Effects of Clinical Trial or Research Program Participation Status on In-Hospital Mortality After Transcatheter Aortic Valve Implantation

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The development of novel devices and the favorable results of several randomized clinical trials have allowed for the rapid expansion of transcatheter aortic valve implantation (TAVI) to elderly patients with aortic stenosis across all risk categories; however, the highly selected populations that are typically enrolled in randomized clinical trials may limit generalizability of the results to the real-world population with aortic stenosis. Furthermore, clinical trial or research program participation itself can facilitate behavior change in patients and health care providers and may contribute to improved patient outcomes, which is known as the “Hawthorne effect.” Previous studies reported that research participation was associated with better survival in patients with acute coronary syndrome. Given the lack of data exploring the effect of research participation on outcomes after TAVI, we compared the short-term survival after TAVI between clinical research participants and nonparticipants using the Nationwide Inpatient Sample.

The data that support the findings of this study are available from the corresponding author upon reasonable request. The Nationwide Inpatient Sample is the largest publicly available all-payer inpatient health care database in the United States and did not require ethical approval. All patients who underwent TAVI between 2013 and 2019 (n=56,648) were identified from the Nationwide Inpatient Sample using the following International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) codes: 02RF37H, 02RF37Z, 02RF38H, 02RF38Z, 02RF3JH, 02RF3JJZ, 02RF3KH, and 02RF3KZ. Patients with age ≤18 years (n=22), cirrhosis (n=760), end-stage renal disease (n=2136), do-not-resuscitate status or palliative care involvement (n=383), and cancer (n=1952) were excluded with reference to previous trials. Patients with missing data (n=12) were also excluded. Research participation status was identified using ICD-10-CM code Z00.6, which was restricted to code as the primary diagnosis or first secondary diagnosis to avoid overcapturing.

The primary outcome in this study was in-hospital mortality. A multilevel logistic regression analysis accounting for strata and hospital clustering was performed to examine the association between clinical research participation status and in-hospital mortality. A sensitivity analysis was performed in the propensity score-matched cohort, which was generated by 1:1 nearest-neighbor matching using a caliper width of 0.01 adjusting for baseline characteristics. Variables for these analyses were chosen on the basis of clinical relevance and the previous work and were included if they were significantly different in the baseline characteristics Table. Differences between groups were tested by 1-way ANOVA and the

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Table. Baseline Characteristics and In-Hospital Outcomes in Clinical Research Participants and Nonparticipants Undergoing Transcatheter Aortic Valve Implantation

| Characteristics          | Before matching | After propensity score matching | P value | Before matching | After propensity score matching | P value |
|--------------------------|-----------------|---------------------------------|---------|-----------------|---------------------------------|---------|
|                          | Research        | Nonparticipants                 | Overall | Research        | Nonparticipants                 | Overall |
|                          | participants    | (n=14,311)                      | (n=51,383) | participants    | (n=14,301)                     | (n=51,301) |         |
| Age, y                   | 80.0±7.9        | 80.0±8.4                        | 80.0±8.3 | 0.736           | 80.0±7.9                       | 80.1±8.5 | 0.344  |
| Female sex               | 46.0%           | 46.9%                           | 46.6%   | 0.075           | 49.7%                          | 50.3%   | 0.281  |
| Race or ethnicity        |                 |                                 |         |                 |                                 |         |        |
| White                    | 88.7%           | 88.7%                           | 82.0%   | <0.001          | 85.5%                          | 85.1%   | <0.001 |
| Black                    | 3.1%            | 3.9%                            | 3.7%    |                 | 2.9%                           | 3.6%    | 3.2%   |
| Hispanic                 | 4.2%            | 4.5%                            | 4.4%    |                 | 3.9%                           | 4.2%    | 4.1%   |
| Asian                    | 1.3%            | 1.2%                            | 1.2%    |                 | 1.2%                           | 1.2%    | 1.2%   |
| Native American          | 0.3%            | 0.2%                            | 0.3%    |                 | 0.3%                           | 0.2%    | 0.3%   |
| None of the above        | 2.4%            | 2.5%                            | 2.4%    |                 | 2.2%                           | 2.8%    | 2.5%   |
| Insurance                |                 |                                 |         |                 |                                 |         | <0.001 |
| Medicare                 | 90.9%           | 89.2%                           | 89.6%   |                 | 90.9%                          | 89.3%   | 90.1%  |
| Medicaid                 | 0.8%            | 1.3%                            | 1.2%    |                 | 0.8%                           | 1.2%    | 1.0%   |
| Private                  | 6.6%            | 7.3%                            | 7.1%    |                 | 6.6%                           | 7.4%    | 7.0%   |
| Self-pay                 | 0.5%            | 0.4%                            | 0.5%    |                 | 0.5%                           | 0.5%    | 0.5%   |
| None of the above        | 1.2%            | 1.8%                            | 1.6%    |                 | 1.2%                           | 1.6%    | 1.4%   |
| Median household income  |                 |                                 |         |                 |                                 |         | <0.001 |
| $1–$38,999               | 18.7%           | 22.1%                           | 21.1%   |                 | 18.7%                          | 20.6%   | 19.7%  |
| $39,000–$47,999          | 26.8%           | 25.0%                           | 25.5%   |                 | 26.8%                          | 24.7%   | 25.8%  |
| $48,000–$62,999          | 28.9%           | 25.9%                           | 26.7%   |                 | 28.9%                          | 25.9%   | 27.4%  |
| $63,000 or more          | 25.6%           | 27.1%                           | 26.7%   |                 | 25.6%                          | 28.8%   | 27.2%  |
| Comorbidities            |                 |                                 |         |                 |                                 |         |        |
| Elixhauser comorbidity    |                 |                                 |         |                 |                                 |         |        |
| score                    |                 |                                 |         |                 |                                 |         |        |
| 0                        | 0.03%           | 0.02%                           | 0.02%   | <0.001          | 0.3%                           | 0.3%    | 0.3%   |
| 1–3                      | 15.3%           | 12.1%                           | 13.0%   |                 | 15.3%                          | 15.2%   | 15.2%  |
| 4–5                      | 38.5%           | 36.4%                           | 37.0%   |                 | 38.5%                          | 38.8%   | 38.6%  |
| 6 or more                | 46.2%           | 51.5%                           | 50.0%   |                 | 46.2%                          | 46.0%   | 46.1%  |
| Hypertension             | 88.5%           | 88.2%                           | 88.3%   | 0.400           | 88.5%                          | 88.8%   | 88.7%  |
| Diabetes                 | 35.6%           | 36.6%                           | 36.4%   | 0.037           | 35.6%                          | 35.3%   | 35.5%  |
| Obese                    | 18.6%           | 18.6%                           | 18.6%   | 0.947           | 18.6%                          | 18.0%   | 18.3%  |

(Continued)
Table. Continued

| Characteristics                                      | Before matching | After propensity score matching | P value | Before matching | After propensity score matching | P value |
|------------------------------------------------------|----------------|---------------------------------|---------|----------------|---------------------------------|---------|
|                                                      | Research       | Nonparticipants                | Overall | Research       | Nonparticipants                | Overall |         |
|                                                      | participants   | (n=14 311)                     | (n=37 072) | participants   | (n=14 310)                     | (n=14 301) | 0.246   |
|                                                      | Overall (n=51 383) |                                     |         | Overall (n=28 602) |                                      |         | 0.105   |
| Chronic kidney disease without end-stage renal disease | 33.5%          | 32.9%                           | 33.1%   | 33.5%          | 32.6%                           | 33.0%   | 0.105   |
| Anemia                                               | 4.5%           | 4.9%                            | 4.8%    | 0.077          | 4.6%                           | 4.3%    | 4.4%    | 0.261   |
| Atrial fibrillation                                  | 37.6%          | 40.1%                           | 39.4%   | <0.001         | 37.6%                          | 38.1%   | 37.9%   | 0.380   |
| Congestive heart failure                             | 71.2%          | 74.9%                           | 73.9%   | <0.001         | 71.3%                          | 72.0%   | 71.7%   | 0.142   |
| Arhythmia                                            | 55.0%          | 58.6%                           | 57.6%   | <0.001         | 55.1%                          | 55.2%   | 55.1%   | 0.831   |
| Prior stroke                                         | 14.1%          | 14.3%                           | 14.2%   | 0.537          | 14.1%                          | 13.3%   | 13.7%   | 0.056   |
| Prior myocardial infarction                          | 11.9%          | 13.1%                           | 12.8%   | <0.001         | 11.9%                          | 11.0%   | 11.5%   | 0.025   |
| Prior percutaneous coronary intervention             | 21.6%          | 22.1%                           | 21.9%   | 0.262          | 21.6%                          | 20.7%   | 21.2%   | 0.066   |
| Prior coronary artery bypass graft                   | 17.0%          | 18.6%                           | 18.2%   | <0.001         | 17.0%                          | 16.0%   | 16.5%   | 0.023   |
| Prior PPM                                            | 9.7%           | 10.1%                           | 10.0%   | 0.240          | 9.7%                           | 9.3%    | 9.5%    | 0.219   |
| Chronic pulmonary disease                            | 28.4%          | 32.8%                           | 31.6%   | <0.001         | 28.4%                          | 28.3%   | 28.3%   | 0.773   |
| Pulmonary circulation disorders                       | 16.7%          | 18.3%                           | 17.9%   | <0.001         | 16.7%                          | 16.3%   | 16.5%   | 0.435   |
| Peripheral vascular disease                          | 22.2%          | 24.7%                           | 24.0%   | <0.001         | 22.2%                          | 22.0%   | 22.1%   | 0.732   |
| Liver disease without cirrhosis                      | 1.8%           | 1.9%                            | 1.9%    | 0.543          | 1.8%                           | 1.5%    | 1.6%    | 0.051   |
| Hypothyroidism                                       | 19.6%          | 20.5%                           | 20.2%   | 0.024          | 19.6%                          | 19.2%   | 19.4%   | 0.362   |
| Hospital characteristics                             |               |                                 |         |               |                                 |         |         |
| Hospital bed size                                    |               |                                 | <0.001  |               |                                 |         | <0.001  |
| Small                                                | 7.4%           | 6.4%                            | 6.6%    | 7.4%           | 5.9%                           | 6.7%    |         |
| Medium                                               | 19.0%          | 20.4%                           | 20.0%   | 19.0%          | 20.5%                          | 19.7%   |         |
| Large                                                | 73.6%          | 73.2%                           | 73.3%   | 73.6%          | 73.6%                          | 73.6%   |         |
| Hospital region                                      |               |                                 | <0.001  |               |                                 |         | <0.001  |
| Northeast                                            | 19.7%          | 25.4%                           | 23.8%   | 19.7%          | 30.0%                          | 24.8%   |         |

(Continued)
| Characteristics                       | Before matching | After propensity score matching |
|--------------------------------------|----------------|--------------------------------|
|                                      | Research participants (n=14,311) | Nonparticipants (n=37,072) | Overall (n=51,383) | Research participants (n=14,301) | Nonparticipants (n=14,301) | Overall (n=28,602) | P value |
| Midwest                              | 24.4%          | 22.3%                       | 22.9%          | 24.4%          | 23.6%                       | 24.0%          | <0.001  |
| South                                | 29.8%          | 35.2%                       | 33.7%          | 29.8%          | 32.4%                       | 31.1%          | <0.001  |
| West                                 | 26.0%          | 17.1%                       | 19.6%          | 26.0%          | 14.1%                       | 20.1%          | <0.001  |
| Hospital location/teaching status    |                |                             |                |                |                             |                | <0.001  |
| Rural                                | 0.4%           | 1.2%                        | 1.0%           | 0.4%           | 1.3%                        | 0.8%           | <0.001  |
| Urban nonteaching                    | 10.5%          | 8.9%                        | 9.3%           | 10.5%          | 8.3%                        | 9.4%           | <0.001  |
| Urban teaching                       | 89.1%          | 89.9%                       | 89.7%          | 89.1%          | 90.4%                       | 89.8%          | <0.001  |
| All-cause mortality                  | 1.0%           | 1.5%                        | 1.3%           | <0.001         | 1.0%                        | 1.4%           | 1.2%    | 0.002   |
| Hospital discharge                   |                |                             |                |                |                             |                | <0.001  |
| Transfer to short-term hospital      | 0.2%           | 0.5%                        | 0.4%           | 0.2%           | 0.5%                        | 0.4%           | <0.001  |
| Skill nursing facility               | 12.5%          | 16.3%                       | 15.2%          | 12.5%          | 15.6%                       | 14.1%          | <0.001  |
| Home health care                     | 17.9%          | 23.5%                       | 22.0%          | 17.9%          | 23.7%                       | 20.8%          | <0.001  |
| PPM implantation                     | 8.8%           | 10.6%                       | 10.1%          | <0.001         | 8.8%                        | 10.4%          | 9.6%    | <0.001  |
| Acute myocardial infarction          | 1.7%           | 1.8%                        | 1.8%           | 0.310          | 1.7%                        | 1.8%           | 1.7%    | 0.556   |
| Cardiac arrest                       | 0.9%           | 1.4%                        | 1.2%           | <0.001         | 0.9%                        | 1.2%           | 1.1%    | 0.009   |
| Cardiogenic shock                    | 1.7%           | 2.0%                        | 1.9%           | 0.012          | 1.7%                        | 1.7%           | 1.7%    | 0.853   |
| Ventricular tachycardia              | 3.1%           | 3.4%                        | 3.3%           | 0.062          | 3.1%                        | 3.1%           | 3.1%    | 0.973   |
| AKI                                  | 9.9%           | 12.1%                       | 11.5%          | <0.001         | 9.9%                        | 11.6%          | 10.8%   | <0.001  |
| AKI leading to dialysis              | 0.5%           | 0.5%                        | 0.5%           | 0.495          | 0.5%                        | 0.5%           | 0.5%    | 0.679   |
| Respiratory failure                  | 1.8%           | 3.8%                        | 3.2%           | <0.001         | 1.3%                        | 2.2%           | 1.7%    | <0.001  |
| Vasopressor use                      | 1.9%           | 2.3%                        | 2.2%           | 0.007          | 1.9%                        | 2.3%           | 2.1%    | 0.014   |
| Intra-aortic balloon pump            | 0.5%           | 0.7%                        | 0.6%           | 0.020          | 0.5%                        | 0.6%           | 0.5%    | 0.286   |
chi-square test, as appropriate. Statistical analysis was performed using Stata 16.1 (StataCorp) and R (R Foundation).

Between 2013 and 2019, 51,383 patients undergoing TAVI met the inclusion criteria: 14,311 (28%) research participants and 37,072 (72%) nonparticipants. Baseline patient characteristics are shown in Table. Compared with nonparticipants, research participants were less likely to have atrial fibrillation, chronic pulmonary disease, history of myocardial infarction, and a higher Elixhauser comorbidity score.

Crude in-hospital mortality after TAVI was lower in research participants than in nonparticipants (1.0% versus 1.5%, \( P < 0.001 \)). Regarding TAVI-related complications, permanent pacemaker implantation, cardiac arrest, cardiogenic shock, acute kidney injury, respiratory failure, vasopressor requirement, and requiring mechanical circulatory support were less frequent in research participants than in nonparticipants. Furthermore, research participants had higher total inflation adjusted costs than nonparticipants.

Crude in-hospital mortality after TAVI in research participants decreased from 4.4% in 2013 to 0.6% in 2019 (Cochran-Armitage trend \( P < 0.001 \)). In nonparticipants, crude in-hospital mortality after TAVI also decreased from 3.6% in 2013 to 1.0% in 2019 (Cochran-Armitage trend \( P < 0.001 \)).

After adjustment for baseline characteristics, adjusted odds ratio of in-hospital death was significantly lower in research participants than nonparticipants (odds ratio, 0.72; 95% CI, 0.60–0.88; \( P < 0.001 \)). The propensity score-matched cohort gave similar results in terms of in-hospital outcomes (Table).

There are several possible explanations for the significant relationship between research participation status and in-hospital mortality after TAVI in this study. First, physicians or hospitals participating in clinical research may have high-level experience and provide cutting-edge care. Previous studies demonstrated an inverse volume-outcome relationship of TAVI.\(^5\) High-volume hospitals seem to offer more opportunity for research participation, which may result in better outcomes. Second, behavior change in operators and postoperative care attributable to research participation may contribute to differences in patient outcomes, that is, the Hawthorne effect.\(^2\) Third, high frailty scores associated with an increased risk of adverse outcomes may preclude research participation.

Several limitations should be acknowledged. First, details on individual trials were lacking, such as inclusion and exclusion criteria and the reason for research participation. The interest of researchers may not be limited to TAVI. Second, the Nationwide Inpatient Sample database did not contain information regarding echocardiographic parameters, the Society

| Characteristic | Research participants (n=14,311) | Nonparticipants (n=37,072) | Overall (n=51,383) | \( P \) value | Research participants (n=14,301) | Nonparticipants (n=14,301) | Overall (n=28,602) | \( P \) value |
|---------------|---------------------------------|---------------------------|-------------------|-------------|---------------------------------|---------------------------|-------------------|-------------|
| Percutaneous ventricular assist device | 0.2% | 0.2% | 0.2% | 0.065 | 0.2% | 0.2% | 0.2% | 0.065 |
| Extracorporeal membrane oxygenation | 0.2% | 0.2% | 0.2% | 0.065 | 0.2% | 0.2% | 0.2% | 0.065 |
| Total inflation adjusted cost, US dollars | $54,420±$24,731 | $53,728±$28,011 | $53,902±$27,225 | <0.001 | $54,423±$24,735 | $53,313±$26,054 | $53,831±$25,452 | 0.002 |
| Length of hospital stay, d | 3.9±4.8 | 4.6±5.6 | 4.3±5.1 | <0.001 | 3.9±4.8 | 4.6±5.6 | 4.3±5.1 | <0.001 |

Values are means±SD or %. AKI indicates acute kidney injury; and PPM, permanent pacemaker.
of Thoracic Surgeons risk scores, frailty scores, and medication use. The impact of research participation status on outcomes should be further evaluated in patients with similar risk scores and frailty.

In conclusion, although our findings are subject to unmeasured confounders and selection bias for patients with favorable characteristics, research participation could be a determinant of better short-term outcomes after TAVI. Further studies are needed to investigate the effect of research participation on long-term outcomes after TAVI.

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REFERENCES
1. Otto CM, Nishimura RA, Bonow RO, Carabello BA, Erwin JP III, Gentile F, Jneid H, Krieger EV, Mack M, McLeod C, et al. 2020 ACC/AHA guideline for the management of patients with valvular heart disease: a report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. Circulation. 2021;143:e72–e227. doi: 10.1161/CIR.0000000000000923
2. Sedgwick P, Greenwood N. Understanding the Hawthorne effect. BMJ. 2015;351:h4672. doi: 10.1136/bmj.h4672
3. Steg PG, López-Sendón J, Lopez de Sa E, Goodman SG, Gore JM, Anderson FA Jr, Himbert D, Allegrone J, Van de Werf F. External validity of clinical trials in acute myocardial infarction. Arch Intern Med. 2007;167:68–73. doi: 10.1001/archinte.167.1.68
4. Matetic A, Mohamed MO, Roberts DJ, Rana JS, Alraies MC, Patel B, Sauer AJ, Diaz-Arocuita C, Sattar Y, Van Spall HGC, et al. Real-world management and outcomes of 7 million patients with acute coronary syndrome according to clinical research trial enrollment status: a propensity matched analysis. Eur Heart J Qual Care Clin Outcomes. 2021;qcab098. doi: 10.1093/ehjqcco/qcab098
5. Vemulapalli S, Carroll JD, Mack MJ, Li Z, Dai D, Kosinski AS, Kumbhani DJ, Ruiz CE, Thourani VH, Hanzel G, et al. Procedural volume and outcomes for transcatheter aortic-valve replacement. N Engl J Med. 2019;380:2541–2550. doi: 10.1056/NEJMsa1901109