Impact of Anesthesia Type on Outcomes of Transcatheter Aortic Valve Implantation From the Multicenter ADVANCE Study

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ABSTRACT

Transcatheter aortic valve implantation (TAVI) has become the standard of care for many patients with symptomatic severe aortic stenosis who are at increased risk of morbidity and mortality during surgical aortic valve replacement. However, there is still no general consensus regarding the use of general anesthesia (GA) versus local anesthesia with sedation (non-GA) during the TAVI procedure. Using propensity score matching analysis, we analyzed the characteristics and outcomes of patients undergoing TAVI with either GA (n=245) or non-GA (n=245) in the fully monitored, international, CoreValve ADVANCE Study. No statistically significant differences existed between the non-GA and GA groups in all-cause mortality (25.4% vs. 23.9%, p=0.78), cardiovascular mortality (16.4% vs. 16.6%, p=0.92), or stroke (5.2% vs. 6.9%, p=0.57) through 2-year follow up. Major vascular complications were more common in the non-GA group. Total hospital stay was similar between the 2 groups. Conversion from non-GA to GA occurred in 13 patients (5.3%) due to procedural complications in 9 patients and discomfort or restlessness in 4 patients. The majority of the procedural complications were related to valve positioning or vascular issues. Two of the 13 converted patients died during the procedure. Both GA and non-GA are widely used in real-world TAVI practice, and the decision appears to be guided by only a few patient-related factors and dominated by local and national practice. The outcomes of both anesthesia modes are equally good. When conversion from non-GA did occur, the complication requiring GA affected outcomes.

Key words: severe aortic stenosis, transcatheter aortic valve replacement; anesthesia; real-world clinical trial

Transcatheter aortic valve implantation (TAVI) has become standard of care for patients with symptomatic severe aortic stenosis at extreme or high risk for surgery.[1] In practice, even lower risk patients are already being treated, while at least 3 TAVI clinical trials are assessing the role of the therapy in patients considered at only intermediate risk from surgical AVR. It is therefore likely the number of patients treated with TAVI will increase, requiring additional numbers of operators and hospitals. Concurrently, the procedure is becoming less complex. Smaller sheath sizes, a reduced need for rapid pacing and balloon valvuloplasty, availability of repositionable and recapturable valves, and decreased reliance upon intraprocedural transesophageal echocardiography will herald a new era of TAVI. A significant proportion of procedures are already being performed using local anesthesia with sedation. Others have reported potential benefits of using local anesthesia, including shorter intensive care unit and overall hospital stays, less hemodynamic instability, and less need for vasopressors.[2-5] It is likely that the proportion of patients treated in this manner will increase. In the ADVANCE study[6], patients were treated according to best local practice in experienced centers, and a significant proportion was treated with local rather than general anesthesia. Local anesthesia was used in approximately 50% of patients in this study, reflecting the real-world practice at the time, and we compared patient characteristics and procedural outcomes in patients administered local versus general anesthesia for TAVI.

Methods

For this report, we analyzed the characteristics and outcomes of patients undergoing TAVI with either general anesthesia (GA) or local anesthesia with sedation

(non-GA) in the Medtronic CoreValve ADVANCE study. Patients treated via the direct aortic approach were excluded from this analysis. The design, methods, and primary results of the ADVANCE study have been previously described.[6] Briefly, the ADVANCE study is a prospective, fully monitored, nonrandomized, international, multicenter study evaluating the acute and long-term results of implantation of the Medtronic CoreValve System (Medtronic, Minneapolis, Minnesota) in "real-world" patients with severe, symptomatic aortic stenosis who were considered to have an inoperable condition or to be at high risk for conventional AVR. All ADVANCE study centers were required to have performed a minimum of 40 TAVI procedures prior to joining the study and to utilize an on-site, multidisciplinary Heart Team consisting of at least 1 TAVI-experienced interventional cardiologist and 1 cardiovascular surgeon.

The ethics committee at each study center approved the ADVANCE investigational protocol. ADVANCE was conducted in adherence to the Declaration of Helsinki, and all patients provided written informed consent prior to the CoreValve implantation procedure.

Detailed device description and implant procedures for the CoreValve System have been previously described.[7,8] The procedures were performed according to standard local hospital practices, which included the selection of access location (transfemoral, or subclavian), the type of access (surgical cutdown or completely percutaneous), and the type of anesthesia (GA or non-GA). Procedural characteristics analyzed for the comparisons between anesthesia groups included access type and site, procedure duration, fluoroscopy time, quantity of contrast agent used, procedural complications, and length and type of hospital stay.

Safety outcomes were analyzed at 30 days and at 1 and 2 years post-procedure and included all-cause mortality, cardiovascular mortality, myocardial infarction, reintervention, stroke, stroke or transient ischemic attack, bleeding, vascular complications, acute kidney injury (stage III), and pacemaker implantation.

Death, stroke, myocardial infarction, and reintervention were adjudicated by an independent Clinical Events Committee consisting of TAVI-experienced interventional cardiologists and a cardiac surgeon using the initial Valve Academic Research Consortium definitions.[9] An independent neurologist reviewed the neurological events and provided a summary of each event to the Clinical Events Committee, which used this information along with any other patient source data to adjudicate all neurological events. A core laboratory (Cardialysis, Rotterdam, The Netherlands) performed a systematic review and assessment of procedural angiograms and ECGs through 1-year follow-up. Data were recorded on a standardized electronic case report form and sent to a central database (Merge, Chicago, Illinois) over the Internet.

Categorical variables are reported as counts and percentages. Continuous variables are reported as means and standard deviations except for non-normal data such as logistic EuroSCORE, Society of Thoracic Surgeons (STS) predictive risk of mortality score, procedure duration, fluoroscopy time, amount of contrast given, and length of stay, which are summarized using medians and interquartile ranges.

Comparisons between anesthesia types are based on chi-square or Fisher's exact tests for categorical variables, and *t*-tests or Wilcoxon tests for continuous variables, as appropriate. Event rates were generated using the Kaplan-Meier method, and log-rank tests were used for group comparisons. For patients without an event, the date of censoring

was the latest date of all follow-up visits (including study exit) and events (including death). A p value < 0.05 was considered statistically significant.

To identify 2 comparable groups of patients undergoing GA or non-GA, we performed a propensity score matching analysis. A multivariable logistic regression model with anesthesia type as the outcome was fit, from which predicted probabilities (i.e., propensity scores) were computed for each patient. Unbalanced variables prior to matching as well as an additional 10 variables were included in the model to achieve balance in baseline characteristics in the anesthesia groups after matching. The baseline covariates included in the model were female, New York Heart Association class III or IV, diabetes mellitus, previous median sternotomy, previous aortic valve intervention, prior coronary artery bypass grafting, history of aortic aneurysm, creatinine clearance < 20 mL/min, baseline left ventricular ejection fraction, moderate or severe tricuspid regurgitation, log transformed age, square root transformed EuroSCORE, history of myocardial infarction, peripheral vascular disease, baseline pacemaker, cerebrovascular disease, and atrial fibrillation. Characteristics were considered to be in balance if the percent standardized difference was < 10%. All statistical analyses were performed using SAS software (version 9.3; SAS Institute, Inc., Cary, North Carolina).

Results

From March 2010 to July 2011, 1,015 patients were enrolled in the ADVANCE study. Of these, 996 patients had undergone an attempted implantation with the CoreValve System. The mode of anesthesia was entirely site-selected and guided by best and customary local practice. Considering the whole group of patients, non-GA was used in 551

(55.3%) patients, and GA was used in 445 (44.7%) patients. Twenty-one patients treated via the direct aortic access were omitted as they are not considered candidates for both anesthesia options, leaving 424 patients in the GA group. Baseline patient characteristics are presented in Table 1. Significant differences existed between the 2 patient groups in diabetes, previous median sternotomy, previous aortic valve intervention, previous coronary artery bypass grafting and left ventricular ejection fraction. Despite these differences, the median STS predictive risk of mortality score and logistic were similar between the 2 groups. There were national differences in the use of non-GA versus GA (Fig. 1), demonstrated by large differences in the use of non-GA among the highest recruiting countries (Germany, 78.6%; Italy, 70.5%; and the United Kingdom, 4.6%).

Since several statistically significant differences in baseline patient characteristics existed between the GA and non-GA groups which could have potentially affected the results of the analysis, we performed a propensity-score matched analysis. A standardized difference of 10% was used as the basis for defining successful matching, where a lower standardized difference corresponds to higher degree of achieved balance. Propensity scoring resulted in 245 matched pairs of patients (Table 1). All of the following outcomes analyses are based on these 2 propensity matched anesthesia groups.

Procedural characteristics and outcomes are listed in Table 2. The vast majority of cases were performed transfemorally. Patients treated using GA had significantly longer median procedure and fluoroscopy times. More patients implanted via the percutaneous approach were treated with non-GA compared with GA, whereas more patients who had surgical cutdown were treated with GA (Table 2). Thus, the method of access may have

affected choice of anesthesia. No statistically significant differences were seen in procedural complications. Total hospital stay was similar between the groups.

Conversion from non-GA to GA occurred in 13 patients during their procedure. A total of 20 procedural complications occurred in 9 of the 13 patients. The remaining 4 converted patients did not experience a procedural complication and thus were most likely converted to GA because of discomfort or restlessness. The majority of the procedural complications were related to valve positioning or vascular issues. The valve was repositioned with snare or retrieved in 3 patients; failure of the vessel closure device requiring surgery occurred in 3 patients; access vessel occlusion (treated with percutaneous balloon) occurred in 1 patient, access vessel perforation (required transfusion) occurred in 1 patient, and 1 patient experienced hemorrhage requiring transfusion and cardiorespiratory arrest. Two of the 13 converted patients died during the TAVI procedure.

Safety outcomes at 30 days and at 1 and 2 years are presented in Table 3. All-cause mortality (Fig. 2), cardiovascular mortality, and stroke were similar between the non-GA and GA patients through 2 years of follow-up. However, non-GA patients had significantly higher incidence of major vascular complications at all time points.

Discussion

In the present study we compared the characteristics and outcome of patients undergoing TAVI with GA versus non-GA. Before discussing the issues identified in this study, it is worth considering the terminology used in previous studies. First, GA is defined by the patient having been placed in a state of “unconsciousness” such that they are

unaware of their physical state and are unable to communicate. Typically this will involve the administration of either inhalational or intravenous anesthetic agents, paralyzing agents, insertion of an endotracheal tube, and artificial ventilation. The terminology of anything that is not general anesthesia (non-GA) is confusing, as evidenced by the wide range of descriptions in the literature. These include "local anesthesia," "regional anesthesia," "conscious sedation," "light sedation," "deep sedation," and "controlled monitored anesthesia." There are 2 components to any non-GA approach. The first component is the relief of pain, and this is administered by true local anesthesia, typically with lidocaine, or with regional or epidural anesthesia. The second component is sedation, and this can range from very mild sedation, where the patient is able to communicate, to deeper sedation, where they cannot. Most anesthesiologists would consider deep sedation a form of GA but without protection of the airway.

Previous studies have suggested potential advantages of a non-GA procedure, including shorter procedure times, shorter intensive care unit and overall hospital stays, lower vasopressor requirements, and equally good outcomes in terms of mortality.[2-5] Others have identified that a non-GA approach may require conversion to GA in up to 5% of cases for cardiac arrest, tamponade, myocardial infarction, or procedural stroke.[10] A higher incidence of paravalvular regurgitation has been recorded in 1 study of patients treated with non-GA, perhaps reflecting a reluctance of operators to prolong the procedure to undertake further post-deployment valvuloplasty or second valve deployment.[11]

In this study we did not prospectively define GA or non-GA, nor was the study randomized; instead, it reflected real-world practice. In the ADVANCE study, the choice of anesthetic and mode of local anesthesia was dependent upon local practice, and this varied

among both hospitals and countries (Fig. 1). It therefore seems that local trends, both within a hospital and within a country, may define the popularity of using local versus general anesthesia.[12] There are numerous factors that influence the decision, including patient-related factors, but more often than not it would appear that the factors determining which type of anesthesia is used are operational and logistic as overall risk scores between the 2 groups were no different.

In our study the baseline patient characteristics between the 2 groups were similar, but some important differences were observed. To account for these differences, we carried out a propensity score matched analysis. In terms of overall outcomes between the propensity score matched groups, non-GA procedures were 18 minutes shorter, less than recently reported from a similarly sized cohort.[13] The only other significant difference was a higher preponderance of major vascular complications, and there was a trend toward a higher number of patients receiving pacemakers at 30 days in the non-GA group. This might possibly be explained by a greater enthusiasm for attempted repositioning of a deeply implanted valve in a patient under GA. Apart from these, there were no significant differences in the very low incidence of procedural complications or in intensive care unit stay. Furthermore, outcomes (i.e., mortality and major adverse cardiac and cerebrovascular events) in the non-GA and GA groups were similar at 30 days, 1 year, and 2 years. Major vascular complications occurred more often in the non-GA group, probably reflecting a higher incidence of surgical cutdown as the initial strategy, whereas conversion to cutdown in the non-GA group was considered a major vascular complication.

While overall outcomes were broadly similar between the 2 groups on an “intention to anesthetize” basis, there was an important subset of patients who converted from non-

GA to GA during the procedure. The rate of conversion in this study was 5.3%, and this is similar to other studies.[4,10,13] The reasons for conversion in this study were predominantly related to valve positioning issues and vascular complications requiring surgery. It is no surprise, therefore, that the need for conversion is actually a surrogate for procedural complications, and the outcomes reflect this. That is not to say that non-GA is not safe—as we have demonstrated, it is. However, it is important to recognize that the need to convert to GA reflects complications that could have occurred in the GA group as well, but would not have mandated any change in anesthesia type.

Limitations associated with this study were that we did not prospectively define GA or non-GA, nor did we require sites to supply specific anesthetic details or the specific reason for conversion. The study was non-randomized, and we relied upon the sites to use best and customary local practice to guide the choice of anesthesia mode, but we did not collect the specifics of the rationale. Our propensity-score matched analysis did however remove the potential confounding influence of baseline characteristics.

Both GA and non-GA are widely used in real-world TAVI practice, and the decision appears to be guided by only a few patient-related factors and dominated by local and national practice. The outcomes of both modes are equally good, and the need for conversion from non-GA to GA was 5.3% in this study. When conversion did occur, the complication requiring GA affected outcome.

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MS (NAMSA, Minneapolis, Minnesota), performed all statistical analyses and verified the accuracy of the data presented. Francesca Barbieri, MD, Rijk de Jong, MSc, and Maarten Hollander, MSc, from Medtronic Bakken Research Centre (Maastricht, The Netherlands) were responsible for overall study management. Medtronic (Minneapolis, Minnesota), funded the ADVANCE study.

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SBr has received consultant fees from Medtronic and Boston Scientific. SBl serves as a consultant to Medtronic and as a proctor for Medtronic and JenaValve and has received travel expenses from Edwards Lifesciences, Medtronic, and Johnson & Johnson. JB serves as a proctor for Medtronic. UG has received consultant and lecture fees and study-related travel expenses from Medtronic and Edwards Lifesciences and serves as a proctor for Boston Scientific and Medtronic. PW has received consultant fees from Medtronic and Edwards Lifesciences and has received remuneration from Medtronic for study-related travel and for development of education materials. AL received speaker honoraria or served as a consultant for the following companies: Medtronic, St. Jude Medical, Claret Medical Inc., Boston Scientific, Edwards Lifesciences, Symetis and Bard; and holds stock options from Claret Medical Inc. In addition, he received grant support from Medtronic and Claret Medical Inc. CT has no conflicts of interest.

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FIGURE LEGENDS

Fig. 1. The distribution of the use of general anesthesia (GA), local anesthesia (non-GA), and changed (non-GA to GA) by country for all patients. The number of centers per country and the number of patients enrolled are shown.

Fig. 2. Kaplan-Meier analysis of all-cause mortality through 2 years by propensity matched anesthesia groups. GA, general anesthesia; Non-GA, local anesthesia.