Eléments d'épidémiologie rénale : Impact du diabète sur la survie des patients insuffisants rénaux chroniques terminaux

Emmanuel Villar

Université Claude Bernard Lyon 1

Année 2010

Demande d'Habilitation à Diriger les Recherches

Eléments d'épidémiologie rénale :

Impact du diabète sur la survie des patients insuffisants rénaux chroniques terminaux

M. Emmanuel VILLAR,

Né le 19 janvier 1973, à Laxou (Meurthe et Moselle, 54)

Jury :
Pr Bertrand DUSSOL (Marseille)
Pr René ECOCHARD (Lyon)
Pr Luc FRIMAT (Nancy)
Pr Michel LABEEUW (Lyon)
Pr Yves PIRSON (Bruxelles)
Pr Charles THIVOLET (Lyon)
Pr Philippe ZAOUI (Grenoble)

TABLES DES MATIERES

Correspondance des références données dans le texte, P : publications (p 50 – 53) ; O : communications orales (p 54 – 58) ; et A : communications affichées (p 59 – 62).

1. CURRICULUM VITAE

1.1 ETAT CIVIL

Emmanuel Christian Robert VILLAR
Ne le 19/01/1973 a Laxou (Meurthe et Moselle)
Nationalité : française
Marié, deux enfants

1.2 ADRESSE PERSONNELLE

✐ 89, avenue de Verdun, 69540 Irigny
☎ 04 78 50 48 07 / 06 03 50 82 87

1.3 ADRESSE PROFESSIONNELLE

Hospices Civils de Lyon
Service de Néphrologie et de Transplantation Rénale
Centre Hospitalier Lyon Sud
✐ 165, chemin du Grand Revoyet, 69495 Pierre Bénite Cedex
☎ 04 72 67 87 00
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Email : emmanuel.villar@chu-lyon.fr

1.4 DIPLOMES ET CERTIFICATS

Habilitation à Diriger les Recherches : autorisation d'inscription à l'HDR donnée par le Président de l'Université Claude Bernard Lyon 1 le 17/02/2009.

FORMATION SCIENTIFIQUE	**ANNEE**
Doctorat d'Epidémiologie (UCB – Lyon 1)	2007
DEA – Méthodes d'Analyse des Systèmes de Santé (UJM – Lyon 3)	2000
MSBM (Université de Bourgogne et UCB – Lyon 1)	1999

FORMATION MEDICALE	**ANNEE**
Doctorat de Médecine (UCB – Lyon 1, Thèse d'exercice)	2001
DES de Néphrologie (UCB – Lyon 1)	2001
Concours de l'internat (zone nord : 99ème ; zone sud : 289ème)	1996
Concours de 1ère année de Médecine (Université de Bourgogne, classé 9ème)	1991
Baccalauréat C	1990

FORMATION COMPLEMENTAIRE	ANNEE
DU de pédagogie médicale (UCB – Lyon 1)	2009
DU d'interprétation des essais thérapeutique (UCB – Lyon 1)	2003
Atelier de rédaction de projet de recherche clinique (HCL)	2002
Formation Logiciel SPSS (HCL)	2002
DIU de Transplantation d'organes (UCB – Lyon 1)	1998

1.5 FONCTIONS HOSPITALIERES ET HOSPITALO-UNIVERSITAIRES

FONCTIONS	ANNEE
Praticien Hospitalier	Depuis le 01/07/2005*
Praticien Hospitalier Contractuel	2004 – 2005
Assistant des Hôpitaux de Lyon Chef de Clinique a la Faculté de Médecine Lyon Sud	2001 – 2004
Interne des Hôpitaux de Lyon	1996 – 2001**
Etudiant en Médecine (CHU de Dijon – Université de Bourgogne)	1990 – 1996

* : disponibilité du 01/01/2007 au 31/12/2007 pour Etudes et Recherche (année post-doctorale)
** : disponibilité du 01/11/1999 au 31/10/2000 pour Etudes et Recherche (DEA)

1.6 MOBILITES HORS UCB – LYON 1 ET HOSPICES CIVILS DE LYON

Diplôme d'Etudes Approfondies MASS (Méthode d'Analyse des Systèmes de Santé) : Université Jean Moulin Lyon 3.
Du 01/11/1999 au 31/10/2000

Année post-doctorale : ANZDATA Registry, The Queen Elizabeth Hospital and University of Adelaide, Adelaide, South Australia, Australia.
Du 01/01/2007 au 31/12/2007

1.7 SOCIETES SAVANTES

Membre de la *Société de Néphrologie*
Membre élu de la Commission d'Epidémiologie (2005, réélu en 2009)
Membre de la *Société Francophone de Transplantation*
Membre de l'association *CERRT Centre Est Réunion Rein Transplant*
Président (2010)
Membre de l'*Association Régionale des Néphrologues de Rhône Alpes*
Membre de l'*European Renal Association – European Dialysis and Transplant Association*
Membre de l'*International Society of Nephrology*

2. PARCOURS HOSPITALO-UNIVERSITAIRE : RESUME

1996 – 2001 : Interne en Médecine, DES de Néphrologie
Hospices Civils de Lyon, Université Claude Bernard Lyon 1

2001 – 2004 : Assistant – Chef de Clinique
Service de Néphrologie – Transplantation rénale, CHLS
Pr Labeeuw, Pr Pouteil-Noble
Hospices Civils de Lyon
Université Claude Bernard Lyon 1, UFR Médecine Lyon Sud

Depuis 2004 : Praticien Hospitalier (nomination le 01/07/2005)
Service de Néphrologie – Transplantation rénale, CHLS
Pr Labeeuw, Pr Pouteil-Noble
Hospices Civils de Lyon

Service de Néphrologie et de Transplantation Rénale du CHLS :

Le Service de Néphrologie du CHLS comprend depuis janvier 2005 :

- un centre de dialyse lourd de 10 postes,
- un hôpital de jour accueillant 20 patients par jour,
- une unité d'hospitalisation conventionnelle de 19 lits
- et une unité de soins lourds, l'unité commune Uro-Néphrologique, de 8 lits.

Responsabilités actuelles :

Responsable médical pour la Néphrologie de l'Unité Uro-Néphrologie depuis son ouverture en janvier 2005,

Responsable du cycle de cours aux Etudiants hospitaliers du Service de Néphrologie du CHLS,

Notre activité clinique est polyvalente, principalement axé vers

- la transplantation rénale,
- le suivi de la maladie rénale chronique avant le stade terminal de l'insuffisance rénale chronique
- et la prise en charge de l'insuffisance rénale aiguë.

Notre parcours hospitalo-universitaire est détaillé en Annexe A, à la fin de notre mémoire.

3. ACTIVITE D'ENSEIGNEMENT

3.1 RESUME DE L'ACTIVITE D'ENSEIGNEMENT

Notre expérience a débuté au cours de notre Internat de Médecine lorsque nous avons été sollicité pour les conférences d'Internat de la Faculté de Médecine Laënnec (UCB – Lyon 1). Elle s'est consolidée au cours de notre clinicat (2001 – 2004) et se poursuit actuellement par notre implication dans l'enseignement de Néphrologie à la Faculté de Médecine Lyon Sud (Pr Pouteil-Noble, Pr Labeeuw), dans l'enseignement du DES de Néphrologie, de Biostatistique et d'Epidémiologie, ou de Diplômes Universitaires.

Cette expérience s'est enrichie en 2008 – 2009 lorsque nous avons suivi les cours du Diplôme Universitaire de Pédagogie Médicale organisé par le Pr G. Llorca à l'Université Claude Bernard Lyon 1 (Cf. §1.4 Diplômes et certificats). Cet enseignement théorique s'est concrétisé :

- par la sélection de notre mémoire par le jury du Diplôme Universitaire pour être publié sous forme de parcours pédagogique sur le site de formation médicale continue des Actualités Claude Bernard en avril 2010 (http://acb.univ-lyon1.fr/).
- par la mise en place d'un cycle d'enseignement de Néphrologie pour les Etudiants Hospitaliers affectés dans le service avec présentations de cas cliniques, présentation théoriques et mise en situation clinique des étudiants.

Au total, nous avons réalisé plus de 500 heures d'enseignement, aussi bien lors de cours magistraux que d'enseignement dirigés, principalement à destination des Etudiants en Médecine, mais également des Internes DES de Néphrologie et DES de Biochimie de la région Rhône – Alpes, des Réanimateurs médicaux (DU de Réanimation Néphrologique), des infirmières ou des étudiants en BTS Diététique.

3.2 ENSEIGNEMENT AUX ETUDIANTS HOSPITALIERS

Cycle d'enseignement aux Etudiants affectés dans le Service de Néphrologie du Centre Hospitalier Lyon Sud (cycle de 3 mois, 1 h toutes les 2 semaines) :

Sémiologie néphrologique
Insuffisance rénale chronique (ECN 253)
Insuffisance rénale aiguë (ECN 252)
Néphropathie diabétique (ECN 233)
Néphropathie vasculaire (ECN 134)
Hypertension rénovasculaire (ECN 130)
Techniques de dialyse (ECN 253)
Néphropathies glomérulaires (ECN 264)
Polykystose rénale (ECN 277)
Néphropathie lupique (ECN 117)
Transplantation rénale (ECN 127)

Chaque question est traitée par un groupe de deux à trois étudiants, autour d'un cas clinique. Nous encadrons la réalisation des présentations (cas clinique, rappels de cours) et animons la séance de cours proprement dite.

Apprentissage par problème :
Avec les Etudiants de DCEM4 affectés au Service, nous avons également mis en place une activité d'apprentissage par problème sur le thème 'augmentation de la créatininémie'.

Par groupe de quatre à six étudiants, à partir d'un cas clinique simple, nous mettons en place une démarche d'apprentissage par problème qui comprend :

- l'analyse initiale du problème,
- une élaboration sur les connaissances antérieures : génération d'hypothèses,
- une recherche de réponse en groupe,
- un retour sur la situation du problème.

3.3 ENSEIGNEMENT MAGISTRAL ET TRAVAUX DIRIGES

Cours aux Etudiants en Médecine :

Etudiants	UFR	Titre du cours	Type de cours	Date
DCEM3	Lyon Sud	Insuffisance rénale aigue Hyperkaliémie Cas cliniques	Cours magistral Cours Magistral Travaux dirigés	12/03/2010
DCEM4	Lyon Sud	Lecture critique d'article : Epidémiologie	Travaux dirigés	11/02/2010
DCEM3	Lyon Sud	Lithiase rénale : aspects médicaux	Cours magistral	03/02/2010
DCEM3	Lyon Sud	Lecture critique d'article : Epidémiologie	Travaux dirigés	23/02/2009
DCEM3	Lyon Sud	Insuffisance rénale aigue Hyperkaliémie Cas cliniques	Cours magistral Cours Magistral Travaux dirigés	15/04/2009
DCEM3	Lyon Sud	Lithiase rénale : aspects médicaux	Cours magistral	16/02/2009
DCEM3	Lyon Sud	Insuffisance rénale aigue Hyperkaliémie Cas cliniques	Cours magistral Cours Magistral Travaux dirigés	21/03/2008
DCEM3	Lyon Sud	Lithiase rénale : aspects médicaux	Cours magistral	13/02/2008
DCEM3	Lyon Sud	Insuffisance rénale aigue	Cours magistral	31/03/2006
DCEM4	Lyon Nord	Examen classant national : Néphrologie	Travaux dirigés	22/02/2006
DCEM3	Lyon Sud	Insuffisance rénale aigue	Cours magistral	13/04/2005
DCEM3	Lyon Sud	Cas clinique : glomérulonéphrite	Travaux dirigés	08/04/2005
DCEM4	Lyon Nord	Examen classant national : Néphrologie	Travaux dirigés	09/02/2005
DCEM2	Lyon Sud	Lithiase rénale : aspect médicaux	Cours magistral	07/04/2004
DCEM1	Lyon Sud	Sémiologie Médicale : Néphrologie	Cours magistral	05/03/2004 26/03/2004 09/04/2004
DCEM4	Lyon Nord	Examen classant national : Néphrologie	Travaux dirigés	07/02/2004
DCEM2	Lyon Sud	Insuffisance rénale aiguë	Cours magistral	10/03/2003
DCEM2	Lyon Sud	Lithiase rénale : aspect médical	Cours magistral	19/02/2003
DCEM2	Lyon Nord	Insuffisance rénale aiguë	Cours magistral	07/01/2003
DCEM3	Lyon Nord	Lithiase rénale : aspect médical	Cours magistral	10/12/2002
DCEM3	Lyon Nord	Hématurie	Cours magistral	10/12/2002
DCEM3	Lyon Nord	Polykystose rénale autosomique dominante	Cours magistral	03/12/2002
DCEM4	Lyon Nord	CSCT de Néphrologie	Cours magistral	29/11/2002
Externes	Néphrologie CHLS	Eléments de Néphrologie	Cours magistral	11/07/2002
DCEM3	Lyon Nord	Insuffisance rénale aiguë	Cours magistral	11/03/2002
DCEM3	Lyon Nord	Insuffisance rénale aiguë	Travaux dirigés	14/03/2002
DCEM3	Lyon Sud	Troubles hydro-électrolytiques	Travaux dirigés	25/02/2002 27/02/2002
DCEM3	Lyon Sud	Hypertension artérielle	Travaux dirigés	04/03/2002

				13/03/2002
DCEM2	Lyon Nord	Insuffisance rénale aiguë	Travaux dirigés	08/01/2002
DCEM4	Lyon Nord	CSCT de Néphrologie	Cours magistral	30/11/2001
DCEM2	Grange Blanche	Glomérulopathies	Travaux dirigés	13/04/2001
Externes	Pavillon N HEH	Pyélonéphrite aiguë Colique néphrétique	Cours magistral	14/02/2001

Enseignement en Biostatistique :

Master 1 : *Biostatistique et Modélisation* (Pr Roy, Biostatistique UCBL1))

Enseignement dirigé : analyse de survie

27 mai 2010

2 juin 2009

Lecture critique d'article :

27 avril 2010

11 février 2010

23 février 2009

Cours aux Internes DES et DIS de Néphrologie de la région Rhône Alpes :

Prise en charge de l'anémie chez le patient IRC avant le stade de la dialyse, 21 avril 2005.
Rejet aigu cellulaire et néphropathie chronique d'allogreffe, 3 mars 2005.
Membranes et solutés de dialyse, 25 mars 2004.
Prise en charge de l'anémie en pré-dialyse, 21 février 2003.

Enseignement pratique de Sémiologie médicale :

Sept étudiants en PCEM 2, Faculté de Médecine Lyon Sud.
Responsable : Pr C. Broussolle.
Année Universitaire 2003 – 2004 (46 heures de travaux pratiques).
Année Universitaire 2002 – 2003 (46 heures de travaux pratiques).
Année Universitaire 2001 – 2002 (46 heures de travaux pratiques).

Cours du DU de Réanimation Néphrologique (Responsable : Pr Guerin, Lyon) :

Prévention de l'insuffisance rénale aiguë, 6 mars 2006.
Syndrome hémolytique et urémique, 6 mars 2006.
Monitoring per-dialytique, 13 avril 2005.
Prévention de la dégradation de la fonction rénale, 15 février 2005.
Désordres acido-basiques, 1er décembre 2004.

Capacité de Médecine d'Urgence :

Colique néphrétique et Pyélonéphrite aiguë
Responsable : Pr P.Y. Gueugniaud
28 mars 2002.

Cours aux Internes DES en Biologie de Lyon :

Eléments de Néphrologie Clinique
DES de biochimie.
Responsable : Dr Mathian, Laboratoire de Biochimie, Centre Hospitalier Lyon Sud
4 mars 2010 et correction de l'épreuve écrite.
3 octobre 2009.
3 juillet 2008.

10 mars 2008 et correction de l'épreuve écrite.
16 mars 2006 et correction de l'épreuve écrite.
12 septembre 2005.
23 septembre 2004 et correction de l'épreuve écrite.
4 mars 2004 et correction de l'épreuve écrite.
6 mars 2003 et correction de l'épreuve écrite.
7 mars 2002.

Cours aux Internes DES de Pharmacie Industrielle et Biomédicale, de Pharmacie Hospitalière et de Pharmacie Spécialisée :
Les traitements immunosuppresseurs
Responsable : Pr Bienvenu, Laboratoire d'Immunologie, Centre Hospitalier Lyon Sud
5 mai 2004.

Cours aux Infirmièr(e)s :
IFSI Clémenceau
Eléments de Néphrologie (1) : Néphropathies, Tableaux clinico-biologiques
Eléments de Néphrologie (2) : Insuffisance rénale chronique, Insuffisance rénale aiguë, Traitements de suppléance de la fonction rénale
29 mars 2010
3 mars 2010

Cours aux Infirmières du service de Néphrologie du Centre Hospitalier Lyon Sud
14 et 28 mars 2006 : Insuffisance rénale chronique, traitement conservateur
18 mars 2002 : Hypotension en cours d'hémodialyse
(en collaboration avec D. Pavan, IDE)
21 janvier 2002 : Néphropathies à Immunoglobuline A
12 décembre 2001 : Diabète de type 2 et dialyse
5 novembre 2001 : Epidémiologie de l'insuffisance rénale chronique terminale.

Cours BTS de diététique :
Eléments de Néphrologie (1) : Néphropathies, Tableaux clinico-biologiques
Eléments de Néphrologie (2) : Insuffisance rénale chronique, Insuffisance rénale aiguë, Traitements de suppléance de la fonction rénale
9 et 15 février 2006.
7 et 8 février 2005.
3 et 4 février 2004.
6 Janvier et 4 février 2003.

3.4 ENCADREMENT D'ETUDIANTS ETRANGERS

M. Philippe Jolicoeur, Université de Montréal, Québec, Canada.
Stage du 30/06/2008 au 25/07/2008 (équivalent 6ème année de Médecine en France).

3.5 CONFERENCES D'INTERNAT

Faculté de Médecine Lyon Sud – Université Lyon I.
Responsable : Pr F. Golfier
DCEM4 : 2003 – 2004, 2004 – 2005, 2005 – 2006, 2008 – 2009, 2009 – 2010.
DCEM 3 : 2009 – 2010
Chargé de la préparation à l'examen classant national, discipline Néphrologie (2008-2009-2010)

Faculté de Médecine Laënnec – Université Lyon I.
Responsable : Pr M. Marie-Cardine.
DCEM 3 : Années universitaires : 1998 – 1999, 1999 – 2000, 2000 – 2001, 2001 – 2002.
DCEM 4 : Année universitaire : 2000 – 2001, 2001 – 2002, 2002 – 2003.

Faculté de Médecine Lyon Nord – Université Lyon I.
Responsable : Pr G. Llorca
DCEM4 : Année universitaire : 2003 – 2004.

3.6 REUNIONS BIBLIOGRAPHIQUES

Encadrement des Internes du service de Néphrologie du Centre Hospitalier Lyon Sud :
- 23 février 2006 : A. Brodin (DES), lecture critique : Efficacy and safety of Benazepril for advanced chronic renal insufficiency. Hou FF et al. *N Engl J Med* 2006 354 : 131 – 140.
- 2 mars 2006 : A Karamé (DES), lecture critique : Effect of inhibitors of the renin angiotensin system and other antihypertensive drugs on reanl outcomes: systématic review and meta-analysis. Casas JP et al. *Lancet* 2005 366 : 2026 – 2033.
- 2 mars 2005 : C. Descamps (DES), lecture critique : Effect of fluvastatin on cardiac outcomes in renal transplant recipients: a multicentre, randomised, placebo-controlled trial. Holdas et al. *Lancet* 2003 361: 2024 – 2031.
- 1er décembre 2004 : M. Bailly (DES), lecture critique : Angiotensin receptor blockade versus converting enzyme inhibition in type 2 diabetes ans nephropathy. AH Barnett et al. *N Eng J Med* 2004 351 (19) : 1952 – 1961.
- 24 mars 2004 : A.C. Latreille (DES), lecture critique : Effects of early and late intervention with epoietin alpha on left ventricular mass among patients with chronic kidney disease (stage 3 or 4) : results of a randomized clinical trial. Roger SD et al. *J Am Soc Nephrol* 2004 15 : 148 – 156
- 17 mars 2004 : A. Benahmed (DIS), lecture critique : Enteric coated Mycophenolate Sodium is therapeutically equivalent to Mycophenolate Mofetil in de novo renal transplant patient. Salvadori M et al. *Am J Transplant* 2003 4 : 231 – 236.
- 18 décembre 2003 : V. Chaigne (DES), lecture critique : Immunoprophylaxis with Basiliximab compared with antithymocyte globulin in renal transplant patients receiving MMF-containing triple therapy. Lebranchu et al. *Am J Transplant* 2002 2 : 48 – 56.
- 27 février 2003 : A. Hendawy (DIS), lecture critique : A randomized controlled trial of N-acetylcysteine to prevent radiocontrast nephropathy in cardiac angiography. *Kidney Int* 2002 62 : 2202 – 2207.
- 3 décembre 2002 : S. Toussaint (DES), lecture critique : Erythropoietin therapy may retard progression in chronic renal transplant dysfunction. *Nephrol Dial Transplant* 2002 17 : 1667 – 1673.

- 19 juin 2002 : M. Ducret (DES), Revue bibliographique : Association IEC – ARA II, quel(s) intérêt(s) en Néphrologie ?

Encadrement des étudiants hospitaliers du service de Néphrologie du Centre Hospitalier Lyon Sud

- 25 février 2005, lecture critique : Preventing microalbuminurie in type 2 diabetes. Ruggenenti P et al. *N Engl J Med* 2004 351 : 1941 – 1951
- 19 novembre 2004, lecture critique : Treating anemia early in renal failure patients slows the decline of renal function: a randomized controlled trial. Gouva C et al. *Kidney Int* 2004 66 : 753 – 760.
- 5 juin 2004, lecture critique : Eléments de méthodologie des essais cliniques (Exemple : étude NEPHRODIAB2), lecture critique : étude RENAAL.
- 21 février 2003, lecture critique : A randomized controlled trial of haemoglobin normalization with epoetin alpha in pre-dialysis and dialysis patients, *Nephrol Dial Transplant* 2003 18 : 353 – 361.
- 20 décembre 2002, lecture critique : Effect of homocystein lowering therapy with folic acid, vitamin B12, and vitamin B6 on clinical outcome after percutaneous coronary intervention, *JAMA* 2002 288 (8) : 973 – 979.

3.7 JURY D'EXAMENS

ECN blanc, UFR Lyon Sud (Pr Glehen) : 28 mars 2008 et correction
CSCT 2ème session, UFR Lyon Nord (Pr Llorca) : 20 mars 2008 et correction
Internat Blanc, Faculté Lyon Sud, épreuve écrite et correction (cas clinique) : 26 mars 2006
Epreuve orale DCEM2 (Pr Gilly) : 3 juin 2009
Epreuve orale DCEM3 (Pr Gilly) : 4 juin 2010

3.8 FORMATION MEDICALE CONTINUE

RMC - Vienne, Médecins Généralistes, 10 avril 2008
Hypertension artérielle secondaire
Association anti-hypertensive

PROBIOQUAL – Lyon, Biologistes
25 juin 2010 : Néphropathie diabétique
26 novembre 2009 : Troubles minéraux et osseux associés à la maladie rénale chronique

Formation Médicale Continue – Commission d'Epidémiologie de la Société de Néphrologie
11ème réunion commune de la Société de Néphrologie et de la Société Francophone de Dialyse. Toulouse, France. Septembre 2009
Villar E, Couchoud C. Epidémiologie : analyse de la survie des patients dialysés.

4. ACTIVITE DE RECHERCHE

Correspondance des références données dans le texte, P : publications (p 50 – 53) ; O : communications orales (p 54 – 58) ; et A : communications affichées (p 59 – 62).

4.1 UNITE DE RECHERCHE

Nous sommes partenaire du :

- **Service de Biostatistique** des Hospices Civils de Lyon dirigé par le Pr R Ecochard
- et du **Laboratoire Biostatistique Santé** de l'Université Claude Bernard Lyon 1 dirigé par le Pr P. Roy
- au sein de **l'UMR CNRS 5558** dirigé par le Pr J.P. Flandrois.

Nous y avons réalisé notre Thèse de Doctorat (Cf. § 4.3) :

Apport des méthodes récentes de modélisation de survie dans le contexte spécifique des patients dialysés
Directeur : Pr R. Ecochard.
Ecole doctorale : Evolution, Ecosystèmes, Microbiologie et Modélisation, UMR CNRS 5558, Directeur : Pr Flandrois
Doctorat soutenu publiquement le 24 mai 2007
Jury : Pr Frimat (Nancy, Président), Pr Brunet (Marseille, rapporteur), Pr Ecochard, Pr Labeeuw, Dr Stengel (Inserm, Paris, rapporteur).
http://tel.archives-ouvertes.fr/tel-00160433/en/

Nous co-encadrons des étudiants avec le Pr R. Ecochard (Cf. §4.7, 6.1 et 6.2) :

M. Liacine BOUAOUN (étudiant Biostatistique, Master 2), année 2009 - 2010
Modélisation de l'espérance de vie des patients insuffisants rénaux terminaux par rapport à la population générale : intérêt de l'utilisation de modèles additif et multiplicatif

Mme F. Vanrietvelde-Sens (Interne DES de Néphrologie HCL, Master 2, Epidémiologie), année 2010 – 2011
Etude de l'adéquation patient - structure de dialyse et des flux de patients entre structures à partir des données REIN

Mme le Dr C. Couchoud, coordinatrice nationale du registre REIN à l'Agence de la Biomédecine
Thèse de Doctorat dirigé par le Pr R. Ecochard
Modèle multi-états, flux des patients entre technique de suppléance de la fonction rénale et survie.

Nous participons enfin à **l'enseignement de biostatistique et d'épidémiologie** (Cf. § 3.2) :

Master 1 : *Biostatistique et Modélisation* (Pr Roy, Laboratoire Biostatistique-Santé, Service de Biostatistique, HCL, UCBL1))
Enseignement dirigé : analyse de survie
Lecture critique d'article (Epidémiologie)

4.2 ACTIVITE DE RECHERCHE AU COURS DU DEA (1999 – 2000)

Notre DEA (Méthode d'Analyse des Systèmes de Santé) a été réalisé à l'Université Jean Moulin - Lyon 3, au sein du Laboratoire GRAPHOS du Pr Claveranne, encadré par M. le Dr Ch. Pascal (PhD, MCU), Mme le Pr Pouteil-Noble et M. le Pr Ecochard.

L'enseignement théorique comportait des cours d'économie et d'économétrie de la Santé, de comptabilité publique, d'analyse des systèmes de santé, de santé publique et de biostatistique.

Notre sujet de recherche était l'analyse du processus d'inscription sur liste d'attente de transplantation rénale. L'étude a été réalisée dans les services de Néphrologie et Transplantation Rénale du CHU de St Etienne (Pr Berthoux), du CHU de Grenoble (Pr Vialtel) et du CHLS (Pr Labeeuw).

L'étude présentait une problématique double de Santé Publique et d'Epidémiologie :

- d'une part nous avons réalisé une enquête concernant le processus d'inscription des patients insuffisants rénaux chroniques terminaux sur liste d'attente de transplantation rénale dans chacun de ces trois services (observation du process, questionnaires médicaux),
- et d'autre part nous avons constitué la cohorte de patients incidents en dialyse en 1995 – 1998 dans ces trois services (cohorte SEGRELYS – St Etienne, GREnoble et LYon Sud) au sein de laquelle nous avons étudiés les déterminants médicaux de l'inscription sur liste d'attente de transplantation rénale.

Le manuscrit de notre DEA comportait donc une partie « analyse organisationnelle » et une partie « analyse médicale ». Son titre est : « Analyse du processus d'inscription sur liste d'attente de transplantation rénale dans trois services de Néphrologie – Transplantation de la région Rhône – Alpes. »

Ce projet a été financé par une bourse de la Société de Néphrologie (1999) et de la Société Francophone de Transplantation (2000).

Ce travail a fait l'objet d'une publication dans *Nephrology Dialysis and Transplantation* [P21], d'une lettre dans l'*American Journal of Kidney Diseases* [P20], de 3 communications orales [O44, O45, 046] et d'une communication affichée [A36]. Il s'agit de la première étude française publiée du processus de sélection des patients insuffisants rénaux chroniques terminaux traités pour la greffe. Son principal résultat est de souligner le très faible accès à la greffe rénale des diabétiques de type 2 qui sont censurés à la fois avant la sélection pour la réalisation d'un bilan pré-greffe et au cours du bilan pré-greffe [P21].

Cette année de DEA nous a permis d'affirmer notre intérêt pour l'épidémiologie et les biostatistiques, de constituer la cohorte SEGRELYS et d'établir un partenariat privilégié avec le service de Biostatistique du Pr Ecochard (Service de Biostatistique, HCL et UCB – Lyon 1, UMR CNRS 558).

Enfin, la cohorte SEGRELYS nous a permis de nous familiariser avec l'analyse de survie des patients dialysés et d'émettre les premières hypothèses qui allaient conduire à notre travail de Doctorat d'Epidémiologie [O30, A25, A31, A32].

4.3 ACTIVITE DE RECHERCHE AU COURS DU DOCTORAT (2003 – 2007)

Nous avons débuté notre Doctorat d'Epidémiologie dirigé par le Pr René Ecochard en 2003 à l'Université Claude Bernard – Lyon 1 au sein de l'école doctorale E2M2 (Evolution, Ecosystèmes, Microbiologie et Modélisation, UMR CNRS 5558, Directeur : Pr Flandrois) dans le Laboratoire Biostatistique – Santé de l'Université Claude Bernard – Lyon 1, dirigé par le Pr Roy. M. le Pr Labeeuw co-encadrait ce travail.

Le sujet de ce Doctorat était « l'apport des méthodes récentes de modélisation de survie dans le contexte spécifique des patients dialysés ».

Ce travail a comporté deux parties :

- l'une technique biostatistique explorant le problème de la prise en compte de la technique de dialyse dans l'analyse de survie des patients insuffisants rénaux chroniques terminaux traités,
- l'autre clinique et épidémiologique s'intéressant d'une part à la mortalité des patients transplantés cardiaques atteignant le stade terminal de l'insuffisance rénale chronique et d'autre part à l'évaluation de l'excès de mortalité des patients dialysés par rapport à la population générale.

Les bases de données analysées comprenaient la cohorte des patients incidents en dialyse au Centre Hospitalier Lyon-Sud entre 1995 et 2005 (n=539), la cohorte des patients incidents en dialyse en Rhône – Alpes entre 1999 et 2003 (n=3025), et la cohorte des patients incidents en dialyse en Lorraine entre 1997 et 2005 (n=2361). Les hypothèses étaient émises sur les deux premières cohortes puis contrôlées sur la cohorte Lorraine.

Sur le plan biostatistique, nous avons montré que :

- l'effet sur la survie associé aux variables modalité de dialyse et diabète variait avec le temps,
- l'ajustement sur la variable « insuffisance rénale terminale rapidement progressive (<6 mois) » permettait de débiaiser en partie l'effet observé en faveur de la dialyse péritonéale la 1ère année après 1ère dialyse,
- l'ajustement sur la variable « inscription sur liste d'attente de transplantation rénale » permettait de débiaiser en partie l'effet observé en faveur de l'hémodialyse après la 1ère année.
- l'analyse en sous-groupe a montré qu'il existait des interactions entre l'âge, le diabète, les comorbidités cardiovasculaires et l'effet de la modalité de dialyse sur la survie.
- les différents codages de la modalité de dialyse, l'utilisation de scores de propension ou d'un modèle de survie relative ne modifiaient pas ces résultats.

Sur le plan technique, nous avons appris la programmation du logiciel de statistique SPLUS 6.0 (Insightful Corp., Seattle, WA, USA) avec M. L. Remontet (Ingénieur Statisticien, Laboratoire Biostatistique – Santé, HCL).

Sur le plan épidémiologique, nous avons étudié :

- la surmortalité des patients transplantés cardiaques et dialysés [P13],
- l'évolution selon l'âge, le sexe et le statut diabétique de l'excès de mortalité des patients dialysés grâce à l'utilisation des ratios standardisés de mortalité. La nouveauté et l'originalité de cette analyse ont conduit à la publication de l'étude dans le *Journal of the American Society of Nephrology* en 2007 [P12].

La production scientifique issue de ce Doctorat a compris :

- 2 publications en tant que premier auteur [P12, P13],
- 1 publication en tant que 3ème auteur [P19],
- 2 publications en tant que 4ème auteur [P15, P17],
- 3 communications orales [O28, O30, O35],
- 2 communications affichées [A23, A25].

Nous avons présenté notre Doctorat devant l'UCB – Lyon 1 le 24 mai 2007. Le Jury était composé du Pr Frimat (Nancy, Président), du Pr Brunet (Marseille, rapporteur), du Pr Ecochard, du Pr Labeeuw, et du Dr Stengel (Inserm, Paris, rapporteur).

Le manuscrit de notre Thèse est disponible à l'adresse Internet suivante :
http://tel.archives-ouvertes.fr/tel-00160433/en/

Ce travail de Thèse a enfin été synthétisé avec Mrs les Prs Frimat, Ecochard et Labeeuw dans un article publié par la revue *Néphrologie et Thérapeutique*, dans la rubrique « Mise au point » [P27]. Cet article s'attache à présenter les spécificités méthodologiques de l'analyse de survie de données d'observation ou d'essai d'intervention dans la population dialysée. Il a été écrit dans un but didactique pour les médecins néphrologues sans formation théorique en épidémiologie et en biostatistique.

Nous avons également été sollicité pour la première séance de Formation Médicale Continue d'Epidémiologie satellite du congrès de la Société de Néphrologie à Toulouse en 2009 dont le sujet était l'analyse de survie des patients dialysés (co-auteur avec Mme le Dr C. Couchoud, Agence de la Biomédecine, Paris) [O6].

Les résultats obtenus au cours de notre Doctorat nous ont conduit à d'autres hypothèses concernant notamment l'interaction entre le diabète, le sexe féminin et la survie en dialyse, ainsi que l'impact de l'état patient sur la survie précoce en dialyse. Elles ont aboutit au projet de recherche principal de notre année post-doctorale, et aux sujets de Thèse de Médecine de :

- M. A. Karamé (Interne DES de Néphrologie, HCL) [Thèse soutenue le 24/09/2007, publication P4, O23, A7, A8],
- Mlle C. Descamps (Interne DES de Néphrologie, HCL) [Thèse soutenue le 20/10/2008, manuscrit soumis à publication, O20, A6],
- Mme S. Ignace – Girerd (Interne DES de Néphrologie, HCL) [Thèse soutenue le 20/10/2009, manuscrit en cours d'écriture, O18]

4.4 ACTIVITE DE RECHERCHE AU COURS DE L'ANNEE POST-DOCTORALE (2007)

En disponibilité du 01/01/2007 au 31/12/2007 pour études et recherches de notre poste de Praticien Hospitalier dans le Service de Néphrologie du CHLS, nous avons réalisé notre année post-doctorale au sein du Registre Australien et Néo-Zélandais de Dialyse et de Transplantation (ANZDATA Registry).

Nous avons été dirigé par le Dr S. McDonald (MD, PhD), néphrologue et biostatisticien responsable du registre au Queen Elisabeth Hospital et à l'Université d'Adélaïde, à Adélaïde en Australie Méridoniale. Cette structure d'épidémiologie rénale et de recherche comporte :

- un médecin néphrologue et biostatisticien à temps plein (Dr Chang),
- un biostatisticien à mi-temps,
- une responsable administratif à temps plein (data management),
- un informaticien à temps plein,
- deux secrétaires à temps plein.

Ce registre couvre l'ensemble des territoires d'Australie et de Nouvelle Zélande (population totale de 25 millions d'habitants environ au 1er janvier 2007). Il existe depuis 30 ans et recueille les données de patients incidents et prévalents en dialyse et transplantés rénaux de manière annuelle. Les données concernant les comorbidités des patients, notamment le type de diabète et les comorbidités cardiovasculaires, sont enregistrées de manière exhaustive depuis 1991. Au 31/12/2005, la base de données comprenait plus de 28 000 patients adultes incidents en dialyse analysables avec ces données de comorbidités et plus de 7 000 nouveaux patients transplantés, et ce avec un recul de 0 à 15 ans. Cette cohorte a constitué notre matériel d'étude.

Le projet de recherche s'intitulait : « Impact du diabète sur la survie en dialyse et en transplantation rénale ». Ce séjour a été préparé dès avril 2005, le financement ayant été finalisé au deuxième semestre 2006 (Hospices Civils de Lyon, Laboratoires Novartis et Roche).

Cette étude a comporté trois parties :

- l'étude de l'impact du diabète de type 1 et de type 2 sur la survie en dialyse,
- l'étude de l'excès de mortalité en dialyse selon le statut diabétique (comparaison ANZDATA Registry / AusDiab Study),
- l'étude de l'impact des comorbidités associées dont le diabète de type 2 sur la survie en transplantation rénale.

La première partie de l'étude est terminée et le manuscrit publié dans *Diabetes Care* [IF 2007 : 7.8] en décembre 2007 [P10]. Nous avons réalisé l'étude de l'incidence, de la prise en charge de suppléance de l'insuffisance rénale terminale, de la survie et de l'effet associé au sexe féminin sur la survie des patients dialysés, selon leur statut diabétique (type 1, type 2, absence de diabète) en Australie et Nouvelle-Zélande entre 1991 et 2005. Cette étude comporte une population de 28 548 patients incidents insuffisants rénaux terminaux. Il s'agit de l'actualisation de l'épidémiologie du diabète associé à l'insuffisance rénale terminale en Australie et Nouvelle Zélande. Elle nous a permis également :

- de montrer que les patients dialysés de sexe féminin, diabétiques de type 2 et âgées de plus 60 ans ont un pronostic péjoratif après 1ère dialyse par rapport aux patients masculins, diabétiques de type 2 et âgés de plus 60 ans. Cette association n'est pas retrouvée chez les non-diabétiques,

- d'introduire dans le champ de la Néphrologie les courbes de survie à partir de la naissance, ce qui est une manière d'ajuster sur l'âge par une technique visuelle simple,
- et de souligner le pronostic très péjoratif des patients diabétiques de type 1 incident en dialyse et ce malgré un accès important à la transplantation rénale seule ou à la transplantation rénale et pancréatique.

Un second article a été publié dans *Diabetologia* [IF 2008 : 6.4] en décembre 2009 [P3]. Cette étude a été rendue possible par la collaboration avec l'équipe de l'étude AusDiab (Australian Diabetes and Obesity Lifestyle, Dr Polkinghorne, Melbourne, et Pr Chadban, Sydney) qui nous a fournit les taux de mortalité annuels dans une population représentative de la population Australienne selon leur statut diabétique (diabétique de type 2, non diabétique). De manière inattendue, lorsque la surmortalité des patients dialysés est comparée à la population générale non dialysée de même statut diabétique, celle-ci est supérieure chez les non-diabétiques par rapport aux diabétiques de type 2. Cette étude complète l'étude réalisée en Rhône – Alpes [P10].

Un troisième manuscrit (Villar E, Chang SH, McDonald SP. Does sex matter? Outcomes after renal transplant differ between males and females depending on comorbidity) est en cours de finalisation et sera soumis au journal *Clinical Journal of the American Society of Nephrology*. Cette étude montre que le pronostic après 1ère transplantation rénale associé au sexe varie selon la présence ou non de comorbidités associées à l'insuffisance rénale chronique terminale traitée : parmi les patients sans comorbidité, les femmes ont un pronostic favorable par rapport aux hommes transplantés rénaux, alors que parmi les patients avec au moins une comorbidité associée (diabète de type 1, diabète de type 2, comorbidités cardiovasculaires et/ou une pathologie respiratoire chronique), les femmes présentent un pronostic péjoratif par rapport aux hommes.

Cette année nous aura donc permis sur le plan scientifique :

- d'approfondir nos connaissances en analyse de survie des patients dialysés et ce notamment sur une cohorte de plus de 28 000 patients, ce que nous n'avions pas fait jusqu'à présent (cohorte Lyon-Sud : 549 patients, cohorte Rhone Alpes : 3025 patients),
- de réaliser l'analyse de la survie de patients transplantés rénaux sur une cohorte importante de plus de 7000 patients, ce que nous n'avions pas réalisé jusqu'à présent. Ce type d'analyse est plus délicat que l'analyse de cohorte de patients dialysés du fait de variables d'ajustement dépendant non seulement du receveur, mais aussi du donneur,
- de faire avancer les connaissances épidémiologiques concernant l'impact du diabète, notamment du diabète de type 2, sur la survie des patients insuffisants rénaux chroniques dialysés et transplantés rénaux, notamment concernant l'effet différentiel associé au sexe des patients.

Les résultats obtenus confirment notamment les interactions entre sexe et diabète chez les insuffisants rénaux chroniques. Ils nous ont conduit à proposer une étude complémentaire sur les données du registre REIN national (Réseau d'Epidémiologie et d'Information en Néphrologie) qui a été réalisée par Mme S. Ignace – Girerd au cours de sa Thèse de Médecine (Interne DES de Néphrologie, HCL) [Thèse soutenue le 20/10/2009, manuscrit en cours de rédaction, O18].

Cette année nous aura également permis de nouer des liens forts avec l'équipe de l'ANZDATA ainsi qu'échanger sur ces sujets biostatistiques et épidémiologiques avec le Dr McDonald [P1], responsable du registre, et le Dr Chang, néphrologue et épidémiologiste à l'ANZDATA. Elle nous aura également permis d'étudier au plus près l'organisation d'un registre bi-national de patients insuffisants rénaux chroniques traités, en ce qui concerne notamment le management des données, le contrôle qualité, l'articulation avec les équipes néphrologiques en amont (recueil des données) et en aval du registre (analyses biostatistiques et épidémiologiques des données).

Enfin, l'équipe de l'ANZDATA et son directeur (Pr G. Russ, The Queen Elisabeth Hospital et University of Adelaïde, South Australia) qui manage également le registre ANZOD recensant les donneurs cadavériques et leurs caractéristiques en Australie et Nouvelle Zélande m'ont demandé d'analyser l'évolution du prélèvement d'organe en Australie et Nouvelle Zélande depuis 1989. Le manuscrit est en cours d'écriture à ce jour.

4.5 ETUDE NEPHRODIAB2

Parallèlement aux projets menés en biostatistique et en épidémiologie de l'insuffisance rénale, nous avons initié avec Mme le Pr Pouteil-Noble l'étude NEPHRODIAB2 [P29].

Il s'agit d'un essai clinique d'intervention prospectif, randomisé, ouvert, multicentrique, évaluant l'effet de deux cibles d'hémoglobine sur la progression de l'insuffisance rénale chez les patients diabétiques de type 2 insuffisants rénaux chroniques. La durée de suivi est de deux ans pour tous les patients. La cible haute d'hémoglobine était 130 – 149 g / L. La cible basse d'hémoglobine était : 110 – 129 g / L.

Les Hospices Civils de Lyon sont le promoteur de l'étude. Nous en sommes co-investigateur principal avec Mme le Pr Pouteil-Noble. M. le Dr Lièvre, Service de Pharmacologie Clinique de la Faculté de Médecine Laënnec, en est le méthodologiste.

Nous en avons écrit le protocole, recherché le financement, et recherché les centres investigateurs avec Mme le Pr Pouteil-Noble et M. le Dr Lièvre. Nous avons été investigateur à Lyon Sud et avons participé au suivi de l'étude et à son comité directeur.

Les centres investigateurs ont été :

ETUDE NEPHRODIAB2, CENTRES INVESTIGATEURS
1. **Centre Hospitalier Lyon Sud**, Hospices Civils de Lyon, Néphrologie, Pr M. Labeeuw
2. **Hôpital E. Herriot**, Hospices Civils de Lyon, Néphrologie, Pavillon P, Pr M. Laville
3. **CHU de Nancy**, Néphrologie, Pr M. Kessler
4. **CHU de Saint Etienne**, Néphrologie, Pr E. Alamartine
5. **CHU d'Amiens**, Néphrologie, Pr G Choukroun
6. **CHU de Lille**, Néphrologie, Pr P. Dequiedt, Dr O. Moranne
7. **CH de Valenciennes**, Néphrologie, Dr V. Lemaitre

8. **CHU de Grenoble**, Néphrologie, Pr P. Zaoui

9. **CHU de Toulouse**, **Hôpital Rangueil,** Néphrologie, Dr Bernardet-Monrozies

10. **CHU de Clermont-Ferrand**, Néphrologie, Pr P. Deteix, Dr A.E. Heng

11. **CH de Bourg en Bresse**, Néphrologie, Dr Boudray

12. **CH de Vichy**, Néphrologie, Dr Meggraoui

13. **CHU de Nîmes**, Néphrologie, Dr Branger

14. **CHU de Tours**, Néphrologie, Dr Francois

15. **CH de Macon**, Néphrologie, Dr Janin

Le comité directeur de l'étude comprend : Mme le Pr Kessler (Nancy), M. le Dr Lemaitre (Valenciennes), M. le Pr Alamartine (St Etienne), M. le Pr Rossert (Paris), Mme le Pr Pouteil-Noble, M. le Dr Lièvre et M. le Dr Villar.

La conduite de l'étude a été confiée à APRET – EZUS, filiale de l'UCB – Lyon 1. L'attachée de recherche clinique de cette étude est Mme J. Gillet (APRET – EZUS).

L'étude est financée par le PHRC national 2002, une bourse de la Société de Néphrologie – Laboratoires Amgen 2002 et une subvention de recherche des Laboratoires Roche. Les sponsors privés ne sont pas intervenus dans la rédaction du protocole ni la conduite de l'étude.

Les inclusions ont été menées de février 2004 à avril 2006, 89 patients sont inclus. Au Centre Hospitalier Lyon Sud, nous avons assuré le recrutement de 31 patients pour cette étude.

Le recueil des données a été terminé en avril 2008. Les événements cliniques ont été validés par le comité de validation des événements indésirables (Dr François, Médecine Interne CHLS, Dr Belot, Néphrologie Pédiatrique HEH, Dr Nony, Cardiologie Hôpital Cardiologique). L'analyse statistique a été réalisée par le service de Biostatistique des HCL (Dr Rabilloud).

Les résultats de l'étude NEPHRODIAB2 sont :

- Pas d'effet bénéfique de la cible haute d'hémoglobine (130 – 149 g / L) chez les patients diabétiques de type 2 présentant une MRC stade 2-4 en terme :
  - De dégradation de la fonction rénale :
    - Bras 110 – 129 g/L : -8.7 ± 12.2 mL/min/1.73m²
    - Bras 130 – 149 g/L : -5.1±7.8 mL/min/1.73m² (p=0.29)
  - Et de qualité de vie,
- Pas d'effet délétère également en terme :
  - D'événements indésirables graves (DC, EER, événements CV),
  - De pression artérielle.
- Mais les posologies moyennes d'érythropoïétine ont été multipliée par 4 pour augmenter le taux d'hémoglobine de 10 g / L :
  - 1558 +/- 2314 UI / semaine dans le bras 110 – 129 g/L
  - versus 6028 +/- 6729 UI / semaine dans le bras 130 – 140 g/L (p<0,001).

L'étude a été présenté en communication orale lors de la 11ème réunion de la Société de Néphrologie – Société Francophone de Dialyse à Toulouse en 2009 [O17] et en communication

affichée lors du World Congress of Nephrology à Milan en mai 2009 [A3] où elle a été primée (best abstracts presented by young authors and top 20% abstracts). Le manuscrit est en cours de finalisation.

4.6 GROUPES DE TRAVAIL REIN NATIONAL

Nous participons à plusieurs groupes de travail au sein du registre REIN national :

- Groupe « Evaluation » dirigée par le Dr B Stengel (INSERM U1018, Villejuif)
- Groupe « Accès à a transplantation rénale » dirigé par le Dr C Jaquelinet (ABM REIN National)

Plusieurs travaux scientifiques auxquels nous avons participé ont été publiés :

> Lassalle M, Labeeuw M, Frimat L, **Villar E**, Joyeux V, Couchoud C, Stengel B, on behalf of the Rein registry. Age and comorbidity explain the paradoxical association of early dialysis start with poor survival. *Kidney Int* in press 2010 ***[IF 2008 : 6,4]*** [P2]
>
> Thilly N, Stengel B, Boini S, **Villar E**, Couchoud C, Frimat L. Evaluation and determinants of underprescription of erythropoiesis stimulating angents in pre-dialysis patients with anaemia. *Nephron Clin Pract*. 108 (1) : 67 – 74, 2008 ***[IF 2007 : 1,5]*** [P9]

4.7 ENCADREMENT D'ETUDIANTS

Nous avons été à l'origine des sujets de recherche et avons encadré les Thèses de Médecine de Mme F. Vanrietvelde-Sens, Mme S. Ignace-Girerd, Mlle C. Descamps et M. A Karamé.

NOM, DIPLOME, IMPLICATION PERSONNELLE	PUBLICATIONS
Mme F. VANRIETVELDE épouse SENS Interne DES HCL, Thèse de Médecine Comparaison de la survie des patients insuffisants cardiaques dialysés selon la technique de dialyse. Données REIN national 2002 – 2009. Encadrement	Publication en cours d'écriture
Mme Sophie IGNACE épouse GIRERD Interne DES HCL, Thèse de Médecine Impact différentiel selon le sexe des comorbidités sur la survie en dialyse. Données REIN national 2002 – 2008. Encadrement	Soutenance : 20/10/2009 Manuscrit en cours d'écriture 1 com. orale [O18]

Mme Anne-Claire LATREILLE épouse DU BESSET Interne DES HCL, Thèse de Médecine Facteurs de risque de cancer chez les transplantés rénaux Participation méthodologique et à la rédaction de la publication Encadrement par Mme le Pr Pouteil-Noble	Soutenance : 15/12/2008 Manuscrit en cours d'écriture 2 com. affichées [A1, A5]
Mlle Chrystèle DESCAMPS Interne DES HCL, Thèse de Médecine Mortalité précoce en dialyse chronique : rôle du type d'insuffisance rénale terminale (chronique vs aiguë) Co-encadrement avec M. le Pr Labeeuw	Soutenance : 20/10/2008 Manuscrit soumis à publication 1 com. orale [O20] 1 com. affichée [A6]
Mlle Aurélie MATRAT Interne en Pharmacie, UCBL1, Thèse de Pharmacie Intérêt prédictif des anticorps anti-C1q dans la néphropathie lupique Participation méthodologique Encadrement par le Dr P. Trolliet et le Dr N. Fabien (Biochimie CHLS).	Soutenance : 18/12/2008 Manuscrit soumis à publication En cours de correction Cf. § 6.1.1 p 36
M. Alexandre KARAME Interne DES HCL, Thèse de Médecine Interaction du sexe et du diabète sur la mortalité en dialyse Co-encadrement avec M. le Pr Labeeuw	Soutenance : 22/09/2007 1 publication [P4] 1 com. orale [O23] 2 com. affichées [A7, A8]
Mme Stéphanie TOUSSAINT Interne DES HCL, Thèse de Médecine Intérêt de la qPCR CMV en transplantation rénale Participation méthodologique et à la rédaction de la publication Encadrement par Mme le Pr Pouteil-Noble	Soutenance : 15/06/2007 1 manuscrit en cours d'écriture 1 com. orale [O27]
M. Hachraf HENDAWY Interne DIS, Mémoire de DIS Transplantation cardiaque et insuffisance rénale Co-encadrement avec Mme le Pr Pouteil-Noble	2 publications [P13, P19] 1 com. orale [O35] 2 com. affichées [A29, A30]

M. Eli NAJJAR Interne DIS, Mémoire de DIS Facteurs de risque cardiovasculaire et insuffisance rénale Co-encadrement avec Mme le Pr Pouteil-Noble	1 com. orale [O40]

Rédaction de cas cliniques :

- M. A. Karamé (2007), co-encadrement avec Mme le Pr Pouteil-Noble : 1 com. affichée [A13].
- Mlle S. Ignace (2007), co-encadrement avec Mme le Pr Pouteil-Noble : 1 publication [P8], 1 com. affichée [A14].
- Mlle A. Koenig (2010), rédaction en cours (SHU atypique chez un patient transplanté cardiaque traité par rituximab).

4.8 BOURSES DE RECHERCHES

Au 31/05/2010, les financements obtenus se chiffrent à **633 700 euros**. Les financements pour le projet « Analyse du processus d'inscription sur liste d'attente de transplantation rénale » (DEA 1999 – 2000) et l'étude NEPHRODIAB2 ont été obtenu avec Mme le Pr Pouteil-Noble.

Dans tous les cas, les sponsors n'ont pas participé à la rédaction du protocole de recherche, à la conduite de l'étude et à la rédaction des publications.

Demande d'Allocation de Recherche en Cours
Appel d'Offre REIN 2010 :
Etude de l'adéquation patient - structure de dialyse et des flux de patients entre structures à partir des données REIN
Projet de Master 2 – Epidémiologie, Mme F. Vanrietvelde-Sens (année 2010 – 2011)
Partenariat : Service d'Epidémiologie – Pr Colin, Pr Schott

SOURCES, PROJET, FINANCEMENT	PUBLICATIONS
Appel d'offre REIN 2009 Modélisation de l'espérance de vie des patients insuffisants rénaux terminaux par rapport à la population générale : intérêt de l'utilisation de modèles additif et multiplicatif 20000 € En partenariat avec le Service de Biostatistique, Pr Ecochard, M. Liacine BOUAOUN (étudiant Biostatistique, Master 2)	Etude en cours

Laboratoire Roche 2007 Impact du diabète de type 2 sur la survie des patients dialysés et transplantés rénaux (registre ANZDATA), 8000 €	3 publication [P1, P3, P10] 2 articles en cours de rédaction 2 com. orales [O10, O11] 2 com. affichées [A9, A10]
Laboratoire Novartis 2007 Impact du diabète de type 2 sur la survie des patients dialysés et transplantés rénaux (registre ANZDATA), 15 000 €	3 publication [P1, P3, P10] 2 articles en cours de rédaction 2 com. orales [O10, O11] 2 com. affichées [A9, A10]
Hospices Civils de Lyon 2007 Impact du diabète de type 2 sur la survie des patients dialysés et transplantés rénaux (registre ANZDATA), Allocation de séjour à l'étranger : 7500 €	3 publication [P1, P3, P10] 2 articles en cours de rédaction 2 com. orales [O10, O11] 2 com. affichées [A9, A10]
Laboratoire Roche 2006 Etude NEPHRODIAB2 : 30 000 €	Publication principale soumise [Nephrol Dial Transplant 18/02/2010] 2 publications [P18, P29] 3 com. orales [O16, O17, O29] 2 com. affichées [A3, A18]
Société de Néphrologie – Bourse Amgen 2002 Etude NEPHRODIAB2 : 184 000 €	Publication principale soumise [Nephrol Dial Transplant 18/02/2010] 2 publications [P18, P29] 3 com. orales [O16, O17, O29] 2 com. affichées [A3, A18]
PHRC national 2002 Etude NEPHRODIAB2 : 351 000 €	Publication principale soumise [Nephrol Dial Transplant 18/02/2010] 2 publications [P18, P29] 3 com. orales [O16, O17, O29] 2 com. affichées [A3, A18]
Société Francophone de Transplantation 2000, Allocation Fujizawa Analyse du processus d'inscription sur liste d'attente de transplantation rénale 60 000 FF (9100 €)	2 publications [P21, P22] 3 com. orales [O44, O45, 046] 1 com. affichées [A33]

Société de Néphrologie 1999, Allocation Baxter Analyse du processus d'inscription sur liste d'attente de transplantation rénale 60 000 FF (9100 €)	2 publications [P21, P22] 3 com. orales [O44, O45, 046] 1 com. affichées [A33]

4.9 ORGANISATION DE REUNIONS SCIENTIFIQUES

Réunion de CERRT (Centre Est La Réunion Rein Transplant, association régionale de transplantation rénale et pancréatique)

Président (2010)
Membre du comité d'organisation de la 11ème réunion scientifique CERRT 2010
20 mai 2010 (programme complet en Annexe B)

Réunion SDRD (Développement et Recherche en Néphrologie en Rhône Alpes)

Membre fondateur (2006), membre du conseil scientifique
Deux réunions scientifiques annuelles : présentation des projets de recherche des différentes équipes de Néphrologie des CHU de Rhône Alpes par les internes et CCA
Une présentation rapportée à l'équipe de Lyon Sud par semestre

Réunion de Internes DES de Néphrologie du CHU de Lyon

Membre fondateur (2005)
Six réunions scientifiques annuelles autour d'un thème clinique

5. IMPACT DU DIABETE SUR LA SURVIE DES PATIENTS INSUFFISANTS RENAUX CHRONIQUES TERMINAUX

Nous présentons ici la synthèse des résultats de cinq études publiés entre 2004 et 2009 formant une analyse cohérente de l'épidémiologie des patients diabétiques insuffisants rénaux terminaux :

Villar E, Polkinghorne K, Chang SH, Chadban SJ, McDonald SP. Effect of type 2 diabetes on mortality risk associated with end-stage renal disease. *Diabetologia* 52 (12) : 2536 – 2541, 2009 ***[IF 2008 : 6,4]***

Karamé A, Labeeuw M, Trolliet P, Caillette-Beaudoin A, Cahen R, Ecochard R, Galland R, Hallonet P, Pouteil-Noble C, **Villar E**. The impact of type 2 diabetes on mortality in end-stage renal disease patients differs between genders. *Nephron Clin Pract*. 112 (4) : 268 – 275, 2009 ***[IF 2008 : 1,7]***

Villar E, Chang SH, McDonald SP. Incidences, treatments, outcomes, and gender effect on survival in end-stage renal disease patients by diabetic status in Australia and New Zealand (1995-2005). *Diabetes Care*. 30 (12) : 3070 – 3076, 2007 ***[IF 2007 : 7,8]***

Villar E, Remontet L, Labeeuw M, Ecochard R, on behalf of the Association Régionale des Néphrologues de Rhône-Alpes and the French Renal Information and Epidemiology Network registry. Effect of age, sex and diabetes on excess death in end-stage renal failure. *J Am Soc Nephrol*. 18 (7) : 2125 – 2134, 2007 ***[IF 2007 : 7,1]***

Villar E, Rabilloud M, Berthoux P, Vialtel P, Labeeuw M, Pouteil-Noble C. A multicentre study of registration on renal transplantation waiting list of the elderly and patients with type 2 diabetes. *Nephrol Dial Transplant*. 19 (1) : 207 – 214, 2004 ***[AO – IF 2004 : 2,7]***

A ces quatre articles originaux, s'ajoutent :

Deux autres publications sur le même thème :

Villar E, McDonald SP, Couchoud C. End stage renal disease among individuals with diabetes or end stage renal disease related to diabetes? Relevance of collected data in renal registries. *Diabetes Care*, in press 2010 ***[Lettre à l'Editeur – IP 2008 : 7,8]***

Couchoud C, **Villar E**, Frimat L, Fagot-Campagna A, Stengel B. L'insuffisance rénale chronique terminale associée au un diabète : fréquence et conditions d'initiation du traitement de suppléance, France, 2006. *Bulletin Epidémiologique Hebdomadaire*. 43 (28/11/2008) : 414 – 418, 2008 ***[Article original – IP : -]***

Les résultats de la Thèse de Médecine de Mme S. Ignace – Girerd (publication en cours d'écriture) :

Impact différentiel selon le sexe des comorbidités sur la survie en dialyse (diabète, artériopathie oblitérante des membres inférieurs, insuffisance cardiaque).
Analyse des données REIN des patients incidents en dialyse en France entre 2002 et 2007.
Soutenue le 20 octobre 2009 devant l'Université Claude Bernard Lyon 1.

Les objectifs de ce projet étaient :

- de mettre à jour de l'épidémiologie du diabète associé à l'insuffisance rénale chronique terminale traitée, notamment concernant les différences de pronostic entre diabétiques de type 1 et diabétiques de type 2,
- d'explorer la surmortalité des patients dialysés par rapport à la population générale selon leur statut diabétique,
- et d'étudier les interactions entre sexe, diabète et survie en dialyse.

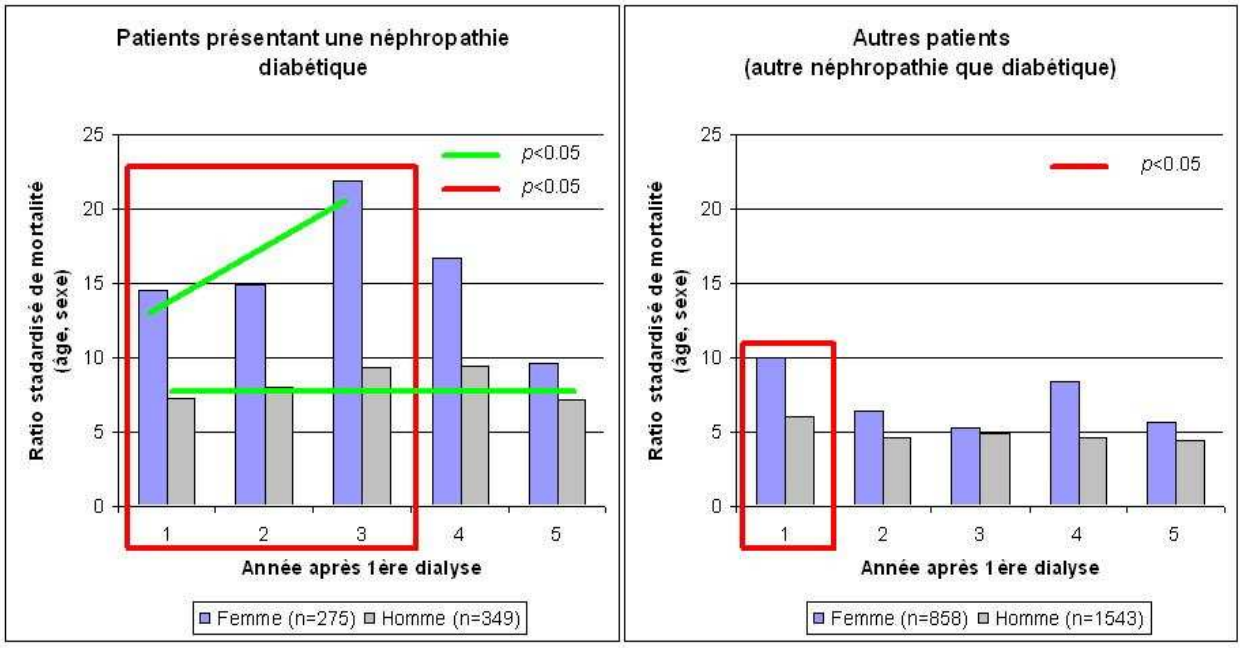
5.1 LE POINT DE DEPART

Au cours de notre Doctorat d'Epidémiologie, nous avons analysé la survie des patients insuffisants rénaux chroniques terminaux avec la technique des ratios de mortalité standardisés (SMR) sur l'âge et le sexe par rapport à la population générale française, méthode développée par Breslow et Day [Breslow et Day 1987]. Cette étude a été réalisée dans la cohorte des patients incidents en dialyse entre 1999 et 2003 en Région Rhône – Alpes (Registre de l'Association Régionale des Néphrologues de Rhône Alpes et Registre REIN à partir de 2002, n=3025) [Villar *et col* J Am Soc Nephrol 2007].

L'objectif de cette étude était d'évaluer la surmortalité des patients dialysés par rapport à la population générale, grâce à une modélisation multiplicative, les SMR.

L'analyse a été stratifiée selon le sexe et la néphropathie initiale (diabétique versus autres néphropathies). Les résultats selon cette stratification sont donnés dans la figure 1 :

Figure 1 : Ratios de mortalité standardisés sur l'âge est le sexe stratifiés selon le sexe et la néphropathie initiale (ligne verte : évolution des SMR au cours du temps après 1ère dialyse ; encadré rouge : différence significative entre SMR selon le sexe), [d'après Villar et col *J Am Soc Nephrol 2007*]



Comme attendu, en tenant compte de l'âge et du sexe, les SMR sont significativement supérieurs chez les patients présentant une néphropathie diabétique quel que soit leur sexe, comparés aux SMR des patients présentant une néphropathie non diabétique (p<0,05), du fait

d'un nombre plus important de comorbidités et donc d'une gravité clinique plus importante chez ces patients diabétiques.

Plusieurs autres observations nous ont interpellé :

- Les SMR étaient significativement plus élevés chez les femmes que chez les hommes. Ce résultat a été observé dans d'autres populations présentant une pathologie chronique, comme les obèses [Bender *et col* JAMA 1999]. Il est lié au fait que la mortalité, à âge égal, est plus faible chez les femmes que chez les hommes en population générale, alors que le sexe n'est pas associé à la mortalité en dialyse : l'insuffisance rénale chronique terminale traitée fait disparaître la meilleure survie féminine observée en population générale.

- Cette association excès de mortalité / sexe féminin existe particulièrement, voire exclusivement, chez les patients présentant une néphropathie diabétique, ce qu'illustre la figure 1 ci-dessus.

- L'évolution des SMR après 1ère dialyse est différente selon le sexe chez les patients présentant une néphropathie diabétique : les SMR augmentaient les trois 1ères années après 1ère dialyse chez les femmes, alors que les SMR restaient stable au cours du temps chez les hommes. Cette évolution était différente de l'évolution observée chez les patients ne présentant pas de néphropathie diabétique (figure 1).

Dès lors plusieurs questions se sont posées à nous, constituant l'architecture de notre projet post-doctoral :

- La première question touchait à la pertinence de la stratification diabétique / non diabétique dans la population dialysée. Chez les patients insuffisants rénaux chroniques, le diabète peut être soit la cause de la néphropathie (glomérulosclérose diabétique dite néphropathie diabétique) soit une comorbidité, la cause de l'insuffisance rénale pouvant ne pas être diabétique. Par ailleurs, il existe deux grands types de diabète, le diabète de type 1, du sujet jeune, insulinoprive, et le diabète de type 2, du sujet âgé, ou diabète gras, avec des étiologies, une prise en charge, des complications et des pronostics différents.

- La seconde question fut celle de la mise à jour de l'épidémiologie de l'insuffisance rénale chronique traitée chez les patients diabétiques, en considérant le diabète comme comorbidité et en différenciant diabétiques de type 1 et de type 2.

- La troisième question fut celle de l'interaction sexe / diabète concernant la survie en dialyse, observée dans la cohorte Rhône Alpes 1999 – 2003.

- La quatrième fut celle de l'évaluation de la surmortalité des patients dialysés grâce à la technique des SMR lorsque ceux-ci sont standardisés sur l'âge, le sexe, mais également sur le statut diabétique.

Ces questions ont été l'objet d'études réalisées dans les cohortes des patients incidents en dialyse :

- au CHLS (Thèse de Médecine de M. A. Karamé [Karamé *et col* Nephron Clin Pract 2009]),
- en France, au sein du Registre REIN national (Thèse de Médecine de Mme S. Ignace – Girerd),
- et en Australie - Nouvelle Zélande en collaboration avec le registre ANZDATA (Dr SP McDonald, Adelaïde) et les promoteurs de l'étude AusDiab (Dr K Polkinghorne, Melbourne, et Pr S Chadban, Sydney).

Les pré-requis méthodologiques de l'analyse de survie en dialyse développés lors de notre Doctorat d'Epidémiologie ne seront pas repris ici, en ce qui concerne notamment la nécessité d'analyser la survie uniquement chez les patients incidents en dialyse et la variation des risques relatifs de survie au cours du temps.

5.2 LE DIABETE COMME NEPHROPATHIE OU COMME COMORBIDITE ?

Jusqu'à nos travaux récents, les principales études épidémiologiques réalisées chez les patients dialysés diabétiques sont issues du registre américain United States Renal Data System (USRDS) et du registre européen de l'European Renal Association – European Dialysis and Transplant Association (ERA – EDTA) qui regroupe des données d'une dizaine de pays européens.

Les diabétiques sont identifiés grâce à leur néphropathie causale ('néphropathie diabétique') dans les deux registres [Burrows *et col* Diabetes Care 2010 ; van Dijk *et al* Kidney Int 2005]. Le registre européen différencie ensuite diabétiques de type 1 et diabétiques de type 2 [van Dijk *et col* Kidney Int 2005]. Le type de diabète chez les patients incidents en dialyse et présentant une néphropathie diabétique n'est connu que depuis 2001 aux USA [www.usrds.org] et, à notre connaissance, n'a pas fait l'objet de publications scientifiques spécifiques à ce jour.

Les diabétiques de type 2 représentent la vaste majorité des patients diabétiques incidents en dialyse [Ritz E *et col* Am J Kidney Dis 1999]. En 2006, dans les 16 régions françaises participant au registre REIN, 2158 patients ayant comme comorbidité un diabète ont débuté la dialyse, soit 34,1% des patients incidents [Couchoud *et col* BEH 2008]. Parmi eux, 87,9% était diabétiques de type 2 [Couchoud *et col* BEH 2008]. En Australie et Nouvelle Zélande, de 1991 à 2005, 9844 patients insuffisants rénaux chroniques terminaux présentaient un diabète associé (34,5% des patients incidents). 87,0% des diabétiques avait un type 2 [Villar *et col* Diabetes Care 2007].

Un tiers des patients diabétiques de type 2 ayant une protéinurie macroscopique présente des lésions histologiques qui ne sont pas en rapport avec une néphropathie diabétique [Fioretto *et col* Diabetologia 2008]. Des atteintes histologiques associées sont possibles également, en particulier néphropathie diabétique et néphropathie vasculaire (néphroangiosclérose) peuvent coexister [Fioretto *et col* Diabetologia 2008].

En France en 2006, parmi les diabétiques de type 2 incidents en dialyse, seuls 10,4% ont eu une biopsie rénale et le néphrologue référent déclarait une néphropathie diabétique pour seulement 52,6% d'entre eux [Couchoud *et col* BEH 2008]. Dans le registre ANZDATA, entre 1991 et

2005, 16,6% des diabétiques de type 2 incidents en dialyse ont bénéficié d'une biopsie rénale et une néphropathie diabétique était déclarée par le néphrologue référent chez 74,1% d'entre eux [Villar *et col* Diabetes Care 2007].

Pour les diabétiques de type 1, 8,9% ont eu une biopsie rénale en France en 2006 et 65,5% ont été enregistrés avec une néphropathie diabétique [Couchoud *et col* BEH 2008]. En Australie et Nouvelle Zélande, de 1991 à 2005, 12,6% ont eu une biopsie rénale et 93,8% ont été déclarés avec une néphropathie diabétique [Villar *et col* Diabetes Care 2007].

Dans le registre ERA – EDTA, la néphropathie diabétique définit le statut diabétique : pour la période 1991 – 2000, 16873 patients avec une néphropathie diabétique déclarée ont débuté la dialyse, soit 16,8% des patients incidents dans ce registre. Parmi eux, la proportion de diabétique de type 2 était de 55,7% [van Dijk *et col* Kidney Int 2005], bien loin des 85% à 90% de patients diabétiques de type 2 parmi les diabétiques incidents en dialyse dans les pays industrialisés [Ritz E *et col* Am J Kidney Dis 1999, Villar *et col* Diabetes Care 2007, Couchoud *et col* BEH 2008].

Ainsi, dans l'analyse des données de registres de patients insuffisants rénaux chroniques terminaux traités, **utiliser la néphropathie diabétique pour déterminer le statut diabétique sous-estime donc le nombre de patients diabétiques**, notamment les diabétiques de type 2. Ce biais n'est pas contrôlable car la néphropathie est déclarée par le néphrologue référent sans contrôle histologique dans la vaste majorité des cas. Il existe par ailleurs, nous l'avons vu plus haut, des variations de déclaration de diagnostic de néphropathie entre pays tels que la France et l'Australie – Nouvelle Zélande. **Utiliser la comorbidité diabétique pour définir le statut diabétique permet de corriger au moins en partie ce biais**, avec des résultats comparables entre la France et l'Australie – Nouvelle Zélande.

Par ailleurs compte tenu des différences d'étiologie et de caractéristiques des patients, des différences de prise en charge thérapeutique et des différences de pronostic, **il est nécessaire de différencier les deux types de diabète** lors d'analyse épidémiologique en dialyse.

Utiliser une stratification sur l'âge, avec un cut-off à 45 ans comme dans l'étude de l'incidence de l'insuffisance rénale terminale due au diabète parmi la population diabétique aux USA [Burrows *et col* Diabetes Care 2010], est également biaisé. En France, en 2006, seulement 58,0% des patients incidents en dialyse, présentant une comorbidité diabétique et âgé de moins de 45 ans était diabétique de type 1 [Couchoud *et col* BEH 2008]. En Australie – Nouvelle Zélande, ce taux passe de 63,4% en 1991 à 48,2% en 2005 [Villar *et col* Diabetes Care 2007]. La stratification sur l'âge ne permet donc pas de différencier diabète de type 1 et de type 2.

Pour l'analyse épidémiologique des données de registres de patients insuffisants rénaux terminaux, concernant l'étude du diabète, nous recommandons donc :

- de définir le statut diabétique en fonction de la comorbidité 'diabète', et non pas en fonction de la néphropathie causale,
- de différencier l'analyse des diabétiques de type 1 et des diabétiques de type 2.

Ces recommandations s'appliquent également a priori aux analyses en transplantation rénale.

5.3 EPIDEMIOLOGIE DU DIABETE DANS LA POPULATION INCIDENTE INSUFFISANTE RENALE CHRONIQUE TERMINALE TRAITEE (1ère DIALYSE OU TRANSPLANTATION RENALE PREEMPTIVE)

Cette étude a été réalisée sur les données du registre Australien et Néo-Zélandais ANZDATA. Dans l'attente du recul suffisant pour les patients français inclus dans le registre REIN, l'ANZDATA est le seul registre (bi)national permettant d'étudier l'épidémiologie et la survie des patients incidents en dialyse selon leur statut diabétique (type 1, type 2 et non diabétique). La comorbidité diabétique est en effet recueillie de façon prospective depuis 1991. La date de point de l'étude a été le 31/12/2005 et a inclus 28548 patients dont 1284 diabétiques de type 1 (4,5%) et 8560 diabétiques de type 2 (30,0%). Elle a été publiée dans Diabetes Care [Villar *et col* Diabetes Care 2007].

Les objectifs étaient de comparer diabétiques de type 1 et de type 2 quant à leurs caractéristiques à la première dialyse, l'évolution de leurs incidences standardisées entre 1991 et 2005, et leurs survies.

Les principaux résultats sont :

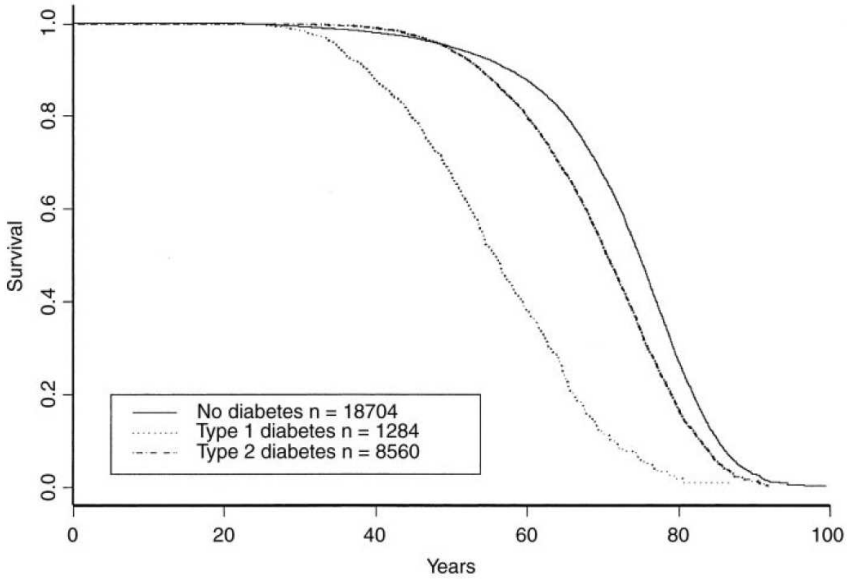
- le très fort taux d'artériopathie des membres inférieurs chez les patients diabétique de type 1 (43,2%), identique à celui des diabétiques de type 2, mais chez des patients âgés en moyenne de 43,1 ans contre 61,2 ans pour les diabétiques de type 2,

- Une très forte augmentation du taux d'incidence des patients insuffisants rénaux chroniques terminaux présentant un diabète de type 2. L'augmentation est de +10,2% [+9,6% ; +10,8%] par an en moyenne entre 1991 et 2005, alors que le taux d'incidence est stable chez les diabétiques de type 1 (variation : -0,3% [-1,6% ; +0,9%]) et qu'il n'augmente qu'assez faiblement chez les non diabétiques (+1,5% en Australie et +2,9% en Nouvelle Zélande).

- un très faible accès à la transplantation rénale pour les diabétiques de type 2 qui ne concerne que 6,5% des diabétiques de type 2 âgés de moins de 70 ans, alors que l'accès à la greffe est identique à celui des non diabétiques pour les diabétiques de type 1 (40 à 42% des incidents en dialyse de moins de 70 ans).

- Malgré un accès important à la greffe rénale et rein-pancréas, les diabétiques de type 1 présente une survie très médiocre illustrée par la figure 2 ci-dessus. Ceci est confirmé par l'analyse multivariée qui montre que le risque relatif ajusté de décès par rapport au non diabétiques est de 1,64 [1,47 – 1,87] chez les diabétiques type 1 et de 1,13 [1,06 – 1,20] chez les diabétiques de type 2.

Figure 2 : Survie à partir de la naissance des patients incidents insuffisants rénaux chroniques terminaux en Australie et en Nouvelle Zélande entre 1991 et 2005.



La représentation de courbe de survie à partir de la naissance est une manière visuelle simple d'ajuster l'analyse sur l'âge des patients à la 1ère dialyse ou transplantation préemptive [Korn *et col* Am J Epidemiol 1997 ; Pencina *et col* Stat Med 2007]. Elle permet d'estimer l'espérance de vie des patients insuffisants rénaux terminaux incidents. Ces courbes sont néanmoins biaisées car pour connaître l'espérance de vie, il faut connaître la survie d'une cohorte de nouveaux nés évoluant vers l'insuffisance rénale terminale traitée.

5.4 IMPACT DU DIABETE DE TYPE 2 SUR LA SURVIE DES PATIENTS INSUFFISANTS RENAUX CHRONIQUES TRAITES SELON LE SEXE

L'observation réalisée par l'étude des SMR dans la population incidente en dialyse en Rhône Alpes concernant les différences entre sexes selon le statut diabétique [Villar *et col* J Am Soc Nephrol 2007] nous a conduit à rechercher une interaction entre sexe et statut diabétique concernant la survie après début de dialyse ou transplantation préemptive.

Ces interactions ont été recherchées et retrouvées :

- Dans la cohorte ANZDATA [Villar *et col* Diabetes Care 2007], il existe une interaction significative entre le sexe féminin, le statut diabétique de type 2 et l'âge :

    - Chez les patients insuffisants rénaux terminaux incidents traités en Australie et Nouvelle Zélande entre 1991 et 2005, le sexe féminin était associée à une surmortalité par rapport aux hommes chez les diabétiques de type 2 âgés de plus de 60 ans : le risque relatif ajusté femme versus homme était 1,19 [1,08 – 1,30], p=0,0003. Les interactions sexe, statut diabétique et âge étaient significatives (p<0,0001).

    - Le sexe n'était pas significativement associé à la mortalité chez les diabétiques de type 1 (risque relatif ajusté : 1,12 [0,87 – 1,46], p=0,38), chez les diabétiques

de type 2 de moins de 60 ans (0,93 [0,83 – 1, 04], p=0,20) et chez les non diabétiques (0,95 [0,91 – 1,005], p=0,07).

- Il est à noter que le risque relatif de décès associé au diabète selon le sexe était constant au cours du temps temps, ce qui n'est pas le cas dans les cohortes françaises (Cf. infra).

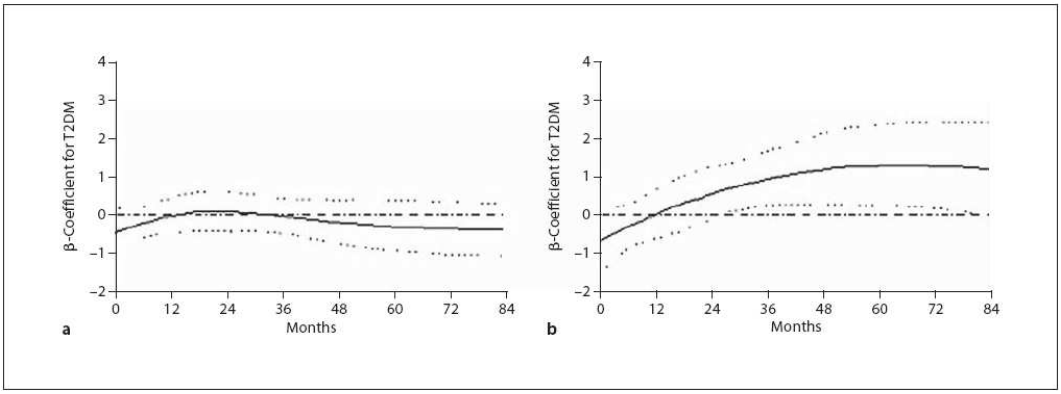
- Dans la cohorte Centre hospitalier Lyon Sud – CALYDIAL 1995 – 2007 [Karamé *et col* Nephron Clin Pract 2009] :

  - Dans cette cohorte de 715 patients incidents en dialyse, le diabète de type 2 n'était pas associé à une surmortalité chez les hommes (risque relatif ajusté diabète de type 2 versus non diabétique : 0,83 [0,62 – 1,10], p=0,20).

  - Par contre le diabète de type 2 était associé à une surmortalité après la 1ère année de dialyse chez les femmes :
    - 1ère année après 1ère dialyse : 0,64 [0,34 – 1,15], p=0,13.
    - Après la 1ère année : 2,40 [1,39 – 4,16], p=0,002.

  - L'évolution du risque relatif de décès a été modélisée de façon continue :

    Figure 3 : Evolution en fonction du temps du coefficient β ajusté (ln du risque relatif) de décès des diabétiques de type 2 versus non diabétique (Cohorte LSCAL 1995 – 2007) selon le sexe.



  - Ces évolutions sont significativement différentes : p=0,009.

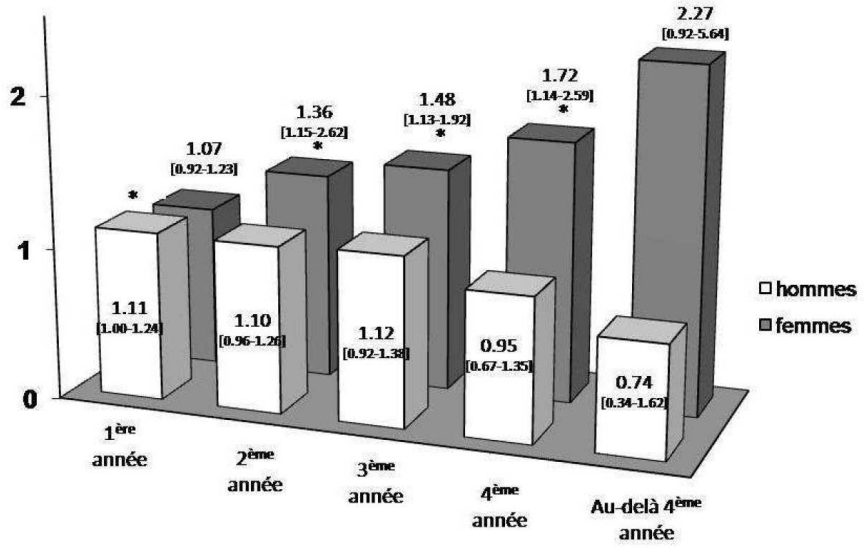
- Dans la cohorte rein 2002 – 2007 [Thèse de Médecine, Mme S. Ignace – Girerd, 2009] comportant 24119 patients incidents en dialyse, des résultats similaires ont été observés :

  - L'impact du diabète était constant au cours du temps chez les hommes avec un risque relatif ajusté de 1,11 [1,02 – 1,21], p=0,019.

  - L'impact du diabète variait avec le temps passé en dialyse chez les femmes :
    - 1ère année après 1ère dialyse : 1,07 [0,92 – 1,23], p=0,39.
    - Après la 1ère année : 1,39 [1,169 – 1,65], p<0,001.

- L'évolution du risque relatif de décès après 1ère dialyse est décrite ci dessous :

Figure 4 : Evolution en fonction du temps des risques relatifs ajustés de décès des diabétiques de type 2 versus non diabétique (Cohorte REIN 2002 - 2007) selon le sexe.



- Ces évolutions étaient significativement différentes : p<0,05.

Il existe donc une interaction entre le sexe féminin et le diabète de type 2 quant à la survie des patients après première dialyse.

L'impact du diabète de type 2 est plus marqué chez les femmes que chez les hommes. Cet effet augmente au cours du temps après première dialyse chez les femmes, alors que cet effet est constant chez les hommes. Ceci a été observé en France, mais pas en Australie – Nouvelle Zélande.

Chez les patients insuffisants rénaux chroniques terminaux, le fait d'être diabétique de type 2 supprime le bénéfice en terme de survie observé chez les femmes dans les pays occidentaux.

Ces résultats concernant l'interaction sexe / diabète de type 2 sur la survie ont été retrouvés en population non insuffisante rénal chronique [Lee *et col* Diabetes Care 2000 ; Huxley *et col* BMJ 2006] et dans d'autres cohorte de patients dialysés [Bloembergen *et col* J Am Soc Nephrol 1994 ; Hocher *et col* Kidney Blood Press Res 2008 ; Cheng *et col* Am J Nephrol 2009].

A ce jour, il n'y a pas d'explication claire à ces observations qui pourraient être liées à des facteurs biologiques, sociaux et comportementaux (Cf. 5. Projets de recherche).

5.5 SURMORTALITE DES PATIENTS INSUFFISANTS RENAUX CHRONIQUES TERMINAUX PAR RAPPORT A LA POPULATION GENERALE

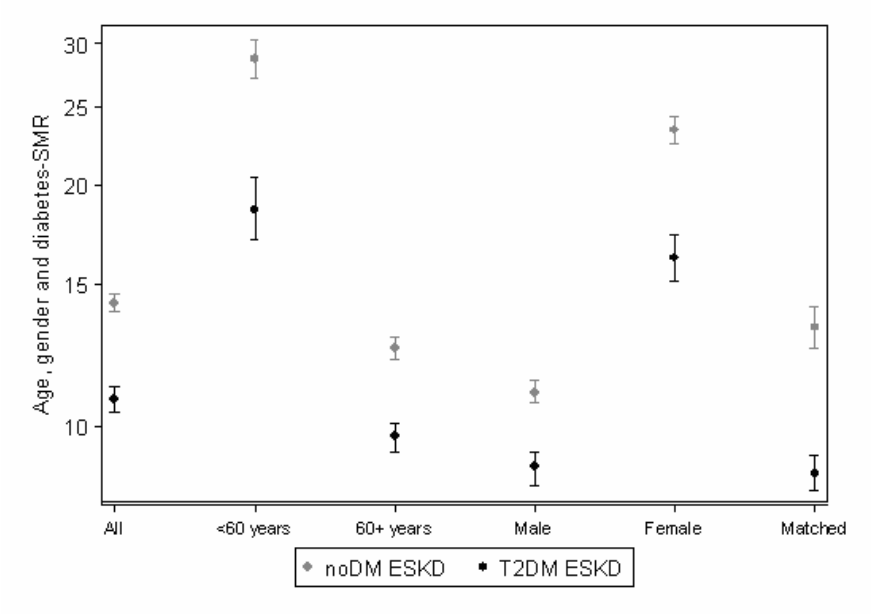
L'utilisation des SMR ajustés sur l'âge et le sexe dans la cohorte Rhône Alpes 1999 – 2003 [Villar *et col* J Am Soc Nephrol 2007] nous a permis de mettre en évidence l'interaction diabète – sexe féminin quant à la mortalité en dialyse. Ces SMR étaient supérieurs chez les patients présentant une néphropathie diabétique par rapport aux patients présentant une autre néphropathie (figure 1, page 17).

La question posée était celle de l'évaluation de la surmortalité des patients insuffisants rénaux chroniques terminaux traités lorsque les SMR sont standardisés sur l'âge, le sexe et le statut diabétique. Le calcul de ces SMR permettrait d'évaluer l'excès de mortalité lié à l'insuffisance rénale terminale chez les diabétiques et les non diabétiques.

L'existence en Australie du registre ANZDATA et de l'étude AusDiab a permis de calculer de tels SMR [Villar *et col* Diabetologia 2009].

L'étude AusDiab est une cohorte nationale représentative de la population australienne pour laquelle est connue entre autre l'âge, le sexe, le statut diabétique et le taux annuel de mortalité [Dunstan *et col* Diabetes Res Clin Pract 2001]. Elle comporte 11247 sujets australiens recrutés en 1999 – 2000 et suivi jusqu'en 2005. Parmi eux, 0,3% étaient diabétiques de type 1 et ont été exclus de l'étude car leur nombre ne permettait pas le calcul des taux de mortalité. 908 sujets avec un diabète de type 2 et 10302 sujets sans diabète ont été utilisés comme population de référence pour calculer les SMR dans la cohorte australienne ANZDATA 1991 – 2005, avec le même statut diabétique (les diabétiques de type 1 n'ont donc pas été étudiés). Les résultats sont présentés dans la figure 5.

Figure 5 : ratio de mortalité standardisés sur l'âge, le sexe et le statut diabétique, chez les diabétique de type 2 et les non diabétiques incidents insuffisants rénaux chroniques terminaux traités en Australie (ANZDATA vs AusDiab). SMR : échelle logarithmique. D'après Villar *et col* Diabetologia 2009. Non diabétique vs diabétique de type 2 : tous $p < 0,01$.



Les SMR standardisés sur l'âge, le sexe et le statut diabétique sont supérieurs chez les non diabétiques (14,2 [13,9-14,6]) par rapport aux diabétiques de type 2 (10,8 [95% CI 10,4-11,2], p<0,01). La comparaison est ajustée sur l'âge et le sexe [Villar *et col* Diabetologia 2009].

Autrement dit, l'excès de mortalité conféré par l'état 'insuffisance rénale terminale' est supérieur chez le non diabétique par rapport au diabétique de type 2 [Villar *et col* Diabetologia 2009], bien que le risque de mortalité absolu soit supérieur chez le diabétique de type 2 dialysé par rapport au non diabétique dialysé [Villar *et col* Diabetes Care 2007].

Ce résultat est probablement lié à un écart de gravité clinique entre sujets non insuffisant rénaux et sujets insuffisants rénaux chroniques terminaux plus important chez les non diabétiques que chez les diabétiques. Comme chez les femmes ou les sujets jeunes, le dénominateur du SMR (le taux de mortalité dans la population de référence) est en effet très faible dans la population non diabétique par rapport à la population diabétique de type 2 [Villar *et col* Diabetologia 2009], expliquant un excès de mortalité (un SMR) plus élevé.

Dans cette dernière étude, nous retrouvons des SMR supérieurs chez les patients jeunes et chez les femmes, quel que soit le statut diabétique. Cela s'explique également par des taux de mortalité très faible dans la population de référence (AusDiab Study).

5.6 DIABETIQUES DE TYPE 2 : ACCES A LA TRANSPLANTATION RENALE

La transplantation rénale est la technique de suppléance de la fonction rénale qui procure la meilleure qualité de vie et la meilleure survie aux patients insuffisants rénaux chroniques terminaux [Wolfe *et col* N Engl J Med 1999].

En Australie – Nouvelle Zélande, nous avons montré que l'accès à la transplantation rénale était comparable pour les diabétiques de type 1 et les non diabétiques, avec 40 à 42 % des patients incidents de moins de 70 ans inscrits sur liste d'attente de transplantation rénale, ou rein-pancréas pour les diabétiques de type 1 [Villar *et col* Diabetes Care 2007].

Pour les diabétiques de type 2, nous avons montré dans la cohorte incidente en dialyse SEGRELYS (St Etienne, Grenoble, Lyon Sud) que ces patients bénéficiaient moins souvent d'un bilan pré-transplantation rénale (33,0% versus 65,8% chez les non diabétiques) et étaient moins souvent listés pour la greffe (24,2% versus 60 ,6%) [Villar *et col* Nephrol Dial Transplant 2004]. Après ajustement sur les caractéristiques médicales, notamment els comorbidités cardiovasculairs, le diabète de type 2 est associé à une diminution de la probabilité d'inscription sur liste d'attente de transplantation rénale (risque relatif ajusté : 0,41 [0,24 – 0,69], p<0,0001) [Villar *et col* Nephrol Dial Transplant 2004].

Ce résultat est confirmé en Australie / Nouvelle Zélande où l'accès à la transplantation rénale ne concerne que 6,5% des diabétiques de type 2 incidents en dialyse de moins de 70 ans entre 1991 et 2005 [Villar *et col* Diabetes Care 2007]. Il est retrouvé dans la cohorte finlandaise de diabétiques de type 2 incidents en dialyse entre 1995 et 2005 où environ 7,5% de ces patients seulement accèdent à la transplantation rénale [Kervinen *et col* Nephrol Dial Transplant 2010].

Comme nous l'avons montré en Rhône Alpes, il existe pour les diabétiques de type 2 à la fois une censure avant tout bilan pré-greffe et un taux plus élevé de non inscription sur liste d'attente après réalisation d'un bilan pré-greffe. La durée du bilan avant inscription est par ailleurs de 12 mois pour les diabétiques de type 2, alors qu'il est moitié moindre pour les non diabétiques [Villar *et col* Nephrol Dial Transplant 2004]. Le bénéfice d'une éventuelle greffe est donc minorée par le processus de sélection pour la greffe chez les diabétiques de type 2, alors que ces patients peuvent s'aggraver rapidement en dialyse en raison du phénomène d'athérome accéléré et des complications micro et macrovasculaires associées au diabète et à l'insuffisance rénale.

5.7 CONCLUSIONS

Ces résultats obtenus et publiés sont d'ordre épidémiologique et analytique.

Sur le plan épidémiologique, nous avons chez les patients insuffisants rénaux terminaux :

- précisé les modalités de stratification selon leur statut diabétique (type 1, type 2, non diabétique),
- décrit en Australie et Nouvelle Zélande (registre ANZDATA) leurs principales caractéristiques épidémiologiques : évolution du taux d'incidence, caractéristiques démographiques et médicales, et mortalité selon le statut diabétique,
- évalué la surmortalité en dialyse par rapport à la population générale sans prise en compte du statut diabétique (en France), puis en le prenant en compte (en Australie).
- décrit le processus d'accès à la transplantation rénale, selon le statut diabétique.

Ces résultats originaux permettent de mieux connaître la population des patients insuffisants rénaux chroniques terminaux traités et diabétiques, notamment de type 2, alors qu'ils représentent plus d'un tiers des patients incidents en dialyse. Concernant la mortalité, ces résultats soulignent le pronostic très péjoratif des patients diabétiques insuffisants rénaux, et plus particulièrement de type 1.

Sur le plan analytique, nous avons mis en évidence :

- qu'il existait une interaction entre le sexe féminin et le statut diabétique en ce qui concerne la mortalité en dialyse. Cette interaction a été mise en évidence dans différentes cohortes locales, régionales ou nationales, en France et en Australie / Nouvelle Zélande.
- que l'impact du diabète n'était pas constant au cours du temps chez les femmes dans les cohortes françaises LSCAL et REIN national (ce qui n'a pas été retrouvé dans le registre ANZDATA). Cet effet délétère sur la survie augmente avec le temps passé après 1ère dialyse.

Toutes ces observations vont constituer la trame de nos projets futurs de recherche, tant en méthodologie biostatistique et en épidémiologie qu'en analyse physiopathologique (Cf. 5. Projets de recherche).

Sur le plan clinique, un des axes de recherche sera l'analyse de l'impact de la transplantation rénale sur la survie des diabétiques de type 2, avec l'hypothèse que la réduction du temps d'attente pour ces patients via une modification du score d'attribution des greffons rénaux (comme cela a été réalisé pour l'attribution des greffons hépatiques en utilisant le score MELD de gravité de la cirrhose) permette d'augmenter la survie des diabétiques de type 2, sans léser les patients non diabétiques.

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6. PROJETS DE RECHERCHE

6.1 PUBLICATIONS EN COURS

Les projets listés ci-dessous sont dans leur phase de publication.

6.1.1 Manuscrits soumis à publication

Marat A, Veysseyre-Balter C, Trolliet P, **Villar E**, Dijoud F, Bienvenu J, Fabien N. Simultaneous detection of anti-C1q and anti-double stranded DNA autoantibodies in lupus: predictive value for renal flares. *Lupus* AO, soumis le 12/01/2010, corrections demandées le 15/03/2010.

Aouizerate J, Matignon M, Kamar N, Thervet E, Randoux C, Moulin B, Raffray L, Buchler M, l **Villar E**, Mahevas M, Desvaux D, Dahan K, Diet C, Audard V, Lang P, Grimbert P. Renal transplantation in patients with sarcoidosis: a French multicenter study. *Am J Transplant* AO, soumis le 09/04/2010.

6.1.2 Manuscrits en cours d'écriture ou de finalisation

Villar E, Lièvre M, Kessler M, Lemaître V, Alamartine E, Rodier M, François M, Zaoui P, Moranne O, Choukroun G, Guerraoui A, Jolivot A, Janin G, Branger B, Heng AE, Boudray C, Bissery A, Rabilloud M, Pouteil-Noble C. Anaemia correction in type 2 diabetes patients with chronic kidney disease stage 2-4: results of the NEPHRODIAB2 randomized trial. AO

Descamps C, Ecochard R, Trolliet P, Cahen R, Pouteil-Noble C, Labeeuw M, **Villar E**. Early death in end-stage renal disease: Respective roles of non-reversible acute kidney injury and dialysis emergency start. AO

Villar E, Chang SH, McDonald SP. Does sex matter? Outcomes after renal transplant differ between males and females depending on comorbidity. AO

McDonald SP, **Villar E**, Chang SH, Russ GR. Reinterpreting the trends in deceased organ donation in Australia, 1989 – 2006. AO

Vanrietvelde-Sens F, Schott-Pethelaz AM, Labeeuw M, Colin C, **Villar E**. Long-term survival advantage of hemodialysis relative to peritoneal dialysis among patients with congestive heart failure. AO

Ignace S, Labeeuw M, **Villar E**. Impact on mortality of peripheral vascular disease and type 2 diabetes is higher in women than in men in dialysis. AO

Toussaint S, Najioullah F, Rabilloud M, **Villar E**, Icard V, Andre P, Pouteil-Noble C. Predicitive value of qPCR as a guide for the initiation of pre-emptive antiviral therapy in kidney transplant cytomegalovirus seropositive recipients. AO

6.2 PROJETS METHODOLOGIQUES

6.2.1 Modélisation de la survie en dialyse : modèles multiplicatifs, modèles additifs

Jusqu'à présent, nous avons utilisé des modèles multiplicatifs, essentiellement le modèle de Cox et les ratios standardisés de mortalité (SMR), pour analyser la survie des patients insuffisants rénaux chroniques terminaux. Des résultats préliminaires obtenus sur la cohorte REIN 2002 – 2007 montrent que l'utilisation de modèles mixtes, multiplicatif et additif, permet de mieux décrire la mortalité en dialyse.

Ces résultats nous ont conduit à proposer avec le Pr Ecochard (Service de Biostatistique HCL, UCB – Lyon 1) un projet d'étude lors de l'appel d'offre REIN 2009 qui a été accepté et financé. Ce projet dont le résumé est reproduit ci-dessous est en cours de réalisation par M. Liacine Bouaoun, étudiant en Biostatistique, dans le cadre de son Master 2 de Biostatistique à l'Université Claude Bernard Lyon 1, lors de l'année 2009 - 2010.

RESUME

Objectifs :
L'insuffisance rénale chronique terminale (IRCT), définie par la nécessité d'un traitement de suppléance de la fonction rénale, est un problème majeur de Santé Publique. Les patients IRCT présentent une mortalité forte. Dans cette population, il est possible de distinguer quatre types de facteurs de risque de décès :

1. ceux directement liés à l'état IRCT et à son traitement (dialyse, transplantation rénale),
2. ceux qui sont liés à la pathologie à l'origine de l'IRCT,
3. ceux découlant des pathologies communes à toute personne, dialysée, greffée ou non,
4. ceux liés à l'impact de l'IRCT et de son traitement sur les risques de décès découlant des pathologies communes,

Une étude préliminaire a montré que l'utilisation combinée de modèles additifs (type Aalen) et multiplicatifs (type Cox) permettait une meilleure analyse de la mortalité des patients IRCT.
Les objectifs de ce projet sont donc de :

1. modéliser ces différents facteurs de risque de décès et leurs interactions en utilisant des modèles souples, additifs et multiplicatifs, et d'évaluer les modalités d'utilisation des ces modèles dans la population IRCT grâce aux données REIN et CRISTAL nationales,
2. évaluer l'espérance de vie brute et par rapport à la population générale (survie relative) des patients IRCT incidents selon leurs caractéristiques.

Résultats attendus :
Les registres REIN et CRISTAL offrent en effet l'opportunité, en utilisant des approches statistiques récentes, d'apporter des informations utiles sur le plan scientifique et pour la pratique clinique dans le domaine de l'étude de la mortalité des patients IRCT. Ce travail permettra de déterminer les conditions d'application des modèles prédictifs de mortalité dans cette population (modèles additifs vs modèles multiplicatifs), ainsi que d'évaluer à la fois le risque de mortalité lié spécifiquement à l'état de dialysé ou de greffé en fonction des autres facteurs connus et l'espérance de vie spécifique de chaque catégorie de patients.

Méthodologie :
Afin d'identifier l'impact de ces facteurs, une analyse statistique orientée sur l'étude de la survie sera réalisée dans un premier temps à l'aide de modèles à la fois additifs et de modèles multiplicatifs avec ajustement sur la mortalité attendue en population générale de même âge et même sexe. Il sera ainsi abordé de manière systématique l'analyse des divers sous groupes de patients afin d'identifier les méthodes adéquates permettant de modéliser les quatre risques de décès listés ci-dessus et leurs interactions.
Sur le plan clinique et épidémiologique, cette modélisation nous permettra dans un second temps d'estimer le risque de mortalité lié à ces quatre types de facteurs de risque de décès, afin d'identifier des sous groupes de patients aux risques particuliers et estimer l'espérance de vie de chaque catégorie de patients au début du traitement de l'IRCT.

Nous assurerons avec M. le Pr Ecochard l'encadrement de cet étudiant lors de son année de Master 2, projet qui pourra se prolonger en Thèse de Biostatistique.

6.2.2 Modélisation de la survie en dialyse : modèles multi-états

Nous avons été sollicités par Mme le Dr C. Couchoud, coordinatrice nationale du registre REIN à l'Agence de la Biomédecine, pour participer au groupe de travail d'encadrement de sa Thèse de Doctorat dirigée par M. le Pr Ecochard (Ecole doctorale E2M2, Université Claude Bernard – Lyon 1).

L'objectif de ce travail est l'analyse des flux de patients entre techniques de suppléance de la fonction rénale qui est un processus dynamique temps-dépendant et leur impact sur la survie des patients.

Les méthodes usuelles d'analyse de survie ne permettent pas de prendre en compte ces changements d'état [Thèse d'Epidémiologie E Villar 2007] et l'objectif du projet de Mme le Dr Couchoud est d'appliquer les modèles multi-états dans le contexte de l'insuffisance rénale chronique terminale.

Les premières réunions de travail se sont tenues :

- à Lyon Sud le 18/01/2010 pour préparer l'analyse de flux de patients entre techniques.
- à St Denis La Plaine (Agence de la Biomédecine) le 01/04/2010.

6.2.3 Objectifs cliniques

Au-delà des objectifs méthodologiques, un des objectifs cliniques est de mieux modéliser l'espérance de vie des patients insuffisants rénaux chroniques, et ce de manière absolue (nombre d'année brute d'espérance de vie après 1ère dialyse ou transplantation préemptive) et de manière relative (nombre d'année perdue par rapport à la population générale de même âge et de même sexe).

Ce type d'information n'existe en effet pas pour les patients insuffisants rénaux chroniques terminaux. Nos travaux utilisant les SMR ne répondent que partiellement à cette question, n'évaluant que l'excès de mortalité (les patients dialysés décédant 6 à 8 fois plus que la population générale [Villar *et col* J Am Soc Nephrol 2007]), sans permettre d'extrapoler de façon fiable une espérance de vie.

6.3 PROJETS EPIDEMIOLOGIQUES

6.3.1 Etude de l'adéquation patient - structure de dialyse et des flux de patients entre structures à partir des données REIN

Ce projet a été soumis à l'appel d'offre REIN 2010 (Cf. Résumé ci-dessous). Il nous permettra d'encadrer Mme F. Vanrietvelde – Sens, interne DES de Néphrologie, au cours de son Master 2 « Santé, Population, Evaluation, Recherche Clinique : option Recherche (C. COLIN, A.M. SCHOTT, F. CHAPUIS, Y. MATILLON) » de novembre 2010 à octobre 2011.

Il permettra de poursuivre le travail réalisé en 2003 par M. le Pr Labeeuw sur cette problématique d'adéquation patient / structure de soin [P30] et de participer sur le versant descriptif au travail de Thèse de Mme le Dr C. Couchoud via le groupe de travail mis en place (Cf. § 6.1.2 ci-dessus).

RESUME

En fonction de leur gravité clinique, les patients insuffisants rénaux chroniques terminaux dialysés peuvent être traités en centre lourd d'hémodialyse, en unité de dialyse médicalisé (UDM), en autodialyse ou en ambulatoire (hémodialyse à domicile ou dialyse péritonéale).

L'enquête transversale SROS/IRCT réalisée en juin 2003 par la CNAMTS, lorsque le déploiement des UDM débutait, a montré que près de 15% des patients traités hors centre lourd avait un profil pouvant relever d'une réorientation soit en UDM, soit en dialyse péritonéale. De la même manière, 7,5% des patients traités en centre lourd avait un profil pouvant relever d'une réorientation soit en autodialyse, soit en hémodialyse à domicile.

Le déploiement du registre REIN sur l'ensemble du territoire français permet de connaître, à une date donnée, les caractéristiques des patients selon leur structure de prise en charge. La connaissance de la trajectoire de ces mêmes patients permet d'appréhender les flux entre structures et éventuellement apporter des explications à la prise en charge de patients dont l'état ne correspond pas à la structure dans laquelle ils sont traités.

L'objectif principal de cette étude est d'analyser l'adéquation entre l'état patient et la structure de prise en charge à la date arbitraire du 1er juin 2009 selon la méthodologie utilisée par l'enquête SROS/IRCT de juin 2003. La typologie des patients utilisée a été :

1. pour les patients traités en centre lourd ou UDM :
   - « lourds typiques »,
   - « lourds atypiques » : patients <60 ans sans comorbidité ni handicap,
2. pour les patients traités en autodialyse ou hémodialyse à domicile :
   - « légers typiques »,
   - « légers atypiques » : patients ≥60 ans avec au moins une comorbidité et un handicap.

Cette analyse permettra une comparaison entre les résultats de 2003 et de 2009 en terme d'évaluation des pratiques médicales.

Les objectifs secondaires sont :

1. affiner la typologie des patients compte tenu des items disponibles dans le registre REIN afin d'étudier l'adéquation état patient / structure,
2. analyser les flux de patients entre structures pour expliquer l'inadéquation de certains patients avec la structure de prise en charge.

Ces analyses seront réalisées au niveau national et régional afin de mettre en perspective les résultats avec l'organisation de l'offre de soin régional. Elles permettront de prendre en compte l'impact des UDM sur l'offre de soin de dialyse et son utilisation.

Les méthodes usuelles d'analyse épidémiologique et biostatistique seront utilisées (étude descriptive : moyenne, écart-type, médiane, effectif, proportion ; comparaison : student, anova, chi-2 ; étude analytique : régression logistique, modèles multivariés usuels)

Les résultats attendus sont une meilleure description des pratiques médicales afin d'une part d'observer si les objectifs quantifiés nationaux en terme de répartition des structures de dialyse et des patients dialysés dans ces structures sont atteints et d'autre part de donner des éléments de réflexion pour mieux adapter l'offre de soin à la demande de soin.

Ce projet sera réalisé par Florence VANRIETVELDE, Interne DES de Néphrologie aux Hospices Civils de Lyon dans le cadre de son Master 2 « Santé, Population, Evaluation, Recherche Clinique : option Recherche (C. COLIN, A.M. SCHOTT, F. CHAPUIS, Y. MATILLON) » de novembre 2010 à octobre 2011.

6.3.2 Impact de l'ancienneté en dialyse avant transplantation rénale sur la survie en post-greffe selon le statut diabétique et les comorbidités cardiovasculaires

Ce projet de recherche sera proposé au Conseil Scientifique du registre REIN lorsque l'ensemble des régions françaises sera passé sous logiciel DIADEM qui permet de rassembler les données de REIN (dont les comorbidités et leur actualisation) et du registre CRISTAL (suivi post-greffe rénale). La plupart des régions françaises utiliseront DIADEM en 2010 (dont Rhône Alpes avec un passage en mai 2010).

L'ancienneté en dialyse est un des facteurs les plus prédictifs de survie après transplantation rénale. L'hypothèse est que l'impact de l'ancienneté en dialyse est plus marqué chez les patients diabétiques (notamment de type 2) et les patients présentant une artériopathie des membres inférieurs, du fait d'un athérome accéléré en dialyse.

Si cette hypothèse est confirmée, il s'agirait d'un argument pour favoriser l'accès à la greffe de ces patients afin d'augmenter leur survie globale. Le cas échéant, des projections devront être faites avec différentes modifications du score d'attribution des greffons afin de maintenir l'équité d'accès à la greffe avec les patients qui ne seraient pas diabétiques ou vasculaires.

6.4 PROJETS PHYSIOPATHOLOGIQUES

6.4.1 Etude SD2D

Ce projet s'inscrit dans la continuité de nos travaux épidémiologiques concernant la survie des diabétiques de type 2 insuffisants rénaux chroniques terminaux.

SD2D : Sex Difference in type 2 Diabetes

RATIONNEL

Différentes études épidémiologiques ont montré en France et en Nouvelle-Zélande que la survie après première dialyse des femmes diabétiques, notamment de type 2, était inférieure à celles des hommes diabétiques alors que le sexe n'influence pas la survie chez les non diabétiques. Cette différence de pronostic entre hommes et femmes selon le statut diabétique n'est pas expliquée par des différences selon le sexe en terme d'âge à la première dialyse, de comorbidités associées (notamment cardiovasculaires), ou de modalités de traitement de l'insuffisance rénale chronique terminale (IRCT) car ces variables disponibles dans les études de cohorte ou de registre ont été prises en compte dans les analyses de survie.

En population générale, un tel effet différentiel selon le sexe a été mis en évidence chez les patients diabétiques de type 2 non insuffisants rénaux. De plus, l'impact sur la mortalité et notamment la mortalité cardiovasculaire d'un certain nombre de comorbidités associées comme les pathologies cardiovasculaires ou les dyslipidémies est en effet différent selon le sexe, plus marqué chez les femmes diabétiques de type 2.

Ces différentes études, menées chez les diabétiques de type 2 quelle que soit leur fonction rénale, ne permettent pas d'expliquer par des facteurs de risque de décès usuels les différences de pronostic selon le sexe des patients.

L'objectif de l'étude SD2D est donc d'explorer cette interaction entre sexe et statut diabétique au sein d'une cohorte de patients insuffisants rénaux chroniques non terminaux et terminaux traités. L'hypothèse est que cette interaction est liée à des différences de facteurs de risque non pris en compte dans les études antérieures, concernant principalement le niveau de stress oxydatif et ses conséquences sur les marqueurs de sénescence cellulaire, l'activité télomérasique et la longueur des télomères des leucocytes, eux-mêmes marqueurs de risque cardiovasculaire.

Nous nous proposons donc d'explorer la relation entre le taux de HDL cholestérol, un des principaux anti-oxydants, et la longueur des télomères des leucocytes selon le sexe et le statut diabétique de patients insuffisants rénaux chroniques non terminaux et terminaux traités.

Les objectifs secondaires de cette étude sont d'analyser les relations entre les marqueurs de sénescence cellulaire et différents critères cliniques (comorbidités cardiovasculaires associées, rigidité artérielle, masse ventriculaire gauche, et survenue d'événements cardiovasculaire au cours du suivi) et d'analyser les différences concernant les facteur de risque de décès non évalués par les études de cohorte ou de registre antérieures
Cette étude pilote pluridisciplinaire sera conduite parmi 96 patients recrutés au Centre Hospitalier Lyon Sud entre le 1er janvier 2011 et le 31 décembre 2012 et suivis jusqu'au 31 décembre 2013 (48 diabétique de type 2 ; 48 non diabétiques ; sex ratio 1/1 ; ratio patients dialysés / non dialysés : 1/1).
Ce projet permettra une meilleure connaissance du stress oxydatif et des déterminants des marqueurs de sénescence cellulaire chez les patients insuffisants rénaux, mécanismes physiopathologiques encore peu explorés en Néphrologie. En cas de résultats positifs à la phase initiale de recueil de données, nous proposerons une augmentation de la taille de la cohorte en incluant d'autres centres investigateurs, le projet devenant alors multicentrique.

OBJECTIF PRINCIPAL
Analyser selon le statut diabétique et le sexe des patients inclus les relations entre marqueurs du stress oxydant et marqueurs de sénescence cellulaire, activité télomérasique et longueur des télomères des leucocytes.

POPULATION ETUDIEE
Critères d'inclusion
Patients IRCT :
Patients adultes de plus de 18 ans et présentant une insuffisance rénale chronique terminale.
Incidents en dialyse entre le 01/01/2011 et le 31/12/2012 dans le service de Néphrologie du CHLS
Quel que soit la néphropathie initiale.
Sevrés de statines, fibrates ou toute autre hypolipémiant depuis 2 mois.
Patients ayant compris les informations données concernant l'étude et ayant signé le formulaire de consentement.
Chaque patient diabétique de type 2 (sexe ratio 1/1) sera matché avec un patient non diabétique selon l'âge (± 5 ans) et le sexe (Cf Calcul du nombre de sujets nécessaires).
Patients IRC non dialysés :
Patients adultes de plus de 18 ans et présentant une insuffisance rénale chronique définit par un débit de filtration
glomérulaire entre 15 et 60 mL/min/1.73 m² mesuré par clairance de l'inuline.
Recrutés entre le 01/01/2011 et le 31/12/2012 dans le service de Néphrologie du Centre Hospitalier Lyon Sud.
Quel que soit la néphropathie initiale.
Sevrés de statines, fibrates ou toute autre hypolipémiant depuis 2 mois.
Patients ayant compris les informations données concernant l'étude et ayant signé le formulaire de consentement.
Chaque patient diabétique de type 2 (sexe ratio 1/1) sera matché avec un patient non diabétique selon l'âge (± 5 ans), le sexe, le niveau de protéinurie (<1 g/24h et ≥1 g/24h) et le niveau de fonction rénale (± 10 mL/min) (Cf Calcul du nombre de sujets nécessaires).
Calcul du nombre de sujets nécessaires
L'étude d'Adaikalakoteswari *et col* publié en 2007 dans Atherosclerosis [*Adaikalakoteswari 2007*] nous permet de connaître a priori la relation linéaire entre le taux d'HDL cholestérol et la longueur des télomères de patients diabétiques de type 2. Le calcul du nombre de patients nécessaires est basé sur l'approche de Dupont et Plummer [Dupont 1998] : Puissance : 0,80 ; Risque alpha : 0,05 ; Pente de régression : + 0,07 ; Déviation standard de l'erreur de régression : 0,016 ; Déviation standard de la variable indépendante (HDL) : 0,2 ; Avec ces contraintes, le nombre de patients à inclure est 12.
Patients IRCT : Nous inclurons donc 24 patients diabétiques de type 2 avec un sexe ratio 1/1, et 24 patients non diabétiques matchés sur le sexe et l'âge (± 5 ans).
Patients IRC : Nous inclurons donc 24 patients diabétiques de type 2 avec un sexe ratio 1/1, et 24 patients non diabétiques matchés sur l'âge (± 5 ans), le sexe, le niveau de protéinurie (<1 g/24h et ≥1 g/24h) et le niveau de fonction rénale (± 10 mL/min)
Le nombre total de patients inclus dans cette étude sera 96.

PLAN EXPERIMENTAL
Chaque année, plus de 50 patients débutent la dialyse (hémodialyse ou dialyse péritonéale) au Centre Hospitalier Lyon Sud, dont 40% de patients diabétiques de type 2, dont 40% de femmes, soit 8 femmes IRCT diabétiques de type 2 en moyenne par an. Une période d'inclusion de 2 ans permettra donc de recruter au moins 12 femmes et 12 hommes IRCT diabétiques de type 2, ainsi que les patients contrôles non diabétiques.

Par ailleurs, le service de Néphrologie reçoit plus de 200 nouveaux patients IRC (fonction rénale < 60 mL/min/1.73m²) par an, dont plus d'un tiers sont diabétiques de type 2, ce qui permettra également de recruter sur cette période de 2 ans le nombre de sujets IRC requis dans chacun des groupes.
Les inclusions seront réalisées au cours des 3 premiers mois après 1ère dialyse pour les patients IRCT.
Les analyses biologiques seront réalisées soit au fur et à mesure des inclusions (biologie standard), soit à la fin de la période d'inclusion (biologie spécialisée).

CRITERE D'EVALUATION
Le critère de jugement principal est la relation entre le taux de HDL cholestérol et la longueur des télomères des leucocytes selon le statut diabétique, le sexe et la fonction rénale (IRCT dialysé / IRC non dialysé).

La recherche de financement pour ce projet sera réalisée en 2010. Son budget est estimé à 50000 euros.

6.4.2 Cohorte DIAB2MRC

Au-delà de l'étude SD2D, l'objectif est de créer une base de données de diabétiques de type 2 au stade 2 à 4 de la maladie rénale chronique, de les enregistrer au moment d'une mesure du débit de filtration glomérulaire et de les suivre au sein d'un registre, comme nous l'avons fait pour la cohorte des patients incidents en dialyse au Centre Hospitalier Lyon Sud.

Les informations recueillies à l'inclusion comprendront :

- des données démographiques et médicales,
- le débit de filtration glomérulaire mesuré (inuline),
- les comorbidités associées dont les comorbidités cardiovasculaires,
- des données de rigidité artérielle : vitesse de l'onde de pouls, index d'augmentation (sphygmocor),
- des marqueurs biologiques du stress oxydant,
- des données hormonales,
- des données métaboliques (répartition des graisses, profil lipidique, insulino-résistance),
- des données psychosociales,
- des données thérapeutiques,
- constitution d'une sérothèque et d'une DNAthèque.

Ce projet est dans sa phase d'étude de faisabilité. Elle implique actuellement le Dr Drai au Laboratoire de Biochimie du Centre Hospitalier Lyon Sud (Inserm U870), pour ce qui concerne notamment l'étude des marqueurs biologiques du stress oxydant (mise au point des dosages biologiques en cours).

Les objectifs sont d'étudier les relations physiopathologiques entre diabète, insuffisance rénale, comorbidités cardiovasculaires, rigidité artérielle et facteurs biologiques. Cette étude comportera également un suivi longitudinal. Elle permettra donc de répéter le recueil des données étudiées et d'analyser la survie des patients inclus. L'objectif est d'émettre des hypothèses physiopathologiques et proposer l'évaluation de thérapeutiques visant à réduire la progression de l'insuffisance rénale et / ou le risque cardiovasculaire de ces patients, comme nous l'avons fait au cours de l'essai randomisé NEPHRODIAB2 (Cf. §4.5 et §6.5.1).

Après la phase de faisabilité au printemps 2010, la recherche de financement sera formalisée et réalisée fin 2010 – début 2011.

6.5 ESSAIS CLINIQUES

6.5.1 Chez les diabétiques de type 2

Fort de notre expérience acquise au cours de l'étude NEPHRODIAB2, notre objectif à moyen terme est la conduite d'essais thérapeutiques en maladie rénale chronique, notamment chez les patients diabétiques de type 2.

Les pistes thérapeutiques seront soulevées par les projets physiopathologiques décrits plus haut (Cf. § 6.4). Néanmoins, les échecs – relatifs – d'essais cliniques conduits en maladie rénale chronique ou en dialyse (concernant les traitement par EPO pour réduire le risque cardiovasculaire ou la dégradation de la fonction rénale, ou par statines, ou par IEC, etc…) doivent nous inciter à proposer des essais incluant plusieurs cibles thérapeutiques optimales à comparer à une prise en charge usuelle.

Ces projets seront l'aboutissement de nos recherches réalisées en épidémiologie rénale et futures en terme de compréhension physiopathologique.

6.5.2 Hémodialyse versus dialyse péritonéale

A plus long terme, un de nos objectifs sera de réaliser un essai clinique comparatif randomisé comparant la survie en hémodialyse et en dialyse péritonéale.

En effet, en raison de biais d'indication et donc de confusion, les études d'observation même sur données de registres nationaux exhaustifs ne permettent pas de répondre à la question de la supériorité d'une technique de dialyse sur l'autre en terme de survie des patients.

L'équipe néerlandaise de l'étude NECOSAD a proposé une telle étude randomisée [Korevaar *et col* Kidney Int 2003] mais n'a pu randomiser que 38 patients entre 1997 et 2000, alors que 773 patients ont été screenés avec 735 refus de participer.

Il est donc clair qu'une telle étude, à mon sens nécessaire en terme d'évaluation de nos thérapeutiques de suppléance, n'est pas réalisable actuellement, du fait d'un choix pour tel ou tel technique de la part des patients en fonction des contraintes propres aux techniques mais également du fait d'une réticence de la communauté néphrologique à une telle étude.

Ce projet ne pourra donc être réalisé qu'après deux études de faisabilité à type d'enquête :

- auprès des néphrologues français : seriez-vous prêt à inclure des patients incidents en dialyse dans un essai randomisé comparant la survie en dialyse péritonéale et en hémodialyse ?

- auprès des patients insuffisants rénaux chroniques lors de l'information pré dialyse : seriez-vous prêt à être inclus dans un essai comparatif avec tirage au sort du traitement de suppléance de la fonction rénale : dialyse péritonéale ou hémodialyse ?

6.6 CONCLUSION : PROJET DE RESEAU DE RECHERCHE CLINIQUE ET EN SANTE DES POPULATIONS

A côté du développement de l'épidémiologie et de la recherche biostatisque en Néphrologie, nos projets de recherche s'inscrivent dans le développement des connaissances physiopathologiques et thérapeutiques, notamment lorsque le diabète de type 2 est associé à la maladie rénale chronique.

Nous souhaitons formaliser les partenariats déjà largement engagés et développés au sein d'un réseau de recherche clinique et en santé des populations en constituant un projet collaboratif à dimension translationnelle incluant néphrologues, diabétologues, cardiologues, biologistes et méthodologistes, et que nous souhaitons étendre aux trois CHU de la région Rhône – Alpes.

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O3. Pasquier A, Berra C, Gesta F, Pothier F, Philibert M, **Villar E**, Paparel P. La transplantation rénale : prise en charge du patient de l'inscription à l'intervention. Association Française d'Urologie, 30ème journée de l'Infirmière en Urologie, Paris, France. Novembre 2009

O4. **Villar E**. Inhibiteur de SGLT2 : le point de vue du Néphrologue. Réunion régionale de Diabétologie, Lyon, Novembre 2009 (invitation du Pr S Halimi, président de la Société Francophone de Diabétologie, ex ALFEDIAM)

O5. **Villar E**. Protéinurie : quels examens ? Actualités Claude Bernard, Faculté de Médecine Lyon Sud – Charles Mérieux, Octobre 2009

O6. **Villar E**, Couchoud C. Epidémiologie : analyse de la survie des patients dialysés. Formation Médicale Continue – Commission d'Epidémiologie de la Société de Néphrologie – Coordonnateurs : Stengel B, Frimat L. 11ème réunion commune de la Société de Néphrologie et de la Société Francophone de Dialyse. Toulouse, France. Septembre 2009

O7. **Villar E**. Epidémiologie du retour en dialyse après transplantation rénale. Conférence Médicale. Centre de Rein Artificiel de Tassin la demi lune. Lyon, Décembre 2008

O8. **Villar E**. Le problème de la douleur chez les insuffisants rénaux chroniques. 8ème journée de la douleur, Hospices Civils de Lyon, Lyon, Octobre 2008

O9. **Villar E**. Transplantation rénale chez les diabétiques de type 2. CERRT, Lyon, avril 2008

O10. **Villar E**. Reinterpreting the trends in deceased organ donation in Australia, ANZOD Registry. Nephrology Seminar. The Queen Elizabeth Hospital. Adelaide, Australia, December 2007.

O11. **Villar E**. A story about ESRD, diabetes and sex. Nephrology Seminar. The Queen Elizabeth Hospital. Adelaide, Australia, June 2007.

O12. **Villar E**. Utilisation des statines en transplantation rénale. Symposium Statine et Transplantation d'Organes. Hospices Civils de Lyon. Lyon, novembre 2006.

O13. Villar E. Gestion de l'anémie chez le patient diabétique insuffisant rénal chronique. Symposium Régional Rein et Diabète, Association Régionale des Néphrologues de Rhône – Alpes. Grenoble, Octobre 2006.

O14. Villar E, Pouteil-Noble C. Qui bénéficie et qui ne bénéficie pas de la transplantation rénale ? 3ème congrès de la Société Française de Transplantation. Paris, novembre 2003.

O15. Villar E, Frimat L. Comparaison de survie selon la méthode de dialyse : description et limites des méthodes statistiques. 5ème réunion commune de la Société de Néphrologie et de la Société Francophone de Dialyse. Nancy, octobre 2003.

9.2 COMMUNICATIONS ORALES :

O16. Villar E, Lièvre M, Kessler M, Lemaître V, Alamartine E, Pouteil-Noble C. Correction de l'anémie des patients diabétiques de type2 insuffisants rénaux chroniques de stade 2 à 4 : résultats de l'essai randomisé NEPHRODIAB2. Association Régionale des néphrologues de Rhône - Alpes, Condrieu, France. Octobre 2009

O17. Villar E, Lièvre M, Kessler M, Lemaître V, Alamartine E, Pouteil-Noble C. Correction de l'anémie des patients diabétiques de type2 insuffisants rénaux chroniques de stade 2 à 4 : résultats de l'essai randomisé NEPHRODIAB2. CO006. 11ème réunion commune de la Société de Néphrologie et de la Société Francophone de Dialyse. Toulouse, France. Septembre 2009

O18. Ignace S, **Villar E**, Labeeuw M. Les facteurs de risque de décès des patients insuffisants rénaux chroniques terminaux varient selon le temps passé en dialyse et le sexe. CO039. 11ème réunion commune de la Société de Néphrologie et de la Société Francophone de Dialyse. Toulouse, France. Septembre 2009

O19. Asselborn M, **Villar E**, Paparel P, Morel-Journel N, Champetier D, Devonec M, Perrin P, Grima F, Campos-Fernandes JL, Ruffion A. Traitement de la cystite interstitielle par cyclosporine : résultats préliminaires. 102ème Congrès Français d'Urologie. Paris, Novembre 2008.

O20. Descamps C, Labeeuw M, Trolliet P, Cahen R, Pouteil-Noble C, **Villar E**. L'insuffisance rénale aiguë non réversible et son impact sur le choix de modalité de dialyse est-il le facteur expliquant la surmortalité précoce en hémodialyse par rapport à la dialyse péritonéale ? CO47. 10ème réunion commune de la Société de Néphrologie et de la Société Francophone de Dialyse. Marrakech, Maroc. Novembre 2008.

O21. Lassalle M, Couchoud C, Donnadieu P, Frimat L, Joyeux V, Labeeuw M, Vérove C, **Villar E**, Stengel B. Initiation précoce de la dialyse et survie des patients. CO54. 10ème réunion commune de la Société de Néphrologie et de la Société Francophone de Dialyse. Marrakech, Maroc. Novembre 2008.

O22. Subtil F, Pouteil-Noble C, Toussaint S, **Villar E**, Rabilloud M. Evaluation des performances dépendantes du temps de la PCR quantitative pour prédire la maladie à CMV. 7ème Congrès de la Société Francophone de Transplantation. O12. Lyon, Décembre 2007.

O23. Karamé A, Labeeuw M, Ecochard R, Trolliet P, **Villar E**. Mortalité des patients diabétiques incidents en dialyse : un profil évolutif différent ? 9ème réunion commune de la Société de Néphrologie et de la Société Francophone de Dialyse. O53. Lyon, septembre 2007.

O24. Dussol B, Cassuto E, Burtey S, Sichez H, Kaaraslan H, **Villar E**, Lasseur C, Mourad G, Berland Y, Delmas Y, Nogier MB, Morange S. Un essai randomisé de traitement par MMF de la glomérulopathie extramembraneuse idiopathique avec syndrome néphrotique. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. Lille, octobre 2006.

O25. Thilly N, Stengel B, Boini S, **Villar E**, Couchoud C, Frimat L. Traitements par érythropoïétine des patients en insuffisance rénale terminale lors de la première dialyse et après un an de suppléance. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. Lille, octobre 2006.

O26. M Pavic, M Chauffer, B Mc Gregor, **E Villar**, M Laville, M Labeeuw, H Rousset. Etude épidémiologique et caractéristiques clinico-biologiques de 44 cas de granulomatoses rénales. Congrès de la SNFMI, juin 2006.

O27. Toussaint S, Rabilloud M, Najioullah F, **Villar E**, Pouteil-Noble C. Stratégie de prise en charge de l'infection à Cytomégalovirus chez les receveurs séropositifs : la PCR quantitative a-t-elle un intérêt ? 5ème congrès de la Société Française de Transplantation. Tours, décembre 2005.

O28. **Villar E**, Remontet L, Labeeuw M, Ecochard R, au nom des Néphrologues de la région Rhône – Alpes. Survie en dialyse par rapport à la population générale : cohorte des patients incidents en dialyse en Rhône – Alpes 1999 – 2003. Réunion annuelle de l'Association Régionale des Néphrologues de Rhône – Alpes, octobre 2005.

O29. **Villar E**, Lièvre M, Pouteil-Noble C, au nom du Comité Directeur de l'étude NEPHRODIAB2. Pourquoi faut-il inclure des patients dans l'étude NPEHRODIAB2 ? Réunion annuelle de l'Association Régionale des Néphrologues de Rhône – Alpes, octobre 2005.

O30. **Villar E**, Remontet L, Labeeuw M, Berthoux F, Vialtel P, Pouteil-Noble C, Ecochard R. Risque relatif de décès en dialyse par rapport à la population générale : données à 5 ans dans la cohorte SEGRELYS. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. Clermont-Ferrand, septembre 2005.

O31. Pavic M, Cruel T, Sève P, **Villar E**, Philippe P, Debourdeau P, Faucompret S, Dupond JL, Vital-Durand D, Rousset H. Granulomes et cancer : étude de 14 observations. 52ème congrès de Médecine Interne, Nantes, Juin 2005.

O32. **Villar E**, Pouteil-Noble C. Protocole de l'étude TRANSREIN. CERRT. Lyon, avril 2005.

O33. Pavic M, **Villar E**, Puget M, Cahen R, Trolliet P, Pouteil-Noble C, Labeeuw M, Vital-Durand D, Rousset H. Granulomatoses rénales : étude de 13 observations. 51ème Congrès de Médecine Interne, Tours, décembre 2004.

O34. Icard V, Pouteil-Noble C, **Villar E**, Boisson RC, Dijoud F, André P. Respective value of Decoy Cells in urine and serum BK virus quantification to identify patients at risk of BKV associated nephropathy (BKVAN) after kidney transplantation. International Congress of Transplantation. Vienne, Autriche, septembre 2003.

O35. Hendawy A, **Villar E**, Sebbag L, Boissonat P, Pouteil-Noble C. Facteurs de progression de l'insuffisance rénale chronique après transplantation rénale. 3ème congrès de la Société Française de Transplantation. Paris, novembre 2003.

O36. **Villar E**, Pouteil-Noble C, Taburet AM. Transplantation rénale chez les patients infectés par le VIH. Réunion annuelle de l'Association Régionale des Néphrologues. Grenoble, octobre 2003.

O37. **Villar E**, Labeeuw M, Registre ARN – REIN Rhône-Alpes. Survie des patients incidents 1999 –2002 en dialyse de la région Rhône-Alpes. Réunion annuelle de l'Association Régionale des Néphrologues. Grenoble, octobre 2003.

O38. **Villar E**, Lièvre M, Labeeuw M, Pouteil-Noble C. Protocole de l'étude NEPHRODIAB2. Réunion annuelle de l'Association Régionale des Néphrologues. Chambéry, novembre 2002.

O39. Pouteil-Noble C, Boisson RC, **Villar E**, Cardozo J, Cahen R, Fontanière B. Valeur de le recherche de cellules decoy pour le diagnostic précoce de l'infection à polyomavirus en transplantation rénale. Congrès de la Société Francophone de Transplantation. Montréal, octobre 2002.

O40. **Villar E**, Najjar E, Rabilloud M, Labeeuw M, Pouteil-Noble C. Les équations de Framingham sous-estiment-elles le risque cardiovasculaire absolu des insuffisants rénaux terminaux ? Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. Tunis, octobre 2002.

O41. **Villar E**, Labeeuw M. Survie à 1 an des patients insuffisants rénaux chroniques terminaux incidents en 1999 en Rhône Alpes. Registre ARN. Réunion annuelle de l'Association Régionale des Néphrologues. Lyon, novembre 2001.

O42. **Villar E**, Moreau-Gaudry X, Trolliet P, Bernon H, Debard AL, Pouteil-Noble C, Labeeuw M. Ponction – Réinjection d'ascite en cours de dialyse : les raisons d'un échec. Réunion annuelle de l'Association Régionale des Néphrologues. Lyon, novembre 2001.

O43. **Villar E**. Epidémiologie de l'insuffisance rénale chronique. 1ère journée nationale de lutte contre l'insuffisance rénale. Lyon, septembre 2001.

O44. **Villar E**, Rabilloud M, Berthoux F, Vialtel P, Labeeuw M, Pouteil-Noble C. Etude Multicentrique du processus d'inscription sur liste d'attente de transplantation rénale : analyse multivariée. Congrès de la Société Francophone de Recherche Clinique et Biologique en Transplantation. Génève, décembre 2000.

O45. Villar E. Processus d'inscription sur la liste d'attente de transplantation rénale (étude rétrospective 1995 – 1998). Réunion annuelle de l'Association Régionale des Néphrologues. Macon, octobre 2000.

O46. Villar E, Pascal C, Claveranne JP, Pouteil-Noble C. L'âge influence-t-il l'accès à la transplantation rénale ? Congrès de la Société de Néphrologie. Tours, juin 2000.

10. COMMUNICATIONS AFFICHEES

A1. Du Besset AC, **Villar E**, Cahen R, Euvrard S, Pouteil-Noble C. Quel sur-risque de cancer pour nos aptients transplantés rénaux par rapport à la population générales française ? AT010. 11ème réunion commune de la Société de Néphrologie et de la Société Francophone de Dialyse. Toulouse, France. Septembre 2009

A2. El M'Barki Kadiri M, **Villar E**, Gagnieu MC, Parant F, Pouteil-Noble C. Cinétique de mycophénolate mofétil lors de la conversion de la ciclosporine vers le tacrolimus. AT026. 11ème réunion commune de la Société de Néphrologie et de la Société Francophone de Dialyse. Toulouse, France. Septembre 2009

A3. **Villar E**, Lièvre M, Kessler M, Lemaître V, Alamartine E, Pouteil-Noble C, and the NEPHRODIAB2 investigators. Anaemia normalisation in patients with type 2 diabetes and chronic kidney disease: Results of the NEPHRODIAB2 randomized trial. World Congress of Nephrology. M561. Milano, Italia, May 2009.

A4. Lassalle M, Couchoud C, Frimat L, Donnadieu P, Joyeux V, Labeeuw M, VéroveC, **Villar E**, Stengel B. Early initiation of dialysis and patient survival. World Congress of Nephrology. M656. Milano, Italia, May 2009.

A5. du Besset AC, **Villar E**, Cahen R, Euvrad S, Pouteil-Noble C. Skin and solid organ cancers in 525 kidney transplant recipients : a real threat. 9th joint American Transplant Congress, Boston, USA, May-June 2009

A6. **Villar E**, Descamps C, Trolliet P, Cahen R, Pouteil-Noble C, Labeeuw M. Higher early mortality in hemodialysis versus peritoneal dialysis patients: Is non reversible acute kidney injury and its impact on dialysis modality choice the explanatory factor? 41st American Society of Nephrology Annual Meeting. F-PO1753. Philadelphia, USA, November 2008

A7. **Villar E**, Karamé A, Trolliet P, Caillette-Beaudoin A, Cahen R, Ecochard R, Pouteil-Noble C, Labeeuw M. Factors associated with mortality in incident renal disease patients differ by diabetes status and by gender. XLV ERA – EDTA Congress. M433. Stockholm, Suede, May 2008

A8. Karamé A, Labeeuw M, Trolliet P, Caillette-Beaudoin A, Cahen R, Ecochard R, Pouteil-Noble C, **Villar E**. Time dependent differential impact of type 2 diabetes between genders in patients with end-stage renal disease. XLV ERA – EDTA Congress. M431. Stockholm, mai 2008

A9. **Villar E**, Polkinghorne KR, Chang SH, Chadban SJ, McDonald SP. Differential impact of end-stage kidney disease on mortality in type 2 diabetics and non-diabetics. First joint meeting of the Francophone Society of Nephrology (Société de Néphrologie) and the UK renal association. Londres, février 2008.

A10. **Villar E**, Chang SH, McDonald SP. Does sex matter? Outcomes after renal transplant differ between males and females depending on comorbidity. First joint meeting of the

Francophone Society of Nephrology (Société de Néphrologie) and the UK renal association. Londres, février 2008.

A11. El M'Barki K, **Villar E**, Gagnieu MC, Parant F, Pouteil-Noble C. Cinétique de Mycophénolate Mofetil lors de la conversion de la ciclosporine A vers le tacrolimus. 7ème congrès de la Société Française de Transplantation. P19. Lyon, décembre 2007.

A12. Cahen R, Savoye E, Aubry-Rosier B, Dubois V, Rennesson-Rey B, **Villar E**, Pouteil-Noble C, Larbre JP. Polyarthrite de novo après transplantation rénale. 7ème congrès de la Société Française de Transplantation. P26. Lyon, décembre 2007.

A13. Karamé A, **Villar E**, Ducret M, Cahen R, Hequet O, Pouteil-Noble C. Traitement par anticorps anti-CD20 (rituximab) d'une récidive précoce de hyalinose segmentaire et focale. 7ème congrès de la Société Française de Transplantation. P35. Lyon, décembre 2007.

A14. Ignace S, **Villar E**, Broussais F, Moncharmont P, Vial T, Pouteil-Noble C. Anémie hémolytique à IgA chez une patiente transplantée rénale. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. AT046. Lyon, Septembre 2007.

A15. Pavic M, Chauffer M, Mc Gregor B, **Villar E**, Laville M, Labeeuw M, Rousset H. Etude épidémiologique et caractéristiques clinico-biologiques de 44 cas de granulomatoses rénales. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. AT046. Lyon, Septembre 2007.

A16. Thilly N, Stengel B, Boini S, **Villar E**, Couchoud C, Frimat L. Anémie des insuffisants rénaux chroniques avant dialyse : évaluation et déterminants de la prise en charge inadéquate. 1ère Conférence d'Epidémiologie Clinique ADELF-RFUEC. Bordeaux, mai 2007.

A17. Dussol B, Sichez H, Burtey S, Cassuto E, Kaaraslan H, **Villar E**, Lasseur C, Mourad G, Berland Y, Delmas Y, Nogier MB, Morange S. Mycophenoloate mofetil (MMF) in patients with idiopathic membranous nephropathy with nephrotic syndrome : A multicenter randomized trial. 39th congress of the American Society of Nephrology. San Diego, USA, Novembre 2006

A18. **Villar E**, Lièvre M, Lemaître V, Kessler M, François M, Alamartine E, Rossert J, Pouteil-Noble C. Etude NEPHRODIAB2 : Caractéristiques des patients à l'inclusion et évolution de la fonction rénale à 1 an chez ces patients diabétiques de type 2 insuffisants rénaux chroniques. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. AN011. Lille, octobre 2006.

A19. **Villar E**, Ducret M, Souquet PJ, Dijoud F, Ffrench M, Carret G, Blandin S, Trolliet P, Pouteil-Noble C, Rousset H, Boibieux A, Labeeuw M. Cause ou conséquence ? Association d'une granulomatose systémique avec atteinte rénale à un cancer bronchique et une infection à *Mycobacterium genavense*. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. AN034. Lille, octobre 2006.

A20. Coulibaly G, Trolliet P, **Villar E**, Dijoud F, Pouteil-Noble C. Atteintes rénales au cours de la sclérodermie systémique. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. AN038. Lille, octobre 2006.

A21. Karamé A, Ducret M, Cahen R, Dijoud F, **Villar E**, Pouteil-Noble. Traitement d'un rejet aigu cortico-dépendant par anticorps anti-CD20. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. AT032. Lille, octobre 2006.

A22. Sartorius A, Guebre-Egziabher F, Fouque D, Cozon G, **Villar E**, Laville M, Juillard L. PTT idiopathique récidivant : un rôle pour le vaccination dans la récidive de la maladie ? Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. AN037. Lille, octobre 2006.

A23. **Villar E**, Remontet L, Labeeuw M, Ecochard R, Association Régionale des Néphrologues de Rhône-Alpes, REIN Registry. Evaluation of excess of death in end-stage renal disease population: a prospective population-based study in Rhône-Alpes region, France. PM514. ERA-EDTA XLIII Congress. Glasgow, United Kingdom, july 2006.

A24. Trolliet P, **Villar E**, Ducret M, Paparel P, Cahen R, Rabodonirina M, Pouteil-Noble C. Anguillulose transmise par le greffon rénal. 5ème congrès de la Société Française de Transplantation. Tours, décembre 2005.

A25. **Villar E**, Labeeuw M, Pouteil-Noble C, Rabilloud M, Frimat L, Berthoux F, Vialtel P, Ecochard R. Comparaison de méthodes statistiques d'analyse de survie en dialyse péritonéale versus hémodialyse (cohorte SEGRELYS). Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. Clermont-Ferrand, septembre 2005.

A26. Combarnous F, Gaillard S, Alamartine E, Boudray C, Zaoui Ph, **Villar E**, Moreau-Gaudry X, Jean G, au nom des Néphrologues de l'Association Régionale des Néphrologues de Rhône-Alpes. Détermination de l'incidence en néphrologie de l'insuffisance rénale chronique en région Rhône-Alpes : Etude épidémiologique prospective « RENALP ». Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. Clermont-Ferrand, septembre 2005

A27. Coulibaly G, Trolliet P, **Villar E**, Dijoud F, Pouteil-Noble C. Crise rénale sclérodermique : à propos de 7 cas. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. Clermont-Ferrand, septembre 2005.

A28. Trolliet P, Rabodonirina M, Paparel Ph, **Villar E**, Ducret M, Lopez JG, Chaigne V, Cahen R, Devonec M, Pouteil-Noble C. Anguillulose transmise par le greffon rénal : à propos d'un cas. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. Clermont-Ferrand, septembre 2005.

A29. Pouteil-Noble C, Hendawy A, **Villar E**, Boissonnat P, Sebbag L. Chronic renal failure (CRF) and End Stage Renal Disease (ESRD) are associated with a high rate of mortality after heart transplantation. International Congress of Transplantation. Vienne, septembre 2004.

A30. A. Hendawy, **Villar E**, Pouteil-Noble C. La survie en dialyse des patients transplantés cardiaques est inférieure à celle des patients non transplantés cardiaques. 3ème congrès de la Société Française de Transplantation. Paris, novembre 2003.

A31. **Villar E**, Labeeuw M, Vialtel P, Berthoux F, Pouteil-Noble C. Aged patients with type 2 diabetes or with cardiovascular comorbidity have a better survival in hemodialysis than in peritoneal dialysis. M 628. World Congress of Nephrology. Berlin, juin 2003.

A32. **Villar E**, Labeeuw M, Vialtel P, Berthoux F, Pouteil-Noble C. No influence of dialysis modality in survival in patients without type 2 diabetes and without cardiovascular comorbidity. M 629. World Congress of Nephrology. Berlin, juin 2003.

A33. **Villar E**, Moreau-Gaudry X, Trolliet P, Debard AL, Bernon H, Pouteil-Noble C, Labeeuw M. Aggravation d'un état cachectique chez un patient traité par réinjection d'ascite en dialyse : rôle de l'IL 6. Congrès de la Société de Néphrologie et de la Société Francophone de Dialyse. Tunis, octobre 2002.

A34. Vial J, Kassir A, Juillard L, **Villar E**, Bret M, Fouque D. Prise en charge de deux purpuras thrombotiques thrombopéniques. Congrès d'Hémovigilance. Aix les Bains, Novembre 2001.

A35. Bencharif L, **Villar E**, Sibille M, Salle G, Felman P, Vital-Durand D, Rousset H. Une leucémie à grand lymphocyte granuleux (GLG) de type NK révélée par l'association d'une uvéite, d'une glomérulonéphrite, d'un purpura vasculaire et d'une lymphocytose NK. Congrès de Médecine Interne. Aix en Provence, juillet 2000.

A36. **Villar E**, Pascal C, Claveranne JP, Pouteil Noble C. Inégalité du processus d'inscription sur liste d'attente de transplantation rénale chez les diabétiques de type 2. Congrès de la Société de Néphrologie. Tours, juin 2000.

11. DISTINCTIONS

WCN 2009, Milano, Italia

BEST ABSTRACTS PRESENTED BY YOUNG AUTHORS AND TOP 20% ABSTRACTS

M561: Villar E, Lièvre M, Kessler M, Lemaître V, Alamartine E, Pouteil-Noble C, and the NEPHRODIAB2 investigators. Anaemia normalisation in patients with type 2 diabetes and chronic kidney disease: Results of the NEPHRODIAB2 randomized trial.

ERA – EDTA travel grant: 500 euros

12. RELECTURES D'ARTICLE ET EXPERTISES

Revues scientifiques

Anaesthesiology
American Journal of Kidney Diseases
American Journal of Transplantation
Heart and Vessels
Journal d'Economie Médicale
Journal of Renal Nutrition
Néphrologie et Thérapeutique
Nephrology Dialysis Transplantation
Nephrology

Congrès

$9^{ème}$, $10^{ème}$, $11^{ème}$ et $12^{ème}$ réunions communes de la Société de Néphrologie et de la Société Francophone de dialyse

Projets de recherche

PHRC
Appel d'Offre Registre REIN – Agence de la Biomédecine

13. CONCLUSIONS

Notre activité de recherche s'est principalement focalisée sur la connaissance de l'épidémiologie du diabète dans la population des patients insuffisants rénaux chroniques terminaux avec des recherches complémentaires à la fois en France, en Australie et en Nouvelle Zélande. Nous nous sommes également impliqué dans l'évaluation de la prise en charge thérapeutique des diabétiques de type 2 au stade 2 à 4 de la maladie rénale chronique avec la conduite de l'étude NEPHRODIAB2.

Nos projets futurs s'inscrivent dans la continuité des ces premières années de recherche scientifique, tant sur le plan biostatistique, qu'épidémiologique ou d'évaluation thérapeutique, en valorisant notre expérience et nos connaissances méthodologiques.

Nos principaux objectifs au cours des années futures sont :

1. de **développer l'épidémiologie et la recherche en biostatistique** dans le contexte de la maladie rénale chronique, en développant notamment la recherche méthodologique grâce aux données du registre REIN dans le cadre de notre partenariat avec le Pr R Ecochard (Biostatistique, HCL, UCLB, UMR CNRS 5558),

2. de **constituer une cohorte de diabétique de type 2 présentant une maladie rénale chronique stade 2 à 4** dans le but d'études physiopathologiques, notamment concernant les facteurs de risque cardiovasculaire non conventionnels,

3. de **développer la recherche thérapeutique** dans le but de diminuer le risque cardiovasculaire et la progression de la maladie rénale chronique, notamment chez le diabétique de type 2, et d'améliorer leur pronostic.

Ces projets devront se formaliser dans la constitution d'un réseau de recherche clinique et en santé des populations incluant des néphrologues, diabétologues, cardiologues, biologistes et méthodologistes de la région Rhône – Alpes

Dans le cadre d'un projet de carrière Hospitalo-Universitaire, nous présentons donc devant l'Université Claude Bernard Lyon 1 l'Habilitation à Diriger les Recherche afin de poursuivre et d'amplifier cette activité scientifique au cours des prochaines années.

13. PUBLICATIONS AU FORMAT PDF

Seuls les 12 articles originaux publiés dans une revue internationale (sur 31 publications à ce jour) auxquels nous avons participé sont reproduits intégralement ci-après, classés par ordre chronologique.

1. Lassalle M, Labeeuw M, Frimat L, **Villar E**, Joyeux V, Couchoud C, Stengel B, on behalf of the Rein registry. Age and comorbidity explain the paradoxical association of early dialysis start with poor survival. *Kidney Int* in press 2010 ***[IF 2008 : 6,4]***

2. **Villar E**, Polkinghorne K, Chang SH, Chadban SJ, McDonald SP. Effect of type 2 diabetes on mortality risk associated with end-stage renal disease. *Diabetologia* 52 (12) : 2536 – 2541, 2009 ***[IF 2008 : 6,4]***

3. Karamé A, Labeeuw M, Trolliet P, Caillette-Beaudoin A, Cahen R, Ecochard R, Galland R, Hallonet P, Pouteil-Noble C, **Villar E**. The impact of type 2 diabetes on mortality in end-stage renal disease patients differs between genders. *Nephron Clin Pract*. 112 (4) : 268 – 275, 2009 ***[IF 2007 : 1,5]***

4. Subtil F, Pouteil-Noble C, Toussaint S, **Villar E**, Rabilloud M. Novel modelling-free method to assess the time-dependant accuracy of a longitudinal biomarker applied to prediction of cytomegalovirus disease after kidney transplantation. *Methods Inf Med*, 48(3), 2009 ***[IF : 0.97]***

5. Dussol B, Morange S, Burtey S, Indreies M, Cassuto E, Mourad G, **Villar E**, Pouteil-Noble C, Karaaslan H, Sichez H, Lasseur C, Delmas Y, Nogier MB, Fathalah M, Loundou A, Berland Y. Mycophenolate mofetil monotherapy in membranous nephropathy: A randomized controlled trial. *Am J Kidney Dis*, 52(4):699 – 705, 2008 ***[IF 2007 : 3.98]***

6. Thilly N, Stengel B, Boini S, **Villar E**, Couchoud C, Frimat L. Evaluation and determinants of underprescription of erythropoiesis stimulating angents in pre-dialysis patients with anaemia. *Nephron Clin Pract*. 108 (1) : 67 – 74, 2008 ***[IF 2007 : 1,5]***

7. **Villar E**, Chang SH, McDonald SP. Incidences, treatments, outcomes, and gender effect on survival in end-stage renal disease patients by diabetic status in Australia and New Zealand (1995-2005). *Diabetes Care*. 30 (12) : 3070 – 3076, 2007 ***[IF 2007 : 7,8]***

8. **Villar E**, Remontet L, Labeeuw M, Ecochard R, on behalf of the Association Régionale des Néphrologues de Rhône-Alpes and the French Renal Information and Epidemiology Network registry. Effect of age, sex and diabetes on excess death in end-stage renal failure. *J Am Soc Nephrol*. 18 (7) : 2125 – 2134, 2007 ***[IF 2007 : 7,1]***

9. **Villar E**, Boissonnat P, Sebbag L, Hendawy A, Cahen R, Trolliet P, Labeeuw M, Ecochard R, Pouteil-Noble C. Poor outcome in heart transplant patients with end-stage renal failure. *Nephrol Dial Transplant*. 22 (5) : 1383 – 1389, 2007 ***[IF 2007 : 3,1]***

10. Asnafi V, Rubio MT, Delabesse E, **Villar E**, Davi F, Damaj G, Irsch I, Dhédin N, Vernant JP, Varet B, Buzyn A, Macintyre E. Prediction of relapse by Day 100 BCR-ABL quantification after allogenic stem cell transplantation for chronic myeloid leukaemia. *Leukemia*. 20 (5) : 793 – 799, 2006 ***[IF 2006 : 6,1]***

11. Frimat L, Durand PY, Loos-ayav C, **Villar E**, Panescu V, Briançon S, Kessler M. Impact of the first dialysis modality on outcomes of patients contraindicated for kidney transplantation. *Perit Dial Int*. 26 (2) : 231 – 239, 2006 ***[IF 2006 : 2,3]***

12. **Villar E**, Rabilloud M, Berthoux P, Vialtel P, Labeeuw M, Pouteil-Noble C. A multicentre study of registration on renal transplantation waiting list of the elderly and patients with type 2 diabetes. *Nephrol Dial Transplant*. 19 (1) : 207 – 214, 2004 ***[IF 2004 : 2,7]***

Age and comorbidity may explain the paradoxical association of an early dialysis start with poor survival

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Starting patients on dialysis early has been increasing in incidence in several countries. However, some studies have questioned its utility, finding a counter-intuitive effect of increased mortality when dialysis was started at a higher estimated glomerular filtration rate (eGFR). To examine this issue in more detail we measured mortality hazard ratios associated with Modification of Diet in Renal Disease eGFR at dialysis initiation for 11,685 patients from the French REIN Registry, with sequential adjustment for a number of covariates. The eGFR was analyzed both quantitatively by 5-ml/min per 1.73 m^2 increments and by demi-decile (i.e., 5 percentiles of the distribution); the 15th demi-decile, including values around 10 ml/min per 1.73 m^2, was our reference point. The patients more likely to begin dialysis at a higher eGFR were older male patients; had diabetes, cardiovascular diseases, or low body mass index and level of albuminemia; or were started with peritoneal dialysis. During a median follow-up of 21.9 months, 3945 patients died. The 2-year crude survival decreased from 79 to 46%, with increasing eGFR from less than 5 to over 20 ml/min per 1.73 m^2. Each 5-ml/min/1.73 m^2 increase in eGFR was associated with a 40% increase in crude mortality risk, which weakened to 9%, but remained statistically significant after adjusting for the above covariates. Analysis by demi-decile showed only the highest to be at significantly higher risk. Hence we found that age and patient condition strongly determine the decision to start dialysis and may explain most of the inverse association between eGFR and survival.

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KEYWORDS: clinical epidemiology; end-stage renal disease; glomerular filtration rate; mortality risk

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The optimal timing for starting dialysis in patients with end-stage renal disease (ESRD) remains uncertain; the decision is based mainly on clinical experience and local dialysis resources.[1,2] International guidelines are consistent in recommending the initiation of dialysis whenever signs of uremia or malnutrition are present, or when blood pressure or hydration status cannot be controlled, but they differ regarding the level of estimated glomerular filtration rate (eGFR) at which dialysis should start in the absence of these conditions, ranging from 8 to 12 ml/min per 1.73 m^2 according to country.[3–6] One of the recommendations is to consider starting dialysis at values of renal function equal to a K_t/V of 2.0 equivalent to an eGFR of about 10.5 ml/min.[3] All agree, however, that it should certainly be started once eGFR reaches 5–6 ml/min per 1.73 m^2.

The so-called healthy start concept, which recommended that dialysis start before overt evidence of uremia, was based on early studies that reported a higher mortality risk with low eGFR at initiation[7] and led to the start of dialysis at higher eGFR levels.[8,9] In the United States,[2] the percentage of patients starting dialysis with eGFR greater than 10 ml/min per 1.73 m^2 more than doubled between 1996 and 2005, from 25 to 54%, whereas in France it has been stable at 30% since the beginning of the Renal Epidemiology and Information Network (REIN) Registry in 2002. The Netherlands Cooperative Study on the Adequacy of Dialysis (NECOSAD) study, however, showed that the apparent gain in survival in these observational studies is more likely to have resulted from lead-time bias than from true effects of an early start.[10] In contrast, more recent studies tend to show decrease of survival with higher GFRs at initiation, an inverse association that appeared to be only partly explained by comorbidity.[11–16] It is important to clarify whether this reflects a potentially harmful effect of early dialysis, indication bias, or confounding from comorbid conditions. Randomized clinical trials are theoretically the most appropriate way to investigate this issue, but the importance of observational studies in evaluating treatment options is increasingly being recognized, particularly those based on large unselected ESRD registry populations.[17]

We, therefore, investigated the association between eGFR level at dialysis initiation and mortality risk in the French REIN Registry, adjusting for a large set of potential explanatory variables and testing for interactions with patient characteristics and treatment conditions.

RESULTS

Distribution of eGFR at start of dialysis

The mean (s.d.) and median (interquartile range) Modification of Diet in Renal Disease (MDRD) eGFR values were 8.8 (4.1) and 7.9 (5.9–10.6) ml/min per 1.73 m^2, respectively; overall values ranged from 0.7 to 35.2 ml/min per 1.73 m^2 (Figure 1). Fourteen percent of the patients started dialysis with eGFR $\leqslant 5$ and 8% with eGFR >15 ml/min per 1.73 m^2.

Baseline patient characteristics and initial dialysis conditions according to eGFR

As MDRD eGFR at start of dialysis increased, patient age and percentage of men also increased significantly, and patients were more likely to have diabetes, vascular nephropathy, malignancy, and cardiovascular diseases, as well as reduced mobility and lower body mass index (BMI) and albuminemia level, independent of age and gender (Table 1). The proportion of those with an eGFR >10 ml/min per 1.73 m^2 was nearly three times higher in the oldest than in the youngest age group (Figure 2). Patients with lower eGFR were more likely to have low hemoglobin levels and to have received predialysis erythropoiesis-stimulating agent treatment. The level of eGFR was not related to history of stroke, liver disease, or chronic respiratory disease, or to smoking or severe disability. Higher the eGFR, higher the percentage of patients starting with planned peritoneal dialysis. There was a U-shaped relation between the percentage of patients with unplanned dialysis and eGFR level. In all, the above significant variables explained 17.5% of the variance of MDRD eGFR treated continuously.

The duration of weekly hemodialysis (HD) decreased and the percentage of patients treated with fewer than three sessions per week increased with increasing eGFR up to 20 ml/min per 1.73 m^2 (Table 2). Patients with eGFR >20 ml/min per 1.73 m^2 were more likely to start with more than three sessions per week. All patients ($n=14$) with more than three sessions began on emergency; 9 (64%) had stage-3–4 heart failure and 11 (79%) received shorter sessions, <4 h per session.

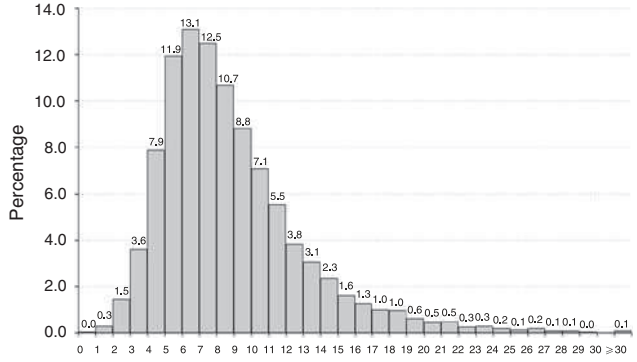

Figure 1 | Distribution of Modification of Diet in Renal Disease estimated glomerular filtration rate in ml/min per 1.73 m^2 at start of dialysis.

Patient survival and transplantation according to MDRD-estimated GFR

Over a median follow-up of 21.9 months, 3945 patients died. Survival decreased strongly with increasing MDRD eGFR (Figure 3, log rank $P<0.0001$). Two-year survival decreased from 79 to 46% for the lowest versus the highest eGFR levels. Of the patients who began dialysis with eGFR $\leqslant 5$, 6–10, 11–15, 16–20, and >20 ml/min per 1.73 m^2, 21, 17, 8, 4, and 6%, respectively, received kidney transplants.

Relation between the level of eGFR at dialysis initiation and mortality

When treated quantitatively, each 5-ml/min per 1.73 m^2 increase in the MDRD eGFR was associated with a 40% increase in the overall mortality risk, and this reduced to half after adjusting for age and gender (Table 3). Further adjustment for comorbidities and nutritional status led to an 8% increased risk, which remained statistically significant after adjusting also for predialysis anemia care, initial treatment conditions, and transplantation or wait listing. Mortality hazard ratios (HRs) (95% confidence interval) at 3 months and 2 years were very similar. Patients with heart failure had a higher fully adjusted mortality HR associated with MDRD eGFR than those without, but the interaction was on the borderline of significance ($P=0.06$). The adjusted HRs tended to differ according to initial dialysis condition, but without significant interaction ($P=0.11$). Other tested interactions had *P*-values higher than 0.10.

Crude analysis by MDRD eGFR 5-percentile groups showed linear rising relation with mortality (Figure 4). Fully adjusted HRs for each group were all close to one, except for the highest demi-decile (HR = 1.3 (1.1–1.6)). It was only of borderline significance for the lowest one (HR = 0.8 (0.6–0.99)). It is noteworthy that these figures showed a similar pattern for both hemo- and peritoneal dialysis patients (data not shown). Subsidiary analysis excluding these two extreme groups (<3.9 and >17 ml/min per 1.73 m^2) led to a non-significant fully adjusted HR associated with 5-ml/min per 1.73 m^2 increase in MDRD eGFR treated quantitatively (1.03 (0.97–1.09)). When we used the Cockcroft–Gault eGFR, the crude relation was U-shaped, and except for the highest group, entirely explained by the covariates.

DISCUSSION

Recent concern about the potential detrimental effect of early dialysis initiation was not confirmed in this study. We found that eGFR at dialysis initiation was strongly related to patient's age, gender, and condition—those who started at higher eGFR levels were older men with particularly high percentage of diabetes (42%), heart failure (50%, of whom 31% with NYHA stage 3–4), and dysrhythmia (42%).

Table 1 | Patient characteristics according to MDRD eGFR at start of dialysis

		MDRD eGFR (ml/min per 1.73 m^2)					
	Total (*n*) (11 685)	⩽5 (1587)	6–10 (6683)	11–15 (2517)	16–20 (633)	>20 (265)	*P*[a]
Mean age	67.0 ± 15.3	60.6 ± 16.7	66.1 ± 15.1	71.1 ± 13.9	73.5 ± 13.0	71.8 ± 14.4	<0.0001
Men	62.1	47.4	62.1	67.2	70.3	84.5	<0.0001
Primary renal disease							<0.0001
Polycystic kidneys	6.9	6.7	8.5	4.7	0.8	1.1	
Glomerulonephritis	12.2	15.8	13.0	9.4	7.3	8.3	
Vascular or hypertensive nephropathy	25.5	18.7	25.0	28.5	34.0	32.1	
Diabetic nephropathy	21.2	15.6	20.9	24.5	26.7	18.9	
Other or unknown	34.2	43.3	32.6	32.9	31.3	39.6	
Comorbidities and disabilities							
Diabetes	35.8	26.3	34.1	42.6	47.2	41.9	<0.0001
Heart failure							<0.0001
None	74.7	84.4	78.1	66.5	58.0	49.8	
Stage I–II	14.4	9.7	13.3	18.4	21.0	15.9	
Stage III–IV	8.9	4.7	6.7	12.8	18.0	31.3	
Stage NA	2.0	1.2	2.0	2.4	3.0	3.0	
Peripheral vascular disease							<0.0001
None	77.6	88.5	79.0	71.8	65.9	60.8	
Stage I–II	13.6	7.7	12.6	17.5	20.1	20.8	
Stage III–IV	6.7	2.8	6.3	8.1	11.5	15.1	
Stage NA	2.1	1.0	2.2	2.5	2.5	3.4	
Coronary heart disease (CHD)							<0.0001
History of myocardial infarction	11.2	5.9	10.4	14.7	16.4	20.4	
CHD without myocardial infarction	14.2	8.0	13.6	17.8	21.2	18.1	
Dysrhythmia	18.8	11.3	16.2	24.8	31.3	41.9	<0.0001
Malignancy	7.5	7.9	7.3	8.0	6.2	10.9	0.0014
Severe disability[b]	5.5	4.2	5.4	5.8	7.0	10.2	NS
Mobility							0.0042
Walk without help	59.6	66.9	62.2	53.1	46.5	43.0	
Need assistance with mobility	10.8	8.8	10.1	12.3	14.2	16.6	
Totally dependent for transfers	4.3	2.8	3.7	5.2	8.1	10.2	
NA	25.4	21.5	24.0	29.4	31.3	30.2	
Predialysis anemia care							
Hemoglobin <11 g/dl	64.0	72.5	57.6	50.7	47.1	41.1	<0.0001
Predialysis ESA treatment	49.9	40.8	53.0	51.0	42.8	32.5	<0.0001
Nutritional status							
Body mass index	25.5 ± 5.3	25.8 ± 5.8	25.6 ± 5.2	25.3 ± 5.4	24.9 ± 5.4	24.5 ± 4.9	0.03
Albuminemia (g/l)	33.6 ± 6.5	33.0 ± 6.2	33.9 ± 6.4	33.5 ± 6.6	32.9 ± 7.0	32.6 ± 6.7	0.0002
Initial dialysis condition							<0.0001
Planned hemodialysis	57.1	44.8	61.6	56.2	50.2	43.4	
Planned peritoneal dialysis	11.7	5.7	10.9	15.6	16.3	19.3	
Unplanned dialysis	31.2	49.5	27.5	28.1	33.5	37.4	

Abbreviations: eGFR, estimated glomerular filtration rate; ESA, erythropoietin-stimulating agent; MDRD, Modification of Diet in Renal Disease; NS, non-significant.
Mean ± s.d. or %.
[a]*P*-value adjusted for age and gender.
[b]Includes severe vision impairment, paraplegia, hemiplegia, and amputation.

Furthermore, patients who began with an eGFR ⩽5 or >15 ml/min/1.73 m^2 were also more likely to have unplanned dialysis than those who began with values within this range. In contrast to other studies,[12–14,16] we found that patient characteristics from this large and unselected population explained most of the inverse association of eGFR with survival except for the 5% of the population with the highest eGFR.

The rationale for commencing dialysis early is supported by a number of observational and interventional studies, reviewed by Canaud,[18] which showed better survival in patients who started dialysis with more preserved renal function. These studies made clear that residual endogenous renal function contributes to the adequacy of dialysis; reduces interdialytic weight gain; and is associated with better nutritional status, lower erythropoietin requirements, and better outcomes.[7,19,20] Although most guidelines provide recommendations about GFR levels at which dialysis should be initiated, they consistently underline the complexity of this decision, in which patients and clinicians must weigh the benefits, disadvantages, and risks of renal replacement therapy. Evidence that several factors other than renal function level have a role in the decision process comes from the wide range of eGFR values at the start of dialysis

that we, like others,[9] have observed, as well as from the 17% of its variance explained here by patient characteristics. As in other studies, we have found older age to be strongly associated with early initiation of dialysis.[2,12,13] Compared with 2005 data from the USRDS, however, the percentage of French patients starting with MDRD eGFR >10 ml/min per 1.73 m^2 was about 10% lower in each age group.[2] Men were also more likely to start with higher eGFR levels than women, probably in part because of their higher rate of cardiovascular diseases. As shown in several other studies, patients started peritoneal dialysis at eGFR levels higher than those started with HD. The fact that 22–26% of those starting with an eGFR >15 ml/min per 1.73 m^2 had impaired mobility clearly indicates sicker patients. Interestingly, not only did patients with very low eGFR begin dialysis on an emergency basis, but so did more than a third of those with eGFR >15 ml/min per 1.73 m^2. The reliability of this variable was recently assessed showing that 83% of the patients labeled with unplanned dialysis were never scheduled for a first dialysis session, and that 80% of them began dialysis within 48 h after the decision was made.[21] Starting dialysis at a high eGFR level thus does not necessarily reflect a 'timely' start. It is indeed clear from this study as well as from others[22] that these patients have more comorbidities, particularly severe heart failure. As discussed in the last KDOQI on Dialysis Adequacy,[3] dialysis initiation at high eGFR in these patients is based on experience and the hope or impression that dialysis therapy may alleviate or attenuate symptoms. The fact that this group started more often with more than three HD sessions per week is further evidence that these high-eGFR patients did not start in a timely progressive manner at a low dialysis dose. Whether this practice, which concerned 14 patients only in this study, is beneficial would need to be evaluated in a larger sample.

Our study is comparable to that of Beddhu *et al.*,[12] Kazmi *et al.*,[13] and Stel *et al.*[16] with respect to study design and population, as well as for both mean or median MDRD eGFR at start: the mean was 8.4 in the study of Kazmi *et al.*[13] and 8.6 in that of Stel *et al.*[16] versus 8.8 ml/min per 1.73 m^2 in ours, and the median was 7.5 in the study of Bedhhu *et al.*[12] and 7.7 in that of Stel *et al.*[16] versus 7.9 ml/min per 1.73 m^2 in our study. Beddhu *et al.*[12] found HRs similar to that in our study for each 5-ml/min per 1.73 m^2 increase in MDRD eGFR: crude HR: 1.36 (1.28–1.44) and fully adjusted HR: 1.14 (1.06–1.22) versus 1.40 (1.36–1.45) and 1.09 (1.05–1.13) in our study. Kazmi *et al.*[13] and Stel *et al.*[16] also observed quite similar adjusted HRs for each 5-ml/min/1.73 m^2 eGFR increase, being 1.17 (1.16–1.18) and 1.15 (1.10–1.15), respectively. However, our study showed that when eGFR was treated semi-quantitatively the statistical significance of the fully adjusted HR resulted mostly from the combination of a very low mortality risk associated with the lowest 5-percentile group of the eGFR distribution and an elevated risk with the highest demi-decile; the mortality risk

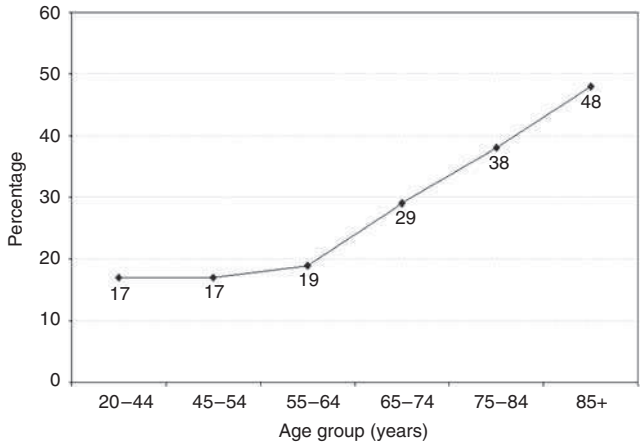

Figure 2 | Proportion of patients starting dialysis at an estimated GFR higher than 10 ml/min per 1.73 m^2 by age group.

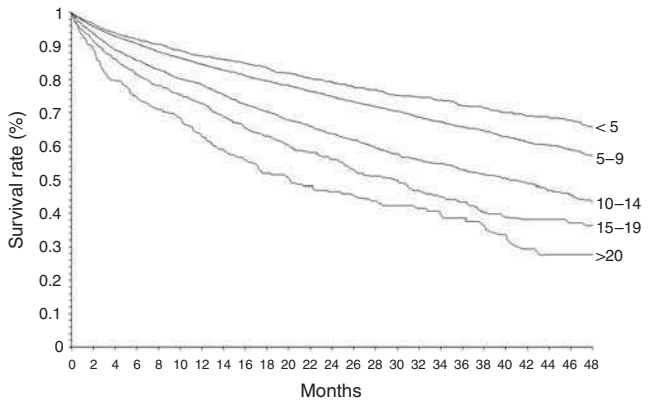

Figure 3 | Kaplan–Meier survival curves according to MDRD eGFR in ml/min per 1.73 m^2 at start of dialysis.

Table 2 | Mean weekly number and duration of hemodialysis sessions according to MDRD eGFR

	MDRD eGFR (ml/min per 1.73 m^2)						
	Total (*n*) (9804)	⩽5 (1411)	5–10 (5646)	10–15 (2040)	15–20 (507)	>20 (200)	*P*[a]
Mean duration of HD sessions (h/week)	11.3 ± 2.2	11.7 ± 1.8	11.4 ± 2.2	11.2 ± 2.4	11.1 ± 2.5	11.3 ± 2.8	<0.0001
Weekly number of sessions (%)							<0.0001
1–2	9	5	9	11	11	7	
3	90	94	90	88	86	86	
>3	1	1	1	1	2	7	

Abbreviations: eGFR, estimated glomerular filtration rate; HD, hemodialysis; MDRD, Modification of Diet in Renal Disease.
[a]*P*-value adjusted for age and gender.

Table 3 | HRs of overall, 3-month, and 2-year mortality associated with 5-ml/min per 1.73 m^2 increase of MDRD eGFR, and of overall mortality by initial dialysis condition and heart failure status

	Model-1: crude		Model-2: adjusted for age and gender		Model-3: 2+ comorbidities[a], mobility, and nutritional status[b]		Model-4: 3+ predialysis anemia care[c], initial treatment condition, wait listing, or transplantation	
	HR	95% CI	HR	95% CI	HR	95% CI	HR	95% CI
Overall	1.40	(1.36–1.45)	1.20	(1.16–1.25)	1.08	(1.04–1.12)	1.09	(1.05–1.13)
Three months	1.41	(1.31–1.51)	1.22	(1.13–1.32)	1.07	(0.99–1.15)	1.09	(1.01–1.17)
Two years	1.41	(1.36–1.46)	1.21	(1.17–1.26)	1.09	(1.04–1.13)	1.09	(1.05–1.14)
Initial dialysis condition								
Planned HD	1.49	(1.41–1.57)	1.26	(1.19–1.34)	1.13	(1.07–1.20)	1.12	(1.06–1.19)
Planned PD	1.38	(1.26–1.51)	1.16	(1.05–1.29)	0.98	(0.88–1.10)	1.00	(0.89–1.12)
Unplanned	1.35	(1.29–1.41)	1.20	(1.13–1.26)	1.09	(1.03–1.15)	1.08	(1.03–1.15)
Heart failure								
Yes	1.27	(1.21–1.34)	1.21	(1.14–1.28)	1.12	(1.06–1.18)	1.11	(1.05–1.18)
No	1.34	(1.28–1.41)	1.12	(1.07–1.18)	1.05	(1.00–1.11)	1.06	(1.01–1.12)

Abbreviations: CI, confidence interval; eGFR, estimated glomerular filtration rate; HD, hemodialysis; HR, hazard ratio; MDRD, Modification of Diet in Renal Disease; PD, peritoneal dialysis.
[a]Comorbidities include diabetes, heart failure, dysrhythmia, peripheral vascular disease, coronary heart disease, malignancy, and severe disability.
[b]Nutritional status includes body mass index and albuminemia.
[c]Predialysis anemia care includes hemoglobin and pre-dialysis erythropoietin-stimulating agent treatment.

associated with all other 5-percentile groups did not differ significantly from the reference. This means that, except at the extreme eGFR values, the covariates we studied entirely explained the inverse crude association observed with mortality. It is noteworthy that once excluding these two extreme groups, the adjusted HR associated with eGFR treated as a continuous variable was no longer statistically significant. Patients starting dialysis with very low eGFR were typically young, had few comorbidities, and had a high rate of early transplantation. This probably reflects common clinical practices aimed at maintaining young patients free of dialysis as long as possible in the hope for a preemptive transplantation. Such practices are likely to select a much healthier subgroup at particularly low mortality risk. In contrast, the significantly higher mortality risk in patients starting HD at very high eGFR levels may result from either residual confounding from unrecorded risk factors, measurement error, indication bias, or a detrimental effect of dialysis. All four hypotheses are plausible. Despite the number and quality of collected comorbidities, which together reduced the mortality HR by 25% in addition to the 50% reduction already due to age and gender, we cannot rule out the potential effect of other unknown factors such as lack of treatment compliance or difficulty in the management of multiple and severe conditions or any other post-initiation issues. Beddhu *et al.*,[23] showed that BMI was not a good measure of the degree of malnutrition, and that MDRD eGFR may overestimate true GFR in patients with advanced kidney failure, low muscle mass, and low creatinine generation. Some of those labeled as early starters may have actually started late as a result of spuriously high eGFR due to low serum creatinine relative to true GFR. Adjusting for BMI and serum albumin may therefore be insufficient to account for the potential confounding effect of malnutrition in the studied association. The extremely high rate of heart failure among patients in this highest demi-decile of the eGFR distribution may argue for indication bias. Conversely, early dialysis initiation may accelerate residual renal function loss and therefore compromise other metabolic functions, which are shown to have a strong impact on outcome.[2,9,18] Patients are also exposed earlier to well-known adverse effects of dialysis, including infections, hemodynamic stress, and membrane bioincompatibility.

The major strengths of this analysis include the study power, which allowed detailed analysis by eGFR level, the number, and the relevance of recorded variables, as well as the unselected nature of the population in comparison with other studies.[10,11,15] Our findings, however, should be interpreted in light of the following limitations. First, this is an observational study and patients were not randomly allocated to eGFR level at dialysis initiation. Therefore, despite careful adjustments for patient conditions, confounding by indication was not controlled as it would be in a randomized trial. Furthermore, because this study was based only on dialysis patients, survival bias cannot be ruled out to explain, for example, the apparent lower risk for death in patients starting at very low MDRD eGFR levels. Some patients reaching such low levels might have died before starting renal replacement therapy, whereas others in better condition may have survived until treatment. It should not be hastily concluded from this study that patients can start dialysis with eGFR below the international consensus value of 5 ml/min per 1.73 m^2. It is nonetheless worth pointing out that about one out of six of the overall French dialysis population were able to do so, likely because of their younger age and a much healthier profile.

Second, GFR was estimated and not measured. The MDRD equation has been shown to perform better than the Cockcroft and Gault equation at low GFR levels in diverse populations.[24–26] Although the latter is in the process of

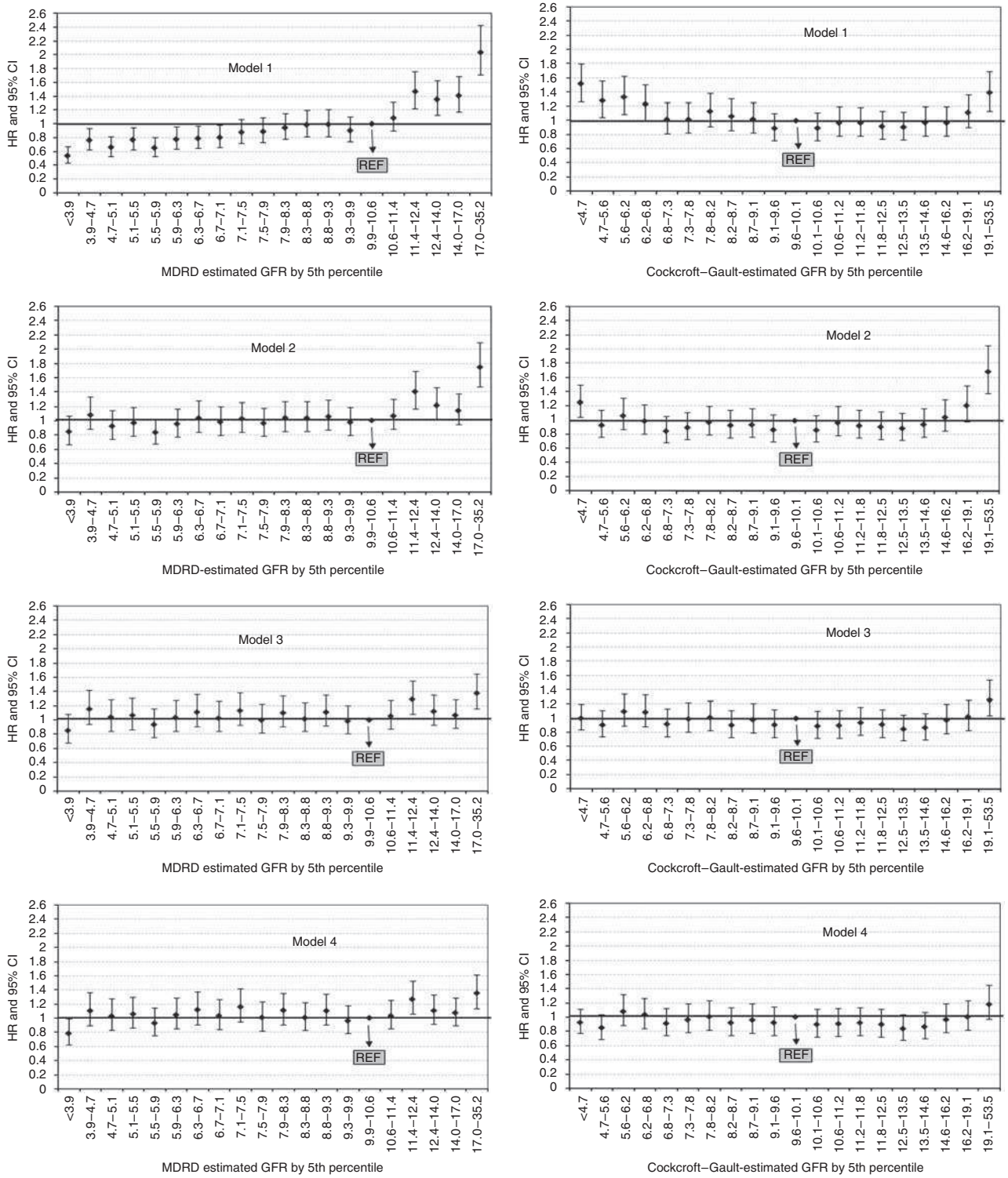

Figure 4 | HRs of mortality by 5-percentile of the GFR distribution in ml/min per 1.73 m^2, estimated with the MDRD and Cockcroft–Gault equations. Model-1: crude HRs; Model-2: HRs adjusted for age and gender; Model-3: HRs also adjusted for diabetes, heart failure, dysrhythmia, peripheral vascular disease, coronary heart disease, malignancy, severe disability, mobility, and nutritional status; Model-4: HRs further adjusted for predialysis anemia care, initial treatment condition, and access to waiting list or transplantation.

replacement by the former, it was still the equation recommended by French health authorities during the study period and the one chosen to randomize patients in the ongoing Initiating Dialysis Early and Late (IDEAL) trial.[27] It is therefore important to point out that the pattern of the crude association of eGFR with mortality differed substantially according to equation. Explanation for divergent findings was related to weight. When using the Cockcroft and Gault equation,

obese patients tend to have higher eGFR and thin patients, lower eGFR for a same level of creatinine.[25] Therefore, because the relation between BMI and mortality is U-shaped, both crude and age- and gender-adjusted HRs also reflect this association. After adjusting for age, gender, and BMI, the pattern of the association was very similar using either equation.

Third, lead-time bias should be taken into account in the interpretation of the results. As described in the NECOSAD study,[10] this bias may result in falsely prolonged survival simply because patients are started at an earlier stage of the disease. In the absence of any effect from early dialysis start, one would therefore expect some negative association between increasing eGFR and mortality, which we did not observe. Consequently, a detrimental effect of early dialysis initiation may be underestimated in this study. Finally, 27% of the patients had missing MDRD eGFR values. These patients, however, did not differ significantly regarding age from those with available data and only slightly for those factors most strongly associated with baseline eGFR, such as gender, heart failure, and diabetes. In the same way, the 1516 patients (11%) with eGFR but missing covariates did not significantly differ from those studied with respect to eGFR distribution at initiation as well as the crude association between eGFR and mortality (data not shown). We thus believe that our findings can be fairly generalized to the entire French population on dialysis.

We conclude that patients' age and comorbidities are strongly related to eGFR at dialysis initiation. In this observational study, these factors explained most of the paradoxical crude association between increasing eGFR and mortality. Considering that early start of dialysis is costly and has major consequences in the personal life of patients, strong evidence is required to justify early start. The ongoing IDEAL trial should provide further evidence regarding the effect that eGFR at initiation has on survival.[27] Our findings, however, emphasize the predominant role of patient condition over eGFR in the decision to initiate dialysis and subsequently on the outcome. Further research is needed to assess whether starting at higher eGFR affects overall quality of life and morbidity.

MATERIALS AND METHODS

Population

The REIN Registry includes all ESRD patients on renal replacement therapy—either dialysis or transplantation—treated in France. Patients with acute kidney failure are excluded, that is, those who recover all or some renal function within 45 days or who die before 45 days and are diagnosed with acute kidney failure by experts. The registry began in 2002 and has grown progressively to include the entire country in 2009. The details of its methods and quality control are described elsewhere.[28] Between 2002 and 2006, a total of 18,891 patients aged over 16 years started dialysis in 16 of 20 regions that together cover 79% of the French population. From these, we excluded 387 patients with preemptive grafts and 232 who recovered renal function within 6 months of dialysis initiation.

Information

Baseline information included age, gender, primary renal disease, BMI, as well as serum albumin, serum creatinine, and hemoglobin levels and use of ESA. In this analysis, we studied the following comorbidities: diabetes, hypertension, congestive heart failure (NYCA stages I–IV), coronary heart disease with or without a history of myocardial infarction, dysrhythmia, stroke or transient ischemic attack, peripheral vascular disease (Leriche classification stages I–IV), chronic respiratory disease, malignancy, liver disease (cirrhosis or viral hepatitis), HIV infection or AIDS, and smoking. We also considered mobility status and severe disabilities that may affect patient independence, such as severely impaired vision, amputation, hemiplegia, and paraplegia. Initial dialysis conditions were classified as planned HD, planned peritoneal dialysis, or unplanned dialysis, defined as any first dialysis begun on an emergency basis, that is, in life-threatening circumstances requiring dialysis within 24 h. We also analyzed dialysis dose related to eGFR, on the basis of the duration and number of weekly HD sessions.

Patients with either creatinine value $<200\,\mu mol/l$ or MDRD (Modification of Diet in Renal Disease study) eGFR >60 ml/min per $1.73\,m^2$ ($n=136$) or with missing creatinine ($n=4935$) were excluded from the analysis. We used MDRD eGFR[24] throughout the analysis, but tested the consistency of our results with the Cockcroft–Gault eGFR, which was used to randomize patients in the IDEAL study.[27]

One of the authors (M. Labeeuw) conducted a validation study of the files of 90 of the 285 patients with MDRD eGFR >20 ml/min per $1.73\,m^2$, to assess the potential for misclassification in these high values. Seven of them (8%) resulted from coding errors and were corrected, one was collected more than 6 months before starting dialysis and was changed to missing value, and another identified a patient with acute kidney failure who was excluded from the database. All the others (90%) proved to be correct. Besides creatinine, the only variables with more than 5% missing data were hemoglobin, albuminemia, BMI, and mobility status. A missing category was added in the multivariate analyses for these four variables. For the others, missing values resulted in the exclusion of 1516 patients, leaving a total of 11,685 patients for this analysis.

Deaths and transplantations were registered on occurrence from the first day of dialysis through the study end-point on 31 December 2007.

Statistical methods

Baseline characteristics were studied by the class of MDRD eGFR ($\leqslant 5$, 5–10, 10–15, 15–20, and >20 ml/min per $1.73\,m^2$) and tested for significant associations after adjusting for age and gender. The percentage of eGFR variance explained by these characteristics was estimated with multivariate analysis, with eGFR treated as continuous. To assess the potential for bias due to missing creatinine values, we compared the characteristics of patients with and without these data. The two groups did not significantly differ regarding age, but those included in the analysis were more often men (62 versus 60%, $P=0.02$), less likely to have diabetes (36 versus 38%, age- and gender-adjusted $P=0.047$) or heart failure (25 versus 28%, adjusted $P<0.001$) and more likely to have started with unplanned dialysis (31 versus 26%, adjusted $P<0.001$).

The Kaplan–Meier method was used to estimate patient survival by eGFR class. Four Cox proportional hazard models were then fit to analyze the relations between eGFR and overall mortality, with sequential adjustment for explanatory variables. Model-1 was crude; Model-2 was adjusted for age and gender; Model-3 added the comorbid conditions and nutritional status indicators significantly associated with eGFR in the first step; and Model-4 also adjusted for predialysis anemia care, initial treatment conditions, wait-listing, and transplantation. In these models, MDRD eGFR was treated both

quantitatively, by 5 ml/min per 1.73 m^2, to compare with others,[12,13,16] and semi-quantitatively, by 5-percentile groups of the distribution (that is, by demi-deciles), with the fifteenth group, including values around 10 (9.9–10.6) ml/min per 1.73 m^2, as the reference category. Interactions between patient or treatment conditions and eGFR were systematically tested. Models 1–4 were applied for the overall population as well as by treatment modality and heart failure status. To assess whether eGFR had a stronger impact on early versus late mortality, we studied HRs at 3 months and at 2 years. Finally, we estimated crude and adjusted HRs with the Cockcroft–Gault eGFR, by 5-percentile groups, with the eleventh group, including values around 10 (9.6–10.1 ml per min/1.73 m^2), as the reference.

The Strata option from SAS PROC PHREG was used to account for the region effect. By using this option, risks were estimated separately within each region and pooled across all regions. The proportional hazards assumption was evaluated by analyzing the scaled Schoenfeld residuals. Significance between the four nested Cox models was tested with the log-likelihood ratio. A *P*-value of 0.05 was the level for statistical significance in all analyses. SAS software, version 9 (SAS Institute, Cary, NC, USA) was used to perform the analyses.

DISCLOSURE

All the authors declared no competing interests.

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SHORT COMMUNICATION

Effect of type 2 diabetes on mortality risk associated with end-stage kidney disease

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Abstract
Aims/hypothesis Patients with end-stage kidney disease (ESKD) and patients with diabetes mellitus experience higher mortality rates than the general population. Whether ESKD imparts the same excess in mortality risk for those with diabetes as it does for those without diabetes is unknown.
Methods Included in the study were all white patients aged ≥25 years with incident ESKD and type 2 diabetes (n=4,141) or with incident ESKD but without diabetes (n=13,289) in Australia from 1991 to 2005, and all the individuals aged ≥25 years without ESKD and with type 2 diabetes (n=909) or without ESKD without diabetes (n=10,302) enrolled in the AusDiab Study—a nationwide Australian representative cohort—from 1999 to 2005. Excess mortality was analysed in patients with ESKD by diabetes status, using age-, sex- and diabetes-status-specific standardised mortality ratios (SMRs) in the first 8 years after first renal replacement therapy among ANZDATA patients relative to AusDiab participants.
Results The SMRs in patients with ESKD were, in non-diabetic patients and in those with type 2 diabetes, respectively: 14.2 (95% CI 13.9–14.6) and 10.8 (95% CI 10.4–11.2) (p<0.01); in people aged <60 years, 28.7 (95% CI 27.2–30.4) and 18.6 (95% CI 17.1–20.4) (p<0.01); in people aged ≥60 years, 12.5 (95% CI 12.1–12.9) vs 9.7 (95% CI 9.3–10.1) (p<0.01); in men, 11.0 (95% CI 10.7–11.4) vs 8.9 (95% CI 8.4–9.3) (p<0.01); and in women, 23.4 (95% CI 22.5–24.3) vs 16.2 (95% CI 15.2–17.3) (p<0.01).
Conclusions/interpretation ESKD was associated with a greater relative increase in mortality in the non-diabetic study populations than in the type 2 diabetes population. Excess mortality was greater among younger people and women.

Keywords ANZDATA Registry · AusDiab Study · Diabetes · End-stage kidney disease · Standardised mortality ratio

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Abbreviations

AusDiab	Australian Diabetes, Obesity and Lifestyle Study
ANZDATA	Australian and New Zealand Dialysis and Transplant Registry
CKD	Chronic kidney disease
CVD	Cardiovascular disease
eGFR	Estimated GFR
ESKD	End-stage kidney disease
RRT	Renal replacement therapy
SMR	Standardised mortality ratio
uPCR	Urine protein/creatinine ratio

Introduction

End-stage kidney disease (ESKD) is associated with an excess mortality compared with the age- and sex-matched general population [1]. An analysis of French patients with incident ESKD reported a standardised mortality ratio (SMR) for that group compared with the general population [2]. In that study, the excess mortality associated with ESKD was higher in patients with diabetic nephropathy than in those with other causes of kidney failure [2]. However, whether ESKD imparts the same relative mortality risk among those with diabetes as it does for those without diabetes is unknown, because that study did not take into account the diabetic status of the non-ESKD reference population [2].

In Australia, the availability of a national treated ESKD Registry (ANZDATA Registry) [3] and mortality rates from a large, population-based cohort study (Australian Diabetes, Obesity and Lifestyle [AusDiab] Study) [4], allowed us to examine mortality rates for Australian patients with ESKD by the presence or absence of type 2 diabetes, and calculate age-, sex- and diabetes-specific SMRs.

Methods

The study was approved by the ANZDATA review board and was carried out in accordance with the Declaration of Helsinki (revised 2000) of the World Medical Association.

Mortality rates in the Australian population The AusDiab Study is a nationally representative cohort study of 11,247 non-institutionalised adults aged >25 years conducted in 1999–2000 in Australia [4]. Participants were predominantly white (92.9%). The proportions of participants with type 1 diabetes, type 2 diabetes and without diabetes were 0.3%, 8.1% and 91.6%, respectively. The 5 year follow-up of AusDiab participants provided population-based 1 year mortality rates in Australia by age band, sex and diabetic status [4].

Australian ESKD patients Data from the ANZDATA Registry were used to calculate mortality rates in Australian patients with incident ESKD [3]. We restricted the ESKD population to all white patients aged >25 years who began chronic dialysis in Australia from 1 April 1991 to 31 December 2005. Patients with type 1 diabetes and ESKD were excluded as the number in the AusDiab population was too small to calculate a mortality rate. Demographic, clinical data and comorbid conditions were prospectively collected at the start of dialysis [3]. Patients were followed until they died or 31 December 2005 [3].

Standardised mortality ratio Age-, sex- and diabetes-status-specific SMR with 95% confidence intervals among ESKD groups were computed using standard methods [5]. SMRs were computed for type 2 diabetic and non-diabetic ESKD patients against corresponding non-ESKD AusDiab groups. To ensure sufficient statistical power, we limited the analysis to the first 8 years of replacement renal therapy (RRT) (>50 remaining patients in all ESKD patient subgroups for each year).

In the ESKD patient groups, we observed the number of deaths (O_{Deaths}) annually from the first RRT, conditional on survival to that year. The expected number of deaths (E_{Deaths}) was derived from the 1 year mortality rates from the AusDiab Study, matched for age band (25–34, 35–44, 45–54, 55–64, 65–74, 75–84, and ≥85 years), sex and diabetic status.

E_{Deaths} was the sum of expected numbers of deaths for each stratum of interest. The SMR was the ratio of O_{Deaths} to E_{Deaths} [5].

When the SMR heterogeneity test [5] over years after first RRT did not reach statistical significance, we presented a single SMR for the 8 year period. Otherwise, we presented the SMR separately for each year.

Comparison of SMR between patient subgroups was performed with the χ^2 test [5], stratified by age band and sex, and computed annually from first RRT using the Mantel–Haenszel method.

All statistical analyses were performed with S-PLUS 6.0 Software Professional Release 2 (Insightful, Seattle, WA, USA). p values <0.05 were considered statistically significant.

Results

Characteristics of type 2 diabetic and non-diabetic ESKD and AusDiab populations Participants with type 2 diabetes and ESKD were older, and more likely to be male and to

Table 1 Baseline characteristics and RRT in type 2 diabetic and non-diabetic Australian patients with ESKD (1991–2005)

Characteristic	With type 2 diabetes (n=4,141, 23.8%)	Without diabetes (n=13,289, 76.2%)	p value
Men, n (%)	2,606 (62.9)	7,841 (59.0)	<0.0001
Age at first RRT (years) (mean ± SEM)	65.5±9.9	60.0±15.0	<0.0001
Age at first RRT (years) (median)	66.7	62.7	
Primary renal disease, n (%)			–
Diabetes	2,627 (63.4)	–	
Renal vascular disease	438 (10.6)	2,290 (17.2)	
GN and related disease	461 (11.1)	5,043 (38.0)	
Polycystic	76 (1.8)	1,432 (10.8)	
Other	539 (13.0)	4,524 (34.0)	
Co-morbidity at first RRT, n (%)			
Chronic lung disease	795 (19.2)	2,138 (16.1)	<0.0001
Coronary artery disease	2,609 (63.0)	4,514 (34.0)	<0.0001
Peripheral vascular disease	2,028 (49.0)	2,477 (18.6)	<0.0001
Cerebrovascular disease	973 (23.5)	1,708 (12.9)	<0.0001
90 day RRT modality, n (%)			<0.0001
Haemodialysis	2,636 (56.4)	8,162 (61.4)	
Peritoneal dialysis	1,487 (35.9)	4,642 (34.9)	
Renal transplantation	18 (0.4)	485 (3.7)	
Renal transplant, n (%)[a]	205 (5.0)	3,604 (27.1)	<0.0001
Median time to transplant (months) (95% CI)	19.9 (16.7–24.4)	18.9 (17.9–19.9)	
Crude median survival (months) (95% CI)	37.4 (35.6–38.8)	70.5 (68.0–72.8)	<0.0001

Data are presented as mean ± SEM, n (%), median or median (95% CI)

[a] Analyses restricted to patients younger than 70 years, including living donor and deceased donor renal transplantation

GN, glomerulonephritis; RRT, renal replacement therapy

have comorbid conditions than the non-diabetic patients with ESKD (Table 1). The overall crude 1 year mortality rate was twofold higher in type 2 diabetic than in non-diabetic patients with ESKD (Table 2).

In the reference population (AusDiab), the mean estimated GFRs (eGFRs) were over 60 ml min^{-1} 1.73 m^{-2} and mean urine protein/creatinine ratios (uPCRs) were within the normal range (<249 mg/mmol) in both groups

Table 2 One year mortality rates and 95% CI by age, sex and diabetic status in Australian patients with ESKD (ANZDATA Registry, 1991–2005)

		1 year death rate per 1,000 person-years	
Age band (years)	Sex	With type 2 diabetes (n=4,141, 23.8%)	Without diabetes (n=13,289, 76.2%)
25–54	Male	129.609 (111.267–150.111)	32.075 (24.100–41.431)
25–54	Female	122.137 (99.931–149.150)	35.848 (32.311–39.666)
55–64	Male	182.690 (165.673–200.980)	112.137 (87.255–140.437)
55–64	Female	198.054 (174.924–223.392)	115.911 (89.706–146.179)
65–74	Male	253.537 (192.907–323.246)	209.039 (175.813–245.729)
65–74	Female	304.205 (277.008–333.349)	208.331 (171.153–250.331)
75–84	Male	327.395 (288.515–370.055)	304.020 (243.547–371.837)
75–84	Female	362.970 (307.208–425.927)	306.872 (227.229–402.428)
≥85	Male	587.919 (281.930–1081.20)	506.664 (378.400–664.422)
≥85	Female	495.770 (160.975–1156.96)	424.189 (279.543–617.173)
Overall	–	224.031 (196.907–253.846)***	111.352 (102.888–120.327)

Data are presented as rate (95% CI)

***p<0.0001 vs without diabetes

Table 3 Baseline characteristics of the AusDiab population (AusDiab Study, 1999–2005) [4]

Characteristic	With type 2 diabetes (n=908)	Without diabetes (n=10,302)	p value
Age (years)	63.2±12.3	50.8±14.2	<0.0001
Men	477 (52.5)	4,551 (44.2)	<0.0001
History of cardiovascular disease[a]	157 (17.3)	582 (5.6)	<0.0001
eGFR[b] (ml min^{-1} 1.73 m^{-2})	71.9±14.7	76.3±12.6	<0.0001
uPCR (mg/mmol)	113±260	51±136	<0.0001

[a] Self-reported history of stroke, heart attack or angina

[b] Modification of Diet in Renal Disease (MDRD) equation

Data are presented as mean ± SD or n (%)

(Table 3). Type 2 diabetic patients were older, more likely to be male and to have a history of cardiovascular disease (CVD) than those without diabetes, and they had lower mean eGFRs and higher uPCRs than non-diabetic participants (Table 3). The overall crude 1 year mortality rate was fivefold higher in type 2 diabetic AusDiab participants than in non-diabetic AusDiab participants (Table 4).

Excess mortality associated with ESKD After adjusting for age and sex, the SMR was significantly higher in non-diabetic than in type 2 diabetic patients with ESKD: 14.2 (95% CI 13.9–14.6) compared with 10.8 (95% CI 10.4–11.2), respectively (p<0.01). When the analysis was restricted to type 2 diabetic patients with diabetic nephropathy (n=2,627, 63.4%), the SMR was 11.5 (95% CI 10.9–12.1) (not significantly different from the SMR in all type 2 diabetic individuals).

Impact of age and sex on excess mortality The SMRs in the non-diabetic group with ESKD vs those with type 2 diabetes and ESKD were: in patients aged <60 years, 28.7 (95% CI 27.2–30.4) vs 18.6 (95% CI 17.1–20.4), respectively, (p<0.01); in participants aged ≥ 60 years, 12.5 (95% CI 12.1–12.9) vs 9.7 (95% CI 9.3–10.1), respectively (p<0.01); in men, 11.0 (95% CI 10.7–11.4) vs 8.9 (95% CI 8.4–9.3) (p<0.01); and in women, 23.4 (95% CI 22.5–24.3) vs 16.2 (95% CI 15.2–17.3) (p<0.01). In both groups, the SMRs were higher in patients aged <60 years than in patients aged ≥60 years (p<0.01) and in women than in men (p<0.01). When the analyses were restricted to type 2 diabetic patients with diabetic nephropathy, the results were not significantly changed (data not shown).

Discussion

The excess relative mortality associated with ESKD was greater in non-diabetic individuals (mortality risk increased ×14) than in those with type 2 diabetes (risk ×10) when compared with the non-ESKD population with the same diabetes status, although patients with type 2 diabetes and ESKD had a mean absolute overall mortality twofold higher than that of non-diabetic patients with ESKD [6, 7]. Restricting the analyses to type 2 diabetes patients with diabetic nephropathy did not change the results.

Table 4 One year mortality rates and 95% CI by age, sex and diabetic status (AusDiab Study, 1999–2005) [4]

		1 year death rate per 1,000 person-years	
Age band	Sex	With type 2 diabetes (n=908)	Without diabetes (n=10,302)
25–54	Male	3.892 (0.471–14.058)	1.192 (0.681–1.935)
25–54	Female	0.000 (–)[a]	0.747 (0.398–1.278)
55–64	Male	14.644 (6.696–27.799)	3.114 (1.743–5.137)
55–64	Female	2.089 (0.052–11.640)	1.200 (0.483–2.474)
65–74	Male	24.022 (13.731–39.011)	11.396 (8.024–15.709)
65–74	Female	17.693 (8.832–31.659)	5.875 (3.725–8.817)
75–84	Male	38.314 (22.707–60.553)	34.821 (25.860–43.784)
75–84	Female	29.779 (17.347–47.679)	16.690 (11.690–23.107)
≥85	Male	135.911 (67.846–243.183)	84.455 (53.537–126.725)
≥85	Female	100.341 (43.320–197.713)	72.841 (47.582–106.730)
Overall	–	20.576 (16.607–25.207) ***	4.870 (4.296–5.500)

Data are presented as rate (95% CI)

[a] No deaths occurred in this group

***p<0.0001 vs without diabetes

The difference in the relative impact of ESKD on individuals with and without type 2 diabetes was not accounted for by differences in the age and sex structures of the groups. However, there are a number of possible explanations. People who develop ESKD have survived a period of chronic kidney disease and other competing risks of death—if these risks were higher among type 2 diabetic than non-diabetic patients, a bias may be introduced. Differences in the prevalence of CVD and the associated mortality between patients with ESKD and the general population by diabetes status are likely to exist: in the US Medicare population aged ≥65 years, the prevalence of peripheral vascular disease was 3.4-fold higher in non-diabetic patients with chronic kidney disease (CKD) than in those without CKD (32.0% vs 9.6%) but was only 2.1-fold higher in diabetic patients with CKD than in those without CKD (38.6% vs 18.0%) [8]. This may confound the diabetes association. Unfortunately, differences in CVD recording methods between the studied cohorts did not allow stratifying analyses by CVD status [3, 4].

The relative mortality among ESKD groups decreased with increasing age, regardless of diabetic status. This is explained in part by very low mortality rates in the younger population without ESKD, leading to a larger 'health gap' between populations with and without ESKD in younger compared with older participants [2]. The SMRs were higher in women as well: mortality rates were similar between the sexes in those with ESKD, but lower in women without ESKD—that is, the female survival advantage seen in the general population was lost in ESKD patients [2].

Our study has limitations. In the AusDiab population, the overall mortality rate was 6.1 per 1,000 person-years [4]. We assumed that the 1 year mortality rates from the AusDiab Study were stable over the 1999–2005 period and applicable to the 1991–2005 period. However, national death rates from the Australian Bureau of Statistics for the Australian population aged >25 years were nine to ten per 1,000 person-years between 1991 and 2005 [9]. This gap reflects the inclusion of a variety of groups in the population-based figures that were excluded from the AusDiab Study. Institutionalised individuals and indigenous people were not included when the AusDiab population was constituted [4]. However, the use of SMR based on a nationally representative cohort without the studied disease may be more accurate than one based on the general population, which will include people with a variety of other chronic diseases leading to an underestimation of excess mortality due to a specific disease [10]. Some bias may remain—the AusDiab population included 7.1% of non-white participants and we were not able to exclude them from this cohort. We excluded the one-quarter of patients with incident ESKD in Australia who were non-white [6]. Although an imbalance in type 2 diabetes prevalence between cohorts by race will introduce bias, this will be limited by the small proportion of non-white members of the AusDiab cohort. At least, the SMR method assessed excess mortality adjusted for a limited number of mortality risks (usually, age and sex) [5]. In our study, comparisons between subgroups should take into account that SMRs were adjusted only for age, sex and diabetic status.

In conclusion, patients with type 2 diabetes and ESKD have an overall higher absolute mortality risk but, when comparing patients with ESKD with a reference non-ESKD population with the corresponding diabetes status, ESKD was associated with a greater excess mortality in non-diabetic individuals than in those with type 2 diabetes. This effect varied with age and sex and may be due to differential cardiovascular risk gaps between patients with and without ESKD in type 2 diabetic and non-diabetic populations. These results underline that the risk for death was increased more than tenfold for the population reaching ESKD.

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Duality of interest The authors declare that there is no duality of interest associated with this manuscript.

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The Impact of Type 2 Diabetes on Mortality in End-Stage Renal Disease Patients Differs between Genders

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Key Words
Dialysis · End-stage renal disease · Type 2 diabetes mellitus · Survival, gender

Abstract
Background/Aims: In diabetics with end-stage renal disease (ESRD), risk of death has been reported to be non-constant after the first dialysis, and different outcomes have been observed between genders. We assessed the impact of type 2 diabetes (T2DM) on mortality in dialysis regarding its differential effect by gender using time-dependent analyses. ***Methods:*** All T2DM and non-diabetic (no-DM) patients who started dialysis in two renal units in Lyon, France, between January 1, 1995, and December 31, 2007, were included. In multivariate analyses, the Cox model and Shoenfeld residual approach were used to assess the effect of T2DM on dialysis mortality by gender. ***Results:*** We included 235 T2DM (males: 57.9%) and 480 no-DM (males: 65.6%) patients. In males, the adjusted hazard ratio (aHR) for death in T2DM versus no-DM was 0.83 (p = 0.20) and was constant over time after the first renal replacement therapy (RRT) (p = 0.88). In females, aHR for death in T2DM versus no-DM patients was not constant over time (p = 0.002). It was 0.64 (p = 0.13) within the first year after the first RRT and 2.10 (p = 0.002) after the first year. Evolutions with time of these aHR by gender were significantly different (p = 0.009). ***Conclusions:*** T2DM was associated with death only in females. This association was not constant over time after the first dialysis.

Introduction

In general and end-stage renal disease (ESRD) populations, type 2 diabetes mellitus (T2DM) is associated with high mortality rates [1–6]. Over the last few decades, a dramatic increase in T2DM prevalence was observed worldwide among ESRD patients [4–8]. In Europe [4–6] and in Australia/New Zealand [7], more than one quarter of incident ESRD patients had associated T2DM. In the

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USA, the proportion of incident dialysis patients with diabetes as cause of ESRD is over 40%, the vast majority due to T2DM [8]. In industrialised countries, population ageing, increased prevalence of diabetes and obesity, improved management of cardiovascular comorbidities and improved access to renal replacement therapy (RRT) explain this epidemic [1, 4–13].

In patients with diabetes, especially with T2DM, worse outcomes have been reported in women compared to men [7, 14–16]. This difference in prognosis has been underlined both in non-renal patients [14, 15] and in ESRD patients, as in France [16] and in Australia/New Zealand [7]. This association between gender and mortality differs from the usual one noted in the general population where females have a higher life expectancy than males [17].

Moreover, the evolution of risk of death in a French regional cohort of incident ESRD patients assessed by standardised mortality ratios against the general population was different by patient nephropathy: the standardised mortality ratio increased significantly during the first 3 years after the first RRT in patients with diabetic nephropathy whereas it decreased with time on dialysis in patients without diabetic nephropathy [16]. This evolution was marked in women with diabetic nephropathy [16]. Nevertheless, this last study had shortcomings regarding this specific issue. Analysis was performed in patients with diabetic nephropathy and not in patients with diabetes as comorbidity, and was not adjusted for confounding factors for death on dialysis [16].

The purpose of the present study was to explore the impact of T2DM on mortality in incident ESRD patients. Our aims were to determine if the effect of T2DM on mortality differed between genders and if this effect was constant over time after the first RRT when medical characteristics, comorbid conditions and RRT modalities were taken into account in multivariate analysis.

Methods

Patients

Patients were recruited in the dialysis units of the Department of Nephrology and Renal Transplantation of the Lyon-Sud Academic Hospital and of the non-for-profit Centre Associatif Lyonnais de Dialyse. Both nephrology services provided care for renal patients including predialysis care, haemodialysis and peritoneal dialysis. Renal transplantation was performed in Lyon-Sud Hospital. The area of patient recruitment was the same for both services and was located in the south of the agglomeration of Lyon in France. Weekly meetings with medical staffs of both services concerning patient care were scheduled over the study period.

Study Design

Data from a previous cohort study performed in our Department [18] and from a study in Australia/New Zealand [7] were used to calculate the study sample size [19]. When the α risk is 0.05, the study power 0.9, the hazard ratio (HR) for death in T2DM females versus non-diabetic (no-DM) females 1.50, the median survival time in the control group (no-DM females) 6 years, the time of recruitment 12 years and the ratio of no-DM females to T2DM females is 2, then the sample size of the cohort of female T2DM ESRD patients should be 76.

About 55 patients per year started dialysis in the units included in the study. Among those patients, 35% were T2DM ESRD patients including 40% of females (i.e. a mean of 8 female T2DM ESRD patients per year). We defined an inclusion period of 13 years with a follow-up period of 0–13 years to respect the sample size specifications (number of expected T2DM females: 104).

Patient Recruitment

All patients who started chronic dialysis (haemodialysis or peritoneal dialysis) between January 1, 1995, and December 31, 2007, in the dialysis units as described above were included. Patients temporarily dialysed for acute renal failure with renal function recovery were excluded. ESRD patients with type 1 diabetes mellitus (T1DM) were excluded (n = 18). ESRD patients who benefited from pre-emptive renal transplantation during the inclusion period were excluded (n = 24).

Patients were prospectively followed up until death or December 31, 2007, with the ESRD patient registry of the Department of Nephrology of the Lyon-Sud Hospital and with the Renal Epidemiology and Information Network Registry [20]. Registration on a renal transplant waiting list was recorded. Transplant patients were followed up with the database of the Agence de la Biomédecine (named CRISTAL). Fourteen patients were lost to follow-up because they moved out of the Rhone-Alpes Region during the study period (<2%).

Studied Parameters

Age, gender, date of first dialysis, original nephropathy, comorbid conditions at first dialysis, modality of dialysis, details of renal transplantation, death with date and cause of death were prospectively collected.

Original nephropathy included diabetic nephropathy, vascular nephropathy, primary and secondary glomerulonephritis (except diabetic nephropathy), polycystic kidney disease, chronic tubulo-interstitial nephritis, malformative uropathy, other causes and unknown cause.

Comorbid conditions at first dialysis included T1DM (used to exclude those patients under analysis), T2DM, arterial hypertension (blood pressure >140/90 mm Hg or antihypertensive medications), peripheral vascular disease (defined as a clinical claudication and/or a peripheral amputation and/or a peripheral artery stenosis >50%), coronary disease (angina, myocardial infarction), congestive heart failure (acute pulmonary oedema and/or left-ventricular ejection fraction <50% over an echocardiograph), cerebrovascular accident, heart transplantation, malignancy, hepatitis B or C virus infection, hepatic insufficiency (defined as a coagulation factor V <50%), liver transplantation, HIV infection and respiratory insufficiency (defined as need for chronic oxygen therapy or mechanical ventilation).

Modality of dialysis was the one used 3 months after first dialysis, or the one at dialysis initiation if death occurred before the fourth month.

Causes of death were pooled in 4 categories: cardiovascular (including sudden death, myocardial infarction, cerebrovascular accident, heart failure, peripheral vascular disease), infectious, malignancy and other causes.

Statistical Analysis

Analyses by diabetes status and by gender included the following: (i) descriptive analysis of baseline patient characteristics; (ii) analysis of survival and of evolution with time of the relative risks for death in T2DM versus no-DM patients by gender, and (iii) assessment of risk factors for death in different intervals of time after first dialysis by gender.

When appropriate, univariate comparisons were done with χ^2 test or Fisher's exact test for category variables and with Student's t test or ANOVA for continuous variables.

In all survival analyses, study start was date of first dialysis, end-point was death of any cause, and patients who benefited from renal transplantation were not right-censored in the analysis at date of transplantation. Crude survivals in T2DM versus no-DM patients by gender were assessed with the Kaplan-Meier method. Evolutions with time of the relative risks for death in T2DM versus no-DM patients by gender were assessed with multivariate analyses using the Cox model and Schoenfeld residual approach [21, 22]. The test based on Shoenfeld residuals explores the assumption of hazard proportionality in Cox regression models by summing the score process array over individuals to give a process that varies over time [22]. Results can be fitted by a line tested for zero slope: a non-zero slope is evidence against proportional hazards. Grambsch and Therneau [22, 23] developed a method from Shoenfeld residuals that models a time-dependent coefficient in Cox regression (instead of the usual constant Cox coefficient). This method allowed us to plot in Cox models the adjusted β-coefficient for death in T2DM versus no-DM ESRD patients by time after first dialysis [22]. The function cox.zph in the S-PLUS 6.0 statistical package was used for these analyses.

At least, the Cox proportional hazard model was used to identify patients' conditions which have independent effects on probability of death after first dialysis, in different intervals of time after first dialysis.

In all multivariate models, the parameter of interest was the diabetic status (T2DM or no-DM). Adjustment factors were age, gender, comorbid conditions at first dialysis (as described above, if the given comorbidity was present in more than 5 patients). Models were stratified on occurrence of renal transplantation during follow-up, first RRT modality and periods of first RRT (1995–1999, 2000–2004 and 2005–2007).

We checked for interactions between variables by including multiplicative terms in the Cox regression. If a significant interaction was found, we performed stratified survival analysis as described above.

Validity of the Cox proportional hazard assumption was checked by tests based on Shoenfeld residuals [21, 22]. All statistical analyses were performed with S-PLUS 6.0 Software Professional Release 2 (© 1988–2001, Insightful Corp., Seattle, Wash., USA).

A p value less than 0.05 was considered statistically significant.

Results

Patient Baseline Characteristics

Overall, 235 T2DM (99 females) and 480 no-DM (165 females) ESRD patients were included in the study. In Lyon-Sud Academic Hospital 615 (86.0%) patients started RRT and 100 (14.0%) in the Centre Associatif Lyonnais de Dialyse. Patient baseline characteristics are presented in table 1.

At first dialysis, T2DM females were older, had more diabetes-related nephropathy and were more likely to have congestive heart failure, coronary heart disease or hepatitis C virus infection than T2DM males. T2DM ESRD females were less likely to be treated by haemodialysis and to be registered on a renal transplant waiting list, but renal transplant rates did not differ between genders in the T2DM group.

In no-DM patients, females were less likely to have renal vascular disease as original nephropathy and to be treated by haemodialysis than males. Access to a renal transplant programme was similar between genders in the no-DM patient group.

Overall, T2DM patients were older, had more cardiovascular comorbidities and were less likely to be transplanted than no-DM ESRD patients.

Crude Survival by Diabetes Status and by Gender

Crude survival after first dialysis is shown in figure 1. In males, non-adjusted HR for death in T2DM against no-DM ESRD patients was 1.53 (95% confidence interval, CI = 1.17–2.00), with p = 0.002. Hypothesis of risk proportionality in the Cox model was achieved (test based on Shoenfeld residuals: p = 0.11). In females, non-adjusted HR for death in T2DM against no-DM ESRD patients was 2.20 (95% CI = 1.55–3.10), with $p < 0.0001$. Hypothesis of risk proportionality was not achieved ($p < 0.001$).

Cause of Death

Causes of death by diabetes status and by gender are described in table 2. In T2DM and in no-DM ESRD patients, causes of death did not differ significantly by gender (table 2). Overall, cardiovascular and sudden deaths were the main causes of death in T2DM, with significantly higher rates than in no-DM patients (table 2).

Time Variation of Adjusted HR for Death in T2DM versus No-DM Groups by Gender

In multivariate analysis, we observed a significant interaction between genders, diabetes status and time on

Table 1. Baseline characteristics of the study population at first dialysis (ESRD patients with T1DM were excluded, n = 18)

	T2DM (n = 235, 32.9%)			No-DM (n = 480, 67.1%)			
	male (n = 136, 57.9%)	female (n = 99, 42.1%)	p[1]	male (n = 315, 65.6%)	female (n = 165, 34.4%)	p[1]	p[2]
Age at first renal therapy, years	67.2 ± 10.3	70.4 ± 9.66	0.01	61.1 ± 17.2	62.9 ± 17.6	0.28	0.01
Primary renal disease, n			0.09			0.01	–
Diabetes	77 (56.7)	67 (67.7)		–	–		
Renal vascular disease	34 (25.0)	23 (23.2)		93 (29.5)	21 (12.7)		
GN and related disease	7 (5.2)	3 (3.0)		76 (24.1)	47 (28.5)		
Polycystic	1 (0.7)	0 (0)		23 (7.3)	22 (13.3)		
Other	17 (12.4)	6 (6.1)		123 (39.0)	75 (45.4)		
Comorbid conditions, n							
Congestive heart failure	45 (33.1)	43 (43.4)	0.10	63 (20.0)	25 (15.1)	0.19	0.01
Coronary heart disease	45 (33.1)	43 (43.4)	0.10	58 (18.4)	21 (12.7)	0.11	0.01
Peripheral vascular disease	54 (39.7)	35 (35.3)	0.49	39 (12.4)	13 (7.8)	0.13	0.01
Cerebrovascular accident	25 (18.4)	13 (13.1)	0.28	42 (13.3)	13 (7.8)	0.07	0.01
Heart transplantation	7 (5.1)	0 (0)	0.06	15 (4.7)	2 (1.2)	0.08	0.70
Malignancy	14 (10.2)	10 (10.1)	0.96	59 (18.7)	24 (14.5)	0.25	0.01
Hepatitis B infection	2 (1.4)	3 (3.0)	0.41	6 (1.9)	2 (1.2)	0.57	0.66
Hepatitis C infection	1 (0.7)	6 (6.0)	0.04	7 (2.2)	2 (1.2)	0.44	0.35
Hepatic insufficiency	12 (8.8)	2 (2.0)	0.06	13 (4.1)	2 (1.2)	0.08	0.07
Liver transplantation	3 (2.2)	0 (0)	0.37	6 (1.9)	1 (0.6)	0.25	0.87
HIV infection	0 (0)	1 (1.0)	0.87	4 (1.2)	1 (0.6)	0.49	0.39
Respiratory insufficiency	5 (3.6)	10 (10.1)	0.08	29 (9.2)	11 (6.6)	0.33	0.36
First modality of dialysis			0.01			0.01	0.48
Haemodialysis	102 (75.0)	59 (59.6)		237 (75.2)	104 (63.0)		
Peritoneal dialysis	34 (25.0)	40 (40.4)		78 (24.7)	61 (37.0)		
Details of renal transplantation							
Waiting list registration	25 (18.4)	8 (8.1)	0.02	112 (35.5)	64 (38.8)	0.48	0.01
Renal transplantation	12 (8.8)	5 (5.0)	0.27	87 (27.6)	45 (27.3)	0.93	0.01

GN = Glomerulonephritis. Figures in parentheses indicate percentages.
[1] Difference between genders in each subgroup by diabetes status. [2] Overall difference between T2DM and no-DM patients.

dialysis with respect to survival after first dialysis (p = 0.009).

In males, the adjusted HR (aHR) for death in T2DM versus no-DM patients was 0.83 (95% CI = 0.62–1.10; p = 0.20) and was constant over time after first dialysis (fig. 2, Shoenfeld residual test: p = 0.88, and table 3).

In females, the aHR was not constant over time (fig. 2, Shoenfeld residual test: p = 0.0019). Within the first year after the first RRT, the aHR for death in T2DM versus no-DM ESRD females was 0.64 (95% CI = 0.34–1.15; p = 0.13; table 3). After the first year after the first RRT, the aHR for death in T2DM versus no-DM ESRD females was 2.40 (95% CI = 1.39–4.16; p = 0.002; table 3).

No other significant interaction was found between variables, especially between first modality of dialysis (haemodialysis or peritoneal dialysis) and sex (p = 0.17) or diabetes status (p = 0.23).

Factors Associated with Death after First Dialysis by Gender

Age was significantly associated with death in both sexes (table 3). Congestive heart failure and peripheral vascular diseases were variables significantly associated with death in males, but not in females (table 3). We did not find a significant aHR variability with time on dialysis for another variable than T2DM in ESRD females.

Discussion

This study performed in a bicentric cohort of incident ESRD patients in France showed that T2DM was associated with death after first dialysis only in female patients. This effect on mortality was time dependent and was noted only after the first year after first dialysis. Moreover,

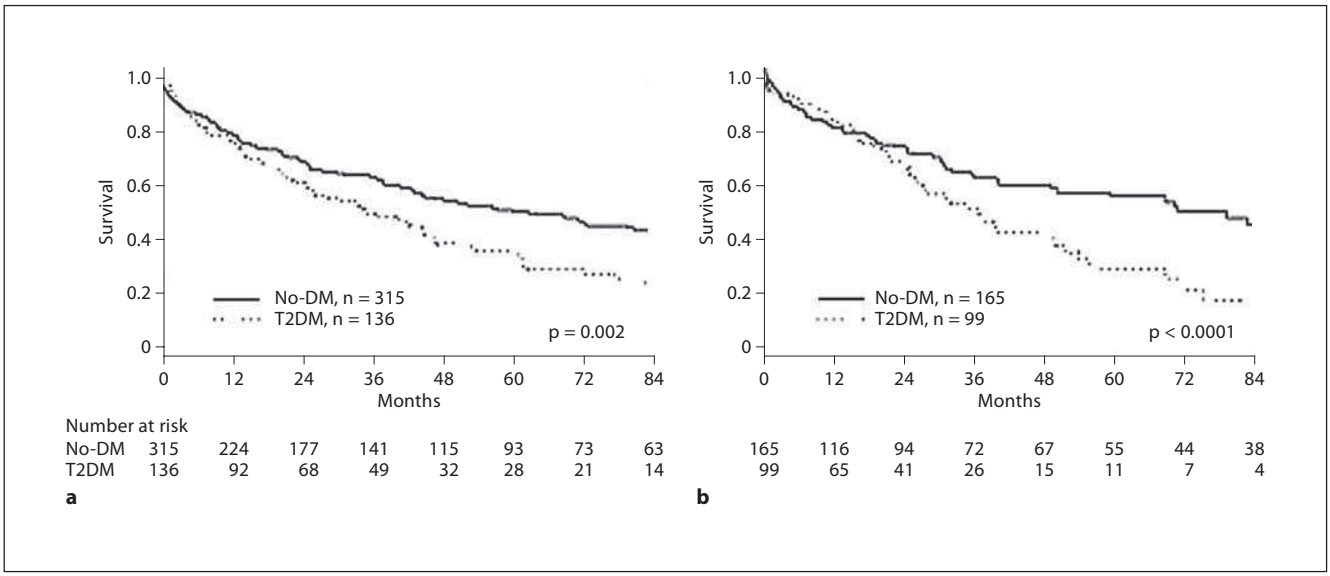

Fig. 1. Crude survival curves after first dialysis, by gender and by diabetes status. **a** Males. **b** Females.

Table 2. Causes of death by diabetes status and by gender

	T2DM (n = 149)			No-DM (n = 226)			
	male (n = 84)	female (n = 65)	p[1]	male (n = 155)	female (n = 71)	p[1]	p[2]
Cardiovascular and sudden death	46 (54.8)	33 (50.8)	0.40	60 (38.7)	20 (28.2)	0.38	0.004
Infection	7 (8.3)	11 (16.9)		15 (9.7)	9 (12.7)		
Malignancy	2 (2.4)	1 (1.5)		20 (12.9)	8 (11.3)		
Other	29 (34.5)	20 (30.8)		60 (38.7)	34 (47.8)		

Figures in parentheses indicate percentages.
[1] Difference between genders in each subgroup by diabetes status. [2] Overall difference between T2DM and no-DM patients.

analysis of death factors on dialysis showed that these differed by gender. Congestive heart failure and peripheral vascular disease were associated with death only in male ESRD patients, whereas T2DM seemed to be the major risk factor for death in females.

These data confirmed the interaction between diabetes status and gender with respect to mortality on dialysis noted in studies performed in France and in Australia/New Zealand [7, 16]. The present results complement both previous studies. In France, unadjusted comparison of age- and sex-standardised mortality ratio in ESRD patients against the general population showed that risk of death was higher in patients with diabetic nephropathy than in other patients [16]. In patients with diabetic nephropathy, especially in females, the standardised mortality ratio increased during the first 3 years after first RRT whereas they decreased continuously with time in patients without diabetic nephropathy [16]. We confirmed here that particular evolution of risk of death in diabetic ESRD patients using multivariate analysis. In Australia/New Zealand, analysis of the ANZDATA Registry showed that female gender was associated with death on dialysis in T2DM incident ESRD patients older than 60 years, whereas no gender effect was found in patients without diabetes and in T2DM patients younger than 60 [7]. In contrast, the overall effect of T2DM on mortality in the whole ANZDATA cohort was constant over time after first dialysis, but a spe-

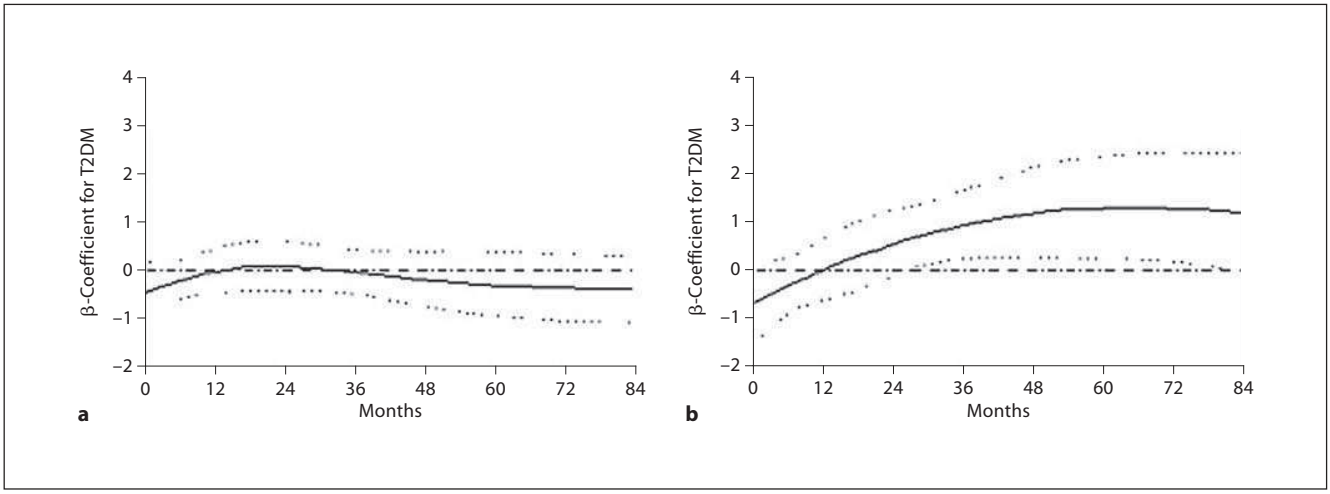

Fig. 2. Evolution with time after first dialysis of adjusted β-coefficient for death in T2DM patients versus no-DM patients, by gender (interaction term with time: p = 0.009; β-coefficient adjusted for age and medical comorbidities; stratified on occurrence of renal transplantation during follow-up, first dialysis modality and periods of first dialysis). **a** Males. **b** Females.

Table 3. aHR for death, 95% CI (in parentheses) and p value by gender and by period of time after first RRT in females

	Males		Females			
	overall (n = 451)	p	within first year (n = 264)	p	after first year (n = 179)	p
Age at first renal therapy (+1 year)	1.04 (1.02–10.5)	<0.001	1.07 (1.04–1.10)	<0.001	1.06 (1.03–1.09)	<0.001
T2DM	0.83 (0.62–1.10)	0.20	0.64 (0.34–1.15)	0.13	2.40 (1.39–4.16)	0.002
Congestive heart failure	2.22 (1.65–2.99)	<0.001	1.07 (0.56–2.03)	0.85	0.74 (0.42–1.30)	0.29
Coronary heart disease	0.80 (0.58–1.10)	0.18	0.95 (0.51–1.77)	0.87	0.82 (0.46–1.44)	0.48
Peripheral vascular disease	1.63 (1.19–2.23)	0.002	1.32 (0.69–2.50)	0.40	0.88 (0.49–1.60)	0.68
Cerebrovascular accident	1.24 (0.88–1.76)	0.22	1.96 (0.98–3.90)	0.056	0.66 (0.29–1.51)	0.32
Heart transplantation	2.02 (1.17–3.47)	0.01	–		–	
Malignancy	1.33 (0.95–1.86)	0.09	1.98 (1.00–3.91)	0.049	1.47 (0.69–3.12)	0.31
Hepatitis B infection	1.87 (0.90–5.81)	0.28	–		–	
Hepatitis C infection	0.75 (0.21–2.78)	0.67	5.74 (2.04–16.1)	<0.001	–	
Hepatic insufficiency	3.29 (1.71–6.30)	<0.001	–		–	
Liver transplantation	0.88 (0.25–3.11)	0.84	–		–	
Respiratory insufficiency	1.02 (0.64–1.65)	0.91	1.13 (0.51–2.50)	0.76	1.77 (0.76–4.03)	0.18

aHR = Adjusted for age and medical comorbidities, stratified on occurrence of renal transplantation during follow-up, first dialysis modality and periods of first dialysis; – = variable not introduced in model because the number of patients with the given comorbidity was lower than 5 in the subgroup.

cific effect of T2DM on mortality by gender was not reported [7]. Analysis of risk factors for death after first dialysis by gender complements those data. To the best of our knowledge, we analysed for the first time risk factors for death by gender, and the results underlined the differential effects of T2DM, heart failure and peripheral vascular disease on ESRD mortality between females and males. These differences between genders were not explained by factors we took into account in multivariate analysis, such as age, comorbid conditions

at first dialysis or RRT modality including renal transplantation.

In a non-renal population, worse prognosis has also been reported among diabetic females [14, 15]. This was not related to the usual risk factors [24], but to differential impacts of coronary disease, cholesterol level, coagulation, obesity and/or hyperinsulinaemia on mortality by gender [14, 15, 25]. Moreover, our study emphasised that risk factors for death in ESRD differed between males and females. Such a differential effect of cardiovascular comorbidities was observed in the general population from Norfolk, UK [25]. Hence, these results underlined the need for individualised management and the need for comprehensive recruitment of diabetic women in further studies and clinical trials performed among ESRD patients.

Our study has limitations. Due to the specificity of patient recruitment in a tertiary Academic Hospital in France, and despite the inclusion of patients from a non-for-profit dialysis association, the particular evolution of aHR for death in T2DM versus no-DM ESRD females with time after first dialysis should be interpreted with caution. We cannot exclude that bias in patient selection modified the aHR for death in T2DM versus no-DM ESRD females in the first year after first RRT, hiding a potential effect of T2DM within this first year. Moreover, several risk factors for death related to being on dialysis were not included in the analysis. Differences by gender and by diabetes status could be due to disparities in body mass index [26], glycaemic control [27], smoking status [7], inflammation [28], nutritional [29], hormonal [30], socio-economic [31], psychological [32] patterns and/or a differential effect of dialysis dose [33] between genders by diabetes status. Unfortunately, these data were not available for analysis in the studied cohort and these were hypotheses to explain such gender differences. In our study, the modality of dialysis had no significant effect to explain these differences by gender and diabetes status.

The strength of the present study was that T2DM was analysed as a comorbid condition. The study performed in Australia/New Zealand underlined that ESRD patients with associated T1DM or T2DM had different clinical characteristics and outcomes, and that 26% of ESRD patients with T2DM had another nephropathy than the diabetic one, when only 16.6% had a biopsy-proven nephropathy [7]. Hence, studies stratifying diabetic patients on diabetic nephropathy could be biased because diabetic nephropathy includes patients with T1DM and T2DM and because a significant proportion of ESRD patients with diabetes may have another original nephropathy than the diabetic one. T1DM patients were not studied here because there were too few T1DM subjects in our cohort (n = 18). Including T1DM in the no-DM control population did not modify the study results (data not shown). Moreover, this analysis underlined the need for checking HR proportionality in the Cox model and the clinical interest to model the aHR against time when risk proportionality was not achieved for a given variable.

In conclusion, this study showed that T2DM was significantly associated with death after first dialysis only in female ESRD patients and that the risk factors for death on dialysis differed between genders. These results confirm and complement previous studies performed in France and in Australia/New Zealand [7, 16]. They deserve further explanatory studies focused on gender differences, and they underline the need for specific care management among ESRD populations by gender and by diabetes status.

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A Simple Modeling-free Method Provides Accurate Estimates of Sensitivity and Specificity of Longitudinal Disease Biomarkers

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Keywords
Sensitivity and specificity, prognosis, early diagnosis, longitudinal study, biological markers

Summary
Objective: To assess the time-dependent accuracy of a continuous longitudinal biomarker used as a test for early diagnosis or prognosis.
Methods: A method for accuracy assessment is proposed taking into account the marker measurement time and the delay between marker measurement and outcome. It dealt with markers having interval-censored measurements and a detection threshold. The threshold crossing times were assessed by a Bayesian method. A numerical study was conducted to test the procedures that were later applied to PCR measurements for prediction of cytomegalovirus disease after renal transplantation.
Results: The Bayesian method corrected the bias induced by interval-censored measurements on sensitivity estimates, with corrections from 0.07 to 0.3. In the application to cytomegalovirus disease, the Bayesian method estimated the area under the ROC curve to be over 75% during the first 20 days after graft and within five days between marker measurement and disease onset. However, the accuracy decreased quickly as that delay increased and late after graft.
Conclusions: The proposed Bayesian method is easy to implement for assessing the time-dependent accuracy of a longitudinal biomarker and gives unbiased results under some conditions.

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1. Introduction

Today, disease diagnosis is made not only on traditional clinical observations, but also on laboratory results; for example, fluorescence polarization, a measure of cellular functionality, is used to make the diagnosis of breast cancer [1]. Methods have been developed to use those results as diagnostic tests and to compare their accuracies [2–4]. Molecular biology has also contributed to the improvement of early diagnosis or prognosis of diseases. Recent research fields, as in genomics or proteomics, led to the development of numerous biomarkers for early diagnosis or prognosis [5, 6]. During patient follow-up, it became frequent to collect repeated measurements of a quantitative biomarker such as the CA19-9 antigen in screening for recurrence of colorectal cancer [7]. The prognostic value of such longitudinal clinical biomarkers has to be carefully assessed and analyzed [8, 9]. For a clinician, a biomarker is useful if it has a good discriminant accuracy and if its test becomes positive early enough to allow an efficient reaction between marker measurement and the disease clinical manifestation. Thus, the progression of a biomarker's accuracy along the delay from marker measurement and disease onset is of major interest. A marker load may also vary along the time elapsed since inclusion of a patient into a study regardless of the progression toward disease. Consequently, accuracy analyses should take into account both the marker measurement time and the delay between marker measurement and disease onset.

When a marker is measured with the disease present, it is conventional to use a ROC curve to summarize the accuracy of continuous or ordinal tests [9–12]. That curve displays the relationship between sensitivity (true-positive rate) and 1-specificity (false-positive rate) across all possible threshold values set for that test. The test accuracy is then measured by the area under the ROC curve (AUC). This area, comprised between 0 and 1, may be interpreted as the probability that the diagnostic test result in a diseased subject exceeds that result in a non-diseased one (for a complete review of classical diagnostic methods, see Pepe [3] and Zhou et al. [13]).

Recently, several methods have been proposed to assess the time-dependent accuracy of a biomarker when the measurements are repeated before disease onset [14–20]. A first approach consists in modeling semi-parametrically the time-dependent sensitivity and

specificity or the ROC curve itself [16, 17]; the model's validity may be checked with methods proposed by Cai and Zheng [21]. A second approach models survival conditional on the marker values [18–20]. A third approach models the marker distribution conditional on the disease status [14, 15]. In each of the previous models, effects related to marker measurement time and to the delay between marker measurement and outcome are introduced. In their comprehensive and very instructive review on the subject, Pepe et al. [22] recommended sensitivity be assessed on events that occur exactly t days after marker measurement (incident sensitivity) and not over a delay following the measurement (cumulative sensitivity). Also, they recommended specificity be evaluated in subjects with follow-up long enough to be considered as subjects who will not develop the disease (static specificity). Five out of the six above-mentioned methods [14–18, 20] use this definition of time-dependent accuracy. However, those methods require sophisticated models that are not currently available in standard statistical softwares.

Considering those facts, we developed a simple method to assess the time-dependent accuracy of a longitudinal biomarker using a Bayesian approach. In agreement with the recommendations of Pepe et al., that method takes into account interval-censored measurements and, possibly, biomarkers with a detection threshold.

The first section of the present article describes the method. Numerical studies were conducted in order to compare the results obtained with and without consideration of the sparse nature of the measurements. The method is also illustrated by an analysis of data stemming from a clinical study where patients were screened by PCR measurements to predict cytomegalovirus (CMV) disease after renal transplantation.

2. Methods

2.1 Time-dependent Accuracy Definition

Heagerthy and Zheng [23] have proposed several ways to integrate time into ROC analysis according to how "cases" and "controls" are defined. As recommended by Pepe et al. [22], the incident sensitivity definition was used here [23]: cases correspond to patients who develop the disease exactly t time units after marker measurement. Thus, for a t time units delay between marker measurement and outcome, sensitivity is estimated with measurements taken exactly t time units before the outcome. Sensitivity is assessed at different delays t to assess its progression along the delay from marker measurement to outcome. In this article, a positive test is defined as a marker value higher than or equal to a certain threshold (though equal or lower values may be elsewhere considered). If $Y_i(s)$ denotes a measurement relative to patient i at time s since his inclusion into the study, and T_i the event onset time, the incident sensitivity for a delay t between marker measurement and outcome and for a threshold c may be formalized as:

$$\text{Sensitivity}\,(c, t) = P[Y_i(s) \geq c \mid T_i - s = t]$$

The progression of sensitivity along t reflects the test ability of early prediction of the outcome.

Controls are defined as subjects who do not develop the disease τ days after inclusion into the study, τ being a fixed delay, long enough to consider as controls patients who will probably never develop the disease. Specificity is estimated using measurements in those patients, which leads to static specificity estimates. A possible progression of specificity after inclusion may be taken into account by estimating specificity using, in the controls, the measurements taken at different periods after inclusion. For each subject of the control group, the highest measurement obtained during the period $[s_j, s_{j+1}]$ is kept, s_j and s_{j+1} denoting successive times since inclusion. The definition of specificity may be formalized as:

$$\text{Specificity}\,(c, \tau, s_j, s_{j+1}) = P\left[\max_{s_j \leq s < s_{j+1}} \left(Y_i(s)\right) < c \mid T_i > \tau\right]$$

2.2 Time-dependent Accuracy Estimation

Estimating incident sensitivity requires that a marker measurement be taken exactly t days before the onset of the disease in each subject who developed that disease, which is not the case in most studies. A first method, called the crude method, consists in using for each cases the last value obtained before $T_i - t$, introducing a bias because the delay between marker measurement and $T_i - t$ might vary widely from one patient to another.

Because of measurements sparsity, a marker threshold value is often crossed between two dates; this leads to "interval-censored data" [24]. For example, for each couple of measurements, the crude method supposes that the marker value was Y_i at time t_i and Y_j at time t_j, whereas Y_j was actually reached and crossed during interval $]t_i; t_j]$. Biomarkers with a detection threshold raise similar issues. All that can be known is that the biomarker has crossed the detection threshold between two dates.

One way to deal with interval-censored measurements is to estimate the exact threshold crossing times using a Bayesian method with non-informative priors and assuming that, for a given threshold, the crossing times of all patients who crossed it follow a Weibull distribution. The Weibull distribution was chosen because it is commonly used to model times to event, in particular failure times, but other positive distributions can be used if appropriate. The moment at which each observed marker value is crossed by each patient can be estimated. Unlike the crude method, that Bayesian method uses all the information contained in interval-censored data or measurements below a detection threshold. Then, in patients who develop the disease, the most recent threshold value crossed at $T_i - t$ is used as a diagnostic test for ROC analysis. In patients who do not develop the disease, the diagnostic test used is the highest threshold value crossed between s_j and s_{j+1} obtained using the Bayesian method.

3. Simulation Study

3.1 Numerical Studies

Numerical studies were carried out to compare the results obtained with the crude method to those obtained with the Bayesian method. Let us consider 200 subjects who developed a given disease at time T_i, and 100 subjects who did not develop that disease. Marker measurements were considered throughout a follow-up duration that did not

Table 1 Estimated mean AUC values and sensitivities for thresholds 1, 2, 3, and 4, with their respective standard errors, obtained with the Bayesian method and the crude method over 100 simulations, for three delays between marker measurement and disease outcome

Delay	Method	AUC	Se 1	Se 2	Se 3	Se 4
2	Theoretical	0.985	0.999	0.971	0.787	0.378
	Bayesian	0.868 (0.037)	0.959 (0.027)	0.842 (0.045)	0.617 (0.056)	0.312 (0.050)
	Crude	0.697 (0.029)	0.885 (0.026)	0.610 (0.029)	0.284 (0.038)	0.085 (0.043)
4	Theoretical	0.791	0.871	0.5	0.129	0.012
	Bayesian	0.616 (0.031)	0.838 (0.025)	0.509 (0.038)	0.175 (0.048)	0.026 (0.029)
	Crude	0.458 (0.045)	0.717 (0.030)	0.299 (0.049)	0.060 (0.055)	0.012 (0.041)
6	Theoretical	0.618	0.664	0.233	0.03	0.001
	Bayesian	0.418 (0.048)	0.682 (0.037)	0.253 (0.055)	0.043 (0.051)	0.006 (0.025)
	Crude	0.342 (0.049)	0.578 (0.041)	0.176 (0.051)	0.027 (0.045)	0.007 (0.032)

True AUCs and sensitivities were estimated according to process of generation of the biomarker values.
Se denotes sensitivity.

exceed 30 days. High marker values were considered indicative of disease onset. The way data were simulated is described in ▶Appendix 1. The biomarker predictive ability was assessed by the crude and the Bayesian method. Sensitivity was estimated at $t = 2, 4$, and 6 days before the outcome. Specificity was estimated only during the period [0, 10[days after inclusion because, in controls, there was no trend for change of biomarker values over time. One hundred simulations were performed. The means obtained for the 100 areas under the ROC curve and for sensitivities at four threshold values (1, 2, 3, and 4) were compared to the theoretical time-dependent area under the ROC curve and sensitivity assessed according to the process of generation of the biomarker values (▶Table 1).

3.2 Results

Except for the delay of six days and the threshold value 4, the Bayesian method led to higher sensitivities with differences ranging between 0.02 and 0.33. The standard errors were roughly of the same order of magnitude with the two methods. The comparisons with the theoretical results showed that, except for the delay of six days and the threshold value 4, the crude method clearly underestimated the test sensitivity and that the use of the Bayesian method corrected this underestimation. Besides, except for a delay of two days, the sensitivities obtained with the Bayesian method were close to the theoretical values with small differences ranging between –0.05 and 0.03. The precision of threshold crossing times estimates depends partly on the measurement frequency. With measurements taken approximately every three days, there is a lack of information to precisely estimate the latest threshold crossed two days before the event, especially when the biomarker values increase as quickly as the onset of disease become closer in time. This explains the differences between the theoretical and the Bayesian results. A way to increase the precision of Bayesian estimates is to make more frequent measurements or to increase the number of cases.

Both the Bayesian and the crude method underestimated the specificities at low thresholds (data not shown). This was not due to the exact estimations of the thresholds crossing times but to the fact that specificity was assessed using the highest value reached in each control during a given period. The longer was the period, the highest was the bias. Hence, the choice of the period should be made with great caution.

The AUC values obtained with the Bayesian method were higher than those obtained with the crude method and corrected partly the underestimation of accuracy with the latter method. The differences between the Bayesian and the theoretical values came from underestimation of sensitivity with a delay of two days, but also and mainly from underestimation of specificity.

The Bayesian methods led to a better estimation of sensitivity, which is the aim of the present article. Underestimation of specificity came from the empirical assessment of specificity and not from the exact threshold crossing times.

4. Example: CMV Disease Prediction after Renal Transplantation

4.1 Study Description

The study involved 68 patients who had undergone kidney transplantation between January 1, 1999 and December 31, 2003, at the Centre Hospitalier Lyon Sud (Lyon, France). All were CMV-seropositive before transplantation; 46 received a CMV-positive graft and 22 a CMV-negative one. They were weekly monitored for CMV by quantitative PCR during eight weeks after transplantation, semi-monthly until the third month, then monthly until the sixth month. Because the probability of developing CMV disease six months after renal transplantation is low, patients who did not present a CMV disease after a six-month follow-up were considered disease-free.

CMV infection was defined as isolation of CMV by early or late viral culture. CMV disease was defined as the presence of the above defined CMV infection plus either: i) an association of two among the following clinical or biological signs: temperature above 38 °C for at least two days, leukopenia (less than 3.5 G/L), thrombocytopenia (less than 150 G/L), abnormalities of liver enzymes (twice or more the reference levels); ii) isolated leukopenia (less than 3 G/L); or iii) tissue injury (invasive disease).

The PCR method had a detection threshold of 200 copies/mL; 321 measurements out of 494 fell below this threshold. Those left-

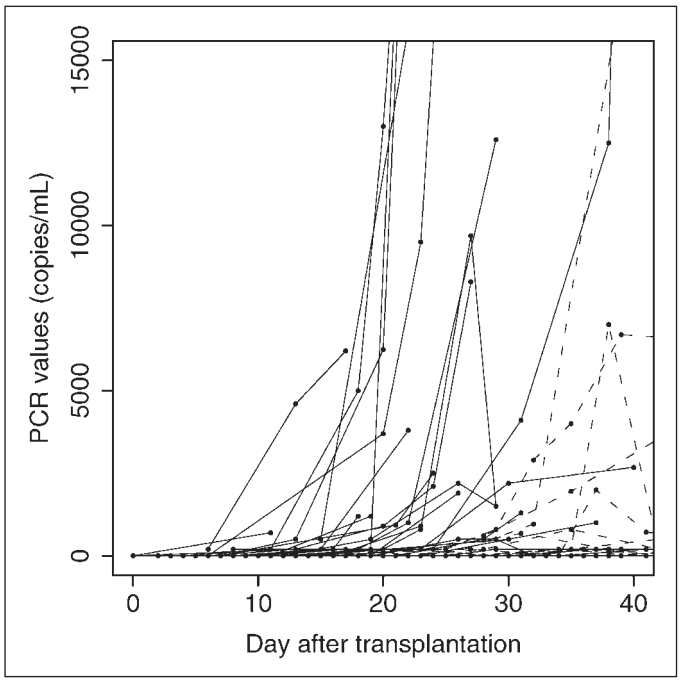

Fig. 1 PCR measurements for cases (solid lines) and controls (dotted lines) versus measurement day after transplantation. *x* and *y* scales have been truncated.

censored measurements were given value 0. Forty-three subjects developed a CMV disease with transplantation-to-disease quartiles 21, 25, and 31 days, respectively. The quartiles relative to the number of measurements in those patients were 3, 4, and 5 measurements, respectively. Most patients who developed a CMV disease had an earlier sharp increase in the viral load (▶Fig. 1). The viral load of the 25 subjects who did not develop the disease remained generally low; however, six of them had a slight increase starting from the 20th day, followed by a decrease starting about the 30th day, then a return to the initial level. This may strongly influence the diagnostic test specificity. However, during the first 30 days, the variability between measurements in subjects who did not develop the disease remained very low.

Specificity was estimated at four periods after transplantation, p_1 to p_4: [0; 10[, [10; 20[, [20; 30[, and [20; 30[days, respectively, with measurements in 25 patients. Sensitivity was estimated at t = 0, 5, and 10 days before the outcome, with measurements in 43 patients. Threshold crossing times were estimated using the Bayesian method. The model was fitted using WinBUGS software package [25]; its corresponding code is given in ▶Appendix 2. ROC curves were then constructed with those sensitivity and specificity estimates. There was a large gap between thresholds 0 and 200 on ROC curves, although there was no information on other in-between thresholds. Therefore, only the partial area above threshold 200 was estimated [26]. The obtained values were transformed in values between 0 and 1, as proposed by McClish [27]. The confidence intervals (CI) for AUC values and the standard errors (SE) for sensitivity and specificity were assessed by bootstrap, based on 1000 samples.

4.2 Results

For a fixed delay between marker measurement and disease onset, the ROC curves corresponding to the first 10 days p_1 and 10–20 days p_2 after transplantation were very close (▶Fig. 2). Regarding the two later periods p_3 and p_4, the ROC curve was as much close to the diagonal as the period was late after transplantation. For each period during which specificity was estimated, the ROC curves were all the more close to the diagonal that the delay between marker measurement and

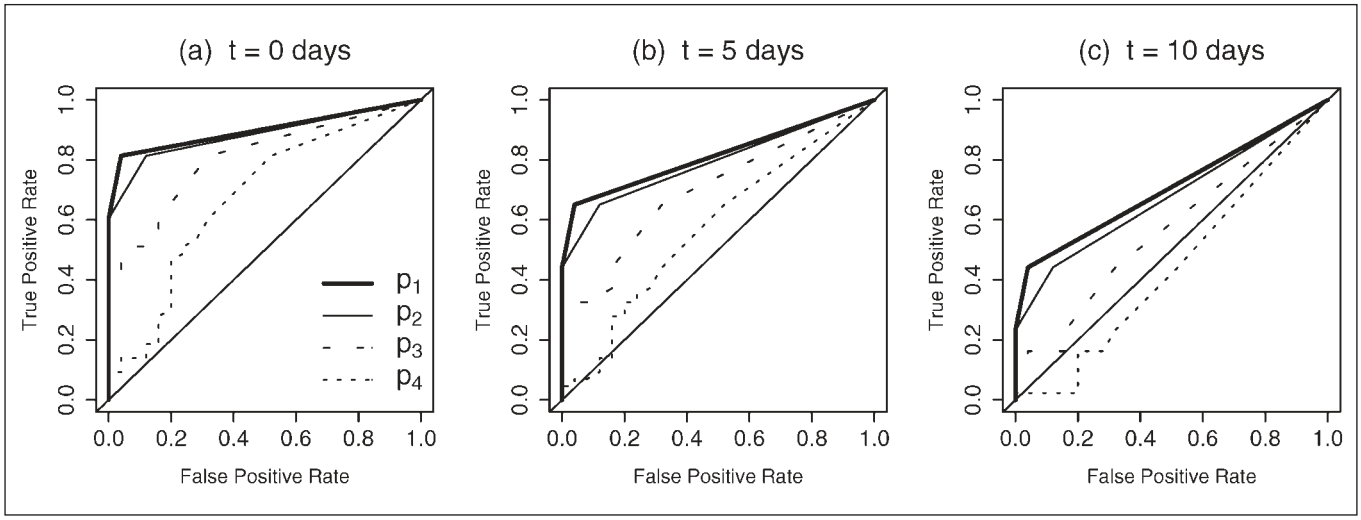

Fig. 2 ROC curves estimated at three delays between marker measurement and disease onset (t = 0, 5, and 10 days) and during four periods after transplantation for specificity: p_1 = [0; 10[, p_2 = [10; 20[; p_3 = [20; 30[, and p_4 = [20; 30[days

disease onset increased. AUC estimates in ▶Table 2 show that the test accuracy was good during the two first periods after graft and at 0- and 5-day delay between test and disease onset ($t = 0$ and $t = 5$). The AUC was then over 75% but it decreased quickly as the period and the delay increased. The AUC decrease with the advance of the period was linked to a decrease of specificity in late periods; thus, specificity depended on the period after graft. The decrease of the AUC along the delay between marker measurement and disease onset was linked to a decrease of sensitivity. The discriminant ability was not significantly greater than 0.5 neither in the third period p_3 with $t = 10$ nor in the fourth period p_4 with $t = 5$ or $t = 10$ (value 0.5 lies within the 95% confidence interval).

At the specific threshold of 200, the sensitivity was above 80% for $t = 0$, but lower than 50% at $t = 10$ (▶Table 3). This threshold was associated with a good specificity during the two first periods p_1 and p_2, but that specificity decreased quickly to less than 50% during the fourth period.

Table 2 Partial AUC values (95% confidence interval) estimated at three delays between marker measurement and disease onset and during four periods for specificity

Period after graft (days)	Delay between test and disease onset (days)		
	0	5	10
[0; 10[	0.852 (0.783; 0.907)	0.769 (0.694; 0.833)	0.662 (0.591; 0.721)
[10; 20[	0.845 (0.780; 0.906)	0.759 (0.684; 0.833)	0.647 (0.574; 0.717)
[20; 30[	0.757 (0.661; 0.844)	0.669 (0.569; 0.761)	0.550 (0.349; 0.642)
[20; 30[	0.634 (0.509; 0.759)	0.555 (0.356; 0.678)	0.344 (0.157; 0.555)

5. Discussion

The Bayesian method to estimate the exact threshold-crossing times described in this article allows estimating incident sensitivity and static specificity of a longitudinal biomarker. The numerical studies showed that the crude method underestimated sensitivity in the case of interval-censored measurements whereas, under some conditions, the Bayesian method corrected that bias.

In the application, quantitative PCR seemed reliable to predict CMV disease within five days preceding the disease onset and within the first 20 days after transplantation. Before that fifth day, the test sensitivity decreased quickly with the increasing delay between marker measurement and disease onset and the test specificity decreased quickly after the 20th day after transplantation. To our knowledge, this is the first study on early diagnosis of CMV disease that took into account the progression of accuracy with both the marker measurement time and the delay between marker measurement and the disease clinical detection. This was found crucial and explained the differences that exist in the literature about quantitative PCR accuracy, where the delay or the measurement period changes from one study to another [28–30].

The use of the highest biomarker value from each control during a given period may lead to an underestimation of specificity; this bias is conservative because we are sure that the true biomarker accuracy is not smaller than the one estimated. There is no consensus throughout the literature on the way to estimate specificity empirically with repeated marker measurements. Our choice was partly motivated by Murtaugh [31], who also kept the highest marker value from each control to estimate specificity. He compared these results to those obtained keeping the average marker value from each control, but the differences were slight. Emir et al. [32, 33], then Slate and Turnbull [15] proposed another way to assess static specificity without modeling it. At a specific threshold, the specificity with each control was estimated by the proportion of negative tests; then the global specificity was defined as the average of all individual specificities, possibly weighted by the number of measurements per subject. The possible bias of this method was not analyzed; the underestimation might be smaller than the one stemming from Murtaugh's method; however, both methods should lead to similar results when estimation periods are short, with few measurements by subject. All those methods could be used after estimation of the threshold-crossing times. A third method would be to model specificity; but then, the bias would depend on the validity of the model assumptions. Certainly, there is still a lot of work to do about estimation of specificity with repeated measurements along time.

Table 3 Estimated sensitivities and specificities (standard error) for quantitative PCR, the threshold being 200 copies/mL

Sensitivity	
Delay between test and disease onset (days)	
0	0.814 (0.063)
5	0.651 (0.073)
10	0.442 (0.077)
Specificity	
Period after transplantation (days)	
[0; 10[	0.960 (0.040)
[10; 20[	0.880 (0.066)
[20; 30[	0.680 (0.091)
[20; 30[	0.480 (0.100)

One contribution of this article is the assessment of specificity over different periods. This is relevant when specificity progresses along time after inclusion.

The exact estimation of the threshold-crossing times relies on the assumption that, for a specific threshold, the crossing times follow a Weibull distribution. This distribution is commonly used to model failure time data; this is the case of parametric regression for interval-censored data [34–37]. Lindsey [35] compared the results obtained from nine different distributions (including the Weibull, the log-normal, and the gamma distributions) and concluded that, except for heavily interval-censored data, the results may change with the distributional assumptions. However, in the above CMV study, the use of a log-normal distribution led to results, and especially ROC curves, which were almost identical to those obtained with a Weibull distribution.

Other forms than incident and static have been proposed for sensitivity and specificity

[23]; for example, estimating the cumulative sensitivity using the measurements taken during the *t* days preceding the outcome and not exactly *t* days before the outcome. However, cumulative sensitivity estimates depend on the time to disease distribution conditional on the marker measurement time and, thus, do not simply reflect biomarker sensitivity. In the concept of dynamic specificity, the controls are the patients who do not develop the disease during the *t* days following a measurement. However, in our study, the patients developed CMV diseases rapidly after transplantation. Among the subjects whose viral load increased during the few days before disease onset, some developed the disease very soon after *t* days following a measurement; these would therefore be considered as controls, inducing a high estimate of the false-positive rate and, thus, an underestimation of the real specificity. Thus, the incident sensitivity/static specificity definition of accuracy is, to our opinion, the best way to integrate the concept of time in ROC analysis. As stated by Pepe et al. [22], this should be used in most studies.

Compared to previous methods [15–20], the one proposed here is really easy to implement using standard statistical softwares (the code for Bayesian computations under WinBUGS is given in ▶Appendix 2). Moreover, there is no need to define and select a model for biomarker progression, sensitivity, specificity, the ROC curve, or the survival conditional to biomarker values; hence, the method can be very quickly adapted to other settings. Despite the need for a complex modeling phase, the method proposed by Cai et al. [17] remains appealing, but it requires large datasets because each biomarker value for which sensitivity or specificity is estimated adds a new parameter to the model; however, biomarker development studies do not always include a high number of patients. Anyway, our method imposes a restriction: it requires control follow-ups be long enough to assume they are real controls, i.e., the method does not allow so far for censoring, but it may be improved to deals with censored data using ideas similar to those proposed by Cai et al. [17]. The next step of our research would be to analyze the effect of the delay between measurements on accuracy estimates when that delay depends on the last measurement value. Within the context of longitudinal biomarker modeling, Shardell and Miller [38], then Liu et al. [39] have directly addressed this problem.

We hope our simple method will help statisticians undertake complete and precise analyses of longitudinal biomarkers accuracy taking into account the marker measurement time and the delay between marker measurement and outcome. In most studies, this is essential.

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Appendix 1

1. Generation of the Simulated Data

1.1 Notation

i = subject index; k = kth marker measurement; s_{ik} = time of the kth measurement for the ith subject; Δ_{ik} = delay between the kth measurement and the diagnosis time for the ith subject

1.2 Sampling Times (s_{ik})

Patients should have a biomarker measurement every three days for 30 days after inclusion into the study; but, actually, the measurement is often delayed. Generate:

$s_{ik} = 3k + \varepsilon_{ik}$, $k = 0, ..., 9$

$$\varepsilon_{ik} = \begin{cases} \text{uniform } (1, 2.95) & \text{if } k = 0, \\ \text{uniform } (0, 2.95) & \text{if } k > 0. \end{cases}$$

1.3 Time of Diagnosis

The time of diagnosis was generated as follows:

$T_i \sim \text{uniform}(15, 20)$ with probability 0.4
$T_i \sim \text{uniform}(20, 30)$ with probability 0.6

1.4 Biomarker Values

For Controls

Throughout each simulation, controls have their own biomarker value normally distributed with mean 1 and variance 0.25; for each measurement, an error is added that follows a normal distribution with mean 0 and variance 0.49.

For Cases

In cases, biomarker values are generated as for controls up to eight days before diagnosis; for later measurements, an extra term is added:

$$\exp(2 - (0.5 + \delta_i)\Delta_{ik})$$

δ_i corresponds to patients' specific biomarker increase with time between marker measurement and diagnosis. It follows a normal distribution, with mean 0 and variance 0.0025.

Measurements taken after the time of diagnosis are removed.

2. Calculation of the Theoretical AUC Values

When biomarkers follow normal distributions in the diseased and non-diseased populations (respectively $N(\mu_D, \sigma_D^2)$ and $N(\mu_{\bar{D}}, \sigma_{\bar{D}}^2)$), Pepe et al. [3] showed that the AUC for the ROC curve is given by

$$\Phi\left(\frac{a}{\sqrt{1+b^2}}\right)$$

where $a = (\mu_D - \mu_{\bar{D}})/\sigma_D$, $b = \sigma_{\bar{D}}/\sigma_D$, and Φ denotes the standard normal cumulative function.

According to the process of generation of biomarker values, during each period, measurements in control subjects follow a normal distribution with mean 1 and variance 0.25 ± 0.49.

In cases, for a delay Δ between the marker measurement and the diagnosis time, the biomarker values follow a normal distribution with mean

$$1 + \exp(0.5(4 - \Delta))$$

and variance

$$\exp(4 - \Delta) \times \text{Var}(\exp(-\delta \times \Delta))$$

where δ follows a normal distribution with mean 0 and variance 0.0025.

For small delays Δ, the variance may be approximated using the delta-method; for our applications, the variance was estimated using 10^7 random values stemming from a normal distribution with mean 0 and variance 0.0025.

Those results allow us to calculate the theoretical AUC for each period and delay between marker measurement and the onset of disease.

Appendix 2

The WinBUGS code for estimating the exact threshold-crossing time (paragraph ROC curve analysis).

```
model
{
for(i in 1:N) ## N corresponds to the
number of crossings
{
crossing_time[i]~dweib(r,mue)I
(left[i],right[i])
## left[i] corresponds to the date of
last PCR measurement whose result was
inferior to the threshold
## right[i] corresponds to the date
of first PCR measurement whose result
was superior or equal to the thresh-
old
}
r~dgamma(1.0E-3, 1.0E-3)
mue<-exp(mu)
mu~dnorm(0,0.000001)
}
```

Mycophenolate Mofetil Monotherapy in Membranous Nephropathy: A 1-Year Randomized Controlled Trial

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Background: Treatment of patients with membranous glomerulonephritis (MGN) is controversial because of the lack of clear benefit of the immunosuppressive regimens on patient or renal survival. The objective of this study is to evaluate the efficacy and safety of mycophenolate mofetil (MMF) for patients with MGN.

Study Design: 1-year prospective, randomized, and controlled clinical trial.

Setting & Participants: 36 patients with biopsy-proven idiopathic MGN and nephrotic syndrome.

Intervention: 19 patients received MMF (2 g/d) for 12 months and 17 patients were in the control group. All patients had the same conservative treatment based on renin-angiotensin blockers, statins, low-salt and low-protein diet, and diuretics in case of edema.

Outcomes & Measurements: End points were the mean proteinuria over creatinuria ratio in mg/g throughout the study and numbers of complete and partial remissions at 1 year (month 12). Data were analyzed on an intention-to-treat analysis.

Results: Mean proteinuria over creatinuria ratio was stable in both groups throughout the study ($P = 0.1$). Mean proteinuria over creatinuria ratio was 4,690 ± 2,212 mg/g in the MMF group and 6,548 ± 4,601 mg/g in the control group (95% confidence interval of the difference, −619 to +4,247; $P = 0.1$). Remission was complete in 3 patients (1 in the MMF group, 2 in the control group; $P = 0.5$) and partial in 11 patients (6 in the MMF group, 5 in the control group; $P = 0.9$). The probability of complete or partial remission did not differ between the 2 groups after 12 months (relative risk, 0.92; 95% confidence interval, 0.48 to 1.75; $P = 0.7$). Kidney function was stable in the 2 groups according to estimated glomerular filtration rate and serum creatinine level.

Limitations: The small number of patients and short follow-up prevent generalizations.

Conclusions: A 12-month regimen of MMF did not decrease mean proteinuria over creatinuria ratio or increase partial and complete remissions. Serious adverse effects were observed in 4 patients (20%) receiving MMF.

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INDEX WORDS: Membranous nephropathy; nephrotic syndrome; mycophenolate mofetil; randomized trial.

Membranous glomerulonephritis (MGN) is the most frequent cause of nephrotic syndrome in adults.[1] Treatment of patients with MGN is a much debated issue because of the natural history of MGN and inconsistencies of therapeutic trials.[2-4]

The natural history of MGN under a conservative approach is known. A minority of patients (~20%) experience end-stage renal failure, whereas 20% to 40% achieve spontaneous remission. The most frequent course is persistence of nephrotic syndrome with slow progression to decreased kidney function.[5,6]

Some risk factors for progression toward end-stage renal failure have been identified, mainly in retrospective studies. The most predictive factors are proteinuria greater than 10 g/d, high serum creatinine level at diagnosis, and deterioration in

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kidney function in the 6 months after the diagnosis.[7] However, it is still difficult for nephrologists to predict which patients will progress to renal failure and thus warrant immunosuppressive treatment.

Randomized controlled trials evaluating immunosuppressive treatments are scarce and results are controversial.[8,9] The most recent systematic review failed to show a long-term effect of steroids, alkylating agents, calcineurin inhibitors, and antiproliferative agents on patient and/or renal survival.[10] There was weak evidence that alkylating agents increased the remission rate.[10] However, 2 recent studies, 1 with tacrolimus and the other with the Ponticelli protocol, have revived the debate because they reported a greater rate of remission in the treated group.[11,12]

Mycophenolate mofetil (MMF) is a specific inhibitor of inosine monophosphate dehydrogenase, which is involved in de novo purine synthesis in activated lymphocytes. MMF has been shown to prevent glomerular lesions in different experimental models of glomerulonephritis.[13,14] MMF monotherapy has been used only in case series of patients with MGN.[15-19] We therefore conducted a randomized controlled study to evaluate the efficacy and safety of MMF monotherapy in patients with MGN.

METHODS

This study was a 1-year, prospective, multicenter, randomized, parallel, open-label, and controlled trial conducted in 6 university hospitals in the South of France between January 2004 and January 2007. The study protocol was reviewed and approved by the Comité Consultatif de Protection des Personnes se Prétant à la Recherche Biomédicale, and written informed consent was provided by all participants.

Entry criteria were idiopathic biopsy-proven MGN, age older than 18 years, nephrotic syndrome (proteinuria $>$ 3 g/day with hypoalbuminemia with albumin level $<$ 3 g/dL [$<$30 g/L] and serum creatinine level $<$ 2.26 mg/dL [$<$200 μmol/L]). Exclusion criteria were secondary MGN regardless of the cause, diagnosis of MGN for more than 6 months, and patients previously treated with an immunosuppressive agent.

Patients were randomly assigned to either a control group (conservative treatment) or a group treated with MMF (conservative treatment plus MMF) for 1 year. Randomization was performed by each center through a centralized Internet on-line application provided by the sponsor (minimization method). Randomization was stratified according to sex and center.

All patients received the same conservative treatment based on angiotensin-converting enzyme (ACE) inhibitors, statins, low-salt and low-protein diet, and loop diuretic in case of edema. Nephrologists were instructed to give the highest dose possible of ACE inhibitors with a target systolic blood pressure less than 130 and greater than 100 mm Hg and a target diastolic blood pressure less than 80 and greater than 60 mm Hg. In case of ACE-inhibitor intolerance (cough or angioedema), patients were prescribed angiotensin receptor blockers (ARBs). For hypertensive patients, other antihypertensive drugs were prescribed in addition to ACE inhibitors/ARBs at each nephrologist's discretion. Target low-density lipoprotein cholesterol level was 1.6 g/L. Statins were prescribed for patients who did not reach this level despite dietary advice. A low-salt ($\leq$4 g/d of sodium chloride) and low-protein (0.8 g/kg/d) diet was initiated in all patients. Loop diuretics were prescribed in case of edema. All patients except 3 (1 in the MMF group, 2 in the control group) had ACE inhibitors before randomization and thus it was not possible to evaluate the effect of the conservative treatment on the mean proteinuria over creatinuria ratio.

Patients randomly assigned to the treatment group started MMF therapy at a dose of 250 mg/d, progressively increased by 250 mg every other day to 2 g/d. White blood cell count was checked every week during the first month, every other week during the second and third months, and once a month until month (M)12. After completion of the trial, MMF therapy was progressively stopped in 15 days.

Follow-up visits were scheduled monthly during the first 2 months (M1, M2) and thereafter every other month until M12 (M4, M6, M8, M10, M12). At each visit, a complete physical examination was performed, including blood pressure). Blood pressure was measured after 5 minutes of rest in a lying position. The average of 2 blood pressure measurements was recorded. Secondary effects of treatments were collected. At each visit, blood was sampled for a standard hemogram, creatinine, urea, ionogram, glucose, total protein, albumin, total cholesterol, low-density and high-density lipoprotein fractions, triglycerides, and calcium. A 24-hour urine sample was collected at each visit, and 24-hour creatinine, urea, ionogram, and protein were measured. Mean proteinuria over creatinuria ratio and estimated glomerular filtration rate (eGFR) according to the 4-variable Modification of Diet in Renal Disease Study equation were calculated at each visit.

End Points

The primary end point was mean proteinuria over creatinuria ratio (milligrams per gram) throughout the study in both groups. The secondary end point was number of patients reaching complete or partial remission. Complete remission was defined as proteinuria with protein less than 0.3 g/24 h plus normal kidney function (eGFR $>$ 60 mL/min/1.73 m^2 [$>$1 mL/s/1.73 m^2]). Partial remission was defined as proteinuria with protein greater than 0.3 and less than 3 g/d with normal kidney function (eGFR $>$ 60 mL/min/1.73 m^2 [$>$1 mL/s/1.73 m^2]). Other secondary end points were number of patients with a 20% decrease in eGFR at the end of the study and a 20% increase in serum creatinine level.

Sample Size

Sample size calculation was based on the largest case series of MGN treatment with MMF using mean proteinuria

over creatinuria ratio as the primary end point.[16] In this study, mean proteinuria over creatinuria ratio decreased from 7.7 ± 4.8 to 3.4 ± 3.8 g/g after a mean of 10 months of treatment (a 44% decrease). Assuming a 50% decrease in mean proteinuria over creatinuria ratio between the 2 groups with a 5% type I error, 90% power, and 10% loss to follow-up, we calculated that we needed 17 patients per group to detect the estimated differences.

Statistical Analysis

Results are presented as group mean ± SD. Statistical analyses were performed using SPSS software (version 13.0; SPSS Inc, Chicago, IL). Student *t*-tests were used to compare differences in patient characteristics and biological parameters within groups. Proportions were compared by means of Pearson χ^2 statistic. Analysis of variance for repeated measures before and after adjustments for covariates was performed to compare groups for change over time. We used unstructured type of correlation because there were no patterns in the covariance matrix.

A Cox regression model was also performed to explore relationships between complete and partial remission and several explanatory variables. Proportional hazards were checked using Schoenfeld residuals, and assumptions of linearity were checked graphically. Variables included in the model were age, sex, body mass index, treatments, mean proteinuria over creatinuria ratio, and eGFR at entry. *P* less than 0.05 is considered significant.

RESULTS

A total of 36 patients with biopsy-proven MGN and who fulfilled the trial entry criteria were randomly assigned to receive MMF plus conservative treatment (MMF group; n = 19) or conservative treatment (control group; n = 17; Fig 1). Table 1 lists demographic, histological, and laboratory characteristics at baseline. The 2 groups did not differ significantly. Most patients were men and had histological stage I or II MGN. All patients had full-blown nephrotic syndrome with proteinuria between 5 and 10 g/d, low serum albumin level, and high levels of serum lipids. At study entry, all patients had normal kidney function estimated by using eGFR. Diastolic and systolic blood pressures of both groups did not differ at baseline and during follow-up (Fig 2).

Table 2 lists types and doses of ACE inhibitors, ARBs, statins, and other treatments during the study. In the control group, 14 patients received ACE inhibitors, 1 received ARBs, and 2 received a combination of ACE inhibitors and ARBs. In the MMF group, 17 patients received ACE inhibitors, 1 received ARBs, and 1 received a combination of ACE inhibitors and ARBs.

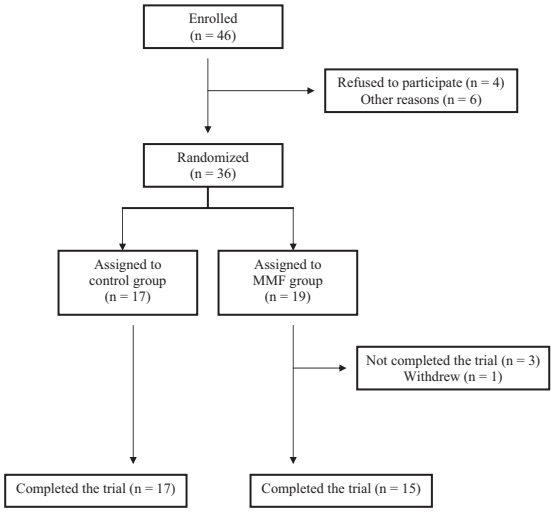

Figure 1. Trial profile. Abbreviation: MMF, mycophenolate mofetil.

Most patients in both groups received diuretics and statins. Mean dose of MMF was 1,850 mg. Sixteen patients could achieve the target dose of 2 g/d. Two patients were maintained on 1.5 g/d, and 1 was maintained on 1 g/d because of gastrointestinal symptoms.

End Points

Mean proteinuria over creatinuria ratio was stable in both groups throughout the study (P = 0.1, analysis of variance). Mean proteinuria over creatinuria ratio was 4,690 ± 2,212 mg/g in the MMF group and 6,548 ± 4,601 mg/g in the control group (95% confidence interval [CI] of the difference, −619 to +4,247; P = 0.1). In the control group, change in mean proteinuria over creatinuria ratio from baseline to M12 was −1,834.60 mg/g, whereas in the MMF group, it was +213.07 mg/g (P = 0.3; 95% CI of the difference, −5,676 to +1,581; Fig 3).

At M6, 1 patient in the MMF group and no patients in the control group experienced complete remission (P = 0.3). Partial remission was observed in 4 patients in the MMF group and 3 patients in the control group (P = 0.8). The relative risk of remission was 1.25 (95% CI, 0.65 to 2.40; P = 0.4). At M12, 1 patient in the MMF group and 2 patients in the control group experienced complete remission (P = 0.5). Partial remission was observed in 6 patients in the MMF group and 5 patients in the

Table 1. Demographic, Histological, and Laboratory Characteristics of Patients at Baseline

	Control Group (n = 17)	Mycophenolate Mofetil Group (n = 19)	*P*
Age (y)	55.9 ± 15.2	47.8 ± 15.2	0.1
Men/women	15/2	17/2	0.9
Body mass index (kg/m^2)	27.2 ± 2.7	26.6 ± 4.1	0.9
Glomerular stage (biopsy; I/II/III)	8/9/0	13/6/0	0.2
Serum creatinine (mg/dL)	1.09 ± 0.39	1.01 ± 0.34	0.5
Estimated glomerular filtration rate (mL/min/1.73 m^2)	80.7 ± 25.4	92.1 ± 29.8	0.2
Proteinuria (g/d)	9.5 ± 5.8	6.2 ± 3.5	0.1
Mean proteinuria over creatinuria ratio (mg/g)	6,548 ± 3,000	4,867 ± 2,831	0.1
Serum albumin (g/L)	20.2 ± 6.0	23.2 ± 7.3	0.2
Serum cholesterol (g/L)	3.4 ± 1.4	3.4 ± 1.2	0.9
Serum triglycerides (g/L)	1.9 ± 1.3	2.5 ± 1.7	0.3
Serum hemoglobin (g/dL)	14.1 ± 2.0	13.8 ± 0.9	0.5
Systolic blood pressure (mm Hg)	136 ± 16	132 ± 15	0.5
Diastolic blood pressure (mm Hg)	81 ± 10	75 ± 9	0.1
Urinary sodium (mmol/d)	125 ± 81	93 ± 88	0.5
Urinary urea (mmol/d)	380 ± 166	361 ± 184	0.4

Note: Estimated glomerular filtration rate calculated by using the 4-variable Modification of Diet in Renal Disease Study equation. To convert serum creatinine in mg/dL to μmol/L, multiply by 88.4; glomerular filtration rate in mL/min/1.73 m^2 to mL/s/1.73 m^2, multiply by 0.01667.

control group ($P = 0.9$) The relative risk of remission was 0.92 (95% CI, 0.48 to 1.75; $P = 0.7$; Fig 4). Thus, complete or partial remission at M12 was observed in 37% of patients in the MMF group and 41% in the control group. Kidney function was stable and not different in the 2 groups according to eGFR (Fig 5). No patient had a more than 20% increase in serum creatinine level.

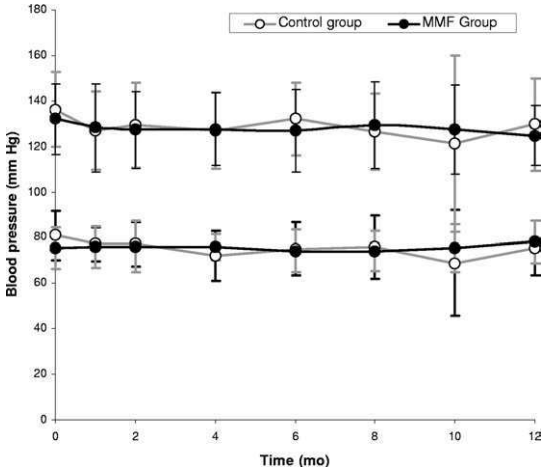

Figure 2. Course of systolic and diastolic blood pressures during the study. All patients were available at each time for these measurements. Abbreviation: MMF, mycophenolate mofetil.

By means of multivariate analysis, we looked for variables that significantly correlated with partial or complete remission. No clinical or biological variables correlated with remission.

Adverse Events

One patient withdrew from the study in the MMF group because a small-cell pulmonary

Table 2. Treatment With ACE Inhibitors, ARBs, Other Antihypertensive Agents, and Statins

	Control Group (n = 17)	Mycophenolate Mofetil Group (n = 19)
ACE inhibitors	16	18
Enalapril (20-40 mg/d)	14	14
Ramipril (10-20 mg/d)	1	3
Perindopril (2-8 mg/d)	1	1
ARBs	3	2
Losartan (50-150 mg/d)	2	1
Irbesartan (150-300 mg/d)	1	1
Diuretics	15	18
β-Blockers	2	4
Calcium channel blockers	2	0
Nicardipine (30 mg/d)	1	
Amlodipine (5 mg/d)	1	
Statins	17	18
Pravastatin (20-40 mg/d)	5	3
Atorvastatin (20-60 mg/d)	12	15

Abbreviations: ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker.

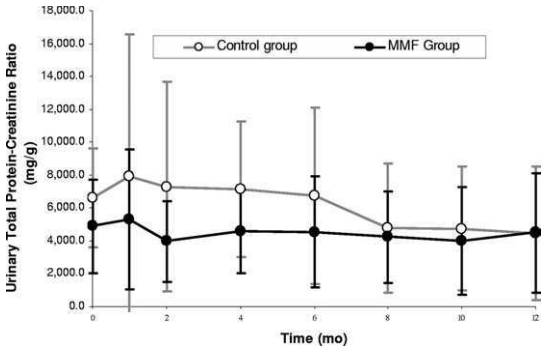

Figure 3. Course of mean proteinuria over creatinuria ratios (mg/g) during the study. All patients were available at each time for these measurements. Abbreviation: MMF, mycophenolate mofetil.

carcinoma was discovered at M10. This patient had a long history of tobacco use. At randomization, chest radiography and pulmonary tomodensitometry had shown no abnormalities. He was successfully treated with chemotherapy and is alive 24 months after the diagnosis.

Three other patients in the MMF group did not complete the trial because of serious adverse events. One experienced persistent diarrhea despite dose reduction and rechallenges after stopping the drug. He eventually stopped MMF therapy at M8. Another experienced acute thoracic varicella-zoster infection at M4. The third patient experienced bullous dermatosis of unknown origin despite extensive investigations. It spontaneously disappeared 4 months after MMF withdrawal at M8.

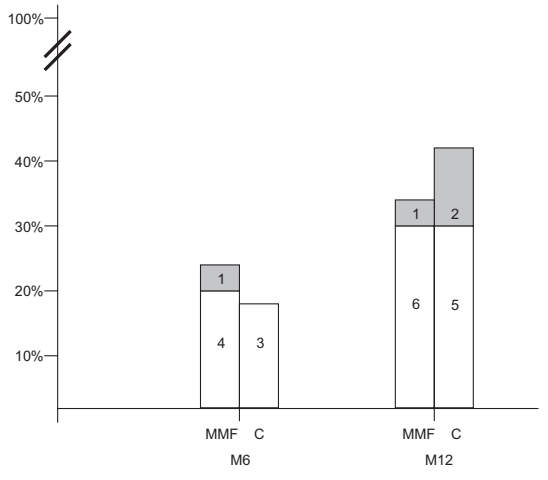

Figure 4. Percentages of complete (grey) and partial (white) remissions in the mycophenolate mofetil (MMF) and control (C) groups. Numbers within columns indicate total numbers of patients in complete and partial remission in both groups. Abbreviation: M, month.

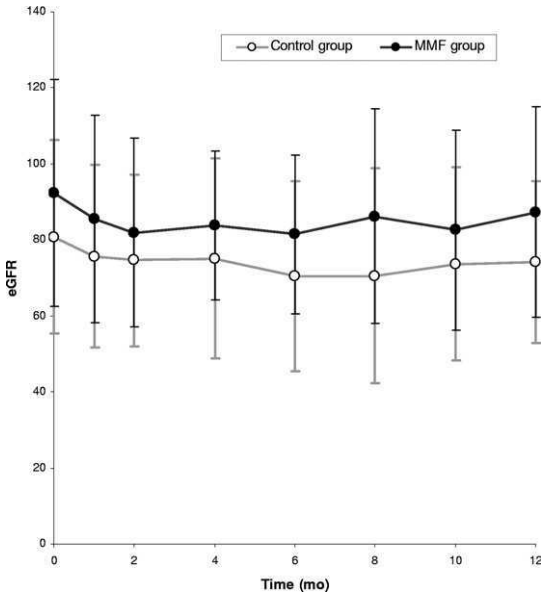

Figure 5. Course of estimated glomerular filtration rates (eGFRs) during the study. All patients were available at each time for eGFR measurements. Abbreviation: MMF, mycophenolate mofetil.

Nine patients (5 in the control group, 4 in the MMF group) experienced muscular pain, probably caused by statins. Other side effects were mild and often transitory. Anemia was observed in 3 patients (2 in the MMF group, 1 in the control group), nausea and vomiting in 3 patients (2 in the MMF group, 1 in the control group), hypotension in 2 patients (1 in each group), and cough in 3 patients (1 in the MMF group, 2 in the control group). One patient had acute bronchitis in the control group and 1 had cytolysis in the MMF group.

DISCUSSION

This study is the first randomized trial comparing MMF alone versus no treatment in patients with MGN. It evidenced the lack of efficacy of MMF monotherapy in patients with MGN, although MMF had a better safety profile and mechanism of action more targeted to the pathophysiological state of MGN compared with previously tested immunosuppressive drugs.

This negative result was obtained in a group of medium-risk patients with moderate proteinuria

according to the Cattran classification because most had proteinuria between 5 and 10 g/d.[20] All patients had recently diagnosed MGN (<6 months) and normal kidney function and were naive of immunosuppressive treatments. We believed they were potential good responders to immunosuppressive treatment, but obviously this was not the case. In most therapeutic trials of patients with MGN, a 6-month regimen of immunosuppressive drugs is given.[21-23] Therefore, the 1-year treatment was long enough to test the drug. The increase in complete and partial remission with time merely reflects the natural history of idiopathic MGN.[5,24] We did not measure blood levels or area under the curve of MMF, but used the usual dose of MMF, 2 g/d. Data for renal transplant patients suggest that with the fixed dose of 2 g/d, only 15% of transplant recipients reach the proposed therapeutic window of the mycophenolic acid area under the curve (30 to 60 mg.h/L) at day 14 after treatment initiation, and 76%, at 3 months.[25] However, the precise therapeutic window for treating patients with MGN is unknown. For all these reasons, we believe MMF is not efficient in medium-risk nephrotic patients with MGN.

Human studies of treatment with MMF monotherapy for patients with MGN are scarce. There are 5 case series including 70 patients; 56 were on MMF monotherapy.[15-19] MMF decreased proteinuria in most patients and induced complete and partial remissions in 7 and 24 patients, respectively. Kidney function was stable, but follow-up was short (4 to 29 months). Because those were not controlled studies, no firm conclusions could be drawn about MMF efficacy for patients with primary MGN.

There are also 2 trials that compared the combination of steroids plus MMF versus steroids plus cyclophosphamide or chlorambucil.[26,27] A Dutch group reported on 32 patients treated with MMF for 12 months and used for comparison 32 matched historic controls treated with cyclophosphamide for the same time. MMF decreased proteinuria and induced partial remission in 66% of patients versus 72% in the cyclophosphamide group ($P = 0.3$).[26] The same features were observed in 20 patients in the only prospective controlled trial comparing MMF and prednisolone for 6 months against a modified Ponticelli regimen with chlorambucil. Complete and partial remission rates were 63% and 67% and kidney function remained stable (P = NS), respectively.[27]

On the basis of the results of these 2 studies, the association of steroids and MMF induced a greater rate of complete or partial remission than that observed in this study (>60% versus 37% in this study), but follow-up was longer in the former (15 and 23 months). Thus, one can speculate that we should have challenged a combination of steroids and MMF versus no treatment or the Ponticelli regimen. We intentionally chose to evaluate MMF monotherapy (versus no treatment) because oral steroid therapy either alone or in association with alkylating agents brought no beneficial effects, evidenced by the systematic review by Perna et al.[10]

This study evidenced some concerns about the safety of MMF for the treatment of patients with idiopathic MGN. Four patients (20%) had to stop treatment for serious adverse effects. For 2 of them, a relationship with the drug was highly probable because diarrhea and viral infection are well-known adverse effects of MMF. It is uncertain whether MMF was implicated in the bullous dermatosis because it disappeared late after MMF withdrawal. The small-cell pulmonary carcinoma was the most serious adverse effect; however, tobacco use was likely the main predisposing factor.

In conclusion, a 12-month treatment with MMF for patients with idiopathic MGN with nephrotic syndrome in adults failed to decrease proteinuria or increase remission. Furthermore, there were some concerns about the safety of this drug. Close to 40% of patients experienced partial and complete remission with conservative treatment at 1 year.

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Evaluation and Determinants of Underprescription of Erythropoiesis Stimulating Agents in Pre-Dialysis Patients with Anaemia

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Key Words
Anaemia · Erythropoiesis-stimulating agents · Dialysis · End-stage renal disease · Registry · Underprescription

Abstract
Background: Inadequate anaemia correction (haemoglobin (Hb) <11 g/dl without receiving an erythropoiesis-stimulating agent (ESA) is common in pre-dialysis patients, but little is known about its determinants. We used data from the French end-stage renal disease (ESRD) registry to investigate these determinants and the patients' anaemia status 1 year after starting dialysis. ***Methods:*** Pre-dialysis anaemia care was studied in 6,271 incident ESRD patients from 13 regions, who were first treated between 2003 and 2005. Data included pre-dialysis Hb measure and ESA use, patient's condition and modalities of dialysis initiation. Anaemia status at 1 year was studied in 925 patients from four regions who started dialysis in 2003 and 2004, were still on dialysis one year later, and had completed the annual registry data form. ***Results:*** Overall, 34.7% of the patients had inadequate pre-dialysis anaemia correction, with variations across regions from 21.1 to 43.2%. Inadequate anaemia correction decreased from 38.0% in 2003 to 33.2% in 2005. It was less likely in patients with diabetic or polycystic kidney disease and more likely in those with malignancy, unplanned haemodialysis, and low glomerular filtration rate or low serum albumin at dialysis initiation. One year after starting dialysis, inadequate correction concerned only 2.6% of the patients. Hb level had risen from 10.3 g/dl in pre-dialysis to 11.7 g/dl, but remained lower in those with inadequate pre-dialysis correction. ***Conclusion:*** Despite improvement over time, inadequate correction with ESAs remains high in pre-dialysis patients in contrast with those on dialysis. As the timing of dialysis initiation is uncertain, continuous management of anaemia is requested.

Data from the French REIN registry.

Introduction

Anaemia is a major complication appearing early in the course of chronic kidney disease (CKD) and affecting nearly all end-stage renal disease (ESRD) patients. The introduction of erythropoiesis-stimulating agents (ESAs) in 1989 offered a new way to manage renal anaemia. Numerous benefits have been associated with anaemia correction in CKD, including lower morbidity and mortality [1] and reduced occurrence of cardiovascular complica-

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tions [2]. A haemoglobin (Hb) level of at least 11 g/dl in all CKD patients is recommended by several clinical practice guidelines [3, 4], but the maintenance of levels above 13 g/dl appears to be unsafe in these patients according to recent randomized control trials [5, 6]. Studies in both pre-dialysis [7–13] and dialysis patients [14–17], however, show that ESA therapy is far from being prescribed to all those who would need it, although anaemia management tends to improve over time [8, 17].

Clinical performance measures to assess the quality of anaemia management are commonly based on the prevalence of both anaemia and ESA use [18]. However, to monitor continuous quality improvement in ESRD patients more straightforwardly, we defined 'inadequate anaemia correction' as an Hb level lower than 11 g/dl in those not prescribed ESAs. Inadequate anaemia correction refers to failure to adhere to guidelines recommending initiation of ESA therapy whenever the Hb level is under 11 g/dl. Non-prescription of ESAs in CKD patients without anaemia is indeed adequate practice. Moreover, below-target Hb levels in patients prescribed ESAs, due to either insufficient ESA dose or hyporesponse to ESAs, are related to other determinants and different interventions.

With the exception of economic constraints, little is known about the determinants of underprescription of ESAs. They are interesting to study in France where these constraints are limited thanks to full reimbursement of ESAs for the treatment of anaemia in all CKD patients since 1996. We therefore used data from the French ESRD registry to investigate pre-dialysis anaemia correction with ESAs and the determinants of inadequate correction. We also studied the patients' anaemia status 1 year after starting dialysis according to pre-dialysis anaemia care.

Patients and Methods

Setting

The French Renal Epidemiology and Information Network (REIN) registry began in 2002 to provide a tool for public health decision support, evaluation and research related to ESRD. It is progressively spreading throughout the country and is aiming for nationwide coverage (i.e. all 22 regions and 4 overseas districts). The design and methods have been described in detail previously [19].

Study Population

The REIN registry includes all patients on renal replacement therapy for ESRD, whether dialysis or transplant. New (incident) patients are considered from the first day of starting treatment. Those with a diagnosis of acute renal failure are excluded. Overall, 10,234 ESRD patients aged 15 years and older began dialysis in seven regions participating in the registry in 2003, eight regions in 2004 and thirteen in 2005. Data on anaemia care were available in 6,271 of them who were included in this analysis. Those with missing data were mainly from three large regions where initial biological data as a whole were missing in more than half of the patients at the beginning of the registry. It is worth noting, however, that these patients were similar to those included with respect to age, gender, primary renal diseases, and most co-morbidities, except cardiac and vascular diseases, slightly but significantly more frequent in participants than in non-participants, 47 vs. 44% and 28 vs. 26%; participants were also more likely to have started renal replacement therapy with unplanned haemodialysis (see definition below), 31 vs. 28% in non-participants.

Information

Data included age, sex, region of care, year of dialysis initiation (2003, 2004 or 2005), body mass index (BMI), primary renal disease, several co-morbidities, and disabilities. Haemoglobin, serum creatinine and albumin in the last month before the start of dialysis as well as pre-dialysis ESA use (yes/no) were also recorded. Other details about anaemia management such as iron supplementation, aluminium levels and inflammatory parameters were not available. Glomerular filtration rate (GFR) was estimated using the simplified modification of diet in renal disease (MDRD) trial equation [20]. Modalities of dialysis initiation were studied as follows: peritoneal dialysis, planned and unplanned haemodialysis. Planned haemodialysis was defined as beginning dialysis with either an arteriovenous fistula or a graft ready for use. Missing data were less than 5% for all variables except BMI and serum albumin which were analyzed as follows: albumin ($\geq$3.5 g/dl; <3.5; 'not available' (NA)); BMI (<18.5 kg/m^2; 18.5–24.9; $\geq$25; NA). GFR was also studied as a dummy with a cut-off point at 10 ml/min/1.73 m^2.

Outcome

The outcome of interest was pre-dialysis inadequacy of anaemia correction, defined as an Hb concentration lower than 11 g/dl in a patient not prescribed ESAs in pre-dialysis. Patients with pre-dialysis Hb level lower than 11 g/dl but prescribed ESAs as well as those with an Hb value of 11 g/dl or greater, were considered as having had adequate anaemia correction.

One-Year Follow-Up

In four regions, annual follow-up was achieved in 1,589 patients who started dialysis in 2003 and 2004. One year after, 69 had received a graft, 319 had died, and 1,201 were still on dialysis. REIN 2004 and 2005 annual data forms were completed, including Hb and ESA use, for 925 patients (77%) from this cohort.

Statistical Analysis

Percentages of pre-dialysis inadequate anaemia correction were first compared between the thirteen regions using the Pearson χ^2 test. Crude associations between baseline patients' characteristics and inadequate anaemia correction were also studied with the Pearson χ^2 test. All factors with a $p < 0.15$ as well as the region of care were then included in a logistic regression model to provide adjusted odds ratios (OR) for inadequate anaemia correc-

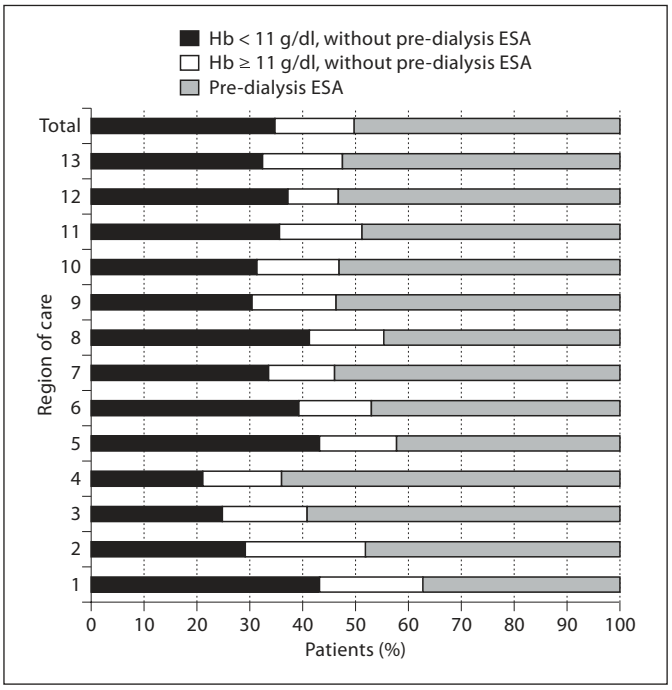

Fig. 1. Distribution of patients according to pre-dialysis anaemia care by regions.

tion and 95% CI. Finally, Hb level, ESA use and inadequate anaemia correction were compared before dialysis and 1 year after using paired χ^2 and Student's t test. All analyses were performed with SAS version 8.2 (SAS Institute, Inc., Cary, N.C., USA).

Results

Baseline Characteristics

Baseline characteristics of the 6,271 incident patients are presented in table 1. Their mean age was 66.6 ± 15.6 years and 61.4% were men. Cardiac diseases and diabetes were the most frequent co-morbidities, and nearly half of the patients had at least two. Nearly one third of the patients started treatment with unplanned haemodialysis and more than two thirds with a glomerular filtration rate lower than 10 ml/min/1.73 m^2.

Pre-Dialysis Haemoglobin Level, ESA Use and Inadequacy of Anaemia Correction

The average level of pre-dialysis Hb was at 10.3 ± 1.8 g/dl and 63.6% of the patients had an Hb value lower than 11 g/dl. This Hb level was at 10.6 ± 1.7 g/dl among patients with pre-dialysis ESAs as compared with 9.9 ± 1.7 g/dl ($p < 0.0001$) among those without pre-dialysis ESAs.

Table 1. Baseline characteristics in 6,271 incident dialysis patients

	Percentage or mean ± SD
Men	61.4
Age, years	66.6 ± 15.6
Dialysis initiation in 2003	19.7
Dialysis initiation in 2004	26.5
Body mass index	25.2 ± 5.2
<18.5 kg/m^2	5.2
18.5–24.9 kg/m^2	38.9
≥25 kg/m^2	37.3
Not available	18.6
Cardiac disease[a]	46.9
Vascular disease[b]	28.4
Diabetes	35.1
Respiratory disease	10.4
Active malignancy	7.1
Patients with at least 2 comorbidities[c]	44.6
Disability	9.5
Primary renal disease	
Polycystic disease	6.8
Diabetes	18.9
Other	74.3
Mode of dialysis initiation	
Unplanned hemodialysis	31.0
Planned hemodialysis	53.6
Peritoneal dialysis	15.4
Estimated GFR	9.0 ± 5.0
<10 ml/min/1.73 m^2	70.3
Serum albumin	3.4 ± 0.6
<3.5 g/dl	38.4
≥3.5 g/dl	27.6
Not available	34.0

[a] Cardiac disease = History of congestive heart failure, coronary heart disease, myocardial infarction or dysrhythmia.

[b] Vascular disease = history of peripheral arterial disease or stroke.

[c] Comorbidities include cardiac or vascular diseases, diabetes, respiratory disease, and malignancy.

GFR = Estimated glomerular filtration rate using the abbreviated MDRD equation.

Overall, 50.4% of the patients were prescribed ESAs in pre-dialysis and more than 1 patient out of 3 (34.7%) had inadequate anaemia correction. Among the subset of patients having an Hb level less than 11 g/dl in pre-dialysis, 68% were not prescribed ESAs.

Pre-Dialysis Anaemia Correction, by Region

Inadequate anaemia correction varied from 21.1 to 43.2% according to the region of care (fig. 1). Overall, 15%

of the patients had an Hb greater than 11 g/dl without receiving ESAs. Among those receiving ESA therapy, 5% of the patients had an Hb level greater than 13 g/dl. After adjusting for patients' characteristics and modalities of dialysis initiation, regional variations in pre-dialysis inadequate anaemia correction remained strongly significant ($p < 0.0001$).

Determinants of Inadequate Pre-Dialysis Anaemia Correction

In the crude analysis, inadequacy of pre-dialysis anaemia correction was neither related to age nor gender (table 2). It was significantly lower in 2005 as compared to 2003. Inadequate anaemia correction was also more frequent in patients with active malignancy, but not in those with other co-morbidities, including diabetes. It was not related to BMI level, but was more frequent in patients with missing BMI data. Patients with inadequate anaemia correction were more likely to start renal replacement therapy with haemodialysis at a low GFR level (GFR <10 ml/min/1.73 m^2) and with a serum albumin <3.5 g/dl or missing and less likely to have polycystic kidney disease. Half of the patients with polycystic kidney disease had an Hb lower than 11 g/dl at the dialysis initiation, as compared with 65% for patients with diabetic nephropathy or other primary renal disease ($p < 0.0001$). After adjustment, factors independently associated with inadequate pre-dialysis anaemia correction included malignancy, unplanned first haemodialysis, low GFR and serum albumin, as well as missing BMI or serum albumin value. Polycystic kidney disease and diabetes as the primary cause of ESRD were associated with its decrease, independent of GFR and mode of dialysis initiation. Improvement of care in 2005 as compared to 2003 was also still statistically significant independent of patients' case mix and region.

Anaemia Status 1 Year after Starting Dialysis according to Pre-Dialysis Anaemia Care

As compared with the 925 patients who remained on dialysis 1 year after starting treatment and whose anaemia status was known, their 276 counterparts with missing data did not significantly differ with respect to either pre-dialysis inadequacy of anaemia correction or any of its determinants except malignancy more frequent in them (data not shown). The mean Hb level rose from 10.3 g/dl in pre-dialysis to 11.7 g/dl 1 year after, and the proportion of patients receiving ESAs from 50.0 to 88.5% (table 3). Overall, inadequate anaemia correction as defined in this study was only 2.6% 1 year after beginning dialysis. However, 28.5% of the patients had still an Hb level lower than 11 g/dl. This percentage was significantly higher in patients with inadequate pre-dialysis anaemia correction as compared with those with adequate correction (34.9 vs. 25.0%). Anaemia status at 1 year was related to pre-dialysis Hb level and anaemia correction; the better the pre-dialysis anaemia status, the higher the haemoglobin level and the better the adequacy of anaemia correction 1 year later.

Discussion

This study showed that pre-dialysis anaemia correction with ESAs is suboptimal in France, although it tended to improve over time. Several risk factors for the underprescription of ESAs were identified including the coexistence of malignancy with ESRD, unplanned first haemodialysis, a GFR less than 10 ml/min/1.73 m^2 and serum albumin less than 3.5 g/dl at dialysis initiation, and non-diabetic and non-polycystic kidney diseases. Some regions also seemed to perform better in achieving the recommended goal than others. In contrast with the pre-dialysis period, anaemia correction with ESAs 1 year after starting dialysis was adequate with respect to the used definition in nearly 100% of the patients, but almost 30% of them remained with an Hb level lower than 11 g/dl.

Adequacy of anaemia correction with ESAs measures the level of adherence to the K/DOQI and ERA-EDTA guidelines recommending the use of ESA therapy in CKD patients whenever the Hb level is less than 11 g/dl. This goal was not reached in 68% of incident ESRD patients who were not prescribed ESAs before starting dialysis despite having clear indications. The present results are quite similar in comparison with practices in other settings, where this percentage ranged from 70 to 80% [7, 9, 11], and confirm the need for improvement in healthcare delivery for CKD patients in the pre-dialysis period. Conversely, only 5% of the patients receiving ESA therapy had an Hb level greater than 13 g/dl, a target level recently appeared to be unsafe according to 2 large clinical trials including CKD patients before dialysis [21].

In the REIN registry, unplanned first dialysis session is used as a surrogate for late nephrology referral. The increased percentage of inadequate anaemia correction when the first dialysis was unplanned is consistent with previous studies showing that the timing of referral to a nephrologist is associated with the quality of pre-dialysis care, including anaemia [22, 23]. In France, only physi-

Table 2. Determinants of inadequate pre-dialysis anaemia correction in 6,271 incident patients

		Inadequate anaemia correction, %	Crude analysis		Multivariate analysis	
			OR (95% CI)	p value	OR (95% CI)	p value
Gender	Men	35.5	1			
	Women	33.3	0.91 (0.81–1.01)	0.073		
Age	≥80 years	32.8	1			
	66–79 years	34.8	1.09 (0.9 5–1.26)	0.265		
	≤65 years	35.5	1.13 (0.98–1.31)			
Year of dialysis start	2005	33.2	1		1	
	2004	35.1	1.09 (0.96–1.23)	0.009	1.13 (0.97–1.32)	0.027
	2003	38.0	1.24 (1.08–1.41)		1.26 (1.06–1.50)	
Body mass index	18.5–25 kg/m^2	34.0	1		1	
	<18.5	37.6	1.17 (0.92–1.49)	0.0002	1.15 (0.88–1.50)	0.006
	≥25	32.4	0.93 (0.83–1.05)		0.95 (0.83–1.09)	
	Not available	39.7	1.28 (1.11–1.48)		1.28 (1.08–1.52)	
Cardiac disease[a]	No	35.2	1			
	Yes	34.2	0.95 (0.86–1.06)	0.376		
Vascular disease[b]	No	35.1	1			
	Yes	33.8	0.94 (0.84–1.06)	0.331		
Diabetes	No	34.9	1			
	Yes	34.5	0.99 (0.88–1.10)	0.796		
Respiratory disease	No	34.5	1			
	Yes	36.5	1.09 (0.92–1.29)	0.321		
Active malignancy	No	34.0	1		1	
	Yes	44.6	1.56 (1.29–1.90)	<0.0001	1.30 (1.01–1.61)	0.021
At least 2 comorbidities[c]	No	34.7	1			
	Yes	34.8	1.00 (0.90–1.11)	0.967		
Disability	No	34.7	1			
	Yes	37.3	1.12 (0.94–1.34)	0.206		
Primary renal disease	Other	35.9	1		1	
	Polycystic disease	25.7	0.62 (0.49–0.77)	<0.0001	0.75 (0.58–0.96)	0.009
	Diabetes	33.2	0.89 (0.78–1.02)		0.83 (0.72–0.97)	
Mode of dialysis initiation	Peritoneal dialysis	24.1	1		1	
	Unplanned haemodialysis	51.4	3.34 (2.81–3.97)	<0.0001	3.16 (2.61–3.82)	<0.0001
	Planned haemodialysis	27.9	1.22 (1.04–1.44)		1.16 (0.97–1.39)	
Estimated GFR	≥10 ml/min/1.73 m^2	30.3	1	<0.0001	1	
	<10	36.5	1.32 (1.17–1.48)		1.34 (1.17–1.52)	<0.0001
Serum albumin	≥3.5 g/dl	26.4	1		1	
	<3.5 g/dl	40.3	1.86 (1.63–2.13)	<0.0001	1.73 (1.49–2.00)	<0.0001
	Not available	35.3	1.52 (1.32–1.74)		1.51 (1.29–1.78)	

OR = Odds ratio; CI = confidence interval; NS = not significant; GFR = estimated glomerular filtration rate.
[a] Cardiac disease = History of congestive heart failure, coronary heart disease, myocardial infarction or dysrhythmia.
[b] Vascular disease = History of peripheral arterial disease or stroke.
[c] Comorbidities include cardiac or vascular diseases, diabetes, respiratory disease, and malignancy.
Results adjusted for the region of care.

Table 3. Anaemia status before and 1 year after starting dialysis according to pre-dialysis anaemia care in 925 incident patients from four regions

	n	Haemoglobin g/dl	Haemoglobin <11 g/dl, %	ESA use %	Inadequate anaemia correction, %
Overall anaemia status					
In pre-dialysis	925	10.3 ± 1.7	64.2	50.0	35.7
One year after starting dialysis	925	11.7 ± 1.4	28.5	88.5	2.6
p value		<0.0001	0.03	0.0005	<0.001
Anaemia status at 1 year by pre-dialysis anaemia status					
Pre-dialysis haemoglobin					
<11 g/dl	594	11.6 ± 1.4	31.0	91.1	3.2
≥11 g/dl	331	11.8 ± 1.3	24.2	84.0	1.5
p value		0.2012	0.0281	0.0012	0.1218
Pre-dialysis ESA use					
No	463	11.6 ± 1.5	31.8	84.9	4.1
Yes	462	11.8 ± 1.3	25.3	92.2	1.1
p value		0.0097	0.0306	0.0005	0.0039
Pre-dialysis adequacy of anaemia correction					
No	330	11.5 ± 1.5	34.9	88.5	5.5
Yes	595	11.8 ± 1.3	25.0	88.6	1.0
p value		0.0391	0.0016	0.9684	<0.0001

cians employed on staff in hospitals and dialysis centres, mainly nephrologists, were authorized to prescribe ESA therapy, so that access to these drugs rested as much on timely referral to nephrologists as on nephrologists' clinical practice. It is worth noting, however, that the percentages of inadequate correction in those starting dialysis with planned haemodialysis or peritoneal dialysis were far from being negligible, i.e. 28 and 24% of the patients, respectively. Therefore, attributing non-adherence to guidelines to non-nephrologists alone may be too hasty, as a large number of patients with pre-dialysis nephrology care were also not prescribed ESAs. GFR level is strongly related to that of anaemia: the greater the severity of renal insufficiency, the greater the degree of anaemia [10, 24]. Consequently, our finding that inadequate correction was independently associated with lower GFR at dialysis initiation was not surprising. The same argument can be used to explain the relationship between low serum albumin and inadequate practices. Indeed, associations between low GFR, hypoalbuminaemia and anaemia are well established [25].

Our data showed that in patients with polycystic kidney disease and diabetic nephropathy, inadequacy of anaemia correction was 25% and 17% lower, respectively, than in those with other primary renal disease. Polycystic patients have been reported as having higher Hb levels than other CKD patients at a comparable degree of renal dysfunction [15]. In our study, only half of them had an Hb lower than 11 g/dl at the dialysis initiation, as compared with 65% for patients with other primary renal disease. Moreover, it has been described that, at any level of GFR, anaemia is more severe in patients with than without diabetes [26]. Our results concerning patients with diabetic nephropathy may reflect greater awareness for anaemia care and higher rate of pre-dialysis ESA prescription in this population. In contrast, inadequate correction was more likely in patients with malignancy even after adjustment for several potential confounders. Yet, we may have expected a better management of anaemia in these patients with intensive medical follow-up.

Inadequate anaemia correction varied across regions from 21 to 43%, which, despite an egalitarian national health system, reveals within-country variations in practices as there are between countries [7, 8, 14–17]. Obrador et al. [8] reported substantial variations in the percentage of patients receiving pre-dialysis ESAs across health service areas in the United States. The question raised is 'What differences between regions could explain this variability?' In our study, neither patients' characteristics nor modalities of dialysis initiation explained variations in anaemia correction, as they persisted after controlling for these factors in the multivariate analysis. Clinical practices and organization of CKD care in each region may play a role, disparities in health care services be-

tween French regions being important [27]. However, it is worth noting that even the absence of variations at the regional (population) level would not necessarily mean that they are none at the centre or at the individual (physician/patient) level. Indeed, heterogeneity within-region may well be as large as between regions.

Patients who began dialysis in 2003 were 26% more likely to have inadequate correction with ESAs as compared with those who began in 2005. This trend towards improvement of anaemia correction is encouraging and consistent with other studies showing greater pre-dialysis use of ESAs over time [10, 28].

Several studies have evaluated the quality of anaemia care either before [7–13] or during maintenance dialysis [14–17]. However, none examined the course of anaemia and ESA use according to pre-dialysis anaemia care. We showed that inadequate correction in the pre-dialysis period, as defined here, was almost inexistent 1 year after the start of dialysis. Administrative constraints in the delivery of ESAs before dialysis may partly explain this difference; in 2003–2005, these were delivered by hospital pharmacies alone and required nurses to inject the drug at home. Therefore, access to ESAs was much more difficult for CKD out-patients than for dialysis patients, in whom ESAs were delivered and directly injected during dialysis sessions. Despite high levels of ESA use 1 year after starting dialysis, however, almost one third of the patients had below-target Hb levels. We showed that inability to reach target Hb in these patients seem to be partially related to pre-dialysis inadequate anaemia correction. Efficacy of anaemia management or compliance to treatment as well as hyporesponsiveness to ESAs are other issues that were beyond the scope of this analysis.

Our results should be interpreted in the light of two limitations. First, more than one third of all incident dialysis patients had missing data on Hb and/or ESA use. In the REIN registry, only a few items, including demographics, primary CKD and treatment modalities, are mandatory for registering a new patient whereas others, including co-morbidities, biological data and ESA treatment are checked for validity but do not preclude patients' registration [19]. This partly explains why, at the start of the registry, some regions focused on achieving complete registration of patients and mandatory items, but failed to do so for some biological items and ESA use. However, missing information about anaemia was not related to most other baseline characteristics, except unplanned first haemodialysis and cardiovascular disease. This patient cohort can thus be considered as fairly representative of the overall dialysis population from the studied regions. In the same way, as missing anaemia status at 1 year was neither related to the pre-dialysis adequacy of anaemia correction nor to most patient's baseline characteristics, our findings about the course of anaemia status are applicable to the entire 2003 and 2004 dialysis cohort. Second, collected data concerned Hb level in the last month before starting dialysis and pre-dialysis ESA use. No information was available about treatment history, particularly pre-dialysis ESA duration or doses and possible adjuvant therapy with iron salts. Therefore, we cannot rule out that the group of patients with adequate pre-dialysis anaemia correction include a number of individuals with very short duration of pre-dialysis ESA therapy, which would tend to underestimate inadequacy of care in this cohort. Nevertheless, it is worth noting that the mean Hb level among patients with pre-dialysis ESAs was significantly higher than that of those without ESAs.

In conclusion, despite full reimbursement of ESAs for treating CKD anaemia since 1996, this study showed that inadequate anaemia correction remains high in pre-dialysis patients in contrast with those on dialysis. These findings underline the difficulties in managing CKD patients not yet on replacement therapy when optimization of pre-dialysis care is the key to improve ESRD outcomes. Their main implication for public health is that interventions to improve anaemia management should target both nephrologists and non-nephrologists in care of CKD patients, as underprescription of ESAs was mainly observed in late referred patients, as characterized by unplanned first haemodialysis, but was also frequent in those with planned haemo- or peritoneal dialysis. In this respect, the 2006 new regulation about ESA prescription authorizing their delivery by out-of-hospital pharmacists may also help improving anaemia care in these patients.

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Incidences, Treatments, Outcomes, and Sex Effect on Survival in Patients With End-Stage Renal Disease by Diabetes Status in Australia and New Zealand (1991–2005)

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OBJECTIVE — We aimed to update the epidemiology of type 1 and type 2 diabetic patients among the incident end-stage renal disease (ESRD) population in Australia and New Zealand (ANZ) and to determine whether outcome is worse for diabetic women, as described in the general population.

RESEARCH DESIGNS AND METHODS — All resident adults of ANZ who began renal replacement therapy (RRT) from 1 April 1991 to 31 December 2005 were included using data from the ANZ Dialysis and Transplant Registry. Incidence rates, RRT, and survival were analyzed. Risk factors for death were assessed using Cox regression.

RESULTS — The study included 1,284 type 1 diabetic (4.5%), 8,560 type 2 diabetic (30.0%), and 18,704 nondiabetic (65.5%) patients. The incidence rate of ESRD with type 2 diabetes increased markedly over time (+10.2% annually, $P < 0.0001$). In patients aged <70 years, rates of renal transplantation in type 1 diabetic, type 2 diabetic, and nondiabetic patients were 41.8, 6.5 ($P < 0.0001$ vs. other patients), and 40.9% ($P = 0.56$ vs. type 1 diabetic patients), respectively. Compared with nondiabetic patients, the adjusted hazard ratio (HR) for death was 1.64 ($P < 0.0001$) in type 1 diabetes and 1.13 ($P < 0.0001$) in type 2 diabetes. Survival rates per 5-year period improved by 6% in type 1 diabetic patients ($P = 0.36$), by 9% in type 2 diabetic patients ($P < 0.0001$), and by 5% in nondiabetic patients ($P = 0.001$). In type 2 diabetic patients aged ≥60 years, the adjusted HR for death in women versus men was 1.19 ($P = 0.0003$).

CONCLUSIONS — The incidence of ESRD with type 2 diabetes increased markedly. Despite high access to renal transplants, type 1 diabetic patients had a poor prognosis after starting RRT. Survival improved significantly in type 2 diabetic patients during the study period. Older type 2 diabetic women had a worse prognosis than older type 2 diabetic men.

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Diabetes is associated with high mortality in the general population (1,2). Worse prognosis has also been reported in diabetic women compared with diabetic men (3,4). End-stage renal disease (ESRD) in patients with type 2 diabetes has increased dramatically worldwide during the last few decades, and diabetes is associated with worse survival among patients undergoing dialysis (5–7).

Nevertheless, a study in Denmark showed that the survival rate of patients with ESRD who had type 2 diabetes has improved during the 1990–2005 period (8). Available studies on patients with ESRD who have type 1 and type 2 diabetes have shortcomings because analyses were limited to patients with diabetic nephropathy (6–7), did not differentiate the two types of diabetes (9), were short-term (10), or were based on single-center experiences (11).

The aim of the present study was to examine the epidemiology and long-term survival of patients with incident ESRD by diabetes status (type 1 diabetes, type 2 diabetes, and no diabetes) in Australia and New Zealand (ANZ) and to determine whether outcomes were different between the sexes among patients with diabetes.

RESEARCH DESIGN AND METHODS

— We performed a prospective study including all patients aged ≥16 years who began chronic renal replacement therapy (RRT) in ANZ from 1 April 1991 to 31 December 2005. We used data from the Australia and New Zealand Dialysis and Transplant (ANZDATA) Registry (5). Patients were followed until death or 31 December 2005. Data collection consisted of information on patient demographic characteristics, cause of ESRD, comorbidities at start of RRT (presence of type 1 diabetes, type 2 diabetes, coronary artery disease, peripheral vascular disease, cerebrovascular disease, or chronic lung disease; BMI; and smoking status), estimated glomerular filtration rate (eGFR) at the first RRT, details of RRT modality and of renal transplantation (RTx), and date and cause of death.

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Abbreviations: ANZ, Australia and New Zealand; ANZDATA, Australia and New Zealand Dialysis and Transplant Registry; eGFR, estimated glomerular filtration rate; ESRD, end-stage renal disease; RRT, renal replacement therapy; RTx, renal transplantation.

A table elsewhere in this issue shows conventional and Système International (SI) units and conversion factors for many substances.

BMI (ratio of weight in kilograms to the square of height in meters at commencement of RRT) was analyzed in categories: underweight <18 kg/m^2, normal weight 18–24.9 kg/m^2, overweight 25–29.9 kg/m^2, and obese ≥ 30 kg/m^2. Smoking status at the start of RRT was categorized as never, former, or current smoker. eGFR was determined by the simplified Modification of Diet in Renal Disease formula (12) in patients who began RRT after 1 April 1998 because data on serum creatinine before the first RRT were collected after this date.

When appropriate, univariate comparisons were performed using a χ^2 test or Fisher's exact test for categorical variables, Student's *t* test for continuous variables between two groups, and ANOVA for continuous variables across the three groups by diabetes status. We calculated age- and sex-standardized ESRD incidence rates by diabetes status among ANZ populations using direct standardization. For 1991, incidence was projected for the entire year. Data on ANZ populations were provided by the Australian Bureau of Statistics and Statistics New Zealand. The reference populations were the 1991–2005 ANZ populations aged ≥16 years. Calculation of average annual changes in incidence and comparisons between subgroups were performed by Poisson regression, and we checked for overdispersion.

Times to RTx or to death were examined with Kaplan-Meier models and Cox regression for multivariate analyses. RTx outcomes were examined in patients aged <70 years. Cox models to analyze variations in access to RTx by diabetes status per 5-year periods (1991–1995, 1996–2000, and 2001–2005) were adjusted for age, sex, primary renal disease, comorbidities at the first RRT, BMI categories, and smoking status and were stratified on racial origin, state where RRT was started (seven states in Australia and one in New Zealand), and initial RRT modality.

Causes of death were classified into sudden death, cardiovascular, infection, malignancy, and other causes. In survival analyses, death from any cause was the end point. In multivariate survival analysis, diabetes status (type 1 diabetic, type 2 diabetic, or nondiabetic) was the variable of interest. We also examined the evolution of all-cause and cause-specific mortality over 1991–2005 by using the period of the first RRT (1991–1995, 1996–2000, and 2001–2005) as the parameter of interest. Models were adjusted for age, sex, primary renal disease, comorbidities at the first RRT, BMI categories, and smoking status. eGFR at the start of RRT was modeled as a fractional polynomial function (analyses restricted to patients who started RRT from 1 April 1998). Cox regression was stratified on racial origin group, year of the first RRT (1991–2005) with the exception of analysis by period of the first RRT, state where RRT was started, initial RRT modality, and RTx during the study period. We checked for interactions between variables by including multiplicative terms in Cox regression. If significant interactions were found, we performed stratified survival analysis as described above. Validity of the Cox proportional hazard assumption was checked by tests based on Shoenfeld's residuals. All statistical analyses were performed with S-PLUS 6.0 Software Professional Release 2 (Insightful).

RESULTS

Baseline patient characteristics

Type 1 diabetic patients were the youngest, and type 2 diabetic patients were the oldest ($P < 0.0001$) (Table 1). Rates of cardiovascular disease were higher in diabetic than in nondiabetic patients ($P < 0.0001$). Type 2 diabetic patients had higher average BMI ($P < 0.0001$). The proportion of current smokers was higher in type 1 diabetic patients ($P < 0.0001$).

Proportions of type 1 and type 2 diabetes in Caucasoid, in Australian Aboriginal, and in Maori/Pacific Islander patients were 5.3 and 20.9%, 1.5 and 70.9%, and 2.6 and 64.1%, respectively ($P < 0.0001$). Sex ratios (male to female) in these groups were 1.5, 0.76, and 1.25, respectively ($P < 0.0001$). Average ages at the first RRT were 58.8 ± 16, 49.9 ± 11.9, and 53.0 ± 12.9 years, respectively ($P < 0.0001$).

ESRD incidence rates by diabetes status

Standardized incidence rates of ESRD with associated type 1 diabetes remained stable over time at about 5 per million populations. Average annual change was −0.3% per year (−1.6 to +0.9%), without significant differences between countries, sex, and age (Fig. 1).

Standardized incidence rates of ESRD with associated type 2 diabetes rose from 10.6 per million populations in 1991 to 48.8 per million populations in 2005 in Australia. In New Zealand, they varied between 23.9 per million populations in 1991 and 68.7 per million populations in 2002. Across countries, the average annual change was +10.2% per year (+9.6–+10.8%). For incidence of ESRD at age <60 years with associated type 2 diabetes, the increase was +8.7% (+7.7–+9.7%) in Australia and +5.3% (+3.9–+6.8%) in New Zealand. For ESRD at age ≥60 years with associated type 2 diabetes, the increase was +11.7% (+10.8–+12.6) and +11.5% (+9.7–+13.4%), respectively ($P < 0.001$ compared with those for patients aged <60 years of the same country).

Standardized incidence rates of ESRD without diabetes increased significantly (+1.5% [+1.1–+1.8%] in Australia and +2.9% [+2.1–+3.8%] in New Zealand).

RRT modalities on the 90th day and access to RTx

Type 1 diabetic patients were more likely to be treated by peritoneal dialysis than type 2 diabetic and nondiabetic patients ($P < 0.0001$) (Table 1). Type 2 diabetic patients were less likely to receive RTx ($P < 0.0001$). Over time, rates of RTx were stable in type 1 diabetic patients (adjusted hazard ratio [HR] 1.02 [95% CI 0.91–1.15] per 5-year period, $P = 0.72$) and in nondiabetic patients (1.00 [0.96–1.03], $P = 0.84$). Adjusted rates of RTx decreased in type 2 diabetic patients (0.78 [0.68–0.90], $P = 0.0005$), without a difference between sexes.

Crude survival and causes of death

Unadjusted median (95% CI) survivals from the first RRT in type 1 diabetic, type 2 diabetic, and nondiabetic patients were 72.5 (66.3–82.1), 40.1 (38.8–41.3), and 80.2 (77.7–83.0) months, respectively. Median survivals from birth were 55.7 (54.4–56.7), 70.5 (70.2–70.9), and 74.7 (74.5–74.9) years, respectively (Fig. 2).

Among type 1 diabetic patients, 627 (48.8%) died during the study period. Proportions of sudden death, cardiovascular, infection, malignancy, and other cause as cause of death were in men and in women 27.2, 40.4, 11.3, 3.3, and 17.8% and 18.7, 34.8, 19.5, 2.0, and 25.0%, respectively ($P = 0.01$). Among type 2 diabetic patients, 4,997 (58.4%) died. Proportions were 17.9, 42.2, 14.7, 4.6, and 20.6% and 15.7, 41.0, 15.9, 3.7, and 23.7%, respectively ($P = 0.01$). Among nondiabetic patients, 8,393 (44.9%) died. Proportions were 14.9, 35.7, 13.4, 11.5, and 24.5% and 12.2, 35.4, 15.4, 8.7, and 28.3%, respectively ($P < 0.0001$). Causes of

Table 1—*Baseline characteristics and renal replacement therapy in type 1 diabetic, type 2 diabetic, and nondiabetic patients*

	Type 1 diabetic	Type 2 diabetic	Nondiabetic	*P**
n	1,284 (4.5)	8,560 (30.0)	18,704 (65.5)	
Male	733 (57.1)	4,943 (57.7)	10,934 (58.5)	0.002
Age at first RRT (years)	43.1 ± 11.3	61.2 ± 11.2	56.5 ± 17.0	<0.0001
Racial origin				<0.0001†
Caucasoid	1,136 (88.5)	4,493 (52.5)	15,882 (84.9)	
Australian Aboriginal	31 (2.4)	1,444 (16.9)	562 (3.0)	
Maori/Pacific Islander	71 (5.5)	1,784 (20.8)	930 (5.0)	
Other people	46 (3.6)	839 (9.8)	1,327 (7.1)	
Primary renal disease				<0.0001†
Diabetes	1,205 (93.8)	6,345 (74.1)	0 (0)	
Renal vascular disease	15 (1.2)	572 (6.7)	3,114 (16.6)	
Glomerular nephropathy and related disease	36 (2.8)	775 (9.1)	7,699 (41.2)	
Polycystic	2 (0.1)	89 (1.0)	1,842 (9.8)	
Other	26 (2.1)	779 (9.1)	6,049 (32.4)	
Biopsy-proven nephropathy	162 (12.6)	1,421 (16.6)	7,032 (37.6)	<0.0001
Comorbid conditions at first RRT				
Chronic lung disease	84 (6.5)	1,496 (17.5)	2,728 (14.6)	<0.0001
Coronary artery disease	435 (33.9)	4,802 (56.1)	5,550 (29.7)	<0.0001
Peripheral vascular disease	555 (43.2)	3,694 (43.2)	2,989 (16.0)	<0.0001
Cerebrovascular disease	153 (11.9)	1,692 (19.8)	2,134 (11.4)	<0.0001
BMI (kg/m^2)	25.0 ± 4.7	28.6 ± 6.4	25.2 ± 5.3	<0.0001
<18	29 (2.3)	128 (1.5)	844 (4.5)	<0.0001[b]
18–24	727 (56.6)	2,574 (30.1)	9,633 (51.5)	
25–29	368 (28.7)	2,878 (33.6)	5,495 (29.4)	
≥30	160 (12.5)	2,980 (34.8)	2,832 (15.1)	
Cigarette smoking				
Never	676 (52.6)	3,725 (43.5)	9,135 (48.8)	<0.0001†
Former	384 (29.9)	3,720 (43.5)	7,131 (38.1)	
Current	224 (17.5)	1,115 (13.0)	2,438 (13.1)	
Serum creatinine at first RRT (μmol/l)‡	686 ± 263	735 ± 306	795 ± 339	<0.0001
eGFR at first RRT (ml/min)‡§	8.5 ± 3.8	7.5 ± 4.0	7.0 ± 3.6	<0.0001
90-day RRT modality				<0.0001†
Haemodialysis	531 (41.3)	4,971 (58.1)	10,860 (58.1)	
Peritoneal dialysis	639 (49.8)	3,554 (41.5)	6,992 (37.4)	
Renal transplantation	114 (8.9)	35 (0.4)	852 (4.5)	
Details of RTx				
n	1,257‖	6,551‖	10,860‖	
Waiting list registration	522 (41.5)	724 (11.1)	5,069 (36.7)	<0.0001
Preemptive renal transplantation	85 (6.8)¶	18 (0.3)	502 (3.6)	<0.0001
Living donor renal transplantation	89 (7.1)#	111 (1.3)	2,024 (14.6)	<0.0001
Cadaveric renal transplantation	436 (34.7)**	340 (5.2)	3,638 (26.3)	<0.0001
Median times to RTx (months)	18.3 (16.7–20.9)	48.8 (45.7–55.9)	26.0 (24.9–26.9)	<0.0001

Data are *n* (%), mean ± SE, or median (95% CI). *Comparisons across the three groups. †Comparisons in categorical variables (racial origin, primary renal disease, BMI categories, cigarette smoking status, 90-day RRT modality). ‡Analysis restricted to patients who started RRT after 1 April 1998: *n* = 17,809; type 1 diabetic, *n* = 694; type 2 diabetic, *n* = 6,176; nondiabetic, *n* = 10;939; for conversion to milligrams per deciliter divide by 88.4. §Estimated by the simplified Modification Diet in Renal Disease formula (12). ‖Analyses restricted to patients aged <70 years. ¶Including 15 living donor renal transplantations, 5 single cadaveric renal transplantations, and 65 simultaneous kidney-pancreas transplantations. #Including 15 preemptive renal transplantations. **Including 159 single renal transplantations and 277 simultaneous kidney-pancreas transplantations.

death were significantly different between patient groups by diabetes status ($P < 0.0001$).

Over time, there was a decrease in adjusted rates of cardiovascular death (adjusted HR 0.96 [95% CI 0.92–0.99] per 5-year period, $P = 0.04$), death from infectious disease (0.89 [0.83–0.95], $P = 0.003$), and sudden death (0.88 [0.83–0.94], $P < 0.0001$), whereas rates of malignancy death increased (1.19 [1.08–1.30], $P = 0.0002$). These trends were similar in the three patient groups.

Multivariate survival analysis in the whole cohort

Multivariate survival analysis showed that the risk for death after the first RRT was 64% higher in type 1 diabetic ($P < 0.0001$) and 13% higher in type 2 dia-

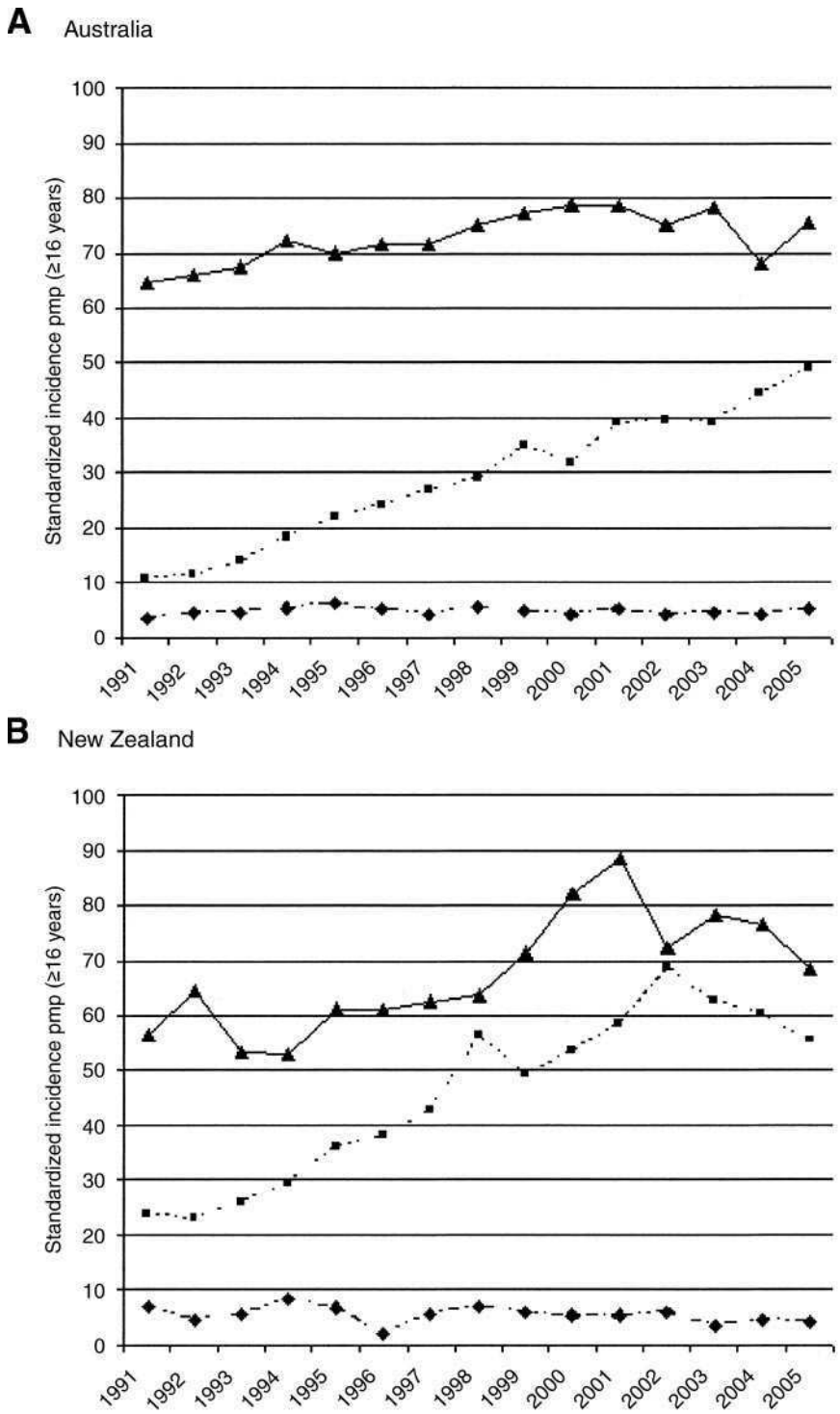

Figure 1—*Age- and sex-standardized ESRD incidence per million population (aged ≥16 years) by diabetes status among the general population in Australia* (A, n = *23,417) and in New Zealand* (B, n = *5,131). -◆-, patients with type 1 diabetes; -■-, patients with type 2 diabetes; -▲-, patients without diabetes.*

betic ($P < 0.0001$) than in nondiabetic patients (Table 2).

Multivariate survival analysis by diabetes status

There was a significant interaction between sex and diabetes status ($P = 0.0004$). Female sex was significantly associated with higher risk for death in type 2 diabetic patients (adjusted HR for death in women versus men 1.08 [95% CI 1.015–1.16], $P = 0.02$). Sex was not associated with survival in type 1 diabetic (1.12 [0.87–1.46], $P = 0.38$) and in nondiabetic patients (0.95 [0.91–1.005], $P = 0.07$).

In type 2 diabetes, there was a significant interaction between sex and age ($P < 0.0001$). The adjusted HR for death in women versus men was 0.93 (95% CI 0.83–1.04) ($P = 0.20$) in type 2 diabetic patients aged <60 years ($n = 3,762$) and 1.19 (1.08–1.30) ($P = 0.0003$) in type 2 diabetic patients aged ≥60 years ($n = 4,798$). This last adjusted HR was similar for cardiovascular and noncardiovascular causes of death.

No other significant interactions were found with race, cause of ESRD (diabetic nephropathy versus other causes of ESRD), and BMI. Results were unchanged when follow-up was censored at the time of transplant and/or RRT modality switches and when analyses were adjusted for eGFR.

In type 1 diabetic patients, survival did not change over time (adjusted HR 0.94 [0.83–1.07] per 5-year period, $P = 0.36$), whereas it significantly improved by 9% per 5-year period in type 2 diabetic patients (0.91 [0.87–0.95], $P < 0.0001$) and by 5% in nondiabetic patients (0.95 [0.92–0.98], $P = 0.001$).

CONCLUSIONS— This study in ANZ showed a large increase in the incidence rate of ESRD with associated type 2 diabetes from 1991 to 2005, which was especially marked in type 2 diabetic patients aged ≥60 years (+11.5% per year). The incidence of ESRD with associated type 1 diabetes remained stable. After adjustment for age, sex, and risk factors for death, type 1 diabetes had a greater effect on survival in patients with ESRD than in type 2 diabetic patients compared with nondiabetic patients. In each patient group, the proportions of cardiovascular, infection, and sudden death decreased over the study period, whereas rates of malignancy death increased. Female sex was associated with worse outcome than male sex in type 2 diabetic patients aged ≥60 years. This difference did not appear to be explained by the different comorbid conditions, age, race, causes of ESRD, BMI at first RRT, or RRT modalities.

The strength of this analysis is that type 1 diabetes and type 2 diabetes are separately reported in a prospective and population-based study. Previous analyses may have been biased because they only included patients with diabetic nephropathy and because nephropathy may have been misclassified if it was not biopsy proven.

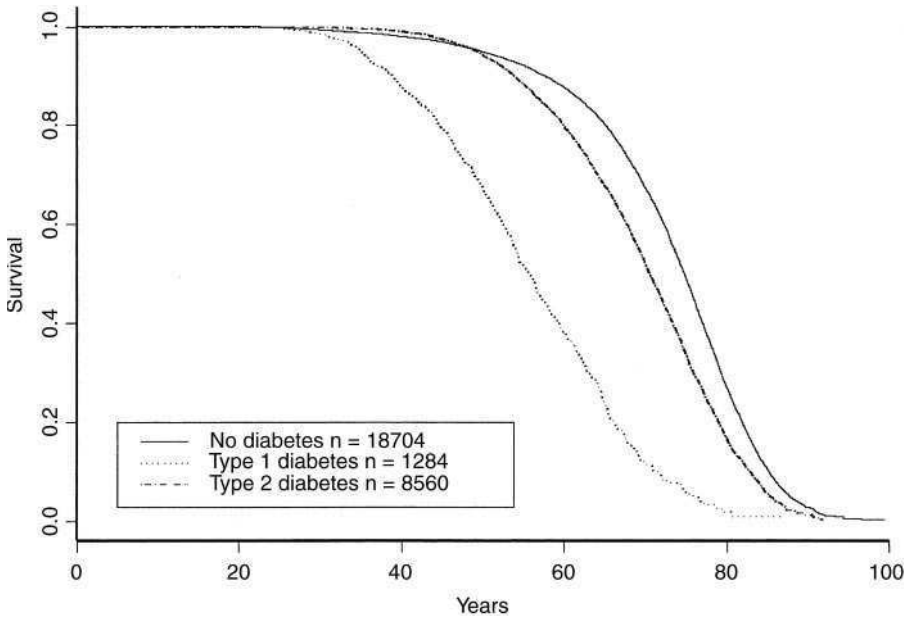

Figure 2—*Survival curve for national cohorts after birth by diabetes status, computed for mortality rates for the period 1991–2005.*

Table 2—*Adjusted HR of death of any cause in the whole cohort, patients not censored at renal replacement modality switches or renal transplantation*

	HR (95% CI)	*P*
Diabetes status		
Patients without diabetes*	1	
Patients with type 1 diabetes	1.64 (1.47–1.84)	<0.0001
Patients with type 2 diabetes	1.13 (1.06–1.20)	<0.0001
Male versus female	1.0 (0.96–1.04)	0.89
Age at first RRT (+1 year)	1.024 (1.022–1.026)	<0.0001
Primary renal disease		
Diabetes	1.21 (1.12–1.31)	<0.0001
Renal vascular disease	1.10 (1.04–1.17)	0.002
Glomerular nephropathy and related disease*	1	
Polycystic	0.76 (0.69–0.83)	<0.0001
Myeloma, light chain deposit, and amyloid	3.0 (2.72–3.32)	<0.0001
Renal cancer	1.67 (1.4–2.0)	<0.0001
Other	1.07 (1.02–1.13)	0.01
Lung disease	1.24 (1.18–1.29)	<0.0001
Coronaropathy	1.22 (1.17–1.27)	<0.0001
Peripheral vascular disease	1.21 (1.15–1.26)	<0.0001
Cerebrovascular disease	1.16 (1.11–1.22)	<0.0001
BMI (kg/m^2)		
<18	1.33 (1.21–1.45)	<0.0001
18–24*	1	
25–29	0.89 (0.86–0.93)	<0.0001
≥30	0.91 (0.87–0.96)	0.0005
Cigarette smoking		
Never*	1	
Former	0.99 (0.95–1.03)	0.72
Current	1.10 (1.04–1.17)	0.001

Whole cohort: n = 28,548. Results were unchanged when patients were censored at time of transplant and/or RRT modality switches, when analyses were adjusted for eGFR, or when analyses were performed only in patients starting RRT with hemodialysis or in patients starting with peritoneal dialysis. *Reference group in categorical variables.

Despite an increase of about +3% per year in the incidence of childhood type 1 diabetes in ANZ during the last decades (13,14), the incidence of RRT with associated type 1 diabetes remained stable between 1991 and 2005. The difference in trends between general and ESRD populations may indicate improvements in care of type 1 diabetic patients due to treatment with ACE inhibitors and aggressive glycemic control available since 1980 (15). High transplant rates, including simultaneous kidney-pancreas transplant, remained stable over time. The higher risk for death in type 1 diabetic than in type 2 diabetic patients was not explained by risk factors in the multivariate analyses. This difference should be accounted for by differences in diabetes duration and severity or glycemic control. These data were not available for analysis, and the result should be interpreted with this limitation in mind.

For type 2 diabetes, the overall 10.2% annual increase in ANZ is consistent with studies in Europe and the U.S. over comparable periods (6,7). The increase was higher in patients aged ≥60 years than in younger patients. Possible explanations for this rise are the increasing incidence and prevalence of overweight, obesity (16), and type 2 diabetes in the general population (17); improved life expectancy in type 2 diabetic patients with earlier stage of kidney disease due in part to better management of cardiovascular diseases (18); and greater access to RRT (5–7).

These results highlighted the specific epidemiology of diabetes and ESRD in the Australasian population. Two-thirds of Australian Aboriginal and Maori/Pacific Islander patients with ESRD had type 2 diabetes at the start of RRT, which was significantly different from the situation in the Caucasoid population (~20% with type 2 diabetes at the start of RRT). The incidence and prevalence of type 2 diabetes and hypertension are high in Aboriginal population (19). This higher incidence of ESRD with associated type 2 diabetes may be explained in part by genetic susceptibility and higher rates of kidney disease progression than in the Caucasoid population (19).

After the first RRT, overall survival was short in type 2 diabetic patients, with median survival times of <3.5 years, similar to reports from Europe (8,11) and the U.S. (9,12). Less than 10% of type 2 diabetic patients received RTx, as in France (20) and the U.S. (21). Adjusted rates of

RTx declined over the study period among type 2 diabetic patients but remained stable in the other two groups. Survival rates improved with a decrease in cardiovascular death. We hypothesize that improvements in dialysis management and in cardiovascular treatments may explain this improvement over time.

Moreover, female sex was significantly associated with death in type 2 diabetic patients aged ≥60 years. Interactions between female sex, diabetes, and excess mortality in the ESRD population compared with the general population have also been noted in France (22). Several dialysis-specific explanations can be proposed, such as sex differences in the effects of the dialysis dose (23) and the importance of glycemic control (12) on survival of patient with ESRD and diabetes.

Although it remains controversial (24), worse prognosis has also been reported in women than in men in the non-ESRD diabetic population who do not have diabetes (3,4). In diabetic subjects without chronic kidney disease, most studies have found that this difference was not accounted for by traditional risk factors (25). Higher risk for death in women may be related to interactions between cardiovascular risk factors and menopause (26), a stronger inverse association between coronary disease and cholesterol level in women, and differences in coagulation and in patterns of obesity and hyperinsulinemia (2–4,25, 26).

In summary, this study confirms that incidences, treatments, and survivals are different between ESRD patients with type 1 and type 2 diabetes. Future studies of patients with ESRD and diabetes should differentiate between these two groups to provide interpretable results. ESRD remains a dreadful complication in patients with type 1 diabetes, and great effort to prevent kidney disease in these young patients is needed. A marked increase in the incidence rate of ESRD with associated type 2 diabetes was seen over the study period. The study emphasizes the burden of ESRD with associated type 2 diabetes in Australian Aboriginal and in Maori/Pacific Islander populations. Prevention of renal impairment (27), nephroprotection in patients with overt nephropathy, early referral to nephrologists (28), and access to RTx (29) may improve the prognosis of type 2 diabetic patients. This study also highlights the poorer prognosis in older type 2 diabetic women compared with older type 2 diabetic men. This finding deserves further explanatory studies.

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Effect of Age, Gender, and Diabetes on Excess Death in End-Stage Renal Failure

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ABSTRACT

Life expectancy is short in elderly individuals with end-stage renal failure (ESRF). This study aimed to compare mortality in patients with ESRF *versus* the general population (GP) to assess the evolution of excess mortality by age, gender, nephropathy, and dialysis modality after first dialysis. All incident adult dialysis patients from January 1,1999, to December 31, 2003, who lived in Rhône–Alpes Region (France) were included and followed up to death or December 31, 2005. Standardized mortality ratios (SMR) in comparison with GP were computed in the first to the fifth years after first dialysis. In the whole cohort (3025 incident patients), SMR decreased during these 5 yr from 7.4 to 5.2 ($P = 0.002$). In the 18- to 44-, 45- to 64-, 65- to 74-, 75- to 84-, and ≥85-yr-old groups, SMR decreased from 26.7 to 6.2 ($P = 0.01$), from 12.8 to 8.1 ($P = 0.03$), from 8.6 to 5.6 ($P = 0.051$), from 7.1 to 4.5 ($P = 0.02$), and from 3.5 to 1.2 ($P = 0.14$), respectively. Among age categories, differences were significant in the first 3 yr ($P < 0.05$). SMR were higher 1.5-fold in women than in men in the first 4 yr ($P < 0.05$). In patients with diabetic nephropathy (DN), SMR increased during the first 3 yr ($P = 0.045$) and were higher than in patients without DN in the second, third, and fourth years ($P < 0.05$). SMR were higher in the peritoneal dialysis than in the hemodialysis group in the fourth year ($P < 0.01$). Patients with ESRF have a high excess mortality compared with the GP. Older patients with ESRF experienced less excess mortality. ESRF cancels out women's survival advantage noted in the GP. SMR evolution in patients with DN was different from that in patients without DN.

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In France in 2003, more than 30,000 patients were treated by dialysis therapy[1] and more than 21,000 lived with a functional renal transplant.[2] As in other industrialized countries,[3–5] the incidence rate of end-stage renal failure (ESRF) increased in France from 62 per 1 million people in 1992[6] to 123 per 1 million people in 2003.[7] During the past decade, the number of elderly patients and patients who had diabetes and received renal replacement therapy (RRT) increased rapidly.[3–9] Population aging, increased prevalence of diabetes, improved management of cardiovascular diseases, and improved access to RRT may explain this evolution.[3–9]

In dialyzed patients, survival after first RRT in the incident cohort is usually analyzed using survival curves drawn by Kaplan-Meier or actuarial methods[10] and using Cox regression in multivariate analysis.[11] Age, after adjustment for other risk factors, is a risk factor for death in the RRT population.[8,12–14] Median survival of patients who were older than 75 yr was <2 yr after first dialysis world-

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wide.[4,8,12,14] The question raised is the efficiency of starting RRT in those patients when quality of life and costs are considered as well.

Part of the answer can be found in the comparison of lifespan of the ESRF and the non-ESRF population in the elderly. Little is known about excess death in patients with ESRF in comparison with the general population (GP). In 1998, Levey *et al.*[15] published a comparison of cardiovascular death rates in prevalent dialysis patients *versus* the GP in United States. The risk for cardiovascular death was higher in the prevalent dialysis population.[15] In comparison with the GP, excess of cardiovascular death decreased when patient age increased.[15]

Our purpose was to explore excess death in incident patients with ESRF in comparison with the GP in a community-based prospective study in France. It was performed with the cohort of all incident dialysis patients between January 1, 1999, and December 31, 2003, who lived in the Rhône–Alpes region, France. We computed age and gender standardized mortality ratio (SMR) in patients with ESRF *versus* the French GP, overall and by patient subgroups (age, gender, original nephropathy, and initial dialysis modality) to analyze SMR variations by age and patient characteristics after first dialysis.

RESULTS

Baseline Characteristics, Events during Study Period, and Survival

Characteristics of the 3025 incident patients with ESRF are presented in Table 1. At first dialysis, mean age was 64.7 yr, and 50% of the population was older than 68.1 yr. Gender ratio (male/female) was 1.7. Vascular (VN) and diabetic nephropathy (DN) were the main causes of ESRF (44%). The majority were treated by hemodialysis (HD) (83%). During the study period, 629 (20.8%) patients received a renal transplant and 1398 (46.2%) died. Mortality rate was higher in the first year after dialysis onset. Cardiovascular disease was the main cause of death in this cohort (38.4%).

Excess Death after First Dialysis in the Whole Cohort

In the whole cohort, SMR decreased significantly from 7.4 to 5.2 with time after first dialysis, with a mean of −6.6% (95% confidence interval [CI] −10.5 to −2.5%) per year after first RRT ($P = 0.002$; Table 2). SMR was significantly higher in the first year after first RRT in comparison with other SMR pooled together ($P < 0.05$).

Excess Death by Age Categories

Gender ratio did not vary by age categories (Table 1). VN and DN were overrepresented in older patients. Rate of cardiovascular disease as cause of death decreased as patient age increased ($P = 0.008$). Crude survival significantly worsened with patient's age ($P < 0.0001$, log rank test; Figure 1, top). Median survival after first dialysis was 44.8 mo in 65- to 74-yr-old patients and 22.7 mo in patients who were older than 75 yr.

Excess of mortality was higher in younger patients (Table 2, Figure 1, bottom): SMR decreased as patient age increased in all studied periods after first dialysis with the exception of the fifth year in 18- to 44-yr-old patients, which was inferior to the fifth-year SMR of 45- to 64-yr-old patients (Table 2). Mean annual changes in SMR in 18- to 44-, 45- to 64-, 65- to 74-, 75- to 84-, and ≥85-yr-old patient groups were −28.8% (95% CI −46.0 to −6.2%; $P = 0.01$), −10.2% (95% CI −18.6 to −1.0%; $P = 0.03$), −6.9% (95% CI −13.5 to 0.1%; $P = 0.051$), −10.7% (95% CI −17.0 to −3.9%; $P = 0.02$), and −12.0% (95% CI −26.1 to 4.8%; $P = 0.14$), respectively. Mean annual changes were not significantly different among age categories.

SMR comparisons between age strata were adjusted on gender structure of the studied strata. In 18- to 44-yr-old patients, SMR were significantly higher than in other age groups during the first 3 yr after dialysis onset ($P < 0.05$). In 45- to 64-yr-old patients, SMR were significantly higher than in 65- to 74-yr-old patients during the first 3 yr ($P < 0.05$), significantly higher than in 75- to 84-yr-old patients during the first 4 yr ($P < 0.05$) and significantly higher than in ≥85-yr-old patients during all of the studied 5 yr after first dialysis ($P < 0.05$). In 65- to 74-yr-old patients, SMR were significantly higher than in 75- to 84-yr-old patients only in the fourth year after first dialysis ($P < 0.05$) and significantly higher than in ≥85-yr-old patients during all 5 yr ($P < 0.05$). In 75- to 84-yr-old patients, SMR were significantly higher than in ≥85-yr-old patients during the first 3 yr after first dialysis ($P < 0.05$).

Excess Death in Women

Mean age was not different between genders ($P = 0.61$; Table 3). DN was overrepresented in women ($P < 0.0001$). Women were more likely to be treated by peritoneal dialysis (PD) as first RRT ($P < 0.0001$). Crude survival was better in women than in men (hazard ratio of death 0.87; 95% CI 0.78 to 0.97; $P = 0.01$). No significant differences in cause of death were observed ($P = 0.44$).

SMR were significantly higher in women during the first 4 yr, after adjustment for age groups ($P < 0.001$ to $P < 0.05$; (Table 4). Mean annual changes in SMR were −5.2% (95% CI −10.2 to −0.1%; $P = 0.046$) in men and −9.3% (95% CI −15.7 to −2.2%; $P = 0.01$) in women. These changes were not different between genders.

Significant differences between genders were observed in patients who were older than 65 yr ($P < 0.001$ to $P < 0.05$ in first, second, and fourth years after first dialysis), in patients with DN ($P < 0.05$ in the first 3 yr after first dialysis), in patients with glomerulonephritis and vasculitis only in the first year after first dialysis ($P < 0.001$), and in patients who were treated by HD as first dialysis modality ($P < 0.001$ to $P < 0.05$ in first, second, and fourth years after first dialysis).

Excess Death in Patients with DN

Mean ages were not different between patients with and without DN ($P = 0.25$; Table 3). Gender ratio (male/female) was lower in patients with DN (1.3 *versus* 1.8; $P = 0.0002$). Renal

Table 1. Characteristics of the studied population in the whole cohort and by age categories (*n = 3025 patients*)[a]

Characteristic	Total Cohort (*n* = 3025)	Age Categories (yr)				
		18 to 44 (*n* = 372)	45 to 64 (*n* = 912)	65 to 74 (*n* = 883)	75 to 84 (*n* = 719)	≥85 (*n* = 139)
Age (yr)						
mean [SD])	64.7 ± 15.5	34.3 ± 7.8	56.4 ± 5.5	70.4 ± 2.9	79.2 ± 2.6	88.8 ± 3.3
median	68.1	35.3	56.7	70.7	78.9	88.1
Gender (*n* [%])						
male	1892 (62.5)	232 (62.4)	561 (61.5)	573 (64.9)	438 (60.9)	88 (63.3)
female	1133 (37.5)	140 (37.6)	351 (38.5)	310 (35.1)	281 (39.1)	51 (36.7)
Original nephropathy (*n* [%])						
VN	698 (23.1)	13 (3.5)	114 (12.5)	255 (28.9)	259 (36.0)	57 (41.0)
DN	624 (20.6)	55 (14.8)	198 (21.7)	237 (26.8)	129 (17.9)	5 (3.6)
glomerulonephritis, and vasculitis	582 (19.2)	143 (38.4)	208 (22.8)	135 (15.3)	78 (10.8)	18 (12.9)
pyelonephritis, and interstitial nephropathy	316 (10.4)	65 (17.5)	112 (12.3)	73 (8.3)	52 (7.2)	14 (10.1)
PKD, adult type	215 (7.1)	30 (8.1)	126 (13.8)	33 (3.7)	23 (3.2)	3 (2.2)
myeloma, light chain deposit disease, amyloid	101 (3.3)	2 (0.5)	28 (3.1)	39 (4.4)	30 (4.2)	2 (1.4)
miscellaneous and unknown	489 (16.1)	64 (17.2)	126 (13.8)	112 (12.5)	148 (20.6)	40 (28.7)
First modality of dialysis (*n* [%])						
HD	2498 (82.6)	321 (86.3)	781 (85.6)	734 (83.1)	564 (78.4)	98 (70.5)
PD	527 (17.4)	51 (13.7)	131 (14.4)	149 (16.9)	155 (21.6)	41 (29.5)
Renal transplant during study period (*n* [%])	629 (20.8)	232 (62.4)	343 (37.6)	53 (6.0)	1 (0.1)	0 (0.0)
Survival (Kaplan-Meier; % [95% CI])						
1 yr	82.2 (80.9 to 83.6)	95.9 (94.0 to 98.0)	91.0 (89.1 to 92.9)	82.0 (79.5 to 84.6)	68.8 (65.5 to 72.3)	59.0 (51.4 to 67.8)
2 yr	70.1 (69.5 to 72.7)	94.3 (92.0 to 96.7)	85.1 (82.8 to 87.5)	69.4 (66.4 to 72.6)	49.7 (46.1 to 53.5)	38.8 (31.5 to 47.9)
3 yr	62.1 (60.3 to 63.9)	91.3 (88.4 to 94.3)	79.0 (76.4 to 81.8)	58.7 (55.4 to 62.1)	36.9 (33.4 to 40.8)	23.4 (17.1 to 32.2)
4 yr	54.5 (52.6 to 56.5)	90.9 (88.4 to 94.3)	74.4 (71.4 to 77.5)	48.3 (44.8 to 52.1)	26.4 (23.0 to 30.3)	11.5 (06.8 to 19.4)
5 yr	48.0 (45.9 to 50.2)	89.9 (86.6 to 93.2)	68.7 (65.3 to 72.3)	39.8 (36.0 to 43.9)	17.8 (14.6 to 21.8)	8.6 (04.5 to 16.7)
Survival (median)	57.2	—	—	44.8	23.8	16.5
No. of deaths during study period	1398	35	249	467	527	120
Causes of death (*n* [%])						
cardiovascular	537 (38.4)	16 (45.7)	107 (43.0)	168 (36.0)	205 (38.8)	41 (34.2)
infectious	141 (10.1)	4 (11.4)	22 (8.8)	51 (10.9)	51 (9.7)	13 (10.8)
malignancy	135 (9.6)	4 (11.4)	27 (10.8)	52 (11.1)	50 (9.5)	2 (1.7)
other known	289 (20.7)	5 (14.3)	35 (14.1)	83 (17.8)	126 (23.9)	40 (33.3)
unknown	296 (21.2)	6 (17.2)	58 (23.3)	113 (24.2)	95 (18.1)	24 (20.0)

[a]Comparisons among age categories: Original nephropathy ($P < 0.0001$), crude survival ($P < 0.0001$), causes of death ($P = 0.008$). No other significant differences among age categories. CI, confidence interval; DN, diabetic nephropathy; HD, hemodialysis; PD, peritoneal dialysis; PKD, polycystic kidney disease; VN, vascular nephropathy.

transplantation rate was lower in patients with DN ($P = 0.01$). Crude survival was significantly worse in patients with DN (hazard ratio of death 1.35; 95% CI 1.20 to 1.53; $P < 0.0001$). Cardiovascular diseases as cause of death were significantly higher in patients with DN ($P < 0.0001$).

In patients with DN (Table 5), SMR annual changes increased significantly from the first to the third years after first dialysis (9.4 to 13.0, with a mean change of 16.8% per year; 95% CI 0.4 to 36.0%; $P = 0.045$) but decreased significantly in the fourth and fifth years (11.5 and 7.8 respectively, with an mean change of −20.9% per year; 95% CI −37.1 to −0.5%; $P = 0.041$). In patients without DN, mean annual changes in SMR were −9.3% (95% CI−15.8 to −2.2%; $P = 0.01$). SMR annual change slopes were significantly different between patients with DN and patients without DN in the first 3 yr after first RRT ($P < 0.0001$).

SMR were significantly higher in the second, third, and fourth years in patients with DN than in patients without DN ($P < 0.001$ to $P < 0.05$). In each patient subgroup by age, by gender, and by RRT modality, SMR were significantly higher in patients with DN in the third year (Table 5). They were significantly higher in the second and in the third years in patients who were older than 65 yr and in female patients (Table 5). They were significantly higher in the second, third, and fourth

Table 2. SMR with 95% CI in patients with ESRF *versus* GP of the same age and the same gender in first, second, third, and fourth years after first dialysis, conditionally of being alive at the beginning of the period

Parameter	First Year	Second Year	Third Year	Fourth Year	Fifth Year	P^b
Total cohort (n = 3025)	7.4 (6.7 to 8.0)[c]	5.9 (5.3 to 6.6)	6.2 (5.4 to 7.1)	6.4 (5.3 to 7.5)	5.2 (4.2 to 6.4)	<0.01
Age categories (yr)						
18 to 44 (n = 372)	26.7 (14.9 to 44.1)	17.0 (7.7 to 32.2)	14.3 (5.2 to 31.2)	9.9 (2.0 to 28.9)	6.2 (0.7 to 22.4)	<0.05
45 to 64 (n = 912)	12.8 (10.2 to 15.9)	9.2 (6.8 to 12.0)	9.3 (6.7 to 12.6)	8.3 (5.4 to 12.2)	8.1 (5.3 to 12.0)	NS
65 to 74 (n = 883)	8.6 (7.3 to 10.1)	7.2 (5.9 to 8.5)	6.7 (5.2 to 8.5)	8.2 (6.3 to 10.7)	5.6 (3.9 to 7.8)	NS
75 to 84 (n = 719)	7.1 (6.2 to 8.1)	5.7 (4.7 to 6.7)	5.4 (4.3 to 6.8)	5.2 (3.8 to 7.0)	4.5 (3.0 to 6.4)	<0.05
≥85 (n = 139)	3.5 (2.7 to 4.6)	2.8 (1.9 to 4.0)	2.8 (1.6 to 4.6)	3.2 (1.5 to 6.2)	1.2 (0.1 to 4.3)	NS
Gender						
male (n = 1892)	6.2 (5.6 to 6.9)	5.2 (4.5 to 5.9)	5.5 (4.7 to 6.5)	5.3 (4.2 to 6.5)	4.9 (3.8 to 6.2)	NS
female (n = 1133)	10.9 (9.4 to 12.5)	8.0 (6.6 to 9.7)	8.2 (6.4 to 10.3)	9.7 (7.2 to 12.7)	6.4 (4.2 to 9.2)	<0.02
Original nephropathy						
VN (n = 698)	5.5 (4.7 to 6.5)	5.2 (4.3 to 6.4)	4.1 (3.0 to 5.4)	6.6 (4.9 to 8.8)	4.1 (2.6 to 6.2)	NS
DN (n = 624)	9.4 (7.7 to 11.3)	10.0 (8.0 to 12.4)	13.0 (10.1 to 16.4)	11.5 (8.0 to 16.1)	7.8 (4.8 to 12.1)	NS
glomerulonephritis and vasculitis (n = 582)	4.5 (3.3 to 6.0)	3.3 (2.3 to 4.7)	4.8 (3.3 to 6.7)	3.5 (2.0 to 5.8)	5.1 (3.0 to 8.1)	NS
pyelonephritis and interstitial nephropathy (n = 316)	5.6 (3.9 to 7.8)	6.0 (4.1 to 8.6)	6.2 (3.8 to 9.5)	6.6 (3.4 to 11.6)	7.4 (3.7 to 13.2)	NS
PKD, adult type (n = 215)	2.4 (1.0 to 4.7)	2.2 (0.8 to 4.9)	2.7 (0.9 to 6.2)	2.3 (0.5 to 6.7)	3.1 (0.8 to 7.8)	NS
myeloma, light chain disease, and amyloid (n = 101)	23.4 (17.1 to 31.3)	17.5 (10.8 to 26.7)	15.3 (6.1 to 31.5)	17.9 (5.8 to 41.8)	25.2 (6.8 to 64.6)	NS
miscellaneous and unknown (n = 489)	11.2 (9.4 to 13.3)[c]	6.3 (4.7 to 8.3)	4.3 (2.6 to 6.7)	5.8 (3.5 to 9.0)	4.1 (2.3 to 6.9)	<0.01
First modality of dialysis						
HD (n = 2498)	7.7 (7.0 to 8.4)[c]	5.8 (5.1 to 6.6)	6.0 (5.1 to 7.0)	5.3 (4.3 to 6.4)	4.9 (3.9 to 6.2)	<0.01
PD (n = 527)	6.1 (5.0 to 7.5)	6.1 (4.8 to 7.7)	7.1 (5.3 to 9.4)	11.7 (8.5 to 15.8)[c]	7.0 (4.2 to 11.1)	<0.01

[a]ESRF, end-stage renal failure; GP, general population; SMR, standardized mortality ratios.
[b]Heterogeneity test for the five periods after first dialysis.[38]
[c]$P < 0.05$ in comparison with other SMR in the given patient subgroup (by row).

years after first RRT in patients who were treated by PD as first RRT modality (Table 5).

Excess Death in Patients without DN

Patients with myeloma or amyloid nephropathy had higher SMR than all other patient groups by original nephropathy during all periods ($P < 0.01$ to <0.05; Table 2). SMR was significantly higher in the first year after first RRT in comparison with other SMR pooled together in patients with miscellaneous and unknown cause of original nephropathy ($P < 0.05$). After taking into account age and gender structure of patient groups by original nephropathy for SMR comparison, no other significant difference was observed between original nephropathies.

Excess Death by Initial Dialysis Modality

In patients who were treated by HD, SMR decreased significantly from 7.7 to 4.9 during the studied period, with a mean annual decrease of −10.8% (95% CI −15.1 to −6.3%; $P < 0.0001$). SMR was significantly higher in the first year in comparison with other SMR pooled together ($P < 0.05$).

In patients who were treated by PD, heterogeneity test was significant ($P < 0.01$) and SMR was significantly higher in the fourth year after first RRT in comparison with other SMR in these patients ($P < 0.05$). A nonsignificant mean annual increase of 1.9% (95% CI −7.8 to 12.6%; $P = 0.7$) in SMR was observed in these patients.

SMR was significantly higher in PD patients than in HD patients only in the fourth year ($P < 0.01$). SMR annual change slopes were not significantly different between the two modalities.

DISCUSSION

This study provides a new view of survival in patients who have ESRF and are on dialysis by changing of analytical perspective. Excess death in this population of interest was specifically explored in a prospective and population-based study of a large cohort of incident dialysis patients.

This study emphasizes the global poor prognosis of patients who start dialysis in comparison with the GP. This result confirms data from US Renal Data System and Australia and New Zealand Dialysis and Transplant Registry in the prevalent ESRD population.[4,5] Excess death, assessed by SMR, decreased significantly during the first 5 yr after first dialysis from 7.4 to 5.2 in the whole cohort. This might be partly explained by selection of patients with lower risk for death by time after first dialysis.

Age is a widely known risk factor for death in the ESRF

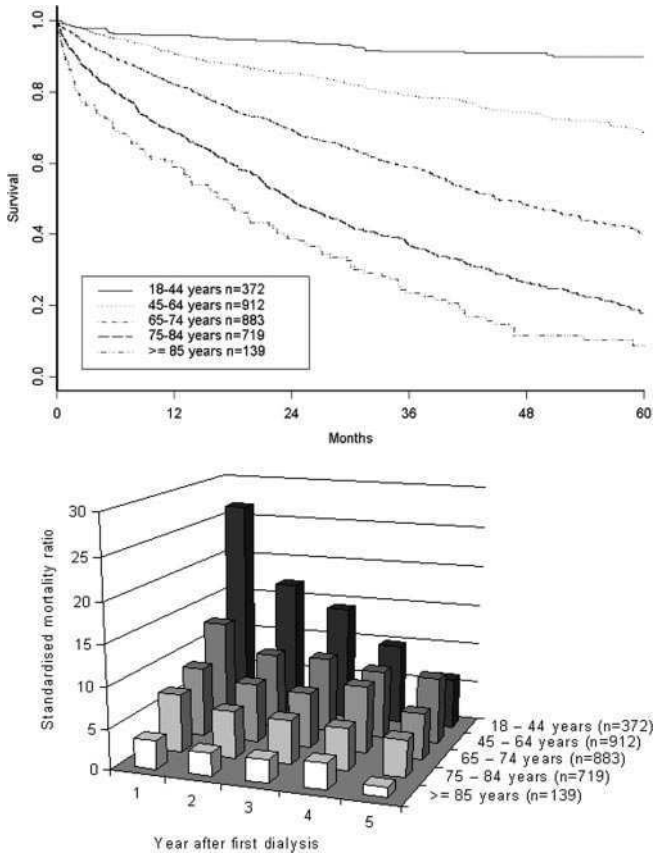

Figure 1. Kaplan-Meier survival curves by age group (top) and standardized mortality ratios by age group (bottom).

population that is treated by dialysis, as in any other populations: Hazard ratio of death, in comparison with younger patients, increases with patient age.[8,12–14] When compared against the GP, this study underlined that excess death is higher in younger patients than in older patients because mortality rates are very low in the young GP: SMR decreases when age increases.

These results are consistent with data from US population.[4,15,16] Ferris *et al.*[16] found that the 10-yr mortality rate was 30-fold increased in adolescents (12- to 19-yr-old patients) who started dialysis compared with the general US adolescent population. Our findings in the 18- to 44-yr-old patient group, in which SMR decreased from 26.7 to 6.2 during the first 5 yr after dialysis onset, are consistent with the results of Ferris *et al.*

When compared with their age-peers, older patients with ESRF experienced lower excess mortality than younger patients with ESRF, especially in the first 3 yr of dialysis. Dialysis therapy should then not be contraindicated by old age *per se*, but this study did not include patients who had ESRF and never underwent dialysis. Cachexia, dementia, and withdrawal of dialysis therapy were important causes of death in patients who were older than 85 yr. Question of indication for starting dialysis needed to be asked in these very old patients, considering survival and quality of life on dialysis.

Moreover, analyzing annual changes in SMR showed that younger patients with ESRF reached the SMR levels of older patients with ESRF in the fifth year after first dialysis, probably because of selection of patients who have ESRF and are long-term survivors. This result warrants further study with a longer observation period.

Gender is usually not considered as a risk factor for death in the ESRF population.[3–5,17,18] In the GP of industrialized countries, life expectancy is longer in women than in men.[19] Although no significant difference in age at first dialysis was observed between women and men in this cohort in which crude survival was better in women than in men, excess death was approximately 1.5-fold higher in women than in men in the first 4 yr after dialysis onset ($P < 0.05$). No difference in causes of death between women and men was observed. As in younger patients, lower mortality rates in the female GP explain higher SMR in women who undergo dialysis: Dialysis therapy cancels out women's survival advantage in the GP.

Considering risks factor for death in the dialysis population and their difference between genders, one can discuss the potential role of body mass index to explain the results of this study. Although its effect remains controversial,[20] the proportions of underweight and overweight patients are different in male and female patients with ESRF, and this could explain in part the results observed. Moreover, different effect of high dialysis dosage on survival was seen in the HEMO Study between genders,[21] and we can hypothesize a role of dialysis dosage delivery to explain this observation.

In patients without chronic kidney disease, most studies have demonstrated that the gap between women and men is not accounted for by conventional risk factors.[22] It has been postulated that cardiovascular risk in women was related to interactions between cardiovascular risk factors and menopause,[23] to a stronger inverse association between coronary heart disease and HDL cholesterol level in women than in men, to differences in coagulation, to differences in patterns of obesity, and to a role for hyperinsulinemia.[22,24,25]

The impact of cardiovascular factors such as diabetes on risk for cardiovascular disease and for death is reported to be greater in women than in men in the GP.[22,24,25] Our results confirm that effect of ESRF as risk factor for death is greater in women than in men, especially in women who are older than 65 and in women with diabetes, indicating deleterious interactions among these cardiovascular risk factors (ESRF, diabetes, and age) in women.

Moreover, differences in women who are on HD and in women who are on PD may be explained by differences in the pattern of cardiovascular risk factor evolution between these dialysis modalities or dialysis dosage. These findings warrant further specific studies that focus on mortality in women with ESRF, especially in women who are older than 65, and in women with diabetes.

SMR evolution was significantly different in patients with DN than in patients without DN: SMR increased from the first to the third years after first dialysis (9.4 to 13.0)

Table 3. Characteristics of the studied population by gender and by DN status ($n = 3025$ patients)[a]

Characteristic	Women ($n = 1133$)	Men ($n = 1892$)	Patients with DN ($n = 624$)	Patients without DN ($n = 2401$)
Age (yr)				
mean ± SD	64.5 ± 15.8	64.8 ± 15.4	65.2 ± 12.6	64.5 ± 16.2
median	67.7	68.5	67.8	68.1
Gender (*n* [%])				
male	—	1892 (100)	349 (55.9)	1543 (64.3)
female	1133 (100)	—	275 (44.1)	858 (35.7)
Original nephropathy (*n* [%])				
VN	216 (19.1)	483 (25.5)	—	699 (29.1)
DN	275 (24.3)	349 (18.5)	624 (100)	—
glomerulonephritis, and vasculitis	169 (14.9)	424 (22.4)	—	593 (24.7)
pyelonephritis, and interstitial nephropathy	146 (12.9)	170 (9.0)	—	316 (13.2)
PKD, adult type	101 (8.9)	114 (6.0)	—	215 (8.9)
myeloma, light chain deposit disease, amyloid	38 (3.3)	63 (3.3)	—	101 (4.2)
miscellaneous and unknown	188 (16.6)	289 (15.3)	—	477 (19.9)
First modality of dialysis (*n* [%])				
HD	889 (78.5)	1609 (85.0)	511 (81.9)	1987 (82.7)
PD	244 (21.5)	283 (15.0)	113 (18.1)	414 (17.3)
Renal transplant during study period (*n* [%])	248 (21.9)	381 (20.1)	106 (17.0)	523 (21.8)
Survival (Kaplan-Meier; % [95% CI])				
1 yr	82.7 (80.6 to 85.0)	81.8 (80.1 to 83.6)	82.2 (79.3 to 85.3)	82.2 (80.7 to 83.7)
2 yr	72.8 (70.3 to 75.5)	70.0 (68.0 to 72.1)	67.8 (64.2 to 71.6)	72.0 (70.2 to 73.8)
3 yr	64.7 (61.9 to 67.6)	60.5 (58.3 to 62.8)	54.1 (50.2 to 58.3)	64.1 (62.2 to 66.1)
4 yr	56.9 (53.8 to 60.1)	53.1 (50.7 to 55.6)	45.2 (41.1 to 49.7)	56.9 (54.8 to 59.1)
5 yr	51.7 (48.4 to 55.2)	45.8 (43.2 to 48.5)	38.1 (33.8 to 43.0)	50.5 (48.2 to 53.0)
Survival (median)	66.4	53.4	40.3	62.6
No. of deaths during study period	492	906	343	1055
Causes of death (*n* [%])				
cardiovascular	181 (36.8)	356 (39.3)	168 (49.0)	369 (35.0)
infectious	51 (10.4)	90 (9.9)	34 (9.9)	107 (10.1)
malignancy	54 (11.0)	81 (8.9)	17 (4.9)	118 (11.2)
other known	94 (19.1)	195 (21.5)	59 (17.2)	230 (12.3)
unknown	112 (22.7)	184 (20.3)	65 (15.0)	231 (21.9)

[a]Women compared with men: Original nephropathy ($P < 0.0001$), first modality of dialysis ($P < 0.0001$), crude survival ($P = 0.01$). No other significant differences between genders. Patients with DN compared with patients without DN: Gender ratio ($P = 0.0002$), rate of renal transplantation ($P = 0.01$), crude survival ($P < 0.0001$), causes of death ($P < 0.0001$). No other significant differences between patients with and without DN.

and decreased during the fourth and fifth years (11.5 and 7.8, respectively) in patients with DN. These trends were not observed in other patient groups. SMR were significantly higher in the second, third, and fourth years in patients with DN compared with patients without DN. We can hypothesize that patients with ESRF and diabetes of this cohort were not homogeneous with regard to risk for death after first dialysis. However, risk for death increased after first dialysis, which was not observed in other groups, suggesting the existence of a population at high risk for death immediately after dialysis onset. Moreover, long-term survivors were observed in this population, suggesting the existence of a population with standard risk for death. This observation warrants further studies in a larger cohort to confirm or refute this evolution. Differential role of accelerated atherosclerosis in these patients should be explored under this assumption.[26–29]

As was expected, patients with myeloma and related diseases presented significant higher SMR as a result of abysmal prognosis of these hematologic diseases.[30]

In patients with polycystic kidney disease (PKD), SMR were low (2.2 to 3.1, with 95% CI always including 1). Survival after first dialysis is better in patients with PKD in comparison with control patients ESRF and without diabetes.[31] Healthier condition, which was underlined by high rates of renal transplantation, may explain why SMR were low in these patients. As described in the United States,[31] most of the mortality in patients with PKD occurred in pa-

Table 4. SMR with 95% CI in women and men with ESRF *versus* the GP of the same age and the same gender in first, second, third, and fourth years after first dialysis, conditionally of being alive at the beginning of the period

Parameter	First Year	Second Year	Third Year	Fourth Year	Fifth Year	P[a]
Women (n = 1133)						
all patients	10.9 (9.4 to 12.5)[b]	8.0 (6.6 to 9.7)[c]	8.2 (6.4 to 10.3)[d]	9.7 (7.2 to 12.7)[d]	6.4 (4.2 to 9.2)	<0.02
age categories						
18 to 64 yr (n = 491)	19.2 (12.7 to 27.7)	12.7 (7.4 to 20.4)	16.4 (9.6 to 26.3)	9.1 (5.4 to 22.6)	11.9 (5.4 to 22.3)	NS
≥65 yr (n = 642)	10.2 (8.7 to 11.8)[b]	7.5 (6.1 to 9.2)[d]	7.1 (5.4 to 9.2)	9.8 (7.1 to 13.1)[d]	5.2 (3.1 to 8.1)	<0.01
original nephropathy						
VN (n = 217)	6.3 (4.6 to 8.6)	5.7 (3.8 to 8.2)	3.5 (1.8 to 6.0)	8.2 (4.8 to 13.1)	6.0 (3.2 to 10.2)	NS
DN (n = 275)	14.5 (10.8 to 19.0)[d]	14.9 (10.6 to 20.3)[d]	21.9 (15.2 to 30.6)[d]	16.7 (9.1 to 28.1)	9.6 (3.8 to 19.8)	NS
glomerulonephritis (n = 168)	10.8 (6.3 to 17.3)[b]	4.1 (1.5 to 9.0)	7.9 (3.4 to 15.6)	7.3 (2.3 to 17.0)	3.2 (0.4 to 11.5)	NS
first modality of dialysis						
HD (n = 889)	12.1 (10.2 to 14.1)[b]	7.8 (6.2 to 9.8)[d]	7.7 (5.7 to 10.1)	8.5 (6.0 to 11.8)[d]	5.9 (3.7 to 9.1)	<0.01
PD (n = 244)	7.7 (5.4 to 10.7)	8.6 (5.9 to 12.2)	9.7 (6.1 to 14.7)	13.8 (7.9 to 22.4)	8.1 (3.3 to 16.8)	NS
Men (n = 1892)						
all patients	6.2 (5.6 to 6.9)	5.2 (4.5 to 5.9)	5.5 (4.7 to 6.5)	5.3 (4.2 to 6.5)	4.9 (3.8 to 6.2)	NS
age categories						
18 to 64 yr (n = 793)	12.5 (9.8 to 15.8)	7.6 (5.4 to 10.5)	10.0 (7.1 to 13.7)	7.5 (4.6 to 11.6)	6.8 (4.0 to 10.8)	NS
≥65 (n = 1099)	5.5 (4.9 to 6.2)	4.9 (4.2 to 5.6)	4.8 (3.9 to 5.8)	4.8 (3.7 to 6.2)	4.4 (3.2 to 5.8)	NS
original nephropathy						
VN (n = 469)	5.3 (4.3 to 6.4)	5.1 (3.9 to 6.4)	4.3 (3.0 to 6.0)	6.0 (4.1 to 8.5)	4.5 (2.7 to 7.1)	NS
DN (n = 349)	7.2 (5.4 to 9.2)	8.0 (5.9 to 10.5)	9.3 (6.5 to 13.0)	9.4 (5.8 to 14.6)	7.1 (3.8 to 12.2)	NS
glomerulonephritis (n = 435)	4.1 (2.9 to 5.6)	3.3 (2.2 to 4.8)	4.8 (3.2 to 6.9)	3.3 (1.7 to 5.7)	5.5 (3.2 to 9.0)	NS
first modality of dialysis						
HD (n = 1609)	6.4 (5.7 to 7.2)	5.2 (4.5 to 6.1)	5.4 (4.5 to 6.5)	4.3 (3.3 to 5.5)	4.6 (3.5 to 6.0)	<0.02
PD (n = 283)	5.4 (4.1 to 7.0)	5.0 (3.5 to 6.8)	6.0 (4.0 to 8.6)	10.8 (7.1 to 15.6)	6.5 (3.2 to 11.6)	0.02

[a]Heterogeneity test for the five periods after first dialysis.[38]
[b]$P < 0.001$ in comparison with men-equivalent cell.
[c]$P < 0.01$ in comparison with men-equivalent cell.
[d]$P < 0.05$ in comparison with men-equivalent cell.

tients who remained on dialysis. Actually, no death was observed during the study period in the 107 patients who had PKD and received a transplant. Survival advantage of renal transplantation in comparison with dialysis[32] may also explain results that were observed in these patients.

Significant higher SMR was observed in the first year after first dialysis in patients with miscellaneous and unknown nephropathy. After that first year, excess death decreased to identical levels as those in patients with VN, glomerulonephritis, or pyelonephritis. This observation may be explained by classification into this group of patients with nephropathies associated with a poor short-term outcome in dialysis, such as acute renal failure without renal recovery of function.[33]

Comparing HD and PD, we found that SMR only in the fourth year after dialysis onset were significantly different between modalities. This was due to an increase in death rate in the fourth year after first dialysis observed in PD patients. This may be specific to this cohort or due to patient outcome after switch from PD to HD. Comparison of outcomes between HD and PD remains controversial.[34,35] Our results suggest that a potential superiority of one modality over the other concerning patient survival is not strongly evident and that comparison between HD and PD outcomes should be studied in a time-dependent analysis.

This study should be interpreted with one restriction. SMR were computed with mortality rates in the French GP for which only age and gender are standardization factors. Specific mortality rates in patients with particular comorbid conditions were unfortunately not available. This leads to an overestimation of excess death in patients with comorbid conditions, especially diabetes, cardiovascular diseases, or malignancy, in comparison with the GP. Moreover, comparisons of patient subgroups have to be interpreted in view of this restriction, because comorbid conditions may not have been equally balanced between patient subgroups.

The strengths of this study are that it was conducted in an exhaustive community-based cohort of incident patients, when excess death was previously usually explored in the prevalent ESRF population.[4,5,15] We were able to describe SMR evolution year by year after first dialysis. Patients who had received a transplant were not censored at date of renal transplantation: The study explored excess death in patients who started dialysis, including natural history of treatment modality management (HD, PD, renal transplant, and switch among these RRT modalities). We did not specifically explore excess

Table 5. SMR with 95% CI in patients with ESRF and with DN and without DN *versus* the GP of the same age and the same gender in first, second, third, and fourth years after first dialysis, conditionally of being alive at the beginning of the period

Parameter	First Year	Second Year	Third Year	Fourth Year	Fifth Year	P[a]
Patients with DN (n = 624)						
all patients	9.4 (7.7 to 11.3)	10.0 (8.0 to 12.4)[b]	13.0 (10.1 to 16.4)[c]	11.5 (8.0 to 16.1)[b]	7.8 (4.8 to 12.1)	NS
age categories (yr)						
18 to 64 (n = 253)	15.9 (10.3 to 23.5)	14.2 (8.7 to 22.0)	28.5 (19.0 to 41.2)[c]	15.9 (7.6 to 29.2)	13.3 (5.7 to 26.3)	NS
≥65 (n = 371)	8.4 (6.7 to 10.4)	9.2 (7.2 to 11.7)[b]	9.5 (6.8 to 12.8)[b]	10.3 (6.6 to 15.4)	6.1 (3.2 to 10.7)	NS
gender						
male (n = 349)	7.2 (5.4 to 9.2)	8.0 (5.9 to 10.5)	9.3 (6.5 to 13.0)[c]	9.4 (5.8 to 14.6)	7.1 (3.8 to 12.2)	NS
female (n = 275)	14.5 (10.8 to 19.0)	14.9 (10.6 to 20.3)[d]	21.9 (15.2 to 30.6)[c]	16.7 (9.1 to 28.1)	9.6 (3.8 to 19.8)	NS
first modality of dialysis						
HD (n = 511)	10.4 (8.4 to 12.7)	9.2 (7.1 to 11.8)	12.7 (9.5 to 16.6)[c]	8.7 (5.4 to 13.3)	7.3 (4.2 to 11.9)	NS
PD (n = 113)	6.0 (3.4 to 9.8)	13.2 (8.4 to 19.6)[b]	14.0 (8.2 to 22.4)[b]	24.4 (13 to 41.7)[b]	10.5 (2.8 to 26.9)	NS
Patients without DN (n = 2401)						
all patients	7.0 (6.3 to 7.7)[e]	5.1 (4.5 to 5.8)	5.0 (4.2 to 5.9)	5.6 (4.5 to 6.7)	4.8 (3.8 to 6.0)	<0.01
age categories (yr)						
18 to 64 (n = 1031)	13.3 (10.5 to 16.8)[e]	7.1 (4.9 to 9.9)	7.0 (4.9 to 9.9)	6.1 (3.5 to 9.7)	6.8 (4.1 to 10.6)	<0.01
≥65 (n = 1370)	6.3 (5.7 to 7.0)[e]	4.9 (4.2 to 5.6)	4.7 (3.9 to 5.6)	5.5 (4.4 to 6.7)	4.4 (3.3 to 5.7)	<0.01
gender						
male (n = 1543)	6.0 (5.4 to 6.8)[e]	4.7 (4.0 to 5.5)	4.9 (4.0 to 5.9)	4.7 (3.6 to 5.9)	4.5 (3.4 to 5.9)	<0.05
female (n = 858)	10.0 (8.4 to 11.8)[e]	6.4 (5.0 to 8.1)	5.3 (3.8 to 7.3)	8.4 (5.9 to 11.5)	5.7 (3.5 to 8.7)	<0.01
first modality of dialysis						
HD (n = 1987)	7.2 (6.4 to 8.0)[e]	5.2 (4.5 to 6.0)	4.8 (3.9 to 5.8)	4.7 (3.7 to 6.0)	4.5 (3.4 to 5.8)	<0.01
PD (n = 414)	6.2 (4.9 to 7.7)	4.8 (3.5 to 6.4)	5.8 (4.0 to 8.0)	9.6 (6.4 to 13.6)	6.4 (3.5 to 10.8)	NS

[a]Heterogeneity test for the five periods after first dialysis.[38]
[b]$P < 0.05$ in comparison with patient without DN–equivalent cell.
[c]$P < 0.001$ in comparison with patient without DN–equivalent cell.
[d]$P < 0.01$ in comparison with patient without DN–equivalent cell.
[e]$P < 0.05$ in comparison with other SMR in the given patient subgroup (by row).

death in transplant patients because this should be performed in incident renal transplant patients.

CONCLUSION

This study indicates that excess death in the ESRF population in comparison with the GP is large and influenced by age, by gender, and by diabetes. Mortality studies that focus on these patient subgroups should be planned.

CONCISE METHODS

Patients

All patients who lived in the Rhône–Alpes region in France and who started long-term dialysis therapy, HD or PD, between January 1, 1999, and December 31, 2003, were prospectively identified at dialysis onset. Patients who were treated by preemptive renal transplantation and patients who were undergoing temporary dialysis for acute renal failure were excluded. Incident study population consisted of 3025 new dialysis patients.

Studied Parameters at Inclusion

Age, gender, date of first dialysis, original nephropathy, and initial dialysis modality were prospectively collected from patients' medical records in the Registry of the Association Régionale des Néphrologues de Rhône–Alpes up to 2002,[36] then in the national Renal Epidemiology, and Information Network (REIN) Registry.[7]

Original nephropathies were divided in eight groups using European Renal Association and European Dialysis and Transplant Association classification[37]: VN, DN, glomerulonephritis and vasculitis, pyelonephritis and interstitial nephropathy, adult-type PKD, myeloma and light chain deposit disease and amyloid, miscellaneous, and unknown. Modality of dialysis (HD or PD) was defined as modality used at 3 mo after first dialysis or modality at dialysis onset if death occurred in the first 3 mo.

Follow-Up

Patients were followed up to death or to December 31, 2005. Follow-up was prospectively performed with the Association Régionale des Néphrologues de Rhône–Alpes Registry up to 2002,[36] then with the REIN Registry.[7] Individual data on outcome (kidney transplantation with date, death with date, and cause of death) were available for each patient. Patients who had received a transplant were followed up with the CRISTAL database of the Agence de la Biomédecine (Paris, France). Patients who were not censored at renal transplant were followed up to death or up to December 31, 2005.

Fifty-eight (2%) patients were lost to follow-up, mostly because of emigration from the Rhône–Alpes region. Observation period was 2 to 7 yr after first dialysis for each patient. Only the

first 5 yr of patient follow-up were used for analysis to ensure sufficient statistical power.

Study End Point

The study end point was death of any cause. Causes of death were divided into five categories: Cardiovascular (sudden death, myocardial infarction, cerebrovascular accident, heart failure, and peripheral vascular disease), infectious, malignancy, other known, and unknown.

Quality Control

The participation rate of dialysis centers in Rhône–Alpes was 100%. A clinical research assistant visited each dialysis center of the region to check for completeness of patient and event registration. Dialysis centers in regions that border Rhône–Alpes region were asked to provide information about patients whom they treated and who lived in Rhône–Alpes.

Statistical Analyses

Analyses included (*1*) descriptive analysis of patient baseline characteristics, events that occurred during the study period (kidney transplantation, deaths and causes of deaths), and crude survival both overall and by patient subgroups (gender, age, original nephropathy, dialysis modality); (*2*) computation of SMR to assess excess death in patients with ESRF *versus* the GP standardized for age and gender, both overall, and by patient subgroups (gender, age, original nephropathy, and initial dialysis modality).

When appropriate, univariate comparisons were done with χ^2 test or Fisher exact test for category variables and with *t* test for continuous variables. Crude survival was explored with the Kaplan-Meier method.[10]

SMR were computing using the method developed by Breslow and Day.[38] In patients with ESRF, we observed number of deaths (O_{Deaths}) by years after first dialysis, conditional on being alive at the beginning of the 1-yr period studied.

Expected number of deaths (E_{Deaths}) was given by 1-yr mortality rate tables provided by the *Institut National de la Statistique et des Etudes Economiques*. For each patient of our cohort and for each studied year after first dialysis, we were able to establish expected number of deaths for a person of the same age and gender in GP:[38]

Expected number of death for patient $i_{age,\ gender}$ = actual length of observation during the 1-yr follow-up × 1-yr mortality $rate_{age,\ gender}$

In the whole cohort and in subgroups, E_{Deaths} was the sum of expected number of death for each patient $i_{age,\ gender}$ of the studied group.[38]

We were able to calculate SMR[38]:

$$SMR = O_{Deaths}/E_{Deaths}$$

The 95% CI were calculated with Breslow and Day's formula.[38] SMR heterogeneity between years after first dialysis, in the whole cohort or in a given patient subgroup, was tested with χ^2 test for heterogeneity developed by Breslow and Day.[38] Comparison of SMR between patient subgroups was performed with χ^2 test developed by Breslow and Day[38] with stratification on age categories (18 to 44, 45 to 64, 65 to 74, 75 to 84, and >85 yr) and gender (male and female) using the Mantel-Haenszel method.[39]

When tests for heterogeneity reach a significant level ($P < 0.05$), we compared the higher SMR, usually the SMR of the first year after first RRT, with SMR of the other years pooled to gether, using the same method.[38]

Mean annual changes in SMR were estimated by Poisson regression.[40] When trends where not linear, we estimated different trends for different periods. Comparisons of mean annual changes in SMR between patient subgroups were performed by Poisson regression.[40]

All statistical analyses were performed with S-PLUS 6.0 Software Professional Release 2 (Insightful Corp., Seattle, WA). $P < 0.05$ was considered statistically significant.

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Original Article

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Poor prognosis of heart transplant patients with end-stage renal failure

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Abstract

Background. Chronic kidney disease (CKD) and end-stage renal failure (ESRF) are major complications after a heart transplant. The aim of this study is to compare survival in heart transplant (HT) *vs* non-heart transplant (non-HT) patients starting dialysis.

Methods. Survival was studied among the 539 newly dialysed patients between 1 January 1995 and 31 December 2005 in our Department. All patients were prospectively followed from the date of first dialysis up to death or 31 December 2005. Multivariate survival analysis adjusted on baseline characteristics was performed with the Cox model.

Results. There were 21 HT patients and they were younger than non-HT patients at first dialysis: 58.6 ± 11.6 *vs* 63.0 ± 16.2 years ($P = 0.09$). Calcineurin inhibitor nephrotoxicity was the main cause of ESRF in HT patients (47.6%). Crude 1, 3 and 5-year survival rates in HT and in non-HT patients were as follows: 76.2%, 57.1%, 28.6% and 79.1%, 58.7%, 46.7% ($P = 0.2$). The adjusted hazard ratio of death in HT *vs* non-HT patients was 2.27 [1.33–3.87], $P = 0.003$. Sudden death was the main cause of death in HT patients, in 33.3% *vs* 10.4% in non-HT patients ($P = 0.01$). Five HT patients benefited from renal transplant. They were all alive at the end of the study period, while one patient among the 16 remaining on dialysis survived.

Conclusion. HT patients with CKD who reached ESRF have a poor outcome after starting dialysis in comparison with other ESRF patients. Improvement in renal function management in the case of CKD is needed in these patients and non-nephrotoxic immunosuppressive regimens have to be evaluated. Renal transplant should be the ESRF treatment of choice in HT patients.

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Keywords: dialysis; end-stage renal failure; heart transplant; renal transplant; survival

Introduction

Chronic kidney disease (CKD) is one of the most important complications in heart transplant (HT) recipients [1]. Using the American Scientific Registry of Transplant Recipients, Ojo *et al*. [2] described in 2003 the natural history of renal failure in HT recipients, that the cumulative 5-year risk of developing CKD, defined as a glomerular filtration rate (GFR) < 30 ml/min/1.73 m^2 of body surface area, was 10.9%. At least 3 to 10% of HT recipients reached end-stage renal failure (ESRF) requiring chronic renal replacement therapy (RRT) during the 10-year post-transplant period [2–6].

Actually, HT recipients are at high risk of CKD because they carry cardiovascular risk factors and specific risk factors associated with renal impairment [1–3]. Risk factors for kidney injury in this population were identified both from single-centre or registry-based studies [1–12]: pretransplant GFR, post-operative acute renal failure, recipient age, presence of diabetes mellitus, hypertension and/or dyslipidaemia, smoking, hepatitis C infection and treatment with calcineurin inhibitors (CNI).

CNI that had made solid organ transplantation successful is paradoxically one of the most important aetiologic factors of CKD in HT patients [1–3]. Myers *et al*. [13,14] first reported in 1984 renal injury associated with cyclosporin A (CsA) immunosuppressive treatment.

Renal impairment and ESRF associated with HT result in an excessive risk of mortality in HT patients [1–3,9,15]. However no conclusive studies compared survival after dialysis onset in HT patients *vs* non-heart transplant (non-HT) patients [15–17].

The aim of our study is to determine if being heart transplanted is a risk factor for death after first dialysis in comparison with non-HT patients.

Materials and methods

Study design

The study design of this comparison of survival in HT patients *vs* non-HT patients entering dialysis was retrospective. With data from a previous explanatory study performed in our Department in an 8-year period [9] and using the approach of Schoenfeld and Richter [18], we were able to calculate sample sizes needed in the present study. When α risk is 0.05, study power is 0.8, hazard ratio (HR) of death between HT patients and non-HT patients is 2.2, median survival in control group (non-HT patients) is 4 years, time of recruitment is 10 years, mean follow-up time is 5 years, and ratio of non-HT patients to HT patients is 25, then sample size of HT patients cohort has to be 20.

About 50 patients per year started dialysis in our department. With an average of two HT patients staring dialysis per year, we defined a study period of 10 plus 1 years with a follow-up period of 0–11 years to respect sample size specifications.

Patients

All patients who started chronic dialysis between 1 January 1995 and 31 December 2005 in the Department of Nephrology, Dialysis and Renal Transplantation of the Lyon-Sud Academic Hospital in France were included. Patients temporarily dialysed for acute renal failure with renal function recovery were excluded. ESRF patients who benefited from pre-emptive renal transplant during this period (2 HT patients and 21 non HT patients) were excluded.

The study population consisted of 539 incident dialysed patients including 21 HT patients.

Origin of the follow-up time and study period

Patients were prospectively included at dialysis onset, i.e. haemodialysis (HD) or peritoneal dialysis (PD). The study period ended on 31 December 2005.

Studied parameters

Age, gender, date of first dialysis, original nephropathy, comorbid conditions at time of first dialysis and modality of dialysis were prospectively collected.

Modality of dialysis was the one used 3 months after the first dialysis, or the one at dialysis initiation if death occurred before the fourth month.

Original nephropathy included diabetic nephropathy, vascular nephropathy, primary and secondary glomerulonephritis (except diabetic nephropathy), polycystic kidney disease, chronic tubulo-interstitial nephritis, malformative uropathy, other causes and unknown cause.

Comorbid conditions at first dialysis included type 1 diabetes, type 2 diabetes, arterial hypertension (blood pressure >140/90 mmHg or anti-hypertensive medications), peripheral vascular disease (defined as a clinical claudication and/or a peripheral amputation and/or a peripheral artery stenosis >50%), coronary disease (angina, myocardial infarction), congestive heart failure (acute pulmonary oedema and/or left-ventricular ejection fraction <50% over an echocardiograph), cerebrovascular accident, heart transplantation, malignancy, alcohol addiction, hepatitis B or C virus infection, hepatic insufficiency (defined as a coagulation factor V < 50%), liver transplantation, HIV infection, and respiratory insufficiency (defined as need of chronic oxygenotherapy or mechanic ventilation).

Follow-up

Patients were prospectively followed-up up to death or up to 31 December 2005. Follow-up was performed with the ESRF patient registry of our Department and with the Renal Epidemiology and Information Network (REIN) registry [19]. Registration on a renal transplant waiting list was recorded. Transplanted patients were followed-up with the database of the Agence de la Biomédecine (named CRISTAL). Ten patients were lost to follow-up (1.8%) because they moved out of Rhône-Alpes region. No HT patient was lost to follow-up.

Study endpoint was death of any cause. Causes of death were pooled in six categories: sudden death, cardiovascular (myocardial infarction, cerebrovascular accident, heart failure, peripheral vascular disease), infection, malignancy, and other known and unknown causes.

Statistical analyses

Analyses included the following: (i) Descriptive analysis of patient characteristics and comorbid conditions in HT patients and non-HT patients at first dialysis; (ii) Univariate comparison of survival and causes of death; (iii) Multivariate survival analyses.

When appropriate, univariate comparisons in case-mix and tabulation were done with χ^2 test or Fisher's exact test for category variables and with Student's t-test for continuous variables. Kaplan–Meier non-parametric survival curves and Log Rank test were used to compare survival in HT and non-HT patients (univariate analysis).

In multivariate analyses, Cox proportional hazards model was used to identify patient conditions which have independent effects on probability of death after first dialysis and to quantify their size effects [20]. Study start was the date of first dialysis. The endpoint was death of any cause. Patients who benefited from renal transplantation were not right-censored in the analysis at the date of transplantation. Heart transplant state was the parameter of interest in the Cox model. Age, gender, nephropathy, comorbidities at first dialysis (as described earlier, if comorbidity was present in more than 5 patients in our cohort) and registration on a renal transplant waiting list were introduced in the model. Analysis was stratified on five periods of first dialysis (1995–96, 1997–98, 1999–2000, 2001–02, and 2003–05).

Age was modelled as continuous variable in a first model and as a polynomial variable (age, age^2 and age^3) in a second model to take into account, by both manners, the effect of age on adjusted HRs of death in other variables.

Step-by-step analysis was done with both backward and forward entrance of variables in order to analyse interactions between variables.

The validity hypothesis of the Cox model (proportional HR) was checked by the test based on Shoenfeld's residuals [21]. When a variable did not respect HR proportionality in Cox regression, we compared results of the model without the variable and the model with variable in order to observe modifications in HRs of other variables.

All statistical analyses were performed with S-PLUS 6.0 Software Professional Release 2 (© 1988–2001 Insightful Corp).

Results

Baseline characteristics

Baseline characteristics of the 539 incident dialysed patients are presented in Table 1 in the HT patient group and in the non-HT patient group. There were 21 HT patients in this cohort. Over the same period of time (1995–2005), 483 heart transplantations were performed in the Department of Heart Transplant of the Hospices Civils de Lyon. Clinical characteristics of HT patients with chronic kidney disease referred to our Department of Nephrology were described elsewhere [9].

In HT patients, causes of cardiac transplantation were ischaemic cardiomyopathy in 16 (76.2%) and dilated cardiomyopathy in 5 (23.8%). Mean time between cardiac transplantation and first dialysis was 9.1 ± 3.1 years with a median time of 9.1 years.

Patient characteristics and comorbid conditions were not equally balanced between groups. HT patients were younger ($P = 0.09$) and sex ratio was 9.5 *vs* 1.6 in non-HT patients ($P = 0.01$). Chronic tubulo-interstitial nephritis (CTIN) was over-represented in HT patients, 47.6% *vs* 6.0% in non-HT patients ($P < 0.0001$). In HT patients, CTIN was related to CNI nephrotoxicity. Type 2 diabetes and cardiovascular diseases were equally represented in both groups. No HT patient presented HBV, HCV or HIV infection, nor hepatic failure and liver transplantation.

HT patients were significantly more often treated by HD as first dialysis modality, as compared to the non-HT patient group (90.5% *vs* 66%, $P = 0.03$).

Outcome: univariate analyses

Survival assessed by Kaplan–Meier method is presented in Figure 1. HR of death in HT patients *vs* non-HT patients was 1.4 with a 95% confidence interval (95% CI) of 0.8–2.3. In univariate analysis, Log-Rank test didn't show any significant difference in survival between the two groups ($P = 0.2$). Median survival time was 33.5 months in HT patients and 50.8 months in non-HT patients.

Registration on a renal transplant waiting list was completed for 5 HT patients (23.8%) and 148 non-HT patients (28.5%), $P = 0.64$. The main reasons for renal

Table 1. Baseline characteristics of the study population at first dialysis

	HT patients ($n = 21$)	Non-HT patients ($n = 518$)
Age at ESRF: mean ± SD (years)	58.6 ± 11.6	63.0 ± 16.2
Median age at ESRF (years)	58.0	66.0
Men	19 (90.5%)	319 (61.6%)*
Original nephropathy (number, %)		
Vascular nephropathy	5 (23.8%)	120 (23.1%)
Diabetic nephropathy	0 (0.0%)	118 (22.8%)
Primary and secondary glomerulonephritis[a]	4 (19.1%)	74 (14.3%)
Polycystic kidney disease	0 (0.0%)	25 (4.8%)
Chronic tubulo-interstitial nephritis	10 (47.6%)	31 (6.0%)*
Malformative uropathy	0 (0.0%)	14 (2.7%)
Other	0 (0.0%)	59 (11.4%)
Unknown	2 (9.5%)	77 (14.9%)
Comorbidity at first dialysis (number, %)		
Type 1 diabetes	0 (0.0%)	17 (3.3%)
Type 2 diabetes	6 (28.6%)	162 (31.3%)
Arterial hypertension	20 (95.2%)	406 (78.4%)
Peripheral vascular disease	5 (23.8%)	105 (20.3%)
Coronaropathy	6 (28.6%)	134 (25.9%)
Congestive heart failure	7 (33.3%)	111 (21.4%)
Cerebrovascular accident	4 (19.1%)	67 (12.9%)
Malignancy	4 (19.1%)	76 (14.7%)
HBV infection	0 (0.0%)	12 (2.3%)
HCV infection	0 (0.0%)	15 (2.9%)
Hepatic failure	0 (0.0%)	23 (4.4%)
Liver transplantation	0 (0.0%)	9 (1.7%)
HIV infection	0 (0.0%)	6 (1.1%)
Chronic respiratory disease	1 (4.8%)	35 (6.7%)
First dialysis modality (number, %)		
Hemodialysis	19 (90.5%)	342 (66.0%)*
Peritoneal dialysis	2 (9.5%)	176 (34.0%)*

[a]Diabetic nephropathy was excluded from secondary glomerulonephritis.
*Comparison between HT and non-HT patients: $P < 0.05$.

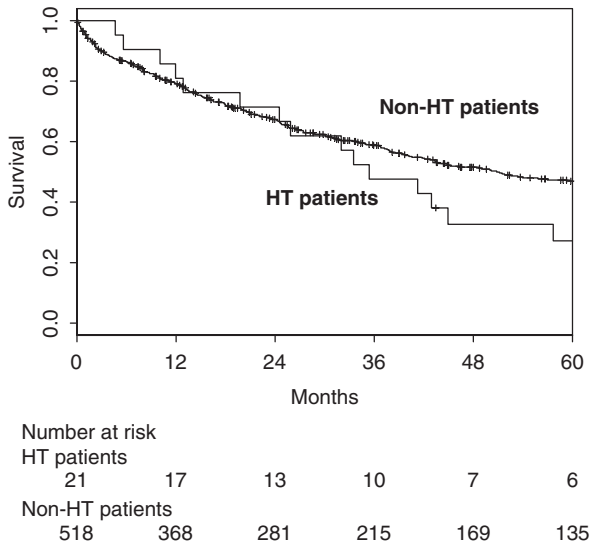

Fig. 1. Kaplan–Meier survival curves in HT patients ($n = 21$) and in non-HT patients ($n = 518$). HR: 1.4 (0.80–2.30), $P = 0.20$, univariate analysis. +: right-censored patients.

transplant contraindication in HT patients were age >70 years in three, neoplasm in four, congestive heart failure in six without indication of a second heart transplantation, and diabetes associated with at least two cardiovascular diseases in three.

Renal transplantation was performed in equivalent rates between the groups during the study period, i.e. in 5 HT patients (23.8%) and in 110 non-HT patients (21.2%).

In the HT patient group, only six patients were alive at the end of the study period, including the five renal transplanted patients. Among them, one benefited from a second heart transplantation with concomitant renal transplantation.

Living HT patients were significantly younger than dead HT patients at first dialysis, 50.1 ± 12.1 years *vs* 62.0 ± 9.9 ($P = 0.048$). They did not present peripheral vascular disease or malignancy at first dialysis.

In the HT patient group, patients contraindicated for renal transplantation ($n = 16$) presented a survival rate at 1, 3 and 5 years after first dialysis of 75%, 31.2% and 6.2%, respectively.

Causes of death

In the HT patients, causes of death were as follows: sudden death in five (33.3%), cardiovascular in three (20%), malignancy in three (20.0%) and unknown in four (26.7%). In non-HT patients, causes of death were the following: sudden death in 27 (10.4%), cardiovascular in 68 (26.2%), infection in 26 (10.0%), malignancy in 20 (7.7%), other known causes in 70 (26.9%) and unknown in 49 (18.8%).

Sudden death and malignancy were significantly over-represented as cause of death in HT patients in comparison with non-HT patients in this cohort ($P = 0.01$). We did not observe death from infectious causes in HT patients.

Survival: multivariate analyses

Because there was no significant difference in survival between HT and non-HT patients in univariate analysis, we first performed survival comparison between these groups with adjustment on age and sex. Actually, HT patients were younger than non-HT patients and sex ratios were different in these groups (Table 1 as well.). These variables are strongly associated with death and especially age may be a confounder in univariate analysis comparing survival in HT and non-HT patients. At this first step, HT was associated with a significant worse prognosis in dialysis: the age and sex adjusted HR of death in HT patients *vs* non-HT patients was 1.84 with a 95% CI of 1.10–3.06, $P = 0.02$ (result did not change if age was introduced as a polynomial in Cox regression).

Because HT was significantly associated with death in this first analysis, we conducted multivariate analysis adjusted on all baseline conditions as described in 'Materials and methods' section. Table 2 shows results of this multivariate analysis. The presented model included age as continuous variable. No change in results was observed with age introduced as polynomial. Original nephropathies were not included in the final model because of colinearity between some nephropathies and comorbid conditions (diabetes and diabetic nephropathy, cardiovascular diseases and vascular nephropathy). The first modality of dialysis variable did not have valid proportionality in HR and was not included in the final model. HRs of other variables were not modified when this variable was introduced in the Cox model.

Table 2. Adjusted HR of death and 95% CI

	HR	95% CI	*P*
Heart transplant	2.27	1.33–3.87	0.003
Age at first ESRF (+1 year)	1.05	1.04–1.07	<0.0001
Men versus women	1.06	0.82–1.37	0.65
Type 1 diabetes	1.67	0.77–3.61	0.19
Type 2 diabetes	1.12	0.85–1.46	0.42
Coronary disease	1.00	0.76–1.32	1.00
Congestive heart failure	1.47	1.10–1.96	0.009
Peripheral vascular disease	1.28	0.96–1.71	0.09
Cerebrovascular accident	1.35	0.97–1.89	0.08
Malignancy	1.03	0.76–1.40	0.86
HBV infection	1.09	0.44–2.70	0.85
HCV infection	1.78	0.84–3.77	0.13
Chronic hepatic insufficiency	2.14	1.10–4.14	0.02
Liver transplant	0.99	0.31–3.16	0.99
HIV infection	2.14	0.62–7.42	0.23
Chronic respiratory insufficiency	1.18	0.72–1.94	0.50
Registration on renal transplant waiting list	0.34	0.22–0.51	<0.0001

In this final model (Table 2), HT was significantly associated with death. Adjusted HR of death in comparison with non-HT was 2.27 with a 95%CI of 1.33–3.87 ($P = 0.003$). The following other conditions were associated with survival in this ESRF patient cohort: age, congestive heart failure, hepatic insufficiency and being registered on a renal transplant waiting list. Liver transplantation was not associated with outcome (adjusted HR: 0.99 (0.31–3.16), $P = 0.99$).

Discussion

This study demonstrates that heart transplantation is associated with a poor outcome in patients starting dialysis. To the best of our knowledge, no direct survival comparison with adjustment on baseline patients' characteristics at first dialysis is available in the literature [4,15–17]. Our study confirms trends observed in previous non-adjusted analyses both in the United Kingdom [16] and in the USA [17].

The strengths of our study are the exhaustiveness of this single-centre cohort concerning ESRF patients starting dialysis with a very low rate of loss to follow-up (1.8% of the patients), the prospective recording of the analysed data and the homogeneity of the recorded data. This HT patient cohort starting dialysis ($n = 21$) is larger than the ones of previously

published series [4,15–17]. Patient characteristics and survival in the whole cohort were comparable with data observed in the French REIN registry and in the Lorraine region in France [19,22]. Survival in HT patients of our cohort was consistent with survival of HT patients in previously published studies [4,15–17]. Those make acceptable generalization of the results of this single-centre study.

We do not include in the analysis patients who benefited from pre-emptive renal transplant as first RRT modality because they constituted a sub-group of ESRF patients with particular conditions and outcomes. In this survival analysis, patients who benefited from renal transplant were not censored at the date of transplant: the study explored survival in patients starting dialysis and then included the natural history of RRT modality management.

In unadjusted comparison, survival seemed equal in HT and in non-HT patients. Adjustment on age and sex underlined the dark prognosis of HT patients starting dialysis. The effect of being heart transplanted on survival in dialysis remained significant after adjustment on baseline patient characteristics. Probability of death after first dialysis was more than 2-fold superior in HT patients than in non-HT patients.

We introduced in regression model the variable 'being registered on renal transplant waiting list' to assess whether age and comorbid conditions, such as cardiovascular diseases and diabetes, influenced patient death or prevented patients from being waitlisted and transplanted. Not introducing this variable in the regression model only slightly influenced the HR of death in HT patients *vs* non-HT patients; 2.05 (1.22–3.44) with $P = 0.007$ [*vs* 2.27 (1.33–3.87), $P = 0.003$]. In this model (without the variable 'being registered on renal transplant waiting list'), new conditions significantly associated with death after first dialysis were type 1 diabetes, peripheral vascular disease and hepatitis C virus infection. This suggests that these last conditions were significant for not being registered on a renal transplant waiting list.

Rates of registration on renal transplant waiting list, rates of renal transplantation, and medical reasons for renal transplant contraindication did not differ in HT patients and in non-HT patients and from contraindication reasons in the general dialysed population [23].

In these HT patients, links between cardiovascular risk factors, heart failure, CKD, dialysis and accelerated atherosclerosis, are hypotheses to explain excess of death in HT patients starting dialysis beyond the role of immunosuppressive regimen [1,3,8,15–17]. It is remarkable that liver transplantation did not modify outcome in dialysis in this study.

In this cohort, ischaemic heart disease was the main cause of heart failure leading to cardiac transplantation, in about 75% of the patients. This confirms the high risk of CKD and ESRF in patients with ischaemic heart disease prior to HT that is a condition associated with ischaemic nephropathy [11]. Cardiovascular diseases and type 2 diabetes as comorbid conditions at first dialysis were equally balanced between HT and non-HT patients. Sudden death was the main cause of death in HT patients, in a significantly higher rate than in non-HT patients. HT patients contraindicated for renal transplantation presented an abysmal prognosis after first dialysis. Only one non-renal transplanted HT patient among 16 HT patients was living 5 years after first dialysis. On the other hand, HT patients selected for renal transplantation presented a higher survival rate related to their younger age and best clinical condition.

These results suggest that mechanisms beyond classical cardiovascular risk factor may be involved and/or accelerated in HT patients by ESRF treatment [8] and that transplanted myocardium may be particularly sensitive to rapid changes in ionic serum concentrations (as kalaemia) and to modifications of fluid overloads between dialysis sessions, especially in patients treated by HD. Accelerated coronary atherosclerosis, plaque rupture and uraemic cardiomyopathy could explain fatal cardiac events in this population [8]. Prospective studies focused on progression of coronary artery disease should be designed to confirm its role in mortality in HT patients undergoing dialysis therapy.

The challenge is then to improve prognosis of HT patients with CKD and ESRF. In our center, we previously observed that HT patients were late in being referred to nephrologist consultation, with an average serum creatinine of 261.5 ± 99 μmol/l and an average GFR of 32 ± 15 ml/min (Cockcroft and Gault formula) [9]. Moreover, progression from CKD to ESRF depended on renal function impairment at the first nephrologist visit [9]. Preventive measures to delay progression of renal dysfunction should be instituted at an early stage of CKD [22], when GFR is over 60 ml/min, i.e. when serum creatinine reached 137 μmol/l in men and 104 μmol/l in women [24]. Kidney protection includes [25] diet, blood-pressure and proteinuria control, use of ACE inhibitor, blood-glucose control in diabetes mellitus, dyslipidaemia treatment and smoking cessation. Control of cardiovascular risk is the cornerstone of CKD patient care. This should be applied to HT patients who are at high risk of CKD [1–3].

But one factor is specific of solid organ transplant patients as HT patients: CNI nephrotoxicity [1–3]. CsA is involved both in aetiology and in progression of CKD in these patients [1–14]. Available data comparing nephrotoxicity of CsA and tacrolimus (Tac) are contradictory [26,27]. No randomized trial is available in this field of clinical research. Similar toxicity profiles of CsA and Tac suggest that CNI-free immunosuppressive regimens are one of the keys of renal function management in HT patients [1,3]. Recent studies with mycophenolate mofetil (MMF) and sirolimus provided substantial optimistic data. In a controlled but non-randomized study, improvement in renal function was observed in HT patients in which CsA dosage was reduced after introduction of MMF, with a reduction of at least 20% of serum

creatinine in 35% of the patients in this arm [28]. Reports of a switch from CNI to MMF and sirolimus as CNI-free immunosuppressive regimen showed significant improvement in renal function without a serious adverse event, especially acute rejection [29,30]. Meiser B *et al*. [31] published in 2005 results of a pilot study where eight HT *de novo* recipients were treated with MMF, sirolimus and corticosteroids without any CNI [31]. Low rejection rate and no renal impairment were observed in a follow-up of 3–12 months after cardiac transplantation.

Our study confirms that renal transplantation is the RRT modality of choice in these ESRF patients [32]. No death was observed in HT patients who benefited from renal transplant in this cohort. Renal transplanted HT patients were clearly selected on comorbid conditions that explain in part a better survival than in non-renal transplant patients. Renal transplantation is associated with a better control of cardiovascular risk factors than dialysis therapy [33]. This decreases risk for fatal cardiovascular events, the major cause of mortality in HT patients [1,3].

Our study should be interpreted in light of few limitations. The factors of death related to being on dialysis, such as inflammation and nutritional parameters, or dialysis dose were not available for analysis. Nevertheless, age seems to be the principal confounding factor to compare survival in HT patients and in non-HT patients reaching ESRF. Adjustment on comorbid conditions and registration on a renal transplant waiting list *vs* adjustment on age and sex alone modified HR of death in HT patients *vs* non-HT in the same proportion as the adjustment on age and sex alone *vs* crude survival comparison did. Despite the fact that this study is observational by nature, and has to be interpreted with limitations of such studies, we can emphasize the strength of the association between being heart transplanted and death after first dialysis.

In conclusion, this study underlines the poor prognosis of HT patients starting dialysis in comparison with non-HT patients. It confirms that ESRF is a major complication of cardiac transplantation. CNI-free immunosuppression regimens with m-TOR inhibitors and MMF have to be studied in large randomized trials in order to assess their efficacy and safety in cardiac transplantation. Referral to nephrologists is recommended at an early stage of CKD, when GFR reaches 60 ml/min/1.73m^2, in order to slow down progression of renal dysfunction. Renal transplant has to be proposed as an RRT modality as early as possible in the case of the absence of medical contraindication, due to maximal gain of life expectancy associated with renal transplant in this population [32–34].

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Conflict of interest statement. None declared.

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ORIGINAL ARTICLE

Prediction of relapse by day 100 *BCR-ABL* quantification after allogeneic stem cell transplantation for chronic myeloid leukemia

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Chronic myeloid leukemia (CML) relapse after allogeneic stem cell transplantation (SCT) is a relatively frequent situation, which is correlated to disease status, time from diagnosis to transplant and T-cell depletion. We evaluated the potential for early minimal residual disease (MRD) *BCR-ABL* quantification to predict relapse of CML patients receiving allogeneic SCT. Minimal residual disease was analyzed by real-time quantitative reverse transcriptase-polymerase chain reaction (RQ-PCR) at day 100 (d100) in 38 patients with >1 year follow-up after conventional non-T-cell-depleted SCT. Normal ABL control values from 1724 follow-up blood samples were used to define an RQ-PCR amplifiability index and the limits of reliable use of *BCR-ABL* ratios. We then compared the 14 patients with a high-level d100 *BCR-ABL/ABL* ratio ($\geqslant 10^{-4}$) to that of the 24 patients with a negative/low-level ratio ($<10^{-4}$). Despite being comparable for all classical parameters, the incidence of relapse was significantly higher in the high MRD group (11/14 (79%)) compared to that of the low/negative MRD group (7/24 (29%)) ($P=0.009$), with d100 MRD values representing an independent risk factor of relapse and disease-free survival, but not of overall survival, in multivariate analysis. These data should facilitate risk-adapted post-transplant immunosuppression and/or tyrosine kinase inhibitor therapy based on an early evaluation of MRD.

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Introduction

Until recently, allogeneic stem cell transplantation (SCT) was considered to be the only curative treatment for patients with chronic myeloid leukemia (CML).[1–3] However, relapse, observed in 20–60% of patients, remains a major adverse outcome after SCT.[4–6] Early recognition of relapse at the molecular level may provide a window for therapeutic intervention when residual disease remains at low levels. Several studies have investigated whether there was a correlation between relapse risk and molecular *BCR-ABL* detection after SCT.[7–13] Most used qualitative polymerase chain reaction (PCR), leading to conflicting results.[7–13] It has, however, been suggested that a single positive qualitative PCR for *BCR-ABL* after SCT was associated with an increased risk of relapse.[14] More recently, Olavarria *et al*. have suggested that early (3–5 months) detection of *BCR-ABL* transcripts by real-time quantitative reverse transcriptase-polymerase chain reaction (RQ-PCR) was associated with an increased risk of relapse in CML patients following standard allogeneic SCT, whereas Lange *et al*.[16] have shown that slow reduction of RQ-PCR for *BCR-ABL* after allogeneic SCT with non-myeloablative conditioning was also associated with a higher relapse risk. Although evaluation of *BCR-ABL* kinetics is useful in individual patient management, a uniform cutoff is necessary for therapeutic stratification within prospective studies. This requires the identification of a reproducible method for the expression of *BCR-ABL* levels, particularly within multicenter trials.

Real-time quantitative reverse transcriptase-polymerase chain reaction is a rapid and sensitive method for quantification of target genes, including at minimal residual disease (MRD) levels, but consensus regarding optimal expression of normalized results has not yet been fully achieved. Raw data need to be normalized for RNA/cDNA quantity and quality and for the efficiency of reverse transcription (RT) (the 'amplifiability') by quantitation of an internal housekeeping gene control from the same cDNA.[17–19] Results then need to be expressed relative to a calibrator. Real-time quantitative reverse transcriptase-polymerase chain reaction can only be considered to be quantitative when the MRD level is within the reproducible range of the standard curve and when cDNA 'amplifiability', reflected by the cycle threshold (C_t) value of the control gene, is within acceptable limits, as excessive correction leads to erroneous results, particularly at levels of MRD below 10^{-2}. Consensus regarding the limits of correction for a given housekeeping gene is also desirable. The use of different control genes and/or different forms of data expression makes it difficult to compare data between studies. The European against Cancer (EAC) framework, after testing 14 potential control genes, concluded that the ABL gene represented an appropriate choice.[20] *ABL* levels do, however, vary between different cell types, including in leukemic blasts and cell lines and between laboratories, when this depends mainly on variable retrotranscription efficiency.

In the present study, we have tested the pertinence of *ABL* normalization on a series of 38 CML patients allografted in chronic or accelerated phase, whose MRD was analyzed by a standardized RQ-PCR technique validated by the EAC network. We show that *ABL* represents a valid housekeeping gene for normalization in CML and have identified the acceptable limits of such normalization, thus contributing to improved inter-center reproducibility. We demonstrate that *BCR-ABL/ABL*

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ratios at one early time point, 100 days after SCT (d100), is a strong independent predictive factor for relapse, thus allowing early therapeutic adjustment in allografted CML patients.

Patients and methods

Patient population

Between 1992 and 2002, 38 CML patients allografted in two Paris hospitals were selected for study according to the following criteria: CML allografted in chronic or accelerated phase; minimum of 12 months survival after SCT and RNA available around d100 (range 82–118 days) after SCT.

Clinical characteristics for these patients are summarized in Table 1. Median ages at diagnosis and at transplant were, respectively, 35.9 years (17–57) and 37 years (18–58). Median interval from diagnosis to transplant was 21 months (3.1–154.3). At the time of transplant, 34 patients (89.5%) were in chronic phase and four in accelerated phase. Most patients (36/38) received a conventional conditioning regimen (busulfan (BU)/cyclophosphamide (CY) or total body irradiation (TBI)/CY) and two received a non-myeloablative conditioning regimen (fludarabine, 6 Gy TBI and antithymocyte globulin) because of co-morbidities. Twenty-nine patients (76%) received related donor grafts and nine (24%) human leukocyte antigen (HLA)-matched unrelated donor grafts. Thirty-two patients (84%) received unmanipulated bone marrow (BM), four (11%) unmanipulated mobilized peripheral blood (PB) grafts and two (5%) received $CD34^+$ selected PB blood mobilized stem cells. Prevention of graft-versus-host disease (GVHD) was based on cyclosporine and methotrexate, with the exception of the two patients who were transplanted with selected $CD34^+$ PBSC, who received no methotrexate.

Clinical samples and RNA/cDNA preparation

Mononuclear cells were isolated by Ficoll–Hypaque density-gradient sedimentation from PB and/or BM aspirates. Cells were

Table 1 Clinical, biological and relapse characteristics of CML patients according to the results of RQ-PCR for *BCR-ABL* (MRD) measured on d100 after allogeneic SCT

n	*All 38*	*Low/negative MRD 24*	*High MRD 14*	P-*value*
Sex				
Male	23 (61%)	13 (57%)	10 (67%)	0.48[a]
Female	15 (39%)	11 (43%)	4 (33%)	
Age at diagnosis	35.9 (17–57)	36.1 (17–52)	35.6 (20–57)	0.88[b]
Age at SCT	37 (18–58)	37 (18–53)	38 (23–58)	1[b]
Interval from diagnosis to SCT (months)	21 (3.1–154.3)	16 (3.1–47.7)	29 (4.4–154.3)	0.216[b]
Disease status at SCT				
Chronic phase	34 (90%)	21 (91%)	13 (87%)	1[c]
Accelerated phase	4 (10%)	3 (9%)	1 (13%)	
Conditioning regimen				
Myeloablative	39 (95%)	23	13	1[c]
Non-myeloablative	2 (5%)	1	1	
Type of donor				
Genoidentical	29 (76%)	16 (65%)	13 (93%)	0.11[c]
Phenoidentical	9 (24%)	8 (35%)	1 (7%)	
Type of graft				
Unmanipulated BM	32 (84%)	20 (82%)	12 (87%)	0.51[c]
Unmanipulated PBSC	4 (11%)	2 (9%)	2 (13%)	
CD34+ selected PBSC	2 (5%)	2 (9%)	0	
Acute GVHD				
0–I	16 (42%)	10 (39%)	6 (47%)	1[c]
II	18 (47%)	11 (48%)	7 (47%)	
III–IV	4 (11%)	3 (13%)	1 (6%)	
Chronic GVHD				
Absence	16 (42%)	12 (52%)	4 (27%)	0.32[c]
Limited	11 (29%)	7 (26%)	4 (33%)	
Extensive	11 (29%)	5 (22%)	6 (40%)	
Relapse				
Frequency	18 (44%)	7 (29%)	11 (79%)	0.009[a]
Time after SCT (months)	26.8 (4.4–61.7)	32.6 (17.3–61.6)	23.1 (4.4–61.7)	0.27[b]
DLI for relapse	13 (72%)	7 (100%)	6 (55%)	0.48[c]

BM = bone marrow; CML = chronic myeloid leukemia; DLI = donor lymphocyte infusion; GVHD = graft-versus-host disease; MRD = minimal residual disease; RQ-PCR = real-time quantitative reverse transcriptase-polymerase chain reaction; SCT = stem cell transplantation; PBSC = peripheral blood stem cells.
Comparison between low and high MRD level groups.
[a]χ^2 test.
[b]Student's *t*-test.
[c]Fisher's exact test.

either frozen using standard techniques for later RNA extraction or used directly to prepare RNA as described previously.[21] ComplementaryDNA was prepared using EAC criteria from 1 μg RNA as described.[20,22] C_t values of samples were determined using a fixed fluorescence threshold of 0.1 for a 7700 real-time PCR machine (AppliedBiosystems, Foster City, CA, USA).

Molecular monitoring

All samples (BM or PBL) were analyzed in duplicate by RQ-PCR on an ABI 7700 (AppliedBiosystems, Foster City, CA, USA) using the EAC M-*BCR-ABL* set.[22] Divergent data were confirmed by a novel duplicate assay. Two non-template control and two non-amplifiable control were added to each assay. The threshold was fixed at 0.2.

Data expression

Two simultaneous *BCR-ABL* quantification methods were evaluated, either relative to a K562 cell line dilution series or a *BCR-ABL*/*ABL* ratio. K562 dilution series were established from 10^{-1} to 10^{-6} serial dilutions of *BCR-ABL* b3-a2-positive K562 cell line RNA from into a *BCR-ABL*-negative cell line RNA (U937). The 10^{-5} dilution of K562 corresponds to approximately 10 copies of *BCR-ABL* plasmid (data not shown). Reproducible sensitivity was at the 10^{-5} K562 dilution point (10 copies of *BCR-ABL* plasmid). *BCR-ABL* to *ABL* ratios were calculated using the difference of C_t values of ABL and BCR-ABL using a threshold of 0.1 by the following formula: $BCR-ABL/ABL = (1 + \text{PCR yield})^{(C_{t_{ABL}} - C_{t_{BCR-ABL}})}$. *BCR-ABL* and *ABL* PCR yields were evaluated by the slope of the dilution series and demonstrated the same range of efficiency, of approximately 100% (data not shown). Consequently, the formula can be simplified to: $BCR-ABL/ABL = 2^{(C_{t_{ABL}} - C_{t_{BCR-ABL}})}$.

Relapse definition

Molecular relapse was defined by increasing *BCR-ABL*/*ABL* ratios at three consecutive evaluations over a period of at least 2 months or *BCR-ABL*/*ABL* ratios above 10^{-3} at two consecutive evaluations.

Statistical analysis

ABL expression comparisons were performed using a Mann–Whitney non-parametric test. The Student *t*-test, the χ^2 test or the Fisher exact test were employed to compare the distribution of clinical characteristics between groups when appropriate. Overall survival (OS) and disease-free survival (DFS) were calculated according to Kaplan–Meier method.[23] Survival curves were compared by the log-rank test.[24] In multivariate analysis, a Cox proportional hazards model[25] was used to identify patients' characteristics that have independent effects on the probability of relapse and to quantify their size effects. Survival curves were analyzed using Prism software (GraphPad Software Inc., San Diego, CA). Statistical analyses were performed with S-PLUS 6.0 Software Professional Release 2 (Insightful Corp., Nanterre, FR).

Results

ABL *expression in CML samples*

The use of *ABL* for *BCR-ABL* normalization is potentially limited by its inclusion in the fusion transcript. We decided to evaluate the usefulness of *ABL* quantification using the EAC set in CML.[20] We first analyzed the distribution of *ABL* C_t values in 1794 follow-up (1263 CML) PB samples (Figure 1a, class interval of 0.4 C_t). The *ABL* C_t distribution peak was centered at 25.8 and corresponded to a normal distribution with a standard deviation of 1.8. We therefore used a reference *ABL* C_t value of 25.8, which was similar to values reported by the EAC from 15 distinct

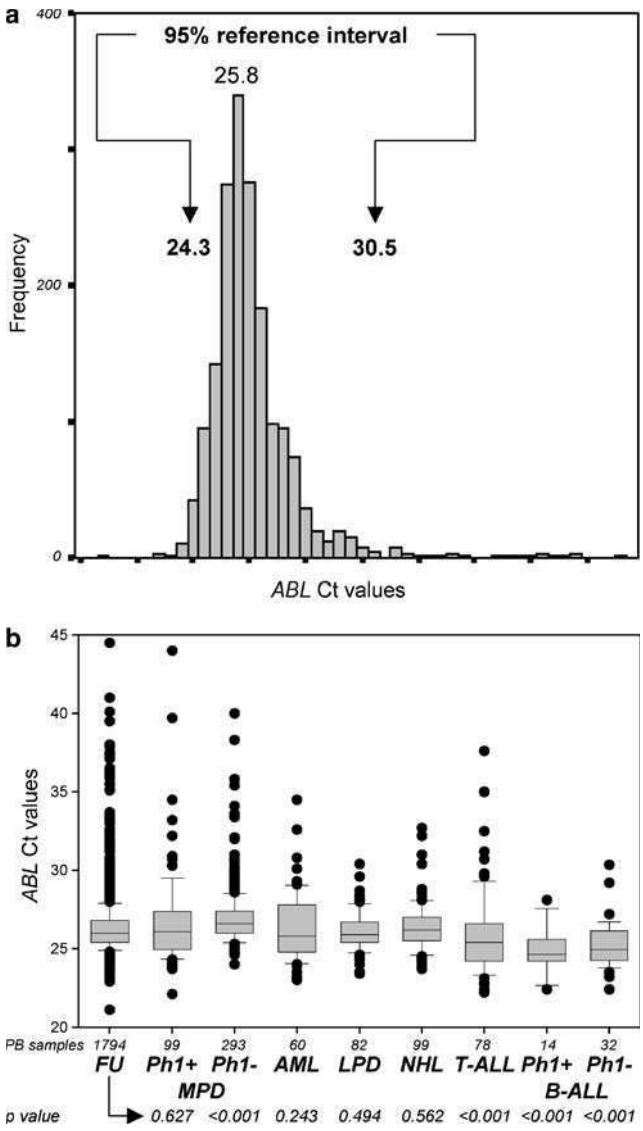

Figure 1 (**a**) Distribution of *ABL* C_t values for follow-up peripheral blood samples, with a 0.4 interval. Peak of distribution and 95% reference intervals are indicated. (**b**) Comparison of *ABL* expression in peripheral blood of follow-up to diagnostic samples. *ABL* C_t values are presented as a box-plot graph using a logarithmic scale. The boundary of the box closest to zero indicates the 25th percentile, a line within the box marks the median and the boundary of the box farthest from zero indicates the 75th percentile. Narrow horizontal bars above and below the box indicate the 90th and 10th percentiles. Outliers are indicated as dots. *P*-values of the results are indicated at the bottom using a Mann–Whitney *U*-test for an identical hypothesis. FU: follow-up; Ph1+ MPD: *BCR-ABL*-positive myeloproliferative disorders; Ph1− MPD: *BCR-ABL*-negative myeloproliferative disorders, AML: acute myeloid leukemias; LPD: lymphoproliferative disorders; NHL: non-Hodgkin's lymphomas; T-ALL: T-cell acute lymphoblastic leukemias; Ph1+ B-ALL: *BCR-ABL*-positive B-cell acute lymphoblastic leukemias; Ph1− B-ALL: *BCR-ABL*-negative B-cell acute lymphoblastic leukemias. The number of samples analyzed is indicated above each category.

laboratories (25.1 ± 1.1).[20] The 95% reference interval was defined between the 2.5 (24.3, 95% confidence interval (CI) 24.2–24.5) and 97.5 (30.5, 95% CI 29.9–31.6) centiles, to give a normal range of C_t 24.3–30.5.

We then compared PB follow-up values of *ABL* to different PB diagnostic samples for *BCR-ABL*-positive and -negative myeloproliferative disorders (MPD), *BCR-ABL*-positive and -negative B-cell acute lymphoblastic leukemias (ALL), lymphoproliferative disorders (LPD), T-cell ALL, acute myeloid leukemias and non-Hodgkin's lymphomas (Figure 1b). No significant differences were found between follow-up samples ($n = 1794$) and *BCR-ABL*-positive MPD diagnosis samples ($n = 99$; $P = 0.627$ using a Mann–Whitney assay), showing that *ABL* is a relevant housekeeping gene at diagnosis and follow-up in CML. In contrast, significantly lower *ABL* values ($P < 0.001$) were seen between follow-up samples and diagnostic T- and B-lineage acute lymphoblastic leukemias samples, *BCR-ABL*-positive B-ALL included.

cDNA and RNA quality index amplifiability index

The quality of a follow-up sample, which results from the quality of the cDNA and RNA and the efficiency of retrotranscription and amplification, should be defined in order to reflect the degree of correction and the limits of negativity. We calculated an 'amplifiability' index (AI) using the ΔC_t method and our reference value of ABL: $AI = 2^{(25.8 - C_{t_{ABL}}\ \text{sample})}$. For instance, the AI of a sample with an *ABL* C_t of 29.1 would be 0.1 meaning that the amplifiability of the cDNA is one-tenth that of an optimal cDNA. All d100 samples were AI superior to 0.1 (C_t range 23.9–29).

Comparison of calibration relative to K562 and BCR-ABL/ABL *ratios*

Although a wide variety of methods of expression of BCR-ABL results have been used, there is increasing consensus for the use of *BCR-ABL* to *ABL* ratios. We compared results expressed relative to K562 cell line dilutions to a ratio of expression between *BCR-ABL* and *ABL* on 80 PB diagnostic samples and 891 PB MRD-positive follow-up samples with an *ABL* C_t lower than 30.5 (Figure 2). The Pearson correlation coefficients were 0.980 and 0.979, respectively, demonstrating the very high redundancy of these two methods, albeit in a single center setting. We decided to use *BCR-ABL*/*ABL* ratios as they can be calculated either from plasmid calibration or from ΔC_t, and are in keeping with current trends in international standardization.

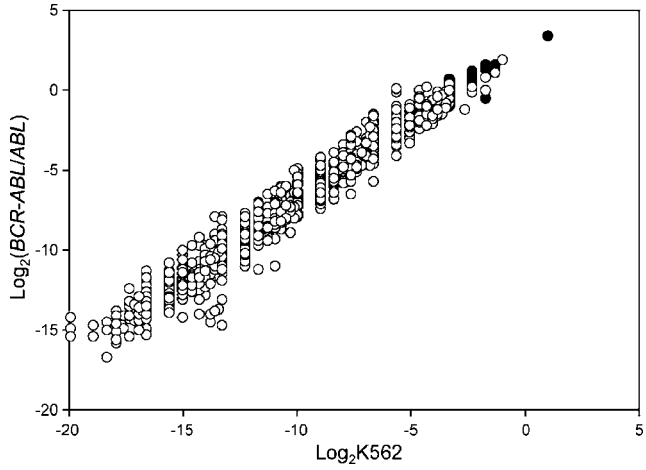

Figure 2 Correlation between calculation from the K562 cell line and *BCR-ABL/ABL* ratios. Closed circles: diagnostic samples; open circles: follow-up samples.

BCR-ABL was considered to be quantifiable if the MRD assay was above the threshold of technical sensitivity (10^{-5} of K562 or 10 plasmid copies) and if AI values were higher than 0.04 (i.e. $\frac{1}{25}$th, *ABL* $C_t < 30.5$ in our laboratory). Below this threshold, samples with detectable *BCR-ABL* transcripts were considered to be positive but not quantifiable, whereas those without detectable *BCR-ABL* transcripts were considered as un-interpretable and were excluded.

BCR-ABL RQ-PCR on d100 post-SCT

At d100 after allogeneic SCT, *BCR-ABL* was detectable by RQ-PCR in 19 of the 38 (50%) patients. Of the 19 d100 *BCR-ABL*-positive patients, five were below the threshold of 10^{-4} of *BCR-ABL*/*ABL* ratios, whereas 14 were above this threshold. Positivity above 10^{-4} was found at the same frequency in BM (6/18) and blood (8/20). Two groups of patients were identified, based on their d100 MRD level by RQ-PCR: low/negative MRD group ($< 10^{-4}$, $n = 24$) and high MRD group ($\geqslant 10^{-4}$, $n = 14$). Within the high MRD group, median MRD positivity was 7.7×10^{-4} (range: 10^{-4} to 1.2×10^{-3}). Amplifiability index values varied from 3.7 to 0.1 (*ABL* C_t 23.9–29).

Comparison of clinical and biological features between high and low/negative MRD groups

As shown in Table 1, the two groups were comparable in terms of sex distribution, age at diagnosis and at SCT and disease status at transplantation. Although the median interval from diagnosis to SCT was longer in the high MRD group, the difference was not statistically significant (median $\pm$ s.d.: 29 ± 38 compared to 16 ± 10 months, $P = 0.216$). There were no differences in conditioning regimen, type of graft or occurrence of acute and chronic GVHD between the two groups (Table 1).

d100 BCR-ABL/ABL *ratio is an independent predictive factor of relapse risk and disease-free survival but not overall survival after allogeneic stem cell transplantation*

At a median follow-up of 76.9 months after SCT (range 44.5–128.9 months), 18 of the 38 patients had undergone molecular relapse. The incidence of relapse was significantly higher in the high MRD group (11/14 (79%)) compared to that of the low/negative MRD group (7/24 (29%)) ($P = 0.009$) (Table 1 and Figure 3a). Relapse was seen in 5/6 patients with MRD high d100 results in BM, which was not different from the 6/8 relapse rate in patients with MRD high positivity in PB. Median time from SCT to relapse was shorter in the high MRD group, but the difference was not statistically significant (Table 1, $P = 0.27$). As shown in Figure 3b, the increased incidence of relapse in the high MRD level group was associated with a significantly shorter DFS compared to that of patients with low/negative MRD levels at d100 after SCT ($P = 0.0006$).

Clinical features potentially associated with relapse were then analyzed in univariate and multivariate models (Table 2). The *BCR-ABL*/*ABL* ratio at d100 was the only significant predictive factor of relapse in both univariate and multivariate analysis. The relative risk of relapse in the high MRD group compared to the low/negative MRD group was of 4.2 (95% CI, 2.2–18.1,

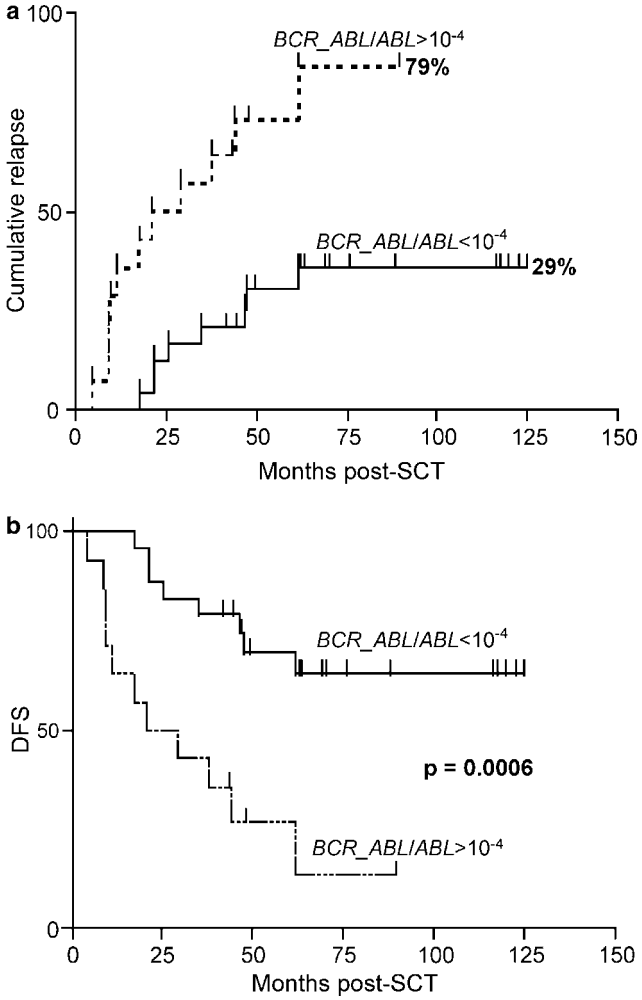

Figure 3 Probability of relapse and disease-free survival (DFS) for CML patients after allogeneic stem cell transplantation based on the results of d100 MRD. (**a**) The probability of relapse in the high MRD group (broken line) is compared to that of the low/negative MRD group (continuous line) ($P<0.01$). (**b**) Probability of DFS in the same groups ($P=0.0006$).

($P=0.0006$)) in univariate analysis and of 8.9 (95% CI, 2.5–31.6, $P=0.0007$) in multivariate analysis.

After a median follow-up of 76.9 months post-SCT, five of the 38 patients (13%) had died, two (9%) in the low/negative MRD group and three (20%) in the high MDR group (not significant). It is noteworthy that the two patients who died in the low/negative MRD group did so from chronic GVHD with no evidence of relapse, whereas the three deaths in the high MRD group had relapsed.

Univariate analysis of clinical features potentially associated with overall survival (identical to those analyzed for relapse) revealed that the d100 MRD level was not a factor influencing overall survival (Table 3). Significant predictive factors of OS in this study were the occurrence of acute GVHD of grade $\geqslant 2$ and the occurrence of chronic GVHD, in particular of extensive chronic GVHD (Table 3).

Discussion

Treatment of CML has considerably changed as the development of specific anti-*BCR-ABL* tyrosine kinase inhibitors such as imatinib mesylate (Gleevec®).[26–29] Despite this, allogeneic SCT remains the only proven curative treatment for CML[1–3] and might be the only efficient alternative for patients who develop resistance to anti-tyrosine kinase therapy.[30,31] Relapse is, however, frequent after allogeneic SCT (20–60%).[4–6] Early detection of molecular relapse before clinical relapse might improve the outcome of these patients by allowing better control of the disease by the use of immunotherapy such as low doses of

Table 2 Univariate and multivariate analysis of clinical features potentially associated with relapse in CML patients following allogeneic SCT

Variable	*Relative risk*	*95% CI*	P-*value*
Univariate model			
Age at SCT >40 years	1.2	0.48–3.15	0.67
Male sex	0.6	0.23–1.57	0.30
Accelerated phase	1.2	0.25–5.57	0.84
BM source of stem cells	1.3	0.35–4.88	0.69
Unrelated donor	0.6	0.21–1.71	0.34
Interval from diagnosis to SCT >1 year	1.2	0.46–3.12	0.71
Occurrence of acute GVHD $\geqslant 2$	0.6	0.23–1.56	0.30
Occurrence of acute GVHD $\geqslant 3$	0.4	0.13–2.22	0.39
Occurrence of extensive chronic GVHD	1.1	0.39–3.23	0.84
d100 BCR-ABL/ABL>10-4	4.2	2.19–18.14	0.0006
Multivariate model			
Age at SCT >40 years	1.6	0.42–6.17	0.48
Male sex	0.4	0.08–1.62	0.18
Accelerated phase	0.7	0.08–6.38	0.76
BM source of stem cells	1.0	0.42–2.22	0.94
Unrelated donor	0.4	0.07–2.26	0.30
Interval from diagnosis to SCT >1 year	2.0	0.49–7.65	0.34
Occurrence of acute GVHD = 2	0.7	0.34–1.64	0.46
Occurrence of acute GVHD $\geqslant 3$	0.7	0.32–1.55	0.38
Occurrence of extensive chronic GVHD	1.2	0.30–5.20	0.77
d100 BCR-ABL/ABL>10–4	8.9	2.52–31.6	0.0007

BM = bone marrow; CML = chronic myeloid leukemia; GVHD = graft-versus-host disease; SCT = stem cell transplantation.

Table 3 Univariate analysis of clinical features potentially associated with overall survival in CML patients following SCT

Variable	*Relative risk*	*95% CI*	P-*value*
Age at SCT >40 years	2.1	0.36–12.6	0.41
Male sex	5.0	0.97–33.7	0.05
Accelerated phase	0	0.02–5.27	0.43
BM source of stem cells	1.9	0.29–36.5	0.33
Unrelated donor	3.3	0.51–62.6	0.16
Interval from diagnosis to SCT >1 year	1.1	0.19–6.69	0.89
Occurrence of acute GVHD $\geqslant 2$	5.4	1.06–36.1	0.04
Occurrence of acute GVHD $\geqslant 3$	6.1	1.57–562.8	0.02
Occurrence of chronic GVHD	5.3	1.05–35.9	0.04
Occurrence of extensive chronic GVHD	10.7	2.0–102.4	0.008
d100 BCR-ABL/ABL >10-4	2.7	0.47–18.26	0.25
Relapse	1.6	0.27–9.02	0.62
DLI	0.4	0.08–2.79	0.40

BM = bone marrow; CML = chronic myeloid leukemia; DLI = donor lymphocyte infusion; SCT = stem cell transplantation.

donor lymphocyte infusion (DLI) or, in chemosensitive patients, by the use of tyrosine kinase inhibitors.

Correlation of *BCR-ABL* transcript levels with the risk of relapse give conflicting results.[7–18] To our knowledge, the only two published quantitative studies showed that detectable *BCR-ABL* within the first 3–5 months following allogeneic SCT was associated with a higher relapse rate.[15,18] None allowed the distinction of clear patient subgroups based on a *BCR-ABL* RQ-PCR level at one precise time point post-SCT. Our study confirms the results of the aforementioned quantitative series, but also shows that the result of d100 *BCR-ABL* RQ-PCR is the only significant factor predictive of relapse in both univariate and multivariate analyses when compared to classical predictive factors of relapse such as time from diagnosis to transplant, disease status at transplant and use of a T-cell-depleted graft.[32–34] The absence of predictive value of these factors in our study is probably explained by the low number of patients, thus emphasizing the predictive power of d100 *BCR-ABL* MRD. We therefore suggest that d100 *BCR-ABL* RQ-PCR values above 10^{-4} should lead to closer molecular monitoring and early treatment of relapse by either low doses of DLI or tyrosine kinase inhibitors. Alternatively, d100 values could be used to randomize patients to 'prophylactic' DLI or use of DLI on confirmed molecular relapse, as defined above. It is to be noted that these data were generated from ficolled mononuclear cells of both blood and BM origin. The proportion of positive samples and of relapsing patients did not differ with the type of sample. As current recommendations are increasingly based on analysis of red cell-depleted un-ficolled samples, it will be important to determine whether such d100 samples have comparable prognostic significance.

Therapeutic stratification in multicenter studies based on a single time point implies reproducible uniform expression of results. There is increasing consensus for expression of *BCR-ABL* results as a *BCR-ABL* ratio, rather than relative to a cell line or plasmid standard curve. This avoids the limitations of expressing results relative to cell lines, which can vary between laboratories and which are not available for many RQ-PCR targets. The use of plasmid copy numbers for expression of individual patient values is unsatisfactory, as copy numbers vary between laboratories for a given target unless fully standardized, complicating interpretation of results. They also represent a contamination risk and their amplifiability reflects only the PCR step and not the efficacy of retrotranscription, when most RQ-PCR variability arises. Although we have demonstrated a very tight correlation between quantification relative to the K562 cell line and BCR-ABL ratios, it should be emphasized that this is in a single centre setting, and it is likely that BCR-ABL ratios will be easier to standardize in a multicenter setting than expression relative to either cell lines or plasmids. The reliability of *BCR-ABL/ABL* ratios is, however, dependent on the RNA quality, as excessive correction can lead to decreased reproducibility, particularly for low-level positivity around the 10^{-4} levels that are increasingly used for therapeutic stratification. It is also important that prescribing clinicians are aware of this. We therefore propose a simple application of *ABL* values (the amplifiablity index or AI) as a method of expressing sample quality/amplifiability to prescribing clinicians, of identifying reasonable limits for correcting target quantification and for assessing inter-laboratory variability in Q-PCR and retrotranscription efficiency. The AI can easily be calculated within each diagnostic laboratory from the normal distribution of *ABL* values either for all samples or, after exclusion of diagnostic samples in order to avoid cases with low C_t *ABL* values, as demonstrated here. These are essentially restricted to ALL, when they are significantly lower than both diverse follow-up and diagnostic CML values. We have set the limits for an acceptable AI at 0.04 ($\frac{1}{25}$th of the median ABL value or $C_t < 30.5$ in our laboratory). It will be interesting to evaluate variability in AI range, both within laboratories using EAC standardized protocols, and those using different ABL amplification primers and RQ-PCR techniques.

Interestingly, although not statistically significant because of low numbers, only six of the 11 patients who relapsed in the high MRD group benefited from DLI compared to all seven of the relapsed patients in the low/negative MRD group. This was owing to more contraindications to DLI because of severe GVHD in the high MRD group. This observation reinforces the relevance of d100 MRD quantification in CML after allograft not only for the identification of patients at a higher risk of relapse but potentially also for those with a higher risk of resistance to immunotherapeutic intervention because of resistance and/or escape from CTL cytotoxicity.

Despite its high correlation with relapse, d100 MRD was not predictive of survival in this study. The high sensitivity of CML cells to immunointervention with DLI and/or to tyrosine kinase inhibitors probably explains the low mortality observed in our series; 2/24 (8.3%) and 3/14 (21.4%) in the low and high MRD groups, respectively, NS. All relapsing patients treated with either DLI and/or imatinib mesylate achieved complete remission. It is, however, noteworthy that the two patients who died in the low MRD group did so from GVHD incomplete remission, whereas the three patients who died in the high MRD group did so from evolving disease.

In conclusion, single-point *BCR-ABL/ABL* d100 ratios allowed identification of distinct CML patient subgroups following allograft, with local *ABL* normal ranges defining the limits of reliable use of these ratios. The potential applicability of these results in a multicenter setting should be tested in a prospective manner.

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IMPACT OF FIRST DIALYSIS MODALITY ON OUTCOME OF PATIENTS CONTRAINDICATED FOR KIDNEY TRANSPLANT

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♦ ***Background:*** **We compared, in patients contraindicated for kidney transplant, outcomes between those patients who were only on hemodialysis (HD) and those who were given peritoneal dialysis (PD) as first renal replacement therapy (RRT).**

♦ ***Design:*** **Prospective, population-based cohort study of incident cases of end-stage renal disease between June 1997 and June 1999.**

♦ ***Setting:*** **A network of dialysis care: NEPHROLOR, that is, all the renal units in Lorraine, one of the 22 French administrative regions (population over 2.3 million people).**

♦ ***Participants:*** **387 patients were contraindicated for kidney transplant during the first 2 years of RRT: 284 were on HD, 103 on PD. Mean age was 67.6 ± 11.3 years for HD patients and 70.8 ± 11.4 years for PD patients ($p = 0.015$).**

♦ ***Main Outcome Measures:*** **Mortality until June 2003, hospitalization over the 2 first years of RRT, and Kidney Disease and Quality of Life Short Form (KDQOL-SF) 6 and 12 months after initiation of RRT.**

♦ ***Results:*** **HD patients were more likely to die from cardiac or cerebrovascular causes, PD from cachexia or withdrawal from dialysis. Whatever mode of RRT, the unadjusted 2-year and 5-year survival rates were similar ($p = 0.98$). The rate of total duration of hospital stay per month of RRT was similar in HD and PD groups: 2.7 ± 4.5 and 2.9 ± 4.2 days respectively ($p = 0.7$). PD was associated with better quality of life than HD. The dimensions Role limitation due to emotional function, Burden of kidney disease, and Role limitation due to physical function ranked first, second, and third for PD.**

♦ ***Conclusion:*** **In Lorraine, end-stage renal disease patients who were given PD as first-line RRT had no excess of death risk or hospitalizations, and better quality of life the first year of RRT.**

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KEY WORDS: Hemodialysis; hospitalization; mortality; health-related quality of life.

The first randomized controlled trial comparing peritoneal dialysis (PD) to hemodialysis (HD) recently suggested a long-term survival advantage for PD patients (1). Unfortunately, as only 38 patients were included rather than the 100 expected, it above all confirmed the non-feasibility of randomized controlled trials in this domain. Nevertheless, as previously published (2–8), these results reinforce the hypothesis that incident dialysis patients might benefit from starting their renal replacement therapy (RRT) on PD. On the other hand, since 2002, several publications issuing from the USA registry (9,10) or from large observational studies (11,12) have pointed out higher mortality rates in some categories of new dialysis patients starting on PD (*i.e.*, elderly diabetic women, patients with coronary artery disease).

It is currently well argued that numerous methodological biases hamper comparison of PD and HD outcomes (4,13). In observational studies, precise control of prescription and delivery of dialysis is limited and the demonstration of a causal relationship between care and outcome is not possible. Ideally, data should be extensive and collected prospectively. In this way, registries have the advantage of including large populations. However, the limited potential to control for possible confounding limits the clinical relevance of results. For example, underreporting of comorbid conditions in the registry may produce false results (14).

Other limitations can be seen in previous studies comparing modes of dialysis. For instance, most published studies ignored outcomes during the first 3 months of dialysis. However, a recent study (15) demonstrated that, for incident dialysis patients, this period is critical in terms of choice of dialysis modality and mortality. On the other hand, due to differences in patients and health

care systems between countries, it is questionable that studies can be generalized (16). Finally, as survival is not the only applicable outcome, it is equally important to consider also hospitalizations and health-related quality of life (QoL). Recent and valid comparisons of these outcomes in incident cohorts are rare (17–21).

From 1997 to 1999, nearly 100% of the patients starting RRT in one French administrative region were assembled in a prospective study and followed until June 2003 (15). This representative sample offers a unique opportunity to compare, with some reliability and consistency, survival, hospitalization, and QoL by dialysis modality. As French nephrologists do not ration access to RRT, they faced a rapid increase in patients contraindicated for kidney transplant because of numerous comorbidities. At the same time, PD effectiveness in elderly patients is still debated. Therefore, we focused on outcome in this population.

PATIENTS AND METHODS

SETTING

Lorraine, one of the 22 administrative regions of metropolitan France, is a region in north eastern France with an urban and rural population reaching 2306 827 inhabitants, according to the 1999 census. The 13 for-profit and not-for-profit nephrology units operating in Lorraine agreed to participate in the study.

INCLUSION CRITERIA AND DATA COLLECTION

EPIREL (EPidémiologie de l'Insuffisance REnale chronique terminale en Lorraine, Epidemiology of end-stage chronic renal failure in Lorraine) was a prospective inception cohort designed to measure the impact of nephrology referral on outcome after the start of RRT (15). All consecutive patients with end-stage renal disease (ESRD) living in Lorraine for at least 3 months, who began RRT between 15 June 1997 and 14 June 1999, were included in the study. In compliance with French legal regulations, general information was given to patients without individual consent. Patients with acute reversible renal failure and patients returning to dialysis following kidney graft failure were not included. All in all, an external audit established that 98.2% of incident ESRD patients starting RRT in the 13 Lorraine facilities during the study period were included. Concurrently, there were 37 patients from Lorraine who started RRT in the neighboring regions.

The detailed protocol of EPIREL has been described elsewhere (15). Data on pre-ESRD medical history and care were collected at inclusion. Data concerning clinical and biological assessment were recorded prospectively using standardized questionnaires at onset of RRT and 6, 12, and 24 months later. During the first 2 years of RRT, reasons for hospital admissions, length of hospital stay, change of RRT modality, survival status, and cause of death were prospectively recorded. Finally, all patients were also requested to fill out Kidney Disease and Quality of Life Short Form (KDQOL-SF) (22) questionnaires when starting RRT and at 6, 12, and 24 months.

For the present study, survival status and cause of death beyond the first 2 years of RRT were extracted from the Lorraine registry of ESRD patients. The follow-up for survival was then extended to 1 July 2003.

DEFINITION OF VARIABLES

Comorbid conditions were considered present if the patient's medical history included clinically significant non-renal diseases (15). The Charlson Comorbidity Index was adapted to take into account the burden of comorbid conditions (23,24). Each patient received a score of 2 for moderate or severe renal disease. A score of 1 was assigned for coronary artery disease, congestive heart failure, peripheral vascular disease, cerebrovascular disease, pulmonary disease, and liver disease, and a score of 2 for diabetes with end-organ damage and for malignancy. Presence of AIDS was scored 6. Age was not added to the comorbidity score. Dementia, connective tissue disorder, peptic ulcer disease, severe liver disease, hemiplegia, and metastatic solid tumor were not taken into account for scoring due to the lack of sufficiently reliable data. Since these diseases occur with relatively low frequency in ESRD patients, the impact on the comorbidity index is likely small.

Patients who were confined to a wheelchair or were bedridden, or who had mild difficulty with activities of daily living due to decreased visual acuity, or who had significant hearing loss were considered to have physical impairment of ambulation, vision, or hearing, respectively.

The date of first visit to a nephrologist and the date when regular RRT began were recorded. Referral to a nephrologist was categorized as absent (<1 month), late (1 – 3 months), middle (4 – 12 months), and early (≥1 year). Initiation of RRT was considered to have been planned if the patient had an arteriovenous fistula/graft or a Tenckhoff catheter ready for use at the first RRT session. If the first RRT session was performed in an emergency setting due to pulmonary fluid overload, hyperkalemia, severe acidosis, anemia with angina pectoris, pericarditis, or uremic stupor, RRT was considered to have begun in life-threatening circumstances.

STUDY POPULATION

The EPIREL cohort included 508 patients. For the present study, we excluded 23 patients: 6 for age under 15 years, 11 who had a kidney transplant as first RRT, and 6 for late restoration of renal function.

Medical check-up for kidney transplantation and dialysis organization were done simultaneously. During the first 2 years of the study, 98 patients were placed on the waiting list for kidney transplantation. At start of RRT, compared to the 387 others, they were significantly younger (42.6 ± 14 vs 68.5 ± 11, $p < 0.0001$), had higher serum albumin (3.6 ± 7 vs 3.3 ± 7 g/dL, $p = 0.002$), and lower prevalence of comorbid conditions, especially cardiovascular disease (11.2% vs 62%, $p < 0.0001$) and diabetes (10.2% vs 38.5%, $p < 0.0001$). In addition, as Lorraine has a relatively high rate of graft supply, kidney transplantation occurred after an average of 6 months after the patient was placed on the waiting list. Moreover, the choice of dialysis modality and patient perception of care are influenced by the waiting list procedure (17). Finally, only 1 patient of this subgroup died during follow-up. To avoid confusing biases related to this significant heterogeneity, we decided not to include these 98 patients in the present comparison of HD and PD outcomes.

Initiation of RRT was planned in 163 patients. For these patients, the first modality was considered the modality used the first day of RRT, that is, HD in 93 patients and PD in 70.

A total of 224 patients had unplanned initiation of RRT. We considered an intentional and voluntary switch from HD to PD in unplanned RRT might be organized most often during the first 3 months of RRT. Using this definition, after a mean of 25.1 days (minimum 4, maximum 52) after the start of RRT, 33 (14.7%) unplanned HD patients were switched to PD, which was then considered the first modality. For the 191 other unplanned RRTs, the first modality was HD. The flow chart presented in Figure 1 describes the respective changes occurring in the HD and PD groups during the first 2 years of RRT.

Ten patients were registered on the waiting list more than 2 years after the start of RRT. They were included in the comparison. The 7 who received a kidney transplant were censored at the day of transplantation.

PRESCRIPTION AND DELIVERY OF PD AND HD

We compared modality choice and the adequacy that was achieved in routine practice in a global network of dialysis care (*i.e.*, the "real world") rather than what could ideally be achieved (*i.e.*, efficacy). It is important

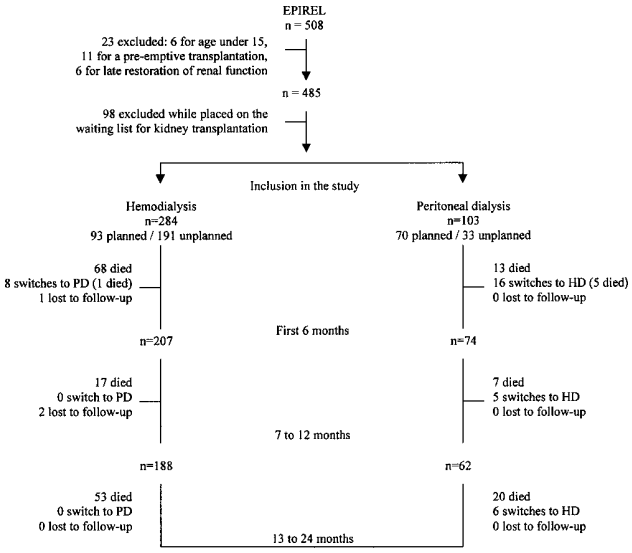

Figure 1 — Patient flow during the first 2 years of the study. EPIREL = EPidémiologie de l'Insuffisance REnale chronique terminale en Lorraine; PD = peritoneal dialysis; HD = hemodialysis.

to note that French PD patients unable to perform PD themselves can be assigned a nurse paid by the health care system for home delivery of PD. Therefore, even older and disabled patients can benefit from home PD. For HD patients, the number of hours weekly and frequency (≥3 vs ≤2 times/week) were, respectively, 13.6 ± 3.1 hours and 92% at 6 months, and 13.9 ± 3.8 hours and 95.1% at 12 months. Kt/V was not recorded in EPIREL; however, in a previous study performed in the same region in 1995 (25), Kt/V was 1.4 ± 0.5. The adequacy targets for PD patients were a weekly Kt/V of 2.0 and a weekly creatinine clearance of 60 L/week per 1.73 m^2. In our patients on continuous ambulatory PD, mean dialysate volume per day was 6.9 ± 1.4 L at 6 months and 7 ± 1.6 L at 12 months. If necessary, automated PD was readily used to reach targets.

STATISTICAL ANALYSIS

We compared, first, baseline characteristics at initiation of RRT; second, survival status and causes of death; third, hospitalizations during the first 2 years of RRT; fourth, Qol. We performed intention-to-treat analysis, because it is the method of choice for treatment comparisons, to reflect the strategy to start with a particular RRT modality. In this way, treatment-received analysis was performed in second instance, because selective dropout in the PD group of those not doing well on PD will favor PD in this type of analysis.

Chi-square, Kruskal–Wallis, t-tests, Kaplan–Meier analysis, and log-rank test were used as appropriate.

For survival comparison, multivariate analysis could not be performed over the entire period of follow-up due to temporary non-proportionality during the first 90 days compared with the post-90-day period (15), which is a violation of the basic hypothesis of the Cox proportional hazards model. As a result, we performed multivariate analyses on 327 patients who survived after the first trimester. Covariates associated with death in unadjusted analyses were included in the multivariable model.

In treatment-received analyses, HD and PD groups were defined according to the first modality but, in case of switch to the other modality, patient follow-up was censored 2 months after this event (Figure 1). To determine the contribution of potential confounders to the relative risk of death in PD versus HD patients, we constructed a series of separate Cox proportional hazards models in which we sequentially adjusted for risk factors. In order to respect Cox model assumption, we divided follow-up after the first day of RRT into 3 discrete time intervals: first and second semesters, and second year. Covariates measured at the beginning of each period associated with death in unadjusted analyses were included in multivariable models.

Quality of life was compared at start of RRT and at the end of the first and second semesters. We could not compare QoL at 24 months because fewer than 30 PD patients filled out the questionnaires. Multivariate analysis was used for analysis of variance and covariance. All models were adjusted for the covariates age, gender, comorbidity index, and first dialysis session (planned vs unplanned).

All analyses were performed with SAS software (v8.2; SAS Institute, Cary, North Carolina, USA).

RESULTS

Of 508 patients enrolled in EPIREL, 387 met the eligibility requirements for this analysis. According to selection criteria, 284 were on HD and 103 were on PD (Figure 1). A total of 6 (1.6%) patients were lost to follow-up, 3 in the first 2 years of RRT, the other 3 after this period.

BASELINE CHARACTERISTICS

Mean age was 67.6 ± 11.3 years for HD patients versus 70.8 ± 11.4 years for PD ($p = 0.015$). At start of RRT, compared with their HD counterparts, PD patients were more likely to have a planned first dialysis session, less likely to start RRT in life-threatening circumstances, and less likely to have physical impairment of ambulation (Table 1).

TABLE 1
Baseline Characteristics by First Dialysis Modality
(Intention-to-Treat Analysis)

	HD (*n*=284)		PD (*n*=103)		
	N	%	*N*	%	*p* Value
Age					
<65 yr	85	29.9	21	20.4	
≥65 and <74	123	43.3	40	38.8	0.020
≥75	76	26.8	42	40.8	
Gender male	170	59.9	58	56.3	0.530
Family support: not alone	211	74.3	75	72.8	0.977
Attributed cause of renal failure					
Glomerulonephritis	34	12.0	7	6.8	
Hypertension	48	16.9	17	16.5	0.509
Diabetes mellitus	88	31.0	33	32.0	
Other or unknown	114	40.1	46	44.7	
Referral to a nephrologist					
Early (≥1 year)	149	52.5	51	49.5	
Middle (4–12 months)	40	14	16	15.5	0.607
Late (1–3 months)	24	8.5	13	12.7	
Absent (<1)	71	25.0	23	22.3	
First dialysis session planned	93	32.8	70	68.0	<0.0001
No life-threatening circumstances	128	45.1	62	60.2	0.008
Creatinine clearance					
≥10 mL/minute	120	42.3	35	34.0	
≥7 and <10	86	30.3	34	33.0	0.402
<7	70	24.6	29	28.2	
Body-mass index					
<20 kg/m²	40	14.1	14	13.6	
≥20 and <30	175	61.6	74	71.8	0.103
≥30	69	24.3	15	14.6	
Albumin					
≥3.5 g/dL	104	36.6	37	35.9	
≥3 and <3.5	64	22.5	28	27.2	0.575
<3	65	22.9	20	19.4	
Hemoglobin ≥11 g/dL	67	23.7	26	25.2	0.736
Comorbidity index					
Low (≤3)	86	30.3	38	36.9	
Moderate (4–5)	115	40.5	43	41.8	0.248
High (≥6)	83	29.2	22	21.2	
Coronary artery disease: Yes	101	35.6	45	43.7	0.145
Congestive heart failure: Yes	106	37.3	33	32.0	0.338
Peripheral artery disease: Yes	110	38.7	31	30.1	0.118
Cerebrovascular disease: Yes	45	15.9	23	22.3	0.138
Diabetes: Yes	111	39.1	38	36.9	0.695
Physical impairment of					
Ambulation: Yes	59	20.8	12	11.7	0.040
Vision: Yes	100	35.2	36	35.0	0.962
Hearing: Yes	21	7.4	11	10.7	0.299

HD = hemodialysis; PD = peritoneal dialysis.

CAUSE OF DEATH AND SURVIVAL

Extending beyond the first 2 years, mean total follow-up was 2.47 years (maximum 6). A total of 270 patients died; 194 (68.5%) benefited only from HD and 76

(72.1%) experienced PD as part of RRT. Hemodialysis patients were more likely to die from cardiac or cerebrovascular causes; patients who had PD were more likely to die from cachexia or withdrawal from dialysis (Table 2).

Comparison of survival curves did not demonstrate any difference between patients who experienced PD as part of RRT and those who benefited only from HD (p = 0.98) (Figure 2). The unadjusted 2-year and 5-year survival rates were 55% and 25% respectively. In the intention-to-treat analysis of survival of patients who survived beyond the first trimester of RRT, the unadjusted relative risk (RR) of death in patients who started on PD versus patients who started on HD was not statistically significant: 1.07 [95% confidence interval (CI), 0.80 – 1.44]. Adjusting for age, comorbidity index, physical impairment of ambulation, albumin level, condition of initiation (planned vs unplanned), and body mass index increased RR to 1.10 (95% CI, 0.79 – 1.51).

Treatment-received analyses of survival of the whole cohort did not demonstrate different results. During the first semester, the unadjusted RR of death in PD patients versus HD patients was not statistically significant: 0.68 (95% CI, 0.40 – 1.14). Adjusting for the condition of initiation, life-threatening circumstances (absent vs present), and physical impairment of ambulation increased RR to 1.06 (95% CI, 0.60 – 1.81), 0.81 (95% CI, 0.48 – 1.36), and 0.75 (95% CI, 0.44 – 1.26), respectively. Additional adjustments for age (<65 years, ≥65 and <74, ≥74) and body mass index (≥20 kg/m^2 and <30, ≥30, <20) reduced the RR to 0.62 (95% CI, 0.36 – 1.04) and 0.67 (95% CI, 0.40 – 1.13) respectively. Simultaneous adjustment for all the above covariates increased RR of death to 0.95 (95% CI, 0.55 – 1.64). None of the other covariates was significantly associated with death in unadjusted analysis.

During the second semester, the unadjusted RR of death in PD patients versus HD patients was not statistically significant: 1.17 (95% CI, 0.48 – 2.82). Adjustment for the covariates serum albumin (≥3.5 g/dL, ≥3 and <3.5, <3) reduced RR to 1.10 (95% CI, 0.33 – 3.60). None of the other covariates was significantly associated with death in unadjusted analysis.

During the second year, the unadjusted RR of death in PD patients versus HD patients was not statistically significant: 1.35 (95% CI, 0.80 – 2.25). Adjustment for age reduced RR to 1.19 (95% CI, 0.70 – 2.00). Adjustment for serum albumin reduced RR to 0.99 (95% CI, 0.53 – 1.83). None of the other covariates was significantly associated with death in unadjusted analysis.

TABLE 2
Attributed Causes of Death by First Dialysis Modality (Intention-to-Treat Analysis) (p = 0.0004)

	HD (Total=194)		PD (Total=76)	
	N	%	*N*	%
Cardiac	62	32.0	14	18.4
Cerebrovascular	28	14.4	6	7.9
Infection	33	17.0	13	17.1
Malignancy	20	10.3	2	2.6
Cachexia	10	5.2	14	18.5
Withdrawal from dialysis	12	6.2	9	11.8
Other and unknown	29	14.9	18	23.7

HD = hemodialysis; PD = peritoneal dialysis.

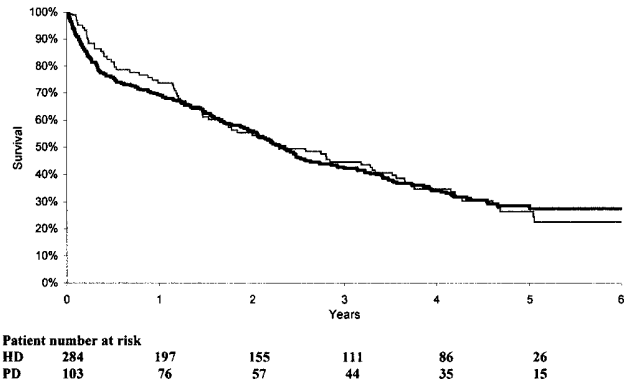

Figure 2 — Kaplan–Meier cumulative survival curves in patients who benefited only from hemodialysis (HD; heavy line) and those who experienced peritoneal dialysis (PD; light line) as part of renal replacement therapy (p = 0.98).

HOSPITALIZATION

The length of the first stay in hospital was similar in HD and PD: 23.8 ± 26.6 and 24.3 ± 16.1 days respectively (p = 0.8). During the first 2 years of RRT, the rate of hospital admissions per month of RRT was 0.26 ± 0.4 for patients who benefited only from HD and 0.24 ± 0.3 for those who experienced PD as part of RRT (p = 0.6). Likewise, the rate of total duration of hospital stay per month of RRT was similar in HD and PD: 2.7 ± 4.5 and 2.9 ± 4.2 days respectively (p = 0.7). Hemodialysis patients were admitted more often for cardiovascular (17.6% in HD vs 13.8% in PD), infectious, and diabetic reasons; PD patients were more likely to be admitted to hospital for reasons related to RRT (Table 3).

HEALTH-RELATED QoL

At start of RRT, 321 (82.9%) patients filled out QoL questionnaires. Baseline QoL was not statistically different in any dimension in the HD versus the PD groups.

TABLE 3
Attributed Causes of Hospital Admission by First Dialysis Modality During the First Two Years of Kidney Replacement Therapy (Intention-to-Treat Analysis) (p=0.0047)

	HD (T=760)		PD (T=288)	
	N	%	*N*	%
Dialysis-related hospitalization	284	37.4	126	43.8
Bacterial infection not related to dialysis	78	10.3	19	6.6
Coronary artery disease	38	5.0	3	1.0
Arrhythmia and conduction problem	15	2.0	10	3.5
Congestive heart failure	10	1.3	3	1.0
Peripheral vascular disease	50	6.6	20	6.9
Cerebrovascular disease	21	2.7	4	1.4
Diabetes mellitus	21	2.7	3	1.0
Malignancy	20	2.6	2	0.7
Cachexia	21	2.7	10	3.5
Other causes	202	26.7	88	30.6

HD = hemodialysis; T = total; PD = peritoneal dialysis.

Six and 12 months after the start of RRT, patients who experienced PD had statistically significantly higher scores in 8 of the 17 dimensions, particularly Role limitation due to emotional function, Burden of kidney disease, and Role limitation due to physical function (Table 4).

DISCUSSION

Our study of ESRD patients contraindicated for kidney transplantation during the first 2 years of RRT suggests that, compared to patients who were only on HD, those who were given PD at initiation of RRT had no excess of hospitalization or risk of death, and better QoL through the first year of RRT. Considering the effectiveness of dialysis prescription and delivery as a whole, our observational study is likely to provide valid insight into the "real world" of the impact of dialysis modality on outcome. First, we focused on the global Lorraine network of dialysis care. In this way, a rate of nearly 100% of potential inclusion was achieved, leading to very good control of selection bias. Second, incident ESRD patients were included on the first day of RRT. Pre-ESRD care was immediately extracted from charts, then deaths in the first 90 days, all modality switches, and facilities' interactions were prospectively noted. Consequently, a bias of misclassification for modality was unlikely. Third, the percentage of patients lost to follow-up was very low (1.6%).

Treatment crossover is frequent in RRT. When outcomes are used to make assumptions about the quality of RRT modalities, the presence of a valid causal linkage between respective modality and outcome signifies only that it is possible to achieve certain outcomes under specified conditions. It does not mean that the outcomes observed in any given situation have actually been produced by the preceding processes. This problem has been defined as "attributional validity" (26), which depends on the prior establishment of a causal linkage between the modality and the outcome on scientific grounds. Unfortunately, the only randomized controlled trial comparing HD and PD failed to enroll the required sample of ESRD patients because the majority of incident ESRD patients declined random assignment to HD or PD (1). Due to unachievable control of crossover, observational studies may not be the proper solution to substitute for randomized controlled trials. However, EPIREL, which included all incident ESRD patients in a population-based network of RRT, represents the strongest feasible study design (*i.e.*, observational study with adjustment for potential confounders) for answering the question.

The EPIREL study demonstrated that the presence of an emergency first dialysis was independently associated with the risk of not being placed on the waiting list for transplant (15). As established in a previous study (17), transplant candidates were highly different from noncandidates. Because we expected that conventional adjustments might not entirely control multifaceted variations in somatic and psychological health, patients placed on the waiting list were not included. As a result, the prevalence of an unplanned first dialysis session, which is associated with poor outcome, was increased (15). On the other hand, in the French health care system, ESRD patients unable to perform PD exchanges themselves could benefit from home nurse care. Consequently, compared with other studies (2,3,5,7,8,10–12), EPIREL had a very high proportion of elderly patients placed on PD. Nevertheless, outcomes were not worse.

In our study, the unadjusted 2-year and 5-year survival rates were 55% and 25% respectively. Peritoneal dialysis patients who were unlikely to be transplanted and were on dialysis for life did not demonstrate any excess of risk of death. One previous study included only ESRD patients >65 years at start of RRT (11). Unlike our findings, that study suggested higher mortality in elderly patients on PD. However, in that study, Winkelmayer performed a retrospective analysis in patients treated before DOQI guidelines were promulgated and reported a huge 90-day death rate (30%). Other studies enrolled patients after a period of 30 – 180 days after start of RRT (3,5,7,8,10,12). The mean age of these cohorts was far below that of EPIREL patients. In the Lombardy registry, as in our study, PD patients were significantly older

TABLE 4
Health-Related Quality of Life (QoL) in Hemodialysis (HD) Versus Peritoneal Dialysis (PD) Patients (Intention-to-Treat Analysis)

		Day 0[a]	6 months[a]	12 months[a]
Physical and mental QoL (SF-36)				
Physical functioning	HD	40.0	42.9	43.3
	PD	42.0	48.5	35.1
Role limitation due to physical function	HD	12.2	24.3[b]	21.4[b]
	PD	13.9	36.7	35.1
Bodily pain	HD	43.0	49.7[c]	46.1[b]
	PD	44.5	59.2	55.2
General health	HD	38.1	40.5[b]	44.1
	PD	39.6	46.8	44.9
Vitality	HD	30.1	35.4[b]	35.3
	PD	30.8	42.1	37.7
Social functioning	HD	55.7	62.4	60.5
	PD	53.4	63.0	62.9
Role limitation due to emotional function	HD	18.9	26.3[c]	27.4[b]
	PD	17.3	44.6	48.3
Mental health	HD	47.7	55.7	52.1
	PD	47.3	58.0	58.3
Kidney disease component summary (KDQOL)				
Symptoms/problems	HD	65.7	68.8[c]	66.9[c]
	PD	68.0	74.8	75.0
Effects of kidney disease on daily life	HD	61.0	57.2[c]	55.9[b]
	PD	58.5	66.3	64.0
Burden of kidney disease	HD	42.5	39.5[d]	38.8[c]
	PD	40.2	53.9	51.0
Work status	HD	14.5	9.5	11.0
	PD	17.0	21.3	17.3
Cognitive function	HD	63.5	66.5	65.8
	PD	63.4	71.7	71.7
Quality of social interaction	HD	79.1	77.3	78.4
	PD	77.4	79.8	80.2
Sexual function	HD	59.3	51.5	49.1[b]
	PD	53.8	56.5	70.8
Sleep	HD	53.1	55.4	54.3
	PD	53.8	58.6	60.3
Social support	HD	70.5	66.4	67.1
	PD	66.2	69.8	66.7

[a] Variance/covariance analysis. Comparison of HD and PD scores at 0, 6, and 12 months adjusted by age, gender, comorbidity index, and first dialysis session (planned vs unplanned).
[b] $p < 0.05$.
[c] $p < 0.01$.
[d] $p < 0.0001$.

than HD patients. Overall survival was better. In contrast, survival in our network was comparable with Canadian and Danish registries. In these two countries, as in Lorraine, PD patients had no excess risk of death. On the other hand, our cohort had prevalences of coronary artery disease, congestive heart failure, and diabetes (10) similar to the USA ESRD population, but we were unable to find an excess of risk of death for PD in these subgroups. Last but not least, cardiovascular causes of death were more frequent in ESRD patients who were only given HD. The question is whether PD is intrinsically superior initially. In the first 90 days of RRT, a period not studied in the USA registry, HD could cause an excess risk of cardiovascular death.

Peritoneal dialysis patients did not spend more time in the hospital than their HD counterparts. Although planned dialysis was more frequent in PD, the length of the first stay in hospital was equivalent in the two groups. During the study period, education for PD was delivered in hospital. Today, education is provided in out-of-hospital centers. This minimizes significantly the duration of the first stay in hospital for PD initiation. On the other hand, causes for hospitalization were different. Dialysis-related hospitalizations were more frequent in PD patients. Time for initial switch from HD to PD, and later a switch back, could account for this difference. Bacterial infections not related to dialysis and cardiovascular causes were more frequent in the HD group. We could assume that residual renal function, which is more prevalent in PD patients, might facilitate the elimination of inflammatory mediators and improve overall health. However, death due to cachexia was more frequent in the PD group. The fact that PD patients are older than HD patients could affect nutritional status.

We demonstrated previously that QoL at onset of RRT was related to pre-ESRD care rather than to respective dialysis modalities (27). Since 2- to 3-point improvements in QoL scores are likely to be clinically pertinent (28), the present study tends to demonstrate that PD has a very significant beneficial effect on QoL over time. We used the KDQOL questionnaire, one of the most valid disease-specific instruments for measuring QoL in ESRD patients (29). It allows for comparisons both across diseases and for specific information relevant to ESRD patients and care providers. Among previous studies, only two (17,18) involved a longitudinal comparison between incident cohorts of PD and HD patients using instruments validated for ESRD. Both suggest better QoL in HD for physical dimensions. In our study, the scores of all dimensions except Social functioning and General health were lower than in the USA and Netherlands studies. However, as these two studies were not population based and had a higher proportion of patients lost to follow-up, our study is probably closer to the "real world." Six and 12 months after the start of RRT, Role limitation due to emotional function, Burden of kidney disease, and Role limitation due to physical function were the three dimensions that ranked first, second, and third for PD. This might be a positive consequence of home nurse care for PD patients, a specific feature of care in France for ESRD. The dimension Burden of kidney disease shows that PD patients perceived dialysis as less restricting than HD. Concurrently, the dimensions Role limitation due to emotional function and Role limitation due to physical function confirm that they become more easily ready to initiate emotional or physical activities. However, dimensions related to mental QoL are similar in PD and HD patients.

In summary, our study provides a comprehensive analysis of outcomes in a French RRT care network. Initial utilization of PD did not increase death and hospitalization rates. Moreover, it was associated with higher QoL in the first year of RRT. Much like three previous studies (5,6,8), our study suggests that an approach to care including PD plus HD is effective for the treatment of ESRD patients. This evidence favors treatment strategies starting with PD.

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Original Article

A multicentre study of registration on renal transplantation waiting list of the elderly and patients with type 2 diabetes

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Abstract

Background. Studies in the USA have shown that some patients (African-Americans, women, the elderly and diabetics) were less likely to receive renal transplants. In order to identify patient characteristics modifying the likelihood of being wait-listed, we studied registration on renal transplantation waiting list (WLR) focusing on elderly (age ≥60 years) and on patients with type 2 diabetes (D2) in three departments of nephrology in the Rhône-Alpes county in France.

Methods. In a cohort of 549 patients who reached end-stage renal disease (ESRD) between 1995 and 1998 in these units, we analysed the rates of pre-transplant evaluation (PTE), the duration of PTE, the rates of exclusion from transplantation by PTE and the rates of WLR. With Cox regression model, we identified the characteristics that have independent and significant effects on the likelihood of being registered after the first renal replacement therapy (RRT).

Results. In this cohort, 185 patients (33.7%) were wait-listed by 31.03.00 and no patient ≥70 years was evaluated or registered. In univariate analysis, PTE and WLR rates were lower in the elderly (21.5 and 20.0%, respectively) than those <60 years (79.1 and 70.2%, $P < 0.001$) and in D2 (33.0 and 24.2%) than in non-D2 (65.8 and 60.6%, $P < 0.001$). The duration of PTE was longer in D2 than in non-D2 (12.7 ± 11.0 *vs* 7.5 ± 7.1 months, $P < 0.01$). Among patients excluded from PTE, more patients without relevant co-morbidities [e.g. rapidly progressive ESRD, cardiovascular disease (CVD), malignancy] were present in the elderly (≥70 years: 14.8%; 60–69 years: 17.0%; <60 years: 6.4%) and in D2 (18.0%) than in non-D2 (10.9%). The adjusted relative risks (aRR) of being wait-listed after first RRT were significantly lowered by age and D2 (aRR, 95% CI): 60–64 year olds (0.44%: 0.26–0.75), 65–69 year olds (0.07%: 0.03–0.20) and D2 (0.41%: 0.24–0.69). Other conditions associated with a lower aRR were rapidly progressive ESRD (0.21%: 0.08–0.55), CVD (0.59%: 0.36–0.94), malignancy (0.13%: 0.04–0.46) and psychosis (0.05%: 0.01–0.35).

Conclusion. Advanced age and D2 were associated with low PTE and WLR rates even after adjustment for other patient characteristics.

Keywords: elderly; end-stage renal disease; recipient selection; renal transplantation; type 2 diabetes; waiting list registration

Introduction

Renal transplantation is the most cost effective treatment of end-stage renal disease (ESRD) [1–6]. Worldwide, shortage of kidneys results in the inability to provide grafts to patients who might benefit from them. In France during the year 2001, just 27.2% of the need for kidneys was satisfied: only 2022 patients have received a transplant out of the 7434 (4903 registered as of 31.12.00 and 2531 registered during 2001) on the national kidney transplantation waiting list managed by the Etablissement français des Greffes (EfG) [7].

In view of the shortage of kidneys, recipient selection and equitable access to renal transplantation should be the cornerstones of the transplantation process. Surveys of the process to select patients for renal transplantation have detected significant variations in the evaluation of candidates both in European and in US transplant centres [8,9]. Moreover, previous studies in the US have showed that African-Americans,

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women, the elderly and diabetics were less likely to receive a renal transplant [10–15].

Therefore, a multicentre study was designed to analyse the pre-transplant evaluation (PTE) and the process of waiting list registration (WLR) and to analyse the influence of patients' medical characteristics and co-morbid conditions on the likelihood of their being registered on the national kidney transplantation waiting list managed by EfG. This study focused on elderly patients and on patients with type 2 diabetes (D2), two groups that are increasing dramatically in the ESRD population [15–17].

Subjects and methods

Nephrology unit selection

This study was performed in the Nephrology, Dialysis and Transplantation departments of three university hospitals in the Rhône-Alpes county in France (Lyon Sud, Grenoble and Saint Etienne). They were selected because of their ability to completely manage the ESRD of their own local patients and to provide all modalities of dialysis as well as an active programme of renal transplantation.

The process of registration on the renal transplantation waiting list in the studied units

In two nephrology departments, PTE was initiated and performed by the patients' attending physicians. The decision in each department to register a patient on the national kidney transplantation waiting list was made by one of the physicians responsible for renal transplantation after a review of the patient's PTE. There was no systematic review of patients with chronic renal failure in those departments.

In one nephrology department, all patients with chronic renal failure followed-up in the unit were identified and listed. Twice a month, during a medical meeting, the question of pre-PTE was routinely raised for each patient, and selection for PTE was made after discussion of doubtful cases. PTE was performed by the patients' attending physicians. All patients undergoing PTE were identified and listed. The decision to register a patient on the national kidney transplantation waiting list was made in a second bimonthly medical meeting after a complete PTE and following discussion of doubtful cases.

Study population

All patients who were followed in the three nephrology units for ESRD (defined as a need for dialysis or pre-emptive renal transplantation) between 01.01.95 and 31.12.98 were included. Patients who were referred by other health care providers only for renal transplantation and patients temporarily dialysed for acute renal failure were excluded. The study cohort consisted of 549 patients, with an exhaustiveness of 98.6%: eight patients were not included because their medical records had been lost. The numbers of patients in each nephrology department were: 209 in Saint Etienne University Hospital, 195 in Lyon Sud University Hospital and 145 in Grenoble University Hospital.

Study period

Patients were identified at the onset of renal replacement therapy (RRT) that included centre haemodialysis, out-centre haemodialysis, peritoneal dialysis or pre-emptive renal transplantation, and were followed until 03.31.00. The minimum duration of follow-up was 15 months after the first RRT.

Study end point

The end point of the study was each subject's status of registration on the French national kidney transplantation waiting list. There were three possibilities for each patient: being registered before the first RRT, being registered after the first RRT or not being registered before or on 31.03.00.

Studied parameters

Age, gender, country of birth, date of the first RRT, rapidly progressive ESRD, late referral, original nephropathy, co-morbid conditions at the time of the first RRT, modality of RRT, PTE performance and WLR were parameters collected retrospectively from patients' medical records between 01.04.00 and 30.06.00.

The country of birth was taken as a dichotomous variable: birth in France or outside France. Rapidly progressive ESRD was defined as a patient's normal renal function 6 months before the first RRT. Late referral was defined as a first referral to a nephrologist <6 months before the first RRT. Original nephropathies included diabetic nephropathy, renal-vascular disease, primary and secondary glomerulonephritis (diabetic nephropathy being excluded from secondary glomerulonephritis), polycystic kidney disease, chronic tubulo-interstitial nephritis, malformative uropathy, other causes and unknown causes. Concomitant conditions associated with the first RRT included: type 1 diabetes; D2; arterial hypertension (blood pressure $>140/90$ mmHg or anti-hypertensive medication); carotid artery disease (defined as a stenosis $>50\%$); peripheral vascular disease (defined as one or more of clinical claudication, a peripheral amputation or a peripheral artery stenosis $>50\%$); coronary disease (angina, myocardial infarction); congestive heart failure (acute pulmonary oedema or left-ventricular ejection fraction $<50\%$ in echocardiography, or both); cerebrovascular accident; malignancy; alcohol addiction; hepatitis B or C; hepatic insufficiency (defined as a coagulation factor V $<50\%$); HIV infection; chronic bacterial infections (defined as a history of bacterial infection treated with antibiotics during >3 months in the 2 years before ESRD or infections relapsing after antibiotic discontinuation); urological disease other than cancer; vasculitis and related diseases (auto-immune diseases); and psychosis. 'Cardiovascular disease' (CVD) encompasses one or more cardiovascular co-morbid conditions, hypertension excepted. The cohort of 391 patients without D2 included 374 non-diabetics and 17 patients with type 1 diabetes. The modality of RRT was the one in use 3 months after the first RRT. PTE was defined as a complete evaluation of the patient in preparation for renal transplantation (including in particular cardiovascular, urologic and anaesthesiologic evaluations). The date of WLR, if any, was the date of the administrative registration on the national list managed by EfG. The duration of PTE was the time between the date of HLA group determination

and the date of registration on the waiting list, and was documented only for patients with PTE leading to WLR.

Statistical analysis

Analyses performed included: (i) tabulation of patients' characteristics and co-morbid conditions in the studied population; (ii) analysis of PTE and WLR processes in the entire cohort, in the elderly and in patients with D2; (iii) analysis of the medical characteristics of patients without PTE, by categories of age and in D2 *vs* patients without D2; (iv) comparisons of characteristics of registered *vs* non-registered patients with calculations of non-adjusted relative risk (NA RR) of being wait-listed by patient characteristics and co-morbid conditions (univariate analysis); (v) analysis of factors having independent effects on the likelihood of being registered on the waiting list (multivariate analysis).

Comparisons were done using the χ^2 test or Fischer exact test when needed for category variables and using the Student's *t*-test for continuous variables. One-year survival rates after the first RRT were determined by the Kaplan–Meier method. The Log-rank test was used to compare 1-year survival rates. Univariate analysis used the χ^2 or Fischer exact tests when needed to compare PTE and WLR rates according to patient characteristics, co-morbid conditions and RRT modalities.

A Cox proportional hazards model was used to identify those patient characteristics and co-morbid conditions with independent effects on the probability of being wait-listed after the first RRT and to quantify their effects. The end-point was WLR after the first RRT, and the patients who were wait-listed before RRT (52 patients) were excluded. Patients older than 70 years on the first day of RRT (189 patients) and HIV-infected patients (two patients) were not included in the Cox regression analysis because none of them were wait-listed in this cohort. Up to that point, only 306 patients were included in the multivariate analysis. Patients not reaching WLR were right-censored at death or at their last follow-up of this study. Patient age in four categories (15–49 years; 50–59 years; 60–64 years and 65–69 years), gender, country of birth, rapidly progressive ESRD, late referral, nephropathy, co-morbidities at the first RRT (as described above), RRT modality, year of the first RRT and nephrology departments were introduced in the model to explore their effects on the likelihood of being wait-listed. Step-by-step analysis was done with both backward and forward introduction of variables to explore interactions between variables. Nephropathy and co-variables of the RRT modalities were not included in the final Cox regression model because of interactions between some co-morbidities and some original nephropathies (diabetes and diabetic nephropathy, CVD and renal-vascular nephropathy, urologic diseases and nephropathy related to malformative uropathy; $P < 0.01$) and between age and RRT modalities ($P < 0.01$). Age, D2 and CVD were studied as parameters of interest in several multivariate Cox regression models, with step-by-step adjustment for other variables. No difference was noted between the estimations of the adjusted relative risks (aRR) of being registered on the renal transplantation waiting list whatever the studied parameter. The result of multivariate analysis shown in Table 3 is the result of analyse using age in four categories as parameters of interest. Significance was defined as $P < 0.05$ for each analysis.

Results

Patients' characteristics

Demographic characteristics of the study population are shown in Table 1.

In the 15–59 year old group ($n = 225$), in the 60–69 year group ($n = 135$) and in patients ≥ 70 years ($n = 189$), the prevalence of CVD was, respectively: 28.9, 51.1 and 58.2% ($P < 0.05$); and of D2: 25.8, 31.8 and 35.4% ($P < 0.05$). In the entire cohort, CVD was present in 68.3% of patients with D2 ($n = 158$) and in 34.5% of patients without D2 ($n = 391$) ($P < 0.001$). In patients younger than 70 years, CVD was present in 65.9% of patients with D2 ($n = 91$) and 27.5% of those without ($n = 269$) ($P < 0.001$).

One-year survival rates after the first RRT were: 85.2% in the entire cohort; 92.9% in the 15–59 year group; 83.7% in the 60–69 year group and 77.2% in patients ≥ 70 years old (univariate analysis, $P < 0.05$). The 1-year survival rates after the first RRT were significantly lower in patients with D2 than in patients without: 78.5 *vs* 87.7% (univariate analysis, $P < 0.05$). Rapidly progressive ESRD (40 patients) was associated with a poorer 1-year survival rate, being 62.5 *vs* 86.8% in 509 patients without rapidly progressive ESRD (univariate analysis, $P < 0.05$).

Analysis of the PTE and the process of waiting list registration

Among the 549 patients studied, 207 (37.7%) were evaluated for renal transplantation and 185 (33.7%) were placed on the renal transplantation waiting list by 31.03.00. In this cohort, the oldest patient registered on the waiting list was 68.8 years old at the time of registration. As no patient older than 70 years was either evaluated or registered in this cohort, further analyses were focused on patients younger than 70 years (360 patients). In this sub-group, the rates of PTE and WLR were, respectively, 57.5 (207/360) and 51.4% (185/360). The rates of PTE and WLR and exclusion after PTE are shown in Figure 1. The duration of PTE was 8.1 ± 7.6 months in the entire cohort, 8.4 ± 8.1 months in 15–59 year group and 6.8 ± 4.3 months in 60–69 year group (NS). The duration of PTE was significantly longer in patients with D2 than in patients without: 12.7 ± 11.0 months *vs* 7.5 ± 7.1 months, respectively ($P < 0.01$).

The PTE and WLR rates according to patients' age, D2 and CVD are shown in Figure 2. The PTE rate was lower in D2 and CVD patients but interaction between D2 and CVD depends on age. The significant difference in the 15–59 year group was restricted to patients having both D2 and CVD ($P < 0.0006$) in comparison with patients without both D2 and CVD. In the older groups, the difference was significant both in D2 patients without CVD ($P < 0.05$) and in D2 patients with CVD ($P < 0.01$) but not significant in patients with only CVD. The WLR rate was also significantly lower in patients with D2, whatever the age and

Table 1. Demographic characteristics of the study population

	Total ($n = 549$)	Age < 70 years ($n = 360$)	Age ≥70 years ($n = 189$)
Age at ESRD: mean ± SD (years)	60.3 ± 16.5	51.8 ± 14.3	76.2 ± 4.2
Median age at ESRD (years)	64.9	55.5	75.3
Age categories (number, %)			
15–49 years	140, 25.5%	140, 38.9%	0, 0%
50–59 years	85, 15.5%	85, 23.6%	0, 0%
60–64 years	65, 11.8%	65, 18.1%	0, 10%
65–69 years	70, 12.8%	70, 19.4%	0, 0%
≥70 years old	189, 34.4%	0, 0%	189, 100%
Men	347, 63.2%	233, 64.7%	114, 60.3%
Born in France	423, 77.0%	274, 76.1%	149, 78.8%
Rapidly progressive ESRD (< 6 months)	40, 7.4%	26, 7.2%	14, 7.4%
Late referral patients (< 6 months)	124, 22.6%	68, 18.9%	56, 29.6%
Original nephropathy (number, %)			
Diabetic nephropathy	115, 21.0%	78, 21.7%	37, 19.6%
Renal-vascular disease	126, 23.0%	52, 14.4%	74, 39.1%
Primary and secondary glomerulonephritis[a]	97, 17.6%	84, 23.3%	13, 6.9%
Polycystic kidneys	31, 5.6%	28, 7.8%	3, 1.6%
Chronic tubulo-interstitial nephritis	48, 8.7%	31, 8.6%	17, 9.0%
Malformative uropathy	37, 6.7%	34, 9.5%	3, 1.6%
Other	48, 6.7%	27, 7.5%	21, 11.1%
Unknown	47, 8.6%	26, 7.2%	21, 11.1%
Co-morbidity at the first RRT (number, %)			
Type 1 diabetes	17, 3.1%	17, 4.7%	0, 0%
D2	158, 28.8%	91, 25.3%	67, 35.4%
Arterial hypertension	455, 82.9%	291, 80.8%	164, 86.8%
CVD[b]	243, 44.3%	133, 36.9%	110, 58.2%
Carotid vascular disease	32, 5.8%	15, 4.2%	17, 9.0%
Peripheral vascular disease	99, 18.0%	52, 14.4%	47, 24.9%
Coronary artery disease	101, 18.4%	51, 14.2%	50, 26.4%
Congestive heart failure	85, 15.5%	44, 12.2%	41, 21.7%
Cerebrovascular accident	49, 8.9%	26, 7.2%	23, 12.2%
Malignancy (history ≤ 5 years)	30, 5.5%	19, 5.3%	11, 5.8%
Malignancy (history > 5 years)	18, 3.3%	9, 2.5%	9, 4.8%
Chronic bacterial infection	6, 1.1%	5, 1.4%	1, 0.5%
Alcohol addiction	43, 7.8%	37, 10.3%	6, 3.2%
HBV infection	10, 1.8%	10, 2.8%	0, 0%
HCV infection	14, 2.5%	12, 3.3%	2, 1.1%
Hepatic failure	20, 3.6%	18, 5.0%	2, 1.1%
HIV infection	2, 0.4%	2, 0.6%	0, 0%
Urologic disease (cancer excepted)	79, 14.4%	54, 15.0%	25, 13.2%
Vasculitis and related diseases	25, 4.5%	18, 5.0%	7, 3.7%
Psychosis	12, 2.2%	9, 2.5%	3, 1.6%
RRT at 3 months after the first RRT (number, %)			
Out-centre haemodialysis	93, 17.0%	89, 24.7%	4, 2.1%
In-centre haemodialysis	324, 59.0%	197, 54.7%	127, 67.1%
Peritoneal dialysis	111, 20.2%	53, 14.7%	58, 30.7%
Pre-emptive transplantation	21, 3.8%	21, 5.8%	0, 0%

[a]Diabetic nephropathy was excluded from secondary glomerulonephritis.
[b]Hypertension excepted.

irrespective of CVD status, than in patients without both D2 and CVD (patients with D2 and without CVD: $P < 0.005$; patients with D2 and with CVD: $P < 0.004$). No significant difference was noted in patients with only CVD.

In the entire cohort, the reasons for exclusion from transplantation by PTE were: CVDs in four (18.2%), non-compliance in dialysis in three (13.6%), death before registration in two (9.1%), multiple co-morbid conditions in two (9.1%), cachexia in one (4.6%), prostate cancer in one (4.6%), patient's refusal during PTE in one (4.6%), alcoholism in one (4.6%), psychiatric disease in one (4.6%) and loss to follow-up for one (4.6%). For the remaining five cases (22.7%), reasons for exclusion during PTE were not specified in the patients' medical records. In the 60–69 year group, the reasons for exclusion were a CVD in one case and unknown in the second. In patients with D2, the reasons for exclusion were a CVD in four (50.0%), death before registration in one (12.5%), alcoholism in one (12.5%) and unknown in two (25%).

Patients without PTE

We identified 49 patients who were not evaluated and who had no apparent reason for exclusion before any PTE. Those patients had no co-morbidities at the first RRT (except D2 alone), no history of cardiovascular

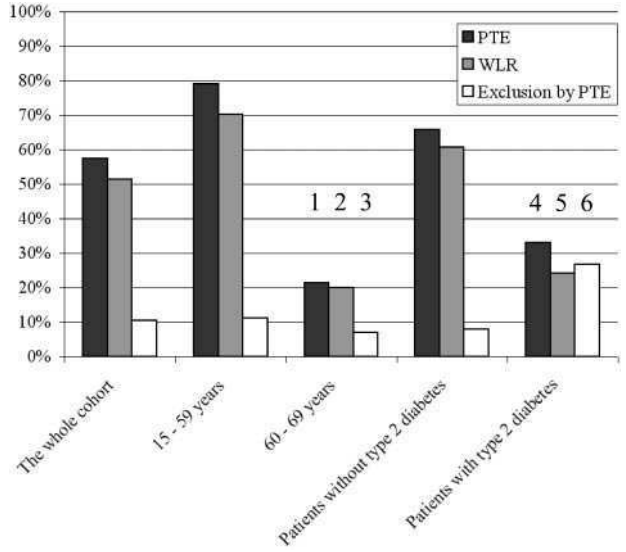

Fig. 1. Rates of PTE, WLR and exclusion after PTE (as a percentage of performed PTE) in the entire cohort, by age categories, and in patients with D2 *vs* patients without D2 (360 patients, age <70 years). In comparison with 15–59 year olds, 1, 2: $P < 0.001$; 3: NS. In comparison with patients without D2: 4, 5: $P < 0.001$; 6: $P < 0.01$.

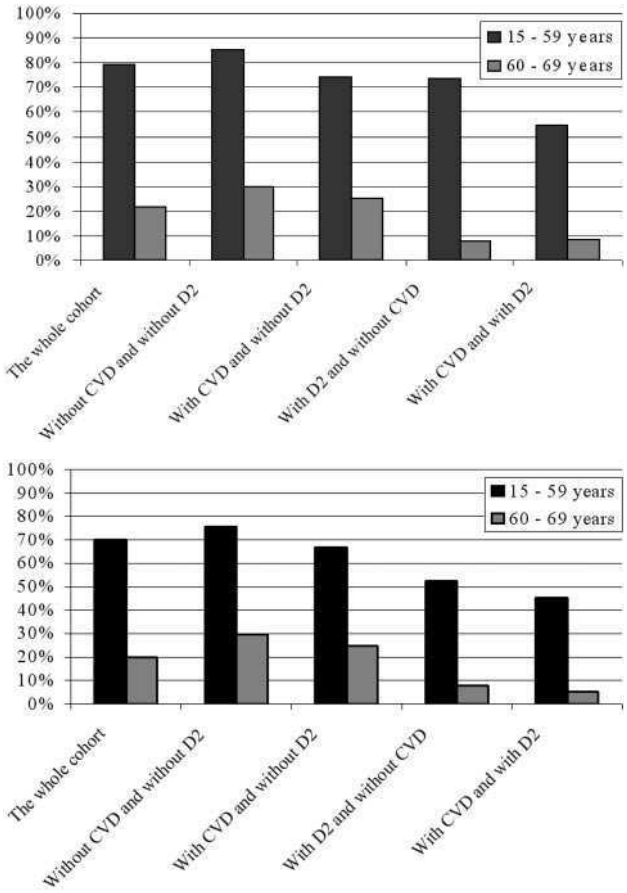

Fig. 2. (Top) Rates of PTE by age categories, according to CVD and D2 (360 patients, age <70 years). (Bottom) Rates of WLR by age categories, according to CVD and D2 (360 patients, age <70 years).

event, no diagnosed neoplasm and no deaths during the year after the first RRT. The rates for such patients were, respectively, in the 15–59 year group, in the 60–69 year group and in patients older than 70 years as follows: 6.4% (3/47 patients without PTE), 17.0% (18/106) ($P = 0.07$ in comparison with the15–59 year group) and 14.8% (28/189) ($P = 0.12$ in comparison with the 15–59 year group). In the 153 patients younger than 70 years who had no PTE, these rates were higher in patients with D2 than in patients without D2: 18.0% (11/61) *vs* 10.9% (10/92) ($P = 0.21$; analysis performed only in patients younger than 70 years).

Registration on the renal transplantation waiting list (univariate analysis)

Characteristics of registered patients *vs* non-registered patients and non-adjusted relative chance of being registered, by patient characteristics and co-morbidities, are shown in Table 2. In univariate analysis, factors associated with a low likelihood of registration were: age $\geq$60 years, D2, all cardiovascular co-morbidities, rapidly progressive ESRD, diabetic nephropathy, renal-vascular disease, neoplasm, alcohol addiction and in-centre haemodialysis as the RRT modality. Polycystic kidneys and malformative uropathy as original nephropathies, type 1 diabetes and urologic diseases (cancer excepted) as co-morbid conditions were associated with high rates of registration.

Registration on the renal transplantation waiting list (multivariate analysis)

Relative risks and 95% confidence intervals for the Cox regression testing of independent co-variables that influenced wait-listing after the first RRT are shown in Table 3. After adjustment for patient characteristics and co-morbid conditions, fewer elderly and D2 patients were registered on the renal transplantation waiting list than young patients and those without D2. A non-linear effect of patient age on wait-listing was observed with a non-proportional decrease in the likelihood of being registered when the age category increased. Other variables having independent and significant effects on the relative risk of being wait-listed were rapidly progressive ESRD, CVD, history of malignancy and psychosis. No significant effect was detected for other characteristics such as year of the first RRT, nephrology centre, gender, country of birth and late referral.

Discussion

Age $\geq$60 years and D2 are associated with poor rates of PTE and WLR. Analysing the PTE process and WLR process showed that patients were evaluated differently.

Table 2. Characteristics of registered and non-registered patients and non-adjusted relative risks (NA RR) of being registered—by patient characteristics and co-morbidities (360 patients, age < 70 years)

	Registered ($n = 185$)	Non-registered ($n = 175$)	NA RR and 95% CI	*P*
Age at ESRD: mean ± SD (years)	45.8 ± 13.5	57.9 ± 12.3		< 0.001
Median age at ESRD (years)	47.3	62.3		
Age categories (number, %)				
15–49 years	104, 56.2%	37, 21.1%	1	–
50–59 years[a]	54, 29.2%	32, 18.3%	0.85, 0.70–1.03	NS
60–64 years[a]	20, 10.8%	44, 25.2%	0.42, 0.29–0.62	< 0.001
65–69 years[a]	7, 3.8%	62, 35.4%	0.14, 0.07–0.28	< 0.001
Men	113, 61.1%	120, 68.6%	0.85, 0.70–1.05	NS
Born in France	137, 74.0%	132, 75.4%	0.97, 0.77–1.21	NS
Rapidly progressive ESRD (< 6 months)	7, 3.8%	19, 10.9%	0.51, 0.27–0.96	< 0.01
Late referral patients (< 6 months)	28, 15.1%	40, 22.8%	0.77, 0.57–1.04	NS
Original nephropathy (number, %)				
Diabetic nephropathy[b]	26, 14.1%	52, 29.7%	0.59, 0.41–0.84	< 0.01
Renal-vascular disease[b]	17, 9.2%	35, 20.0%	0.58, 0.37–0.88	< 0.01
Primary and secondary glomerulonephritis[c]	50, 27.0%	38, 21.7%	1	–
Polycystic kidneys[b]	24, 13.0%	4, 2.3%	1.5, 1.19–1.91	< 0.01
Chronic tubulo-interstitial nephritis[b]	16, 8.6%	15, 8.6%	0.91, 0.62–1.34	NS
Malformative uropathy[b]	26, 14.1%	8, 4.6%	1.35, 1.04–1.75	< 0.01
Other[b]	13, 7.0%	10, 5.7%	0.99, 0.66–1.49	NS
Unknown[b]	13, 7.0%	13, 7.4%	0.88, 0.57–1.35	NS
Co-morbidity at the first RRT (number, %)				
Type 1 diabetes	14, 7.6%	3, 1.7%	1.65, 1.29–2.11	< 0.01
D2	22, 11.9%	69, 39.4%	0.40, 0.27–0.58	< 0.001
Arterial hypertension	145, 78.4%	135, 77.1%	1.04, 0.82–1.32	NS
CVD[d]	45, 24.3%	85, 48.6%	0.50, 0.37–0.67	< 0.001
Carotid vascular disease	1, 0.05%	14, 8.0%	0.07, 0.02–0.83	< 0.001
Peripheral vascular disease	16, 8.6%	36, 20.6%	0.56, 0.37–0.85	< 0.01
Coronary artery disease	11, 5.9%	40, 22.9%	0.38, 0.22–0.65	< 0.001
Congestive heart failure	12, 6.5%	32, 18.3%	0.50, 0.30–0.82	< 0.001
Cerebrovascular accident	7, 3.8%	19, 10.9%	0.50, 0.27–0.96	< 0.01
Malignancy (history ≤ 5 years)	1, 0.05%	15, 9.1%	0.12, 0.02–0.78	< 0.001
Malignancy (history > 5 years)	6, 3.2%	6, 3.4%	0.97, 0.55–1.72	NS
Chronic bacterial infection	1, 0.05%	4, 2.3%	0.39, 0.07–2.23	NS
Alcohol addiction	13, 7.0%	24, 13.7%	0.66, 0.42–0.98	< 0.05
HBV infection	5, 2.7%	5, 2.9%	0.97, 0.52–1.82	NS
HCV infection	5, 2.7%	7, 4.0%	0.80, 0.41–1.58	NS
Hepatic failure	8, 4.3%	12, 6.9%	0.77, 0.44–1.33	NS
HIV infection	0, 0.0%	2, 1.1%	–	–
Urologic disease (cancer excepted)	36, 19.5%	18, 10.3%	1.37, 1.10–1.71	< 0.05
Vasculitis and related-diseases	7, 3.8%	11, 6.3%	0.75, 0.41–1.34	NS
Psychosis	1, 0.05%	7, 4.0%	0.24, 0.04–0.96	< 0.05
RRT 3 months after the first RRT (number, %)				
Out-centre haemodialysis	62, 33.5%	25, 14.3%	1	–
Centre haemodialysis[e]	76, 41.1%	123, 70.3%	0.53, 0.43–0.67	< 0.001[f]
Peritoneal dialysis[e]	26, 14.0%	27, 15.4%	0.69, 0.51–0.94	< 0.01[f]
Pre-emptive transplantation	21, 11.4%	0, 0.0%	–[f]	

[a]NA RR calculated in comparison with the 15–49 year group.
[b]NA RR calculated in comparison with the glomerulonephritis group.
[c]Diabetic nephropathy was excluded from secondary glomerulonephritis.
[d]Hypertension excepted.
[e]NA RR calculated in comparison with out-centre haemodialysis group.
[f]Comparison without pre-emptive transplantation.

PTE, as defined in this study, was a process leading to a low rate of exclusion from renal transplantation (~10% of the patients beginning PTE).

Patients older than 60 years were less frequently evaluated for renal transplantation, but the rate of exclusion resulting from PTE and the mean duration of PTE were not different from those in younger patients. PTE seemed to have been performed in only pre-selected elderly patients with a low rate of exclusion (< 7%). The percentages of patients without obvious reasons for not being taken through PTE were twice as high in elderly patients than in young ones.

Patients with D2 were highly excluded at all stages of the selection process for registration on the renal transplantation waiting list. They were less frequently considered for PTE, more frequently excluded after PTE, with a longer PTE duration, and then less likely to be registered on the renal transplantation waiting list

Table 3. aRR of being wait-listed for renal transplantation after the first RRT. Cox regression analysis with all variables[a] (306 patients[b], age < 70 years)

	aRR	95% CI	*P*
1995 (year of the first RRT)	1		
1996 (year of the first RRT)	0.73	0.44–1.20	0.21
1997 (year of the first RRT)	1.16	0.69–1.96	0.57
1998 (year of the first RRT)	0.59	0.32–1.08	0.09
Saint Etienne	1		
Grenoble	0.95	0.56–1.61	0.84
Lyon Sud	1.15	0.73–1.80	0.54
0–49 years	1		
50–59 years	0.95	0.59–1.53	0.83
60–64 years	0.41	0.23–0.73	0.0022
65–69 years	0.07	0.03–0.20	< 0.0001
Female	1.19	0.78–1.80	0.42
Born outside France	1.05	0.52–1.78	0.63
Rapidly progressive ESRD	0.21	0.08–0.55	0.0014
Late referral (*< 6 months*)	0.87	0.50–1.46	0.57
Type 1 diabetes	1.24	0.57–2.70	0.58
D2	0.32	0.18–0.56	< 0.0001
CVD[c]	0.59	0.36–0.94	0.029
Malignancy	0.13	0.04–0.46	0.002
Chronic bacterial infection	0.20	0.03–1.55	0.12
Alcohol addiction	0.42	0.17–1.02	0.056
HBV infection	0.98	0.27–3.54	0.98
HCV infection	0.52	0.17–1.57	0.25
Hepatic failure	1.19	0.57–2.48	0.64
Urologic disease (cancer excepted)	0.82	0.49–1.40	0.48
Vasculitis and related disease	0.47	0.18–1.24	0.13
Psychosis	0.05	0.01–0.35	0.003

[a]Nephropathy and RRT modality were not included in the model because of interactions between nephropathy and co-morbidity and between age and RRT modality.
[b]Patients older than 70 years and HIV infected patients were not included because none of them were wait-listed.
[c]Hypertension excepted.

than patients without D2. In patients with D2, the diagnosis of CVD was the main reason for exclusion from transplantation after PTE. Cardiovascular investigations needed in patients with D2 [18–20], such as invasive angiography or coronarography, may explain the longer PTE. Among patients without apparent reasons for exclusion from PTE, patients with D2 were twice as likely to be excluded than patients without.

Moreover, because the process of selection for renal transplantation starts before PTE, the combination of age ≥60 years and D2 seemed to be the most important reason for exclusion from renal transplantation before any PTE (Figure 2 top). Elderly patients with D2 were significantly less likely to be evaluated than elderly patients without D2. CVD seemed to have no significant effect on the decision to begin PTE in the elderly. This suggests that age and D2 were thought by clinicians to be limiting factors for renal transplantation, independently of other co-morbidities. Unfortunately, the reasons for patients being excluded from renal transplantation before any PTE—for example patient's choice—were documented in < 50% of medical records, and those data were not analysed here.

Advanced age, D2 and CVD are linked characteristics [15–17] and confounders in an analysis of factors influencing renal transplantation wait-listing. Multivariate analysis confirmed that old age and D2 have independent and significant effects on the likelihood of being registered on a renal transplantation waiting list. With equal co-morbidities, elderly patients and patients with D2 had a lower probability of being wait-listed than young patients and patients without D2.

Several other characteristics decreased the likelihood of being registered on the renal transplantation waiting list—such as rapidly progressive ESRD, probably because of a high 1-year death rate. Other significant factors were the classic relative or absolute medical contraindications of renal transplantation [18–20]: CVD, history of malignancy and psychosis.

In univariate analysis, type 1 diabetes was associated with a high rate of WLR: 14 of 17 patients in this cohort (82.3%). Those data are comparable with USRDS data [15]. This high rate could be explained by the registration of six of our patients on the kidney–pancreas transplantation waiting list and their age at the first RRT (mean age: 40.6 ± 10.1 years). The lack of statistical power and adjustment for age may explain why this characteristic was not a significant factor in multivariate analysis.

No statistical association was noted in this study between registration and gender or country of birth. Previous American studies have shown that females, Native Americans, African-Americans and Asian patients had a lower probability of receiving a renal transplant than males and whites [10–15]. National health care systems may explain the differences of data between France and USA.

Late referral was not a factor influencing the decision to wait-list a patient, after adjustment for patient characteristics and co-morbidities—if, in case of late referral, the patient's characteristics and co-morbid conditions allowed wait-listing.

No difference in access to the renal transplantation waiting list was detected between the three nephrology units studied. These units are all in university hospitals where both dialysis and transplantation are performed and where the interest and the educational level of physicians in renal transplantation are widespread and high.

Although advanced age and D2 are not considered as contraindications for renal transplantation [1–5,7–8], we found that these conditions have influenced adversely the likelihood of being registered on renal transplant waiting list. In both conditions, renal transplantation is beneficial, with an increased survival and quality of life compared with dialysis [1–6]; but some studies have shown that because of higher rates of morbidity and mortality the prognosis of renal transplantation was poorer in those groups than in younger patients and in patients without D2 [1–4]. As a result, the collective benefit of renal transplantation might decrease when the elderly or patients with D2 are transplanted leading physicians to allocate kidneys to other patients given organ shortage. This utilitarian

approach to kidney transplantation may explain our results, but it has to be discussed in view of actual epidemiological data on ESRD. In Western countries >50% of incident ESRD patients are older than 60 years (59% in our cohort) [15,17]. The incidence of patients with D2 in the ESRD population has increased in the last 20 years—now over 25% in Europe [16] (28.8% in this 1995–1998 university hospitals cohort) and >40% in USA [15]. A recent medico-economical study by Jassal *et al.* [4] showed that, compared with dialysis, the cost-effectiveness of cadaveric renal transplantation declines as age increases over 65 years and with prolonged waiting times in dialysis. Elderly patients may benefit if transplanted after a short time awaiting and with organs from living donors. To our knowledge, such a study is not available for patients with D2. When matched with respect to the year of transplantation, sex, age, immunological parameters and duration of graft cold-ischaemia, Boucek *et al.* [5] showed that transplantation outcomes were not different in highly selected patients with D2 compared with patients without D2.

Thus, in those patients, prognostic factors of renal transplantation have to be better analysed. The criteria for the selection of high-risk recipients should be discussed in the community of nephrology-transplantation physicians, in order to respect both individual and collective benefits, to improve equity and effectiveness of recipient selection and access to renal transplantation, to offer information to the elderly and patients with D2 regarding results of transplantation and, finally, to improve the cost-effectiveness of renal transplantation.

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Conflict of interest statement. None declared.

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ANNEXE A

PARCOURS HOSPITALO-UNIVERSITAIRE

PARCOURS HOSPITALO-UNIVERSITAIRE

INTERNAT DE MEDECINE : de 1996 à 2001, Hospices Civils de Lyon

Service de Néphrologie, unité de Néphrologie Clinique, Dr Béruard, Clinique du Tonkin
Service de Réanimation polyvalente, Pr Boulétreau, Hôpital de l'Hôtel Dieu
Service de Réanimation Médicale, Pr Boulétreau, Pavillon N, Hôpital E. Herriot
Service de Néphrologie, unité de Néphrologie – Transplantation, Pr Labeeuw, CHLS
Service de Médecine Interne, Pr Vital-Durand, CHLS
Service de Cardiologie, Dr Boutarin, Hôpital St Joseph
Service de Néphrologie, unité de Néphrologie, Pr Laville, Pavillon P1, Hôpital E. Herriot
Service de Néphrologie, unité d'Hémodialyse, Pr Labeeuw, CHLS

ASSISTANAT ET CLINICAT : du 01/11/2001 au 31/10/2004

Nous avons été responsable en alternance avec le second CCA du Service de :

- ***l'unité d'hospitalisation*** : 20 lits, dont 4 lits en secteur protégé et 6 lits permettant d'hémodialyser les patients dans le service, activité de Néphrologie clinique, d'appel de greffe, de suivi post-transplantation immédiat, de repli de dialysés (dialyse péritonéale et hémodialyse) et de transplantés, de prise en charge de patients présentant une insuffisance rénale aigue. Gestes réalisés : biopsie rénale (reins propres et greffons) sous contrôle échographique continu, pose de voies centrales (tous types dont cathéters tunélisés double voie pour hémodialyse chronique).
- ***l'unité d'hémodialyse chronique conventionnelle*** : 12 postes d'hémodialyse dont 2 postes de patients en repli.

L'activité d'hospitalisation correspondait à plus de 700 séjours par an et le nombre de séances d'hémodialyse à plus de 6000 par an. Dans l'unité d'hospitalisation nous encadrions 2 internes et dans l'unité d'hémodialyse 1 interne en formation.

UNITE COMMUNE UROLOGIE-NEPHROLOGIE (janvier 2005) :
BATIMENT UROLOGIE-NEPHROLOGIE DU CENTRE HOSPITALIER LYON SUD

Nous sommes responsable médical de cette unité pour le service de Néphrologie depuis son ouverture. Elle comprend 8 lits partagés avec le service d'Urologie du CHLS (Pr Perrin, Pr Ruffion).

Sur le plan néphrologique, cette unité a pour vocation de prendre en charge :

- les patients transplantés (appel de greffe et post-greffe immédiat),
- les patients présentant une insuffisance rénale aiguë,
- les patients en repli de dialyse (hémodialyse et dialyse péritonéale) en fonction de leur état clinique,
- les patients en suite de Réanimation avec séquelles fonctionnelles rénales,

- et depuis décembre 2008, début du programme d'échange plasmatique (plasmafiltration sur PRISMAFLEX), 125 séances en 2009 :
    - microangiopathie thrombotique (centre de compétence régionale), rejet aigu humoraux, récidive de hyalinose segmentaire et focale sur greffon rénal, …

Notre rôle est celui de Médecin référent de Néphrologie de l'Unité. Nous sommes responsable :

- de l'organisation médicale,
- de la prise en charge des patients,
- de la rédaction des procédures de soins médicaux et infirmiers (appel de greffe, post-greffe immédiat, hémodialyse urgente et chronique),
- des relations avec les autres unités de Néphrologie et d'Urologie du CHLS,
- des relations avec les services de Réanimation du CHLS mais également de l'agglomération lyonnaise du fait de notre capacité unique sur les HCL à prendre en charge des patients nécessitant des soins paramédicaux lourds et non sevrés d'hémodialyse en sortie de Réanimation.

L'activité de l'unité représente sur le plan néphrologique plus de 50 greffes par an, 250 séances d'hémodialyse aigue par an, 30 patients en sortie de réanimation par an. Le taux d'occupation des lits (Urologie + Néphrologie) est supérieur à 95% (99,4% en 2009).

Nous y encadrons un interne DES en formation.

Par ailleurs nous assurons le suivi des patients dont nous avons la responsabilité en Hôpital de Jour et en Consultation externe (néphrologie clinique, insuffisance rénale chronique, transplantation rénale).

ACTIVITES TRANSVERSALES AU SEIN DU SERVICE DE NEPHROLOGIE DU CHLS

Nous participons à l'ensemble des activités institutionnelles du service :

- Suivi des patients insuffisants rénaux chroniques (1 réunion / 2 semaines),
- Suivi des patients en bilan pré-greffe et inscrit sur liste d'attente de greffe (1 réunion / 2 semaines),
- Réunion d'anatomopathologie (1 réunion / 2 semaines),
- Suivi des patients transplantés (1 réunion / 2 semaines),
- Réunion de Service (1 réunion / 2 semaines)
- Evaluation des pratiques professionnelles,
- Information aux patients (pré-dialyse, dialyse, transplantés rénaux),
- Constitution d'un dossier informatisé des patients insuffisants rénaux chroniques,
- Responsable de l'informatisation des prescriptions médicales (logiciel OPIUM), effectif en janvier 2010,
- Organisation des lectures critiques d'article faites par les internes du Service,
- Enseignement aux Etudiants Hospitaliers affectés au Service (1 heure / 2 semaines),
- Enseignement aux IDE du service.

Actuellement, un effort particulier est produit dans le service concernant :

- l'évaluation des pratiques professionnelles et de l'information donnée aux patients,
- l'informatisation des prescriptions (logiciel OPIUM – effectif en janvier 2010).

ACTIVITE DE GARDES EN NEPHROLOGIE

Nous participons depuis octobre 2001 au tour de garde du Service de Néphrologie du Centre Hospitalier Lyon Sud, réalisant 70 à 75 gardes par an en moyenne.

ACTIVITE DE GARDE EN REANIMATION

De novembre 1998 à décembre 2002 nous avons réalisé 121 gardes de Médecin senior dans le Service de Réanimation de l'Hôtel Dieu, Service du Pr Chassard (réanimation polyvalente).

ANNEXE B

PROGRAMME DE LA REUNION SCIENTIFIQUE CERRT 2010

Lyon 20 mai 2010

Programme

CERRT Jeudi 20 mai 2010

Château de Montchat, Lyon

9 h 00 :
Accueil des participants

9 h 15 – 10 h 30 :
Diabète de type 1 : transplantation rein – pancréas, rein seul, ilôts pancréatiques
Indications et place de la greffe d'ilôts versus greffe pancréatique ?
Pr Lionel Badet, Urologie, Transplantation rénale et pancréatique, HCL (20 min + discussion 10 min)
Priorité nationale et accès à la greffe rein – pancréas : que proposer aux non prioritaires ?
Pr Emmanuel Morelon, Néphrologie, Transpl rénale et pancréatique, HCL (10 min + discussion 5 min)
Résultats des greffes d'ilots : L'expérience du réseau GRAGIL.
Pr Pierre Yves Benhamou, Endocrinologie, CHU de Grenoble (20 min + discussion 10 min)

Pause

10 h 45 – 12 h 15 : Les receveurs limites
Non compliance au traitement et transplantation / retransplantation rénale
Conduites addictives (alcoolisme)
Problèmes posés au Néphrologue : cas cliniques
Dr Stéphanie Fourré – Toussaint, Néphrologie CH de Bourg en Bresse (20 min)
Le point de vue du Psychologue :
Jean-Loup Clément, Transplantation rénale et pancréatique, HCL (20 min)
Discussion : 15 min

Transplantation chez les patients obèses :
Pour : *Dr Bénédicte Janbon, Transplantation rénale, CHU de Grenoble (10 min)*
Contre : *Dr Anne-Elisabeth Heng, Transplantation rénale, CHU de Clermont-Ferrand (10 min)*
Discussion : 15 min

12 h 15 – 12 h 45 : Cas clinique

Pause déjeuner

14 h 00 – 15 h 00 : Interface CERRT – ABM
Activité de greffe rénale et pancréatique en 2009
Dr Frédéric Brun, ABM Lyon (20 min + discussion 10 min)
Activité de prélèvement en 2009
Dr Olivier Dubosc de Pesquidoux, Coordination hospitalière, HCL (20 min + discussion 10 min)

15 h 00 – 15 h 30 : Cas clinique

Pause

15 h 45 – 16 h 45 : Le cœur et les vaisseaux du transplanté rénal
Bilan cardiovasculaire pré-greffe et suivi post-greffe rénale
Dr Cyril Bergerot, Cardiologie, HCL (20 min + discussion 10 min)
Prise en charge de l'HTA du transplanté : *table ronde (20 min + discussion 10 min)*

Fin

Nous vous remercions de confirmer votre participation par mail : *emmanuel.villar@chu-lyon.fr*