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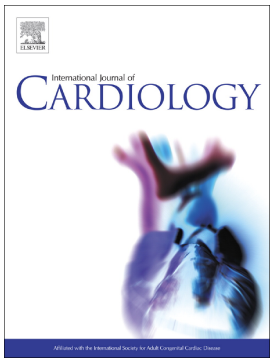

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Outcomes associated with dual antiplatelet therapy after myocardial infarction in patients with aortic stenosis

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Keywords: Aortic stenosis, epidemiology, myocardial infarction, dual anti-platelet therapy

Abstract

Background

Acquired loss of the largest von Willebrand factor multimers is a common hemostatic disturbance in patients with aortic valve stenosis (AS), resulting in impaired platelet adhesion and increased bleeding risk. AS is also associated with atherosclerosis and myocardial infarction (MI). Our aim was to study the clinical outcomes associated with AS in MI patients treated with dual antiplatelet therapy (DAPT) in a nationwide hospital-based register study.

Methods

Based on nationwide hospital discharge registers from Sweden (2005-2010) and Denmark (2005-2015), we calculated 1-year incidence rates and hazard ratios of bleeding, recurrent MI, and all-cause mortality in MI patients with and without AS treated with DAPT. Results from both countries were also combined in a meta-analysis.

Results

We included 50,460 MI patients from Sweden and 50,307 MI patients from Denmark, of which 3% had AS. The bleeding rates (per 100 person-years) in Sweden and Denmark were 3.2 and 3.3 among patients without AS vs. 9.2 and 8.3 among patients with AS. All-cause mortality rates were 7.1 vs. 28.7 in Sweden and 5.8 vs. 30.7 in Denmark among patients without and with AS, respectively. Patients with AS had an increased risk of bleeding, recurrent MI and all-cause mortality. Combined results from both countries were similar for bleeding (hazard ratio 1.59 [0.98-2.59), recurrent MI (1.78 [1.25-2.54]), and all-cause mortality (1.76 [1.26-2.47]).

Conclusion

AS was associated with an increased risk of bleeding, recurrent MI and mortality after MI when treated with DAPT. Individualized selection of antiplatelet therapy may be warranted in this high-risk population.

Introduction

Cardiovascular mortality is a leading cause of death worldwide with an estimated 17.3 million deaths annually (1). Much of the cardiovascular disease burden is due to myocardial infarction (MI) (2). Recognition and treatment of risk factors associated with the atherosclerotic process, together with early revascularization therapy and antiplatelet therapy with dual antiplatelet therapy (DAPT) have resulted in greatly improved outcomes for patients presenting with acute MI (3-4). Although DAPT treatment is associated with improved outcomes (4-6), the antithrombotic effect is offset by increased bleeding risk (8).

Aortic valvular stenosis (AS) is one of the most common valvular disorders in western countries (8-9). AS is mainly a disease of the elderly, with a steeply increasing prevalence with age (8-9). Similar to coronary artery disease, AS is associated with calcific degeneration of the aortic valve leaflets with features of lipid accumulation and inflammation (10-11). The overlap of risk factors between AS and MI is considerable (12). AS therefore also frequently occurs concomitantly with coronary artery disease and MI, but the prognostic implications of having both conditions remain incompletely understood. One particular concern is the bleeding risk associated with AS. A clustering of AS, intestinal angiodysplasia, and bleeding was described by Heyde in the 1950s and has subsequently been referred to as Heyde's syndrome (13). Heyde's observation has been confirmed in several case series, with higher rates of gastrointestinal bleeding in patients with AS compared to controls (14-15). The mechanism has been attributed to, at least in part, an acquired loss of the largest multimers of von Willebrand factor (vWF), a large glycoprotein secreted from the endothelium which is central for platelet adhesion (16-18).

AS have also been associated with a prothrombotic state, likely influenced by flow condition and concurrent atherosclerotic vascular disease (19). An increase in factor XI and activated tissue factor with an elevation in markers of thrombin generation in severe AS have previously been reported with possible implications for the risk of recurrent MI (20-21). The outcomes associated with AS after acute MI in the era of widespread DAPT have not previously been investigated and the risk-benefit profile of DAPT might be different in the presence of vWF abnormalities. We hypothesized that patients with AS would have a higher risk for bleeding events and recurrent MI following MI. The current study aimed to examine the relationship of AS with bleeding, recurrent MI, and all-cause mortality in MI patients treated with DAPT in a large population-based study using hospital-discharge registers in Sweden and Denmark.

Methods

All patients in Sweden and Denmark with a hospital discharge diagnosis of MI and a DAPT prescription were included in the study, using nationwide registries for each country. Inclusion was from 2005 until 2010 in Sweden and 2005 until 2015 in Denmark. Patients were followed for up to 1 year, as DAPT is recommended 1 year after MI by contemporary guidelines (4). Follow-up ended on December 31, 2010 in Sweden and on December 31, 2015 in Denmark. Observational time started 30 days after initial MI to allow subjects time to claim DAPT prescriptions and to possibly undergo delayed revascularization therapy. Prevalent AS was defined as a diagnosis any time up to 30 days after MI, when follow-up started.

The Swedish and Danish National Patient Registries (NPR) were used to identify patients with a first MI, concurrent AS, bleeding requiring hospitalization and recurrent MI. Data on mortality and cause of death were obtained from the national Cause of Death Registry (CDR), which is nationwide in both Sweden and Denmark (22). The NPR includes information on hospital discharge diagnoses of all patients cared for in a hospital setting (23-24). In the study period the NPR also included diagnoses from specialized outpatient clinics. Both Sweden and Denmark have tax-financed healthcare systems with fiscal compensation to the departments based on mandatory reporting of discharge diagnoses. A unique and anonymous serial number based on the personal identification number that all Swedish and Danish citizens receive at either birth or immigration was used to link the NPR and CDR (25). Diagnosis codes were based on WHO's International Classification of Disease (ICD) version 10; found in online Supplementary table 1.

Patients were considered under treatment with various medications if they had claimed a prescription within 90 days of the index event or up to 30 days after the event, in accordance with previous studies (26). Information regarding pharmacotherapy was based on the Danish Registry of Medicinal Product Statistics and the Swedish Pharmaceuticals Registry. Pharmacotherapy is also subsidized by the tax-financed healthcare system and is considered nationwide and accurate.

Cardiovascular diagnoses in these registries have previously been validated and have a high positive predictive value (23,27-28). Most diagnoses of aortic valvular stenosis captured in these registries are based on echocardiographic examination and generally represent moderate to severe valvular disease (27). Comorbidities were identified from discharge diagnoses in the NPR at any time prior to the index event.

In both Sweden and Denmark, MI diagnoses are defined according to European guidelines and international consensus. Both non-ST-elevation and ST-elevation infarction were included in the study. DAPT in combination with coronary revascularization, statins, and anti-ischemic drugs such as beta blockers, nitrates and angiotensin receptor blockers are the recommended treatment for patients presenting with a myocardial infarction (4). During the study period the most common combination for DAPT was acetylsalicylic acid and clopidogrel, but other adenosine diphosphate receptor inhibitors (e.g. ticagrelor or prasugrel) were also included in the Danish analyses (ending in 2015). The addition of oral anticoagulant treatment to DAPT in patients with and without AS was explored separately.

Diagnostic definitions

The main outcomes of the study were bleeding, recurrent MI and all-cause mortality. Bleeding was defined as one of the following ICD-10 codes (non-fatal and fatal): I60, I61, I62, D50, D60, R04, R31, S064-S066, J942, K250, K252, K254, K260, K262, K264, K270, K272, K280, K282, K920, and K922. AS was defined as diagnosis code I35. MI was defined as diagnosis code I21. Recurrent MI was defined as a new diagnosis of MI by diagnosis code I21 or I22 later than 30 days after the primary event including both non-fatal and fatal MIs.

Statistical analysis

Data for Sweden and Denmark were analyzed separately, as data access restrictions did not allow individual-level data to be exported from the official authorities' data servers. MI patients with DAPT were grouped according to presence or absence of AS at baseline and according to concomitant use of warfarin treatment. Treatment was analyzed by the intention to treat principle, i.e., any breaks in treatment were not considered. Kaplan-Meier curves were constructed to visualize unadjusted mortality rates after MI for patients with and without AS in each country. Unadjusted incidence rates (per 100 person-years) of bleeding, recurrent MI and mortality were also calculated for the separate exposure groups. Cox proportional hazards regression analysis was used to calculate hazard ratios, adjusted for potential confounders including age, sex, calendar year, percutaneous interventions and CABG performed within 30 days after index event, treatment with certain drugs (NSAIDs, proton pump inhibitors, beta blockers, statins, calcium blockers, thiazides, loop diuretics, spironolactone, and/or insulin), previous diagnosis of ischemic heart disease, cerebrovascular disease, peripheral arterial disease, liver disease, chronic kidney

disease, peptic ulcer disease, chronic obstructive pulmonary disease, rheumatic disease, atrial fibrillation, cancer, bleeding, and congestive heart failure. Patients without AS and without the use of oral anticoagulants served as the reference group in all analyses. Hazard ratios were also analyzed in random-effects meta-analysis using the R package "metafor" (29).

An independent ethics committee approved the study in Sweden. In Denmark, no such approval is necessary for unidentifiable data, but the study was approved by the Danish data protection agency (reference number 2007-58-0015; internal reference GEH-2014-013 I-suite no. 02731). A two-sided p-value <0.05 was considered statistically significant for all analyses. Statistical analyses were performed using SAS versions 9.2 and 9.4 (SAS Institute, Cary, NC) and R version 3.3.2.

Results

A total of 50,460 MI patients (mean age 70±12 years, 36% women) from Sweden and 50,307 MI patients (mean age 66±13 years, 33% women) from Denmark were included in the current study (Table 1). Concurrent AS was present in 3% in both countries, comprising 1287 patients in Sweden and 1525 patients in Denmark. In Sweden 12% and 16% had concurrent atrial fibrillation (in individuals without and with AS, respectively). In the Danish population 8% and 22% were diagnosed with atrial fibrillation. A large proportion of individuals were treated with statins and beta-blockers after MI in both countries. RAAS-inhibitors were also used frequently.

Revascularization therapy within 30 days was performed in 60% of the Swedish population and 75% in the Danish population without AS. For patients with AS revascularization therapy was less common; only 28% in Sweden and 40% in Denmark were treated with either percutaneous coronary intervention (PCI) or coronary artery bypass grafting (CABG) within 30 days after MI. During follow-up 106 (8%) with AS were censored due to valve replacement surgery (mean time after follow-up to surgery 78, SD: 77 days) in Sweden and 197 patients (13%) in Denmark (mean time to surgery 78, SD:85 days).

Bleeding rates

The bleeding rates (per 100 person-years) in Sweden and Denmark were 3.2 and 3.3 among patients without AS vs. 9.2 and 8.3 among patients with AS (Table 2). The increased risk for bleeding among patients with AS persisted after adjustments in Sweden (hazard ratio [HR]: 2.04, 95% confidence interval [CI]=1.61-2.59, Table 3) but not in Denmark (HR: 1.24, 95% CI=0.98-1.57). In the combined analysis with

data from both countries there was a trend towards increased bleeding risk but it was not statistically significant (Figure 1, HR: 1.59, 95% CI=0.98-2.59). In a sensitivity analysis, patients with AS who had revascularization performed the results remained almost identical with an increased risk of bleeding events in Sweden but not in Denmark (Supplementary Table 1)

Recurrent MI rates

For patients without AS recurrent MI rates per 100 person-years were 8.7 in Sweden and 8.2 in Denmark. For patients with AS corresponding rates were 29.5 and 23.9, respectively. Patients with AS also had a significantly higher risk for recurrent MI in both countries in the adjusted model (Sweden, HR: 2.13, 95% CI=1.85-2.44, Denmark HR: 1.48, 95% CI=1.28-1.71). Combining results from both countries resulted in an HR of 1.78 (95% CI=1.25-2.54). In both countries, patients who underwent percutaneous revascularization had similar findings (HR: 2.19, 95% CI 1.58-3.03 and 1.62, 95% CI=1.24-2.12 for patients with DAPT and AS).

Mortality rates

Mortality analyses indicated a substantially higher mortality for patients with aortic stenosis compared to patients without aortic stenosis. All-cause mortality rates are shown in Table 2. Patients with bleeding events had higher subsequent mortality rates than those without bleeding events; the mortality rates were 49.1 (95% CI 43.3-55.7) and 21.7 (95% CI 19.4-24.3) vs 7.7 (95% CI 7.4-7.9) and 6.1 (95% CI 5.9-6.3) per 100 person-years in Sweden and Denmark respectively. Mortality rates after a bleeding event were 73.5 (95% CI 51.7-104.6) in Sweden and 34.2 (95% CI 25.7-

45.6) in Denmark for those with aortic stenosis vs 46.8 (95% CI 40.9-53.9) and 20.4 (95% 18.0-23.0) per 100 person-years in patients without aortic stenosis.

In the adjusted analyses patients with AS had approximately 2-fold increased risk of mortality in Sweden (HR: 2.09, 95% CI=1.85-2.35) and a 1.5-fold increased mortality risk in Denmark (HR: 1.48, 95% CI=1.32-1.67) compared to patients without AS. Combined results from both countries rendered an HR of 1.76 (95% CI=1.26-2.47). The risk for all-cause mortality for patients with AS was increased in the subgroup who underwent PCI in both Sweden (HR: 2.35, 95% CI 1.54-3.59) and Denmark (2.17 95% CI=1.71-2.75).

Oral anticoagulant therapy

Patients receiving oral anticoagulant treatment in addition to DAPT had higher bleeding rates; 5.6 and 8.4 in Sweden and Denmark, respectively. Recurrent MI and all-cause mortality were also more common, with incidence rates of 10.1 and 12.8 for recurrent MI and 7.8 and 11.2 for all-cause mortality in Sweden and Denmark. After combining the results from both countries patients without AS on DAPT and receiving warfarin therapy had an increased risk for bleeding (HR 1.48, 95% CI=1.27-1.73). Patients with AS receiving both DAPT and oral anticoagulant therapy had an increased risk for bleeding (HR 2.47, 95% CI=1.56-3.90), recurrent MI (HR 1.73, 85% CI=1.22-2.45) and all-cause mortality (HR 1.34 95% CI=1.00-1.80), compared with individuals without AS not receiving oral anticoagulant therapy.

Sensitivity analysis

Due to potential changes in PCI techniques and safety and efficacy of antiplatelet therapy, we also tested for interactions between calendar year and PCI in the cohorts. P-values for interactions were 0.36 (Sweden) and 0.84 (Denmark) for bleeding, 0.52 (Sweden) and 0.25 (Denmark) for recurrent myocardial infarction, and 0.95 (Sweden) and 0.18 (Denmark) for all-cause mortality, respectively.

Sources of bleeding

Gastrointestinal bleeding was most common bleeding site for both patients with AS (34.5%) and without AS (31.0%). Hematuria (18.9% and 22.0% respectively) and epistaxis (12.1% and 13.5%) were also common sites of bleeding in these patients. Cerebral bleeding events were rare in both patient groups (3.9% for AS patients and 4.3%). Iron-deficiency anemia due to chronic blood loss without a specified site of bleeding was common (20.9% for AS patients and 16.1% for non-AS patients).

Discussion

In the current study, including nationwide data from two countries, we observed that AS was associated with an increased risk of bleeding after MI in Sweden but not in Denmark, but also a significantly increased risk for both recurrent MI and all-cause mortality in both countries. The differences remained after adjustments for age, sex and common comorbidities and were robust when pooling data from both countries.

Patients with AS were older and had a higher burden of comorbid conditions such as diabetes, heart failure and previous ischemic heart disease. It is possible that they represent a group with more advanced cardiovascular and atherosclerotic disease, which in part could explain some of the findings in the current study. However, the observations remained after adjustment for both age and comorbidity, suggestive that factors related to AS itself might confer an increased risk. AS has previously been shown to be associated with an increased bleeding risk due to loss of large vWF multimers with impaired hemostasis as a result (16). Impaired hemostasis mainly occur in subjects with severe AS and less frequently in cases with mild to moderate disease. Previous validation of AS cases in the Swedish registers have found that a diagnosis of AS mainly represent moderate to severe disease implicating acquired von Willebrand disease as one of the potential mechanisms behind the results observed in this study. It is possible that the lower risk estimates in the Danish population might reflect different diagnostic traditions with relatively milder disease being diagnosed in Denmark. Interestingly, the proportion of bleeding events due to gastrointestinal or iron-deficiency anemia (most likely due to gastrointestinal bleeding) were higher in patients with AS, in line with current understanding of the pathophysiology behind AS related bleeding.

In patients with AS, it is possible that reducing the time of DAPT could prove beneficial. To our knowledge, this is the first report on the worse clinical outcomes associated with AS in an era of modern aggressive antiplatelet therapy.

Increased risk for recurrent MI

Although we observed that the bleeding risk was increased for patients with AS, these patients were also at a higher risk for recurrent MI, consistent with previous studies which have reported a procoagulative state for some patients with AS (20).

Our findings thus highlight the complexity of antiplatelet therapy in this high-risk population, and suggest that individualized decisions on selection of antiplatelet inhibitors guided by vWF analysis may be warranted. However, additional studies are needed to characterize the prevalence of vWF abnormalities in AS patients with moderate and severe AS, and comparisons of different antiplatelet therapies in this context.

AS results in obstruction of the outflow tract of the left ventricle, increasing strain on the left ventricle. In combination with comorbid conditions such as anemia, infection or trauma, this increasing strain may result in insufficient oxygen delivery to myocardial cells resulting in a strain-induced form of MI not necessarily due to coronary obstruction, referred to as MI type 2. AS patients are at increased risk for MI type 2 compared to patients without AS, which could contribute to the higher risk for recurrent MI and lower use of revascularization observed in this study. Revascularization therapy within 30 days for AS patients was only utilized in 28% and 40% in Sweden and Denmark, respectively. Although the restriction of our study population to patients with DAPT is likely to results in exclusion of a number of

patients with MI type 2, to whom DAPT is not uniformly prescribed, our findings of high bleeding rates further highlight the risks of DAPT in this context. As already shown in previous studies, bleeding events were associated with higher subsequent mortality rates (30). There were no significant discrepancies in findings between the group who had revascularization performed and the main analysis, supporting the validity of the findings.

Similar findings were observed in both countries, however, small differences between the countries were noted, and previous ischemic heart disease was strikingly more common in Denmark than in Sweden. This might reflect different risk factor exposure in the two countries and when comparing the actual rates between the countries caution is advised.

Added treatment of oral anticoagulants enhanced the bleeding risk for patients with AS quite substantially. A small but statistically significant increase in bleeding risk was noticed in the population without AS. The added bleeding risk associated with oral anticoagulant therapy was more pronounced for patients with AS compared to patients without AS when combining data from both countries. The results from the combined model suggests that the loss of vWF multimers have an additive effect when antiplatelet therapy is combined with anticoagulant therapy, as would be expected. However, there were few AS patients receiving both oral anticoagulants and DAPT.

Study limitations

This study was based on nationwide registries and as such has some inherent limitations. For example, echocardiographic data was unavailable which leads to uncertainty in diagnostic accuracy. The diagnosis of both AS and MI were based upon a registry diagnosis requiring hospitalization which could potentially lead to missed cases. Nevertheless, acute myocardial infarction is typically a medical emergency and these patients are highly unlikely to be treated for in a non-hospital setting. After MI, patients undergo rigorous examinations, normally including both echocardiography and coronary angiography. In both Sweden and Denmark these patients are generally treated in a cardiology ward. Clinically significant AS is likely to be diagnosed upon routine echocardiographic examination post-MI, resulting in a limited proportion of undiagnosed AS but also an increased probability of clinically insignificant cases of AS. Bleeding is traditionally considered difficult to evaluate in register studies. The few validation studies which have evaluated bleeding events however have shown a high positive predictive value in Scandinavian registers and that bleeding events are unlikely to be miss-diagnosed (31). As with all observational studies, residual confounding cannot be ruled out. The meta-analysis comparing data from registries gathered in two different countries and during different time periods could possibly contain some heterogeneity in the population and therefore the effect estimates and should be interpreted with some caution. Despite these limitations, there were also several strengths in our nationwide data from two countries. For example, the coverage in these registries is exceptional and the validity of the cardiovascular diagnoses has proven to be high (23,27-28).

Conclusions

AS is associated with a substantially increased occurrence of recurrent MI and all-cause mortality after MI. Bleeding events were numerically more common in patients

with AS and a statistically significant increased risk was found in the adjusted analysis in Sweden, but not in Denmark. Careful evaluation and monitoring of these patients are recommended and the risk-benefit of DAPT might be different for these patients after MI. Prospective studies of vWF abnormalities and randomized studies of antiplatelet regiments are needed to determine optimal therapy in patients with AS.

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Figure legends

Figure 1. Forest plot illustrating the results from meta-analysis, combining results from both countries. AS = Aortic stenosis. DAPT = Dual antiplatelet therapy.

Table 1. Patient characteristics in Denmark and Sweden separated into patients with or without concurrent AS.

	Denmark		Sweden	
	No Aortic Stenosis	**Aortic stenosis**	**No Aortic Stenosis**	**Aortic stenosis**
N	48782 (97%)	1525 (3%)	49173 (97%)	1287 (3%)
Age	66 (13)	79 (10)	70 (12)	76 (11)
Male sex	68%	51%	64%	56%
Diabetes	11%	17%	15%	20%
Previous IHD	46%	54%	26%	39%
Congestive heart failure	14%	31%	16%	23%
Kidney disease	2%	6%	3%	4%
Prior bleeding	3%	8%	4%	6%
Atrial fibrillation	8%	22%	12%	16%
COPD	6%	12%	4%	5%
Cerebrovascular disease	5%	12%	7%	9%
Treatment				
PCI within 30 days post-MI	71%	38%	58%	26%
CABG within 30 days post-MI	4%	2%	2%	2%
Use of oral anticoagulants	5%	10%	3%	5%
Use of statins	90%	73%	85%	75%
Use of beta blockers	84%	78%	90%	88%
Use of RAAS-inhibitors	50%	50%	74%	68%
Use of insulin	4%	6%	8%	12%
Use of loop diuretics	20%	54%	27%	49%

Table 1. Patient characteristics. N = Number of subjects. IHD = Ischemic heart disease. COPD = Chronic obstructive pulmonary disease. PCI = Percutaneous coronary intervention. CABG = Coronary artery bypass grafting. RAAS = Renin-angiotensin-aldosterone system.

Table 2. Association with all-cause mortality, recurrent MI and bleeding after myocardial infarction in patients with DAPT comparing patients with and without aortic stenosis.

	All-cause mortality		**Recurrent MI**		**Bleeding**	
Events / person-years (PY)	Sweden	Denmark	Sweden	Denmark	Sweden	Denmark
DAPT, no AS	2,885 / 40,868	2,495 / 42,755	3,314 / 38,246	3,267 / 40,211	1,254 / 39,183	1,367 / 41,305
DAPT with oral anticoagulants, no AS	106 / 1,366	234 / 2,086	123 / 1,214	203 / 1,584	69 / 1,236	135 / 1,613
DAPT and AS	263 / 916	344 / 1,121	226 / 767	215 / 898	75 / 817	77 / 928
DAPT with oral anticoagulants, AS	8 / 44	36 / 112	8 / 41	26 / 79	3 / 43	17 / 76
Incidence rate (events / 100 PY)						
DAPT, no AS	7.1 (6.8-7.3)	5.8 (5.6-6.1)	8.7 (8.4-9.0)	8.2 (7.9-8.4)	3.2 (3.0-3.4)	3.3 (3.1-3.5)
DAPT with oral anticoagulants, no AS	7.8 (6.4-9.4)	11.2 (9.9-12.8)	10.1 (8.5-12.1)	12.8 (11.2-14.7)	5.6 (4.4-7.1)	8.4 (7.1-9.9)
DAPT and AS	28.7 (25.4-32.4)	30.7 (27.6-34.1)	29.5 (25.9-33.6)	23.9 (20.9-27.4)	9.2 (7.3-11.5)	8.3 (6.6-10.4)
DAPT with oral anticoagulants, AS	18.0 (9.0-36.1)	32.2 (23.2-44.6)	19.6 (9.8-39.3)	32.8 (22.3-48.1)	7.1 (2.3-21.9)	22.3 (13.9-35.9)

Table 2. DAPT: Dual-antiplatelet therapy, AS: Aortic valvular stenosis, MI: Myocardial infarction, PY: Person-years.

Table 3. Adjusted hazard ratios for all-cause mortality, recurrent MI and bleeding after myocardial infarction in patients with DAPT comparing patients with and without aortic stenosis.

	All-cause mortality		**Recurrent MI**		**Bleeding**	
	Sweden	Denmark	Sweden	Denmark	Sweden	Denmark
DAPT, no AS	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)	1.00 (reference)
DAPT with oral anticoagulants, no AS	0.97 (0.80-1.18)	1.07 (0.92-1.24)	1.09 (0.91-1.31)	1.10 (0.94-1.28)	1.43 (1.11-1.84)	1.51 (1.23-1.85)
DAPT and AS	2.09 (1.85-2.35)	1.48 (1.32-1.67)	2.13 (1.85-2.44)	1.48 (1.28-1.71)	2.04 (1.61-2.59)	1.24 (0.98-1.57)
DAPT with oral anticoagulants, AS	1.67 (0.90-3.12)	1.26 (0.90-1.77)	1.75 (0.87-3.50)	1.73 (1.16-2.57)	1.73 (0.56-5.38)	2.65 (1.61-4.36)

Table 3. DAPT: Dual-antiplatelet therapy, AS: Aortic valvular stenosis, MI: Myocardial infarction, Adjusted for age, sex, percutaneous interventions and CABG performed within 30 days after index event, treatment with NSAIDs, proton pump inhibitors, beta blockers, statins, calcium blockers, thiazides, loop diuretics, spironolactone, and/or insulin, previous diagnosis of ischemic heart disease, cerebrovascular disease, peripheral arterial disease, liver disease, chronic kidney disease, peptic ulcer disease, chronic obstructive pulmonary disease, rheumatic disease, atrial fibrillation, cancer, bleeding, and congestive heart failure.

Outcomes associated with dual antiplatelet therapy after myocardial infarction in patients with aortic stenosis

Highlights

Bleeding was more common in AS patients treated with DAPT after MI

Recurrent MI and all-cause mortality were more frequent in AS patients

Patients with AS represents a group with high risk after incident MI

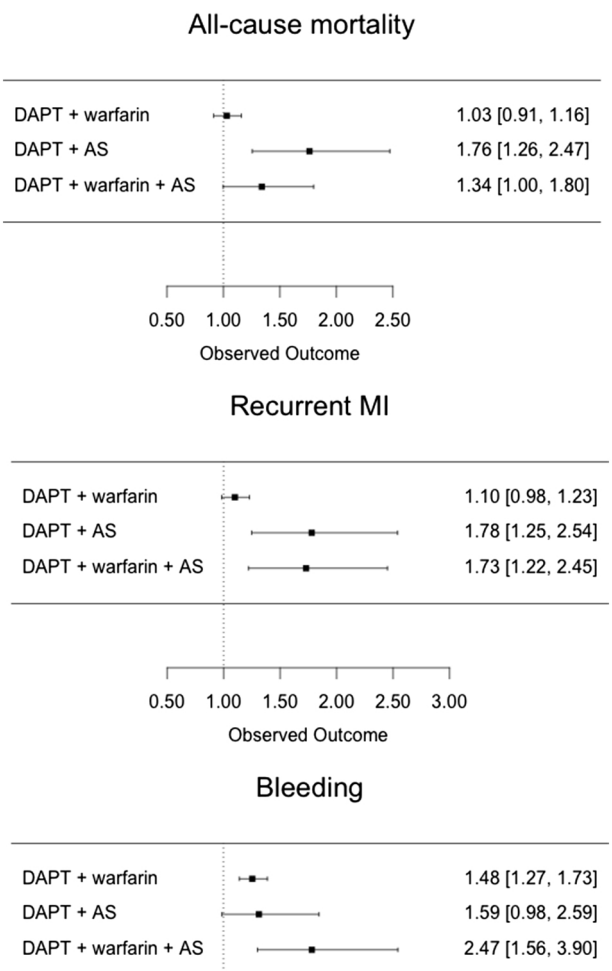
All-cause mortality
DAPT + warfarin
DAPT + AS
DAPT + warfarin + AS
1.03 [0.91, 1.16]
1.76 [1.26, 2.47]
1.34 [1.00, 1.80]
0.50 1.00 1.50 2.00 2.50
Observed Outcome
Recurrent MI
DAPT + warfarin
DAPT + AS
DAPT + warfarin + AS
1.10 [0.98, 1.23]
1.78 [1.25, 2.54]
1.73 [1.22, 2.45]
0.50 1.00 1.50 2.00 2.50 3.00
Observed Outcome
Bleeding
DAPT + warfarin
DAPT + AS
DAPT + warfarin + AS
1.48 [1.27, 1.73]
1.59 [0.98, 2.59]
2.47 [1.56, 3.90]
0.00 1.00 2.00 3.00 4.00
Observed Outcome

Figure 1