Patients with end-stage renal disease (ESRD) on long-term dialysis therapy have very high mortality due to predominantly cardiovascular causes (Figure 1). Sudden cardiac death (SCD) is the single most common form of death in dialysis patients, accounting for 20% to 30% of all deaths in this cohort. These patients indeed have a very high burden of coronary artery disease (CAD), and a proportion of SCD events could be due to obstructive CAD. However, epidemiological and observational studies have reported that the overall incidence of SCD in this population is much greater than the incidence of coronary events, and the risk of SCD persists even after coronary revascularization. These findings suggest a possibility of a primary increase in the risk of fatal ventricular arrhythmias, which is the most common cause of SCD. Dialysis patients with ESRD have several factors that could predispose them to a high risk of ventricular arrhythmias (Table 1). A large number of dialysis patients have diabetes, and thus, autonomic neuropathy as a consequence of both chronic uremia and coexisting diabetes is very common, resulting in alterations in autonomic control with a sustained increase in the sympathetic tone reported to be proarrhythmic. Similarly, hypertension is very common, and uremia leads to secondary hyperparathyroidism, both of which lead to considerable left ventricular hypertrophy (LVH). In addition, chronic uremia leads to endothelial dysfunction, and the combination of endothelial dysfunction and LVH compromises perfusion reserve and makes the individual susceptible to arrhythmias precipitated by ischemia. Long-standing uremia leads to uremic cardiomyopathy, with typical changes of diffuse myocardial fibrosis, which could lead to slowing of conduction and increased dispersion of repolarization, both of which have been shown to be proarrhythmic. Significant sudden shifts in electrolytes and fluid volume that surrounds a dialysis session acts as a trigger and can initiate life-threatening arrhythmias in patients with a susceptible substrate. Hence, it is conceivable that risk assessment tests that evaluate these variables could be used to identify dialysis patients at risk of SCD. In this review, we discuss the rationale behind the use of specific risk assessments to evaluate the risk of SCD in the dialysis cohort and review the current evidence on the use of some of these tests in dialysis patients with ESRD.

Left Ventricular Systolic Dysfunction and Risk of SCD in Dialysis

Severe left ventricular systolic dysfunction (LVSD) is reported to be a reliable indicator of high risk of SCD and has been used as the single most important variable in selecting patients for implantable cardioverter defibrillators (ICDs). Notably, clinical trials on ICD either actively excluded or had very few patients with ESRD. When patients with ESRD received an ICD, the main parameter used to decide on the need for an ICD was severe LVSD. A large number of dialysis patients who died suddenly did not have significant LVSD, and 1 prospective study of mortality in a dialysis population reported that severe LVSD was not an independent predictor of SCD. Thus, it is likely that a significant proportion of patients with ESRD with a high risk of SCD may have preserved left ventricular systolic function and by using LVSD as the main risk identifier, these patients who arguably might have lower risk of nonarrhythmic mortality, particularly that related to pump failure, will be missed. In that context, 1 study reported that the current risk assessment model identifies far fewer patients than would be expected to have a potential risk of SCD, thus indicating a need for specific risk assessment to address the unique features that predispose dialysis patients to SCD and enable appropriate intervention, such as an ICD, to be tested in those found to be at highest risk.

ICD in Dialysis Patients: Current Evidence

Several therapeutic interventions have the potential of reducing the risk of SCD in a high-risk population of which the most effective is an ICD. As yet, no prospective data are available on the effect of ICDs in the dialysis population. Much of the currently available data are obtained from retrospective analysis of major ICD trials and these studies have raised doubts about the benefit of ICD therapy in this subgroup of patients. However, such analyses also confirmed that dialysis patients have a higher incidence of appropriate ICD therapy. Another retrospective analysis that compared ICD recipients within the dialysis group, reported that those with ICD have had a better survival rate. These facts seem to suggest that ICD therapy is likely to be useful in dialysis patients if appropriate risk stratification...
was used to identify high-risk individuals. The main issue affecting the outcome of ICD therapy in dialysis patients in these retrospective analyses is a high risk of nonarrhythmic mortality often related to deaths due to pump failure or infective complications. This observation could have been influenced by the selection criteria for an ICD in these studies, which was mainly severe LV dysfunction. It is therefore essential to prospectively identify dialysis patients at high risk of SCD who may not have severe LV dysfunction so that the effect of an ICD in this high-risk group could be evaluated appropriately.

ECG and Risk of SCD in Dialysis
Several ECG markers, such as mean QRS duration, corrected QT interval, and QT dispersion, have been suggested as potential predictors of ventricular arrhythmias in dialysis patients. However, the relationship between these episodes of ventricular arrhythmias and risk of SCD has not been established. In a large prospective study in patients with diabetes undergoing hemodialysis, Krane et al reported that absence of sinus rhythm in ECG predicted high risk of all-cause mortality, whereas presence of LVH predicted high risk of SCD (P = 0.027).

LVH and Risk of SCD in Dialysis
LVH has been shown to be a major predictor of SCD independent of left ventricular systolic function in several clinical conditions, such as systemic hypertension and ischemic heart disease. Significant LVH is a common feature of uremic cardiomyopathy, with 60% to 80% of patients with ESRD commencing dialysis while showing echocardiographic evidence of LVH. In addition to systemic hypertension, both as a common cause of ESRD and as a consequence of it, other factors unique to ESRD, such as hyperparathyroidism, high cardiac output due to anemia and arteriovenous fistula, and activation of the neuroendocrine systems, contribute to this high incidence of LVH.

LVH has been reported to be a predictor of cardiac death in dialysis patients independent of blood pressure, and its progression has been clearly linked to risk of SCD. In addition, regression of LVH with therapy has been reported to improve survival. Hence, assessment of this variable using a conventional imaging mode, such as echocardiography or MRI, would provide information that could be used to prospectively assess the risk of SCD in dialysis patients. However, it is important to realize that this variable is very common in the dialysis population, which could limit its usefulness as an independent risk predictor on its own.

Heart Rate Variability in Dialysis
Alterations in the balance between the sympathetic and parasympathetic control of the heart with higher sympathetic tone, parasympathetic (vagal) withdrawal, or both have been reported to increase the risk of SCD. ESRD is characterized by high sympathetic output, which has been reported to be a result of increased chemosensitive reflex from the failing kidney. This is supported by studies reporting association between high circulating levels of norepinephrine in ESRD and cardiac events, including SCD.

Heart rate variability (HRV) is a measure of physiological variation in the beat-to-beat interval of heart rate. This variability is an end product of various inputs to the sinoatrial...
node but is predominantly controlled by the autonomic input. There are various components of HRV that can be used to determine individual axes (sympathetic and parasympathetic) of the autonomic neural input. The most widely used method of analysis uses either a short 5-minute recording of ECG or a 24-hour recording to analyze various components. The 2 common methods used to express HRV are the time domain and the frequency domain parameters. Time domain uses continuous measurements of the R-R intervals, whereas frequency domain uses spectral analysis to express the variation in heart rate as a frequency function.32,33 Several studies have reported that abnormal HRV in dialysis patients is associated with higher risk of cardiac and all-cause mortality.34,35 A typical example of altered HRV in 2 dialysis patients, 1 a survivor and 1 who died, is shown in Figure 2 to highlight this fact. More recently, studies have reported HRV, either on its own or in combination with other noninvasive parameters, to be a reliable predictor of SCD in dialysis patients.36,37 In this context, of the numerous variables that could be evaluated, the most relevant parameter in the dialysis cohort would be the ratio of low frequency (predominantly driven by sympathetic activity) to high frequency (a measure of pure vagal tone), which would provide an estimate of the sympathovagal balance. This parameter has been shown to be a reliable predictor of SCD in the dialysis population,37 with higher values suggesting increased risk.

Baroreceptor Sensitivity and Baroreflex Effectiveness Index in Dialysis Patients
Baroreceptor sensitivity is a measure of the response of the autonomic nervous system to pharmacological stimulation with a pure IV-administered α-adrenergic agent, phenylephrine. A standard dose of 200 μg of phenylephrine increases the systolic blood pressure about 20 to 30 mm Hg above the baseline. At this range, a linear relationship between increase of systolic blood pressure and a decrease in heart rate is observed. The slope of such a curve is determined by the relative input of sympathetic and parasympathetic control on the heart, with a flat slope indicating sympathetic dominance and higher risk of SCD.38 A more recent addition is the baroreflex effectiveness index, which estimates the number of times the baroreflex is active in controlling the heart rate in response to blood pressure fluctuations.39 One recent study reported that reduced baroreflex effectiveness index and baroreceptor sensitivity are independent predictors of all-cause mortality and SCD, respectively, in a cohort of patients with hypertension and chronic kidney disease.40

Microvolt T-Wave Alternans in Dialysis
T-wave alternans, or repolarization alternans, is a periodic, beat-to-beat variation in the morphology, amplitude, or timing of the T-waves in ECG sinus rhythm. Subtle alternans at microvolt levels can be reliably amplified and revealed by computer-aided signal processing techniques, and a measure of such alternans is known as microvolt T-wave alternans (MTWA). Regional (spatial) or temporal dispersion of repolarization is the most likely mechanism that underpins MTWA.41 MTWA typically is measured at heart rates of 100 to 110 bpm using either exercise or atrial pacing to accelerate the heart rate. Two methods of performing MTWA assessment have been reported: conventional spectral analytic method during an exercise session and modified moving average method using tracings from an ambulatory ECG recorder. Both methods have been validated in clinical studies.42,43

Figure 2. Comparison of HRV parameters in 2 adult men on hemodialysis. Trendgrams, histograms, and power spectra of 24-hour normal-to-normal R-R intervals from 1 survivor (follow-up of 34 months) (left) and 1 nonsurvivor (cardiovascular death) during follow-up of 23 months after this measurement (right).35 HF indicates high frequency; LF, low frequency; NN, normal to normal; SDNN, standard deviation normal-to-normal interval; ULF, ultra-low frequency; VLF, very-low frequency. Reprinted with permission.
ESRD is associated with LVH and dilation, diffuse cardiac fibrosis, and a high incidence of CAD either overtly symptomatic or occult, which results in transient ischemia a known cause for dispersion of repolarization. Studies have reported increased regional and transmural dispersion of repolarization in ESRD. Such abnormalities of repolarization could be quantified by estimating MTWA. Small pilot studies in dialysis patients reported altered behavior at baseline in some patients, whereas in some others who tested negative at baseline became nonnegative after dialysis, thus suggesting that dialysis itself may have an influence on cardiac repolarization and consequently arrhythmogenicity. This technique has not been extensively evaluated in the dialysis population but has the potential to be useful in risk assessment of SCD in these patients.

Late Potentials in Signal-Averaged ECG in Dialysis
Signal-averaged ECG (SAECG) is a high-resolution ECG technique where multiple electric signals are averaged to remove interference and reveal small variations in the terminal deflection of the QRS complex, commonly referred to as the late potential (LP). LPs in SAECG are high-frequency, low-amplitude waveforms in the terminal portion of the QRS complex (≥40 milliseconds) and represent areas of slow and abnormal ventricular activation, which increase the risk of reentrant malignant ventricular arrhythmias. LPs in SAECG have been reported to predict SCD in patients with various ischemic and nonischemic cardiac conditions. The common denominator in all these conditions is the presence of abnormal areas of ventricular myocardium where activation is delayed by slow conduction, thus predisposing to reentrant tachycardia.

In ESRD, diffuse myocardial fibrosis appears to be characteristic of uremic cardiomyopathy, which is supported by a study reporting diffuse late gadolinium enhancement in MRI. In addition, prolonged high sympathetic output, characteristic of ESRD, also leads to myocardial fibrosis. These changes would alter regional conduction, rendering the substrate prone for reentry and serious ventricular arrhythmias. LVH, seen in a large proportion of patients with ESRD, also would result in abnormally delayed impulse conduction, leading to the appearance of late potentials on the SAECG.

Clinical studies on dialysis patients have shown that approximately 20% to 25% of the dialysis population show evidence of LPs at baseline, which mirrors the incidence of SCD in this population. Studies evaluating the role of dialysis on these parameters suggests that dialysis could have both a detrimental influence (in particular, in those who had high serum potassium before dialysis) and a beneficial influence (probably due to fluid removal and consequent reduction in left ventricle stretch), thus suggesting that dialysis itself with its attendant hemodynamic alterations and electrolyte shifts would alter myocardial electrophysiology.

Nonsustained Ventricular Tachycardia in Holter Monitoring and Risk of SCD in Dialysis
High-grade ventricular ectopic activity and nonsustained ventricular tachycardia are commonly seen in dialysis patients, particularly around a dialysis session. The cause and significance of these arrhythmias are still not clear. Silent myocardial ischemia and sudden changes in electrolytes have been reported to be associated with higher risk of such arrhythmias. The predictive value of such nonsustained arrhythmia recorded during routine hemodialysis sessions in the risk assessment of SCD has not been explored adequately.

Dialysis Disequilibrium as a Trigger for Arrhythmias
The unique difference between the patients with other forms of cardiomyopathy and those with ESRD (uremic cardiomyopathy) is the fact that these patients will be on a renal replacement therapy that most commonly is intermittent, long-term dialysis. A session of dialysis results in sudden shifts in volume and electrolytes within a short time that alters the physiological milieu and could lead to sudden changes in the myocardial vulnerability to serious arrhythmias. Although various factors such as the middle molecules have been implicated, the most frequent cause of arrhythmias appears to be related to changes in fluid status and electrolytes, particularly potassium. The most convincing evidence for the role of dialysis in SCD comes from a temporal relationship between the days of dialysis and SCD (Figure 3). It is well-known that the rate of SCD in center-based, intermittent hemodialysis is greatest during the first 12 hours of starting dialysis and the last 12 hours of the 72-hour dialysis-free interval. However, changes to these regimes by prolonging the duration of dialysis, use of hemodiafiltration, and use of low-potassium dialysate have not made a significant impact in reducing the incidence of SCD in dialysis. Hence, it is essential to identify substrate level changes that would increase the risk of sustained arrhythmic episodes when a triggering metabolic alteration occurs during dialysis.

Combined Testing
The major reason why these noninvasive tests are not applied routinely in clinical practice to risk stratify patients at risk of SCD is their poor positive predictive value, which could be overcome by combining tests that would complement one another and thus provide incremental data on the risk of SCD. In addition, several tests that assess similar physiological parameters could be combined to provide a composite that might be superior to each of them alone as is the case with the composite index of cardiac autonomic function where HRV; baroreceptor sensitivity; baroreflex effectiveness index; and a newer measure of baroreceptor function, heart rate turbulence, are all combined to provide 1 composite index. The role of noninvasive assessment to predict risk of SCD in ESRD and dialysis has not been adequately explored, and current evidence is limited to a few small studies evaluating a few parameters. Of the parameters studied, HRV is the most elaborately investigated and appears to be useful. Even within these limited data, it is apparent that a combination of noninvasive tests would confer better predictive value (Table 2) in assessing risk in dialysis patients. Hence, a combination of noninvasive tests carefully chosen to reflect the underlying pathology that predisposes...
dialysis patients to such high risk of SCD would help to identify those at highest risk.

When Is the Best Time To Do the Noninvasive Tests in Dialysis Patients?
An important caveat in the risk assessment of dialysis patients, particularly with ECG-based parameters, is timing. It is well documented that the results of many of these noninvasive tests are influenced by diurnal changes that occur normally in most individuals but is clearly an issue with dialysis patients because their hemodynamics change significantly around the time of dialysis. Although structural changes such as LVH could be assessed at any time, functional assessments have to be done both at baseline and during dialysis. This limitation could be largely overcome by deriving most of the ECG data using continuous ambulatory monitoring recordings commenced before dialysis, allowing adequate time to obtain baseline data, and run through a dialysis session so that the total effect of dialysis is evaluated.

Summary
Patients with ESRD on long-term dialysis therapy have a very high risk of SCD. The incidence of SCD in dialysis is much higher than the incidence of myocardial infarction and severe LVSD, which are the current indications for ICDs. It is likely that ESRD and its consequent influence on the heart, both

Table 2. Summary of Studies on Noninvasive Risk Assessment in Dialysis Patients

<table>
<thead>
<tr>
<th>Studies</th>
<th>Investigated Marker</th>
<th>Outcome Measure</th>
<th>Patient Characteristics</th>
<th>Salient Findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Krane et al, 2009²⁴</td>
<td>LVH</td>
<td>SCD</td>
<td>1253 patients with type 2 diabetes on HD</td>
<td>LVH associated with a 60% higher relative risk of SCD</td>
</tr>
<tr>
<td>Nishimura et al³⁷</td>
<td>HRV+LVH</td>
<td>SCD</td>
<td>196 asymptomatic HD patients with LVH</td>
<td>LF/HF ratio in HRV was an independent predictor of SCD</td>
</tr>
<tr>
<td>Oikawa et al³⁶</td>
<td>HRV</td>
<td>All-cause mortality</td>
<td>383 patients on chronic HD</td>
<td>SDNN &lt;75 ms; independent predictor of mortality (after adjusting for diabetes)</td>
</tr>
<tr>
<td>Fukuta et al³⁵</td>
<td>HRV</td>
<td>Cardiovascular mortality</td>
<td>120 chronic HD patients, 38% diabetic</td>
<td>Decreases in T1 and ULF; independent predictors of mortality</td>
</tr>
<tr>
<td>Johansson et al³⁹</td>
<td>BRS and BEI</td>
<td>All-cause mortality and SCD</td>
<td>Hypertensive patients with ESRD on HD or PD</td>
<td>BEI predicts all-cause mortality whereas BRS predicts SCD</td>
</tr>
<tr>
<td>Freidman et al⁴⁴</td>
<td>MTWA pre- and post-HD</td>
<td>Abnormalities in MTWA and effect of dialysis</td>
<td>9 patients with ESRD on HD</td>
<td>5 out of 9 had nonnegative TWA, and 2 more became nonnegative after an HD session</td>
</tr>
<tr>
<td>Morales et al⁴⁵</td>
<td>SAECG LPs</td>
<td>Abnormalities in SAECG in ESRD at baseline and effect of dialysis</td>
<td>48 patients with ESRD on HD, SAECG before and after HD</td>
<td>25% showed evidence of LP before HD, and HD had an adverse influence</td>
</tr>
<tr>
<td>Girgis et al⁴⁷</td>
<td>SAECG LPs</td>
<td>Abnormalities in SAECG in ESRD at baseline and effect of dialysis</td>
<td>28 patients with ESRD before and after HD</td>
<td>25% had LP in SAECG; fluid removal during HD improved SAECG</td>
</tr>
</tbody>
</table>

BEI indicates baroreflex effectiveness index; BRS, baroreceptor sensitivity; HD, hemodialysis; HF, high frequency; LF, low frequency; TI, triangular index; ULF, ultra low frequency.
directly and by virtue of the sudden shifts in volume and electrolytes associated with dialysis therapy, could be the cause for such high risk of SCD. Thus, applying the criteria of severe LVSD and prior myocardial infarction as the major indications for a primary prevention ICD in dialysis patients, we may be choosing those at highest risk of dying from other causes such as progressive pump failure or a further ischemic coronary event as reported in some retrospective analyses of ICD recipients. This issue would further discourage the physician implanting the device from considering this very-high-risk patient group for an ICD and further worsen the current situation of very low implantation rates in this group despite having a very high event rate. Hence, a targeted risk assessment strategy possibly using a combination of various tests that evaluate factors unique to this subset of patients may help to identify those at highest risk of SCD. There is evidence, albeit very limited, to show that some of these tests could be used to predict SCD in the dialysis patients. We believe that a combination of noninvasive risk assessments, carefully chosen to reflect the underlying pathology and changes in the myocardial substrate in ESRD, could help to identify patients at high risk of SCD within the dialysis cohort. Hence, there is a need for a prospective clinical study evaluating the benefits of a combination of various noninvasive risk assessment strategies possibly using a combination of various tests that evaluate factors unique to this subset of patients so that therapeutic interventions to reduce the risk could be applied appropriately.

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Dr Davidson has received research funding from Medtronic UK, Watford, Herts, UK, and St Jude Medical UK Ltd, Bourne End, UK, both manufacturers of ICDs. Dr Saravanan reports no conflicts.

References


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Palaniappan Saravanan and Neil C. Davidson

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