Incidence and Outcomes of Acute Coronary Syndrome after Transcatheter Aortic Valve Replacement

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Abstract

Background: Evidence about incidence and outcomes of acute coronary syndrome (ACS) after transcatheter aortic valve replacement (TAVR) is scarce.

Methods: We identified Medicare patients who underwent TAVR from 2012 to 2017 and were admitted with ACS during follow-up. We compared outcomes based on the type of ACS; ST-segment elevation myocardial infarction (STEMI), non-STEMI (NSTEMI), and unstable angina. In patients with non-ST elevation ACS (NSTE-ACS), we compared outcomes based on the treatment strategy (invasive versus conservative) using inverse probability weighting (IPW) analysis.

Results: Out of 142,845 TAVR patients, 6,741 patients (4.7%) were admitted with ACS after a median time of 297 days (IQR 85–662), with 48% of admissions occurring within 6 months. The most common presentation was NSTEMI. Predictors of ACS were history of coronary artery disease, prior revascularization, diabetes, valve-in-TAVR, and acute kidney injury. STEMI was

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associated with higher 30-day and 1-year mortality compared to NSTEMI (31.4% versus 15.5% and 51.2% versus 41.3% respectively, p<0.01). Overall, 30.3% of NSTE-ACS patients were treated with invasive approach. On IPW analysis, invasive approach was associated with lower adjusted long-term mortality (aHR 0.69, 95% CI 0.66–0.73, p<0.01) and higher risk of repeat revascularization (aHR 1.29, 95% CI 1.16–1.43, p<0.001).

Conclusion: After TAVR, ACS is infrequent (<5%), and the most common presentation is NSTEMI. Occurrence of STEMI after TAVR is associated with a high mortality with nearly one-third of patients dying within 30-days. Optimization of care is needed for post-TAVR ACS patients and if feasible, invasive approach should be considered in these high-risk patients.

Graphical abstract
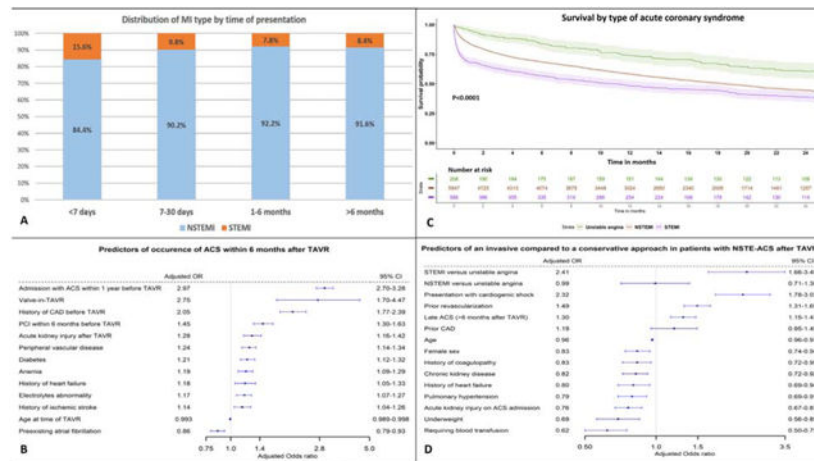
CONDENSED ABSTRACT

Among 142,845 Medicare patients who underwent transcatheter aortic valve replacement (TAVR) from 2012 to 2017, 6,741 patients (4.7%) were admitted with acute coronary syndrome after a median time of 297 days (IQR 85–662). The most common presentation was NSTEMI. STEMI was associated with higher 30-day and 1-year mortality compared to NSTEMI (31.4% versus 15.5% and 51.2% versus 41.3% respectively, p<0.01). After propensity score matching and inverse probability weigh analyses, invasive approach was associated with lower 30-day and long-term mortality (aHR 0.69, 95% CI 0.66–0.73, p<0.01), as well as reduction in HF and bleeding admissions.

Keywords

Transcatheter aortic valve replacement; Acute coronary syndrome; Percutaneous coronary intervention

INTRODUCTION

Transcatheter aortic valve replacement (TAVR) has revolutionized the management of severe aortic stenosis (AS) worldwide. After the recent results from PARTNER 3 and EVOLUT low risk trials, it is expected that the indications for TAVR will expand to include low risk

patients(1,2). Furthermore, in light of evidence about potential long-term durability of TAVR valves and improved survival of patients following TAVR (3), it becomes crucial to study long-term cardiac events after TAVR and identify strategies for optimal management.

Aging is a major risk factor for both coronary artery disease (CAD) and AS (4). More than 50% of patients with severe AS who undergo TAVR have concomitant CAD, and majority of these patients have undergone coronary revascularization (5). Evidence about incidence, timing and outcomes of ACS after TAVR at long-term follow up remain scarce (6,7). Furthermore, studies about the optimal management of ACS after TAVR are lacking. The technical considerations involved in performing percutaneous coronary intervention (PCI) in the presence of a TAVR prosthesis raise the question of applicability of prior studies of utility of PCI in management of ACS in TAVR patients (8,9).

The aim of this study is to address this knowledge gap by examining the incidence, timing and predictors of ACS after TAVR in Medicare beneficiaries. We also examined short- and long-term outcomes with different types of ACS and treatment using an invasive approach versus conservative management.

METHODS

Study population

The study cohort included patients who underwent TAVR from January 2012 to December 2017 and were enrolled in Medicare Fee-for-service. These patients were identified using the 100% Medicare Provider and Analysis Review (MEDPAR) Part A files from the Center for Medicare and Medicaid Services (CMS) which include all hospital admissions for Medicare fee-for-service beneficiaries nationwide. TAVR procedures were identified using ICD-9 procedure codes (35.05 and 35.06) for the period until September 2015, and ICD-10 procedure codes (02RF37Z, 02RF38Z, 02RF3JZ, 02RF3KZ, 02RF37H, 02RF38H, 02RF3JH, 02RF3KH, or X2RF332) for the period after September 2015. Patient demographics including age, sex, and race were extracted from Medicare enrollment files, while comorbidities were identified using ICD-9 and ICD-10 codes on inpatient claims during the three years prior to the TAVR admission (Supplemental Table 1). We used comorbidity algorithms originally defined by Elixhauser et al (10), as well as additional conditions that are relevant to our cohort. The dates of beneficiary Medicare enrollment and death were obtained from the 100% Beneficiary Summary file for the study period. Patients were excluded if they had been enrolled in Medicare fee-for-service for less than three years prior to the TAVR.

The Institutional Review Board of the University of Iowa approved this study with waiver for individual informed consent.

Study Outcomes

We identified patients who were admitted after TAVR with a diagnosis of acute coronary syndrome (ACS) including unstable angina (UA), non-ST-segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI) using ICD-9 and ICD-10 codes (Supplemental Table 1). We restricted the diagnosis of ACS to the

primary diagnosis or the first secondary diagnosis to ensure that the ACS was the main indication for the hospital admission. We excluded ICD-10 code (I21.A1) for type II MI. Patients were followed from the date of TAVR discharge through the end of the follow-up period (December 2017), and were censored due to death, Medicare disenrollment, or end of the study period (December 31, 2017). We also classified ACS admission based on the timing of occurrence after the index TAVR admission into very early (7 days), early (>7 to 30 days), delayed (>1 to 6 months) and late (> 6 months) post-TAVR. In the total ACS cohort, we studied 1) the incidence and timing of ACS after TAVR; 2) predictors associated with occurrence of ACS within 6 months after the TAVR procedure; and 3) rate and predictors of invasive approach (coronary angiogram, balloon angioplasty, bare metal stent [BMS], or drug eluting stent [DES]) versus a conservative management in ACS.

We then divided the cohort in 3 groups, patients with UA, NSTEMI and STEMI based on ICD code algorithms that were validated extensively in prior studies with positive predictive value of >90% (11,12). In these 3 groups, we compared 1) differences in in-hospital management (i.e. invasive versus conservative approach, and use of mechanical circulatory support [MCS]); 2) in-hospital outcomes including in-hospital mortality, cardiogenic shock, cardiac arrest, and heart failure; 3) short-term outcomes including 30-day mortality, heart failure (HF), and bleeding admissions; and 3) long-term outcomes including all-cause mortality, readmissions for HF, bleeding, recurrent ACS and need for revascularization. ICD-9 and ICD-10 codes used to define the study outcomes are reported in Supplemental Table 1.

The short- and long-term outcomes with invasive versus conservative approach were further studied among patients with non-ST-segment elevation ACS (NSTE-ACS) patients. Outcomes were reported both pre- and post-propensity score matching that was utilized to balance 41 clinical covariates between the two groups. Dates of deaths occurring through September 1,2018 were available, while data on readmissions was available through December 31,2017.

Statistical analysis

Continuous patient characteristics were described as mean and standard deviation or median and interquartile range as appropriate and were compared between patients with different types of ACS using analysis of variance or Wilcoxon test. Categorical characteristics were described as percentages and were compared using Chi-Square or Fisher Exact test as appropriate.

We used a multivariable logistic regression model to determine factors associated with ACS occurrence within 6 months after TAVR. To determine the predictors of PCI in management of ACS, we created a mixed-effects multivariable logistic regression with hospitals as random-effects to account for clustering of patients within hospitals. Adjusted odds ratios (ORs) are reported with 95% confidence intervals (CI) derived from sandwich estimates of standard errors.

Finally, we compared invasive versus conservative approach in NSTEACS using propensity scores that were created by a logistic regression model with the dependent variable of PCI

and a list of 41 covariates as the independent variables (Supplementary Table 3). Propensity score matching with 1 (conservative) to 1 (PCI) was performed with greedy match method and a caliper of 0.01 and robustness of the match algorithm was assessed by comparing the variables between both groups post-matching with a standardized difference lower than 0.1 considered balanced. To account for the matched design, short-term outcomes were compared with conditional logistic regression and asymptotic and exact odds ratio were estimated.(13) For long-term outcomes, we used Cox proportional hazards regression with Breslow method to break ties, which gives identical results to conditional Poisson regression (14), and hazard ratios (HRs) with 95% confidence intervals (CIs) were calculated. Unadjusted Kaplan-Meier (KM) curves with 95% CIs were generated to determine the cumulative proportion of patients with events as a function over time and compared using log-rank or Generalized Wilcoxon statistic, as appropriate. To assess the proportional hazards assumption, Kolmogorov-type supremum test and graphical inspection of Schoenfeld residuals plotted against time were performed. For the long-term outcomes of bleeding and HF admissions, multivariable survival analyses were performed by competing risk regression analysis to account for death using the Fine-Gray proportional sub hazards model, and subdistribution hazard ratios (sHRs) were calculated, along with 95% CIs.(15)

As a sensitivity analysis, we then performed survival time inverse probability weighting to estimate the average treatment effects.(16) First, the unstabilized inverse probability weights (IPWs) for the whole cohort were derived from the propensity scores from the non-parsimonious logistic regression model. Then, survival models to determine the adjusted effect of SAVR/TAVR on the study outcomes were created using the IPWs.(16) The model was generated using a robust sandwich covariance matrix estimate and robust standard error estimates to account for the clustering of patients within hospitals.(17) We also generated IPW-adjusted KM survival curves and adjusted KM estimator compared with log-rank test as proposed previously.(18,19)

A P value of 0.05 was the cutoff for statistical significance. The analysis was done with SAS version 9.4 (SAS Institute, Cary, North Carolina) and R 3.4.3 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Incidence and timing of ACS

Out of 142,845 patients who underwent TAVR during the study period, 6741 patients (4.7%) were admitted for an ACS with a total of 8,862 ACS admissions (single ACS admission n= 4,620, 2 ACS admissions n= 827, 3 ACS admissions n= 405, > 3 ACS admissions n= 242). Table 1 shows baseline characteristics of TAVR patients who experienced ACS during follow up compared to those who did not. Patients who had ACS were younger, more likely to be males and of black race, with a higher burden of comorbidities including hypertension, diabetes mellitus, HF, lung disease, chronic kidney disease, prior CAD, and prior revascularization. Valve-in-TAVR (repeat TAVR) procedure was more common in patients who experienced ACS.

Out of the 6741 first ACS admissions, 586 had STEMI (anterior STEMI n=163, non-anterior STEMI n=423), and 6155 had NSTE-ACS (NSTEMI n= 5,947, UA n= 208) (Supplemental Figure 1). Median time from TAVR to first ACS admission was 297 days (IQ range 85–662) days. Post-TAVR ACS occurred very early (7 days) in 562 patients (8.3%), early (7–30 days) in 488 patients (7.2%), delayed (1–6 months) in 1509 patients (22.4%), and late (>6 months) in 4,182 patients (62.0%) (Supplemental Figure 2).

Predictors of ACS within 6 months after TAVR

Important factors associated with occurrence of ACS within 6 months after TAVR included younger age at TAVR (adjusted (aOR) 0.993, 95% CI 0.989–0.998, p=0.008), prior ACS within one year before TAVR (aOR 2.97, 95% CI 2.70–3.28,P<0.0001), history of CAD (aOR 2.05, 95% CI 1.77–2.39, p<0.0001), TAVR-in-TAVR valve (aOR 2.75, 95% CI 1.70–4.47, p<0.0001), prior PCI within 6 months before TAVR (aOR 1.45, 95% CI 1.30–1.63, p=<0.0001), DM (aOR 1.21, 95% 1.12–1.32, p=<0.0001), PAD (aOR 1.24, 95% CI 1.14–1.34, p<0.0001) and post-TAVR acute kidney injury (AKI) (aOR 1.28, 95% CI 1.16–1.42, p<0.0001) (Figure 1).

Predictors of invasive management

Overall, 30.3% of the patients were treated with invasive approach (13.9% with coronary angiogram without intervention and 16.6% with PCI). Important predictors of an invasive versus conservative approach included STEMI presentation (aOR 2.41, 95% CI 1.66–3.49, p<0.0001), cardiogenic shock (aOR 2.32, 95% CI 1.78–3.03, p<0.0001), history of prior revascularization (aOR 1.49, 95% CI 1.31–1.69, p<0.0001), and presenting >6 months after TAVR (aOR 1.30, 95% CI 1.15–1.47, p<0.0001) (Figure 2).) In contrary, important predictors that favored conservative approach were older age, female sex, chronic kidney disease, need for blood transfusion, history of coagulopathy or presenting with AKI. Importantly, NSTEMI was not associated with higher rates of invasive approach compared to UA.

Outcomes by type of ACS

Table 2 summarizes the baseline characteristics of the three ACS groups. While patients who presented with NSTEMI were relatively younger compared with the other two groups, overall, no significant difference in the prevalence of comorbidities (e.g. DM, hypertension, HF, lung disease, liver disease, or kidney disease) was observed between groups. STEMI patients were also more likely to undergo an invasive approach with half of the patients undergoing coronary angiogram (21.3% had PCI with a drug eluting stent, 6% with bare metal stent, 7% had angioplasty without stenting, 14% had coronary angiogram without intervention and 0.7% had urgent CABG). In patients who underwent intervention, data on number of vessels treated and number of stents placed were available for 99% of the patients. The majority of patients had one stent placed and one vessel treated during the index ACS admission. (Table 3).

In-hospital and short-term outcomes

STEMI was associated with significantly higher in-hospital mortality (24.1% compared to 7.6% and 1.4% for NSTEMI and UA, respectively, p<0.001). Also, STEMI patients had higher rates of cardiogenic shock, cardiac arrest, AKI, and need for mechanical circulatory support. NSTEMI patients had the highest incidence of in-patient acute HF (34.7% compared to 25.1% and 4.8% for STEMI and UA, respectively, p<0.001). At 30-days, STEMI was associated with higher mortality (31.4% compared to 15.5% and 4.8% for NSTEMI and UA, respectively, p<0.001). STEMI and NSTEMI both had higher 30-day HF readmission compared to UA (5.5% and 4.4% compared to 1.5%, p=0.04). There were no differences in 30-day bleeding between types of ACS. One-year mortality was highest in STEMI compared to NSTEMI and UA (51.2% versus 41.3% and 26.0% respectively, p <0.01).

Long-term outcomes

Median follow up after ACS was 373 days (IQR 91–676). Long-term mortality remained higher with STEMI compared to NSTE-ACS (58.7 deaths vs 45.8 deaths per 100 person-years in NSTEMI, HR 1.28, 95% CI 1.15–1.43, p<0.0001; and 24.3 deaths per 100 person-years in UA, HR 2.04, 95% CI 1.65–2.51, p<0.0001). NSTEMI also had higher mortality compared to UA (HR 1.59, 95%CI 1.32–1.92, p<0.0001) (Figure 3 and Supplemental Table 2). STEMI was also associated with higher risk of readmission with ACS compared to NSTEMI (HR 1.91, 95% CI 1.63–2.24) and UA (HR 2.89, 95% CI 2.08–4.03) (P<0.001 for both). There was no difference between the three groups in long-term bleeding or HF admissions.

Outcomes with invasive versus conservative approach in NSTE-ACS patients

Prior to propensity score matching, invasive approach was associated with lower in-hospital mortality (4.8% versus 8.4%, p<0.0001), 30-day mortality (8.8% versus 17.7%, p<0.0001) and 1-year mortality (51.2% versus 41.3, P<0.001). Invasive approach was also associated with significantly lower long-term mortality, and bleeding readmissions, but a higher risk for repeat revascularization at follow up compared to the conservative approach. There was no difference in the risk of recurrent ACS admissions or heart failure admissions between both management approaches (Supplemental figures 3A–E).

Propensity-matching and Inverse-probability weighting analyses

After propensity-matching, there were 1750 matched pairs managed with invasive versus conservative approach. The two groups were well balanced in all variables (Supplemental Table 3). Invasive approach remained associated with significantly lower in-hospital, 30-days and 1-year mortality (4.8% versus 8.4%, aOR 0.54, 95% CI 0.40–0.72, 8.8% versus 16.9%, aOR 0.47, 95% CI 0.38–0.58, and 29.6% versus 43.8%, aOR 0.52, 95% CI 0.47–0.63, p<0.0001 for all). On IPW-adjusted analysis, Invasive management was also associated with significantly lower long-term mortality (aHR 0.69, 95% CI 0.66–0.73, p<0.0001), lower risk for heart failure (aHR 0.90, 95% CI 0.81–0.99, P=0.03) and bleeding (aHR 0.88, 95% CI 0.78–0.98, P=0.03). There was no difference in long-term risk for recurrent ACS admissions between both groups (aHR 1.00, 95% CI 0.93–1.09, p=0.87. Invasive approach

was associated with higher risk of need for revascularization at follow up (aHR 1.29, 95% CI 1.16–1.43, p<0.001). (Figures 4A–D).

DISCUSSION

In this study from Medicare population, we report several important findings. First, the incidence of ACS after TAVR was 4.7%, and the majority of ACS admissions were due to NSTEMI. Second, 48% of ACS admissions occurred within 6 months after TAVR and were associated with prior history of CAD, prior revascularization within 6 months before TAVR, diabetes, post-TAVR AKI and valve-in-TAVR procedures. Third, STEMI was associated with the highest rates of short- and long-term mortality followed by NSTEMI compared to UA with one half of the patients dying within one year. Fourth, about one-third of post-TAVR ACS patients were managed with an invasive approach, especially when presenting with STEMI, cardiogenic shock, late (>6 months) after TAVR, or had prior revascularization. Last, this approach was associated with significantly lower long-term mortality when compared to conservative management (Central Illustration).

There is scarce literature about the true incidence of ACS in long-term follow-up after TAVR in real world. Plausible mechanisms of ACS after TAVR include plaque rupture with intra-coronary thrombus formation, valve thrombosis with embolization into the coronaries, and mechanical obstruction of coronary ostia with the valve structure. In our study, over a median of one year, 4.7% of TAVR patients developed ACS. In a prior single center study, the incidence was higher (10%) (7). This can be explained by its less contemporary cohort, and likely higher risk TAVR population from as early as 2007, its longer follow up compared to our study, and the inclusion of patients with type II MI. In our study, we divided ACS admissions into earlier than or after 6 months post TAVR. ACS occurring earlier than 6 months could be probably related to the TAVR procedure. In one study, delayed coronary obstruction occurring in the first 7 days after the procedure was most probably due to continued expansion of the valve, while obstruction that occurred after 7 days was most likely related to valve thrombosis (6). In that study, 40% of cases of coronary obstruction related to the valve occurred more than two months after the procedure (6). In another study by Vilalta and his colleagues, half of ACS admissions happened in the first year following TAVR. This is consistent with our study where 40% of ACS admissions occurred in the first 6 months. It appears that NSTEMI is the most common type of ACS following TAVR, representing 65% of the cases in the prior study and 85% of the cases in our study (7).

It is crucial to study factors associated with occurrence of ACS after TAVR given the morbidity and mortality associated with ACS. In our study, younger age at TAVR, history of CAD and occurrence of AKI after TAVR were all significantly associated with ACS after multivariable analysis. However, it is interesting that valve-in-TAVR valve was associated with a significantly higher risk of ACS. Valve-in-valve procedures were shown in the past to be associated with delayed coronary obstruction after TAVR in one study (6), and this could be due to high risk of thrombosis or due to crowding of the aortic root with two valve structures. In our study, we were not able to study outcomes with valve-in-surgical valves, because of the limitation of ICD codes in specifying location of prior prosthetic valves (aortic vs mitral) when the surgery was remote.

Some of the factors that were associated with a higher likelihood of an PCI in managing NSTE-ACS in the current study are consistent with the ACC/AHA guidelines in NSTE-ACS in general population, such as hemodynamic instability, ST-segment elevation on presentation, and history of revascularization (20). Furthermore, patients with chronic kidney disease or AKI on presentation were less likely to be treated invasively probably to avoid further kidney injury with exposure to contrast. Similarly, patients with coagulopathy, liver disease and need for transfusion, are likely to be at a higher risk of bleeding with antithrombotic agents, which could explain the lower rates of invasive approach in this population. Interestingly, similar to prior studies in NSTE-ACS, in our study female sex and older age were both associated with less likelihood of PCI (21,22). How prior TAVR affects decision of PCI in ACS patients remains unclear.

Multiple case reports have raised concerns about technical challenges in performing PCI in patients post-TAVR, including challenges in selective cannulation of the right coronary artery (8,23), retrieval of the guiding catheter due to entrapment within the stent frame (9), and the usual difficult location of the culprit lesion in the ostium of the vessel (24). However, procedural success was reported to be around 70–90% in prior studies (6,7). In our study, PCI in patients who presented with NSTE-ACS was associated with lower mortality compared with conservative approach. This indicates that the known benefit of PCI in NSTE-ACS patients may as well extend to include patients with prior TAVR despite the technical challenges (25,26). However, it is worth mentioning that PCI in our study was associated with an increase in the need for revascularization at follow-up. Two plausible explanations include 1) staged PCI for non-culprit lesions found on coronary angiogram; and 2) the risk of in-stent restenosis or thrombosis with PCI. Among the important potential causes of ACS in TAVR population is leaflet thrombosis and subsequent embolization, and the magnitude, prevention as well as the appropriate management of such complication remain under extensive investigation (27).

Limitations

The current study represents the largest and most comprehensive analysis examining the incidence, outcomes and management of ACS after TAVR. However, our study has several limitations. First, we only had inpatient files available for the analysis, so patients who received coronary interventions on an outpatient basis would not be captured. However, our main interest was ACS and coronary intervention in the acute setting. Second, information on serum biomarkers levels such as troponin and EKG tracings were not available for our study cohort. However, we used ICD-codes algorithms that were validated extensively in prior studies (11,12). Third, to avoid including type II MI patients, we excluded ICD codes (I21.A1, 410.9*) and we restricted our cohort to patients with diagnosis of ACS in the first two positions in the inpatient claim. However, there is a possibility that some of NSTEMI patients in our cohort could still represent type II MI, and outcomes could potentially be different in these two etiologies. Fourth, we lacked information on important medications known to affect ACS outcomes including antiplatelets, anticoagulation and statins. Fifth, we lacked information on surgical risk scores such as STS score, coronary anatomy, culprit lesion, success of PCI, and repeat revascularization site. Last, despite propensity score

matching analysis to adjust for measured confounders, residual confounding cannot be entirely excluded.

CONCLUSION

In TAVR patients, ACS after TAVR is infrequent (4.7%), and the most common presentation is NSTEMI. Although incidence of STEMI after TAVR is low (<1%), it is associated with a high mortality with nearly one-third of patients dying within 30-days. ACS is most frequently treated with conservative approach and although invasive approach was associated with better outcomes in our study, the role invasive versus conservative approach requires further investigation.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

ABBREVIATIONS AND ACRONYMS

ACS	Acute coronary syndrome
AKI	Acute kidney injury
CAD	coronary artery disease
HF	Heart failure
NST-ACS	Non-ST elevation acute coronary syndrome
NSTEMI	Non-ST elevation myocardial infarction
PCI	percutaneous coronary intervention
STEMI	ST-elevation myocardial infarction
TAVR	Transcatheter aortic valve replacement
UA	unstable angina

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PERSPECTIVES

WHAT IS KNOWN?

Because of the age and comorbidities of patients who undergo transcatheter aortic valve replacement (TAVR), they are at high risk of coronary artery disease and acute coronary syndromes (ACS).

WHAT IS NEW?

Incidence of ACS after TAVR is low (4.7%) and is most commonly non-ST elevation myocardial infarction (NSTEMI). STEMI is associated with higher short- and mid-term mortality than other ACS types. Invasive approach in post-TAVR patients with ACS is potentially associated with better outcomes.

WHAT IS NEXT?

Future studies are encouraged to examine the appropriate preventive and therapeutic approaches to lower the risk and improve the outcomes of post-TAVR ACS in this high-risk population.

	Adjusted OR		95% CI
Admission with ACS within 1 year before TAVR	2.97		2.70-3.28
Valve-in-TAVR	2.75		1.70-4.47
History of CAD before TAVR	2.05		1.77-2.39
PCI within 6 months before TAVR	1.45		1.30-1.63
Acute kidney injury after TAVR	1.28		1.16-1.42
Peripheral vascular disease	1.24		1.14-1.34
Diabetes	1.21		1.12-1.32
Anemia	1.19		1.09-1.29
History of heart failure	1.18		1.05-1.33
Electrolytes abnormality	1.17		1.07-1.27
History of ischemic stroke	1.14		1.04-1.26
Age at time of TAVR	0.993		0.989-0.998
Preexisting atrial fibrillation	0.86		0.79-0.93

Adjusted Odds ratio: 0.75 1.0 1.4 2.8 5.0

Figure 1: Predictors of occurence of ACS within 6 months after TAVR
Predictors of occurrence of acute coronary syndrome within 6 months after TAVR on multivariable logistic regression.
ACS= acute coronary syndrome; CAD= coronary artery disease; CI= confidence interval; OR= odds ratio; PCI= percutaneous coronary intervention; TAVR= transcatheter aortic valve replacement

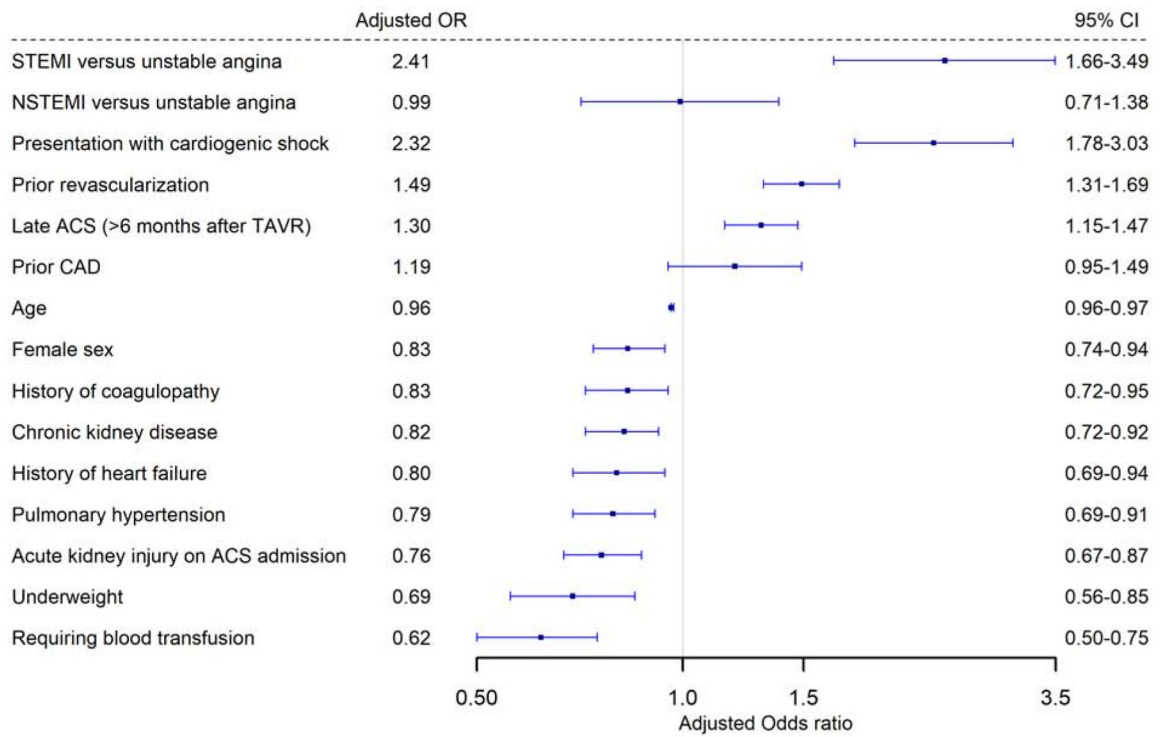|	Adjusted OR		95% CI
STEMI versus unstable angina	2.41		1.66-3.49
NSTEMI versus unstable angina	0.99		0.71-1.38
Presentation with cardiogenic shock	2.32		1.78-3.03
Prior revascularization	1.49		1.31-1.69
Late ACS (>6 months after TAVR)	1.30		1.15-1.47
Prior CAD	1.19		0.95-1.49
Age	0.96		0.96-0.97
Female sex	0.83		0.74-0.94
History of coagulopathy	0.83		0.72-0.95
Chronic kidney disease	0.82		0.72-0.92
History of heart failure	0.80		0.69-0.94
Pulmonary hypertension	0.79		0.69-0.91
Acute kidney injury on ACS admission	0.76		0.67-0.87
Underweight	0.69		0.56-0.85
Requiring blood transfusion	0.62		0.50-0.75

Figure 2: Predictors of an invasive compared to a conservative approach in patients with NSTF-ACS after TAVR

Predictors of an invasive compared to a conservative approach in patients with NSTE-ACS after TAVR.

NSTEMI= Non-ST elevation myocardial infarction; STEMI= ST-elevation myocardial infarction; rest of abbreviations as figure 1.
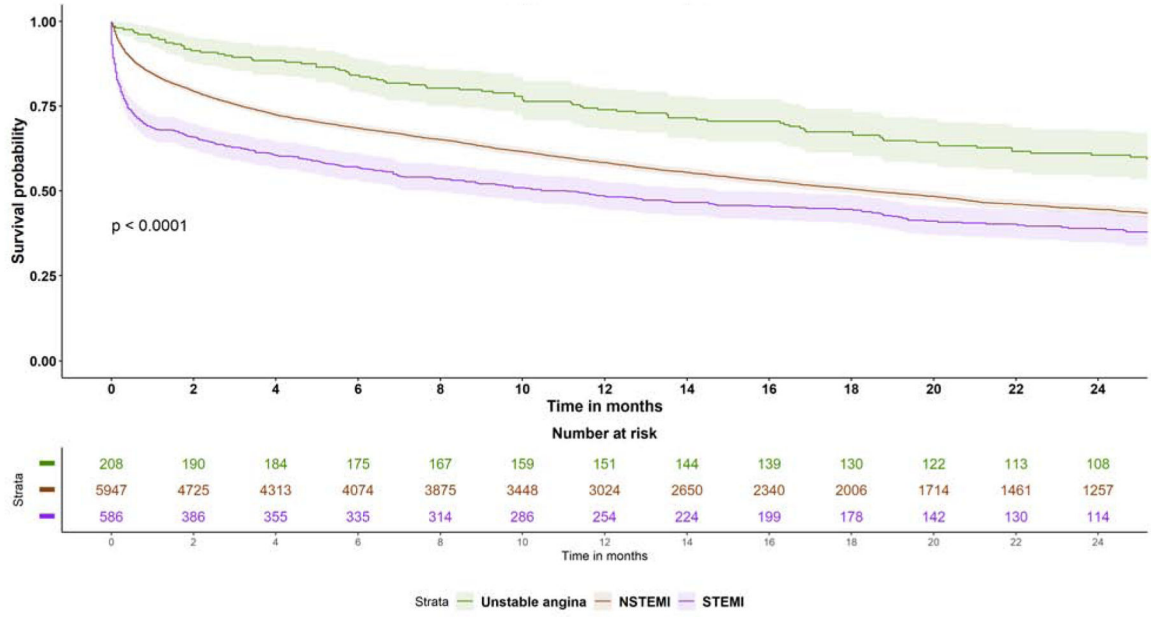
Figure 3: Survival by type of Acute coronary syndrome
Kaplan Meier curves for survival probability in the three ACS types after TAVR.

Abbreviations as figure 2.

A

IPW-Adjusted survival Post TAVR ACS patients with treatment choice
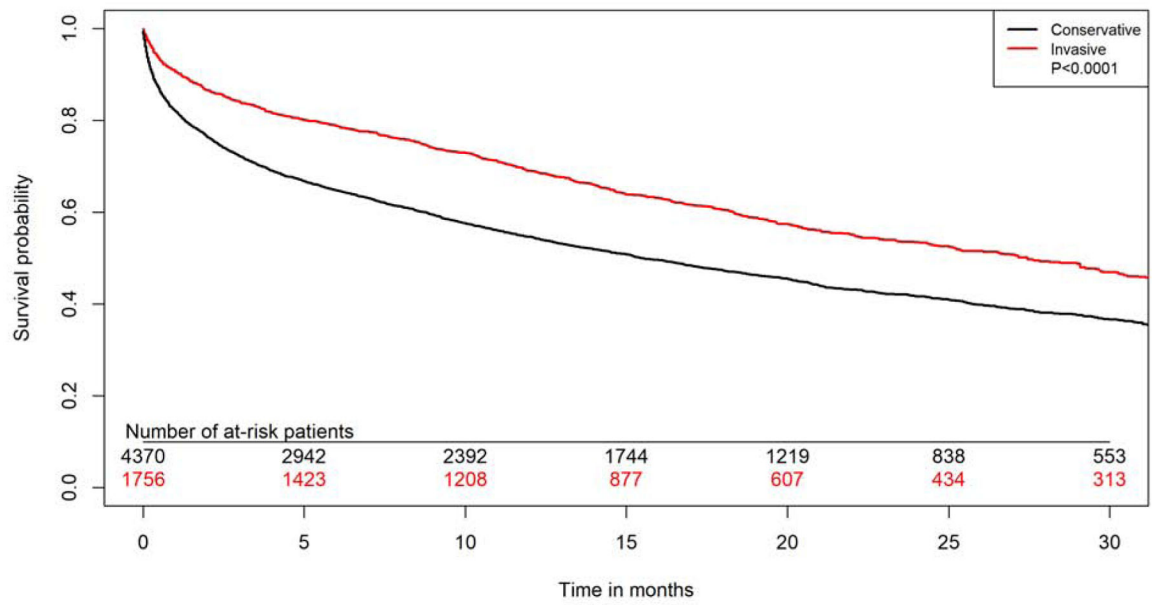
B

IPW-Adjusted heart failure Post TAVR ACS patients with treatment choice

C

IPW-Adjusted bleeding Post TAVR ACS patients with treatment choice

D

IPW-Adjusted need for intervention in Post TAVR ACS patients with treatment choice
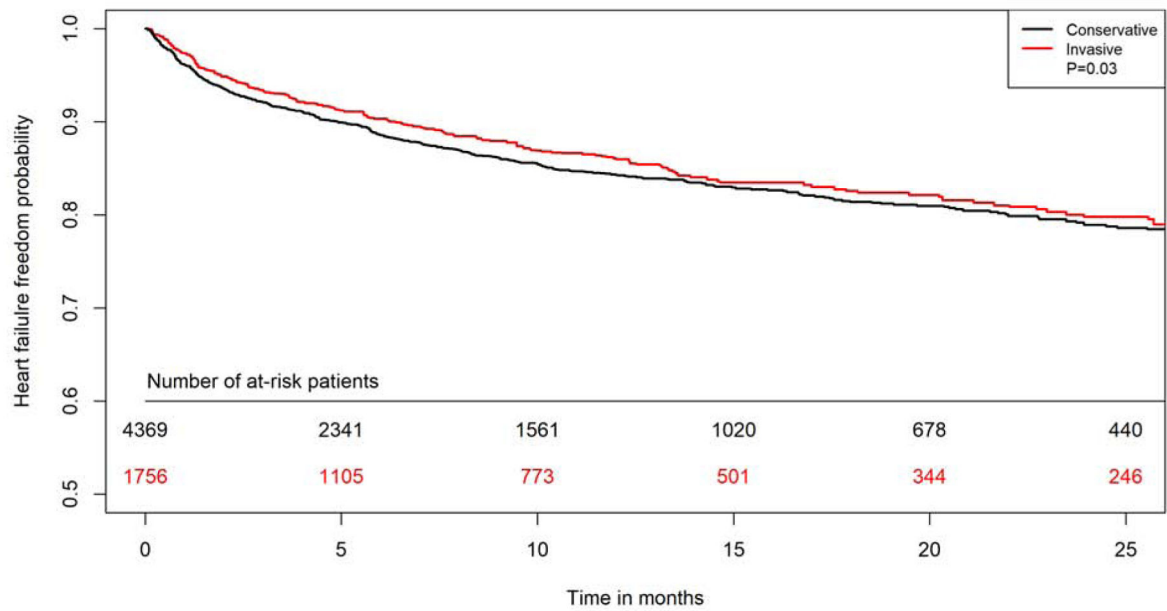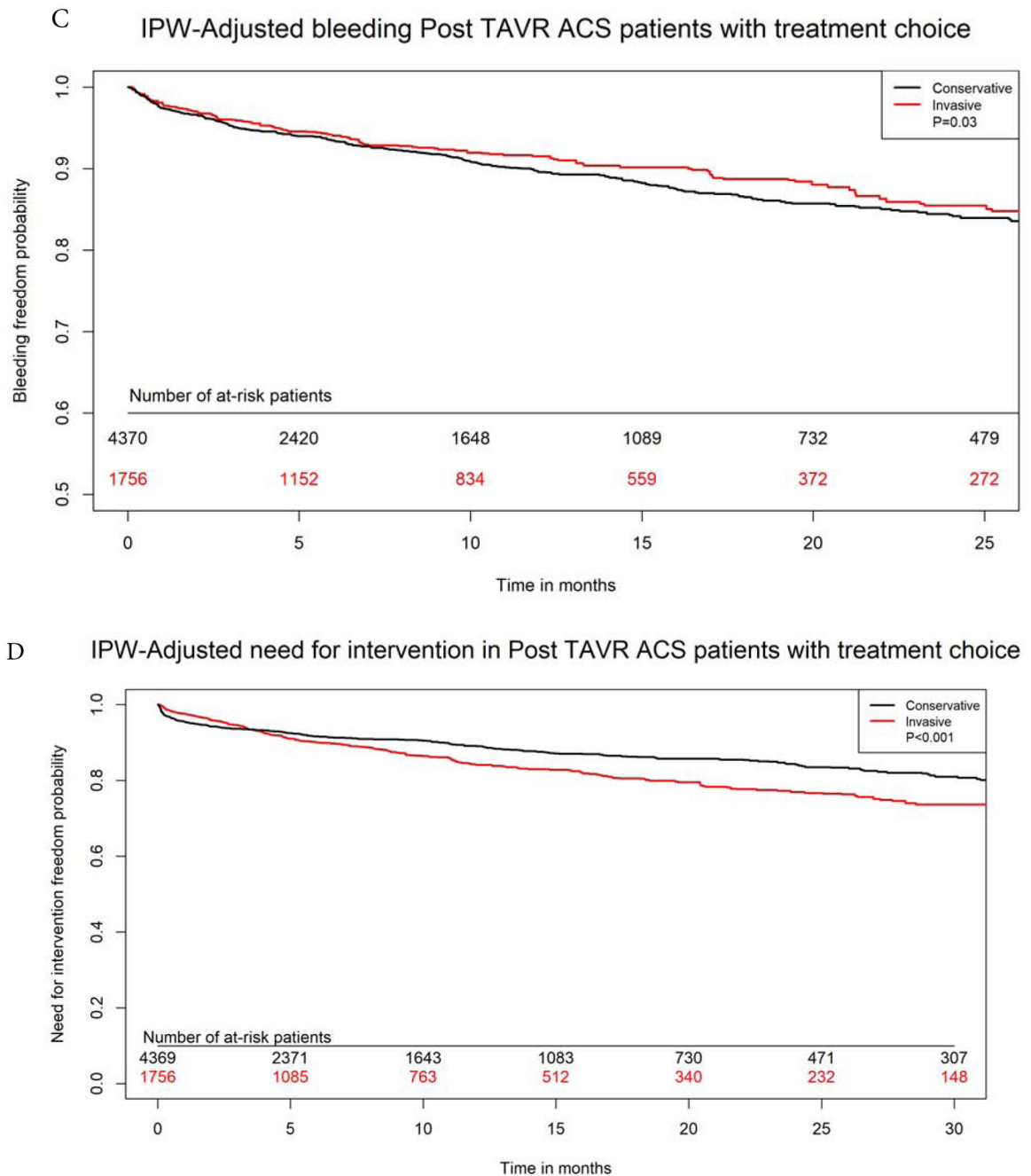
Figure 4: IPW Adjusted Kaplan-Meier Curves
Inverse probability weighting adjusted Kaplan Meier curves of A) survival, B) heart failure, C) bleeding, and D) need for revascularization with invasive versus conservative approach in patients with NSTE-ACS after TAVR

IPW=inverse probability weighting; rest of abbreviations as figure 1.

Central illustration: Panel A: Distribution of types of myocardial infarction by timing of presentation **Panel B:** Predictors of occurrence of acute coronary syndrome within 6 months after TAVR on multivariable logistic regression. **Panel C:** Kaplan Meier curves for survival

probability in the three ACS types after TAVR. **Panel D:** Predictors of an invasive compared to a conservative approach in patients with NSTE-ACS after TAVR

Table 1:

Baseline characteristics of patients with versus without acute coronary syndrome after TAVR

Variable	Without ACS	With ACS	P value
N	136,104	6,741	
Age	81.7±8.1	80.7±8.8	<0.0001
Male	52.7	55.3	<0.001
White	92.5	91.2	<0.001
Black	3.9	5.3	
Other	3.5	3.4	
Hypertension	93.8	95.1	<0.0001
Diabetes mellitus	40.9	51.5	<0.0001
Heart failure	79.3	83.9	<0.001
Deficiency anemia	40.8	50.3	<0.001
Alcohol abuse	2.0	1.7	0.10
Connective tissue disease	6.7	7.7	<0.001
Chronic lung disease	38.5	43.8	<0.001
Coagulopathy	22.4	24.1	0.001
Depression	15.2	12.7	0.002
Drug abuse	0.7	1.0	0.02
Hypothyroidism	25.7	26.1	0.44
Liver disease	3.8	3.8	0.90
Lymphoma	1.8	1.9	0.70
Electrolyte abnormality	43.6	51.9	<0.001
Metastasis	1.2	0.9	0.04
Obesity	24.3	27.0	<0.0001
Paralysis	4.0	4.9	0.0004
Peripheral arterial disease	35.6	46.4	<0.0001
Psychosis	2.7	3.5	0.0002
Pulmonary hypertension	18.2	25.5	<0.0001
Tumor without metastasis	5.1	5.4	0.32
Underweight	1.7	1.4	0.10
Weight loss	8.7	9.5	0.02
Prior bleeding	34.1	41.8	<0.0001
Cerebral hemorrhage	0.7	0.8	0.31
Prior stroke	16.6	22.6	<0.0001
End stage renal disease on dialysis	3.5	7.0	<0.0001
Chronic kidney disease	28.7	34.7	<0.0001
Prior coronary artery disease	79.8	90.8	<0.0001
Prior smoking	26.3	38.7	<0.0001
Prior revascularization (within 3 years prior to TAVR)	35.3	55.2	<0.0001

Variable	Without ACS	With ACS	P value
Prior ACS (within 1 year prior to TAVR)	7.9	21.6	<0.0001
PCI (within 6 months prior to TAVR)	7.4	14.9	<0.0001
Prior ICD	4.2	5.1	0.0004
Preexisting atrial fibrillation	43.6	40.7	<0.001
Prior pacemaker	13.9	13.7	0.70
Apical TAVR	7.2	12.8	<0.001
Valve-in-TAVR valve	0.4	1.1	<0.001
Aortic aneurysm	1.9	1.0	<0.0001
TAVR in Bicuspid AS	1.2	1.0	0.18

ACS=Acute coronary syndrome, ICD=intracardiac defibrillator, TAVR=transcatheter aortic valve replacement; PCI= percutaneous coronary intervention

Table 2:

Baseline characteristics of patients according to the type of ACS after TAVR

	Unstable angina (n = 208)	NSTEMI (n = 5,947)	STEMI (n = 586)	p value
N	208	5,947	586	
Age, yrs	82.7 ± 7.7	80.6 ± 8.8	80.9 ± 9.1	0.003
Male	56.7	55.7	50.5	0.05
White	94.2	91.0	91.8	0.70
Black	-	5.3	6.0	
Other	-	3.7	2.2	
Hypertension	94.2	95.0	95.6	0.73
Diabetes mellitus	43.8	51.9	50.7	0.07
Heart failure	83.2	84.1	82.9	0.74
Deficiency anemia	46.6	50.3	51.4	0.50
Alcohol abuse	-	1.7	1.9	0.37
Connective tissue disease	5.8	7.8	8.0	0.54
Chronic lung disease	45.2	44.0	41.1	0.37
Coagulopathy	20.2	24.2	23.9	0.41
Depression	21.2	17.8	15.5	0.16
Hypothyroidism	31.3	25.7	28.7	0.07
Liver disease	-	3.8	5.1	0.05
Lymphoma	-	1.8	2.1	0.24
Electrolyte abnormality	47.6	52.0	52.1	0.46
Obesity	29.8	27.0	25.9	0.56
Paralysis	-	4.8	5.6	0.67
Peripheral arterial disease	47.6	46.6	44.2	0.52
Pulmonary hypertension	27.4	25.7	22.0	0.12
Tumor without metastasis	5.8	5.3	5.5	0.96
Weight loss	6.3	9.6	9.2	0.26
Prior bleeding	40.4	41.7	43.3	0.68
Prior stroke	23.6	22.5	22.9	0.92
ESRD	-	7.2	6.5	0.10
CKD	31.7	35.0	32.6	0.32
Prior coronary artery disease	93.8	90.6	91.1	0.30
Prior smoking	44.2	38.7	36.5	0.15
Prior revascularization (within 3 yrs before TAVR)	66.8	55.5	47.8	<0.001
Prior ACS (within 1 yr before TAVR)	18.8	22.0	18.4	0.08
Prior PCI (within 6 months before TAVR)	14.9	14.8	15.9	0.77
Prior cardiac device	22.6	17.6	13.3	0.004
Preexisting atrial fibrillation	42.3	40.6	41.0	0.88
Apical TAVR	16.8	13.0	9.6	0.01

Values are mean ± SD or %.

Cells with N <10 were suppressed with (–).

CKD = chronic kidney disease; ESRD = end-stage renal disease on dialysis; NSTEMI = non–ST-segment elevation myocardial infarction; STEMI = ST-segment elevation myocardial infarction; other abbreviations as in Table 1.

Table 3:

Management and in-hospital outcomes of different types of ACS after TAVR

	Unstable angina (n = 208)	NSTEMI (n = 5,947)	STEMI (n = 586)	p value
N	208	5,947	586	
Length of hospital stay, days	3 (1–4)	4 (2–7)	4 (2–8)	<0.0001
Early discharge (72 h)	66.4	38.3	29.2	<0.0001
Discharge destination				
Home	62.5	37.4	32.9	<0.001
SNF	-	19.3	12.3	
Home health care	15.4	19.1	12.8	
Acute rehabilitation	-	2.8	2.2	
Cardiogenic shock	-	3.5	15.0	<0.001
Cardiac arrest	-	2.9	13.0	<0.001
Blood transfusion	7.7	11.2	9.9	0.19
Acute kidney injury	8.2	33.2	32.4	<0.001
Acute heart failure	-	34.7	25.1	<0.0001
In-hospital mortality	-	7.6	24.1	<0.0001
30-day readmission for recurrent ACS	4.9	12.1	28.5	<0.0001
30-day need for intervention (after discharge from index ACS admission)	6.8	4.0	4.0	0.1
30-day heart failure	-	4.1	5.5	0.04
30-day bleeding	-	2.5	-	0.07
30-day mortality	-	15.5	31.4	<0.0001
1-yr mortality	26.0	41.3	51.2	<0.0001
ACS inpatient management				
Invasive approach	30.3	28.5	48.1	<0.001
Drug eluting stenting	—13.9	11.8	21.3	<0.001
Bare metal stenting	-	1.4	6.0	<0.001
Number of vessels treated [*]				
1	80.0	80.4	82.7	0.59
2	16.7	16.6	12.2	
3	-	3.0	5.1	
Number of stents placed [*]				
1	65.6	75.4	73.1	0.16
2	28.1	18.0	14.7	
3	6.3	6.6	12.2	
Coronary angiography without intervention	13.0	13.9	13.8	0.92
Plain old balloon angioplasty alone	-	1.4	7.2	<0.001
Urgent CABG	0.0	0.5	-	0.48
Use of coronary intravascular ultrasound	-	1.2	2.4	0.02
Mechanical circulatory support (IABP, ECMO, Impella)	-	1.4	7.2	<0.001

	Unstable angina (n = 208)	NSTEMI (n = 5,947)	STEMI (n = 586)	p value
Nuclear myocardial perfusion imaging testing	12.5	10.4	3.8	<0.001

Values are median (interquartile range) or %.

Cells with N <10 were suppressed with (–).

CABG = coronary artery bypass grafting; ECMO = extracorporeal membrane oxygenation; IABP = intra-aortic balloon pump; SNF = skilled nursing facility; other abbreviations as in Tables 1 and 2.

*
These are proportions out of patients who had PCI with drug-eluting stent or bare-metal stent. Missing data are <1% for both variables.

Table 4:

Adjusted short outcomes with invasive compared to conservative approach in NST-ACS patients after propensity score matching.

	Conservative	Invasive	Adjusted OR	95% CI	P value
	N=1750	N=1750			
In-hospital mortality	8.4%	4.8%	0.54	0.40–0.72	<0.0001
30-day readmission for ACS	12.7%	10.6%	0.85	0.67–1.06	0.10
30-day need for intervention	6.1%	3.2%	0.50	0.34–0.73	0.0002
30- day mortality	16.9%	8.8%	0.47	0.38–0.58	<0.0001
30-day HF	4.4%	3.2%	0.70	0.47–1.03	0.07
30-day bleeding	2.6%	2.0%	0.72	0.43–1.20	0.22
1 -year mortality	43.8%	29.6%	0.52	0.47–0.63	<0.0001

NST-ACS=Non-ST elevation acute coronary syndrome, OR=Odds ratio, CI=Confidence interval, HF=Heart failure, ACS=Acute coronary syndrome.

Table 5:

Cox regression analysis for long-term outcomes for invasive versus conservative approach in NSTE-ACS patients after inverse probability weigh analysis

Outcome	HR	95% CI	P value
Mortality	0.69	0.66–0.73	<0.0001
Heart failure	0.90	0.81–0.99	0.03
Bleeding	0.88	0.78–0.98	0.03
Need for intervention	1.29	1.16–1.43	<0.0001
Admission with ACS	1.00	0.93–1.09	0.87

NST-ACS=Non-ST elevation acute coronary syndrome, HR=Hazard ratio, CI=Confidence interval, ACS=Acute coronary syndrome