Circulation: Heart Failure

ON MY MIND

When the VEST Does Not Fit

Representations of Trial Results Deviating From Rigorous Data Interpretation

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Sudden cardiac death (SCD) prevention in patients with newly diagnosed ventricular dysfunction or heart failure with reduced ejection fraction is an important clinical issue. A lack of strong evidence has led to uncertainty in medical decision making and variable clinical practice in the use of wearable cardioverter-defibrillators (WCDs). In this context, the results of VEST (Vest Prevention of Early Sudden Death Trial)[1] at the American College of Cardiology Scientific Sessions on March 10, 2018, in Orlando, FL were highly anticipated. However, interpretations of the trial results have been presented that we find difficult to reconcile. We wish to call attention to what we think is the most rigorous interpretation of VEST: the primary results were negative.

The WCD is designed for patients at risk of SCD who are not immediate candidates for implantable cardioverter-defibrillator (ICD) therapy. This is most commonly because of a new diagnosis of left ventricular dysfunction, often after acute myocardial infarction (MI).[2] Although ICDs improve survival over years of treatment in appropriately selected patients, reductions in the first 40 days postinfarction have not been conclusively demonstrated.[3,4] Despite this lack of evidence, the Food and Drug Administration approved the WCD for use in 2002, primarily because of the ability of this noninvasive technology to deliver appropriate shocks in laboratory settings and case series.[5]

Although the WCD may seem benign—prompting a philosophy among some of why not, or better safe than sorry—there are reasons its efficacy and value should be investigated. The device can be burdensome and uncomfortable, with skin rash and inappropriate shocks possible. The device is resource intensive in terms of hardware, initiation, and monitoring; at the time of the VEST presentation, the average charge was >$3000 per month. A large, randomized, patient-centered outcomes trial of WCD was therefore important.

VEST was that trial, and we applaud its conduct and completion. It screened 13 774 patients between 2008 to 2017, of whom 2302 with acute MI and left ventricular ejection fraction≤35% were randomized within 7 days of hospital discharge to open-label WCD or not (2:1). Clinicians were blinded to an arrhythmia detection, and crossovers and ICDs were prohibited except for secondary prevention (2.6% of control participants crossed over). Initially, >80% of intervention patients wore the WCD, which declined to 50% by 90 days; average use per day was 14.1 hours. During a median follow-up of 84 days, 1.6% of the WCD group and 2.4% of the control group experienced the primary end point of SCD or death from ventricular arrhythmia (P=0.18). Of 1524 patients in the WCD arm, 20 patients received an appropriate shock, of whom 14 (0.9%) survived to 90 days. There were 10 inappropriate shocks and 70 aborted shocks.

Unexpectedly, non-SCD occurred in 1.4% of the WCD group and 2.2% of the controls (P=0.15) driven by 4 fatal strokes in controls and none in the WCD arm

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(*P*=0.01). When combined, all-cause death, a secondary end point, occurred in 3.1% of participants in the WCD arm and 4.9% in the control arm, with a *P*=0.04. Possible explanations for lower all-cause death are speculative. SCD may have been adjudicated incorrectly, although non-SCD deaths in the study, largely stroke and progressive heart failure, should be accurately attributed in most cases. The study was not blinded, which may have led to bias. Random variation is always possible, noting that with Bonferroni correction for multiple comparisons the *P* value of 0.04 for all-cause death is not significant. Finally, it should be noted that the WCD, like the ICD, was designed to prevent arrhythmic SCD, and by doing so, to reduce all-cause death. In previous trials of ICD therapy, the reduction in SCD has been of greater magnitude and more clear statistical significance than the reduction in all-cause death.[6] Therefore, the observation of an apparent reduction of all-cause death without a clear reduction in SCD observed in VEST should be interpreted with extreme caution.

Despite these considerations, the overall mortality difference of 36% was a prominent message carried forward in news coverage and was the primary finding immediately touted by the manufacturer. De-emphasis of the primary end point in favor of a secondary and less mechanistically consistent end point carries an appearance of bias. Also atypical is how the late-breaking trial presentation at American College of Cardiology concluded with prescribing the WCD is reasonable to protect high-risk patients with a low left ventricular ejection fraction post-MI until evaluation for an ICD at 40 to 90 days. Words have meaning. In the American College of Cardiology/American Heart Association Clinical Practice Guideline Recommendation Classification System, Class (strength) of Recommendation IIa is defined as is reasonable. Treatment/strategy A is probably recommended/indicated in preference to treatment B. We do not think that VEST results are consistent with such a definition.

In our view, among a group of patients selected for their perceived risk of SCD, the VEST results did not demonstrate a clear, clinically meaningful reduction in arrhythmic death. Thus, the VEST results as presented at the American College of Cardiology suggest that for most patients hospitalized with acute MI and an left ventricular ejection fraction≤35%, it is reasonable to wait without a WCD and reassess the need for an ICD 40+ days later. There may be higher-risk groups for whom the chance of benefit is larger and thus for whom WCD may be of higher value (eg, patients with incomplete revascularization, greater myocardial damage, lower left ventricular ejection fraction, hemodynamic compromise at presentation, or short-duration ventricular arrhythmia on telemetry), but exactly who these patients are is not immediately apparent. In the meantime, it also seems appropriate to incorporate patient preferences, where a small potential reduction in early SCD is weighed against the cost, side effects, and lifestyle burdens of WCD. Or perhaps even better, we should focus on treatments for our patients with new heart failure with reduced ejection fraction that are strongly evidence-based. For example, mineralocorticoid receptor antagonist use in VEST was 44%, and is even lower in clinical registries of EPHESUS-like patients (Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study), despite its demonstrated efficacy in SCD prevention.[7]

Whereas medical decisions are often made on imperfect evidence, we urge our colleagues to be critical of recommending therapies on the basis of secondary findings alone, particularly when they are not yet peer-reviewed. Patients want to be healthy and clinicians want to keep them safe. The best way to do that is through a rigorous review of the evidence and a focus on those treatments with a clear benefit. Based on information available at this time, for patients with acute MI and new heart failure with reduced ejection fraction, the VEST does not fit.

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