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Off-Label Use of High-Risk Cardiovascular Devices Widening the Lens

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Transcatheter aortic valve replacement

(TAVR) has transformed the treatment of symptomatic severe aortic stenosis. Randomized clinical trials have demonstrated the clinical effectiveness of TAVR for patients at extreme, high, and intermediate risk for undergoing a surgical valve replacement.^{1–4} These well-designed clinical trials necessarily involved trade-offs between a focused, carefully defined study population and subsequent generalizability. Current US Food and Drug Administration (FDA) labeling for TAVR reflects this balance, illustrating that the manufacturers have met the standard of demonstrating a reasonable assurance of its safety and effectiveness through rigorous clinical studies among selected patients with severe aortic stenosis.

Even when these procedures are approved for marketing, patient access to novel technology, such as TAVR, also depends on insurance coverage, for which evidentiary standards may differ from those embedded in the premarket approval process. Data from the Transcatheter Valve Therapy (TVT) Registry suggest that the median age of patients undergoing TAVR in the United States is 84 years,⁵ and most of these patients will depend on Centers of Medicare and Medicaid Services (CMS) coverage for their procedures. By mandate, CMS covers services that meet the bar of “reasonable and necessary,” and in practice most treatments that are FDA-approved also become covered by CMS.⁵

However, some services are subjected to additional review, a process typically reserved for interventions that may raise particular concerns regarding cost, safety, or effectiveness specific to Medicare beneficiaries. A subset of these reviews generate “coverage with evidence development” memoranda, in which reimbursement is provided only if beneficiaries are also enrolled in a clinical study specifically approved by CMS to collect additional data that evaluate outcomes related to the service at issue.⁶ In 2012, CMS issued a coverage with evidence development decision on TAVR, under which TAVR was covered if it adhered to the following requirements: (1) TAVR would be used in an on-label manner, (2)

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2 cardiac surgeons would participate in clinical decision-making and determine TAVR to be appropriate, (3) the patient would be cared for by a heart team at a hospital with adequate technical infrastructure to perform the procedure, (4) a cardiac surgeon and interventional cardiologist would participate jointly in the procedure, and (5) the heart team and hospital would participate in a prospective, national, and audited registry.⁷ Procedures performed as a part of a qualifying clinical trial also received coverage under the TAVR coverage memo.

In this issue of *JAMA Cardiology*, Hira et al⁵ draw from the TVT registry to explore off-label TAVR use and outcomes from 2011 to 2014. Among 23 847 procedures, nearly 10% were considered off-label, with most (76%) of these related to coexisting aortic or mitral regurgitation and an additional 19% performed in patients with bicuspid aortic valves. The implantations were successful in nearly all procedures (92% off-label, 93% on-label). In-hospital mortality was significantly higher in the group who underwent an off-label TAVR, at 6.3% vs 4.7%, as was residual moderate or severe perivalvular leak. Among the subset of patients for whom postdischarge out-comes could be ascertained, the adjusted 30-day mortality rate was higher for off-label use, but survival at 1 year appeared similar between the 2 groups.

The strengths of this study include its rigorously adjudicated prospective data source and the use of well-validated claims to characterize clinically relevant outcomes. Though heterogeneous, the cohort who underwent an off-label TAVR that was evaluated by Hira et al⁵ clearly needs effective treatments, and a registry such as TVT can provide useful estimates for acute procedural success and acute safety outcomes. Advanced aortic stenosis combined with mitral regurgitation in particular portends a grim prognosis, and the predominance of these indications in the group who underwent an off-label TAVR may reflect a particular area of clinical need and perhaps even potential for benefits. For example, data from the PARTNER clinical trial estimated a 2-year mortality rate that approached 50% for patients with moderate or severe mitral regurgitation treated with surgery vs 37% when treated with TAVR.⁸ Thus, the study from Hira et al⁵ provides a useful glimpse at procedural outcomes for patients currently excluded from FDA labeling and CMS coverage that may benefit from access to TAVR.

However, several aspects of the analysis point to the limitations of using uncontrolled registry data to evaluate clinical effectiveness. First, by design the TVT Registry only includes patients who received a TAVR. Understanding whether off-label use carries acceptable risks and is associated with meaningful benefits requires data on patients with similar comorbidities who did not undergo a TAVR, including those who underwent surgery and those who received no intervention. While perhaps such individuals could be identified through administrative claims, these data typically lack the necessary clinical detail on comorbidities, such as renal function, as well as the disease characteristics (eg, left ventricular ejection fraction and the severity of valvular disease) required to make accurate comparisons. Decision making regarding valvular interventions, whether surgical or transcatheter, may also be sensitive to hard-to-measure confounders, such as frailty or overall clinical impressions of patient fitness, that may further complicate attempts to leverage observational data. In addition, the coverage memo for TAVR implies that any off-label procedures performed in Medicare beneficiaries from the Hira et al⁵ cohort should not

have been submitted for reimbursement to CMS. This begs the question of whether the institutions involved provided these services for free or through some other mechanism, which may introduce additional confounding by socioeconomic status or other patient characteristics. A more ambitious condition-specific registry, rather than a procedure-specific registry, would be more valuable to advance our understanding of aortic stenosis and its emerging treatments, particularly in subgroups perhaps too small for a standalone clinical trial.

A related problem is that the TVT Registry cannot answer important long-term effectiveness questions that are essential to evaluating emerging technologies, particularly in the case of off-label use. For example, patients with bicuspid aortic valve are typically younger than the mean for candidates for aortic valve intervention and may have coexisting thoracic aortic pathologies, raising additional questions about valve durability and subsequent procedures. Such individuals are particularly unlikely to be captured in Medicare data, which allow longer-term passive follow-up, and make up a sufficiently small proportion of the population with aortic stenosis that conducting trials limited to this group is improbable. Thus, while the TVT Registry is a useful tool for tracking the adoption, dissemination, and outcomes of TAVR nationally, it falls short of delivering maximal clinical insights into the potential expanded uses for, and limitations of, this important technology.

Taken together, the strengths and weaknesses of the Hira et al⁵ study and the TVT Registry represent an opportunity to reconsider tools used by the FDA and CMS to incentivize evidence generation. Pivotal trials for multiple TAVR devices, conducted under close FDA guidance, have provided the scientific basis for clinical effectiveness as well as quality of life and economic assessments.^{9–11} The TVT Registry, and the important analyses it has facilitated, also demonstrate the synergy between the authority of the FDA to include registries as a part of a postmarket surveillance strategy and the requirements for CMS coverage. However, we can, and should, do better. Expanding data collection to not just device recipients but to all patients referred for consideration for undergoing a TAVR, for example, could be explored as a way to capture more robust comparative effectiveness data and truly drive transformative advances in knowledge. While a referral will necessarily include potential biases and confounders, broadening the scope of postmarket registries might provide a much more robust control population, even for relatively unusual phenotypes. Of course, requiring the manual submission of all data on patients considered for undergoing a TAVR would be unreasonably burdensome for clinicians and teams who are already busy, but we must begin to harness the potential of distributed research networks based on electronic health records. Transcatheter aortic valve replacement, and other procedures like it, would benefit immensely from the type of learning health care system that could be facilitated by electronic data capture. Efforts under way via PCORNet,¹² for example, could make such analyses feasible without undue burden.

Transcatheter aortic valve replacement has fundamentally altered the treatment of patients with aortic stenosis. The next steps in evidence generation will require more ambitious data collection focused not just on device recipients, but on all patients potentially eligible for this transformative technology.

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