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Cardiac Rhythm Disturbances in Hemodialysis Patients

Early Detection Using an Implantable Loop Recorder and Correlation With Biological and Dialysis Parameters

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ABSTRACT

OBJECTIVES The aim of this study was to identify using implantable loop recorder (ILR) monitoring the mechanisms leading to sudden death (SD) in patients undergoing hemodialysis (HD).

BACKGROUND SD accounts for 11% to 25% of death in HD patients.

METHODS Continuous rhythm monitoring was performed using the remote monitoring capability of the ILR device in patients undergoing HD at 8 centers. Clinical, biological, and technical HD parameters were recorded and analyzed.

RESULTS Seventy-one patients (mean age 65 ± 9 years, 73% men) were included. Left ventricular ejection fraction was <50% in 16%. Twelve patients (17%) had histories of atrial fibrillation or flutter at inclusion. During a mean follow-up period of 21.3 ± 6.9 months, 16 patients died (14% patient-years), 7 (44%) of cardiovascular causes. Four SDs occurred, with progressive bradycardia followed by asystole. The incidence of patients presenting with significant conduction disorder and with ventricular arrhythmia was 14% and 9% patient-years, respectively. In multivariate survival frailty analyses, a higher risk for conduction disorder was associated with plasma potassium >5.0 mmol/l, bicarbonate <22 mmol/l, hemoglobin >11.5 g/dl, pre-HD systolic blood pressure >140 mm Hg, the longer interdialytic period, history of coronary artery disease, previous other arrhythmias, and diabetes mellitus. A higher risk for ventricular arrhythmia was associated with potassium <4.0 mmol/l, no antiarrhythmic drugs, and previous other arrhythmias. With ILR monitoring, de novo atrial fibrillation or flutter was diagnosed in 14 patients (20%).

CONCLUSIONS ILR may be considered in HD patients prone to significant conduction disorders, ventricular arrhythmia, or atrial fibrillation or flutter to allow early identification and initiation of adequate treatment. Therapeutic strategies reducing serum potassium variability could decrease the rate of SD in these patients. (Implantable Loop Recorder in Hemodialysis Patients [RYTHMODIAL]; NCT01252823) (J Am Coll Cardiol EP 2017;■:■–■) © 2017 by the American College of Cardiology Foundation.

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ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation or flutter

AV = atrioventricular

CMP = cardiomyopathy

HD = hemodialysis

HR = hazard ratio

ICD = implantable cardioverter-defibrillator

IQR = interquartile range

ILR = implantable loop recorder

SD = sudden death

VA = ventricular arrhythmia

VF = ventricular fibrillation

VT = ventricular tachycardia

Patients with chronic kidney disease undergoing maintenance hemodialysis (HD) experience a high annual mortality rate of 17%. The primary cause of death in these patients (53% of deaths of known cause) is cardiovascular, with sudden death (SD) constituting a significant proportion (25% of all-cause mortality in a U.S. registry) (1). In the French REIN registry from 2014 (2), the annual mortality rate for patients undergoing HD was 15.5%, with 25% of these being cardiovascular deaths and 11% unexpected deaths. Cardiac arrhythmias are highly sensitive to volume and electrolyte shifts, which occur frequently in HD patients. In addition, other conditions leading to cardiac arrhythmias such as ischemic, hypertrophic, or dilated cardiomyopathy (CMP) are extremely prevalent in this population. However, so far, little is known about the occurrence of significant arrhythmias, specifically terminal rhythms, because studies have used only standard Holter monitoring of 24 to 48 hours in duration (3-5). We therefore sought to investigate the potential mechanisms of SD in HD patients and their relationship to clinical, biological, and HD parameters.

METHODS

STUDY DESIGN, SETTING, AND POPULATION. In this multicenter, interventional-observational, prospective cohort study, patients were prospectively enrolled at 8 HD centers from 2010 to 2013. They were followed for at least 18 months. HD centers were university hospitals (Bordeaux, Nantes, Rennes, Strasbourg, and Toulouse), public hospitals (Haguenau and Libourne), and 1 private practice dialysis clinic (Clinique St. Augustin, Bordeaux). Patients included were 45 to 80 years of age and undergoing long-term HD. Exclusion criteria were the presence of a pacemaker or an implantable cardioverter-defibrillator (ICD), an active infection, pregnancy, and the inability to give written informed consent. All patients provided written informed consent to the study protocol, which was approved by the Bordeaux Hospital Health Human Research Ethics Committee.

CARDIAC ARRHYTHMIA MONITORING. Patients were implanted subcutaneously with implantable loop recorders (ILRs) (Reveal XT, Medtronic, Minneapolis, Minnesota) with remote monitoring capabilities (Carelink, Medtronic). They were asked to transmit information every week; for those who were unable to do so, transmissions were performed once a week during their HD sessions. Storage of the electrocardiogram was triggered automatically when arrhythmic events fulfilled preprogrammed cutoff criteria, including sinus bradycardia ≤30 beats/min for ≥4 beats, pauses or asystole ≥3 seconds, high-degree atrio-ventricular (AV) block (second- or third-degree AV block) <40 beats/min lasting >3 seconds, ventricular tachycardia (VT) ≥150 beats/min lasting ≥16 beats, fast VT (heart rate >200 beats/min for 12 of 16 beats), and atrial fibrillation or flutter (AF; irregular RR interval over a 2-minute period). In the case of symptoms (lightheadedness, syncope, etc.), patients and witnesses were encouraged to manually activate the device to store an electrocardiographic strip. Transmission at the time of death was encouraged but was not required in the protocol. All tracings (automatic or manual) were reviewed by an electrophysiologist blinded to the patient. Episodes were then classified accordingly as: 1) significant conduction disorder (sinus bradycardia ≤30 beats/min for ≥4 beats, pauses or asystole ≥3 s, high-degree AV block [second- or third-degree AV block] <40 beats/min lasting >3 s); 2) significant ventricular arrhythmia (VA) (nonsustained VT ≤150 beats/min for ≥16 beats lasting <30 s, sustained VT ≥150 beats/min lasting ≥30 s, or ventricular fibrillation [VF] [irregular rhythm in the fast VT zone]); 3) AF; or 4) a false episode (artifact, undersensing, or oversensing). In uncertain cases, the tracings were interpreted by 2 other electrophysiologists blinded to the patient situation.

VARIABLES. Clinical events were collected at study inclusion and during follow-up. SD was defined as sudden, unexpected death within 1 h of symptom onset or unwitnessed, unexpected death without obvious noncardiac cause in patients known to be well within the past 24 h.

The primary endpoint was the occurrence of a significant conduction disorder and/or VA as defined earlier. Potential determinants of these arrhythmias were patients' baseline characteristics (sex, age, history of coronary artery disease or ischemic CMP, cardiac treatments, diabetes) and time-dependent variables such as antiarrhythmic medication, monthly routine biological measurements (serum concentrations of potassium [K^+], calcium, bicarbonates, phosphate, hemoglobin, C-reactive protein), and HD parameters (day of HD, length of HD session, body weight variation and systolic blood pressure changes during HD, systolic blood pressure

TABLE 1 Population Baseline Characteristics as a Function of Outcome

		Patients Alive at End of FU (n = 55)	Patients Who Died During FU (n = 16)	Patients Who Died of SD (n = 4)	Total (n = 71)
Follow-up (months)		23.7 ± 4.5	13.1 ± 7.4	18.7 ± 5.1	21.3 ± 6.9
Clinical characteristics	Age (yrs)	63.9 ± 8.9	69 ± 6.3	69.6 ± 5.6	65 ± 8.6
	Male	43 (78%)	9 (56%)	2 (50%)	52 (73%)
Main cause of ESRD	Diabetes mellitus	22 (40%)	10 (63%)	4 (100%)	32 (45%)
	Hypertension	14 (26%)	5 (31%)	1 (25%)	19 (27%)
	Glomerulonephritis	5 (9%)	0 (0%)	0 (0%)	5 (7%)
	Polycystic kidney disease	4 (7%)	0 (0%)	0 (0%)	4 (6%)
Medical history	Atrial fibrillation/flutter	8 (15%)	4 (25%)	0 (0%)	12 (17%)
	Ischemic CMP	14 (25%)	8 (50%)	1 (25%)	22 (31%)
	Diabetes mellitus	30 (55%)	12 (75%)	4 (100%)	42 (59%)
	Hypertension	46 (84%)	14 (88%)	4 (100%)	60 (85%)
Current vascular access	AV fistula	43 (78%)	9 (56%)	3 (75%)	52 (73%)
	AV graft	8 (15%)	4 (25%)	0 (0%)	12 (17%)
	Catheter	4 (7%)	3 (19%)	1 (25%)	7 (10%)
Dialysis	Duration (median in months)	16	45	33	19
	Initiation <3 months ago	6 (11%)	1 (6%)	0 (0%)	7 (10%)
Medications (n = 66)	Beta-blocker	29 (58%)	9 (56%)	2 (50%)	38 (58%)
	Amiodarone	4 (8%)	2 (13%)	0 (0%)	6 (9%)
	Calcium inhibitor	3 (6%)	2 (13%)	0 (0%)	5 (8%)
	Class 1 antiarrhythmic drug	1 (2%)	1 (2%)	0 (0%)	2 (3%)
	ACE inhibitor or ARB	19 (34%)	3 (19%)	1 (25%)	22 (31%)
	Anticoagulant agent	15 (27%)	7 (44%)	1 (25%)	22 (31%)
	Antiplatelet agent	37 (67%)	12 (75%)	4 (100%)	49 (69%)
ECG parameters	Heart rate (beats/min)	72 ± 14	68 ± 12	67 ± 13	71 ± 13
	PR (ms)	180 ± 31	200 ± 41	217 ± 48	185 ± 34
	QRS (ms)	96 ± 21	87 ± 26	100 ± 17	94 ± 22
	QRS >120 ms	5 (10%)	1 (6%)	0	6 (9%)
	QTc (ms)	426 ± 38	435 ± 27	424 ± 21	428 ± 36
Echocardiographic parameters		(n = 39)	(n = 12)	(n = 3)	(n = 51)
	LVEF (%)	61 ± 11 (n = 39)	59 ± 14 (n = 12)	63 ± 1.5 (n = 3)	61 ± 11 (n = 51)
	Patients with LVEF >50%	33 (85%)	10 (83%)	3 (100%)	43 (84%)
	Patients with LVEF 35%-50%	5 (12.8%)	0 (0%)	0	5 (10%)
	Patients with LVEF <35%	1 (2.6%)	2 (17%)	0	3 (6%)
Baseline biological parameters	Potassium (mmol/l)	4.6 ± 0.7	4.9 ± 0.7	4.8 ± 0.5	4.7 ± 0.7
	Total calcium (mmol/l)	2.2 ± 0.2	2.5 ± 0.3	2.4 ± 0.1	2.3 ± 0.2
	Phosphate (mmol/l)	1.6 ± 0.4	1.4 ± 0.4	1.3 ± 0.5	1.5 ± 0.4
	Bicarbonate (mmol/l)	23.2 ± 2.8	24.3 ± 4.3	22 ± 2.1	23.4 ± 3.2
	Hemoglobin (g/dl)	11.2 ± 1.1	11.1 ± 1.7	12.1 ± 1.6	11.2 ± 1.2

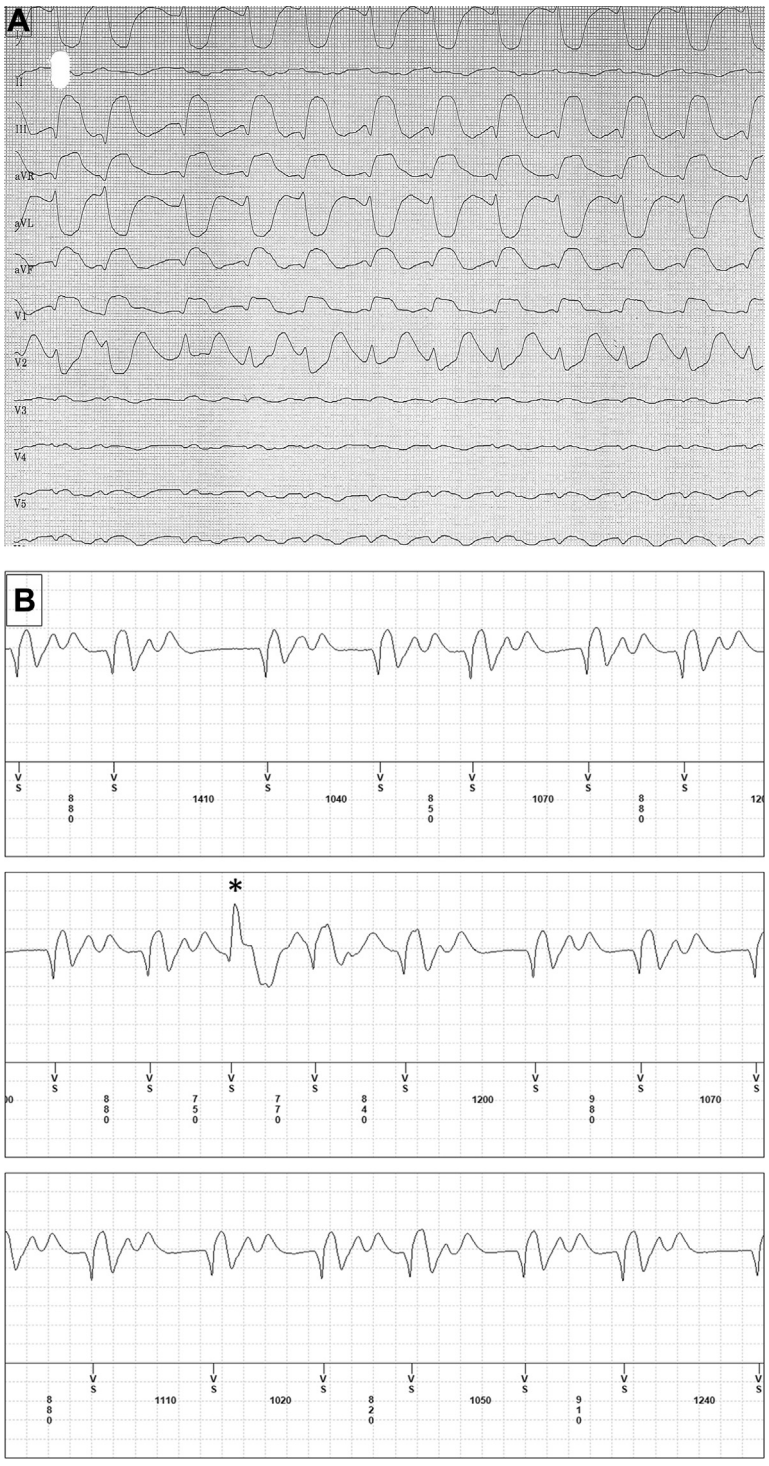
Values are mean ± SD or n (%).

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blockers; AV = atrioventricular; CMP = cardiomyopathy; ECG = electrocardiographic; ESRD = end-stage renal disease; FU = follow-up; LVEF = left ventricular ejection fraction; SD = sudden death.

before and after HD, and dialysate calcium and K^+ concentrations). A period at risk for arrhythmic events was defined as ±24 h around the first HD session of the week after the long interdialytic period. The latter was defined as the 72-h break between HD sessions, whereas the other two 48-hour interdialytic periods were each defined as the short interdialytic period.

To address the nonlinear relationship between arrhythmic events and quantitative explicative variables, several variables were categorized: serum K^+ (<4, 4 to 5, and >5 mmol/l), serum phosphate (<0.8, 0.8 to 1.45, and >1.45 mmol/l), serum calcium (<2.18, 2.18 to 2.3, and >2.3 mmol/l), serum bicarbonate (<22, 22 and 24, >24 mmol/l), CRP (<4, 4 to 10, and >10 mg/l), hemoglobin level (<10.5, 10.5 to 11.5, and >11.5 g/dl), systolic blood pressure (≤140 and >140 mm Hg), and dialysate calcium (<1.5, 1.5, and >1.5 mmol/l) and K^+ (<2, 2, and >2 mmol/l) levels.

FIGURE 1 Tracing of a Patient With Sudden Death



(A) Twelve lead ECG of a patient who died suddenly, following myocardial infarction. The ECG is typical of major acidosis with pulseless electrical activity with extremely wide QRS. **(B)** ILR tracings recorded at the same time but displaying a premature ventricular contraction **(*)** in addition to the wide QRS. ECG = electrocardiogram; ILR = implantable loop recorder.

STATISTICAL ANALYSIS. Sample size calculation was based on an expected mean number of 4 episodes of cardiac arrhythmias per patient within a 2-year follow-up period (2 episodes/year). The inclusion of 100 patients would have yielded a 95% confidence interval (defined by an approximation of the Poisson distribution by a normal distribution) of 1.8 to 2.2 episodes of cardiac arrhythmias per patient-year. Recruitment difficulties due to the low acceptance rate in this specific population led us to stop inclusion before 100 patients were recruited.

Data are described using standard statistics: mean ± SD, interquartile range (IQR), minimum value, and maximum value for quantitative variables and frequencies and percentages for qualitative or ordinal variables.

Analyses were based on available data. The incidence of significant cardiac arrhythmias expressed as a proportion for 100 patient-years and its confidence interval were estimated by an approximation of the Poisson distribution by a normal distribution.

The possible relationship between arrhythmic events and baseline characteristics, HD dialysis parameters, and biological measures was evaluated with survival analyses. A Cox model could not be used in this situation, as it would not take into account recurrent events. Therefore, a frailty model (survival model for recurrent events) was used because: 1) a patient could have a cardiac event several times (11 patients had more than 1 conduction disorder, 1 patient had more than 1 significant VA episode, and 16 patients had more than 1 AF episode); 2) the hazard of having a cardiac event was dependent on previous events; and 3) several covariates were likely to change over time, particularly those influenced by the HD procedure.

This model can be written as follows:

$$\lambda_{ij}(t|\upsilon_i) = \upsilon_i \lambda_0(t) \exp(\beta_1' X_{1i} + \beta_2' X_{2ij})$$

where i is the patient, j the recurrent event, X_{1i} fixed covariates, X_{2ij} time-dependent covariates, and υ_i the random effect (frailty), which follows a gamma distribution of variance $1/\theta$. Because events are recurrent, the random effect allows taking into account the correlation between events in a given patient.

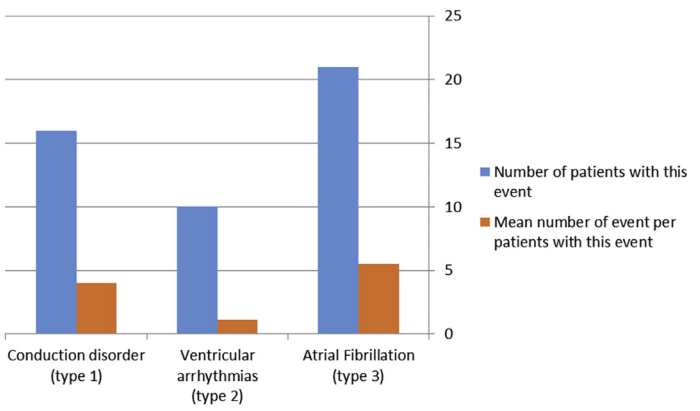
To analyze recurrent event data, the time variable ("calendar time") was the time between the date of first HD and the event date or date of censored data.

For the time-dependent covariates, we considered values collected at the last visit before an event. These variables were selected in a 2-step procedure. First, variables were selected according to a univariate model with $p < 0.20$. Second, the final multivariate model was established according to a stepwise backward procedure, and an association was considered significant at $p < 0.05$.

Multivariate analyses were systematically adjusted on age, sex, history of coronary artery disease, diabetes, and occurrence of other cardiac arrhythmias other than that of interest during follow-up.

The frailty models were performed using the freely available R package "Frailty pack," (6).

FIGURE 2 Number and Type of Events Recorded by Implantable Loop Recorders per Patient



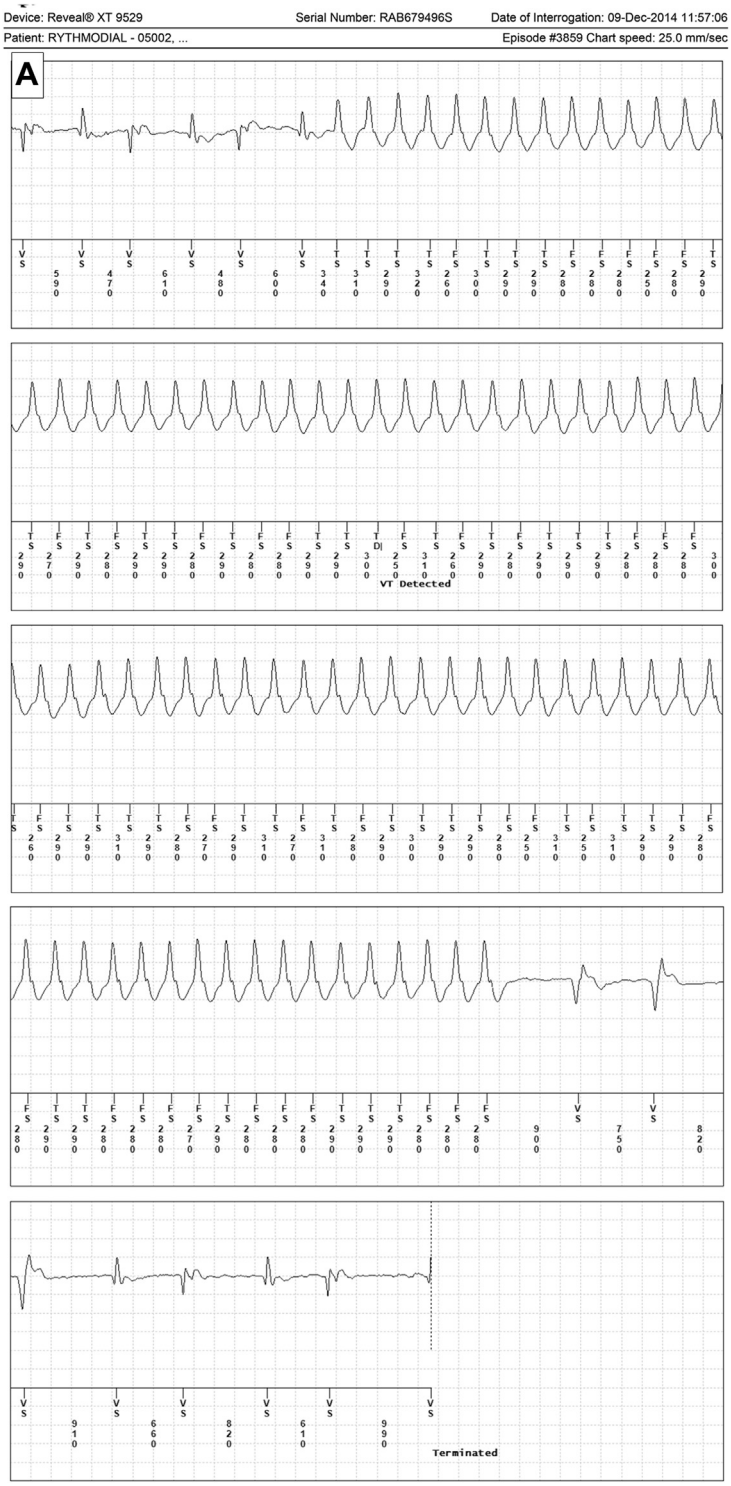
For atrial fibrillation or flutter (AF), patients with permanent AF at inclusion in the study are excluded from this figure. Among patients developing permanent AF during follow-up, only the first episode was counted.

RESULTS

POPULATION. Baseline. Seventy-one patients (mean age 65 ± 8.6 years, 52 men) undergoing maintenance HD for 1.6 years (IQR: 0.6 to 4.2 years) were included. Seven patients (9.8%) had been undergoing HD for <3 months. Diabetes (n = 32 [45%]) and hypertension (n = 19 [27%]) were the most common causes of end-stage renal disease, followed by glomerulonephritis (n = 5 [7%]), polycystic kidney disease (n = 4 [6%]), and other causes (n = 11 [15%]), with some patients having multiple causes. An ischemic CMP was present in 22 patients (31%), and left ventricular ejection fraction was <50% in 16%. A history of AF was noted in 12 patients (17%) at inclusion. Baseline characteristics are reported in Table 1.

Clinical events during follow-up. During a mean follow-up period of 21.3 ± 6.9 months, 16 patients (mean age 69 ± 6 years, 9 men) died and 3 underwent renal transplantation. The incidences of total mortality

FIGURE 3 Examples of Significant Ventricular Arrhythmias Recorded by the Implantable Loop Recorders



(A) Monomorphic nonsustained ventricular tachycardia (VT). **(B)** Runs of polymorphic VT.

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FIGURE 3 Continued

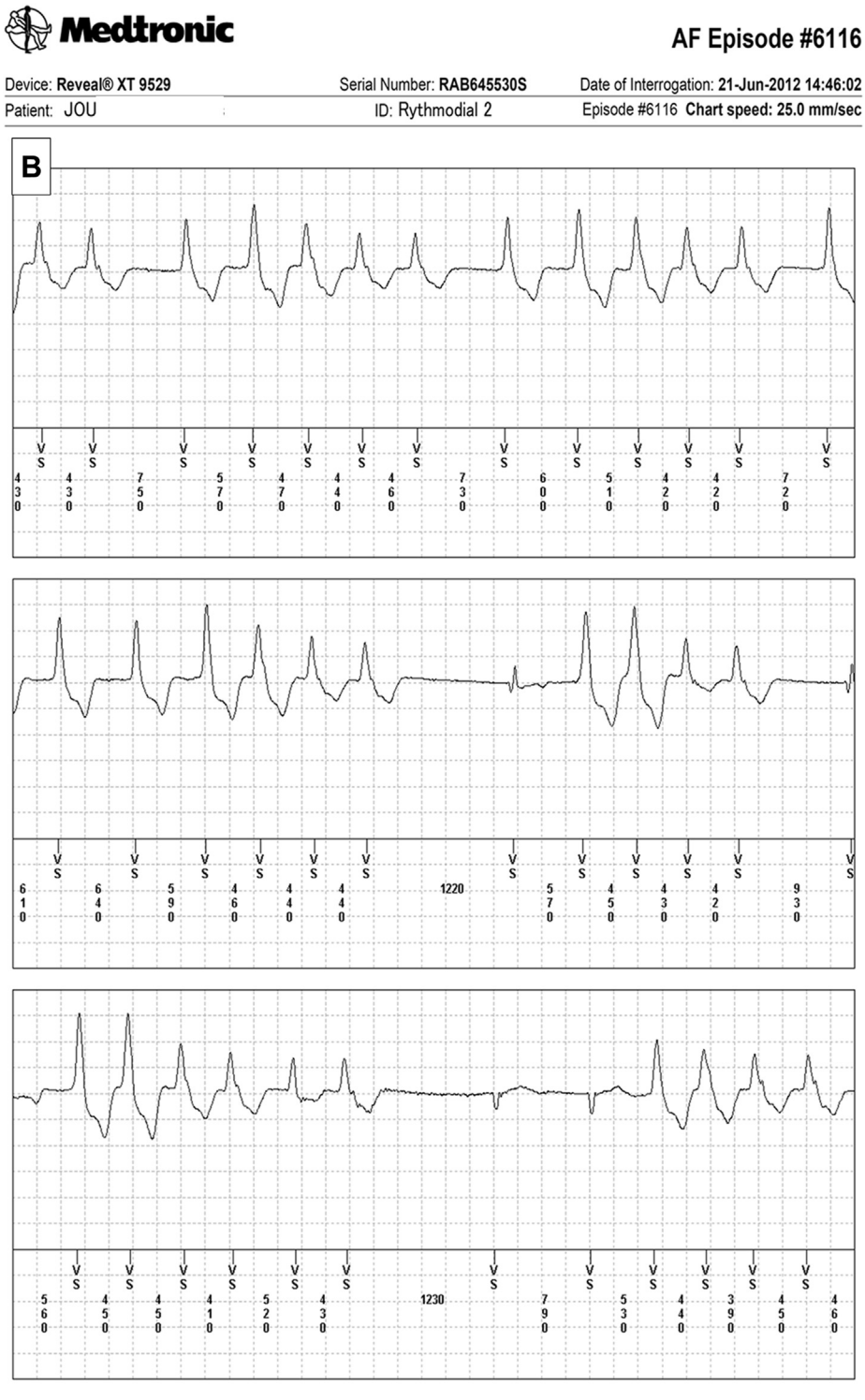
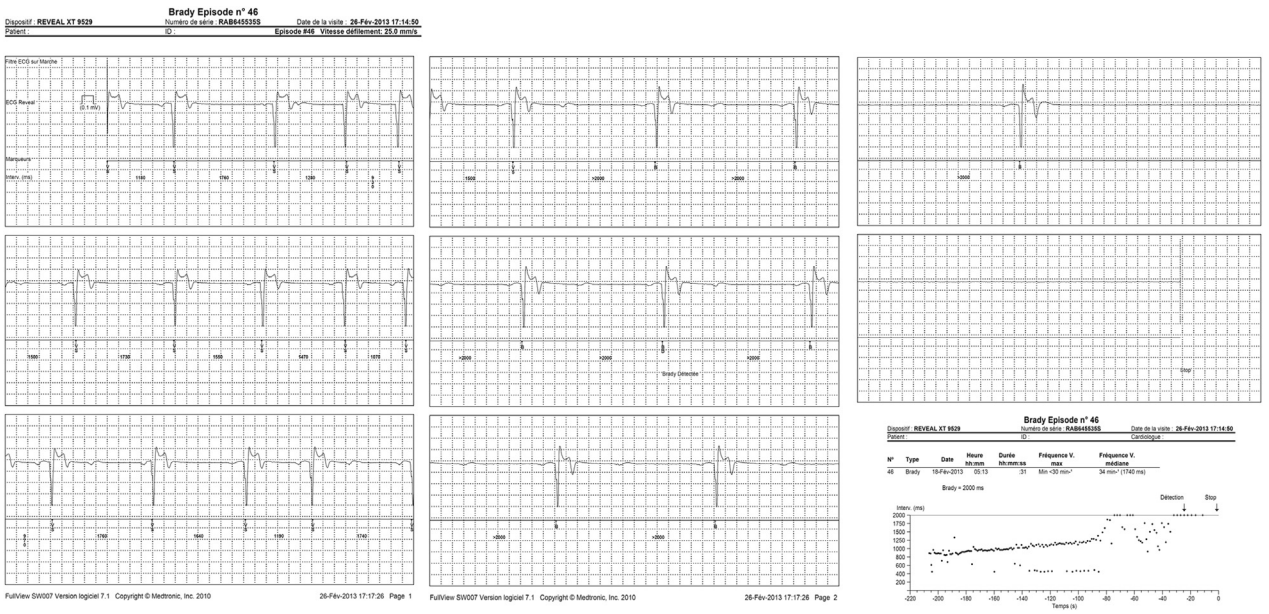


FIGURE 4 Implantable Loop Recorder Tracings in a Patient With Sudden Death



Similar tracings were seen in 3 patients with sudden death. It shows progressive rhythm lengthening followed by asystole without ventricular arrhythmia at the time of death.

and SD were 14% and 3% patient-years, respectively. The cause of death was cardiac in 5 patients and noncardiac in 11 patients (sepsis in 7 patients, stroke or complications of stroke in 2 patients, massive hemorrhage in 1 patient, and HD withdrawal for terminal illness in 1 patient). Concerning cardiac death, 1 patient had a massive myocardial infarction during hospitalization following femoral arterial graft surgery and died of terminal pulseless activity without a VT or VF episode. Four patients experienced SD, of whom 1 had an agonal rhythm with QRS widening (Figure 1) following myocardial infarction. In the 3 remaining patients, progressive bradycardia followed by asystole was recorded by the ILR, and no cause for these bradycardias leading to death could be identified.

ILR RECORDINGS DURING FOLLOW-UP. No adverse event related to the ILR occurred at implantation or during follow-up. Real events were recorded in 39 patients (55%). The mean number of events per patient is reported in Figure 2. Sixty-six patients had at least 1 oversensing or artifact recording, with a median of 95.5 (IQR: 11 to 522) of these episodes per patient. Remote monitoring capabilities allowed early transmission of arrhythmic events leading to specific treatment in 19 patients in our study.

Incidence of significant conduction disorders and/or VA. Sixteen patients experienced significant conduction disorders and 10 significant VA (nonsustained VT in all 10 patients) (Figure 3). The median time to occurrence of significant conduction disorder or VA was 12 months (IQR: 4 to 17 months). These were identified early because of the remote monitoring capabilities of the ILR. The incidence rates of such events were 56 (IQR: 42 to 70) and 10 (IQR: 4 to 16) per 100 patient-years, respectively. The incidence rates of patients' experiencing either significant conduction disorders or VA were 14 (IQR: 7 to 21) and 9 (IQR: 4 to 14) per 100 patient-years. Of the 4 patients with SD, 3 had severe bradycardia and ensuing asystole as the terminal event (Figure 4). The fourth patient was in the hospital for scheduled surgery and died suddenly in the context of low cardiac output due to a probable massive myocardial infarction. She rapidly developed severe metabolic acidosis with QRS widening (Figure 1) and experienced pulseless electric activity.

Pacemakers were implanted in 3 patients during follow-up for significant conduction disorders. No ICD was implanted in this population; however, the occurrence of nonsustained VT in ILR recordings provoked cardiologic work-up. Although no specific etiology was found in these cases, specifically no significant coronary artery disease, ILR-based diagnosis provoked tight control of serum K^+ levels between 4 and 5 mmol/l and administration of beta-blockers.

DETERMINANTS OF SIGNIFICANT CONDUCTION DISORDERS. Results of the univariate and multivariate analysis of the determinants of significant conduction disorder are presented in **Table 2 and** Online Table 1. In the multivariate analysis, pre-dialysis serum concentrations of K^+ >5 mmol/l (hazard ratio [HR]: 3.9; $p < 0.001$), bicarbonate <22 mmol/l (HR: 3.5; $p = 0.001$), hemoglobin >11.5 g/dl (HR: 3.2; $p = 0.005$), high-risk period (HR: 6.5; $p << 0.001$), history of coronary artery disease (HR: 23.3; $p = 0.004$), occurrence of other cardiac arrhythmias during follow-up (HR: 10.1; $p << 0.001$), and diabetes (HR: 9.7; $p = 0.04$) were associated with a higher risk for significant conduction disorders (**Table 2**). Conversely, systolic blood pressure ≤140 mm Hg after HD was associated with a lower risk for significant conduction disorder (HR: 0.34; $p < 0.001$). There was no relationship with several other parameters linked to HD, such as dialysate calcium and K^+ concentrations, ultrafiltration rate, and percentage body weight loss during HD.

DETERMINANTS OF SIGNIFICANT VAs. In the multivariate analysis of the determinants of significant VA (**Table 3**), the occurrence of other cardiac arrhythmias (conduction disorders or AF) during follow-up (HR: 46.2; $p << 0.001$) and serum K^+ <4 mmol/l (HR: 17.9; $p = 0.004$) were associated with a higher risk for VA. Conversely preventive treatment of VA with beta-blockers and strict serum K^+ blood level control significantly decreased the risk for such events (HR: 0.16; $p = 0.01$). None of the parameters linked to HD were significant in the multivariate analysis.

AF. Twelve patients had histories of AF at inclusion, and 14 developed AF during follow-up with early identification because of the remote monitoring capabilities of the ILR. AF prevalence was 37% in our population, and the incidence of patients' experiencing AF was 18 (IQR: 1 to 26) per 100 patient-years. In 8 patients (57%), AF identification by ILR recordings led to anticoagulation initiation. New AF episodes occurred a median of 6.7 months after inclusion, and the median number of episodes of AF per patient was 2.5 (IQR: 2 to 10).

Results of the univariate and multivariate analysis of the determinants of AF are presented in Online Table 3 **and Table 4**. In the multivariate analysis, male sex (HR: 67.5; $p = 0.004$), serum K^+ <4 mmol/l (HR: 2.5; $p = 0.01$), and serum phosphate >1.45 mmol/l (HR: 1.9; $p = 0.006$) were associated with an increased risk for AF. Specific drugs such as amiodarone, beta-blockers, calcium-channel blockers, and sodium channel blockers were not associated with reduced occurrence of AF.

TABLE 2 Multivariate Survival Frailty Model of the Determinants of Significant Conduction Disorder in Patients With Chronic Kidney Disease Undergoing Hemodialysis (n = 71)

		Hazard Ratio	95% Confidence Interval	p Value
Systolic blood pressure (mm Hg)	≤140 vs. >140	0.34	0.18–0.64	0.0009
Serum potassium (mmol/l)	<4 vs. 4–5	1.43	0.29–7.16	0.663
	>5 vs. 4–5	3.88	1.88–8.02	0.0002
Serum bicarbonate (mmol/l)	<22 vs. 22–24	3.46	1.60–7.51	0.001
	>24 vs. 22–24	0.74	0.30–1.85	0.519
Hemoglobin (g/dl)	<10.5 vs. 10.5–11.5	0.85	0.41–1.75	0.657
	>11.5 vs. 10.5–11.5	3.17	1.41–7.15	0.005
High-risk period	Yes vs. no	6.45	3.64–11.42	1.58×10^{-10}
History of coronary artery disease	Yes vs. no	23.35	2.74–199.18	0.004
Occurrence of other cardiac arrhythmias	Yes vs. no	10.07	4.55–22.27	1.17×10^{-8}
Gender	Male vs. female	0.71	0.08–6.11	0.753
Age (yrs)	58–73 vs. <58	25.87	2.13–314.24	0.011
	>73 vs. <58	14.99	0.75–298.05	0.076
Diabetes mellitus	Yes vs. no	9.72	1.17–80.97	0.035

DISCUSSION

The actual incidence rates of patients with significant conduction disorders, VA, and AF were, respectively, 14 (IQR: 7 to 21), 9 (IQR: 4 to 14), and 18 (IQR: 1 to 26) per 100 patient-years in HD patients implanted with ILRs for continuous rhythm monitoring over a mean period of 21.3 ± 6.9 months. The incidence rates of total mortality and SD were 14 and 3 per 100 patient-years, respectively. We showed that variations in serum K^+ concentrations are of critical importance. High K^+ was associated with conduction disorder, while low K^+ was associated with VA and AF.

TABLE 3 Multivariate Survival Frailty Model of the Determinants of Significant Ventricular Arrhythmia in Patients With Chronic Kidney Disease Undergoing Hemodialysis (n = 71)

		Hazard Ratio	95% Confidence Interval	p Value
Serum potassium (mmol/l)				0.011
	<4 vs. 4–5	17.94	2.54–126.67	0.004
	>5 vs. 4–5	4.21	0.61–28.92	0.144
Serum phosphate (mmol/l)				0.690
	<0.8 vs. 0.8–1.45	2.88	0.25–32.63	0.394
	>1.455 vs. 0.8–1.45	1.21	0.25–5.93	0.811
Ventricular antiarrhythmic drugs	Yes vs. no	0.16	0.04–0.69	0.014
History of coronary artery disease	Yes vs. no	0.16	0.03–1.03	0.053
Occurrence of other cardiac arrhythmias	Yes vs. no	46.23	7.96–268.48	1.9×10^{-5}
Gender	Male vs. female	0.39	0.12–1.32	0.131
Age (yrs)				0.569
	58–73 vs. <58	0.49	0.13–1.83	0.292
	>73 vs. <58	5.8×10^{-6}	0.00–∞	0.886
Diabetes mellitus	Yes vs. no	3.03	0.46–19.82	0.246

TABLE 4 Multivariate Survival Frailty Model of the Determinants of AF in Patients With Chronic Kidney Disease Undergoing Hemodialysis (n = 71)

		Hazard Ratio	95% Confidence Interval	p Value
Serum potassium (mmol/l)				0.010
	<4 vs. 4–5	2.48	1.21–5.10	0.013
	>5 vs. 4–5	0.73	0.46–1.17	0.198
Serum phosphate (mmol/l)				0.016
	<0.8 vs. 0.8–1.45	0.60	0.08–4.75	0.632
	>1.455 vs. 0.8–1.45	1.89	1.20–2.97	0.006
AF antiarrhythmic drugs	Yes vs. no	3.93	1.45–10.68	0.007
History of coronary artery disease	Yes vs. no	0.74	0.20–2.77	0.654
Occurrence of other cardiac arrhythmias	Yes vs. no	0.0002	0.00–∞	0.478
Gender	Male vs. female	67.50	3.94–∞	0.004
Age (yrs)				0.634
	58–73 vs. <58	1.63	0.34–7.79	0.540
	>73 vs. <58	2.62	0.36–19.09	0.342
Diabetes mellitus	Yes vs. no	0.57	0.15–2.13	0.402

SD is a major cause of death in HD patients. Unexpectedly, the terminated rhythm in the 4 patients with SD was not VF but progressive bradycardia followed by asystole. Wong et al. (7) reported similar findings using an ILR from another company in a similar population to ours, albeit with a longer duration of HD therapy (mean 5 ± 4 years vs. a median of 1.6 years in our study). No other study has so far observed cardiac rhythm at the time of death in such a population. Karnik et al. (8) described a cardiac arrest rate during HD of 7 per 100,000 HD sessions (400 cardiac arrests). Cardiac arrest occurred more frequently during the session following the long interdialytic period, a finding confirmed in other studies (9,10).

The presenting rhythm in those with documented arrhythmias was VF in 42.4%, VT in 19.7%, and asystole in 15.2%; however, in a study by Foley et al. (9), only 16.5% had electrocardiographic documentation at the time of arrest, and the study was confined to HD sessions and not to daily life. In our population, no SD events occurred during HD session.

Possible explanations for the significant proportion of bradycardia followed by asystole in our population as opposed to VA, which is the main cause of SD in the general population, include the small proportion of patients with left ventricular ejection fractions <35% (6%). However, when examining the published research on SD in long-term HD patients, the autopsy series reported by Takeda et al. (11) found that causes of SD in this population were stroke in 26%, dissecting aortic aneurysm in 14%, hyperkalemia in 11%, pulmonary edema in 9%, arrhythmia in 9%, and acute myocardial infarction in 6%. Therefore, cases of SD may not be all of cardiac origin, which could explain why prophylactic ICD implantation in this population has only a marginal effect on survival (12,13). Subcutaneous ICDs do not require venous access but have no true pacing mode. Their use has the potential to limit complications such as central vein stenosis or thrombosis or infections (14–16) but would not be expected to improve survival in SD related to asystole. In our series, 16 patients experienced significant conduction disorders leading to the cessation of bradycardic drugs when relevant, optimization of serum K^+ levels to <5 mmol/l, and pacemaker implantation in 3 cases. Of note, serum bicarbonate < 22 mmol/l and hemoglobin >11.5 g/dl were also associated with conduction disorders in multivariate analysis and should be carefully monitored in this population.

FACTORS ASSOCIATED WITH ADVERSE EVENTS IN PATIENTS UNDERGOING HD. Because of the limited number of patients with SD, we could not identify predictive factors. However, HD- and patient-related factors have previously been associated with SD. The initiation of HD is a crucial period with a high risk for SD, which then decreases after the second month before progressively increasing over time on HD (1,17). In our population, 7 patients were on HD for <3 months, and we therefore could not extrapolate the cause of SD early after HD initiation.

Several parameters, which may increase the risk for SD, have been identified. Coronary artery disease is the primary cause of significant VA in the general population, with an estimated prevalence in HD patients of 28% to 38% (18,19) compared with 31% in our study. The prevalence of microangiopathy is also important and may partly explain why revascularization does not improve VA or mortality in this specific population (20). Left ventricular hypertrophy is also a well-recognized risk factor for SD (21,22). Its incidence in HD patients may increase from 25% to 40% at the initiation of HD to 70% to 90% after several years (23). Left ventricular hypertrophy is multifactorial and has been associated with hypertension, anemia, chronic fluid overload, increased arterial stiffness, chronic inflammation, and increased sympathetic activity (23). Hyperphosphatemia was also found to increase myocardial fibrosis, left ventricular hypertrophy, and microangiopathy (24) and has been identified as a predictor of SD (25).

The deleterious effects of high hemoglobin levels in HD patients have been shown in several studies, including the seminal Normal Hematocrit Trial (26), in which mortality was higher in patients targeted to a high hemoglobin level. However, in that trial, the number of deaths from cardiac arrest was the same in the low- and high-hematocrit groups.

Myocardial fibrosis is frequently observed even without previous myocardial infarction (27) and is described as uremic CMP, which may in turn lead to heart failure and increased mortality.

Other well-known risk factors of SD are directly linked to HD. For practical reasons, HD is generally performed 3 times a week. The long interdialytic period (3 days) is a period of increased risk for SD (9,10,28,29). The 24-hour period around the HD session following the long interdialytic period was associated with the occurrence of significant conduction disorders, emphasizing the relationship between conduction disorder and SD.

In our study, low K^+ dialysate was associated with VA. Conversely, high serum K^+ was associated with conduction disorder. These results highlight the importance of a tight control of pre-dialysis serum concentration in patients treated with HD. We did not find any association with serum calcium concentration, probably because of the narrow range of variation. Jadoul et al. (30) clearly showed that low dialysate potassium is associated with a higher risk for death. In our cohort, 49.3% of patients were treated with dialysate potassium at 2 mmol/l and 35.2% with dialysate potassium at 3 mmol/l: this narrow range of variation due to homogeneous practices among centers explains the lack of association between dialysate potassium concentration and cardiac rhythm events.

Shorter HD sessions, higher ultrafiltration rate and volume (31), and a higher percentage of ultrafiltered fluid as a marker of fluid accumulation between HD sessions (32) have also been associated with a higher mortality risk.

AF. The prevalence of AF in HD patients has been estimated variably at about 20% (1), but ILR monitoring found higher figures of 42% in the series by Wong et al. (10) and 37% in ours. Of note, we found that half of episodes occurred in asymptomatic patients, suggesting that AF is largely underdiagnosed in this population using standard methods of detection (symptoms and electrocardiography), as has been similarly demonstrated for cryptogenic stroke with Reveal XT monitoring (33).

The most important complication of AF is ischemic stroke (3 or 4 events per 100 patient-years), which is 10 times more prevalent in patients with chronic kidney disease than in the general population (34). In the present study, ILR monitoring proved to be effective in detecting asymptomatic AF. Despite controversial data on the benefit of AF anticoagulation in patients undergoing HD (35,36), if anticoagulation of such patients can be shown to reduce stroke with acceptable bleeding rates, routine ILR insertion in such patients may be potentially beneficial and cost effective.

ILR IMPLANTATION IN HD PATIENTS. ILR implantation has been shown to be safe in this population. Remote monitoring capabilities allowed early transmission of arrhythmic events leading to specific treatment in 19 patients in our study.

CONCLUSIONS

ILR monitoring with remote monitoring capabilities may be useful in HD patients prone to significant conduction disorder, VA, or AF to allow early identification of such arrhythmias and initiation of adequate treatment. Using ILR monitoring in a population with ischemic CMP and/or lower left ventricular ejection fraction may increase the proportion of patients with VA as a cause for SD.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Remote monitoring capabilities allowed early transmission of arrhythmic events leading to specific treatment. Whereas VA is the main cause of SD in the general population, bradycardia followed by asystole seems frequent in patients with end-stage renal disease undergoing HD. The incidence rates of patients presenting with significant conduction disorder and with VA were 14 and 9 per 100 patient-years, respectively.

COMPETENCY IN PATIENT CARE: Significant conduction disorders were associated with plasma K^+ >5.0 mmol/l, bicarbonate <22 mmol/l, hemoglobin >11.5 g/dl, pre-HD systolic blood pressure >140 mm Hg, the longer interdialytic period, history of coronary artery disease, previous other arrhythmias, and diabetes mellitus. A higher risk for VA was associated with K^+ <4.0 mmol/l, no antiarrhythmic drugs, and previous other arrhythmias. Tight potassium control may limit significant conduction disorders and VA. With ILR monitoring, de novo AF was diagnosed in 14 patients (20%).

TRANSLATIONAL OUTLOOK: ILRs with remote monitoring capabilities may be of interest in patients with end-stage renal disease undergoing HD prone to significant conduction disorder, VA, or AF. A randomized control trial will determine the potential improvement of this strategy.

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APPENDIX For supplemental tables, please see the online version of this article.