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Wearable Cardioverter Defibrillator in Hemodialysis Patients (WED-HED) Study

Principal Investigators:

Wojciech Zareba, MD, PhD
University of Rochester Medical Center, Rochester, NY

and

Charles Herzog, MD
Chronic Disease Research Group
Minneapolis Medical Research Foundation
University of Minnesota, Minneapolis, MN

I have read and understand the information in the protocol and I understand my requirements for executing the protocol based on sound knowledge of GCP and ICH Guideline for Good Clinical Practice (E6).

PRINTED NAME OF INVESTIGATOR	SITE NUMBER
INVESTIGATOR SIGNATURE	DATE
Steven J. Szymkiewicz. MD Vice President of Medical Affairs ZOLL (SPONSOR)	10-Mar-2015 DATE

PROTOCOL SUMMARY

Objective

To study the impact of wearable cardioverter defibrillator (WCD) use on sudden cardiac death in hemodialysis patients.

Study Population

Participants will be patients beginning hemodialysis (<2 months from initiation) who are ≥ 50 years old.

Intervention

A WCD will be used for protection against sudden cardiac death (SCD).

Study Design

The study will be a multi-center, prospective, randomized controlled trial with 1:1 assignment of treatment and control.

Study Size

The study will enroll up to 2,600 subjects. A maximum of 200 sites will be used for enrollment.

1. INTRODUCTION

End-stage renal disease (ESRD) affects over 400,000 people in the United States. Due to the aging population and increasing burden of comorbidities, it is expected that by 2030 the ESRD population could significantly increase and reach over 2.2 million. Recent data indicate that the treatment of ESRD patients accounts for 6.4% of total Medicare expenditure.[1,2]

1.1 Incidence and Mortality

The risk of mortality among ESRD patients, including sudden cardiac death (SCD), continues to gain attention among the scientific community as indicated by the recent Kidney Disease: Improving Global Outcomes (KDIGO) committee convened in London. The high mortality rate of these patients, and the sudden cardiac death rate in particular, was one of the main topics among the 80 international experts that attended this meeting to discuss the current state of knowledge about chronic kidney disease (CKD) patients. KDIGO concluded that every effort should be made to decrease the high mortality rate of ESRD patients.[1]

Paralleling the scientific community, the USA government initiative called Healthy People 2020 has set goals to reducing the mortality among hemodialysis patients. Specifically, one goal is a 10% reduction in the number of deaths in dialysis patients within the first 3 months of initiation of renal replacement therapy. This goal specifically targets incident hemodialysis patients as they have a significantly higher mortality. Another goal is a 10% reduction in the number of cardiovascular deaths for persons on dialysis. SCD contributes significantly to the cardiovascular death tally.[45]

According to United States Renal Data System (USRDS), there were approximately 388,000 patients on hemodialysis in the USA in 2011 and the death rate for all dialysis patients was 198 deaths per 1000 patient-years.[2] Mortality rates are substantially higher among incident patients, comparable to the mortality of patients with advanced heart failure or advanced cancer. The first months are particularly high risk and patients new to dialysis experience approximately 14% mortality in the first 6 months.[3]

The USRDS database also reveals that 65% of all cardiac deaths are attributable to cardiac arrhythmias, making SCD the single largest cause of death in hemodialysis patients and responsible for approximately 26% of all mortality in this population.[2,9,10] Other studies in this population such as the German Diabetes and Dialysis (4D) study, the Hemodialysis (HEMO) study and the Evaluation of cinacalcet therapy to lower cardiovascular events (EVOLVE) reported similar proportions of mortality attributable to sudden death.[6,8,44]

The SCD rate of hemodialysis patients in the US is over 50 times greater than the general population, with 53 deaths per 1000 patient-years compared to the approximately 1 death per 1000 patient-years in the general population, and SCD accounts for a smaller portion (6% to 13%) of deaths in the general population.[2,9,10,11] Compared to other modalities such as peritoneal dialysis, hemodialysis patients die of sudden cardiac arrest (SCA) and arrhythmia at a higher rate (62.2 vs. 42.8 events/1,000 patient-years).[12] Still, the majority of SCD occurs outside of dialysis centers where it is very unlikely to be witnessed or have resuscitation equipment available. Several studies show the incidence of sudden cardiac arrest (SCA) in dialysis patients is only 4.5 per 100,000 hemodialysis sessions or about 7 per 1000 patient-years based on an average of three hemodialysis sessions per week.[13,14,15]

The survival rate following SCA in the general population is poor, with a median survival rate of 8%, and hemodialysis patients would not be expected to have better results.[16] Even

for SCA occurring within the dialysis center where supportive care may be available, the survival rate is poor with 60% mortality within 48 hours of the arrest, including 13% in the unit and 47% en route or in the hospital.[14] In a population-based study of SCA within hemodialysis centers, survival of SCA to hospital discharge was reported as 24% with a 15% one year survival rate.[16] In a three year study of 24 patients who had CPR conducted during a hemodialysis session, Lai et al. reported that only two patients survived more than one month, and none survived to hospital discharge.[17]

Even the introduction of the Automated External Defibrillator (AED) into dialysis units has not been associated with improved outcomes. Two groups independently reported the lack of AED benefit within dialysis centers, finding that available AEDs were used only 50% of the time prior to EMS arrival.[15,31] At the same time, devices such as wearable cardioverter defibrillators (WCD) have shown to be very effective in terminating SCA in other high-risk populations through rapid response without the need for bystander intervention.

In summary, large registries and clinical studies have shown SCD in hemodialysis patients accounts for about one fourth of total mortality and for 60 to 80% of cardiovascular deaths (Table 1). Sudden cardiac arrest survival is very poor in this patient population with the majority of SCA events occurring outside the dialysis unit. Even within the dialysis unit, where supportive care is available, survival is low. The alarming SCD rate in this population is a growing concern within the scientific community. In their recent position statement, KDIGO emphasized that preventative strategies for SCD should be a public health concern, specifically noting research is needed regarding the impact of the WCD on survival in the dialysis population. Reducing SCD through the use of modalities such as the WCD is thus anticipated to significantly reduce total mortality.

1.2 Hemodialysis as an Independent Risk Factor

The high rate of SCD in hemodialysis patients is not only related to the high prevalence of underlying cardiac diseases but also associated with the stress and duration of the dialysis sessions. Several studies show that hemodialysis treatment is itself an independent risk for SCD.

1.2.1 Stress from the Hemodialysis Sessions

Dialysis treatment-related stresses are important in the genesis of SCA. Bleyer and colleagues examined the timing of SCD in hemodialysis patients and identified that SCD events increased both before and after starting treatment. They found a 1.7-fold increased SCD risk occurring in the 12-hour period after starting dialysis procedure and a 3-fold increased risk at the end of the dialysis-free weekend interval. In this study, the occurrence of SCD was unrelated to the patient's left ventricle function.[18]

Rapid changes in serum electrolytes, specifically serum potassium concentrations, and extracellular fluid during dialysis are known to trigger malignant arrhythmias. Potassium fluxes during the hemodialysis interval are associated with established risk markers for SCD such as increased ventricular ectopy, increased QT interval, and an increased QT dispersion. In addition, the increased sympathetic activity occurring with hemodialysis is associated with sudden cardiovascular events.[18]

In a small study, Bleyer et al. did not find a significant difference in coronary artery disease (CAD) prevalence between patients who experienced sudden and non-

sudden deaths. Prevention of CAD or its progression through the use of statins did not improve survival of chronic kidney disease (CKD) patients in the Study of Heart and Renal Protection (SHARP) despite a decrease in cardiovascular events. Similarly, 4D and AURORA (A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis) failed to show any benefit of statins in decreasing cardiovascular mortality in dialysis patients despite significant decreases in cholesterol levels.[6,18,19]

Table 1. Summary of Clinical Studies: Risk of SD in Hemodialysis Population

Study/Data Source	Description	Sample Size/HD Cohort	% Female	Age (mean±SD)	Presence of DM (%)	Hx CD (%)	%Pts EF > 40	Sudden Death (%)*	% SCA of CV deaths	Sudden death definition
USRDS[2]	United States Renal Data System 2013. (2011 data)	n= 395,656 (Total study N=430,273)	44.0 (n=174,111)	≥50yrs =80.0%	45.1 (n=178,269)	85 (Incidence of HTN)	NR	24	65	SCA/cardiac arrhythmia
4D[6]	Atorvastatin RCT in HD+ DM (type II) pts, composite endpoint of cardiac death, nonfatal MI, stroke. (1998-2002)	n=1255 (control group=636, treatment group=619) European HD patients	46.1	65.7 ± 8.3	100	>43	NR	25.9	59.2	Unexpected death without K+ > 7.5 mmol per liter before the start of the three most recent sessions of HD (sudden cardiac death)
HEMO[7,8]	RCT of high-flux dialyzer membrane on survival or morbidity with cardiac event sub-analysis. (1995-2000)	n=1846 HD patients	56.2	57.6 ± 14.0	44.6	80.1 (pre-existing CD)	NR	24.9	23.9	Witnessed or unwitnessed unexpected death; symptoms onset < 24 hours if witnessed or < time since last dialysis session if unwitnessed.
DOPPS (US)[20]	Prospective, observational study of HD patients in EU, Japan, and US (1996-2002)	n=3856 US HD pts (Total study N=16,720)	46.6	60.5 ± 15.5	45.7	83.2(HTN)	NR	NA	NR	NA
Bleyer[18]	Retrospective examining sudden death in HD patients.	n=80 sudden deaths (total N=228)	58.8	60.3 ± 14.1	57.5	92.5 (HTN) 56.3 (CAD)	75.3 (EF >35%)	35	80	Cardiovascular related (73% of SD due to SCA)
EVOLVE[44]	Prospective study of cinacalcet	3883 hemodialysis patients	40	55.4	33.4%	NR	NR	24.5	45	NR
Mangrum[21,22]	Single-center, retrospective mortality analysis of prevalent hemodialysis pts evaluating SCD and LV function (1999-2003)	N= 241 HD patients		NR	NR	NR	63.0 (89 pts echo available)	35	74	Arrhythmias/SCA
Pun (2009)[23]	Retrospective study of GFR and risk of SCD in a CKD cohort. Duke Databank for Cardiovascular Disease (DDCD) was used. (1995-2006)	n=424 HD (58.7%) and non-HD pts (eGFR<15 ml/min) with documented CAD	48.6	61 (median)	63.0	89.4 (HTN)	52 (IQR 40, 60)	24.2 per 1000 patient years (HD pts)	NR	Death resulting from the sudden, unexpected cessation of cardiac activity with hemodynamic collapse

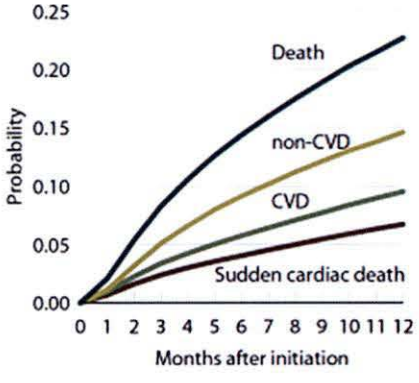
*Out of total mortality

1.2.2 Duration of Hemodialysis

The 2011 annual overall mortality for prevalent dialysis patients in US was 198 deaths per 1000 patient years, which rose to 224.5 deaths per 1000 patient years for patients between the ages of 65 and 74 years. The 2011 death rate in patients within the first three months of dialysis initiation was markedly higher with 335.4 deaths per 1000 patient years for all patients and 368.2 per 1000 patient years for patients between the ages of 65 and 74 years. Like overall mortality, the hazard of cardiovascular mortality and SCD is not uniform over the duration of dialysis therapy and patients who are initiated on hemodialysis have a 1.7 to 2 fold increased risk of SCD during first few months on dialysis.[2] According to the USRDS, total mortality for the first six months following dialysis initiation is approximately 14% and sudden cardiac death is approximately 4% (Figure 1).[2]

Figure 1

Probability of death in incident dialysis patients, by cause of death, 2009
Figure 4.8 (Volume 2)

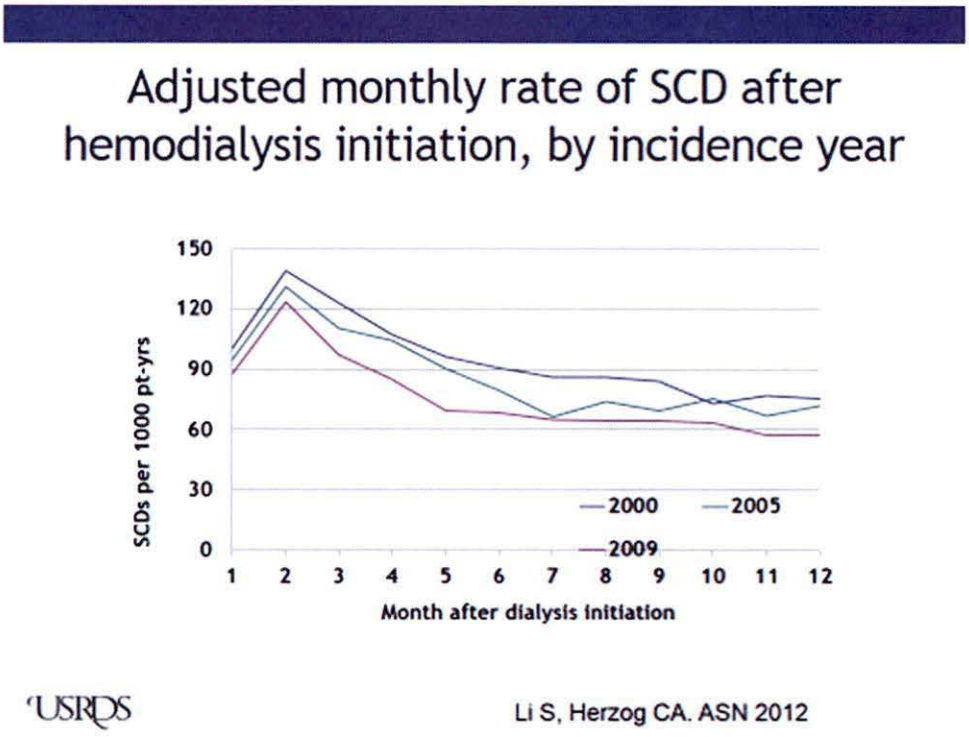


Incident dialysis patients, age 20 & older, unadjusted.

USRDS 2012 ADR

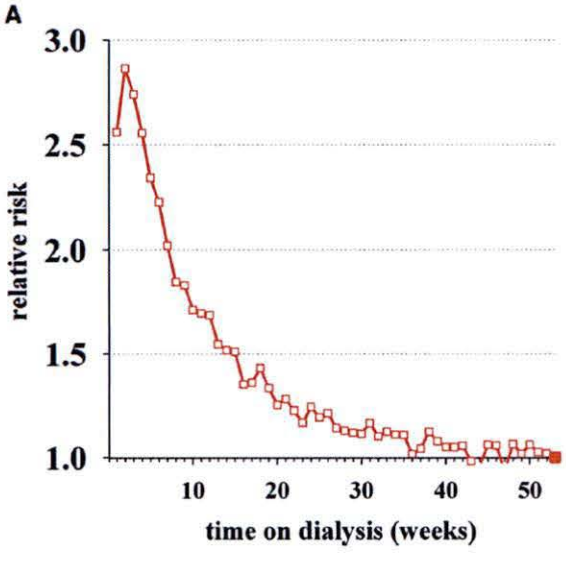
Herzog et al. found that the rate of SCD was approximately 50% higher for hemodialysis patients within three months of dialysis initiation, compared with patients on dialysis longer.[24] The USRDS 2009 report revealed that sudden death rates averaged >100 deaths per 1000 patient-years in the first 3 months, and nearly 90 deaths per 1000 patient-years over the first 6 months (Figure 2). As the SCD rate reported by Herzog trends similar to the USRDS cardiovascular mortality, it is clear that the risk of SCD is highest in the first six months as opposed to the last six months of the first year of dialysis, paralleling total mortality.[24,25]

Figure 2.



The DOPPS study confirms the USDRS data, and shows the higher mortality in the first six months after dialysis initiation is not unique to the US population.[43] The trend is more pronounced in the older population but still exists for those under 65 years of age. Closer examination of data from a commercial hemodialysis provider indicates that mortality is highly time dependent and declines weekly following hemodialysis initiation (Figure 3).[46]

Figure 3. Relative risk of death at one week intervals after starting chronic dialysis, compared to a reference group who survived one year of dialysis.



1.3 Hemodialysis and Preserved Left Ventricular Function

Left ventricular dysfunction, as measured by the left ventricle ejection fraction (LVEF), is well-known as an independent risk stratifier for SCD in the general population. However, LVEF does not provide the same utility in assessing risk of SCD in end stage renal disease (ESRD) patients, despite the high risk of arrhythmic events in this group. The rationale for LVEF and other risk factors for determining the proposed patient population are supported by three US based studies.

In a retrospective study by Bleyer and colleagues it was shown that LVEF was not predictive of the occurrence of SCD in 80 hemodialysis patients. In fact, 75% of the patients who suffered sudden death had preserved LVEF (>35%). Arrhythmias accounted for 35% of the total sudden deaths.[18]

Similarly, in a study which evaluated overall cardiac function and SCD in the hemodialysis population, low LVEF alone did not account for the high risk of SCD associated with advanced CKD. On the contrary, the majority of the SCD (71%) occurred in patients with an EF > 30%.[21,22] Additionally, Duke University examined the risk of SCD in a large cohort of their CKD patients and found that the subgroup of 424 patients with glomerular filtration rates (GFR) < 15 ml/min, of whom 66% of patients were on hemodialysis, had a median LVEF of 52% (IQR 40, 60). The rate of SCD for the patients on hemodialysis was 24.2 per 1000 patient-years, nearly double the SCD rate for those patients with similar GFRs of <15 ml/min but not yet on dialysis.[23]

Although the USRDS database does not capture LVEF data, it is the opinion of our investigators that the risk of SCD in hemodialysis patients with preserved EF shown in these studies, totaling 448 cases of hemodialysis patients suffering SCD, are representative of the risk inherent in the US hemodialysis population.

1.4 Hemodialysis Patients ≥50 Years

Published data indicates both hemodialysis and mortality rates rise as age progresses. According to the USRDS database, approximately 87.9% of the dialysis population is over 45 years of age, while approximately 50.3% of the dialysis population is over 65 years of age.[2]

Ample data shows that age is also independently associated with increased risk for SCD in this population. SCD risk increases at least 1.5 times with every incremental age range. Results from randomized controlled trials, prospective observational, and retrospective studies report similar findings.[8,18,20] In the DOPPS study, patients who were older than 65 years had more than double the risk of dying compared to younger patients.[20] The HEMO study showed that the risk of SCD increased by 41% with every 10-year increment. Age was one of the strongest predictors of death in this randomized trial.[7,8] Bleyer et al. also reported that the incidence of SCA was 93.7/1000 patient-years at risk for dialysis patients >65 years of age.[18] Among non-diabetic hemodialysis patients in the United States, those 45 years old or older have double the SCD rates of those below 45 years of age.[25] Details are shown in Tables 1 and 2.

In the DOPPS study, patients >65 years old (who constitute the majority of dialyzed patients) had exceptionally high mortality rates ranging from 211-412 deaths per 1000 patient-years in the first 8 months after initiation of hemodialysis. [43] This translates to cumulative 6-month mortality of up to 15.4% for subjects beginning follow-up within a

month of initiating dialysis, and 14.1% for subjects beginning 6-month follow-up 1 to 2 months post-initiation.

Table 2. US Renal Database System: SCD Rates by Primary Cause of ESRD and Age

Unadjusted cardiac arrest/arrhythmia mortality rates combined 2005-2007 period prevalent hemodialysis patients (deaths per 1,000 patient years), by primary cause of ESRD and age

	Cause of ESRD: Diabetes				Cause of ESRD: Non-Diabetes			
	Cardiac Arrest				Cardiac Arrest			
AGE	N=	Death Count	Yrs at Risk	Rate	N=	Death Count	Yrs at Risk	Rate
20-44	39,052	1,380	31,334	44.0	120,887	1,920	106,525	18.0
45-64	227,994	10,054	184,152	54.6	229,133	7,151	192,998	37.0
65-74	143,528	8,395	112,626	74.6	118,032	5,644	92,434	61.1
75+	94,462	7,333	68,880	106.5	160,556	11,231	116,694	96.4

Population: period prevalent hemodialysis patients combined 2005-2007 who were age 20 and above, resided in the US 50 states, Washington D.C.

U.S. Renal Data System, USRDS 2009 Annual Data Report: Atlas of End-Stage Renal Disease in the United States, National Institutes of Health, National Institute of Diabetes and Digestive and Kidney Diseases, Bethesda, MD, 2009.

1.5 Management of SCD Risk in Hemodialysis Patients

The in-center SCA rate is reported to be as low as 3.5 per 100,000 hemodialysis sessions.[14,15,29,30,31] Therefore, the majority of arrhythmic events occur at home where patients are not supervised. The accumulation of electrolytes and fluids between dialysis sessions contributes to the arrhythmogenic predisposition. Even SCA occurring during hemodialysis has a poor survival rate, despite attendance by trained personnel. About 60% of patients die within 48 hours of the SCA, including 13% while still in the dialysis unit.[14] In another population-based study of hemodialysis facilities, survival to discharge from the hospital was reported as 24% with 15% survival at 1 year.[15] Moss et al and Lai et al reported even worse in-hospital death rates of 92% and 100%.[17,32] There is a tremendous need to improve survival of these very high-risk patients. Rapid treatment with defibrillation remains the best option when SCA occurs.

1.5.1 Automatic External Defibrillator (AED)

Automated external defibrillators have been broadly introduced into dialysis units. However, published data indicate that even when available these devices were attached in only half of cases prior to EMS arrival. Furthermore, the introduction of AED in dialysis unit has not shown improved outcomes for patients experiencing SCA. Two groups independently reported lack of benefit in SCA victims among outpatient dialysis centers with versus without AED availability.[15,31] One-year survival after in-center SCA was reported as low as 8.4% despite AED availability.

1.5.2 Implantable Cardioverter Defibrillator (ICD)

Implantable cardioverter defibrillators provide protection from SCD, but these devices are underused or not practical in patients undergoing hemodialysis. Physicians are less likely to refer patients in with ESRD for ICD implantation not only due to potential complications (infections, difficulties with venous access) but also due to lack of data from randomized trials as patients with ESRD have been

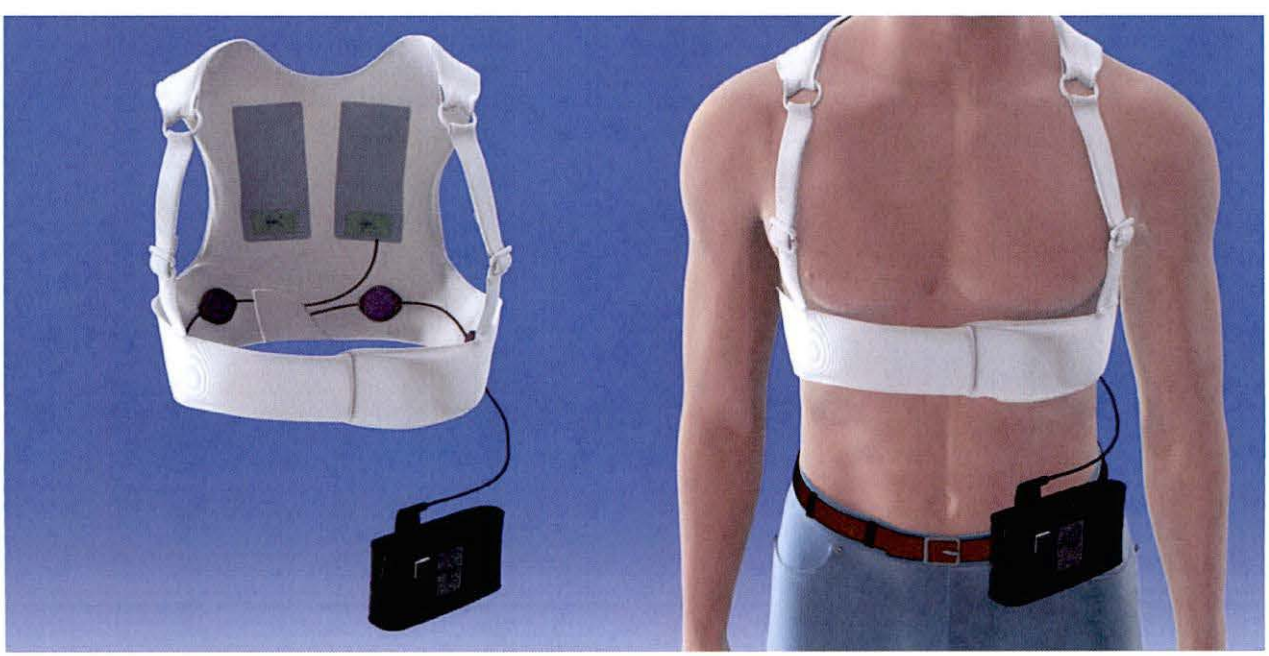
traditionally excluded from major ICD clinical trials. Therefore, there are very limited data on ICD use in dialysis patients. A study by Herzog et al reported that of 6,000 dialysis patients eligible for ICDs, only 8% received them.[4] Despite the low proportion of implantation, ICD use was associated with a significant 42% reduction in death risk as compared to non-ICD group. Charytan and colleagues conducted a similar analysis but found a lower yet statistically significant reduction in all-cause mortality with ICDs.[33]

1.5.3 Wearable Cardioverter Defibrillator (WCD)

The life-saving effects of the WCD were documented in the WEARIT/BIROAD studies designed and conducted by Drs. Klein, Hall, and Moss.[5] Following these studies, CMS approved WCD use in patients who meet coverage criteria for ICD implantation, but without the waiting periods established after a significant cardiac event. A small proportion of dialysis patients meet these criteria. Since ICDs are underutilized in dialysis patients, the WCD provides an opportunity to save the lives of numerous hemodialysis patients.[40]

2. WEARABLE CARDIOVERTER DEFIBRILLATOR DESCRIPTION

The LifeVest™ wearable cardioverter defibrillator is composed of four dry, non-adhesive capacitive electrodes and three dry-to-wet non-adhesive defibrillation electrodes incorporated into a chest strap assembly, along with a 0.8 kg defibrillator unit carried on a waist belt or shoulder strap. The monitoring electrodes are positioned circumferentially around the chest and held in place by approximately 0.5 kg of tension. The defibrillation electrodes are positioned for apex-posterior defibrillation. If an arrhythmia is detected, an escalating alarm sequence starts, including a vibration against the skin, audible tones, and a voice cautioning bystanders of an impending shock. Patients are trained to hold a pair of response buttons during these alarms. Responding acts as a test of consciousness: if no response occurs, the device extrudes gel from the defibrillation electrodes and delivers up to five 150-Joule biphasic shocks.



3. OBJECTIVES

3.1 Primary Objective

The study will test the hypothesis that ESRD patients, who are at least 50 years of age and beginning hemodialysis (either scheduled for their first session or within two months of the initial treatment), will experience a 60% relative risk reduction in SCD mortality through WCD use as measured at six calendar months after randomization. The primary objective will be evaluated using intention-to-treat analysis.

WCD therapies are anticipated to reduce the risk of SCD by 60% over the course of use, similar to other personal defibrillation therapies such as ICDs. The hypothesized relative reduction in SCD translates to a 2.1% absolute reduction in the risk of SCD mortality over 6 months of follow-up, given that the SCD rate during that period is expected to be 3.5%. The hypothesized 60% reduction in SCD is also expected to result in a 15% reduction in total mortality over 6 months for this patient group, a consequence that would be of major clinical importance.

3.2 Secondary Objectives

The specific secondary objectives are:

3.2.1 Evaluate the effect of WCD use on total mortality at 6 calendar months

The relative risk reduction in SCD at 6 months is anticipated to be 60%. Given that total mortality during the same time period is 14% and that SCD comprises 25% of the total mortality, the relative risk reduction in total mortality is anticipated to be 15%. The absolute reduction in total mortality is expected to be the same as the reduction in SCD, 2.1%.

3.2.2 Evaluate the effect of WCD use on sudden cardiac death at 6 calendar months (as-treated analysis)

Intention-to-treat analyses have several advantages but are generally conservative in estimating the treatment effect, due to noncompliance in the treatment arm, crossover of subjects to opposing study arms, etc. Therefore secondary as-treated analyses will be used to estimate the relative risk of wearing versus not wearing WCD. Detailed data will be obtained regarding actual daily use of WCD in each subject enrolled in the trial. The as-treated analysis will be based on a Cox model with a time-dependent indicator for wearing versus not wearing WCD, allowing subjects to dynamically move back and forth between the "wearing WCD" and "not wearing WCD" groups every time the WCD is put on and taken off. Thus, events occurring while wearing WCD will be attributed to "wearing WCD," while events occurring while not wearing WCD will be attributed to "not wearing WCD." A likelihood ratio test will be used to obtain a p-value for the resulting hazard ratio for wearing WCD, and the estimated hazard ratio along with a 95% confidence interval will also be reported.

3.2.3 Evaluate the clinical status of SCA survivors 48 hours after the event

Resuscitation from SCA due to VT/VF is high in commercial use of WCD. Similar results are anticipated in hemodialysis patients. Survival will be evaluated at 48 hours after the SCA event.

3.2.4 Evaluate the incidence of potentially life-threatening arrhythmias as documented by the WCD, regardless of treatment by the WCD, at 6 calendar months

Some patients who experience VT may not lose consciousness and will use the WCD response buttons to prevent a treatment from occurring. Such patients, after the documentation of a sustained VT event, are indicated to receive an ICD. This may reduce the incidence of SCD without actual WCD therapy being delivered. Likewise, asystole may be the initial rhythm during an SCA event and impact SCA resuscitation success. Alternatively, surviving an asystole event and receiving a pacemaker may reduce SCD without defibrillation.

3.2.5 Evaluate the risk of inappropriate WCD therapy at 6 months

The rate of inappropriate therapies (i.e., a treatment shock in the absence of a VT/VF arrhythmia) during commercial WCD use is low, occurring less than 0.9% per patient-month of use. This rate will be confirmed for hemodialysis patients.

3.2.6 Evaluate compliance with WCD therapy

Compliance is high in commercial use of WCD, exceeding 90%. Similar results are anticipated in hemodialysis patients.

3.2.7 Evaluate quality of life

Psychosocial issues are one of the major concerns in the overall health of hemodialysis patients. Patients with ESRD, especially those undergoing dialysis, are under continuous stress related not only with a disease itself but also with the mode of treatment. Depression and anxiety disorders are among the most frequently encountered in ERDS patients. Social and family issues related with end-stage illness and dialysis-dependency should also be emphasized.

Quality of life will be assessed by means of a specific Kidney Disease and Quality of Life (KDQOL) survey. This questionnaire is composed of 36 questions evaluating overall health perception, kidney disease-related issues and its influence on patient's daily life as well as satisfaction with care. Kidney Disease Quality of Life Working Group website: http://gim.med.ucla.edu/kdqol/

3.2.8 Evaluate clinical variables that may be predictive for mortality and arrhythmic events

4. SUBJECT SELECTION CRITERIA

The population for this study will be ESRD patients who are beginning hemodialysis.

4.1 Inclusion Criteria

The specific inclusion criteria are (all must be true):

4.1.1 The patient has end stage renal disease requiring hemodialysis.

4.1.2 The patient is on hemodialysis for ≤ 2 calendar months or scheduled to begin hemodialysis within 1 calendar month.

4.1.3 The patient is ≥50 years of age.

4.1.4 The patient has a documented EF > 35% within the previous calendar year.

4.1.4.1 If the patient has been hospitalized for a myocardial infarction or heart failure decompensation, the EF measurement must have occurred during the last hospitalization or after discharge.

4.2 Exclusion Criteria

The specific exclusion criteria are (none may be true):

4.2.1 The patient is receiving or will receive hemodialysis due to acute kidney injury and is not expected to receive subsequent chronic hemodialysis therapy.

4.2.2 The patient has an active ICD.

4.2.3 The patient has a unipolar pacemaker.

4.2.4 The patient has physical or mental conditions preventing him/her from interacting with or wearing a WCD. For example, patients unable to understand device use, unable to hear alarms, or unable to use response buttons.

4.2.5 The patient has a chest circumference at the level of the xiphoid of < 24 inches.

4.2.6 The patient has a chest circumference at the level of the xiphoid of > 56 inches.

4.2.7 The patient has an advance directive prohibiting resuscitation.

4.2.8 The patient has cancer or other terminal disease (excluding ESRD) with expected survival less than 6 months.

4.2.9 The patient is medically unstable for reasons not specifically related to kidney disease.

4.2.10 The patient is scheduled for live-donor kidney transplantation within 6 calendar months.

4.2.11 The patient is unable to consent.

5. STUDY SIZE

A minimum of 1,300 and a maximum of 2,600 subjects will be enrolled into this study. A maximum of 200 sites will enroll patients into the trial.

6. STUDY PROCEDURE

6.1 Screening

Patients undergoing hemodialysis or those with a scheduled start date for the initiation of dialysis will be screened regarding their eligibility for the study based on age, EF and length of time on hemodialysis.

6.1.1 Left ventricular ejection fraction (EF) assessment

EF must be assessed within one calendar year prior to enrollment. The most recent test must be used. In patients with a history of myocardial infarction or heart failure hospitalization within the past year, it is expected that an echocardiogram or other method for measuring EF should have been obtained during or after the time of the event. If there is more than one hospitalization for myocardial infarction or heart failure, the EF measurement used must be associated with the most recent

hospitalization. If there is no EF measurement available from the last hospitalization for myocardial infarction or heart failure, potential subjects should be treated as if no EF measurement is available.

Potential subjects who have never had an EF evaluation or whose EF was obtained greater than one calendar year prior to randomization will be required to have an echocardiogram to assess cardiac function prior to enrollment, ideally within 14 days prior to enrollment but in no circumstances later than one calendar month prior to enrollment.

Echocardiographic assessment of LVEF is most frequently performed in clinical practice. Nevertheless, similar to ICD trials, other imaging modalities (MUGA, MRI) may be used to document LVEF. Also similar to ICD trials, local assessment of LVEF will be accepted. Although there are likely to be differences in EF assessment among enrolling sites and practices, these differences are not expected to affect the outcome of the trial.

6.1.2 Patients on home hemodialysis will be eligible for enrollment in the study.

6.2 Pre-study Visit (only required if EF needs to be collected)

6.2.1 Inclusion/exclusion will be verified

6.2.2 Informed consent will be obtained.

6.2.3 Patients requiring collection of LVEF must have an echocardiogram (or other appropriate EF assessment) prior to enrollment at Visit 1. The EF assessment must be completed within 1 calendar month of the pre-study visit but ideally should be completed within 14 days.

6.2.4 Enrollment will occur once all screening criteria have been met, including EF.

6.3 Visit 1 (Day 1)

Prior to Visit 1, call ZOLL to schedule a Patient Service Representative (PSR) to be present the day of enrollment. A PSR should be available to fit the patient with a WCD in the event that the patient is randomized to the WCD arm.

For all subjects:

6.3.1 Inclusion/exclusion will be verified.

6.3.2 Informed Consent will be obtained.

6.3.3 Subjects will be randomized to WCD or conventional therapy.

6.3.4 Clinical history data will be collected, including laboratory and ECG if available.

6.3.5 Subjects will be asked to complete quality of life questionnaire.

6.3.6 If the patient has started hemodialysis, general hemodialysis data will be collected.

6.3.7 Medication usage will be collected.

For subjects randomized to WCD only:

6.3.8 Subjects will be instructed and trained regarding usage of WCD by a ZOLL representative.

6.3.9 Subjects will be instructed to wear the WCD for six months.

6.4 Visit 2 (2 calendar months from enrollment ± 14 days)

6.4.1 For all subjects:

6.4.1.1 Subjects will be asked to complete quality of life questionnaire reflecting their experience over the previous 4 weeks.

6.4.1.2 Collect general hemodialysis data.

6.4.1.3 Collect any changes to medications.

6.4.1.4 Collect device, adverse, and cardiac event information including laboratory data from the medical record as available.

6.4.2 For subjects randomized to WCD therapy:

6.4.2.1 Compliance will be evaluated and encouraged.

6.5 Visit 3 (4 calendar months from enrollment ± 14 days)

6.5.1 For all subjects:

6.5.1.1 Collect general hemodialysis data.

6.5.1.2 Collect any changes to medications.

6.5.1.3 Collect device, adverse and cardiac event information including laboratory data from the medical record as available.

6.5.2 For patients randomized to WCD therapy:

6.5.2.1 Compliance will be evaluated and encouraged.

6.6 Visit 4 (at least 6 calendar months from enrollment, with up to 14 additional days)

6.6.1 For all subjects:

6.6.1.1 Collect general hemodialysis data.

6.6.1.2 Collect any changes to medications.

6.6.1.3 Collect device, adverse and cardiac event information as needed.

6.6.1.4 Subjects will be asked to complete quality of life questionnaire reflecting their experience over the past calendar month.

6.6.2 Collect survival data.

6.7 Unscheduled Visit (e.g., if resuscitation from SCA)

6.7.1 For all subjects:

6.7.1.1 Collect general hemodialysis data.

6.7.1.2 Collect any changes to medications.

6.7.1.3 Collect device, adverse and cardiac event information as needed, including laboratory data as available from medical record.

6.7.2 For patients randomized to WCD therapy:

6.7.2.1 Compliance will be evaluated and encouraged.

6.8 Final survival assessment (1 calendar year from enrollment, with up to 14 additional days)

Sites will be asked to determine survival for all subjects enrolled in the study through either routine dialysis records and appointments, or a phone call to the subject.

6.9 Post-study follow-up

Long-term outcome assessment may be performed using databases maintained by the United States Renal Data System and the Centers for Medicare and Medicaid.

Table 3: Visit and Data Collection Schedule

	Pre-study Visit [a]	Visit 1 (Enrollment)	Visit 2 (Month 2)	Visit 3 (Month 4)	Visit 4 (Month 6) or Terminal Event or Withdrawal	Unscheduled Visit or SCA Event
Consent	X	X				
Confirm Inc/Exc (confirm presence of EF or schedule echocardiogram)	X [b]	X				
Medical History/ESRD History		X [c]				
Laboratory Assessment [e]		X	X [f]	X [f]	X [f]	X
WCD Introduction/Training		X				
Randomization		X				
WCD Fitting (WCD subjects only)		X [d]				
WCD Compliance (for WCD subjects only)		X [d]	X [d]	X [d]	X [d]	X [d]
Collection of Dialysis Information and Medication Use		X	X	X	X	X
Collect device, adverse and cardiac events (includes defibrillation events)			X	X	X	X
KDQOL (Quality of Life)		X	X		X [g]	

[a] for patients without EF data
[b] LVEF must have been collected within 1 calendar year prior to enrollment, or during or after MI or CHF hospitalization, whichever is more recent. LVEF may be collected from Echocardiogram, MUGA, MRI.
[c] included ECG if available
[d] for WCD subjects only
[e] collected at local lab
[f] only if cardiac event/shock occurs
[g] if not terminal event

6.10 Managing WCD Therapy

6.10.1 The WCD System continuously monitors and records critical patient data to help diagnose and treat arrhythmic conditions. Device data will be uploaded at least weekly to a central server located in Pittsburgh, PA. In the event that uploads are not occurring on a routine basis, subjects should call ZOLL Technical Support for instructions.

6.10.2 Subjects having questions or difficulty managing their WCD should be instructed to call ZOLL Technical Support.

6.10.3 Clinicians will be blinded to the arrhythmia recordings in the group assigned to wear the WCD. This is necessary to prevent co-interventions with inappropriate anti-

arrhythmic drugs or early implantation of an ICD. If unblinding is required, the investigator may be able to view the device recorded data through a secure website and/or receive ECG strips recorded by the WCD. The following provisions for unblinding are available when clinically indicated.

6.10.3.1 Automatic unblinding will be initiated by ZOLL, and results in electronic notification to the site as well as the transmission of ECG data. Automatic unblinding will be initiated when any of the following events occurs:

6.10.3.1.1 The subject receives a treatment by the WCD.

6.10.3.1.2 VT/VF lasting $\geq$ 30 seconds is detected and recorded by the WCD, regardless of treatment by the device.

6.10.3.1.3 Asystole or bradycardia less than 20 BPM is detected and recorded by the WCD.

6.10.3.2 Clinical sites can request unblinding and receive ECG strips recorded by the WCD under the following circumstances:

6.10.3.2.1 Subject suffers a cardiac arrest or reports receiving a shock.

6.10.3.2.2 Subject complains of excessive alarms or alarms suspicious of an arrhythmic event that is not associated with syncope, pre-syncope or palpitations. In this circumstance, a protocol deviation will be reported.

6.10.3.2.3 Subject complains of syncope or pre-syncope associated with WCD alarms.

6.10.3.2.4 Subject complains of palpitations associated with WCD alarms.

6.10.3.2.5 A treating physician deems it to be medically necessary. In this circumstance, a protocol deviation will be reported.

7. STUDY DESIGN

This study will employ a group sequential two-arm randomized clinical trial to test the hypothesis that the wearable cardioverter defibrillator (WCD) reduces overall mortality within a 6 calendar month period beginning at the time of randomization, which is to occur no later than 2 calendar months after the initiation of hemodialysis.

Enrolled subjects will be 1:1 randomized to WCD or non-WCD, stratified by enrolling site and, implicitly, by calendar time of enrollment. All subjects will be followed for at least 6 calendar months regardless of compliance. The primary endpoint is the binary event of whether or not sudden cardiac death occurs within the 6 month follow-up period. The primary analysis will be an intention-to-treat analysis based on the randomization, ignoring the fact that some subjects randomized to WCD may discontinue use of the device early while some subjects randomized to the non-WCD arm may obtain and wear a WCD.

Overall mortality at 6 calendar months in the non-WCD arm is expected to be 14%, with one quarter of all deaths due to sudden cardiac death (SCD rate of 3.5%).[2] Taking some anticipated noncompliance into consideration, as some subjects are expected to discontinue WCD prior to 6 months, we hypothesize that the WCD will provide a relative reduction in SCD of 60%. Thus, we

expect an absolute reduction of 2.1% in SCD mortality, corresponding to a relative risk (RR) of 0.40 and an odds ratio (OR) of 0.39.

The exact number of subjects to be randomized is uncertain since the group sequential trial was designed to have 46% power to stop at the first interim look at 650 (50%) subjects per arm, and 69% power to stop at the second interim look at 975 (75%) subjects per arm, while controlling the overall significance level at $\alpha = 0.05$. But if the study continues to the third and final look, a maximum of 1,300 subjects will be enrolled in each arm, for a total of 2,600 subjects providing 91% power to detect the hypothesized 60% relative reduction in overall 6-month SCD mortality from 3.5% down to 1.4%.

7.1 Endpoint Assessment

A Mortality Committee will provide an assessment regarding mortality events with a categorization of the death based on underlying cause and mechanism of death. All deaths will be adjudicated by the Mortality Committee and classified as 'sudden (SCD)', 'not sudden' or 'indeterminate'. In addition, the death will be classified as 'cardiac', and 'non-cardiac'. All deaths will be used as endpoints in the primary analysis and the adjudicated results used as endpoints in the secondary analyses.

This committee will be blinded to information regarding the use of a WCD. The death reports from enrolling sites will be transcribed by an unblinded individual and provided in a uniform format to the adjudication committee. Transcribed notes will be redacted of information regarding WCD or WCD therapy to maintain the blinding of the committee. The Mortality Committee will not utilize WCD or AED interrogation information when classifying death as cardiac or non-cardiac, and as sudden or non-sudden.

7.1.1 SCD definitions

For witnessed deaths, sudden cardiac death (SCD) will be defined as an unexpected, non-traumatic, non-self-inflicted fatality in otherwise stable subjects who die within one hour of the onset of the terminal symptoms (and for whom dialysis-noncompliance or withdrawal have been excluded). Subjects dying more than one hour after a sudden cardiac arrest (SCA) from a ventricular arrhythmia will be designed as non-sudden death due to ventricular arrhythmia.

For unwitnessed deaths, participants will meet the definition of sudden cardiac death if they are found dead within 24 hours of being well, assuming there is no evidence of another cause of death during that time period including dialysis-noncompliance (or withdrawal). Autopsy results may be used when available.

7.1.2 Arrhythmia Adjudication

A separate Wearable Defibrillator Interrogation Adjudication Committee will focus on assessing cardiac arrhythmias triggering WCD therapy regarding its appropriateness and effectiveness. All events will be reviewed by an independent committee and will be categorized as appropriate, inappropriate, or indeterminate. Details of arrhythmic events and related therapy will be recorded.

7.2 Statistical Methods

The primary analysis will be based on a 1-df likelihood ratio test (LRT) of the null hypothesis that the 6 calendar month SCD mortality rate is identical for subjects randomized to WCD versus non-WCD (i.e. odds ratio of 1), conditional on enrolling site and date of enrollment (stratification variables that define randomized blocks), and further

parametrically adjusted for five additional pre-specified risk factors via conditional logistic regression (CLR):

- age (continuous, and flexibly modeled via a 4-df continuous piecewise linear spline with knots at 60, 70, and 80 years of age, allowing for a separate odds ratio per year within each decade of age),
- ejection fraction (continuous, and modeled via a 2-df continuous piecewise linear spline with a knot at 50%, allowing for a separate odds ratio per year above and below 50%, given that it is expected that mortality risk likely decreases smoothly up to about 50% but then perhaps levels off thereafter),
- race/ethnicity (binary: white non-Hispanics versus all others),
- diabetes (binary: yes versus no),
- myocardial infarction (binary: yes versus none),
- dialysis access (binary: catheter versus no catheter).

The adjusted odds ratio (OR) for WCD along with its corresponding 95% confidence interval (CI) will be estimated via CLR. Note that, in stark contrast to case-control studies, there is essentially no loss of efficiency due to heavy stratification resulting in a large number of strata, provided almost every stratum contains at least 1 patient from each group (WCD, non-WCD). This condition is guaranteed, given the plan to stratify on only those variables defining blocks for randomization. This was verified by simulation and supported by results in DeStavola and Cox, which states that there is no loss of efficiency if the strata are perfectly balanced (e.g. via stratified randomization).[39] Thus, there is no concern of "over-stratifying," even if SCD were independent of enrolling site and date of enrollment. In fact, in order for CLR to be computationally feasible it is necessary that no stratum be too large. Furthermore, even if SCD were independent of some or all of the 5 variables (8 df) parametrically adjusted for, the loss of efficiency and precision would be negligible since randomized treatment is completely independent of all risk factors. On the other hand, to the extent that SCD is associated with any of the adjustment or stratification variables, failing to control for them at the analysis stage could result in a substantial loss of efficiency. Standard power calculations assume that subjects are independent and identically distributed, at least given the adjustments, but this assumption would be violated if important predictors of SCD were not controlled for, thus resulting in lower power than that suggested by standard sample size and power calculations.

Exploratory analysis of the secondary endpoint of all-cause mortality will be based on a single 2-sided nominal 0.05 level LRT, using the same CLR method as used to analyze SCD, with whatever sample size (650, 975, or 1300 patients per arm) happens to be available when the trial ends. A simple nominal 0.05 level test will be performed for the analysis of all-cause mortality, treating the resulting data as a fixed sample size.

Secondary analyses will test interactions between WCD and SCD risk factors in order to investigate whether there are subgroups for whom WCD might be especially effective. Interactions between pairs of SCD risk factors will also be explored in secondary analyses.

7.3 Group Sequential Design

Standard group sequential methods[38] can be applied, given the large-sample approximate normality of the estimated log(OR), and PASS 11 software was used to compute the alpha and power values for our custom group sequential stopping rule. We plan to conduct 2

interim analyses once the 6 calendar month SCD outcome has been observed for 1/2 and 3/4 of the subjects. Our custom stopping boundaries retain 4% nominal alpha for the third and final look, provided the study doesn't stop early, while testing each of the 2 interim analyses at the nominal alpha level of 0.01375 (see Table 4). The overall alpha level for the study is .05.

Table 4: Group sequential design for the two-arm randomized clinical trial.

Look	Relative Information	# WCD subjects	# non-WCD subjects	# Total subjects	Nominal Alpha	Corrected Alpha
1	50%	650	650	1,300	0.01375	0.01375
2	75%	975	975	1,950	0.01375	0.02231
3	100%	1,300	1,300	2,600	0.04000	0.05000

7.4 Sample Size and Power

Although the odds ratio (OR) is the canonical parameter for our CLR analysis, we have specified power here in terms of the relative risk (RR), which is generally easier to interpret. As is well known, the OR will always be more extreme than the RR, though not by much if the outcome is rare in both groups (as it is here) or if the effect size is small.

This study is designed to provide 91% power to detect RR = 0.40 (OR = 0.39), assuming the SCD rate in the non-WCD arm is 3.5%. Our group sequential design increases the maximum sample size by just 4%, relative to a non-sequential study (1,250 per arm), while yielding —if the true RR = 0.40— a 36% reduction in expected sample size (804 per arm), as there is 69% chance of stopping early, and 46% chance of stopping at the very first look with just 650 subjects per arm.

Power is tabulated in Table 5 for 9 scenarios, varying the RR (.30, .40, .50) as well as the SCD mortality rate among controls (3.0%, 3.5%, 4.0%).

Table 5: Power as a function of RR and the SCD rate in the control arm.

Power (%) at Look 3	Power (%) at Look 2	Power (%) at Look 1	% SCD (WCD)	% SCD (non-WCD)	Absolute Reduction in % SCD	Relative Risk (RR)
96	80	57	0.90	3.00	2.10	0.30
85	60	38	1.20	3.00	1.80	0.40
67	40	23	1.50	3.00	1.50	0.50
98	*87*	***66***	*1.05*	*3.50*	*2.45*	*0.30*
91	***69***	***46***	***1.40***	***3.50***	***2.10***	***0.40***
74	*47*	*28*	*1.75*	*3.50*	*1.75*	*0.50*
99	92	73	1.20	4.00	2.80	0.30
94	76	53	1.60	4.00	2.40	0.40
80	54	33	2.00	4.00	2.00	0.50

A relative risk of 0.50 (OR = 0.49), i.e. a relative reduction of 50% and an absolute reduction of 1.75% in SCD, corresponds with a 12.5% reduction in all-cause mortality due to WCD,

assuming the all-cause mortality rate is 14% with about 25% of deaths attributable to SCD (3.5% SCD rate). Even under these conservative assumptions, our study maintains 74% power, as shown in Table 5. We believe that the risk reduction will be higher (at least 60% reduction in SCD, corresponding with at least a 15% reduction in all-cause mortality), thus providing 91% power. Furthermore, this study maintains 85% power to detect RR = 0.40 (OR = 0.39) even if the SCD rate were only 3% (rather than 3.5%) among controls.

7.5 Randomization Scheme

Enrolled subjects will be 1:1 randomized to WCD or non-WCD, stratified by enrolling site and, implicitly, by calendar time of enrollment given the prospective nature of the study. That is, each enrolling site will have its own randomization sequence, ensuring treatment balance within each enrolling site. Each such randomization sequence will consist of a string of random 4- and 6-blocks. That is, there will be a 50% chance that the first block will consist of 4 subjects (2 WCD + 2 non-WCD, in random order), and a 50% chance that it will contain 6 subjects (3 WCD + 3 non-WCD, in random order). Each subsequent block size will similarly be randomly selected. This procedure makes it very difficult for anyone to predict whether the next treatment assignment will be WCD or non-WCD, helping to ensure integrity of the study. In contrast, if each block were of size 4, then it would be trivial to perfectly predict every 4^{th} treatment assignment (as well as the 3^{rd}, if the first two were both WCD, or both non-WCD) which would be undesirable. Using such small blocks will also guarantee near perfect balance no matter where the sequence is truncated, i.e. regardless of how many subjects are enrolled in each site, and it will further guarantee temporal balance not only overall but also within each enrolling site (i.e. balanced treatment x time interaction strata) since each randomization block will contain an equal number of WCD and non-WCD subjects, with the possible exception of the last (incomplete) block in each enrolling site.

7.6 Statistical Analysis

Upon completion of the trial, a two-tailed p-value will be computed as the probability of the realized stopping point (under null conditions) plus the probability of all more extreme stopping points, defined via the stagewise ordering of the sample space.[38] If the study stops at the first look, $p \leq 0.01375$ and inference proceeds as if there were no future potential stopping rules. If the study stops at the second look, we know $0.01375 < p \leq 0.02231$; and if the study continues to the third and final look, then either $0.02231 < p \leq 0.05$ (if nominal $p \leq 0.04$) or else $p > 0.05$ (if nominal $p > 0.04$). SAS PROC SEQTEST will be used to compute the actual p-value, as well as a median unbiased estimated OR, along with 95% confidence intervals (CI).

A point estimate of the true OR, a *median unbiased estimate*, is that value for OR for which the probability of stopping points more extreme than the reached stopping point equals the probability of stopping points less extreme than the reached point — and hence the estimate is just as likely to underestimate as to overestimate the true risk ratio. Confidence bounds for the OR are found similarly: the value of OR for which the probability of more extreme values is at most 2.5% and the value of OR for which the probability of less extreme values is at most 2.5% together yield a 95% confidence interval for OR.

8. RISKS AND BENEFITS

Resuscitation success rates decline approximately 10% per minute of delayed defibrillation. The LifeVest is designed to deliver defibrillation within one minute of syncopal VT/VF. Although emergency medical service response times vary by location, the device is expected in general to defibrillate faster than the local emergency medical services response and possibly result in a better resuscitation success rate.

Without LifeVest use, the patient is dependent on outpatient emergency medical services for treatment in the event of a sudden cardiac arrest. If the device is not worn, if the device fails to detect an episode of VT/VF, or if having detected the arrhythmia it fails to convert the VT/VF, then the patient would again be dependent on emergency medical services.

Prior investigations and current use indicate that the probability of an unnecessary shock episode is less than one per 100 months of patient use.[5,41,42] The experience of an unnecessary shock may be painful and startling, but is not likely induce heart damage or arrhythmia. However, there is a small risk that an unnecessary shock will induce a fatal arrhythmia. Non-sustained VT following an inappropriate shock from a wearable cardioverter defibrillator has been observed in about 0.25% of inappropriate shocks (about one in 350 to 400 inappropriate shocks).[41,42]

If standard defibrillation is required on a patient wearing the device, the electrode belt should be unbuckled and the monitor disconnected. If the monitor is not disconnected prior to standard defibrillation, there is a possibility that some of the defibrillation current could be shunted through the electrodes. Although not directly harmful to the patient, such shunting might reduce the effectiveness of the rescue defibrillation. A warning label on the garment instructs emergency medical personnel to disconnect the system before using a standard defibrillator.

9. SUBJECT CONSENT AND CONFIDENTIALITY

Each patient will be informed of the purpose of the investigation, as well as the potential risks and benefits of the study prior to their enrollment in the study. The patient must freely sign the current IRB reviewed Informed Consent Form prior to enrollment. In the event that the information regarding potential risks and benefits contained in the Informed Consent Form changes, the subject must sign the new Informed Consent Form at the next return visit or be informed as directed by the reviewing IRB.

Each subject will receive a unique subject identification number. The subject's name and identity will be known to the local principal investigator and the Sponsor, as necessary for device use and study conduct, but will be kept confidential. Authorized personnel from the IRB and regulatory authorities may have access to original subject records.

At the end of the data collection period, a fully de-identified, HIPAA-compliant dataset will be created using all variables available from the Case Report Forms and device data contained within LifeVest network. This dataset will be used for analysis and publication purposes.

10. ETHICAL CONSIDERATIONS

The protocol, informed consent form, and relevant supporting information must be submitted to the IRB for review and must be approved before the study is initiated. In addition, any patient recruitment materials must be approved by the IRB prior to being used. This study will be conducted in accordance with the ethical principles that have their origin in the Declaration of Helsinki and that are consistent with Good Clinical Practice and applicable regulatory

requirements. The study must be conducted in accordance with the regulations of the United Stated Food and Drug Administration (FDA) as described in 21 CFR 50, 56 and 812, applicable laws and the IRB requirements.

11. ADVERSE EVENTS

The Investigators are responsible for recording and reporting adverse events deemed to be related to the use of the WCD in the Adverse Event Case Report Form. The Investigator must first assess whether the adverse event may be or is clearly not causally related to the WCD device. Adverse events must be reported to reviewing IRBs per local reporting requirements.

The Investigator must next assess the seriousness of the adverse event. Serious adverse events include any event which is fatal or life-threatening, requires or prolongs hospitalization, is permanently disabling, or requires medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.

The Investigator should also assess whether the adverse event is anticipated or unanticipated. An unanticipated adverse event is any adverse event not identified by nature, severity or frequency prior to the investigation. The following events are commonly reported in patients having hemodialysis and therefore should not be reported unless deemed related to WCD wear: infection, hypotension, access site cellulitis, anemia, electrolyte imbalance, dyspnea, muscle cramps, pruritus, restlessness, and seizures. Anticipated events that may be caused by WCD use are as follows: skin rash or irritation, sleeplessness due to WCD alarms occurring at night and inappropriate shocks.

If the adverse event may be causally related, and is serious and unexpected, the Investigator must immediately record the event in the Case Report Form. These events will be reported to the Sponsor from the Data Coordination Center (DCC) upon entry to into the CRF. The reviewing IRB must also be notified within 10 working days.

11.1 Unanticipated Adverse Device Effect (UADE)

The investigational device exemption (IDE) regulations define an unanticipated adverse device effect (UADE) as "any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects". UADEs must be reported by the clinical investigator to the sponsor and the reviewing IRB, as described below:

- For device studies, investigators are required to submit a report of a UADE no event than 10 working days after the investigator first learns of the event. UADE information must be entered into the CRF as soon as possible so notification of the event to the sponsor can occur through the DCC.
- Sponsors must immediately conduct an evaluation of a UADE and must report the results of the evaluation to FDA, all reviewing IRBs, and participating investigators within 10 working days after the sponsor first receives notice of the effect.

12. DATA MANAGEMENT

The Data Coordinating Center (DCC) for the study will be Heart Research Follow-up Program at the University of Rochester. The Heart Research Follow-up Program has provided program coordination and data management for several large NIH clinical studies during the past 25 years and for major clinical intervention trials related to the series of Multicenter Automatic Defibrillator Implantation Trials (MADIT) involving thousands of subjects. The DCC will develop and coordinate data management through dedicated personnel. In this study, electronic web-based data entry using the clinical data-management system developed by Omnicomm. This system permits data expansion, easy updating, and rapid retrieval; it has simplified report-generating routines and an audit trail component.

As with any study, accurate and timely completion of documentation is essential for the successful completion of the trial. The Investigators will be responsible for obtaining and maintaining Informed Consent Forms (90D0126_ICD) and completing Case Report Forms (90D0126_CRF) through the electronic web-based data entry system maintained by the DCC. A copy of the Informed Consent Form will be given to every subject.

The Sponsor stores ECG and compliance information from the WCD, obtained through periodic downloading during device use. A subset of this information containing at a minimum daily device use (compliance) and ECG recordings, including baseline and those recorded during alarms lasting at least 30 seconds, will be periodically sent to the DCC. This information will be de-identified and assigned a study identification number prior to transmission to the DCC.

13. ADMINISTRATIVE RESPONSIBILITIES

ZOLL, the Sponsor, is responsible for study administration as well as providing devices and related materials for the study. The Sponsor will select appropriate investigators, assure collection of investigator agreements, assure IRB approval of the protocol, and monitor informed consent records.

The Sponsor will designate appropriately trained and qualified individuals to monitor the investigation. These individuals will verify the adherence to procedures specified in the protocol, and verify maintenance of required subject and data records. Monitoring activities will be conducted according to ZOLL's Monitoring of Clinical Studies Standard Operating Procedure (ZOLL 90D0013) and will be documented.

The Sponsor will provide trained and qualified individuals to fit subjects randomized to wear the WCD and to provide training on the use of the WCD.

The Steering Committee will be responsible for general scientific oversight and progress of the study. Steering Committee Members will be appointed by the Sponsor. The committee will be chaired by Dr. Wojciech Zareba and co-chaired by Dr. Charles Herzog, and include a representative from the Sponsor. The Steering Committee will be responsible for overseeing study progress including ancillary studies, scientific policies, integrity and direction. It will appoint the analysis and publications committee and writing groups, ensuring that information from the study is disseminated in the scientific literature and at scientific meetings. The Steering Committee will meet at least twice in the first year, and then at least once yearly in person or by conference call. An executive subgroup of the Steering Committee will be responsible for decisions that require attention between Steering Committee meetings, and for major financial, administrative, and operational decisions. The Executive Committee will consist of Dr. Zareba (chair), Dr. Herzog (co-chair), and a representative from the Sponsor.

The Data Coordination Center (DCC) will be the Heart Research Follow-up Program at the University of Rochester, and have responsibility for clinical data coordination. The DCC will provide management of data for the overall project independent of the Sponsor. All case report forms will be collected directly by the DCC.

The study will be monitored by an independent Data Safety Monitoring Board (DSMB). The DSMB will be appointed by the Sponsor. The DSMB will review and validate all events used for the stopping rule. They will also periodically review all aspects of the trial, including inappropriate therapies, to ensure the safety of the participants. The DSMB is responsible for appointing adjudication committees for significant endpoints including deaths (through the Mortality Committee) and ECG analysis (through the Wearable Defibrillator Interrogation Adjudication Committee). The DSMB will communicate directly with the DCC and the adjudication committees.

The Investigators are responsible for obtaining and maintaining ethics approval of the study protocol. The Investigators are responsible for obtaining patient consent, and maintaining Informed Consent Forms and Case Report Forms for each subject. All forms must be signed by the Investigator or by the Investigator's designee. If the Investigators designate an individual to sign these forms, written notification must be provided to the Sponsor. The Investigators are responsible for maintaining records of study protocol deviations and amendments and all correspondence relating to the study. The Sponsor will provide an Investigator Notebook to serve as a study reference and regulatory binder. At the conclusion of the study, the Investigators will provide a summary report to the Sponsor and the reviewing IRB.

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