The benefit of implantable cardioverter-defibrillators (ICDs) in improving mortality in populations at risk for sudden cardiac death has been firmly established by multiple randomized controlled trials (RCTs). However, patients receiving ICDs in clinical practice differ substantially from those enrolled in landmark RCTs. In the most recent report of the US National Cardiovascular Data Registry (NCDR) ICD Registry, including more than half a million ICD implants, ICD recipients were older and sicker, with higher prevalences of diabetes mellitus, hypertension, and atrial fibrillation, than those enrolled in the Sudden Cardiac Death in Heart Failure Trial (SCD-HeFT) and the Multicenter Automatic Defibrillator Implantation Trial II (MADIT-II). Whether these patients enjoy a similar survival benefit to those enrolled in the clinical trials is less well understood. Determining the benefits of ICDs in the real world is a subject of increasing importance, especially as healthcare costs continue to rise.

In this issue of Circulation: Arrhythmias and Electrophysiology, Parkash et al compared the mortality rates in real-world patients in Nova Scotia receiving ICDs for primary prevention of ischemic or nonischemic cardiomyopathy (n=290) with comparable patients not receiving ICDs (n=601), using data from 2 registries. The study also described ICD utilization rates. They found that the ICD patients had significantly improved survival and also that ICD referral/implantation rates suggested significant underutilization. Because Nova Scotia has a province-wide registry of all patients admitted to any hospital in the province with acute coronary syndrome, heart failure (and atrial fibrillation), the investigators were able to identify patients who met the standard criteria for a primary prevention ICD but who did not receive one. Because all patients underwent ICD implantation at a single center in the province, a similar cohort of ICD recipients could be identified. Similarly, Nova Scotia’s universal healthcare system registers all deaths in a single database, allowing complete follow up. Thus, this analysis is truly population based. The investigators found a dramatic survival benefit from the ICD, with an unadjusted hazard ratio for mortality of 0.46, ranging from 0.55 to 0.59 after multivariable and propensity analyses, with high statistical significance.

How best to determine benefit from any intervention in real-world populations remains a matter of debate. Informed medical decision making requires reliable evidence. But what makes evidence reliable? Types of evidence are often considered as a hierarchy, with RCTs at the pinnacle, followed by various types of nonrandomized data. Certainly, a well-designed randomized trial has high internal validity, that is, the findings are likely correct in the context of the trial. However, RCTs have strict entry criteria, which can limit generalizability to broader populations. Other factors may also contribute to the issue of generalizability. The fact that control groups in RCTs tend to do better than patients receiving routine medical care suggests that other factors—the overall enhanced medical care patients receive in trials and the involvement of physicians who may have unique clinical expertise—may make their results hard to generalize. Population-based observational studies, on the other hand, contain a diversity of patients and hospitals. Although these studies are limited by potential differences in the groups being compared, which may then threaten the validity of the treatment-outcome relationship, that is, confounding or susceptibility bias, appropriate statistical design, such as the propensity scoring techniques used in the current study, can minimize this limitation. Concorato et al performed meta-analyses of observational and randomized studies of the same treatments and found remarkable similarities between the findings, with the observational studies actually demonstrating less heterogeneity among themselves and less variability around the point estimate than the RCT results.

A limitation of the current study is its identification of the non-ICD cohort from an inpatient myocardial infarction/congestive heart failure population. Although this is a good starting point for identifying ICD-eligible patients, these patients are only truly eligible if their low ejection fraction (EF)/congestive heart failure persists after time/appropriate treatment, and thus this population may not all have met guidelines-based criteria for an ICD. Although patients with a documented improvement in EF after myocardial infarction were excluded from the study, follow-up EFs were available only in a minority of patients (12%), and confirmation of continued congestive heart failure was available in only 33%. This weakness to the study design limits what can be said regarding utilization. As it is unknown in how many patients an improvement in EF would have removed them from the denominator of ICD candidates, underutilization may have been exaggerated. Other studies have also demonstrated a low rate of appropriate utilization of ICDs for primary
prevention, however, suggesting this remains a significant problem.

The inclusion of subjects in the non-ICD group who were earlier in the time course of their disease than is recommended for ICD implantation may have underestimated the survival benefit. Including an early postmyocardial infarction population in the non-ICD group whose EF may have subsequently increased, or including those whose congestive heart failure had improved would have more likely blunted an effect of ICD, rather than create an effect artifactually. Because these non-ICD patients may in fact have been healthier than the group receiving ICDs, the benefit may have been even greater without these patients. The mortality rate in the non-ICD group was lower than that in the placebo groups in SCD-HeFT or MADIT-II, further suggesting that the ICD benefit in the present study was not artifactually increased by susceptibility bias.

A prior observational study has used Medicare data to investigate ICD benefit in the general population. Groeneveld et al\textsuperscript{15} compared 7125 ICD recipients to a propensity-score-matched group and found a similar hazard ratio for mortality of 0.62 with the ICD. Like any study using administrative data, that study was limited by lack of detailed clinical data, such as EF or markers of renal function.\textsuperscript{9} In both the Medicare study and the Parkash study, however, the use of observational data, including both treated and untreated groups, is an important strength. Although many studies attempt to define ICD benefit in various subgroups, using surrogate end points, such as appropriate shocks, or comparing mortality among subgroups of patients receiving ICDs, only approaches comparing treated and untreated patients can define benefit.

It has been suggested that hierarchies of evidence are less useful than approaches combining evidence from a range of study designs.\textsuperscript{8} This and other observational studies complement the well-known RCTs, showing improved survival with primary prevention ICDs\textsuperscript{1–3} to provide compelling evidence that the benefit of primary prevention ICDs can and should be generalized to the real world.

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References

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