Observational Comparative Effectiveness Research
Comparative Effectiveness and Caveat Emptor

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Recent legislation has emphasized comparative effectiveness, including both the American Recovery and Reinvestment Act of 2009 and the Patient Protection and Affordable Care Act of 2010, which established the Patient Centered Outcomes Research Institute (PCORI) to foster comparative effectiveness research (CER).1,2 Defined as “the generation and synthesis of evidence that compares the benefits and harms of alternative methods to prevent, diagnose, treat, and monitor a clinical condition or to improve the delivery of care,”3 the intent of CER is to assist stakeholders, including patients and clinicians, with making informed decisions to improve health. Although many stakeholders are hopeful that CER will improve health and increase the value of care provided, it is not uniformly accepted that CER will achieve these important goals. In particular, the use of nonexperimental observational methods is questioned by some.4,5

Skepticism around observational CER is warranted. Indeed, observational studies have inherent limitations, including several potential sources of bias and confounding that may threaten the validity of findings.6 The effect of hormone replacement therapy (HRT) on cardiovascular outcomes is a notorious example. In the 1990s, high-profile publications using complex multivariable statistical modeling approaches in a variety of observational settings and datasets demonstrated lower risk of cardiovascular outcomes associated with use of HRT in women.7–9 Subsequently, randomized trials determined that HRT was actually harmful with respect to cardiovascular outcomes.10,11 With the proper perspective, however, observational studies can contribute useful evidence and have an important role in CER. In fact, there is great appeal to using observational data to efficiently answer multiple important scientific questions where costs and/or other factors make performing trials impractical.

In this issue, Reynolds and colleagues present an observational clinical comparative effectiveness analysis of catheter ablation versus antiarrhythmic therapy for the prevention of stroke or transient ischemic attack among patients with atrial fibrillation (AF).12 The comparative effectiveness and safety of medical antiarrhythmic therapy and catheter ablation of AF are of great importance. AF is a common and increasingly more prevalent problem that carries an increased risk of stroke. The authors used a large administrative claims dataset to identify patients with a diagnosis of AF who received an ablation procedure or antiarrhythmic therapy. In a propensity score-matched analysis, further adjusted for multiple measured confounders, ablation therapy was associated with a 40% lower risk of stroke or transient ischemic attack and no significant difference in heart failure admissions compared with antiarrhythmic drug therapy. The authors clearly and appropriately state that the advanced statistical methods used cannot account for unmeasured differences between the patient groups. We agree and believe that the observed association of AF ablation with apparently lower risk of stroke in this study should be interpreted with great caution.

A key concern in comparative effectiveness analyses using observational data are confounding by indication, or treatment selection bias. Investigators do not have control over treatment assignment, but, rather, clinicians and patients make treatment decisions. Propensity score analysis balances the observed characteristics of patients nonrandomly assigned to different treatments and reduces treatment selection bias.13 Many factors that influence patient selection for AF ablation, however, may not be documented in a medical chart and are certainly not available through claims data. For example, duration of atrial fibrillation, left atrial size, functional status, and symptom burden may influence the choice of treatment and also affect outcomes but were not available for analysis. It is remarkable that the majority of ablation patients could not be paired with nonablation control subjects. The match rate of 25% highlights that the patients who received ablation generally differed substantially from those receiving antiarrhythmic therapy on measured variables and suggests that confounding by indication, or treatment selection bias, is an important concern in the study interpretation.

Similar to confounding by indication, other unmeasured confounding, and the “healthy user effect” may also threaten the validity of findings in CER. When a number of measured variables are available, they can collectively represent, in part, the effect of unmeasured confounders. In this sense the propensity score, which uses available measured variables, serves as a proxy for unmeasured factors that are dependent on measured factors.14 However, propensity score methods cannot balance unobserved confounders that are independent of the observed confounders. To assess for potential healthy user effect, Reynolds and colleagues examined admission for...
pneumonia. A difference in the rate of pneumonia between the 2 groups was not observed but, if such a difference had been present, it might have indicated an imbalance in the overall health risk of the study groups unaccounted for by propensity matching.

The story of HRT demonstrates that no amount of multivariable adjustment or complex statistical modeling can completely address the potential issues of treatment selection bias, confounding, or healthy user effect. These exact issues are very likely to be at play with this current study as well, or, at a minimum, they cannot be excluded. Of particular concern is treatment selection bias, or confounding by indication. One could argue that candidacy for AF ablation, an invasive procedure where the periprocedural risks are so closely tied to age, comorbidity, and the operating electrophysiologist’s intangible impression of the patient’s risks, could magnify these issues even more than the decision to initiate hormone therapy.

Regardless of the statistical methods applied, a primary determinant of the quality of any study is the quality of the data. An advantage of the dataset used by Reynolds and colleagues is the large size and national sample of patients from real world practice settings; however, claims data have several limitations of particular importance in CER. Properly assessing comparative effectiveness requires the capacity to identify 1) appropriate comparison groups; 2) factors that influence clinical decision-making; and 3) potential confounding factors. In general, administrative datasets such as the one employed in the current study are based on administrative codes (CPT and ICD9/10 codes) and, as such, are often lacking in granularity and nuance of the clinical information required for the ascertainment of specific procedures, clinical burden of disease severity and comorbidity, and clinical outcomes. In this study, the accuracy of identifying those who underwent ablation using claims data are uncertain because an administrative code specific to AF ablation did not yet exist at the time the data for this study were collected. This results in an important possibility of misclassification and calls into question the validity of the comparison groups. Additionally, as discussed above, a number of clinical variables that likely influenced treatment selection and that may be potential confounders may have been incompletely captured or not captured by claims data at all. Inability to adequately account for such factors in the analysis increases the likelihood of bias and confounding.

This study highlights the need for high quality data to perform CER. Databases are needed that 1) reflect routine community-based clinical practice; 2) include broad patient populations receiving and not receiving therapies; 3) include detailed clinical information for risk adjustment; 4) include information on treatment decision-making from the patient and provider perspective; and 5) track longitudinal outcomes, including patient-centered outcomes, such as health status. Although a number of observational data sources are available, many lack 1 or more of these components. Integrated health care systems such as the VA provide the most robust data, but also have limitations. Creating robust clinical datasets, as described above, is costly and complex. Challenges include the protection of private health information and connectivity of health information systems, in addition to ensuring that the data collected are valid. The investment in creating such rich datasets, financial and otherwise, is necessary for CER to achieve its intended goals.

Of critical importance is how the results of observational studies are interpreted and used. In the case of HRT, millions of women received therapy, in the absence of other indications, with the sole intent of reducing cardiovascular risk. The findings of the current study of AF therapies should stimulate further study; however, they should not be interpreted as adequate to advocate for the use of catheter ablation of AF as a stroke-reduction strategy. A randomized trial, CABANA, is underway, which will provide additional data on the longitudinal safety and efficacy of atrial fibrillation ablation and the procedure’s effects on the risk of stroke.

Although this study should be interpreted with caution and should not change practice, it does provide important insights into the real world outcomes of patients undergoing catheter ablation. Even with the limitations of observational data, the authors used the most rigorous possible statistical methods and appropriately framed the findings in the context of the limitations of the data. Further, the finding of a relatively low risk of hospitalizations for stroke among the patients who underwent AF ablation is somewhat reassuring about the safety of AF ablation, as it is currently employed in practice.

It is certain that observational studies will play an important role in CER, particularly, if the various emtors (stakeholders) adequately consider the relevant caveats. It is critical that researchers apply the highest quality methods and are honest about potential limitations, exactly as Reynolds and colleagues have done. Similarly, healthcare decision-makers must understand the relative strengths and weaknesses of various types of evidence. Finally, it is critical that all stakeholders interpret results cautiously and in the context of a larger body of evidence. Meanwhile, concerted efforts to develop data sources that enhance the validity of observational CER will ensure that such studies provide the most useful information to clinicians and their patients.

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References

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