Challenges and Importance of Finding Hidden Confounders When Conducting Comparative Effectiveness Studies Using Registry Data

The Impact of Surgical Turn-Down on Percutaneous Coronary Intervention Mortality

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In this issue of Circulation, Waldo and coworkers¹ report the results of a study designed to provide insight into the frequency and impact of coronary artery bypass grafting surgery (CABG) surgical turn-down, that is, how often patients with an indication for CABG were declared unsuitable for it by a surgeon and how that decision affected outcomes. The analyzed data were extracted from the Partners Long-Term Outcomes Database, which aligns its variables and definitions with the National Cardiovascular Data Registry (NCDR) CathPCI Registry and the Society of Thoracic Surgeons Adult Cardiac Surgery Database. Looking at >1000 patients undergoing nonemergent percutaneous coronary intervention (PCI) over a 3-year period at 2 Boston hospitals, these investigators found that 22% had been deemed ineligible for CABG, usually because of poor bypass target vessels, advanced age, or renal insufficiency. CABG-ineligible patients were sicker than CABG-eligible patients, and they had higher mortality rates: CABG ineligibility was independently associated with a roughly 6-fold increase in adjusted in-hospital death and an ≈3-fold increase in adjusted late death compared with CABG-eligible patients. CABG-ineligible patients had more complex PCI procedures (more lesions, more stents) but fewer vessels were treated compared with CABG-eligible patients despite similar burdens of 3-vessel disease, suggesting the ineligible patients may have had less complete revascularization and hence greater residual ischemic burden after PCI. Inserting CABG ineligibility as an independent term into the NCDR PCI mortality risk model improved the predictive capability of the model significantly. The authors concluded that CABG ineligibility occurs frequently enough to be important to practice statistics and appears to affect outcomes powerfully, but the authors note that it has not been incorporated into current risk adjustment models.

Registry analyses are important to clinical medicine because they provide information about the performance of techniques, products, and approaches in less selected patient groups (and applied by less selected practitioners) than appear in randomized clinical trials. Because they are much less expensive to conduct, registry studies are abundant. Registry data are commonly used for descriptive purposes and may also be used to compare outcomes between treatments or approaches. The limitations of registry analyses, however, are well known. Of their potential pitfalls, perhaps the most distressing is the risk that unaccounted clinical factors may affect measured outcomes when comparative effectiveness studies are done and produce erroneous conclusions. Pundits use this limitation effectively. Those in favor of the conclusions of a given study argue that well-crafted registry studies are structured to capture all important variables, so unmeasured factors ought to have a small effect. Those who do not like a given finding lean on the uncertainty introduced by the notion of unmeasured confounders.

Sensitivity to unmeasured confounders has increased as medicine has become more regulated, and regulators look to published studies to determine policy. On the topic of revascularization for coronary artery disease, contemporary randomized clinical trials have generally found a mortality advantage with CABG over PCI only for patients with complex disease or important comorbidities such as those with high Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) scores² or diabetes mellitus.³ In comparison, some registry-based studies have found benefit with CABG in less complicated patients. For example, an oft-cited analysis of data from a pair of state-level registries, the Cardiac Surgery Reporting System and Percutaneous Coronary Intervention Reporting System registries, reported better adjusted 3-year survival after CABG than PCI for all patients treated in New York except those with single-vessel disease.⁴ Cardiac surgeons were generally gratified, but interventional cardiologists complained that surgeons had declined to treat undesirable patients in a state with public reporting; these patients were then left with PCI as, perhaps, a second-best choice for treatment and thus were bound to have worse outcomes. To assess revascularization at a national level, the NCDR and Society of Thoracic Surgeons registries are perhaps the most important to American cardiovascular care; collectivelly, they have produced hundreds of useful reports on coronary revascularization. Two years ago, the results of a multiyear, National Heart, Lung, and Blood

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Institute–funded, collaborative effort called American College of Cardiology Foundation and the Society of Thoracic Surgeons Collaboration on the Comparative Effectiveness of Revascularization Strategies (ASCERT) were published. In ASCERT, investigators linked data from the NCDR CathPCI Registry and the Society of Thoracic Surgeons Adult Cardiac Surgery Database to the Centers for Medicare & Medicaid Services database to evaluate long-term outcomes in Medicare patients treated with either PCI or CABG. The largest registry-based coronary revascularization comparative effectiveness analysis ever conducted, ASCERT found that CABG was associated with a longer life and was cost-effective relative to PCI. It is hard to avoid a conclusion that CABG is preferable over PCI. Could an unmeasured confounder have led investigators astray?

The ASCERT exercise included construction of a probability model that estimated how prevalent a confounding factor would have to be in the 2 populations being compared and how strongly that factor would need to affect the outcome measure to nullify the analysis conclusion. This complex model predicted that a single confounder could abolish the finding of a mortality difference between groups if that confounder increased the risk of death by >3-fold, was present in >20% of the PCI group, and was present in <5% of the CABG group. Was such a confounder likely to be present in the ASCERT patients? At the time, most ASCERT investigators felt it was unlikely. Patients appeared to get suitable treatment; the appropriateness of the revascularization method selected for each ASCERT patient seemed to be supported by a treatment propensity analysis. However, risk adjustment modeling methods, including propensity analyses, have limited ability to account for treatment selection bias related to an unmeasured variable, especially when the confounding influence of that variable is strong.

A 2012 study by McNulty and colleagues underscored this fact. McNulty et al found that surgical ineligibility had been declared in more than half of a consecutive group of patients with unprotected left main coronary artery disease who were treated with PCI (remember, these patients had a Class III indication for PCI at that time and thus had at least 1 factor strongly in favor of CABG). In that unique cohort, surgical ineligibility increased the intermediate-term risk of adjusted death by 5- to 6-fold, depending on the risk adjustment model. Additionally, ≥1 clinical factors believed to affect survival but not measured in the NCDR CathPCI Registry were found to be present in more than three fourths of patients with unprotected left main disease treated with PCI. The conclusions were that surgical ineligibility and other variables not captured in standard databases seem to be present in a sizable portion of patient with an indication for coronary revascularization and that standard risk adjustment models cannot adequately account for the impact of such variables.

The present article by Waldo et al extends the observations of McNulty and colleagues by broadening the studied population to include patients with multivessel coronary artery disease and unprotected left main disease, and it is perhaps most remarkable for making very similar observations and conclusions. Have Waldo and coworkers and McNulty et al really found a poison dart that threatens the validity of the many registry analyses that came before them, including ASCERT? It is hard to be sure. It is tempting to fit the figures reported by Waldo et al into the elegant ASCERT confounder model, but the numbers from the present study and the model constructed for ASCERT cannot be simply combined. Still, it is an interesting thought experiment: If the proportion of PCI patients with declared surgical ineligibility in ASCERT were similar to that observed by Waldo et al and if the impact of surgical ineligibility was a 3- to 6-fold increase in risk of death for the Centers for Medicare & Medicaid Services population, as Waldo et al observed for their patients, then the principal findings of ASCERT would have been overturned. The works by Waldo et al and McNulty and coworkers collectively make a strong case that a single unmeasured confounder may, in fact, exist in a coronary artery disease patient cohort that is sufficiently powerful and sufficiently prevalent that retrospective, observational outcome comparisons of revascularization methods may lead to erroneous conclusions despite risk adjustment.

If a single confounder might have this effect, what if there are others? Indeed, several potential candidate variables have been nominated, including cachexia and frailty (likely factors in determining CABG ineligibility), poor adherence to prescribed medications (especially dual antiplatelet therapies), aortic calcification, systemic infection, immunosuppression, and lack of patient acceptance of recommended treatment (Some patients simply refuse CABG even when told it is the best choice and may extend their lives). The prevalence and magnitude of these factors are not well studied or well understood.

Going forward, large registries must manage, not just acknowledge, the issue of unmeasured confounders to remain relevant for comparative effectiveness research. To the extent that new factors are demonstrated to be important through studies like the one published here, registries must account for them. Tracking a variable as complicated as surgical turn-down is challenging. Waldo and colleagues describe how difficult it was to find the needed information. Formal, consistent use of a heart team to review treatment options for patients with multivessel coronary artery disease, as recommended by PCI practice guidelines, would provide a helpful structure for tracking clinical decisions and complex patient characteristics. Better integration between clinical databases (with deep clinical information such as laboratory values and imaging study findings) and administrative databases (with broad patient information such as comorbidities and outpatient medication use) would allow better characterization of individual patients without overwhelming any single registry. Voluntary unblinding of patient identifiers in research databases, now forbidden, should be considered as a means of improving the accuracy of pooled database studies that depend currently on probabilistic matching techniques. NCDR is now assembling a team to craft version 5 of the CathPCI Registry, so the Waldo et al publication is timely. This assembly will provide an opportunity to discuss changes in the structure and operation of the NCDR CathPCI Registry, as much as how to improve its data element list. My hope is that the Society of Thoracic Surgeons
will follow suit and look to make important changes to its Adult Cardiac Surgery Database as well.

**Disclosures**

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