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Review

Arrhythmias and Sudden Cardiac Death in End Stage Renal Disease: Epidemiology, Risk Factors, and Management

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ABSTRACT

Patients with end-stage renal disease (ESRD) are predisposed to heart rhythm disorders resulting in significant morbidity and mortality. Bradyarrhythmia appears to be more prevalent than ventricular tachyarrhythmias. There is also a high incidence of sudden cardiac death (SCD) in this group of patients, which cannot be explained only by traditional cardiac risk factors. The reported incidence and prevalence of arrhythmias and SCD is quite variable mainly because of the different study populations and recording techniques. The mechanism of SCD in patients with ESRD is also not clear. Although traditionally the thinking has been that ventricular arrhythmias are the main contributor to SCD, recent studies with implantable loop recorders have highlighted the role of bradyarrhythmias. The pathophysiological processes resulting in arrhythmia and SCD in patients with ESRD are

RÉSUMÉ

Les patients atteints d'insuffisance rénale en phase terminale (IRPT) sont prédisposés à des troubles du rythme cardiaque qui entraînent une augmentation considérable de la morbidité et de la mortalité. La bradyarythmie semble avoir une plus grande prévalence que les tachyarythmies ventriculaires. Dans ce groupe de patients, on note également une forte incidence de la mort subite d'origine cardiaque (MSOC), qui ne peut être expliquée que par les facteurs de risque cardiaque traditionnels. L'incidence et la prévalence des cas déclarés d'arythmies et de MSOC sont très variables principalement en raison des différentes populations étudiées et des techniques d'enregistrement. On ne connaît pas non plus le mécanisme de la MSOC chez les patients atteints d'une IRPT. Bien que traditionnellement on ait pensé que les arythmies ventriculaires contribuaient principalement à la

Patients with end-stage renal disease (ESRD) are predisposed to heart rhythm disorders, including bradyarrhythmias, atrial fibrillation (AF), ventricular tachyarrhythmias, and sudden cardiac death (SCD). Arrhythmias and SCD are a major cause of mortality in patients with ESRD.[1] According to the 2016 United States Renal Data System Annual Data Report, cardiovascular diseases contributed to more than half of all deaths in patients with ESRD and known causes.[2] Cardiac arrhythmias and cardiac arrest alone were responsible for 38.7% of the deaths. In another study, 50% of dialysis patients experienced a cardiac arrest within 5 years of initiating hemodialysis (HD).[3] In a study by Pun et al. involving 19,440 patients with coronary artery disease and chronic kidney disease (CKD), the rate of SCD per 1000 patient-years was 175 in patients with glomerular filtration rate < 15 mL/min and 249 in patients receiving dialysis.[4] The high rate of SCD in this group of patients, however, cannot be explained only by traditional risk factors noted in the general population and is likely a result of unique proarrhythmic risk factors. In addition to the fact that patients with ESRD have a high prevalence of underlying cardiac disease, the stress of HD itself might also contribute to increased rates of SCD. The purpose of this review is to discuss the epidemiology and risk factors of cardiac arrhythmias and SCD in ESRD. We also review the use of pharmacologic and device-based therapies for the management of cardiac arrhythmias and the prevention of SCD.

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Epidemiology of Arrhythmias in ESRD

Cardiac arrhythmias have been well described in patients with ESRD. There has been, however, significant variability in the incidence and type of arrhythmias reported in these patients. Notably initial studies that assessed cardiac arrhythmias in patients with ESRD were on the basis of electrocardiogram (ECG) and ambulatory ECG recording systems. These traditional tools have obvious limitations including inability to detect

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unique. Some of the risk factors, including dialysate composition, timing, and frequency, are modifiable and hence provide an option for interventions to potentially reduce SCD. In addition, there might be a relationship with the timing of dialysis with SCD tending to occur during the long interdialytic period. Patients with ESRD have a higher likelihood of requiring pacemaker implantation; however, they also have a higher risk of device-related complications. The limited data available regarding the role of the implantable cardioverter defibrillator to prevent SCD in patients with ESRD have shown conflicting results. Future research is needed to develop appropriate risk stratification tools to identify patients who will benefit from such interventions and to assess their safety and efficacy.

MSOC, de récentes études sur les enregistreurs en boucle implantables ont mis en évidence le rôle des bradyarythmies. Les processus physiopathologiques qui entraînent l'arythmie et la MSOC chez les patients atteints d'une IRPT sont uniques. Certains des facteurs de risque, dont la composition, le moment et la fréquence de la dialyse, sont modifiables et, par conséquent, offrent aux interventions la possibilité de réduire la MSOC. De plus, il se pourrait qu'il existe une relation entre le moment de la dialyse et la tendance de la MSOC à survenir pendant les longues périodes interdialytiques. Les patients atteints de IRPT sont plus susceptibles d'avoir besoin de l'implantation d'un stimulateur cardiaque. Cependant, ils sont également exposés à un plus grand risque de complications liées au dispositif. Les quelques données disponibles sur le rôle du défibrillateur cardioverteur implantable dans la prévention de la MSOC des patients atteints d'une IRPT ont montré des résultats contradictoires. Des recherches ultérieures sont nécessaires à l'élaboration d'outils appropriés de stratification du risque pour déterminer les patients qui bénéficieront de ces interventions et pour évaluer leur innocuité et leur efficacité.

temporal trends and circadian variation, which might explain the variability in results. In recent studies, the availability of the implantable loop recorder (ILR) has overcome these limitations and provided a clearer picture regarding the type of arrhythmias and also the cause of SCD death in this group of patients.

Bradyarrhythmias

Bradyarrhythmias (heart rate < 40 beats per minute [bpm]) have been consistently documented in patients with ESRD.[5,6] Studies using ILR have given us more insight into the incidence and prevalence of bradyarrhythmias in this group of patients (Table 1). Recently, there has been more evidence to suggest that they contribute significantly as a cause of SCD. In a study by Silva et al.,[6] involving 100 consecutive renal transplantation candidates with ILR, bradyarrhythmia was detected in 25% of the patients, which constituted asystole (4%), heart rate < 40 bpm (24%), and advanced atrioventricular (AV) block (1%). Roy-Chaudhury et al.[5] used ILR to study arrhythmias in 68 HD-dependent patients. Notably, in this study, bradyarrhythmia accounted for a much higher proportion of clinically significant arrhythmias than ventricular arrhythmias. Over a 6-month period, 1678 events were recorded in 44 of 66 subjects (66.7%), which included 19.7% bradycardia and 9.1% asystole. Although these studies are limited in the number of patients enrolled, they do consistently highlight the fact that bradyarrhythmia rather than ventricular arrhythmias are the predominant clinically significant arrhythmia in patients with ESRD.

Atrial fibrillation

AF frequently complicates the management of CKD, especially in patients with ESRD.[7] Deterioration in renal function is a well-documented independent risk factor for AF.[8,9] In patients with CKD, AF hastens the progress to ESRD and is associated with adverse clinical outcome.[10] The prevalence of AF varies between 11% and 27%[11-14] and has been reported as high as 32% in older HD-dependent patients (Table 1).[15] Previous investigators have also reported an increase in incidence and prevalence of AF in patients who commence dialysis. The incidence of AF has been reported as between 1 and 14.8 per 100 patient-years.[16-19] The incidence of AF is also higher in HD-dependent patients compared with peritoneal dialysis (PD)-dependent patients,[10,20] which might be explained by the nonphysiological nature of HD.[10] The difference in baseline characteristics, including age of the studied populations, type and documentation of the recorded AF episodes, and the associated risk factors might explain the marked difference in the reported incidence and prevalence.

Ventricular arrhythmias

Ventricular arrhythmias have been well documented in patients with ESRD,[21] however, variable figures have been quoted in descriptions of incidence and prevalence (Table 1). In a study involving 127 HD-dependent patients who were randomly selected from 13 centres, the incidence of ventricular arrhythmias was 76%, of which 6% were sustained ventricular arrhythmias.[22] Bozbas et al.,[21] in a study involving 94 HD-dependent patients who underwent 24-hour Holter monitoring, detected ventricular premature contractions in 80 (85%) patients, of whom 35 (37%) were classified as complex ventricular arrhythmia. In a study by Silva et al.,[6] sustained ventricular tachycardia (VT) or ventricular fibrillation (VF) were detected in 1% of patients. In the **C**ardio **R**enal **A**rrhythmia **S**tudy in **H**emodialysis Patients Using **I**mplantable **L**oop **R**ecorders (CRASH-ILR) study, the event rate for VT/VF was 46 per 1000 patient-years.[23] The significant variability in the incidence of ventricular arrhythmia is most likely dependent on the specific characteristics of the population and on the different diagnostic criteria and monitoring technique used for each study.

Epidemiology and Mechanism of SCD in ESRD

SCD is the single largest cause of death in patients with ESRD[6] accounting for 25%-29% of all-cause mortality in HD-dependent patients.[2,24,25] The reported incidence of SCD in patients with ESRD shows significant variation and there is a paucity of studies specifically designed to determine the incidence of SCD in this group of patients (Table 1).[26] Recent

Table 1. Incidence and prevalence of atrial fibrillation, bradyarrhythmias, ventricular arrhythmias, and SCD in ESRD

Reference	Sample size	Follow-up duration	Mode of monitoring	Incidence of arrhythmia	Prevalence of arrhythmia
All arrhythmias					
Roy-Chaudhury et al.[5]	66	6 Months	Reveal XT or LINQ	Bradycardia 4.7 (1.53-14.69)* Asystole 0.08 (0.03-0.26)* Ventricular arrhythmias 2.45 (1.6-3.74)*	Bradycardia 25.8% Asystole 10.6% VT 1.5%
Silva et al.[6]	100	424 ± 127 Days	Reveal XT	N/A	Bradycardia 25%† Asystole 4% AF 13% VT/VF 1%
Wong et al.[34]	50	12 ± 4 Months	ICM St Jude Medical	N/A	SCD 10%
Sacher et al.[35]	71	21.3 ± 6.9 Months	Reveal XT	Bradyarrhythmia 14% patient-years Ventricular arrhythmias 9% patient-years	Bradycardia 22% SCD 5%
Bozbas et al.,[21]	94	N/A	Holter	N/A	Complex ventricular arrhythmia 37.2%
[Gruppo Emodialisi e Patologie Cardiovasculari][22]	127	N/A	Holter	N/A	Ventricular arrhythmias 6% Bradycardia 9%
Atrial fibrillation					
Ansari et al.[16]	106	3 Years	ECG	N/A	5%
Abbott et al.[20]	3374	4 Years	ECG	12.5 per 1000 person-years	N/A
de Castroviejo et al.[17]	164	47 ± 29 Months	ECG	3.1 per 100 patient-years	N/A
Vazquez et al.[18]	333	25 ± 14 Months	ECG	5.9 per 100 patient-years	N/A
Zimmerman et al.[105]	(Meta-analysis)	25 Studies	ECG/Holter	2.7 per 100 patient-years	12.1%
Shen et al.[10]	15,947	8-10 Years	ECG/Holter	2.07 (1.93-2.23)*	N/A
Sudden cardiac death					
Karnik et al.[31]	N/A	N/A	N/A	7 Cardiac arrests per 100,000 HD sessions	N/A
Parekh et al.[28]	1041	Median 2.5 years	N/A	1.8% per year	N/A
Wang et al.[29]	230	5 Years	N/A	4.9% Per year	N/A
Ramesh et al.[26]	80,382 (meta-analysis)	N/A	N/A	0.4-10.04 Per 100 patient-years	N/A

AF, atrial fibrillation; ECG, electrocardiogram; ESRD, end stage renal disease; HD, hemodialysis; ICM, implantable cardiac monitor; N/A, not available; SCD, sudden cardiac death; VF, ventricular fibrillation; VT, ventricular tachycardia.

*Incidence ratio with 95% confidence interval.

†Bradycardia, ventricular rate < 40 beats per minute.

data also suggest an increased proportion of HD-dependent patients dying from SCD.[27] In the **C**hoices for **H**ealthy **O**utcomes **i**n **C**aring for **E**SRD (CHOICE) trial, a prospective study involving 1041 dialysis participants over 8 years of follow-up, there were 658 deaths, of which 146 were due to SCD (SCD rate of 1.8% per year).[28] In a 5-year prospective study in 230 ESRD patients, 24% of all deaths were attributed to SCD.[29] The cumulative incidence of SCD over a period of 3 years was 6.9% in a study involving 476 HD-dependent patients with ESRD.[30] Karnik et al.[31] analyzed 400 reported cardiac arrest episodes over a period of 9 months in HD-dependent patients. The incidence of cardiac arrest was 7 per 100,000 HD sessions. Finally, in a meta-analysis including 42 studies (80,382 patients), the incidence of SCD among adults with ESRD ranged from 0.4 to 10.04 deaths per 100 person-years.[26]

Ventricular arrhythmias

Most SCDs in the general population occur as a result of ventricular arrhythmias related to coronary artery disease. There is however, limited data supporting the relationship between SCD and ventricular arrhythmias in patients with ESRD. In a retrospective study involving 110 dialysis patients with cardiac arrest, ventricular arrhythmias were predominant among those who arrested during dialysis. In this study, the initial electrocardiographic rhythm was VF in 70 (65%) cases, VT in 2 (2%), pulseless electrical activity in 25 (23%) cases, and asystole in 11 (10%) cases.[32] Also, VF was significantly more likely to be reported as the initial cardiac rhythm than non-VF rhythms. In a study involving HD-dependent patients with a wearable cardiac defibrillator, a total of 75 HD patients experienced 84 sudden cardiac arrest events (119 arrhythmia episodes).[33] Of these, 35.7% occurred at home, 15.5% in hospital, 27.4% in the dialysis unit, 1.2% in rehab/nursing home, others (1.2%), and 19% unknown. Sixty-six (78.6%) sudden cardiac arrest events were due to VT/VF and 18 (21.4%) were due to asystole.

Bradycardia

Recent studies involving patents with ESRD and ILR have shown that bradyarrhythmia might result in SCD in patients with ESRD. In the Predictors of Arrhythmic Events Detected by ILRs in Hemodialysis Renal Transplant Candidates (PRETRANSPLANT) study of 100 ESRD patients, bradyarrhythmia was the predominant cause of SCD.[6] There were 7 incidences of SCD in this study of which 3 were attributed to bradycardia. Other causes included 1 VF, 1 acute myocardial infarction, and, in the remaining 2 cases, the ILR could not be analyzed. In a study involving 50 HD-dependent patients, after a mean follow-up of 12 ± 4 months, all deaths occurred in the long interdialytic period with severe

bradycardia followed by asystole. Notably, no ventricular arrhythmias were detected in these patients.[34] Sacher et al.[35] used ILRs in a study involving 71 HD-dependent patients. After a mean follow-up period of 21.3 ± 6.9 months, 4 (5.6%) SCDs were reported. During each of these episodes, there was progressive bradycardia followed by asystole. Fourteen percent and 9% of patients presented with significant conduction disorder and with ventricular arrhythmia, respectively. These relatively recent studies highlight the fact that although ventricular arrhythmias are common in patients with ESRD, fatal incidents are usually due to bradycardia.[36]

Risk Factors/Predictors of Arrhythmias and SCD in ESRD

Risk factors for bradyarrhythmia

A significant percentage of fatal arrhythmic events in patients with ESRD are bradycardic.[36] Taking this into consideration, efforts should be made to identify risk factors for bradyarrhythmia in this population specifically identifying those who might benefit from pacemaker implantation. Older age and coronary artery disease have been identified as predictors of bradyarrhythmias in several studies (Figure 1).[6,35,37] In the PRETRANSPLANT study of 100 ESRD patients,[6] the presence of a long QTc interval (ie, for men $>$ 450 ms, for women $>$ 470 ms; odds ratio [OR], 7.28; $P = 0.002$), and a prolonged PR interval (OR, 1.05; $P < 0.001$) were independently associated with bradyarrhythmias.[6] For each 10-ms increase in the PR interval, the likelihood of a bradyarrhythmia increased by 5% during follow-up. Sacher et al.[35] identified plasma potassium $>$ 5.0 mM, bicarbonate $<$ 22 mM, hemoglobin $>$ 11.5 g/dL, pre-HD systolic blood pressure $>$ 140 mm Hg, a longer interdialytic period, previous other arrhythmias, and diabetes mellitus as predictors of conduction disorders, defined as sinus bradycardia $\leq$ 30 bpm for $\geq$ 4 beats, pauses or asystole $\geq$ 3 s, or high-degree AV block (ie, second- or third- degree AV block) $<$ 40 bpm lasting $>$ 3 s.

Risk factors for ventricular arrhythmias

The frequency of ventricular ectopic beats during HD might vary from 18% to 76% depending on the study.[22,31,38-40] Predictors of ventricular ectopic beats during HD include age $>$ 55 years,[22] impaired left ventricular (LV) function, LV hypertrophy, systolic hypertension, increased concentrations of calcium, phosphorus, parathyroid hormone, and digoxin use (Fig. 1). However, importantly, the presence of ventricular ectopic beats during HD has not been identified as a predictor of SCD in this population. Silva et al.,[6] in a study of 100 ESRD patients, showed that LV dilatation was independently associated with nonsustained VT (OR, 2.83; $P = 0.041$). In a study by Bozbas et al.[21] involving 94 patients with ESRD, hypertension, coronary artery disease, and QTc dispersion were identified as independent predictors of ventricular arrhythmias.

Risk factors for SCD

Potassium homeostasis. Hyperkalemia and hypokalemia might play a role in the pathogenesis of SCD in ESRD. Genovesi et al.,[30] in a study involving 465 HD-dependent patients, showed that hyperkalemia was a significant predictor of SCD whereas hypokalemia was not associated with this outcome. Kovesdy et al.,[41] in a study involving 81,013 HD-dependent patients showed that serum potassium between 4.6 and 5.3 mEq/L was associated with greatest survival, whereas potassium $<$ 4.0 or $\geq$ 5.6 mEq/L was associated with increased mortality. The death risk of serum potassium $\geq$ 5.6 mEq/L remained consistent after covariant adjustments. Underlying mechanisms of hyperkalemia-related SCD include arrhythmias from overactivation of voltage-gated potassium channels resulting in shortening of ventricular repolarization, and inactivation of voltage-gated sodium channels, leading to slower depolarization and broadening of QRS complexes.[42] In contrast, hypokalemia-induced arrhythmogenicity has been attributed to prolonged ventricular repolarization, slowed conduction, and abnormal pacemaker activity.[43]

Dialysate composition. HD is associated with rapid fluid and electrolyte shifts, which might result in increased risk of SCD. Alteration in blood cation concentration, particularly potassium and calcium are usually unavoidable during HD sessions.[44] The gradients of these cation concentrations across the cardiac conduction and muscle cells have the potential to induce automaticity or re-entry, hence predisposing to arrhythmias. Most studies on the role of dialysate electrolyte composition have investigated changes in potassium concentration. In a study involving 23 HD-dependent patients, Morrison et al.[38] showed that compared with a dialysate potassium of 2 mEq/L, using a dialysate of 3.5 mEq/L potassium resulted in reduced frequency and complexity of ventricular arrhythmias. Karnik et al.[31] showed that HD patients with presenting cardiac arrest were nearly twice as likely to have been dialyzed against a low potassium (ie, 0 or 1.0 mEq/L) dialysate on the day of cardiac arrest (17.1% vs 8.8%). Pun et al.,[45] in a study of 43,200 ESRD patients, did not observe a strong relationship between traditional cardiac arrest risk factors and the occurrence of SCD. However, patients with SCD were significantly more likely to have been exposed to low potassium dialysate $<$ 2 mEq/L. Santoro et al.,[46] in a study involving 30 arrhythmia-prone HD patients, showed that the use of a low potassium dialysate resulted in greater arrhythmogenic activity compared with smoother potassium removal. A threefold reduction in intradialytic ventricular ectopic beats was seen in subjects whose dialysate potassium concentration was reduced gradually. Hence, there seems to be evidence to suggest a detrimental effect of aggressive potassium removal and the importance of regular assessment of serum potassium levels (Fig. 1). The potential proarrhythmic milieu is unlikely solely from the low dialysate concentration of potassium, but rather the gradient between serum and dialysate electrolytes combined with the short dialysis duration. It is unknown whether using a modified dialysate prescription would result in a reduction in SCD.

Dialysis modality. Electrolyte and acid base changes are less likely with PD compared with HD. Hence, theoretically SCD rates might be less in PD patients. The reported sudden death incidence is 49 per 1000 patients per year in the HD

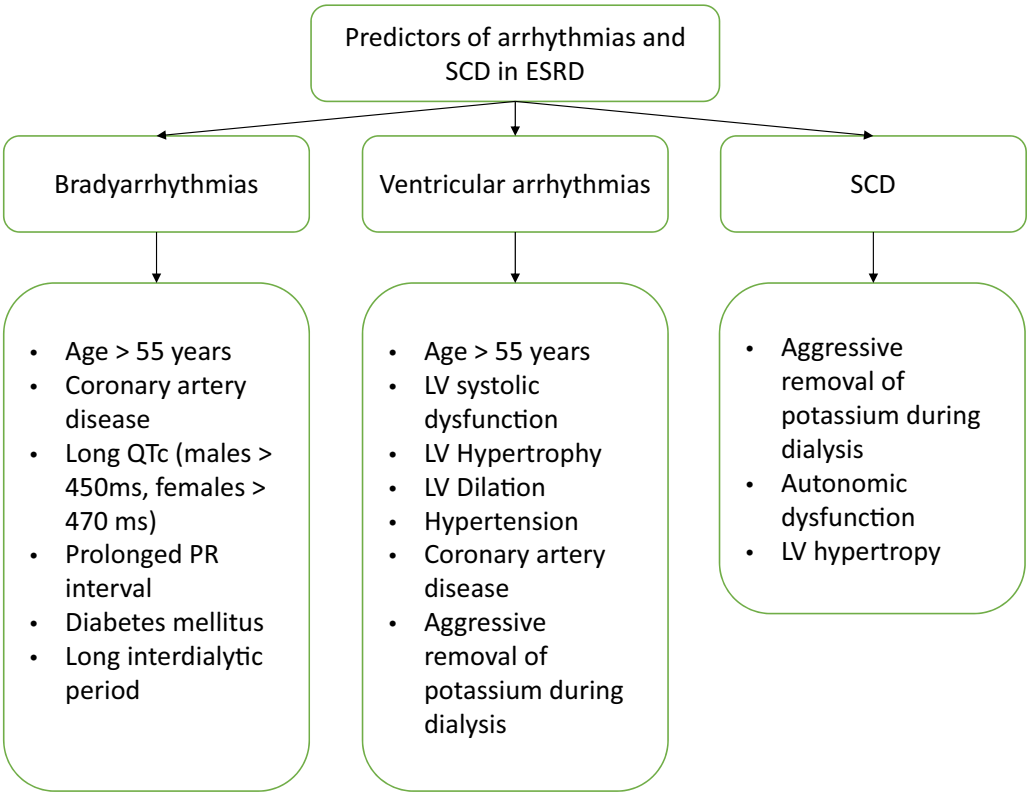

Figure 1. Predictors of arrhythmias and sudden cardiac death (SCD) in end stage renal disease (ESRD). LV, left ventricular.

population and 36 per 1000 patients per year in the PD population. Although the reported annual rate is low, this might reflect therapy selection bias because PD patients are usually younger with fewer comorbidities.[47] Notably, in the aforementioned study, the prevalence of subjects with LV ejection fraction (LVEF) $\leq$ 35% was higher in PD compared with HD patients. In one prospective study of 230 PD patients followed for 5 years, 28 patients suffered sudden death, 24% of all mortality, and at a rate as high as 5.6% per year. In contrast, in a multicentre prospective study involving 1823 HD and 249 PD patients, the incidence of sudden death did not differ in the 2 populations.[48] SCD is hence an important clinical problem in PD patients as well and more research is required to identify the pathophysiological process unique to PD that results in SCD.

LV systolic dysfunction. In the general population, LV systolic dysfunction is one of the major predictors of SCD. However, this is not the case in patients with ESRD. In studies by Pun et al.,[45] Genovesi et al.,[30] and Parekh et al.,[28] which included ESRD patients, LV systolic dysfunction was not a predictor of SCD. In a study by Nishimura et al.,[49] involving 196 patients with ESRD, death from acute myocardial infarction and congestive heart failure was associated with LV systolic dysfunction, but not SCD. Also, most patients with ESRD and cardiac arrest do not have an LVEF $<$ 35%.[50] Mangrum et al.[51] showed that LV systolic dysfunction was a significant predictor of SCD in HD-dependent patients. However, most (71%) of SCD occurred in patients with LVEF $>$ 30%. Hence, the most ESRD patients with SCD do not have impaired LVEF, which is similar to the general population.

LV size. In patients with uremic cardiomyopathy, LV dilatation associated with volume overload is a major determinant of increase in LV mass index. In a study by Satyan et al.,[52] N-terminal fragment of B-type natriuretic peptide was a marker of fluid overload and myocardial damage. N-terminal fragment of B-type natriuretic peptide was more strongly associated with mortality than cardiac troponin in asymptomatic HD patients suggesting that volume overload might play a role in predicting outcome.

LV hypertrophy is found in approximately 60%-80% of patients starting renal replacement therapy mainly as a result of increased preload from hypervolemia and increased afterload from greater peripheral resistance.[53] Studies have shown LV hypertrophy to be a predictor of cardiac death in dialysis patients (Fig. 1).[54] In a study involving 123 HD-dependent patients, the difference between LV mass indexed to body surface area between the time of recruitment and occurrence of the end point was the strongest predictor of SCD.[55] Adding weight to these findings, London et al.[56] showed that partial LV hypertrophy regression in patients with ESRD had a favourable and independent effect on patients' all-cause and cardiovascular survival. Although this variable may be used to estimate SCD risk, the fact that it is a common finding in this group of patients might limit its utility as an independent predictor.[57]

Coronary artery disease. In patients with ESRD, myocardial ischemia might be a contributor to SCD risk, however it is unlikely to play a significant role.[58] In support of this, an observational study of > 19,000 patients who underwent cardiac catheterization, showed that the severity of coronary artery stenosis did not explain the heightened risk of SCD among CKD patients.[4,59]

QT prolongation. QT prolongation is well documented in dialysis patients and hence might be an underlying cause for SCD. In a retrospective study by Matsumoto et al.[60] involving 102 HD patients, ECG data were analyzed at 1, 4, and 7 years after HD initiation. The control group comprised 68 age-matched individuals with normal renal function and 2 available ECG reports at an interval of more than 4 years. The average QTc interval at 4 and 7 years after HD initiation was significantly longer than that at 1 year after HD initiation (443, 445, and 437 ms, respectively; $P < 0.05$). However, QTc interval in the control group was 425 ms in the first year and 426 ms after an average of 6 years. In patients with ESRD, QTc prolongation appears to be the result of a gradual reduction in potassium channels[61] and an increase in sensitivity of the remaining potassium channels, resulting in diminished repolarization reserve and acquired long QT syndrome. Hence, drugs capable of inhibiting potassium currents, in particular I-Kr, might lead to further QTc prolongation and should be avoided.

Autonomic imbalance. Sympathetic overactivity is highly prevalent in patients with ESRD.[62] Enhanced cardiac sympathetic activity might act as a trigger of malignant ventricular arrhythmias in ESRD (Fig. 1).[49] In a study involving 71 HD-dependent patients, the presence of autonomic neuropathy was associated with increased supraventricular and ventricular arrhythmias.[63] Hayano et al.,[64] in a study involving 31 HD-dependent patients, identified reduced heart rate variability as an independent predictor for all-cause and sudden death. In a prospective cohort study involving 196 asymptomatic HD-dependent patients who had LV hypertrophy, cardiac sympathetic activity, assessed according to heart rate variability frequency analysis, was an independent predictor of SCD.[49]

Timing of Arrhythmias/SCD in Relation to the Dialysis Session

Patients with ESRD are limited in their ability to maintain homeostasis in the presence of metabolic and volume-related stressors. Several studies have shed light into the timing of arrhythmias and SCD in dialysis patients. In a study involving 110 HD-dependent patients who presented with cardiac arrest, the proportion of those with VF differed depending on whether the patient arrested before (30%), during (69%), or after (85%) HD ($P < 0.007$),[32] potentially indicative of different mechanisms of ventricular arrhythmia before, during, and after dialysis, respectively. In a Case Mix Adequacy Study in patients who were designated as Monday, Wednesday, and Friday dialysis candidates, 20.8% of sudden deaths occurred on Monday compared with the 14.3% expected ($P < 0.002$).[65] Similar trends were noted for Tuesday, Thursday, and Saturday dialysis patients. Another study by the same group identified the HD procedure as a major stressor leading to increased sudden death in the 12-hour period starting with the dialysis session.[24] In their study involving 80 HD patients who met the criteria for sudden death, a bimodal distribution of death occurrences was noted. There was a 1.7-fold increased risk of death in the first 12 hours starting with the dialysis procedure and also a threefold increased risk of death in the 12 hours preceding HD.[24] In a study by Karnik et al.,[31] involving 400 cardiac arrest episodes in HD-dependent patients with ESRD, 93 cardiac arrests were on Mondays compared with 54 on Wednesdays ($P < 0.001$) and 58 on Fridays ($P < 0.004$). There was no day-of-the-week effect for patients on a Tuesday-Thursday-Saturday schedule. In agreement with these findings, Foley et al.,[66] in a study involving 32,065 HD-dependent participants, showed that patients with long interdialytic intervals had significantly increased mortality from cardiac arrest (1.3 vs 1.0; $P = 0.004$) and dysrhythmia (20.9 vs 11.0; $P < 0.001$). Similarly, Roy-Chaudhury et al.[5] described the temporal relationship with arrhythmias and dialysis sessions. They noted arrhythmias reach a peak during the first weekly dialysis session and another peak during the last 12 hours of the long interdialytic period. Notably, the period toward the end of the interdialytic period was also significant for bradycardias.

Conventional 3 times a week HD is designed to provide adequate renal replacement therapy only. However, because of the obligatory long interdialytic gap, there are significant oscillations of extracellular fluid volume, electrolytes, and hemodynamics[67] within each HD session and during a typical week. Indeed, recent observational studies have documented the morbidity and mortality associated with a 2-day gap without renal replacement therapy.[66] It is possible that mechanisms of cardiac arrest involved in the periods before, during, and after dialysis therapy are not the same. Immediately before a patient begins dialysis, they might be at greater risk of cardiac arrest because of volume overload and accumulation of toxins. During dialysis, the rapid shift of fluid and rapid changes in electrolyte concentrations might increase cardiac stress and trigger arrhythmias or SCD.[45] These results hence emphasize the possible need for dialysis on a more frequent basis than 3 times a week.

Management and Prevention of Arrhythmias/SCD in ESRD

Prevention of cardiac arrhythmias and SCD in patients with ESRD had proven difficult because traditional cardiac risk factors play a less significant role. Important risk factors for arrhythmias and SCD relevant to this population are summarized in Figure 1.

Modification of dialysate

Modification of dialysate in terms of timing and composition might have a role in reducing SCD. Because of the increased risk of SCD during the long interdialytic period, there might be an argument for performing HD more frequently. To date, there is no evidence that this would result in reduction in arrhythmia or SCD; however this has been shown to reduce LV hypertrophy which is a predictor of SCD. Chan et al.,[68] in the Frequent Hemodialysis Network daily trial, showed that frequent HD (6 vs 3 sessions per week) resulted in significant reductions in LV end diastolic volume

Table 2. Antiarrhythmic drugs in patients with ESRD

Class	Drug	Indication	Renal clearance	Dosing in ESRD
IA	Quinidine	AF rhythm control and VT, VF	15%-40% Renal excretion[98]	Dose reduction required[99]
IA	Procainamide	Hemodynamically stable VT and AF cardioversion	60% Renal excretion[99]	Dose reduction required[99,100]
	Disopyramide	AF rhythm control	> 50% Renal excretion	Not recommended in ESRD
IB	Mexiletine	VF, VT, PVC	15% Renal excretion[99]	No adjustment required[99]
	Lidocaine	VT, VF	< 10% Renal excretion[99]	No adjustment required[99]
IC	Propafenone	VT, PVC in the absence of structural heart disease, AF cardioversion, and rhythm control	<1% Renal excretion[99]	No adjustment required[99]
	Flecainide	VT and PVC in the absence of structural heart disease, AF cardioversion, and rhythm control	35% Renal excretion[99]	Dose reduction required
II	Atenolol	VT, PVC, AF rate control	40% Renal excretion[101]	10%-50% dose reduction (GFR 10-50 mL/min/1.73 m^2) and 25% dose reduction (GFR < 10 mL/min/1.73 m^2)[102]
	Bisoprolol	VT, PVC, AF rate control	50% Renal excretion[101]	75% dose reduction (GFR 10-50 mL/min/1.73 m^2) and 50% dose reduction (GFR < 10 mL/min/1.73 m^2)[102]
	Carvedilol	VT, PVC, AF rate control	Primarily through feces	No adjustment required
	Metoprolol	VT, PVC, AF rate control	< 5%-10% Renal excretion	No adjustment required
	Nadolol	VT, PVC, AF rate control	Excreted predominantly via kidneys[101]	50% dose reduction (GFR 10-50 mL/min/1.73 m^2) and 25% dose reduction (GFR < 10 mL/min/1.73 m^2)[102]
	Propranolol	VT, PVC, AF rate control	Cleared predominantly by the liver[103]	No adjustment required
III	Sotalol	VT, VF, PVC, AF cardioversion and rhythm control	70% Renal excretion[99]	Once-daily dosing with CrCl 40-60 mL/min. Not recommended if CrCl < 40 mL/min[104]
	Amiodarone	VT, VF, PVC, AF rhythm and rate control	No renal excretion[99]	No adjustment required[99]
	Dofetilide	AF cardioversion and rhythm control	60%-70% Renal excretion[99]	Contraindicated with GFR < 20 mL/min/1.73 m^2;[99]
IV	Verapamil	Idiopathic VT, AF rate control	70% Renal excretion[101]	25%-50% dose reduction with CrCl < 10 mL/min. Not cleared by hemodialysis[101]
	Diltiazem	Idiopathic VT, AF rate control	2%-4% Renal excretion	No adjustment required

AF, atrial fibrillation; CrCl, creatinine clearance; ESRD, end stage renal disease; GFR, glomerular filtration rate; PVC, premature ventricular contraction; VF, ventricular fibrillation; VT, ventricular tachycardia.

and LV end systolic volume. Additionally, less aggressive removal of potassium and fluid with intensive monitoring of electrolytes might be useful in this setting. At this time, there is no evidence to suggest that these strategies would be antiarrhythmic.

Rhythm control and stroke prevention with AF

Management of AF in ESRD continues to pose a challenge, mainly as a result of these patients being excluded from most major clinical trials. It also is not clear whether maintenance of sinus rhythm would benefit these patients. In a study involving 102 patients with CKD who underwent successful cardioversion, Schmidt et al.[69] showed that severely decreased renal function significantly predicted recurrence of AF at 1 month. Pharmacotherapy for AF would include propafenone, lipophilic β-blockers (eg, metoprolol and carvedilol) and nondihydropyridine calcium channel blockers (eg, diltiazem). Amiodarone is highly effective, however its use is limited because of the long-term risk of pulmonary, renal, and thyroid toxicity. Table 2 shows a summary of renal dose adjustment for these and other commonly used antiarrhythmic drugs. Data regarding catheter ablation are limited. Sairaku et al.[70] assessed outcomes in a retrospective study involving 30 HD and 60 age- and sex-matched control patients who underwent pulmonary vein isolation. Six (54%) of the HD patients were free from AF recurrence vs 47 (78%) of the control patients after the initial ablation ($P = 0.013$). Twelve patients underwent a second procedure. After a follow-up of 747 ± 221 days, 20 (67%) of the HD patients were in sinus rhythm compared with 53 (88%) of control participants ($P = 0.012$). Hayashi et al.[71] assessed the long-term clinical outcomes of 16 HD patients and 111 non-HD patients as controls. In patients who underwent multiple procedures, they found no significant difference in AF rate after the last procedure. On the basis of these studies, there might hence be a role for AF catheter ablation in HD-dependent patients, if medical therapy including amiodarone is ineffective or contraindicated.

Although dialysis patients with AF have an increased risk of ischemic stroke, there seems to be no clear consensus regarding stroke risk reduction therapy. Anticoagulation in patients with AF and ESRD is an area where evidence-based knowledge is limited. Observational studies have shown

Table 3. Pacemaker usage and complications in ESRD

Reference	Study patients	Study design	PPM implantation rates	PPM complication rates
Wang et al.[37]	HD and PD patients	Case control study (2000-2010) Cases: HD (n = 18,771) and PD (n = 9700) Controls: no renal disease (n = 113,769)	Rates of PPM implantation were 5.93- and 3.50-fold greater in HD and PD than in controls	N/A
Leman et al.[79]	ESRD patients	Case control study (1973-1983) Cases: ESRD (n = 1029) Controls: no renal impairment	Higher rate of PPM implantation in ESRD vs controls (0.68% vs 0.29% over 10 years)	N/A
Dasgupta et al.[80]	ESRD patients	Case control study Cases: ESRD (n = 41) Controls: no renal impairment (n = 123)	N/A	Major complications in 29% with ESRD vs 5% of controls ($P = 0.001$) Minor complications in 17% and 6%, respectively ($P = 0.03$)

ESRD, end stage renal disease; HD, hemodialysis; N/A, not available; PD, peritoneal dialysis; PPM, pacemaker.

mixed results with regard to the use of warfarin.[72-74] In a meta-analysis including 14 observational studies (20,398 participants), warfarin did not significantly decrease risk of ischemic stroke. In addition, there was no significant association between warfarin use and intracranial hemorrhage, gastrointestinal bleeding, or all-cause mortality. However, when a more comprehensive definition of bleeding was evaluated, warfarin did show a greater risk of hemorrhage.[75] The novel oral anticoagulants (NOACs) have some degree of renal excretion, and become difficult to dose with creatinine clearance < 25-30 mL/min.[76] Hence, these patients are under-represented in the large NOAC randomized controlled trials. In a retrospective cohort study involving 25,523 patients with ESRD, standard-dose apixaban (5 mg twice a day) was associated with significantly lower risks of stroke/systemic embolism and death compared with either reduced-dose apixaban (2.5 mg twice a day) or warfarin.[77] Apixaban has been approved for use in HD patients by the Food and Drug Administration on the basis that it has a lesser degree of renal excretion compared with other NOACs. There are at present several ongoing studies pertaining to stroke risk reduction in patients with AF and ESRD. **Ren**al Hemodialysis Patients **All**ocated Apixaban Versus Warfarin in **A**trial **F**ibrillation (RENAL-AF) (NCT02942407) is an open-label, blinded end point clinical trial, randomizing HD patients with AF to 5 or 2.5 mg apixaban twice daily or to warfarin.[78] An open-label randomized controlled trial, AXADIA, will assess the safety of apixaban vs phenprocoumon in HD-dependent patients with AF. The **S**trategy **to** **P**revent **H**emorrhage Associated with **A**nticoagulation in **R**enal Disease **M**anagement (STOP-HARM) (NCT02885545) trial will compare warfarin, rivaroxaban, or apixaban with left atrial appendage occlusion with a Watchman device (Boston Scientific) in dialysis-dependent AF patients.[78]

Permanent pacemaker in ESRD

Because of the prevalence of bradyarrhythmias and their major contribution to SCD in patients with ESRD, there may be a role for pacemaker implantation. However, there is limited information regarding the outcome of permanent pacemaker implantation in this group of patients. Compared with the general population, patients with ESRD have a higher rate of pacemaker implantation. This was shown by Leman et al.,[79] who reported a higher rate of pacemaker implantation with ESRD (0.68% vs 0.29% in the general population) over a 10-year span (Table 3). Furthermore, in a study involving 28,471 newly diagnosed patients with ESRD and 113,769 randomly selected patients, the incidence of permanent pacemaker implantation in the HD and PD population was 5.9 and 3.5 times, respectively, compared with controls. We have previously discussed predictors of bradyarrhythmia in patients with ESRD. Wang et al.[37] identified older age, coronary artery disease, and AF as risk factors for permanent pacing in dialysis patients. It is also important to take into consideration the complications associated with pacemaker implantation in patients with ESRD. In the study by Wang et al.,[37] the complication rates resulting in pacemaker removal or revision were higher in dialysis patients compared with the control population (29.5 vs 18.6 per 1000 person-years after implantation). In an observational study involving 41 patients with ESRD and 123 without ESRD, who had permanent pacemaker or implantable cardioverter defibrillator (ICD) implantation, patients with ESRD had significantly higher complication rates (39% vs 11%; $P < 0.001$).[80] The risk was also higher for HD patients than for PD patients. These factors must be taken into consideration when making decisions regarding pacemaker implantation in this group of patients.

ICD therapy in ESRD

The role of ICD to prevent SCD in patients with ESRD is not clear. This is mainly because of the lack of randomized studies that have evaluated ICDs in patients with ESRD.[81] As a result, we are guided mainly by single-centre studies and registry data when deciding on ICD implantation. Mortality remains high in patients with ESRD despite that they are more likely to receive appropriate ICD therapy.[82] The unique metabolic derangements might make these patients refractory to ICD therapy. Also, in a study by Wase et al.[83] involving 95 patients with CKD, there was a progressive increase in defibrillation thresholds with worsening renal failure potentially from worsening LV hypertrophy and fibrosis. Another fact that needs to be taken into consideration is the elevated risk of periprocedural infection.[82] Charytan et al.[82] reported a device infection rate of 42/1000 patient-years in patients with ESRD who underwent ICD implantation. Dasgupta et al.[80] reported

Table 4. ICD usage and complications in renal disease

Reference	Study patients	Study design and ICD Therapy	ICD-related outcomes
Hreybe et al.[86]	HD patients (2001-2002)	Case control study (2001-2002) Cases: primary prevention ICD (77% of cohort; n = 230) Controls: primary prevention ICD but patients not receiving HD	Appropriate ICD shocks were more in HD patients vs patients not receiving HD (57% vs 11%; $P = 0.006$)
Hager et al.[106]	Chronic kidney disease patients (2000-2006)	Two-centre retrospective study (n = 958) Primary prevention ICD	Chronic kidney disease was an independent predictor of mortality
Herzog et al.[87]	HD patients	Case control study (1996-2001) Cases: secondary prevention ICD for VF/cardiac arrest (n = 460) Controls: no ICD (n = 5582)	ICD implantation independently associated with a 42% reduction in death (relative risk, 0.58; 95% CI, 0.50-0.66)
Goldenberg et al.[107]	Cardiomyopathy patients with chronic kidney disease (eGFR < 35 mL/min/1.73 m^2)	Subanalysis of MADIT II (randomized control trial; n = 80) Group 1: primary prevention ICD Group 2: no ICD	No mortality benefit from ICD
Pun et al.[85]	HD patients	Case control study Cases: primary prevention ICD (n = 108) Controls: no ICD (n = 195)	Comparing the propensity-matched cohorts, 1-year (3-years) mortality was 43.4% (74.0%) in the ICD cohort and 39.7% (76.6%) in controls (P = not significant)
Pun et al.[85]	Cardiomyopathy patients with impaired renal function (eGFR < 60 mL/min/1.73 m^2)	Pooled analysis of MADIT I, MADIT II, and SCD-HeFT (randomized control trial; n = 1032) Group 1: primary prevention ICD Group 2: no ICD	No mortality benefit from ICD

CI, confidence interval; eGFR, estimated glomerular filtration rate; HD, hemodialysis; ICD, implantable cardioverter defibrillator; MADIT, **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial; SCD-HeFT, **S**udden **C**ardiac **D**eath in **He**art **F**ailure **T**rial; VF, ventricular fibrillation.

a nonsignificant trend ($P = 0.1$) in increased risk of infection in 41 patients with ESRD vs 123 control participants without ESRD who received a permanent pacemaker or ICD.

Primary prevention ICD

In the **M**ulticenter **A**utomatic **D**efibrillator **I**mplantation **T**rial (MADIT) II randomized control trial involving 1232 patients with ischemic cardiomyopathy and LVEF < 35%, all-cause mortality and SCD was reduced in patients randomized to primary prevention ICD and an estimated glomerular filtration rate > 35 mL/min/1.73 m^2 compared with those randomized with no ICD.[84] However, this survival benefit was not apparent in the subset of patients (n = 80) with estimated glomerular filtration rate < 35 mL/min/1.72 m^2,[84] hence raising questions regarding the benefit of primary prevention ICD in ESRD (Table 4). Pun et al.,[85] in a study involving 108 dialysis patients with primary prevention ICDs and 195 dialysis patients without ICDs, reported that there was no significant difference in 1- and 3-year mortality between the 2 groups. In a comparison of the propensity-matched cohorts, 1-year (3-years) mortality was 43.4% (74.0%) in the ICD cohort and 39.7% (76.6%) in the control cohort.

Secondary prevention ICD

Patients with renal dysfunction are at higher risk of receiving appropriate ICD therapies for ventricular arrythmias.[86] Charytan et al.[82] compared 2232 dialysis patients who received an ICD for secondary prevention with 8928 control participants. There was a small, but significant reduction in mortality up to 2 years in those who received an ICD. When the patients were followed up to 3 years, this survival advantage was no longer present. Herzog et al.[87] assessed the effect of ICD implantation in dialysis patients hospitalized with VF arrest and having ICD implantation within 30 days of admission. In this study, 460 patients (7.6%) received an ICD, whereas the remaining patients (n = 5582; 92.4%) who presented with cardiac arrest did not receive an ICD and served as the control group. ICD implantation was independently associated with a 42% reduction in death (relative risk, 0.58; 95% confidence interval, 0.50-0.66; Table 4). This study highlighted the underutilization of ICDs in this population. Renal impairment itself might influence the beneficial effects of ICDs. The findings from the previously mentioned studies emphasize the need for randomized trials of ICD therapy in this patient population. In the 2017 American Heart Association/ American College of Cardiology/Heart Rhythm Society guideline for management of patients with ventricular arrhythmias and the prevention of SCD[88]—the writing committee concluded there were not enough data to inform a recommendation on ICD implantation in HD-dependent patients with ESRD. In agreement with these guidelines, we believe that decision-making regarding ICD implantation should be made on an individualized basis taking into consideration the risk benefit ratio, functional status, and patient wishes.

Vascular access

Another factor relating to device implantation that should be taken into consideration in patients with ESRD is vascular access.[89] Central vein stenosis is a significant complication in patients who undergo transvenous lead implantation with ESRD. In one study, subclavian vein stenosis was noted in 71% of patients with AV fistula ipsilateral to the lead.[90] Superior vena cava syndrome has also been described in up to

18% of HD-dependent patients.[91] Traditionally, transvenous placement of devices contralateral to existing HD access has been the treatment of choice. Some authors have suggested avoidance of transvenous lead placement because of the potentially disastrous complications of central vein stenosis and spreading infection from an infected vascular prosthesis/central venous catheter to the transvenous leads.

Other options include epicardial lead placement and leadless pacemaker. Epicardial leads have been traditionally avoided, however, recently minimally invasive epicardial approaches have been made available.[92,93] In a study involving 201 HD-dependent patients, 197 patients (98%) underwent successful implantation of a leadless pacemaker in the right ventricular endocardium using the Micra (Medtronic Inc) transcatheter pacemaker.[94] Reasons for failure included increased pacing threshold (n = 2) and pericardial effusion (n = 2). There were 3 procedure-related deaths. One occurred because of metabolic acidosis in the context of prolonged procedure time. Two deaths occurred in the context of lead perforation.

Subcutaneous ICD (S-ICD) placement remains another option in those without a pacing indication.[95] In a study involving 86 S-ICD patients of whom 18 (21%) were HD-dependent at the time of implantation, there was no difference in procedural complications between the HD and non-HD cohort.[96] In another study involving 79 patients with S-ICD implants of whom 27 were HD-dependent, no patient in the dialysis cohort had complications requiring surgical reintervention vs 6 patients in the nondialysis cohort ($P = 0.086$).[97] Lack of pacing capability with S-ICDs might be an important limitation because ESRD patients are more likely to develop bradyarrhythmias. Finally, wearable cardiac defibrillators might be used as a temporary option.[33]

Conclusion

SCD is the single largest cause of mortality in patients with ESRD. Traditional thinking was that SCD in patients with ESRD was because of lethal ventricular arrhythmias, similar to the general population. However, recent studies involving ILRs have revealed that a significant proportion of the terminal arrhythmias in these patients comprised bradycardia followed by asystole. It is important to note that the pathophysiological processes resulting in arrhythmia and SCD in patients with ESRD are unique to this group of patients. Some of the risk factors, including dialysate composition, timing and frequency, are modifiable and hence provide a possibility for interventions to potentially reduce SCD. On the basis of recent evidence, there might be a role for pacemaker implantation to manage bradyarrhythmias and prevent SCD. Also, ICDs might have a role in preventing SCD in this population. Using LV dysfunction only as a SCD risk factor would result in omission of a significant proportion of ESRD patients who present with SCD. Future research is needed to develop appropriate risk stratification tools to identify patients who would benefit from such interventions and to assess their safety and efficacy.

Disclosures

The authors have no conflicts of interest to disclose.

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