

EDITORIAL COMMENT

Why Are Clinically Indicated, But Lower-Risk, Patients Less Likely to Receive Implantable Cardioverter-Defibrillator and Cardiac Resynchronization Therapy?*

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High-voltage device therapy is one of cardiology's great success stories of the past 20 years. Patients known to be at risk of sudden death—principally those with left ventricular systolic dysfunction—can be identified in advance of their arrhythmic events and prophylactic implantable cardioverter-defibrillator (ICD) therapy initiated. When the patient has disordered intraventricular conduction, addition of cardiac resynchronization therapy (CRT) has a further beneficial, albeit smaller, effect on mortality in addition to the desirable reduction in heart failure symptoms and heart failure hospitalizations that CRT brings. Although the results of major prospective randomized trials of transvenous ICD and CRT therapy have all been consistent, implantation of high-voltage devices in indicated patients is declining.

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Prophylactic high-voltage device implantation began in 1996 with the publication of the first primary prevention trial, MADIT (Multicenter Automatic Defibrillator Implantation Trial) (1), and volume grew up to about 2005 (2). The early CRT trials (COMPANION [Comparison of Medical Therapy, Pacing, and Defibrillation in Heart Failure] (3) and MIRACLE [Multicenter InSync Randomized Clinical Evaluation] (4)) and the subsequent introduction of the idea

that CRT could be administered prophylactically (MADIT CRT (5) and REVERSE [Resynchronization Reverses Remodeling in Systolic Left Ventricular Dysfunction] (6)) bolstered the growth of high-voltage device implantation. Since then, however, implantation rates have been declining such that current rates are down by about one-quarter compared with their peak period (Jeffries Group Inc., unpublished data, 2013) (CitiGroup Investments, unpublished data, March 23, 2011).

Why are high-voltage device implantation rates so low? There are many possible reasons. It may be that the number of appropriate patients is in fact smaller than anticipated despite a larger pool of patients meeting indications. Recent technological problems may influence physicians to shy away from referring indicated patients. In addition, convincing referring physicians of the clear mortality benefit seems to be an ongoing challenge.

This last point is addressed in the current article by Finegold et al. (7) in this issue of the *Journal*. The authors reviewed mortality benefit from CRT in 7 major trials comparing biventricular pacing versus no biventricular pacing. They used the measurement of life span gained, which has the advantage of providing a clinical context in which to relate clinical trial results to individual patients. Over 24 months of follow-up (the typical length of a prospective randomized trial), they observed that life span gained grew at a greater rate over time. The observed life span gain at 24 months was >4 times greater than that at 12 months. Although it is widely accepted that CRT positively affects mortality, the authors eloquently demonstrate the durability of the benefit.

Due to the overwhelming cost, clinical trials are designed to last as long as necessary to prove or disprove benefit. In the case of CRT trials, this is approximately 2 years. However, the life of a CRT device is about 5 years, and many patients live long enough to receive >1 device. The authors (7) extrapolated the hazard ratios over the life of a device (i.e., 5 years), thus enabling them to estimate the life span gained. Although clearly relying on assumptions, this is a practical way of looking at longer-term results without prolonging expensive clinical trials. When the authors reviewed the life span gained for the compiled trial data at 1, 2, 3, and 5 years after device implantation, it grew over time, and the number-needed-to-treat (NNT) decreased. In fact, in COMPANION (3), the NNT was 101.8 at 1 year and dramatically dropped to 7.4 at 3 years. In CARE-HF (CArdiac REsynchronization Heart Failure), the NNT was 75.8 and 6.0 at 1 and 3 years, respectively; in RAFT (Resynchronization-defibrillator Ambulatory Heart failure), the NNT dropped from 91.3 at 1 year to 4.8 at 5 years.

Even more interesting were the findings of Finegold et al. (7) when extrapolated to 15 and 20 years. At 5 and 10 years, there was greater benefit (more life span gained) in the higher-risk patients. However, lower-risk patients live longer (they have less nonsudden cardiac and noncardiac mortality), and at 15 and 20 years, they gained more benefit

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in life span than high-risk patients from device implantation. These findings have a direct impact on clinical practice. It is easy for us as clinicians to evaluate our New York Heart Association functional class III and IV patients and feel a need to do everything we can to prolong their lives as fast as possible. We may not see the same urgency in treating our patients who are better compensated, especially with device therapy. However, the authors have demonstrated that over time, these patients actually receive more benefit from CRT.

This concept of durability of benefit is not unique to CRT, and we believe it is evident in the non-CRT ICD trials as well. In MADIT II, the benefit of ICD therapy was not seen until 18 months (8). The 8-year follow-up data showed that the absolute risk reduction was 13% and that the NNT was 8 compared with 17 at 2 years (9). These findings suggest that clinical benefit extends at least throughout the life span of the device. During the trial phase of MADIT II, two-thirds of the patients did not receive appropriate ICD therapy. However, this relatively large group of low-risk patients derived benefit over the longer-term follow-up.

In a substudy of SCD-HeFT (Sudden Cardiac Death in Heart Failure Trial), Levy et al. (10) divided the subjects into risk quintiles. Implantation of an ICD reduced the relative risk of sudden cardiac death by 88% in the lowest-risk group versus a 24% reduction in the highest-risk group. The mortality reduction was 54% in the lowest-risk group compared with no mortality benefit in the highest-risk group. They then looked at life span gained and found that the lowest-risk group gained approximately 6 years but required multiple ICDs (about 3 over their predicted life span). This is markedly longer than the 0.2 life-year gained for the highest-risk patients.

There is further evidence regarding the nonuniformity of benefit of ICD therapy in the MADIT II data. Goldenberg et al. (11) looked at their own clinical risk score to determine who benefits the most from primary prevention ICD therapy. They chose several clinical risk factors, including New York Heart Association functional class >II, age >70 years, blood urea nitrogen level >26 mg/dl, QRS duration >0.12 s, and atrial fibrillation. They also identified a group of very-high-risk patients with a blood urea nitrogen level >50 mg/dl and/or serum creatinine level >2.5 mg/dl. Patients with at least 1 risk factor had a 49% reduction in mortality, whereas patients with no risk factors or who were deemed very high risk had no benefit (hazard ratio: 0.96 and 1.00, respectively).

In conclusion, it seems intuitively obvious that the sickest patients will derive the most life span benefit from prophylactic high-voltage device implantation. But defibrillators, unlike other therapies commonly used in patients with heart

failure, have a benefit that continues long after the device is implanted. It is only by assessing this over a period of many years and several devices that the full impact of therapy will become apparent. The current article (9) and more contemporary analyses of prophylactic ICD trials in different groups of patients indicate that it is the lower-risk patients who derive the most life span gain from these therapies. The implication of this finding is that guideline-appropriate patients should receive implants at an earlier stage in their course than is currently common. The mortality benefit will take time to become apparent, but it is real and is of importance to individual patients.

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