There is a general agreement that before a therapy can be accepted into widespread clinical use, demonstration of efficacy in randomized clinical trials (RCTs) is absolutely necessary. There are, however, a growing number of experts who believe that demonstration of RCT efficacy might not be a sufficient basis for widespread acceptance. RCTs may not enroll subjects representative of patients in community settings, who may differ from RCT subjects in age, gender distribution, disease severity, comorbidity burden, and intensity of ancillary therapy. Additionally, randomized trials may not enroll sufficient numbers of subjects to demonstrate safety from rare adverse events. As a result of these differences, some therapies with demonstrated efficacy may have a smaller effect or no effect at all in community patients. For example, spironolactone reduced mortality in a randomized trial, but in community-based studies, its effectiveness was limited by rates of adverse events significantly higher than in the trial.

Payers and consumers are increasingly concerned about unmeasured gaps between efficacy and effectiveness. As a result, calls are escalating for comparative effectiveness research to guide decisions regarding which new treatments to pay for. For example, the state of Washington has a health technology assessment committee that recently recommended limiting reimbursement for drug eluting stents to patients with diabetes mellitus, treatment of left main coronary disease, treatment of in stent restenosis, or situations in which stent diameter is 3 mm or less or stent length is 15 mm or more, on the grounds that effectiveness beyond these relatively narrow indications has not been demonstrated.

These strong arguments for making effectiveness research customary, however, run headlong into the reality of a healthcare system poorly able to conduct such work. First, funding for routine collection of effectiveness data is scarce, and financially squeezed healthcare organizations have few resources to devote to this important work. Second, the healthcare system is disjointed. Doctors and hospitals, inpatient and outpatient care, and primary and subspecialty care are often administratively separate. Third, computer-based storage and transfer of medical information is rudimentary. Finally, well-meaning but zealous privacy laws stifle data collection.

Implanted cardioverter-defibrillators (ICDs) illustrate both the need for comparative effectiveness research and the barriers to carrying it out successfully. Carefully conducted RCTs have consistently demonstrated the efficacy of ICDs for the primary prevention of sudden cardiac death. As a result, the Centers for Medicare and Medicaid Services and other payers have substantially expanded coverage for ICDs for patients with left ventricular systolic dysfunction. More than 140,000 ICDs are implanted annually in the United States with an estimated 500,000 Medicare beneficiaries eligible for ICDs. Despite the potential benefits of ICDs for primary prevention, important questions have emerged about the effectiveness of this technology in community-based populations.

A meta-analysis conducted in 2007 identified 12 randomized trials of ICDs for primary prevention of sudden death involving a total of 6553 subjects (3367 of whom received devices) and concluded that the devices resulted in a significant 19% reduction in the risk of all-cause mortality. The degree to which subjects in the RCTs are representative of patients in the community has been questioned. The mean age of subjects in the trials varied from 52 to 65 years, whereas the mean age of the patients with heart failure in community registries is typically 70 to 75 years. Similarly, men comprised 67% to 92% of trial subjects, compared with community populations with heart failure that are typically closer to 50% men, depending on the age distribution of the sample. In fact, recent studies have demonstrated that the risk of ICD-associated adverse events is higher in women, and the efficacy is questionable.

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contemporary population-based surveys. If patients receiving ICDs in community settings are older, have more severe heart failure, greater comorbidity, and lower rates of guideline-based ancillary therapy than RCT subjects, a greater likelihood of nonarrhythmic death might substantially diminish the reduction in all-cause mortality attributable to ICDs. Effectiveness research is needed.

That there are formidable barriers to ICD effectiveness research is illustrated in the study by Hernandez et al in this issue of *Circulation: Heart Failure*. Starting with a registry of 76,824 elderly patients with heart failure, the investigators were forced to exclude 44% of the sample because of incomplete data, including lack of information about ejection fraction and inability to match with a data set that contained follow-up information. An additional 9% were excluded for relative contraindications such as having left the hospital against medical advice or being older than 85 years. After applying standard exclusion criteria, such as an ejection fraction >35% or discharge to hospice, an additional 29% of the sample was excluded. Finally, only 8% of the eligible patients received an ICD during the index hospitalization, leaving 376 patients with an ICD implanted during the index hospitalization available for study. This number is smaller than the number of subjects receiving ICDs in 7 of the 12 efficacy studies cited by Ezekowitz et al. Yet, larger rather than smaller sample sizes are customary for observational studies assessing the external validity of randomized trials. Also of concern is that this sample size neither allow for the adequate study of separate subgroups, such as severely versus moderately reduced ejection fraction, women, or the elderly, nor can it give us reliable data on complication rates and other safety issues. A previous study of the effectiveness of ICDs investigated ~97,000 Medicare patients with acute myocardial infarction and subsequent heart failure or cardiomyopathy and found no difference in mortality at ~1 year associated with ICD implantation. Although the sample size was much larger in this latter study, the ability to assess eligibility or to adjust for confounders was limited by reliance on administrative data and a lack of clinical data.

Another barrier in effectiveness research is tying detailed clinical information to longitudinal outcomes. In part, this reflects the disconnection of inpatient and outpatient care present in many US healthcare data systems. Hernandez et al made these ties by linking a cross-sectional registry containing detailed clinical information from hospitalization to Medicare claims data to obtain outcomes. However, data use agreements limit linkages of the hospital-based registries with Medicare claims data and resulted in <80% matching. Ideally, data used to evaluate the effectiveness of ICDs would contain longitudinal data on both outcomes and detailed clinical factors that influence clinical decision making and outcomes so that adequate risk adjustment could be performed.

Despite these concerns, it would be a mistake to discount the results of this study completely. The age and gender distributions of the sample reflect the population of patients with heart failure. Approximately 35% of patients had atrial arrhythmias and ~15% had chronic kidney disease, again more similar to the community population than the RCT subjects were. Few other data are available. Most importantly, despite the small sample size, ICDs were associated with survival benefit.

So, what would it take to answer the question of whether or not ICDs are effective therapy in elderly patients with heart failure?

First, someone has to pay for the work. Although patients, doctors, and payers have a critical need for this information, funding for effectiveness research has been slow in coming. Construction of a registry large enough to answer the question requires more effort than is commonly appreciated, whether the registry is constructed solely from existing data or makes use in part of data entered prospectively. Although they clearly have an interest in the question, the Food and Drug Administration or Centers for Medicare and Medicaid Services do not have a legislative mandate to conduct such inquiries. It is therefore encouraging that research funds are being made available for effectiveness research through the National Institutes of Health and the Agency for Healthcare Research and Quality.

Second, integrated healthcare systems must be studied. At the very least, a single electronic medical record that contains clinical data from both inpatient and outpatient encounters is necessary. Without this integration, large losses of sample size from missing data are inevitable. Examples of integrated systems include the Veterans Administration system and large health maintenance organizations such as Kaiser Permanente.

Finally, the issue of trade-off between quality of life and quantity of life must be answered. Patients with heart failure in community samples and patients with heart failure enrolled in RCTs have quantified this trade-off differently. As with mortality, there is every reason to believe that health status assessments may differ between RCT subjects and community patients. Potential ICD recipients deserve to have a clear idea of what their lives might look like if they opt for the therapy. Prospective collection of health status should, therefore, be a high priority for future efforts.

In the longer run, effectiveness research will be bolstered by the thoughtful development of connectivity in health information systems. Issues related to the protection of private health information need to be solved. Although society has an obligation to individuals to protect their privacy, this must be balanced against the obligation that individuals have to the common good. In concrete terms, this may mean that patient identifiers that allow linking between data sources can be included in registries, provided data security standards for confidential information are met.

The most interesting questions concern whether or not readily available high quality effectiveness research will affect healthcare policy. Will payers use it to limit the introduction of expensive new technology of limited value? Will this stifle innovation? Will clinicians learn to use it to guide practice as they have learned to use RCT data? Will it be ignored? As with the effectiveness of ICDs in general, these questions cannot be answered until they are properly asked.
Disclosures

None.

References


Key Words: defibrillators implantable elderly
Are Implanted Defibrillators Effective Therapy in the Elderly?: Asked, Not Answered
Edward P. Havranek and Pamela N. Peterson

Circ Heart Fail. 2010;3:4-6
doi: 10.1161/CIRCHEARTFAILURE.109.931204
Circulation: Heart Failure is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2010 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-3289. Online ISSN: 1941-3297

The online version of this article, along with updated information and services, is located on the World Wide Web at:
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