Arrhythmia and Sudden Death in Hemodialysis Patients: Protocol and Baseline Characteristics of the Monitoring in Dialysis Study

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Abstract

Background Dialysis patients have high rates of cardiovascular morbidity and mortality, but data on arrhythmia burden, arrhythmia type, arrhythmia triggers, and the identity of terminal arrhythmias have historically been limited by an inability to monitor heart rhythm for prolonged periods.

Objectives To investigate arrhythmia and its association with sudden death in dialysis-dependent ESRD, describe the potential for implantable devices to advance study of dialysis physiology, review the ethical implications of using implantable devices in clinical studies, and report on the protocol and baseline results of the Monitoring in Dialysis Study (MiD).

Design, setting, participants, & measurements In this multicenter, interventional-observational, prospective cohort study, we placed implantable loop recorders in patients undergoing long-term hemodialysis. The proportion of patients experiencing clinically significant arrhythmias was the primary endpoint. For 6 months, we captured detailed data on the primary endpoint, symptomatic arrhythmias, other electrocardiographic variables, dialysis prescription, electrolytes, dialysis-related variables, and vital signs. We collected additional electrocardiographic data for up to 1 year.

Results Overall, 66 patients underwent implantation in sites in the United States and India. Diabetes was present in 63.6% of patients, 12.1% were age ≥70 years, 69.7% were men, and 53.0% were black. Primary and secondary endpoint data are expected in 2016.

Conclusions Cardiac arrhythmia is an important contributor to cardiovascular morbidity and mortality in dialysis patients, but available technology has previously limited the ability to estimate its true burden and triggers and to define terminal rhythms in sudden death. Use of implantable technology in observational studies raises complex issues but may greatly expand understanding of dialysis physiology. The use of implantable loop recorders in MiD is among the first examples of such a trial, and the results are expected to provide novel insights into the nature of arrhythmia in hemodialysis patients.


Introduction

Dialysis patients experience high cardiovascular and all-cause mortality. The death rate for all United States dialysis patients in 2011 was 198 per 1000 patient-years, with cardiac disease accounting for roughly 40% (1). In the US Renal Data System database, two thirds of cardiac deaths are attributed to arrhythmia, making up 26% of mortality. Similarly, in the Hemodialysis Study and Die Deutsche Diabetes Dialyse Studie trials, 22% and 26% of deaths, respectively, were sudden (2,3). The most convincing validation of registry data is provided by the Evaluation Of Cinacalcet HCl Therapy to Lower CardioVascular Events study, the largest randomized dialysis trial, which enrolled 3883 hyperparathyroid hemodialysis (HD) patients. Overall, 25% of deaths were adjudicated as sudden deaths (4), resolving speculation on the relative importance of (presumed) sudden cardiac death (SCD) in HD patients (Figures 1 and 2) (1,4).

The underlying mechanisms of SCD, particularly the specific type of terminal arrhythmia (which has profound implications for prevention), remain controversial. Nearly 5 years ago, the Kidney Disease Improving Global Outcomes Clinical Update Conference on cardiovascular disease in CKD presciently concluded, “Implantable loop recorders (ILRs) used to identify terminal arrhythmias could prove useful, but a coordinated effort would be necessary given low enrollment rates anticipated in such studies” (5). Furthermore, the potential value of ILRs is not restricted to lethal arrhythmias—the detection of clinically unsuspected bradyarrhythmia and atrial fibrillation (AF)
markedly widens their potential utility. In this manuscript, we review data on arrhythmia in HD patients and present the protocol and baseline data from the Monitoring in Dialysis Trial (MiD), which used ILR to detect arrhythmia in the setting of HD.

SCD

Hemodialysis initiation is a time of markedly increased risk. Healthy People (HP) is a federally mandated program established to improve the health of Americans; one major goal of HP2020 is to “reduce new cases of CKD and its complications, disability, death, and economic costs” (1). Commensurate with the singularly high mortality rate in incident dialysis patients, the HP2020 CKD-14.2 goal is to reduce the death rate within the first 3 months of dialysis initiation to 319.9 deaths per 1,000 patient-years (from the 2011 rate of 335.4 per 1000 patient-years). Figure 3 shows the early hazard of SCD (and other cause-specific mortality) at dialysis initiation (6).

One major knowledge gap in understanding of SCD in dialysis patients is ambiguity regarding the “terminal event,” particularly in distinguishing between sudden death due to arrhythmia and sudden death not preventable with cardiac devices. Kidney Disease Improving Global Outcomes (5) identified the paucity of autopsy data in dialysis-related SCD as a major knowledge gap and highlighted the problematic nature of conventional definitions: “sudden, unexpected death within an hour of symptom onset, or unwitnessed, unexpected death without obvious non-cardiac cause in patients known to be well within the past 24 hours.” What exactly is “unexpected death” in a population with a high burden of comorbid illness who spend a disproportionate amount of time in health care facilities? Furthermore, following withdrawal from dialysis, patients ultimately die of terminal arrhythmias, but this is death due to withdrawal. Without patient-centered context, one could easily (and wrongly) infer SCD as the “primary” event from an ILR. Similarly, such diseases as subarachnoid hemorrhage or aortic dissection may mimic SCD in the absence of rhythm tracings.

Many publications have highlighted strategies for risk stratification to predict SCD in dialysis patients. For example, biomarkers indicating inflammation and malnutrition (e.g., albumin) are associated with SCD risk (7,8). Additionally (but perhaps not surprisingly), there may be heritability to SCD propensity in dialysis patients. Chan et al. recently reported that genetically related family members on dialysis had a 1.7-fold increase in the odds of cardiac arrest compared with matched, unrelated controls (9). In the general population, rare mutations in ion channel genes cause several distinct long-QT syndromes, which are associated with a markedly higher risk of SCD (10). However, polymorphisms in long-QT syndrome genes are relatively common (approximately 1% of general population) (11). These genetic polymorphisms may be highly relevant and more dangerous in the context of conventional HD given the rapid declines in serum potassium, magnesium, and calcium, coupled with frequent exposure to drugs that cause QT prolongation (such as fluoroquinolones).

Conventional 12-lead electrocardiography is a reasonable method for assessment of the QT interval and the QT interval corrected for heart rate (a value >460 msec for the latter is considered prolonged). Although measurement of QT dispersion as a predictor of risk has been studied in dialysis patients, its role in clinical practice is still uncertain. Although ventricular arrhythmias (primarily premature atrial contractions) are common in dialysis patients (based on 48-hour Holter monitoring), a prospective study of 127 Italian HD patients followed for 4 years showed they were not predictive of overall mortality (12,13).

Few data are available on the types of lethal arrhythmias in dialysis patients. One paper detailed 84 sudden cardiac arrest events in dialysis patients with wearable cardioverter-defibrillators (14). In this selected cohort, 78% of initial rhythms were ventricular tachycardia (VT; 64.3%) or...
ventricular fibrillation (VF; 14.3%), and 21.4% were asystole (i.e., not shockable). Unpublished data (kindly supplied by Linda Becker) covering emergency medical services data on 47 cardiac arrests in nine outpatient dialysis centers in Seattle/King County between 1990 and 1996 showed that in 29 (62%) arrests the rhythm was VT or VF. A recent Australian study using ILRs, however, implicates bradycardia and asystole as the major contributors to SCD in HD patients; this finding suggests pump failure or non-cardiac causes for the final sequence of clinical events leading to death (15,16). An important caveat was the exceptionally long dialysis vintage of the study patients (mean ± SD, 6 ± 4 years); the type of arrhythmia (and terminal event) might be different in patients of newer versus older dialysis vintage.

Role of Dialysis Baths
Low-potassium dialysate of 0 or 1 mEq/L (17) or <2 mEq/L (18) and lower calcium dialysate (<2.5 mEq/L) (19) have been implicated as risk factors for SCD in large database studies. Similarly, low serum magnesium levels were associated with higher all-cause mortality in Japanese dialysis patients (20), but few data exist on SCD risk and magnesium dialysate levels.

Dialytic Cycle
Although great enthusiasm exists among nephrology professionals for more frequent maintenance HD, most patients dialyze three times weekly, necessitating two gaps of 1 day and one gap of 2 days. This has long been viewed as physiologically challenging in patients with limited capacity.
to maintain homeostasis in the presence of metabolic and volume-related excursions from normality, where background cardiovascular disease is the norm.

In a nationally representative United States sample between 2004 and 2007, one study compared rates of death and cardiovascular admissions on the day after the 2-day interdialytic interval with rates on other days (21). As shown in Figure 4, although overall mortality, cardiovascular mortality, and cardiovascular admission rates were higher on the day after the long interval, relative event disparities were especially marked for congestive heart failure (by a factor of 1.8) and dysrhythmia (by a factor of 1.9).

Similar associations have been seen in several large studies (22–24). For example, in a recent study of newly incident HD patients in the United Kingdom between 2002 and 2006, hospital admission rates after the 2-day gap were 1.7-fold higher, whereas all-cause mortality rates were 1.22 times higher. As with almost all of the literature to date, this study was not specifically configured to compare rates of SCD. Nevertheless, out-of-hospital death rates were 1.59 times higher after the long interval than after the shorter interval and only 1.06 times higher for in-hospital death (23).

Pathophysiology of Arrhythmia in CKD

Multiple cardiovascular risk factors, including atherosclerotic heart disease, left ventricular hypertrophy (LVH), and accelerated cardiac fibrosis, appear to contribute to arrhythmia pathogenesis in ESRD (25). Although arrhythmia and ultimately sudden cardiac death can occur in patients (in the general population) with apparently structurally normal hearts, most patients (particularly those with CKD) have underlying structural heart disease, and some type of acute event interacts with the underlying substrate to produce the fatal arrhythmia (26,27).

Although many triggers have been identified, acute myocardial ischemia is felt to be the most common initiating event in the general population (28). In patients with advanced CKD (particularly those undergoing dialysis), myocardial ischemia is likely to be a contributor, but it is also plausible that myocardial ischemia (of the type mediated by epicardial coronary artery disease) may play a less predominant role and that other factors, such as inflammation and autonomic imbalance or increased sympathetic activity (including sleep apnea), may be important contributors to sudden cardiac death (29,30). Hypertrophic myocardium is predisposed to both atrial and ventricular arrhythmia through the induction of prolonged action potentials and increased repolarization defects in areas of ischemia, with underlying fibrosis serving as a favorable substrate for propagation of arrhythmia. While hypertension, diabetes, and other typical risk factors undoubtedly contribute, dialysis and uremia may directly contribute to LVH and fibrosis, which appears to accelerate after

![Figure 4](image-url)
dialysis initiation. In a prospective study of 596 patients with ESRD who had no history of cardiovascular disease, for example, serial echocardiography demonstrated that left ventricular mass index increased significantly during the first 2 years of dialysis (31).

Processes unique to CKD and ESRD may largely account for increasing left ventricular mass index. Mall et al. analyzed myocardial histology in patients with advanced renal disease and noted that >90% of patients exhibited diffuse and uniform cardiac fibrosis with significantly greater levels of myocardial collagen than observed in hypertensive and valvular cardiomyopathies and diffuse rather than the “patchy” fibrosis characterizing other conditions (32). Amann et al. subsequently demonstrated that myocardial matrix expansion was associated with a reduction of capillary density (33). Low capillary density may partly explain sudden reductions in myocardial perfusion induced during dialysis. For example, McIntyre et al. studied patients with ESRD who did not have significant coronary disease using intradialytic position emission tomography and noted marked, regional reductions in myocardial perfusion during dialysis. Changes in perfusion were accompanied by regional wall-motion abnormalities, suggesting that functional ischemia during dialysis is not caused by flow-limiting atherosclerosis (34).

The full pathogenesis of myocardial fibrosis and capillary rarefaction in ESRD is beyond the scope of this review. Further study is needed to fully elucidate the pathways involved. However, several circulating factors, including asymmetric dimethyl arginine (35,36), parathyroid hormone (37), aldosterone (38), fibroblast growth factor-23 (39), angiotensin-2 (40), endogenous cardiac glycosides (41), vitamin D (42), and circulating angiogenesis inhibitors, have been implicated (35).

These observations suggest that in addition to the effect of LVH and coronary disease, transient myocardial ischemia induced by a mismatch between capillary supply and the hypertrophied myocardium may be critical to the generation of arrhythmias (43). Conversely, myocardial fibrosis may slow or disrupt normal conduction, leading to bradycardia, asystole, and reentrant arrhythmias (43). Peridialytic changes in BP, volume status, sympathetic tone, and electrolytes are likely to further contribute to arrhythmogenesis, but their exact contributions remain largely unstudied.

AF

Incidence and Prevalence of AF

Although asystole or ventricular arrhythmias are the most likely types of arrhythmia to result in sudden death, atrial arrhythmias, particularly AF, may result in significant morbidity in patients with ESRD. AF is increasingly common in HD patients. In a study of 258,605 older participants, the AF incidence in incident dialysis patients was 14.8/100 person-years, and adjusted probabilities of developing AF during the first year of dialysis increased from 11.3% in 1995 to 14.3% in 2007 (44). Similarly, the prevalence of AF (diagnosed from administrative claims) was 10.7% in 2006—a three-fold increase from 1992 (45). Finally, the overall AF prevalence in a meta-analysis of 25 dialysis studies was 11.6% (46).

Dialysis as a Trigger

Most evidence that HD triggers AF is indirect. Echocardiographic intra-atrial and interatrial activation times, for example, correlate with ultrafiltration volume and shorten significantly toward the end of HD (47). Similarly, there are peridialytic changes in P-wave dispersion (standard electrocardiography), P-wave duration, and the root mean square voltage of the final 20 ms of the filtered P wave (signal-averaged electrocardiography)—parameters that measure atrial conduction delay and are associated with AF (48,49). In several studies, intradialytic changes were prominent and were attenuated at the conclusion of dialysis (50,51). In others, changes were not detected or were seen only at the conclusion of dialysis and then quickly attenuated (52). However, in one study, P-wave duration decreased and root mean square voltage of the final 20 ms of the filtered P wave decreased from the beginning to the end of dialysis, changes suggesting a reduced risk of AF after HD (53). Changes in electrolytes were associated with P-wave parameters in several studies (51,52), but associations with ultrafiltration appear more robust (50,51). On balance, this literature suggests that rapid ultrafiltration or other factors during HD acutely affect conduction in a way that could trigger AF but that effects rapidly attenuate after HD.

More recently, implanted defibrillators were used to monitor patients enrolled in the Implantable Cardioverter Defibrillator-2 Trial. AF was detected in 14 of 40 dialysis patients—11 receiving HD, 3 receiving peritoneal dialysis, and 9 without known AF (54). AF frequency was three-fold higher on dialysis days (P=0.001) but did not differ with duration of the interdialytic interval. Intradialytic AF was 13-fold more frequent than in the 7 hours before dialysis (P=0.03) and two-fold higher than in the 7 hours after dialysis (P=0.001), although results were largely driven by two patients. Lower dialysate potassium concentration and higher ultrafiltration volumes were associated with AF occurrence. More recently, a trial using an ILR in 50 HD patients found that the long interdialytic interval was the most frequent period of arrhythmia. AF was detected in 42% of patients, and new-onset AF was asymptomatic in 86% (16).

Consequences of AF

Associations with stroke are similar in the ESRD and general populations (44–46,55,56). In a recent study, for example, stroke incidence was 5.2/100 patient-years in patients with AF compared with 1.9/100 patient-years in dialysis patients without AF (46). AF is also strongly associated with mortality due to fatal stroke and other causes, the rate of which is roughly doubled (26.9 versus 13.4/100 patient-years) when AF is present (44–46). In addition, AF is an independent risk factor for mesenteric ischemia, a frequently fatal event (57), and amputation (58); although this has not been studied in the setting of ESRD, AF may lead to tachyarrhythmia-induced cardiomyopathy when sustained (59). Frequent AF could thus be an important cause of an extended array of morbidity and mortality, including fatal stroke, heart failure, and deterioration in LV ejection fraction in HD patients.

Relevance of Subclinical AF

Although associations of subclinical AF with clinical outcomes have not been studied in ESRD, multiple studies
suggest that clinically silent AF is an important stroke risk factor in the general population. In one randomized pacemaker trial, the pacemaker monitoring function was used to record rapid atrial events (rate ≥220 beats/min [BPM] lasting ≥5 minutes) presumed to represent AF (60). Overall, 51.3% of patients had events at a median onset of 100 days. Atrial events were independently associated with stroke (hazard ratio, 2.8; \( P = 0.001 \)). Other studies have demonstrated similar associations between subclinical AF and subsequent overt AF or stroke (61–63). More recently, the Cryptogenic Stroke and Underlying AF (CRYSTAL AF) (64) study randomly assigned 441 stroke patients without AF who were undergoing 24-hour monitoring to an ILR or conventional follow-up. AF lasting >30 seconds was detected in 30% of intervention versus 3% of control patients at 3 years.

These data suggest that subclinical AF is an important contributor to stroke while illustrating the limits of clinical observation and standard diagnostics for advancing scientific discovery. In CRYSTAL AF, newly developed implantable technologies enabled long-term, continuous monitoring, thereby facilitating discovery of a high frequency of “silent” AF and a paradigm shift in the understanding of cryptogenic stroke. Improving understanding of SCD and its association with dialysis is an obvious extension. More broadly, CRYSTAL AF highlights a new paradigm in which the expanding capabilities and decreasing size of wearable or implantable technologies will facilitate capture of previously unmeasurable parameters and collection of more granular physiologic data, thereby improving understanding of dialysis physiology.

### LINQ and Reveal XT System

Subcutaneous ILRs have been clinically available since 1998 (Medtronic Reveal; Medtronic, Minneapolis, MN), and ILR use for detecting heart rhythm abnormalities in patients with syncope, palpitations, AF, and other conditions in which arrhythmia is suspected has been well described in the literature. These small loop recorders are placed in the subcutaneous space and are leadless. ILRs continuously record the heart rhythm, and when programmed alert criteria are met for diagnosis of arrhythmia, the event is captured and stored until retrieved in person or via remote home monitoring. Most patients in the MiD study had a Medtronic Reveal XT ILR implanted, but recently enrolled patients received an updated device, the Medtronic Reveal LINQ (Figure 5). These monitors are implanted subcutaneously with a simple outpatient procedure using local anesthesia. In patients without ESRD, device-related complications associated with ILR implantation include

![Figure 5](image_url)
 infection (1.2%), device migration, and pain at the implant site (<1%) (65). Battery life is approximately 3 years, and both devices are conditionally approved for magnetic resonance imaging (1.5 and 3.0 T) without reprogramming, although waiting for 6 weeks after insertion with the XT device is recommended (65,66). Medicare reimbursement for an ILR is generally in the range of $6000–$7000, which includes the device and insertion-related costs.

Both Reveal XT and Reveal LINQ can detect and record AF as well as home monitoring capabilities, but the LINQ device is 87% smaller (about a one third the size of a triple-A battery), offers more memory (20% more), and provides automatic nightly downloads of detected arrhythmias. While Reveal XT required holding a landline-connected transmitter over the chest wall, automatic nightly downloads from the LINQ monitor to a bedside cellular phone-based monitor (MyCareLink monitor [Medtronic, Minneapolis, MN]), allow daily assessment of patient’s heart rhythms (Figure 5). This capability allows physicians to follow patients daily instead of receiving the data only when the patient has symptoms or at the time of scheduled interrogation, as was the practice with the XT device.

ILRs offer the ability to monitor patients for an extended period (up to 3 years) (65). For patients with infrequent symptoms or who require long-term rhythm evaluation, these monitors provide more information than shorter-term Holter monitoring, wearable patch technology, external loop recorders, or intermittent monitoring devices (67). Patient compliance may also be issue with external monitors, which limits their effectiveness (68).

### MiD Protocol

#### Overview

The primary objective of the MiD study (NCT01779856) was to estimate the proportion of HD patients experiencing clinically significant arrhythmias during a 6-month primary observation period using the Reveal ILR system. Secondary goals were to broadly characterize the occurrence of arrhythmia in HD-dependent ESRD and quantify associations with electrolytes, HD procedure, and volume parameters.

#### Study Population

Eligibility criteria were designed to maximize generalizability and patient safety (Table 1). All research complied with the Declaration of Helsinki and was approved by applicable institutional review boards.

#### Study Procedures

Echocardiography (if not performed within the preceding 6 months), 12-lead electrocardiography, medical history, and medications were obtained at baseline, and ILRs were implanted within 14 days. For the first 6 months after implantation, patients transmitted Reveal data immediately before all dialysis sessions and after each session associated with a study blood draw. Postmortem transmission was encouraged but was not specifically required by the protocol. Symptoms, dialysis prescription, ultrafiltration volumes, and peri- and postdialysis vital signs were collected at every dialysis session during the first 6 months. Blood was drawn both before and after dialysis: twice weekly for 4 weeks and once weekly thereafter through 6 months (Table 2 and 3). After 6 months, transmissions occurred at least weekly but data collection was otherwise limited to adverse events.

Study coordinators reviewed transmissions after the dialysis session to identify prespecified, potentially dangerous arrhythmias, which mandated investigator review: VT $\geq$180 BPM for $>15$ seconds, asystole $>5$ seconds, waking (6 a.m.–10 p.m.) heart rate $\leq$40 BPM for $\geq$6 seconds, AF for $>24$ hours or for $>12$ hours over consecutive days, or symptomatic arrhythmia.

During months 0–6, the study sponsor reviewed patient-marked events and transmissions with potential arrhythmias. A core laboratory adjudicated those possibly consistent with the primary endpoint. Long-term follow-up continued for a maximum of 12 months. The study concluded when the last study participant had completed 6 months of follow-up. ILR removal at study termination was optional.

#### Endpoints

The primary study objective was to estimate the proportion of HD patients experiencing clinically significant

<table>
<thead>
<tr>
<th>Table 1. Inclusion and exclusion criteria</th>
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<tr>
<td><strong>Inclusion Criteria</strong></td>
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<tr>
<td>Age $\geq$ 21 yr</td>
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<tr>
<td>In-center HD $\geq$ 3 times/wk or</td>
</tr>
<tr>
<td>eGFR $&lt;15$ ml/min per 1.73 m$^2$ with expected HD</td>
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<tr>
<td>initiation within 2 mo</td>
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<tr>
<td>Ability to comply with protocol</td>
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<tr>
<td><strong>Exclusion Criteria</strong></td>
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<tr>
<td>Not suitable for implantation (e.g., cachexia, severe dermatologic conditions)</td>
</tr>
<tr>
<td>Expected survival $&lt;6$ mo</td>
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<tr>
<td>Left-sided HD catheter in position expected to interfere with implantation</td>
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<tr>
<td>Thoracic surgery within 6 mo</td>
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<tr>
<td>Infection with 14 d</td>
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<tr>
<td>Bacteremia within 60 d</td>
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<tr>
<td>Hemoglobin $&lt;10$ g/dl on consecutive measurements within prior 2 mo</td>
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<tr>
<td>Transplantation expected within 6 mo</td>
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<tr>
<td>Modality transfer expected within 6 mo</td>
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<td>Existing pacemaker or ICD</td>
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HD, hemodialysis; ICD, implantable cardioverter-defibrillator.
cardiac arrhythmias (CSAs) over 6 months. CSAs are arrhythmias considered most likely to be associated with syncope and cardiac arrest or to cause symptoms of hypoperfusion. They were based on standard definitions (69–71), recommendations of an advisory panel, and the detection capabilities of the Reveal device and included the following:

- VT≥115 BPM lasting ≥30 seconds (the rate limit was subsequently changed to ≥130 BPM with a protocol amendment).
- Bradycardia with heart rate ≤40 BPM for ≥6 seconds.
- Asystole for ≥3 seconds.
- Patient-marked (symptomatic) events where electrocardiographic review showed an arrhythmia considered clinically relevant in the judgment of the site cardiologist.

Secondary objectives were designed to assess device safety, characterize cardiac rhythm and associations with dialysis or clinical events, and assess the ability of the Reveal device to detect short-term changes in electrocardiographic morphology and their association with treatment parameters.

The following secondary objectives were specified: (1) quantifying device and procedure-related adverse events; (2) recording health-related events, specifically death, cardiovascular events, and health care utilization; (3) analyzing the association of arrhythmic events with health-related events and HD treatment parameters (this objective included CSA, other arrhythmias [e.g., AF], and parameters such as heart rate variability and heart rate trend); (4) quantifying atrial arrhythmia burden and analyzing associations with HD treatment parameters; and (5) assessing association of captured electrocardiographic morphology and pre- and postdialysis serum electrolyte levels.

**Table 2. Schedule for blood draws**

<table>
<thead>
<tr>
<th>Weekly Session</th>
<th>First Session Predialysis</th>
<th>First Session Postdialysis</th>
<th>Second or Third Session Predialysis</th>
<th>Second or Third Session Postdialysis</th>
</tr>
</thead>
<tbody>
<tr>
<td>Wk 1</td>
<td>A+B+LTS</td>
<td>D+E&lt;sup&gt;4&lt;/sup&gt;</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Wk 2</td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Wk 3</td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Wk 4</td>
<td>C</td>
<td>D</td>
<td>C</td>
<td>D</td>
</tr>
<tr>
<td>Wk 5–26</td>
<td>B&lt;sup&gt;9&lt;/sup&gt; or C</td>
<td>D</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

For laboratory tests performed in panels A–E, see Table 3. LTS, sample long-term storage.
<sup>4</sup>Optional blood draw.
<sup>9</sup>Hemoglobin, hematocrit, and iron collected monthly according to standard of care.

**Table 3. Blood collection panels**

<table>
<thead>
<tr>
<th>A</th>
<th>B</th>
<th>C</th>
<th>D</th>
<th>E (Optional)&lt;sup&gt;a&lt;/sup&gt;</th>
</tr>
</thead>
<tbody>
<tr>
<td>Brain natriuretic peptide</td>
<td>Albumin</td>
<td>Bicarbonate</td>
<td>Albumin</td>
<td>Albumin</td>
</tr>
<tr>
<td>CK/CK-MB</td>
<td>Bicarbonate</td>
<td>Bicarbonate</td>
<td>Albumin</td>
<td>Albumin</td>
</tr>
<tr>
<td>Hemoglobin A1c</td>
<td>BUN</td>
<td>Calcium</td>
<td>BUN</td>
<td>Bicarbonate</td>
</tr>
<tr>
<td>High-sensitivity C-reactive protein</td>
<td>Creatinine</td>
<td>Calcium</td>
<td>Creatinine</td>
<td>Calcium</td>
</tr>
<tr>
<td>Parathyroid hormone</td>
<td>Hematocrit</td>
<td>Magnesium</td>
<td>Magnesium</td>
<td>Creatinine</td>
</tr>
<tr>
<td>Troponin-T</td>
<td>Hemoglobin</td>
<td>Phosphorous</td>
<td>Phosphorous</td>
<td>Magnesium</td>
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<tr>
<td></td>
<td>Iron</td>
<td>Potassium</td>
<td>Potassium</td>
<td>Phosphorous</td>
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<tr>
<td></td>
<td>Magnesium</td>
<td>Sodium</td>
<td>Sodium</td>
<td>Potassium</td>
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<td></td>
<td>Phosphorous</td>
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<td>sodium</td>
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CK, creatine kinase; CK-MB, creatinine kinase muscle brain; BUN, blood urea nitrogen.
<sup>a</sup>Optional blood collections 15 and 30 minutes after dialysis on first session after Reveal implantation.
was capped at 66 implanted patients. This final sample size of 66 enables the estimation of the proportion of patients experiencing CSA with a 95% CI half-width of <0.13 for any proportion.

The primary CSA proportion will be calculated from the cohort completing 6-month follow-up with 95% CI bounds estimated by the Clopper–Pearson “exact” method using the Mid-p modification (72). The analysis will be repeated in two populations: (1) patients with complete follow-up, plus those with incomplete data who experienced CSAs, and (2) all implanted patients, assuming that those with incomplete follow-up and no CSAs while under observation had no events during unobserved follow-up. This will be supplemented with Kaplan–Meier survivor plots of CSA-free survival. A negative binomial model, appropriate for recurrent events and allowing for variable follow-up (73), will be used to estimate mean and 95% CI of CSA per patient-year.

Special Considerations

Use of an invasive monitoring device in a clinical study is an unusual feature of MiD and raises unique issues by exposing patients to risk in an otherwise observational study. The ethical issues are not unique to this design. Radiographic endpoints are frequently used in studies, for example, and also require radiation exposure without clear benefit; phase 1 drug studies or “first-in-human” device studies also expose people to risk without clear benefit.

Given the need to understand SCD and arrhythmia cause in the dialysis population, the minimally invasive nature of ILR devices, and the low rate of infections when used in other populations, the use of Reveal XT and LINQ in MiD was felt to be ethically acceptable. In general, we advocate assessing “interventional-observational” research designs, with an ethical framework that balances the importance of the knowledge gained against potential risks. High-risk, non-minimally invasive devices would rarely be acceptable without a potential for individual benefit. Conversely, as devices become smaller and less invasive, they may enable observational studies of nonserious conditions. Use of non-invasive tools should generally be considered as an alternative, and investigators are obligated to carefully review individual risk before enrolling patients in an observational study requiring use of an implantable monitor.

A particularly thorny issue is that monitoring data can alter observed outcomes and bias estimated event rates. Detected arrhythmias in MiD, for example, could mandate changes in clinical care (e.g., pacemaker implantation, change in dialysis prescription) that modify the risk of subsequent arrhythmia, thereby reducing CSAs and resulting in underestimation of the true population CSA rate.

Full disclosure to participants and clinicians maximizes potential benefits to participants but also maximizes bias. Sequestering the monitoring data eliminates outcome contamination, but nondisclosure of potentially harmful and treatable conditions discovered during research is ethically unacceptable.

With end-of-study batch analysis of raw monitoring data, results and interpretation of the monitoring data do not become available until after the study has concluded. This is similar to storing blood samples for batch analysis at the end of a study. Because the samples (in this case monitoring information) are not analyzed or interpreted until after the study, this approach eliminates the ethical problems inherent to withholding analyzed data; however, it imposes substantial data storage requirements and may inhibit the ability to optimally understand clinical features of events or to determine the best clinical response. Batch analysis at regular intervals offers a useful intermediate approach. Finally, it may be possible to select endpoints, monitoring time frames, or data disclosures in order to limit biasing of important endpoints while allowing clinical use of research data. In MiD, arrhythmias felt to be dangerous, such as asystole and sustained VT, were reviewed in an ongoing manner and shared with study patients and their clinicians. Conversely, disclosure of arrhythmias of uncertain importance, such as nonsustained VT, was not required.

Baseline Characteristics of the Study Population

Patients were enrolled in India (23 of 66) and the United States (43 of 66). Several characteristics of the study population differed from those of the United States dialysis population (1). Mean age was lower; only 12.1% of patients were ≥70 years of age. A higher percentage of patients were black (53.0%), Asian (34.8%), and male (69.7%). Diabetes was present in 63.6% of patients, while nearly half of the patients (48.5%) had a history of ischemic heart disease. A minority of patients had a history of arrhythmia (31.8%), and 10.6% had a history of AF (Table 4). Use of cardiovascular medications was common, with 55%, 33%, and 48% of patients using β-blockers, angiotensin-converting enzyme inhibitors, or angiotensin-receptor blockers or statins, respectively. Laboratory parameters (Table 5) suggested adequate potassium (5.0±1.0 mEq/L), hemoglobin (10.6±1.2 g/dL), and phosphorous (5.5±2.0 mg/dL) were each mildly elevated but within the expected range for patients undergoing long-term dialysis.

Several characteristics differed significantly between United States and Indian patients. In particular, Indian patients weighed less (66.5 versus 97.6 kg), were more likely to have diabetic kidney disease (56.5% versus 34.9%), were more likely to dialyze with an arteriovenous fistula (91.3% versus 59.5%), had a shorter dialysis vintage (2.2 versus 3.5 years), and were less likely to have hypertension (60.9% versus 97.7%) than participants in the United States. Laboratory characteristics were generally similar, but bicarbonate (18.8 versus 23.8 mEq/L) and sodium (134.1 versus 138.4 mEq/L) concentrations were lower in India.

This regional variation and increased variability in laboratory and clinical characteristics present challenges and opportunities. Analysis of country-specific arrhythmia rates is important, but the wide range of characteristics, such as body mass index, hypertension, and bicarbonate concentrations, may provide a greater ability to analyze associations of these factors with arrhythmia than would have been possible had the study recruited only within the United States. Global enrollment should thus limit the effect of country-specific dialysis practices on our findings and may enhance relevance to the global HD population while requiring more cautious extrapolation to the United States population.
MiD as a Paradigm
The MiD study illustrates the potential of invasive monitoring to improve understanding of the pathophysiology of ESRD and elucidate the true nature or cause of clinical events in dialysis patients. From our experience, it seems clear that when investigators are engaged, risks are reasonably low, research questions are important, and clinical benefit is possible, dialysis patients can be engaged

<table>
<thead>
<tr>
<th>Table 4. Baseline characteristics of enrolled patients</th>
</tr>
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<tbody>
<tr>
<td>Characteristics</td>
</tr>
<tr>
<td>Mean age at implant±SD, yr (n/N)</td>
</tr>
<tr>
<td>Male sex</td>
</tr>
<tr>
<td>Race</td>
</tr>
<tr>
<td>Asian</td>
</tr>
<tr>
<td>Black</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>White</td>
</tr>
<tr>
<td>Hispanic ethnicity</td>
</tr>
<tr>
<td>Cause of ESRD</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>GN</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Other</td>
</tr>
<tr>
<td>Median ESRD vintage (IQR), yr (n/N)</td>
</tr>
<tr>
<td>Prior kidney transplant</td>
</tr>
<tr>
<td>Previous peritoneal dialysis</td>
</tr>
<tr>
<td>Current vascular access</td>
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<tr>
<td>AV fistula</td>
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<tr>
<td>AV graft</td>
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<tr>
<td>Catheter</td>
</tr>
<tr>
<td>Diabetes</td>
</tr>
<tr>
<td>None</td>
</tr>
<tr>
<td>Type 1</td>
</tr>
<tr>
<td>Type 2</td>
</tr>
<tr>
<td>Mean diabetes duration±SD, yr (n/N)</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
</tr>
<tr>
<td>Hypertension</td>
</tr>
<tr>
<td>Ischemic heart disease</td>
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<tr>
<td>Congestive heart failure</td>
</tr>
<tr>
<td>Coronary artery bypass surgery</td>
</tr>
<tr>
<td>History of arrhythmia</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
</tr>
<tr>
<td>Smoking</td>
</tr>
<tr>
<td>Current</td>
</tr>
<tr>
<td>Never</td>
</tr>
<tr>
<td>Past</td>
</tr>
<tr>
<td>Mean weight±SD, kg (n/N)</td>
</tr>
<tr>
<td>Body mass index ≥40 kg/m²</td>
</tr>
<tr>
<td>Mean systolic BP±SD, mmHg (n/N)</td>
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<tr>
<td>Mean diastolic BP±SD, mmHg (n/N)</td>
</tr>
<tr>
<td>Medications</td>
</tr>
<tr>
<td>Nonaspirin anticoagulants or anti platelet agents</td>
</tr>
<tr>
<td>β-Blockers</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
</tr>
<tr>
<td>ACEI or ARB</td>
</tr>
<tr>
<td>Statin</td>
</tr>
<tr>
<td>Aspirin</td>
</tr>
</tbody>
</table>

Unless otherwise noted, values are the number/number of patients (percentage). Categorical P value is based on a two-sided Fisher exact test. Continuous P value is based on an unpaired t test. IQR, interquartile range; AV, arteriovenous; ACEI, angiotensin-converting enzyme inhibitor; ARB, angiotensin-receptor blocker.
and their collaboration secured in observational studies using invasive monitoring procedures.

Future research on ILR technology in ESRD should include studies to determine the association between subclinical AF and the risk of stroke, long-term studies with sufficient sample size to capture terminal cardiac rhythms at the time of SCD, and interventional studies testing the effect of individualization of the dialysis prescription on arrhythmia. Devices with miniaturized impedance technology will facilitate studying associations of volume status with arrhythmia and more sophisticated investigations into links between ultrafiltration rate, BP, volume status, cardiovascular death, and intradialytic hypotension. Outside of the cardiovascular arena, implantable glucose monitors stand out as a technology that could be readily used to definitively determine the true relationship between serum glucose levels and hemoglobin A1c or clinical outcomes in ESRD (74). Similarly, one can envision using pressure or flow monitoring devices to better understand access physiology and trajectories of access maturation and failure.

**Summary**

Understanding the causal sequence of events in the pathway to death is critical to identifying opportunities for prolonging life in ESRD. Despite advances in renal care, the period from the last clinical assessment until out-of-hospital death remains ripe for investigation (75–78). In persons undergoing in-center HD, regular health care contact limits the time during which no vital information is recorded; however, out-of-center SCD remains common, with little information about the hours and days leading up to the final minutes of life. Information on these periods in home-care patients is more limited with respect to cardiac rhythm and vital status (79).

Conventional cardiac pacemakers have reduced the mortality associated with bradycardia and allow bradycardic patients to have normal actuarial survival compared with age- and sex-matched cohorts (80). In those with accepted indications for implantable cardioverter-defibrillators (ICDs), the rate of appropriate therapy for lethal rhythms is approximately 20% over the life of the implant (80), and primary and secondary prevention of SCD with ICDs in patients with left ventricular dysfunction improves survival of these groups. In a subset of patients with left ventricular dysfunction who have ventricular dysynchrony (e.g., prolonged left bundle-branch block morphology QRS complex on electrocardiography), the addition of a left ventricular lead and biventricular pacing improves survival from both sudden and pump failure death (82).

Nevertheless, the specific translation of these therapies to patients with advanced CKD and ESRD is limited, as noted above, by a lack of data that allow inferences on their potential risks and benefits. ICDs, for example, face higher defibrillation thresholds that may inhibit successful cardioversion of VT/fibrillation in patients with ESRD (83). This may reflect greater degrees of overall left ventricular fibrosis and hypertrophy compared with those without years of CKD. There is also limited information about the need for backup bradycardia pacing in patients with ESRD who have ICDs implanted yet may have a clinical event where bradycardia is the complicating rhythm. Finally, and most critically, the proportion of death that is truly avoidable with device therapy versus how much is truly attributable to pump failure or noncardiac primary causes that cannot be influenced by any form of device therapy remains unknown.

The MiD study is uniquely designed to gain critical insights into patients both in the clinic and hospital and, more important, in the community and households in which they live. Recording the most recent baseline rhythm, critical triggers (premature depolarizations, pauses), pathologic intermediate rhythms (monomorphic, polymorphic VT), and terminal patterns (heart block, VT, VF, systole, and other forms of pulseless electrical activity) will provide crucial data allowing investigators to begin piecing together the sequence of events and proximate causes of the last minutes of life in ESRD. Similarly, identification of clinical, demographic, or electrophysiological variables associated with the final electrical sequence may prove useful for predicting lethal, yet
treatable, rhythms, for the potential utility of and identi-
ifying those most likely to benefit from ICD insertion, for
determining whether back-up pacing functions are needed,
or for determining whether patients would benefit from
withdrawal of nodal blockade (e.g., β-blockers).

By capturing the full constellation of cardiac rhythm
during a prolonged period, the MiD study will provide
information on the extent to which previously undetected
AF or other tachyarrhythmias and bradyarrhythmias con-
tribute to morbidity in ESRD. Finally, as noted previously,
the detailed capture of clinical data in MiD is critical for
correlating captured rhythms with concurrent clinical
symptoms to avoid confusing “agonal” rhythms that appear
secondary to some other life-ending event, such as sepsis or
stroke (for which application of cardiac pacing devices is not
appropriate), with primary arrhythmia as a cause of death.

Analysis of blood chemistries and data on the dialysis
prescription from MiD may alternatively identify prescription
characteristics or electrolyte levels strongly associated
with the occurrence of arrhythmia. Thus, the final results
could suggest ways to tailor the dialysis prescription in order
to limit arrhythmia. In this regard, associations between
blood-dialysate potassium or calcium gradients and arrhyth-
mia occurrence in MiD are eagerly anticipated.

In the future, particularly as point-of-care information
becomes available, long-term monitoring may allow neph-
rologists to alter the dialysis prescription in response to
minute-by-minute changes in electrocardiographic mor-
phology or the peridialytic occurrence of arrhythmia.
Long-term monitoring might allow the identification of
patients with subclinical AF likely to benefit from anti-
coagulation. ILR studies may also facilitate determination of
whether certain dialysate-serum electrolyte gradients are
associated with a higher likelihood of arrhythmia and
should be avoided. Finally, clinical trials comparing
outcomes following randomization to an ILR with detection
of the study. D.M.C. received consulting from Questcor Pharma-
aceuticals (Anaheim, CA), expert witness fees related to dialysate
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Disclosures

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aceuticals (Anaheim, CA), expert witness fees related to dialysate
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