Effectiveness in a Real-World Observation Confirms Efficacy of Controlled Clinical Trials*

Arie Pieter Kappetein, MD, PhD, Alec Vahanian, MD, PhD

The efficacy of an intervention can be defined as the performance under ideal and controlled circumstances, whereas effectiveness refers to its performance under “real-world” conditions. Randomized clinical trials (RCTs) provide the strongest empirical evidence of a treatment’s efficacy and safety because they allow for the analysis of a homogenous study population. The generalizability of RCTs, however, is compromised due to the use of strict inclusion and exclusion criteria in selecting participants.

In this issue of the Journal, the study by Brennan et al. (1) determines the safety and effectiveness of transcatheter aortic valve replacement (TAVR) versus surgical aortic valve replacement (SAVR) in a nationally representative real-world cohort. A total of 9,464 intermediate- and high-risk patients (patients with a Society of Thoracic Surgeons [STS] score ≥3%) of the Transcatheter Valve Therapy (TVT) registry and STS database were propensity-matched. Outcomes that were compared include death, stroke, discharge home, and days alive out of the hospital. The current study comprises an elderly patient population with a mean age of 82 years and an increased risk with a mean STS score of 5.8.

The valve prosthesis used was CoreValve (Medtronic, Dublin, Ireland) in 33% and Sapien (Edwards Lifesciences, Irvine, California) in 67%. In the current study, transfemoral access was used in 76%. However, the difference with more contemporary practice is that changes in delivery catheter with smaller sheath sizes have made transfemoral the preferred access in more than 90% of the cases, and transapical access rates have decreased below 10% (2,3).

TAVR and SAVR patients experienced no difference in 1-year rates of death (17.3% vs. 17.9%) and stroke (4.2% vs. 3.3%), and no difference was observed in the proportion of days alive and out of hospital at 1-year (hazard ratio 1.00) (1). However, TAVR compared with SAVR patients were more likely to be discharged home after treatment (69.9% vs. 41.2%). Results were consistent across most subgroups, including among intermediate- and high-risk patients.

This study provides a unique insight into whether the results of RCTs are comparable to the results of routine clinical practice. It confirms the findings of randomized trials (4). Only stroke rates are 50% lower in this real-world population compared with the incidence in randomized trials. The most likely explanation is that in trials, a more rigorous neurological examination pre- and post-procedure was part of the study protocol, and in the current study, there is possibly underreporting of strokes.

There are some caveats in interpreting the data. Effectiveness trials can also exclude patients, and the exclusion criteria of the current study show that a substantial number of patients undergoing TAVR in clinical practice were excluded, such as those >90 years of age, or patients with hostile chest or porcelain aorta. One should be aware that even this “all-comers TAVR population” does not include

*Editorials published in the Journal of the American College of Cardiology reflect the views of the authors and do not necessarily represent the views of JACC or the American College of Cardiology.

From the *Department of Thoracic Surgery, Erasmus Medical Centre, Rotterdam, the Netherlands; and the †Cardiology Department, Hôpital Bichat, Université Paris VI, Paris, France. Dr. Kappetein is on steering committees for the SURATVI trial sponsored by Medtronic and the UNLOAD trial sponsored by Edwards Lifesciences. Dr. Vahanian has received consulting honoraria from Edwards Lifesciences, Abbott, and Valtech.
patients that are usually treated with TAVR. The main limitation is the nonrandomized nature of the study. Propensity matching is unable to correct for all confounding factors in a population. The authors compare their results with those of the Sapien 3 cohort (5), which had a lower mortality and stroke rate. Although a newer generation of transcatheter heart valves are expected to show better outcomes, even the propensity-matched analysis of this Sapien 3 cohort has been criticized because of suboptimal methods in propensity-score analysis. There was no adjustment for some important covariates, and no adjustment in Kaplan-Meier estimates (6).

On the other hand, propensity matching has the advantage to identify independent risk factors. In randomized trials comparing TAVR and SAVR, female subjects had lower mortality with TAVR (7), whereas in the current propensity-matched analysis, there were no significant differences in treatment effect across the male/female subgroups. This outlines the fact that not sex in itself, but rather sex-related comorbidities play a role in a better outcome of TAVR in female patients.

The database here is essentially of an administrative nature, with inherent pitfalls. Examples of a systematic bias include surgical patients being followed longer, resulting in observation bias. They are also more commonly discharged to feeder hospitals or rehabilitation facilities, resulting in a bias in the discharge-to-home outcome. Other outcomes, which are particularly important in an elderly patient population, are usually not captured in registries such as quality of life, physical functioning, and New York Heart Association functional classification. Prognostic factors such as paravulvular leak and left ventricular remodeling are also absent, and although this is understandable, it shows that it is difficult to obtain precise information from registries. It would also be of interest to break down the results according to device type with a dedicated propensity matching.

The authors note that GARY (German Aortic Valve Registry) showed a difference in mortality between TAVR and SAVR in favor of surgery (8), whereas the current data do not show any difference. It is, however, likely that those intermediate-risk patients in the GARY registry had severe comorbidities that would have led to exclusion in the current registry, which may explain the more unfavorable outcome in the TAVR patients in the GARY registry.

Defining the best available evidence on which physicians base their decisions and translate these into practice guidelines is not always easy. Both efficacy data from RCTs and effectiveness data, as more relevant to real-world clinical practice decisions, are necessary to make informed decisions (9).

This study contains important data about the daily practice of TAVR and SAVR and further confirms the potential expanding role of TAVR in the population of elderly patients with severe aortic stenosis. In the future, executing RCTs using registries, as is done in Sweden, would be desirable (10). This latter approach limits selection bias, but long-term data are of course needed and registries could provide this. However, RCTs to avoid bias, remain a crucial part of the regulatory process whereby a new device can gain access to the market.

ADDRESS FOR CORRESPONDENCE: Dr. Arie Pieter Kappetein, Department Thoracic Surgery, Room BD 569, Erasmus Medical Centre, PO Box 2040, 3000 CA Rotterdam, the Netherlands. E-mail: a.kappetein@erasmusmc.nl.

REFERENCES


KEY WORDS randomized trials, registries, transcatheter valves