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Guideline-directed medical therapy for secondary prevention after coronary artery bypass grafting in patients with depression ☆

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ABSTRACT

Background: We hypothesized that depressed patients would have lower use of guideline-directed medical therapy for secondary prevention of cardiovascular events following coronary artery bypass grafting (CABG).
Methods: We included all patients who underwent primary isolated CABG in Sweden between 2006 and 2008. We cross-linked individual level data from national Swedish registers. Preoperative depression was defined as at least one antidepressant prescription dispensed before surgery. We defined medication use as at least two dispensed prescriptions in each medication class (antiplatelet agents, beta-blockers, angiotensin-converting enzyme inhibitors (ACEI)/angiotensin II receptor blocker (ARB), and statins) within a rolling 12 month period. We calculated adjusted risk ratios (RR) for the use of each medication class, and for all four classes, after one and four years, respectively.
Results: During the first year after CABG, 93% of all patients (n = 10,586) had at least two dispensed prescriptions for an antiplatelet agent, 68% for an ACEI/ARB, 91% for a beta-blocker, and 92% for a statin. 57% had prescriptions for all four medication classes. After four years (n = 4034), 44% had filled prescriptions for all four medication classes. Preoperative depression was not significantly associated with a lower use of all four medication classes after one year (RR 0.98, 95% confidence interval (CI) 0.93–1.03) or after four years (RR 0.97, 95% CI 0.86–1.09).
Conclusions: Preoperative depression was not associated with lower use of guideline-directed medical therapy for secondary prevention after CABG. These findings suggest that the observed higher mortality following CABG among depressed patients is not explained by inadequate secondary prevention medication.

1. Introduction

Prior research has shown that depression is common in patients with coronary artery disease and that it is independently associated with increased cardiovascular morbidity and mortality [1,2]. Approximately 30 to 45% of all patients with coronary artery disease are suffering from clinically significant depression [3]. Optimal secondary prevention medications after coronary artery bypass grafting (CABG) include antiplatelet agents, statins, beta-blockers and angiotensin-converting inhibitors (ACEI) and are important to reduce the risk for recurrent cardiovascular events [4]. Clinical practice guidelines provide information and recommendations about patient lifestyle and medical therapy after CABG [5,6]. Because depression has been established as a strong and important independent risk factor for recurrent cardiovascular events and mortality in patients with coronary heart disease, the use of evidence-based secondary prevention is even more essential among these patients. However, the coexistence of depression and coronary heart disease may complicate several aspects of secondary prevention for coronary heart disease. Psychosocial risk factors such as smoking, unhealthy food choice, less physical exercise tend to accumulate in the same individuals and behavioral phenomena common in depressed patients, e.g. social isolation, a feeling of hopelessness and little belief in that anything is worthwhile, may act as barriers to secondary preventive efforts [7,8]. Based on these observations, it is not unlikely that depressed patients could face an increased risk of receiving less than optimal secondary prevention medications. Lower use of secondary prevention medications may partly explain the higher mortality observed in patients with depression and coronary heart disease. The hypothesis

☆ All authors take responsibility for all aspects of the reliability and freedom from bias of the data presented and their discussed interpretation.

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was that depressed patients would have lower use of medications recommended for secondary prevention of cardiovascular events following CABG than patients without preoperative depression. The primary aim was to analyze the association between preoperative depression and guideline-directed medical therapy after CABG. A secondary aim was to investigate possible changes in medication use over time. We also investigated possible gender differences in secondary prevention medication use.

2. Methods

2.1. Study design

We performed a nationwide population-based cohort study. The study complied with the Declaration of Helsinki and was approved by the regional Human Research Ethics Committee in Stockholm, Sweden.

2.2. Study population

We identified all patients who underwent CABG in Sweden between 2006 and 2008 from the SWEDEHEART (Swedish Web-system for Enhancement and Development of Evidence-based care in Heart disease Evaluated According to Recommended Therapies) registry [9]. We excluded patients who had undergone previous cardiac surgery, and patients who had concomitant procedures in addition to CABG. We also excluded patients who underwent surgery within 24 h from decision to operate. Finally, we excluded patients who died within one year of surgery, because the outcome of interest was dispensed prescriptions after a minimum of one year of follow-up. The final study population consisted of patients who underwent primary isolated non-emergent CABG in Sweden between 2006 and 2008.

2.3. Data sources

The Swedish personal identity number [10] was used by The National Board of Health and Welfare to cross-link individual level data from national Swedish registers to assemble the study database. Baseline patient characteristics were obtained from SWEDEHEART [9], The National Patient Register, The Prescribed Drug Register and The Total Population Register (Statistics Sweden). The National Patient Register covers all diagnoses for all patients hospitalized in Sweden from 1987 [11,12]. The Prescribed Drug Register [13] was used to identify patients using antidepressants (Anatomical Therapeutic Chemical [ATC] code N06A) and who had at least one dispensed prescription with ATC-code N06A before the date of surgery. Patients were divided into an exposed group (preoperative antidepressant use) and an unexposed group (no preoperative antidepressant use).

2.4. Outcome measures

We identified patients using the personal identity number who had at least two dispensed prescriptions with the following ATC-codes: B01AC (antiplatelet agents), C09 (ACEI/angiotensin receptor blockers (ARB)), C07 (beta-blockers), and C10AA (statins) from the national Prescribed Drug Register [13]. The Prescribed Drug Register contains information about the ATC-code and the date of dispensing covering the whole population of Sweden since July 2005. The primary outcome measure was medication use defined as at least two dispensed prescriptions in each ATC group (medication class) after at least one year of follow-up, and at least four years of follow-up, respectively.

2.5. Statistical analyses

To describe baseline characteristics means and standard deviations were used for continuous variables and frequencies and percentages for categorical variables. We used modified Poisson regression [14] with a robust estimator of variance to calculate risk ratios (RR) for the use of each medication class for depressed patients with non-depressed patients as reference category. We reported unadjusted and multivariable adjusted RR with 95% confidence intervals (CI). The following variables were included in the full multivariable model: age (continuous variable), sex, current smoking (no/yes), atrial fibrillation (no/yes), diabetes mellitus (no/yes), hyperlipidemia (no/yes), hypertension (no/yes), chronic obstructive pulmonary disease (no/yes), peripheral vascular disease (no/yes), prior myocardial infarction (no/yes), prior stroke (no/yes), left ventricular ejection fraction (normal, moderate, or poor), and preoperative heart failure (no/yes). We also analyzed the distribution of medication class and medication use in men and women separately. Finally, we investigated the time trend in secondary prevention medication by comparing the distribution of medication class for patients who underwent surgery in 2006 to that of patients who underwent surgery during 2008.

2.6. Missing data

Data were missing for some variables: diabetes mellitus (2.8%), current smoking (13%), hyperlipidemia (10%), hypertension (10%), peripheral vascular disease (0.9%), and preoperative left ventricular function (0.9%). We used multiple imputation [15] to handle missing data and imputed 50 datasets. All multivariable analyses were performed on the imputed data.

Stata version 13.0 (StataCorp LP, College Station, TX) was used for all data management and statistical analysis.

3. Results

From the SWEDEHEART registry 14,032 patients who underwent CABG between January 2006 and December 2008 were identified. We excluded 227 patients who had previous heart surgery, 2261 patients who had another cardiac procedure than isolated CABG, 660 patients who were operated within 24 h from decision, and 298 patients who had a shorter follow-up time than one year. The final study population included 10,586 patients (1132 depressed and 9454 non-depressed) who underwent primary isolated non-emergent CABG. The baseline characteristics are presented in Table 1. Female sex, current smoking,

Table 1
Characteristics of the study population.

	All patients	Antidepressant use	
		No	Yes
Number of patients	10,586	9454	1132
Percent of study population	100	89	11
Age (years)	67.1 (9.2)	67.3 (9.1)	65.2 (9.4)
Female sex (%)	20	19	34
Estimated GFR (mL/min/1.73 m^2)	82 (25)	82 (25)	83 (24)
Diabetes mellitus (%)	24	23	33
Atrial fibrillation (%)	3	3	2
Hypertension (%)	59	58	62
Hyperlipidemia (%)	60	59	64
Peripheral vascular disease (%)	8	8	10
Current smoking (%)	18	17	28
COPD (%)	6	6	10
Prior myocardial infarction (%)	46	45	47
Prior heart failure (%)	3	3	4
Prior stroke (%)	5	5	10
Left ventricular function			
Ejection fraction >50% (%)	71	71	70
Ejection fraction 30–50% (%)	25	25	26
Ejection fraction <30% (%)	4	4	4

GFR = glomerular filtration rate, CABG = coronary artery bypass grafting, COPD = chronic obstructive pulmonary disease. Age and GFR are given as means with standard deviations. All other values are percentages.

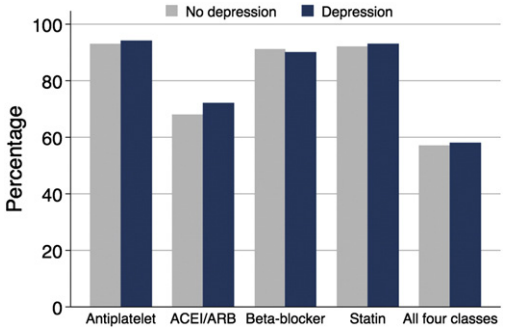

Fig. 1. Distribution of medication use one year after surgery in 10,586 patients who underwent primary isolated CABG between 2006 and 2008 in Sweden. ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CABG = coronary artery bypass grafting.

a history of stroke, and diabetes were more common in patients with depression.

3.1. Medication use

The distribution of secondary prevention medications after one year of follow-up is shown in Fig. 1. During the first year after CABG, 93% of all non-depressed patients had at least two dispensed prescriptions for an antiplatelet agent, 68% for an ACEI/ARB, 91% for a beta-blocker, and 92% for a statin. Fifty-seven percent of all non-depressed patients had prescriptions for all four medication classes. Among depressed patients 94% had at least two dispensed prescriptions for an antiplatelet agent, 72% for an ACEI/ARB, 90% for a beta-blocker, and 93% for a statin. Fifty-eight percent of all depressed patients had prescriptions for all four medication classes. During the fourth year after CABG, compliance was generally lower (Fig. 2). Among non-depressed patients, 44% used all four medication classes, compared to 46% among depressed patients.

Unadjusted and multivariable adjusted associations between depression and guideline-directed medical therapy for secondary prevention (antiplatelet agents; ACEI/ARB; beta-blockers; statins and all four classes) after a minimum of one year of follow-up are shown in Table 2. After multivariable adjustment, there was no significant association between depression and all four classes of guideline-directed medical therapy for secondary prevention (RR 0.98, 95% CI: 0.93 to 1.03). The corresponding adjusted associations between depression and guideline-directed medical therapy after a minimum of four years of follow-up are shown in Table 3. After multivariable adjustment, there was no significant association between depression and all four classes of guideline-directed medical therapy for secondary prevention (RR 0.97, 95% CI: 0.86 to 1.09) four years after surgery.

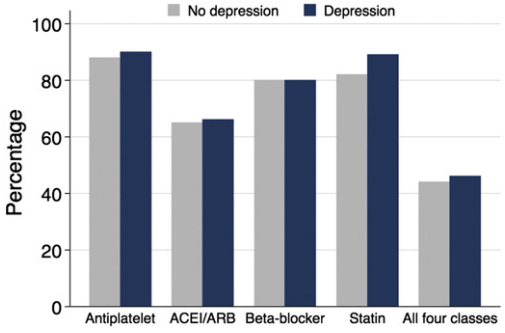

Fig. 2. Distribution of medication use four years after surgery in 4034 patients who underwent primary isolated CABG between 2006 and 2008 in Sweden. ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CABG = coronary artery bypass grafting.

Table 2
Crude and multivariable adjusted associations between antidepressant use and guideline-directed medical therapy for secondary prevention in 10,586 patients after CABG between 2006 and 2008 in Sweden. Risk ratios (95% confidence interval).

	Antidepressant use	
	No[a]	Yes
Number of patients	9454	1132
Antiplatelet agent		
Unadjusted	1.00	1.00 (0.99–1.02)
Multivariable adjusted[b]	1.00	1.00 (0.98–1.02)
ACEI/ARB		
Unadjusted	1.00	1.06 (1.02–1.10)
Multivariable adjusted[b]	1.00	1.02 (0.98–1.06)
Beta-blocker		
Unadjusted	1.00	0.99 (0.97–1.01)
Multivariable adjusted[b]	1.00	0.99 (0.97–1.01)
Statin		
Unadjusted	1.00	1.00 (0.99–1.02)
Multivariable adjusted[b]	1.00	1.00 (0.99–1.02)
All four classes		
Unadjusted	1.00	1.03 (0.97–1.08)
Multivariable adjusted[b]	1.00	0.98 (0.93–1.03)

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker.
[a] Reference category.
[b] Multivariable adjustment was made for age, gender, current smoking, atrial fibrillation, diabetes mellitus, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease, prior myocardial infarction, prior stroke, left ventricular ejection fraction, and preoperative heart failure.

3.2. Compliance to guideline-directed medical therapy during four years after surgery

Adequate compliance was defined as at least two filled prescriptions for each medication class for every rolling 12 months period during a minimum of four consecutive years. In other words, patients who was on continuous treatment with an antiplatelet agent, an ACEI/ARB, a beta-blocker, and a statin during at least four consecutive years after surgery were deemed adequately compliant to guideline-directed medical therapy. Among a total of 4034 patients with a minimum of four years of follow-up, 32% non-depressed, and 32% depressed, had adequate compliance. Adequate compliance was similar in depressed and non-depressed patients after multivariable adjustment (RR 0.91, 95% CI: 0.77 to 1.07).

3.3. Results stratified by gender

The distribution of medication use and multivariable-adjusted RR (95% CI) for guideline based medication use associated with antidepressant use are shown in Table 4. After multivariable adjustment, there was

Table 3
Adjusted[a] associations between antidepressant use and guideline-directed medical therapy for secondary prevention in 4034 patients four years after CABG. Risk ratios (95% confidence interval).

	Antidepressant use	
	No[b]	Yes
Number of patients	3698	336
Antiplatelet agent	1.00	1.01 (0.97–1.05)
ACEI/ARB	1.00	0.97 (0.90–1.05)
Beta-blocker	1.00	0.99 (0.94–1.05)
Statin	1.00	1.08 (1.03–1.12)
All four classes	1.00	0.97 (0.86–1.09)
All four classes during four consecutive years	1.00	0.91 (0.77–1.07)

ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker.
[a] Multivariable adjustment was made for age, gender, current smoking, atrial fibrillation, diabetes mellitus, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease, prior myocardial infarction, prior stroke, left ventricular ejection fraction, and preoperative heart failure.
[b] Reference category.

Table 4
Distribution of medication use and multivariable-adjusted risk ratios (95% confidence intervals) for guideline-directed medical therapy associated with antidepressant use in 10,586 patients who underwent primary isolated CABG between 2006 and 2008 in Sweden stratified by gender.

	Men N = 8447		Women N = 2139	
	Antidepressant use		Antidepressant use	
	No[a]	Yes	No[a]	Yes
Distribution (%)				
Antiplatelet agent	93	94	94	94
ACEI/ARB	67	72	71	72
Beta-blocker	91	91	93	89
Statin	92	93	93	92
All four classes	56	60	58	58
Risk ratio (95% CI) [b]				
Antiplatelet agent	1.00	1.00 (0.98–1.02)	1.00	1.00 (0.97–1.03)
ACEI/ARB	1.00	1.03 (0.98–1.08)	1.00	1.00 (0.94–1.07)
Beta-blocker	1.00	1.00 (0.97–1.02)	1.00	0.97 (0.93–1.00)
Statin	1.00	1.01 (0.99–1.03)	1.00	1.00 (0.97–1.03)
All four classes	1.00	0.99 (0.93–1.05)	1.00	0.97 (0.88–1.06)

CI = confidence interval, ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker.
[a] Reference category.
[b] Multivariable adjustment was made for age, current smoking, atrial fibrillation, diabetes mellitus, hyperlipidemia, hypertension, chronic obstructive pulmonary disease, peripheral vascular disease, prior myocardial infarction, prior stroke, left ventricular ejection fraction, and preoperative heart failure.

no significant association between depression and all four classes of guideline-directed medical therapy for secondary prevention in neither men (RR 0.99, 95% CI: 0.93 to 1.05) or women (RR 1.00, 95% CI: 0.97 (0.88–1.06)).

3.4. Time trends in medication use

Medication use for patients going through surgery in 2006 compared to 2008 is shown in Fig. 3. Antiplatelet agent and beta-blocker use was similar for patients going through surgery in 2006 as compared to those who underwent surgery in 2008. During the same time period, a small increase in the use of ACEI/ARB and statins was noted.

4. Discussion

The main finding in this nation-wide population-based cohort study of 10,586 patients with coronary heart disease who underwent primary isolated non-emergent CABG from 2006 to 2008 was that preoperative depression was not associated with lower use of guideline-directed medical therapy for secondary prevention of cardiovascular events. Secondary prevention medications were similar between men and women, and ACEI/ARBs and statins were the only medication classes where a small increase in use was noted during the study period. Guideline-directed medical therapy for secondary prevention in patients with coronary heart disease is important, because approximately half the decrease in deaths from coronary heart disease during 1980–2000 in the United States could be attributable to evidence-based medical therapies [4].

Several studies have investigated the medication use for secondary prevention in patients with coronary heart disease [16–18]. However, the use of guideline-directed medical therapy for secondary prevention medications after CABG in patients with depression has not been thoroughly explored.

The use of guideline-directed medical therapy was studied in European patients with acute coronary syndromes who underwent PCI [17]. Despite common management guidelines [6], a large variation in the use of guideline-directed medical therapy was found between the

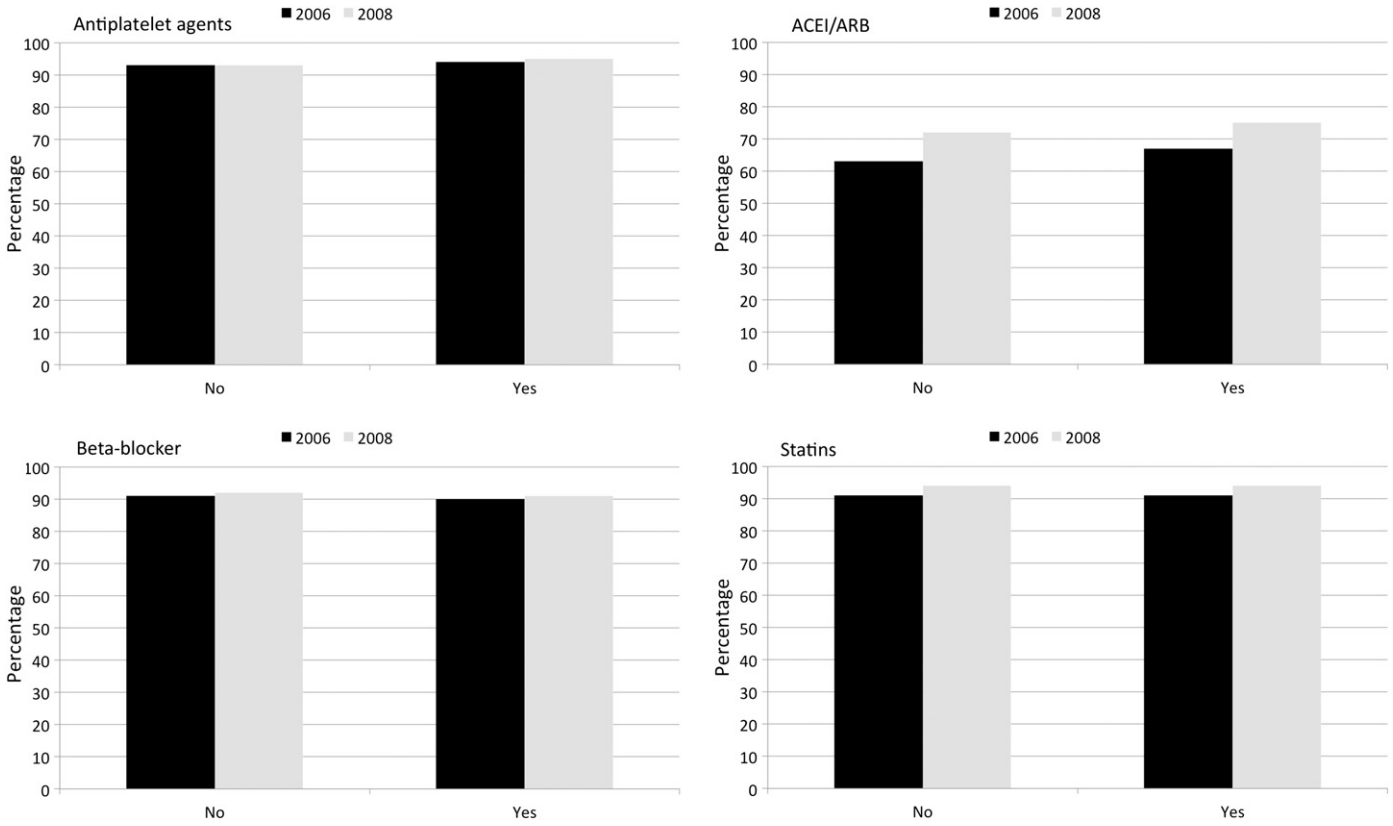

Fig. 3. Distributions of medication use in patients with or without depression who underwent CABG in 2006 compared to 2008. ACEI = angiotensin-converting enzyme inhibitor, ARB = angiotensin II receptor blocker, CABG = coronary artery bypass grafting.

different countries. In the Nordic countries, the use of statins was 86%, beta-blockers 82%, ACEI 64%, and dual antiplatelet therapy 58% after one year. In our study, the guideline-recommended medication use was generally higher: the use of statins was 92%, beta-blockers 91%, an antiplatelet agent 93%, and ACEI/ARB 68%, but it should be noted that the patient populations were not directly comparable because the patients in our study underwent CABG, not PCI. It is unclear if patients with coronary heart disease receive equal medical therapy for secondary prevention after CABG and PCI. In contrast to our findings, secondary prevention medication use after CABG and percutaneous coronary intervention (PCI) was examined in 23,353 patients by Hlatky et al. [16], and they found that patients who underwent PCI were more likely to fill a prescription for statins (95.2% vs. 92.9%), ACEI/ARB (77.6% vs. 70.9%) and beta-blockers (93.9% vs. 93.6%) than patients who underwent CABG. In another Western European study, secondary prevention was investigated in a global, high-risk population with established coronary heart disease [18]. The use of antiplatelet agents was 94%, beta-blockers 80%, ACEI/ARB 77%, and statins 98%. The generally high use of secondary prevention medications in this study could possibly be explained by the design of the study. It was a randomized, prospective study and patients taking part in this study may be more compliant to recommended treatments than patients who declined participation. Kronish et al. [8] studied the effect of depression on adherence to secondary prevention behaviors and medications at three months after acute coronary syndrome and found that persistently depressed patients had a lower adherence to medications than persistently non-depressed patients. We studied the association between depression before CABG and the use of guideline-directed medical therapy one year after surgery, and in patients with a minimum follow-up of four years, respectively. We did not find a lower use of secondary prevention medications among patients with pre-operative depression, and thus our results differ from the observations by Kronish et al. [8]. Even though we did not evaluate postoperative depressive status, it has been shown that preoperative depression is associated with the highest risk for postoperative depression [19]. Depression is a risk factor for mortality after CABG [2,20,21] and studies have shown that improvement of depression symptoms was consistently associated with better adherence to medications in patients hospitalized with cardiac conditions [22]. Future studies should focus on detection and treatment of depression before CABG, in order to increase the likelihood of adequate adherence to secondary prevention medications.

4.1. Study limitations

There are several limitations of this study that should be considered. A certain degree of misclassification of exposure was present because the Swedish national Prescribed Drug Register only contains information about prescribed medicines since July 2005. Therefore, some patients in our study could have been prescribed antidepressants before that date and consequently classified into the unexposed group. Moreover, not all patients with clinical depression receive pharmacological treatment, but instead non-drug therapy e.g. cognitive–behavioral therapy or no treatment at all. Some patients could have been prescribed anti-depressants for other medical conditions than depression, such as panic disorder. Other limitations were lack of information regarding why some patients were not prescribed secondary prevention medications, perhaps due to medical contra-indications. Other factors which may affect patients' inclination to fill a prescription could be physician specialty, distance to a pharmacy, social network, and number of out-patient visits. This information was no available in the national registers used in this study. We also lacked information regarding socio-economic status.

A strength of the study was the nationwide population-based design which allowed us to include a large number of patients from all centers performing cardiac surgery in Sweden, which improved the generalizability of our results.

5. Conclusions

Preoperative depression was not associated with lower use of guideline-directed medical therapy for secondary prevention of cardiovascular events in a nationwide population-based cohort study of 10,586 patients who underwent primary isolated non-emergent CABG. These findings suggest that the observed higher mortality following CABG among depressed patients is not explained by inadequate secondary prevention medication.

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