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FULL RESEARCH PAPER
Gender-specific conditions

Sex differences in medication adherence and medication-associated mortality after coronary artery bypass grafting

Jouko Nurkkala [1,2]*, Aleksi Winstén[3], Jenni Toivonen[1,2]; FinnGen, and Teemu Niiranen[3,4,5]

[1]Division of Perioperative Services, Intensive Care and Pain Medicine, Turku University Hospital, Kiinamyllynkatu 4-8, Turku 20521, Finland; [2]Department of Anesthesiology and Intensive Care, University of Turku, Kiinamyllynkatu 4–8, Turku 20014, Finland; [3]Department of Internal Medicine, University of Turku, Turku, Finland; [4]Division of Medicine, Turku University Hospital, Turku, Finland; and [5]Department of Public Health Solutions, Finnish Institute for Health and Welfare, Turku, Finland

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Aims Higher mortality rates after coronary artery bypass grafting (CABG) have been reported in women than in men. We examined whether adherence to secondary prevention medications could explain these sex differences.

Methods and results We used data from 9857 participants (18% women) who underwent CABG between 1998 and 2021. Medication adherence for statins, beta-blockers, and renin-angiotensin-aldosterone system (RAAS) inhibitors was assessed using nationwide drug purchase registers. Multivariable-adjusted Cox regression models with a sex interaction term were used to analyze the association between adherence and all-cause mortality. Use of statins (90%), RAAS inhibitors (62%), and beta-blockers (93%) was similar in men and women immediately after CABG ($P \geq 0.57$ for all). After 10 years, adherence remained high for statins (84%), beta-blockers (85%), and RAAS inhibitors (66%), with a non-significant trend towards greater adherence in women. Use of medications was associated with lower mortality in men and women, and particularly for statins [HR, 0.49; 95% confidence interval (CI), 0.41–0.59 for women; HR, 0.54; 95% CI: 0.50–0.59 for men; *P* for interaction 0.08]. Beta-blocker adherence was associated with a greater mortality benefit in women compared with men (HR, 0.66; 95% CI: 0.55–0.78 vs. HR, 0.82; 95% CI: 0.75–0.90; *P* for interaction 0.04).

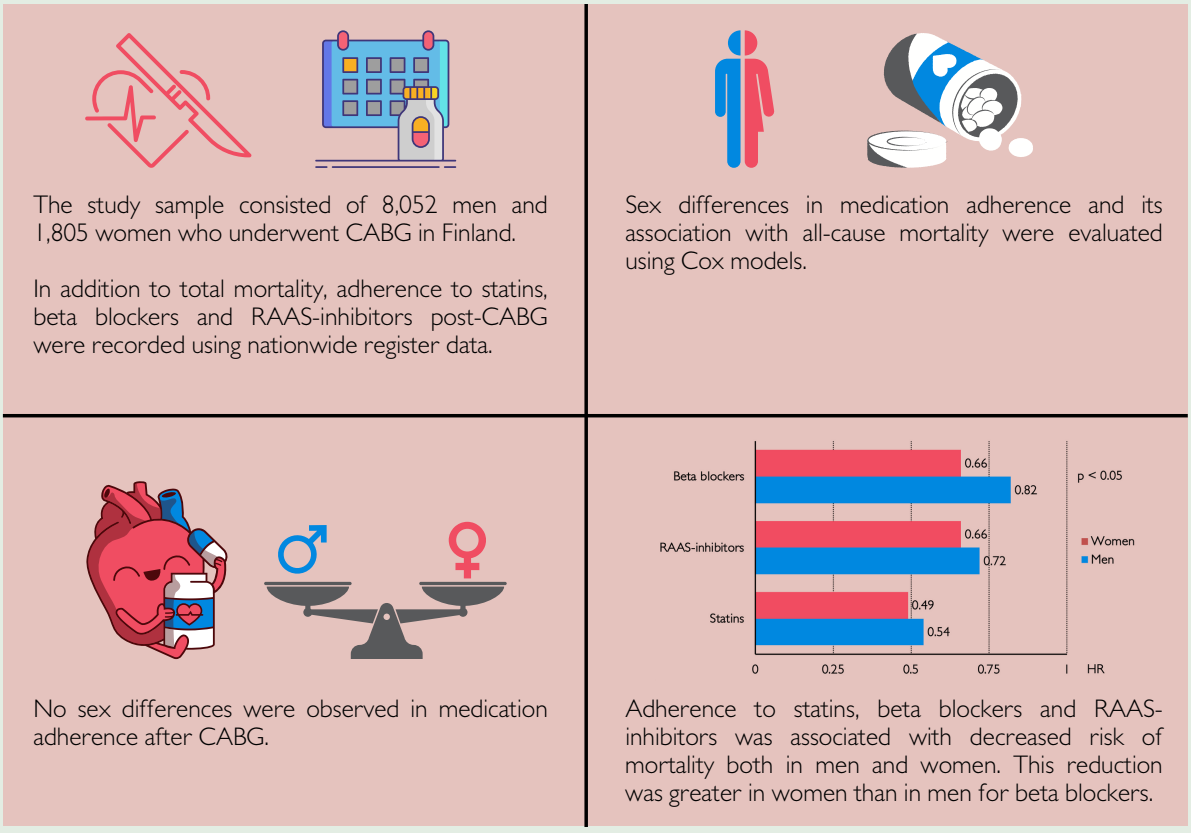
Conclusion No major sex differences in medication adherence were observed during 10 years of follow-up. Use of beta-blockers was associated with lower risk of mortality in women compared with men. Future interventional trials should focus on the potential sex differences in efficacy of secondary prevention medication in CABG patients.

Lay summary Women have a higher risk of complications and death after coronary artery bypass grafting (CABG) compared with men, and one possible factor could be poorer adherence to protective medications. This study investigated sex differences in secondary prevention drug adherence after CABG to explore whether these differences could explain the previously observed disparities in mortality.

- No sex differences in drug adherence were observed in this study.
- Statins, RAAS inhibitors, and beta-blockers adherence after CABG was associated with lower mortality risk in men and in women. However, women derived a significantly greater mortality benefit from beta-blocker use compared with men.

* Corresponding author. Tel: +358 2 313 9074, Email: jouko.nurkkala@tyks.fi.

Graphical Abstract



Keywords Revascularization • Secondary Prevention • Sex Differences • Medication Adherence • CABG • Mortality

Introduction

Coronary artery bypass grafting (CABG) is used to alleviate ischaemic symptoms and improve outcomes in patients with coronary artery disease.[1,2] CABG is particularly beneficial for specific groups, including those with multivessel or complex disease, left main disease, or diffuse coronary artery disease combined with diabetes.[1,2] However, several sex-based differences in perioperative outcomes, long-term survival, and complications have been observed in patients undergoing CABG.[3–5] Namely, women seem to face a significantly higher risk of cardiac death after CABG when compared with men.[6] These sex differences have been partly attributed to a greater number of complex comorbidities at the time of surgery, older age, gender-based selection bias, in addition to differences in anatomy, physiology, and urgency of surgery.[3,4]

Improved survival and reduced morbidity have been demonstrated with the use of secondary prevention medications after CABG.[1,2] Moreover, reduced adherence to these medications can negatively impact long-term survival after CABG.[7–9] The recommended secondary prevention regimen following revascularisation includes statins, antiplatelet therapy, renin-angiotensin-aldosterone system (RAAS) inhibitors (for patients with reduced left ventricular ejection fraction, hypertension, or diabetes), and beta-adrenergic blockers (for those with reduced left ventricular ejection fraction or a history of myocardial infarction).[10] However, adherence to these medications has been shown to decline during long-term post-operative follow-up, particularly in elderly patients.[8] In addition, women have been reported exhibit a slight but statistically significant decrease in the use of statins and beta-blockers compared with men.[8] This sex difference in adherence to secondary prevention medications could potentially contribute to the observed mortality differences after CABG.

In this study, we analyzed data from 9857 individuals (1805 women, 18%) who underwent a CABG. We investigated the sex-differences in the association between adherence to secondary prevention medications and long-term mortality, as well as potential sex differences in medication adherence.

Methods

Study participants

The study cohort included 500 348 individuals (282 064 women) from the FinnGen cohort study Data Freeze 12. The FinnGen cohort consists of participants of randomly selected population cohorts and of hospital biobank patients.[11]

Of the whole cohort, 14 036 individuals (11 359 men, 2322 women, and 355 with unknown sex) had undergone CABG. The first CABG procedure was selected as the index procedure for follow-up. The follow-up period spanned from 1 January 1998, to 30 June 2021, and the follow-up time was limited to a maximum of 10 years. This time frame was chosen because it ensured the existence and completeness of all relevant health and drug reimbursement registers in Finland and FinnGen. Due to this restriction, 10 362 individuals were included in further analyses.

From the remaining 10 362 individuals, patients who died within the first 6 months after the index procedure (197 men and 41 women) were considered to represent early perioperative mortality (rather than medication adherence) and were therefore excluded from the study. Sex was defined based on genotype data. Individuals whose genotype-based sex was either uncertain or was inconsistent with sex assigned at birth ($n = 267$) were excluded. Furthermore, patients whose index procedure occurred ≤6 months before the end of the study period were excluded. Thus, the final study sample consisted of 9857 revascularized patients (8052 men and 1805 women).

Register data

Patient data was obtained from the nationwide Causes of Death Register, the Hospital Discharge Register, the Inpatient Operations Register, and the Kela Drug Purchase and Reimbursement Register. These data were merged using unique personal identification numbers assigned to everyone living in Finland. Diagnoses, medication use, and procedures are recorded in these registers using International Classification of Diseases codes, Anatomical Therapeutic Chemical codes, and Nordic Classification of Surgical Procedures codes, respectively. A more detailed description of the variables used in this study is reported in Supplementary material online, *Table S1*.

Medication adherence follow-up

The primary endpoint for this study was all-cause mortality. The exposure variable was medication use following CABG. The medications of interest in this study were: (i) statins, (ii) RAAS inhibitors (angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers), and (iii) beta-adrenergic blockers.

The drug adherence of individual patients was monitored using the Drug Purchase and Reimbursement Register at 3-month intervals. Due to legislative restrictions, pharmacies can dispense a maximum of 3 months' worth of medication at a time, ensuring adherence could be tracked within this interval. Acetylsalicylic acid is an over-the-counter drug in Finland and, as a result was not evaluated in this study.

A patient was considered non-adherent if they missed drug purchases on two consecutive 3-month periods, at which point they were categorized as a non-user. However, the same individual could return to being categorized as an adherent drug user with any new drug purchase of the same class during the follow-up period. Each patient was censored at 3-month intervals based on drug purchases, at the time of death, or at the end of the study. Baseline and individual follow-up for medication adherence began 6 months post-operatively.

Ethics

All participants gave written informed consent for the FinnGen study, which was approved by the Ethics Committee of the Hospital District of Helsinki and Uusimaa (HUS/990/2017). The participants were recruited from Finnish hospital districts, national biobanks, and other Finnish cohort studies.

Statistical analysis

In a *post hoc* power analysis, we calculated that with an alpha level of 0.05, 70% of individuals in the exposed (medicated group), and 3189 deaths, we had 80% power to detect a relative hazard of 0.90.[12]

Statistical differences in baseline characteristics were evaluated using Student's *t*-test for continuous variables and the Chi-square test for categorical variables. Differences in prescriptions at baseline were evaluated by assessing the sex differences in prescribed medication strengths in milligrams for the most commonly used (i) RAAS inhibitor (ramipril); (ii) statin (atorvastatin); and (iii) beta-blocker (bisoprolol). Differences in medication strengths were compared using a two-sample *t*-test. Temporal trends in adherence to three study medications after CABG were evaluated with local polynomial regression models. A Cox proportional hazards model was applied to examine the associations between drug adherence and all-cause mortality. Drug adherence was included as a time-dependent variable (3-month periods) in the Cox models. In these models, follow-up time was limited to a maximum of 10 years.

Two Cox models were constructed for each drug with different sets of covariates. Model 1 included age, operation year, and a sex interaction term. Model 2 expanded on Model 1 by including two additional study medications, hypercholesterolaemia, heart failure, hypertension, obesity, Type 1 and Type 2 diabetes, chronic kidney disease, stroke, atrial fibrillation, and chronic obstructive pulmonary disease (COPD). Age, as a covariate, was defined as the difference between the patient's age at the time of the operation and the mean age of the cohort. Similarly, the covariate for operation year was defined as the difference between the year of the patient's operation and the mean operation year. Both models were used to assess long-term survival, with analyses conducted separately for each study medication.

In all statistical analyses, a two-tailed *P*-value of <0.05 was considered statistically significant. All analyses were conducted using R software (version 4.2.1).

Results

Of the 9857 individuals who underwent CABG, 1805 (18%) were women. The mean age was 65.9 ± 9.2 for men and 67.7 ± 9.8 for women ($P < 0.001$ for difference). In the study sample, men were more likely to have atrial fibrillation (22.9% vs. 19.6%, $P = 0.009$) and COPD (5.3% vs. 2.9%, $P < 0.001$), whereas women were more likely to have diabetes (37.1% vs. 32.4%, $P < 0.001$), heart failure (30.1% vs. 22.9%, $P < 0.001$), and hypertension (65.9% vs. 56.8%, $P < 0.001$) at baseline. More detailed characteristics of the study sample are presented in *Table 1*.

There were no statistically significant sex differences in medication adherence at 6 months after CABG. The adherence rate for beta-blockers was 92.6% in men and 93.3% in women. The corresponding adherence rates for RAAS inhibitors were 62.0% in men and 62.4% in women, and for statins 89.8% in men and 90.3% in women (*Table 1*). At baseline, the prescription strengths of atorvastatin (34.9 vs. 32.1 mg, $P = 0.001$) and ramipril (3.83 vs. 3.68 mg, $P = 0.043$) were slightly, but significantly higher in men, whereas no sex differences were observed for bisoprolol (4.52 vs. 4.43 mg, $P = 0.269$) (see Supplementary material online, *Table S2*).

Long-term drug adherence was mainly similar between men and women, with no major significant sex differences observed across the three drug classes (*Figure 1*; Supplementary material online, *Table S3*). RAAS inhibitor use at 2 years and beta-blocker use at 6 years was slightly greater in women than in men. After 10 years of follow-up, 84.4% of men and 84.9% of women who were still alive remained statin users. Similarly, 83.3% of men and 86.7% of women continued using beta-blockers, while 65.5% of men and 68.4% of women purchased RAAS inhibitors ($P \geq 0.054$ for all; Supplementary material online, *Table S3*). During the follow-up period, drug use increased, particularly for RAAS inhibitors, at baseline (i.e. 6 months after surgery) across all drug categories (*Figure 2*).

A total of 3189 (32.3%) individuals died during the 10-year follow-up. Adherence to all three secondary prevention medications was associated with lower risk of death in men and in women (*Table 2*, *Figure 3*). This risk reduction was the greatest for statins, but no sex differences were observed (*P* for interaction 0.26). Beta-blocker use was associated with a greater decrease for all-cause mortality in women (HR, 0.66; 95% CI: 0.54–0.80) as compared to men (HR, 0.82; 95%

Table 1 Baseline characteristics of the study sample 6 months after CABG

	Total ($n = 9857$)	Men ($n = 8052$)	Women ($n = 1805$)	*P*-value
Characteristics at baseline				
Age (years)		65.9	67.7	<0.001
Atrial fibrillation	2201 (22.3%)	1847 (22.9%)	354 (19.6%)	0.009
CKD	256 (2.6%)	202 (2.5%)	54 (3.0%)	0.51
COPD	479 (4.9%)	427 (5.3%)	52 (2.9%)	<0.001
Diabetes	3278 (33.3%)	2608 (32.4%)	670 (37.1%)	<0.001
Heart failure	2386 (24.2%)	1842 (22.9%)	544 (30.1%)	<0.001
Hypercholesterolaemia	1932 (19.6%)	1588 (19.7%)	344 (19.1%)	0.81
Hypertension	5764 (58.5%)	4575 (56.8%)	1189 (65.9%)	<0.001
Stroke	832 (8.4%)	694 (8.6%)	138 (7.6%)	0.41
Secondary medication use at baseline				
Beta-blockers	9138 (92.7%)	7454 (92.6%)	1684 (93.3%)	0.57
RAAS inhibitors	6122 (62.1%)	4995 (62.0%)	1127 (62.4%)	0.95
Statins	8863 (89.9%)	7233 (89.8%)	1630 (90.3%)	0.83

CABG, coronary artery bypass grafting; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; RAAS, renin-angiotensin-aldosterone system.

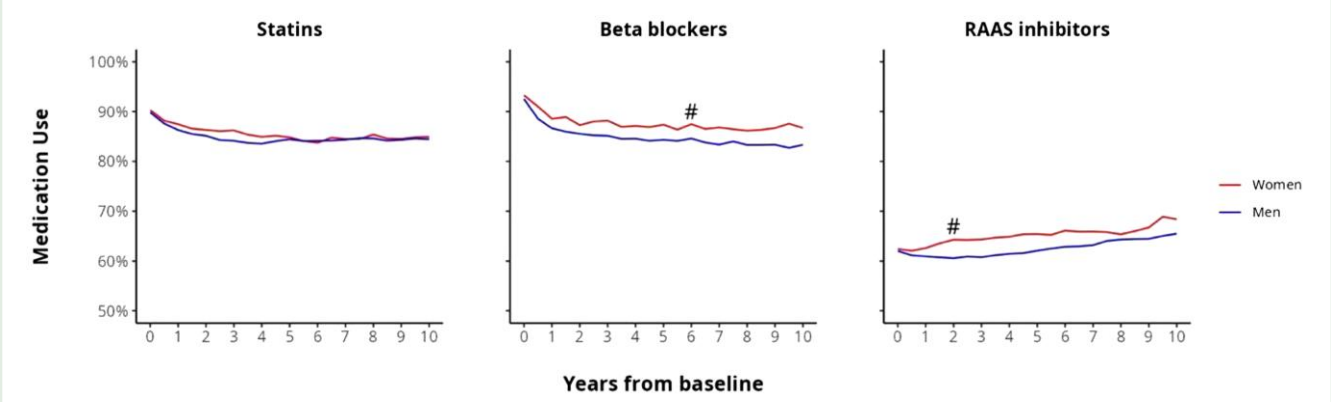


Figure 1 Medication adherence by sex after coronary artery bypass grafting. The hashtag indicates statistically significant difference in medication use between men and women at that time point. RAAS, renin-angiotensin-aldosterone system.

CI: 0.75–0.90; *P* for interaction 0.043; *Figure 3*). No significant differences between women and men were observed for the other risk factors (*Figure 3*).

Discussion

In this study, we investigated the sex differences in medication adherence and adherence-associated long-term mortality in 9857 CABG patients (18% women). In general, we observed no major sex differences in adherence to statins, RAAS inhibitors, or beta-blockers during a maximum 10-year follow-up period and thus, the previously observed sex differences in mortality after CABG cannot be attributed to differences in drug adherence based on the results of this study. Both men and women benefited from the use of secondary prevention medication, and particularly from the use of statins. However, the use of beta-blockers was associated with a lower risk of death in women than in men.

Our results demonstrate that secondary prevention medications in all three categories were initiated similarly for both sexes at baseline. Adherence at 6 months to statins and beta-blockers exceeded 90% in both men and women, while RAAS inhibitor adherence was 62% in both sexes combined. At baseline, the mean strength of atorvastatin and ramipril prescriptions was slightly, but significantly, greater in men than in women, whereas no differences were observed for bisoprolol. In general, women are prescribed high-dose statins less often than men, which can reduce the possible mortality benefits they could derive from statin use.[13,14] Also, women receive less often guideline-directed medical therapy for CAD and HF compared with men, which could potentially mask possible sex differences concerning statin and RAAS-inhibitor use.[15,16] However, as the sex interaction was observed only for beta-blockers in our study and the differences in drug dosage were clinically insignificant, it is unlikely that our findings are a result of these factors.

These adherence rates align with findings from a registry study conducted in Sweden, where initial adherence rates for statins, beta-

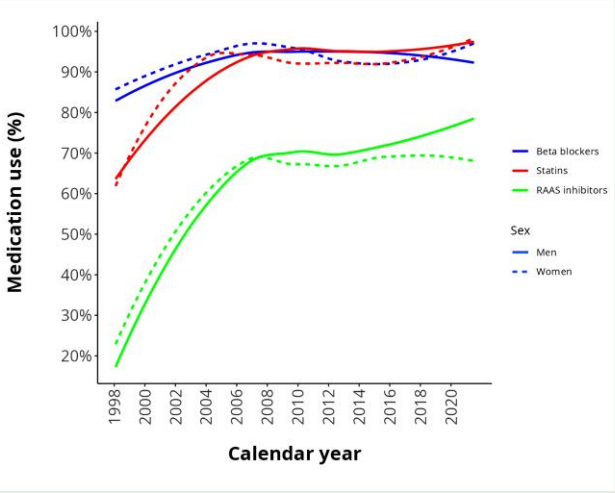


Figure 2 Temporal trends in secondary prevention medication initiation 6 months after coronary artery bypass grafting.

Table 2 Effect of secondary prevention medication use on survival after CABG

	Women HR (95% CI)	Men HR (95% CI)	Interaction *P*-value
Model 1			
Statins	0.46 (0.39–0.55)	0.53 (0.48–0.58)	0.083
Beta-blockers	0.69 (0.56–0.84)	0.88 (0.80–0.96)	0.009
RAAS inhibitors	0.74 (0.63–0.88)	0.86 (0.79–0.93)	0.055
Model 2			
Statins	0.49 (0.41–0.59)	0.54 (0.50–0.59)	0.262
Beta-blockers	0.66 (0.54–0.80)	0.82 (0.75–0.90)	0.043
RAAS inhibitors	0.66 (0.55–0.78)	0.72 (0.66–0.78)	0.240

The survival models were based on the Cox proportional hazards model, where the independent variable was medication use, and the dependent variable was all-cause mortality. Model 1 was adjusted for age at the time of operation, operating year, and a sex-interaction term. Model 2 included all adjustments from Model 1 and was further adjusted for the following comorbidities: two other study medications, atrial fibrillation, stroke, chronic obstructive pulmonary disease (COPD), hypertension, diabetes, hypercholesterolaemia, heart failure, and chronic kidney disease. CI, confidence interval; CABG, coronary artery bypass grafting; RAAS, renin-angiotensin-aldosterone system.

blockers, and RAAS inhibitors were 94%, 91%, and 73%, respectively, for both sexes.[8] However, the Swedish study observed a small but significant decline in adherence across all drug classes, particularly among elderly women.[8] Also, the adherence rate for statins observed in our study at baseline and after 2 years was considerably higher than what was reported by an Italian study of patients who underwent a percutaneous coronary intervention procedure in the setting of ST-elevation myocardial infarction.[17] In that study, statin adherence after 1 year of follow-up was only 69%.[17] In a Swedish register study, adherence to statins 8 years after CABG was 77%,[8] and in another smaller Greek study, long-term adherence to statins after CABG was 81%.[18] Also, a study using Bayesian regression model demonstrated that drug adherence at 90 days after myocardial infarction could accurately predict adherence behaviour at 1 year indicating that behavioural changes and patterns established early after the primary intervention are crucial for the formation of long-term adherence.[19,20] Furthermore, the 1-year adherence to statins in that study was 80%, which is in line with the 84% adherence observed in our study.[19,20] Thus, it is possible that cultural differences may explain some of the differences in long-term statin adherence.

In contrast, drug adherence in our study remained relatively stable during the 10-year follow-up period for all three drug categories, with no significant differences between sexes. However, these differences could be explained also by between-study differences in years of data collection. Our findings contradict the previous notion that women tend to be less adherent to primary and secondary prevention medications.[21] Therefore, the differences in long-term mortality between men and women after CABG, as reported in earlier studies,[3,6] cannot be attributed to differences in drug adherence based on the results of our study.

The greatest reduction in long-term mortality was observed with adherence to statins, which was associated with an approximate halving of mortality. However, this risk reduction was similar in men and women. However, we observed a non-significant trend towards statin use being associated with lower risk of death in women than in men (*P* for interaction 0.08). This trend has not been observed in previous drug trials in this domain, which have demonstrated an equal benefit for men and women in both primary and secondary prevention of cardiovascular disease.[22,23] Furthermore, in a Swedish cohort study of >35 000 CABG patients, statin use was associated with similar reduction in major adverse cardiovascular events and dementia in both sexes.[24]

Similarly to statins, the use of RAAS inhibitors after CABG was associated with a significant all-cause mortality benefit for both sexes. These observed effect size for statins and RAAS inhibitors are consistent with findings from previous studies, with hazard ratios ranging from 0.24 to 0.46 for statins and 0.66 to 0.78 for RAAS inhibitors.[8,9] These findings therefore underline the importance of adherence to RAAS inhibitors and particularly to statin therapy after CABG in both women and men.

The use of beta-blockers was also associated with a reduction in long-term mortality in both sexes, even after adjusting for covariates such as atrial fibrillation and heart failure. In contrast to statins and RAAS inhibitors, beta-blocker use after CABG was associated with a greater mortality benefit in women compared with men. Previous randomized controlled trials and observational studies support the postoperative use of beta-blockers in patients with reduced left ventricular function or previous myocardial infarction to reduce recurrent coronary events, atrial fibrillation, other arrhythmias, and stroke, thereby decreasing post-CABG mortality.[1] However, evidence on the long-term benefit of beta-blockers in patients without left ventricular dysfunction or previous MI has been challenged in more recent observational studies, as they have failed to demonstrate mortality benefit from beta-blocker use.[1] Conversely, a recent register study from Sweden demonstrated reduction in major adverse coronary events, but not in mortality, with selective beta-blocker use in patients after CABG irrespective of their previous MI or LV-function status.[25] However, sex-specific analyses were not performed.[25]

The possible mechanisms underlying the lower mortality risk in women could be potentially explained by the sex differences in beta-adrenergic pathways, hormonal modulation of β-receptor activity or sensitivity, ischaemic heart disease phenotypes, pharmacodynamics, pharmacokinetics, and responses to beta-blocking agents.[26] Namely, the β1-, β2-, and β3-receptors mediate cardiac and vascular function in response to sympathetic nervous system (SNS) stimulation, but these effects differ between sexes.[26] First, women and men both

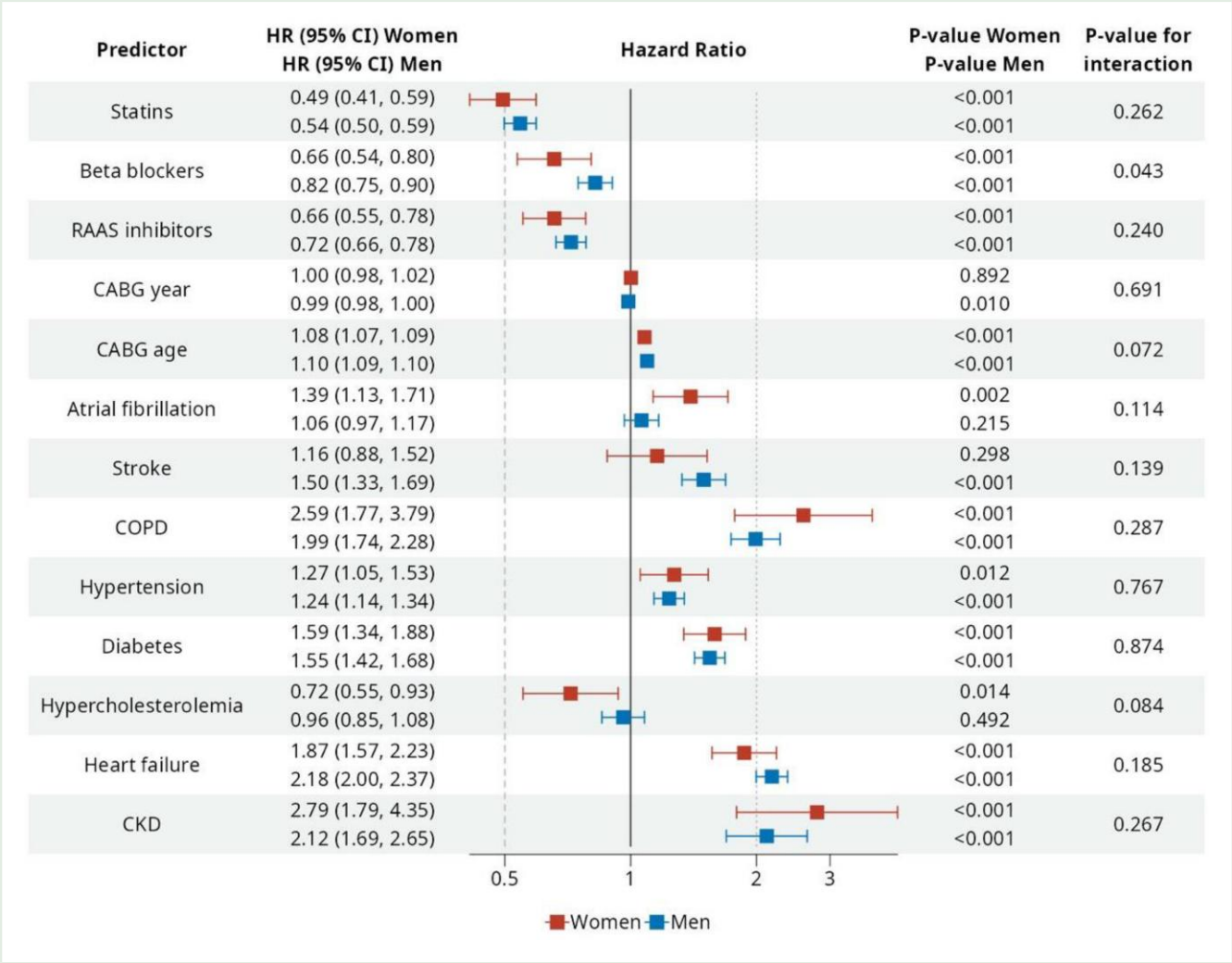


Figure 3 Sex-stratified effect of secondary prevention medication use and patient characteristics on all-cause mortality after coronary artery bypass grafting. HR, Hazard Ratio. CABG, coronary artery bypass grafting; CI, confidence interval; CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; RAAS, renin-angiotensin-aldosterone system.

express all β-receptors in the cardiomyocytes (mostly β1) and vasculature or endothelium (mostly β2 and β3). However, young women express more vasodilatory β1 and β3 receptors in the endothelial cells compared with men, making their vessels more resistant to vasoconstriction and more prone to vasodilatation.[27] Furthermore, this β-receptor expression and responsiveness is modulated and maintained by oestrogen through stimulation via oestrogen receptors and this protective benefit is lost after menopause leading to down-regulation and desensitising of β1-receptors.[27,28] In addition, oestrogen receptors exist in all types of cardiovascular cells and are shown to modulate gene expression and interact with β-adrenergic pathways offering a mechanistic background for these observed sex differences.[29] Second, oestrogen production in women down-regulates the activity of the SNS, reducing the release of epinephrin and norepinephrine and thus reducing β-stimulation.[26] After menopause, loss of oestrogen results in a hyperactivated SNS and β-stimulation, reduced β-responsiveness, down-regulation of β-receptors, increased heart rate, systemic vascular resistance, and hypertension in women.[30] Third, women are shown to respond to beta-blocker medication with greater reduction in heart rate and blood pressure compared with men.[26,31] Also, due to enhanced absorption, smaller drug distribution volume and reduced CYP enzyme activity for beta-blockers, women are more prone to increased drug concentrations and are thus potentially at increased risk for adverse drug effects such as bradycardia and fatigue which again may require dose reduction in women.[32] However, beta-blocker therapy is shown to re-sensitize and up-regulate β-receptors and prevent direct catecholamine toxicity, thus ameliorating the increased SNS-stimulation in menopausal women.[26]

Clinically, both sexes are shown to derive equal mortality benefit from beta blockade in heart failure with reduced ejection fraction.[33] Conversely, in one study, women with previous hypertension and beta-blocker medication had more frequent episodes of heart failure in the setting of acute coronary syndrome.[34] Also, women present less often with obstructive epicardial coronary artery disease and are more often observed with coronary microvascular disease (CMD) characterized by endothelial dysfunction, reduced coronary blood flow (CBF), and concurrent ischaemia.[35,36] In CMD, beta blocking agents reduce myocardial ischaemia and angina by lowering heart rate, reducing contractibility,

blood pressure and myocardial oxygen consumption and increase CBF by increasing diastolic filling time.[35,36] Especially, third generation beta-blockers such as nebivolol and carvedilol are shown to reduce endothelial dysfunction and promote vasodilatation making beta-blockers first line of treatment in CMD.[35,36] Thus, due to greater prevalence of CMD in women, beta-blocker use could potentially benefit women more than men. Therefore, women, or certain subpopulations of women, may benefit from beta-blocker medication more than men due to sex differences in beta-adrenergic physiology. This hypothesis, however, warrants further research and particularly sex-stratified clinical trials in CABG patients.

During the follow-up period from 1998 to 2021, the initiation and adherence to statins and RAAS inhibitors became more frequent, aligning with evolving guidelines for secondary drug prevention in CAD. In contrast, the use of beta-blockers remained consistently high after CABG and even increased over the follow-up period. Interestingly, the year in which CABG was performed (between 1998 and 2021) was not associated with differences in survival for either sex in this study. This finding can be explained by the fact that, despite advancements in medical therapy and surgical techniques, more elderly and higher-risk patients are undergoing CABG now compared with one or two decades ago.[1,2] As a result, the benefits of surgery in these more challenging patient groups may be offset by the increased risk of death from other comorbidities.

Although this study has several strengths, including up to 10 years of individual follow-up spanning over two decades, over 9000 CABG patients with high-quality registry data,[37] and comprehensive drug purchase records, its results must be considered in the light of several limitations. First, as seen in other CABG studies,[38] only 18% of our study sample were women, which may limit statistical power for detecting sex-specific effects or interactions among CABG patients as well as lead to biased effect sizes. Women have always been underrepresented in cardiac clinical studies and especially in CABG studies.[38] This underrepresentation of women in previous and current research may also limit the generalizability of these results. However, as women are referred to and undergo CABG surgery less often than men in many nationwide real life cohorts (24.5% of operated patients in an American cohort and 19.7% in a Swedish cohort), it can be argued that the proportion of women in our study represents the current clinical practice of CABG enrolment in Finland, Europe, and in the United States.[24,38,39] Second, individuals with lower socioeconomic status are less likely to participate in studies and may also have lower adherence to medication after surgery. As a result, this study cohort may overestimate the true adherence rates. However, this potential bias is likely to affect both sexes equally. Third, information on potential confounders such as physical activity, diet, and body mass index was not available. Women are shown to obtain greater all-cause- and CV mortality benefits from physical activity compared with men, which could partially explain the sex differences and mortality benefits observed in this study.[40] Also, women are shown to benefit differently from healthy diet in terms of CV disease risk[41,42] whereas obesity may be a stronger risk factor for CV disease in men than in women.[43–45] While we adjusted for several confounders, the study results may be subject to residual confounding. Fourth, this study cohort consisted of mainly Finns which may limit the generalizability of these results to other cultures and ancestries. Cultural differences, access to medications and surgical interventions and differences in genetic background could influence the results of our study.[46,47] Finally, adherence to antiplatelet medication could not be evaluated in this study. Nevertheless, adherence to the three other classes of medications in this study remained stable over 10 years, suggesting that the observed adherence rates for statins, beta-blockers, and RAAS inhibitors could also reflect participants' general medication adherence behaviour.

Our findings highlight the importance of long-term adherence to secondary prevention medications for men and women who have undergone CABG. Efforts should be made to encourage patients to remain committed to these medications. Future research should focus on strategies to improve drug adherence in both men and women after CABG. Additionally, trials and studies assessing the benefits of beta-blocker use in CABG patients should include subgroup analyses by sex, as our findings suggest that women may benefit more from the use of these drugs than men.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contribution

J.N. interpreted the results and drafted the manuscript. A.W. performed statistical analyses, drafted the figures, and reviewed the manuscript critically for important intellectual content. J.T. and T.N. designed the study, interpreted the results, and reviewed the manuscript critically for important intellectual content. All authors approved the final version of the manuscript.

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Conflict of interest: none declared.

Data availability

The data underlying this article cannot be shared publicly due to sensitive nature of individual genetic and register data. Requests to access the dataset from qualified researchers trained in human subject confidentiality protocols may be submitted through the Finnish Biobanks' Finngenious portal (https://site.fingenious.fi/en/).

References

1. Lawton JS, Tamis-Holland JE, Bangalore S, Bates ER, Beckie TM, Bischoff JM, *et al.* 2021 ACC/AHA/SCAI guideline for coronary artery revascularization: a report of the American College of Cardiology/American Heart Association joint committee on clinical practice guidelines. *Circulation* 2022;**145**:e18–e114.
2. Neumann F-J, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, *et al.* 2018 ESC/EACTS guidelines on myocardial revascularization. *Eur Heart J* 2019;**40**:87–165.
3. Harik L, Perezgrovas-Olaria R, Soletti G Jr, Dimagli A, Alzghari T, An KR. Sex differences in coronary artery bypass graft surgery outcomes: a narrative review. *J Thorac Dis* 2023;**15**:5041–5054.
4. Johnston A, Mesana TG, Lee DS, Eddeen AB, Sun LY. Sex differences in long-term survival after Major cardiac surgery: a population-based cohort study. *J Am Heart Assoc* 2019;**8**:e013260.
5. Robinson NB, Naik A, Rahouma M, Morsi M, Wright D, Hameed I, *et al.* Sex differences in outcomes following coronary artery bypass grafting: a meta-analysis. *Interact Cardiovasc Thorac Surg* 2021;**33**:841–847.

6. Nurkkala J, Kauko A, Palmu J, Aittokallio J, Niiranen T. Sex differences in coronary artery bypass grafting-related morbidity and mortality. *Front Cardiovasc Med* 2022;**9**:1021363.
7. Javaid I, Zhang Y-J, Holmes DR, Morice MC, Mack MJ, Kappetein AP, *et al.* Optimal medical therapy improves clinical outcomes in patients undergoing revascularization with percutaneous coronary intervention or coronary artery bypass grafting: insights from the synergy between percutaneous coronary intervention with TAXUS and cardiac surgery (SYNTAX) trial at the 5-year follow-up. *Circulation* 2015;**131**:1269–1277.
8. Björklund E, Nielsen SJ, Hansson EC, Karlsson M, Wallinder A, Martinsson A, *et al.* Secondary prevention medications after coronary artery bypass grafting and long-term survival: a population-based longitudinal study from the SWEDEHEART registry. *Eur Heart J* 2020;**41**:1653–1661.
9. Kawashima H, Serruys PW, Ono M, Hara H, O'Leary N, Mack MJ, *et al.* Impact of optimal medical therapy on 10-year mortality after coronary revascularization. *J Am Coll Cardiol* 2021;**78**:27–38.
10. Kulik A, Ruel M, Jneid H, Ferguson TB, Hiratzka LF, Ikonomidis JS, *et al.* Secondary prevention after coronary artery bypass graft surgery. *Circulation* 2015;**131**:927–964.
11. Kurki MI, Karjalainen J, Palta P, Sipilä TP, Kristiansson K, Donner KM, *et al.* FinnGen provides genetic insights from a well-phenotyped isolated population. *Nature* 2023;**613**:508–518.
12. Schoenfeld DA. Sample-size formula for the proportional-hazards regression model. *Biometrics* 1983;**39**:499.
13. Peters SAE, Colantonio LD, Zhao H, Bittner V, Dai Y, Farkouh ME, *et al.* Sex differences in high-intensity statin use following myocardial infarction in the United States. *J Am Coll Cardiol* 2018;**71**:1729–1737.
14. Johnston N, Schubert J, Svensson MK, Taufer Cederlof E, Cars T, Gustafsson S, *et al.* Lipid-lowering treatment pattern in chronic coronary syndrome—lower proportion of treatment observed among women during 3 years of follow-up. *Eur J Prev Cardiol* 2024;**31**:zwae175.039.
15. Hambraeus K, Tydén P, Lindahl B. Time trends and gender differences in prevention guideline adherence and outcome after myocardial infarction: data from the SWEDEHEART registry. *Eur J Prev Cardiol* 2016;**23**:340–348.
16. Sumarsono A, Xie L, Keshvani N, Zhang C, Patel L, Alonso WW, *et al.* Sex disparities in longitudinal use and intensification of guideline-directed medical therapy among patients with newly diagnosed heart failure with reduced ejection fraction. *Circulation* 2024;**149**:510–520.
17. Giacobbe F, Giannino G, Annone U, Morena A, Di Vita U, Carmagnola L, *et al.* Impact of statin adherence and interruption within 6 months after ST-segment elevation myocardial infarction (STEMI): results from the real-world regional registry FAST-STEMI. *Int J Cardiol* 2024;**405**:131933.
18. Bampali T, Efstathopoulos A, Siminelakis S. The trajectory of statin compliance after coronary artery bypass grafting surgery. *Eur J Prev Cardiol* 2023;**30**:zwad125.105.
19. Tannous EE, Selitzky S, Vinker S, Stepensky D, Schwarzberg E. Predictive modelling of medication adherence in post-myocardial infarction patients: a Bayesian approach using beta-regression. *Eur J Prev Cardiol* 2025;**32**:649–658.
20. Magne J, Jost J. Ninety days to predict a year: a Bayesian journey into medication adherence post-myocardial infarction. *Eur J Prev Cardiol* 2025;**32**:659–660.
21. Venditti V, Bleve E, Morano S, Filardi T. Gender-related factors in medication adherence for metabolic and cardiovascular health. *Metabolites* 2023;**13**:1087.
22. Cholesterol Treatment Trialists' (CTT) Collaboration; Fulcher J, O'Connell R, Voysey M, Emberson J, Blackwell L, *et al.* Efficacy and safety of LDL-lowering therapy among men and women: meta-analysis of individual data from 174,000 participants in 27 randomised trials. *Lancet* 2015;**385**:1397–1405.
23. Kostis WJ, Cheng JQ, Dobrzynski JM, Cabrera J, Kostis JB. Meta-analysis of statin effects in women versus men. *J Am Coll Cardiol* 2012;**59**:572–582.
24. Pan E, Nielsen SJ, Mennander A, Björklund E, Martinsson A, Lindgren M, *et al.* Statins for secondary prevention and major adverse events after coronary artery bypass grafting. *J Thorac Cardiovasc Surg* 2022;**164**:1875–1886.e4.
25. Lindgren M, Nielsen SJ, Björklund E, Pivodic A, Perrotta S, Hansson EC, *et al.* Beta blockers and long-term outcome after coronary artery bypass grafting: a nationwide observational study. *Eur Heart J Cardiovasc Pharmacother* 2022;**8**:529–536.
26. Liccardo D, Arosio B, Corbi G, Cannavo A. Sex/gender- and age-related differences in β-adrenergic receptor signaling in cardiovascular diseases. *J Clin Med* 2022;**11**:4280.
27. Al-Gburi S, Deussen A, Zatschler B, Weber S, Künzel S, El-Armouche A, *et al.* Sex-difference in expression and function of beta-adrenoceptors in macrovessels: role of the endothelium. *Basic Res Cardiol* 2017;**112**:29.
28. Lindenfeld J, Cleveland JC, Kao DP, White M, Wichman S, Bristow JC, *et al.* Sex-related differences in age-associated downregulation of human ventricular myocardial β1-adrenergic receptors. *J Heart Lung Transplant* 2016;**35**:352–361.
29. Machuki JO, Zhang HY, Harding SE, Sun H. Molecular pathways of oestrogen receptors and β-adrenergic receptors in cardiac cells: recognition of their similarities, interactions and therapeutic value. *Acta Physiol (Oxf)* 2018;**222**:e12978.
30. Sherwood A, Park SB, Hughes JW, Blumenthal JA, Hinderliter A, Trivedi R, *et al.* Cardiovascular hemodynamics during stress in premenopausal versus postmenopausal women. *Menopause* 2010;**17**:403–409.
31. Stolarz AJ, Rusch NJ. Gender differences in cardiovascular drugs. *Cardiovasc Drugs Ther* 2015;**29**:403–410.
32. Tamargo J, Rosano G, Walther T, Duarte J, Niessner A, Kaski JC, *et al.* Gender differences in the effects of cardiovascular drugs. *Eur Heart J Cardiovasc Pharmacother* 2017;**3**:163–182.
33. Kotecha D, Manzano L, Krum H, Rosano G, Holmes J, Altman DG, *et al.* Effect of age and sex on efficacy and tolerability of β blockers in patients with heart failure with reduced ejection fraction: individual patient data meta-analysis. *BMJ* 2016;**353**:1855.
34. Bugiardini R, Yoon J, Kedev S, Stankovic G, Vasiljevic Z, Miličić D, *et al.* Prior Beta-blocker therapy for hypertension and sex-based differences in heart failure among patients with incident coronary heart disease. *Hypertension* 2020;**76**:819–826.
35. Tjoe B, Barsky L, Wei J, Samuels B, Azarbal B, Merz CNB, *et al.* Coronary microvascular dysfunction: considerations for diagnosis and treatment. *Cleve Clin J Med* 2021;**88**:561–571.
36. Soleymani M, Masoudkabir F, Shabani M, Vasheghani-Farahani A, Behnoush AH, Khalaji A. Updates on pharmacologic management of microvascular angina. *Cardiovasc Ther* 2022;**2022**:6080258.
37. Sund R. Quality of the Finnish hospital discharge register: a systematic review. *Scand J Public Health* 2012;**40**:505–515.
38. Gaudino M, Di Mauro M, Fremes SE, Di Franco A. Representation of women in randomized trials in cardiac surgery: a meta-analysis. *J Am Heart Assoc* 2021;**10**:e020513.
39. Gaudino M, Chadow D, Rahouma M, Soletti G Jr, Sandner S, Perezgrovas-Olaria R, *et al.* Operative outcomes of women undergoing coronary artery bypass surgery in the US, 2011 to 2020. *JAMA Surg* 2023;**158**:494–502.
40. Ji H, Gulati M, Huang TY, Kwan AC, Ouyang D, Ebinger JE, *et al.* Sex differences in association of physical activity with all-cause and cardiovascular mortality. *J Am Coll Cardiol* 2024;**83**:783–793.
41. Yao H, Wang X, Wu X, Liu Y, Chen Y, Li L, *et al.* Sex differences in association of healthy eating pattern with all-cause mortality and cardiovascular mortality. *BMC Public Health* 2024;**24**:2363.
42. Tindall AM, Stallings VA. Sex differences in cardiovascular risk may be related to sex differences in diet patterns: a narrative review. *Ann Hum Biol* 2021;**48**:517–524.
43. Song X, Tabák AG, Zethelius B, Yudkin JS, Söderberg S, Laatikainen T, *et al.* Obesity attenuates gender differences in cardiovascular mortality. *Cardiovasc Diabetol* 2014;**13**:144.
44. Appelman Y, van Rijn BB, ten Haaf ME, Boersma Eric, Peters SAE. Sex differences in cardiovascular risk factors and disease prevention. *Atherosclerosis* 2015;**241**:211–218.
45. Kohansal K, Afaghi S, Khalili D, Molavizadeh D, Hadaegh F. Gender differences in midlife to later-life cumulative burden and variability of obesity measures and risk of all-cause and cause-specific mortality. *Int J Obes* 2024;**48**:495–502.
46. McQuaid EL, Landier W. Cultural issues in medication adherence: disparities and directions. *J Gen Intern Med* 2017;**33**:200–206.
47. Abbes H, Soria-Chacartegui P, Omezzine A, Abad-Santos F, Zubiaur P. Impact of genetic variation in adrenergic receptors on β-blocker effectiveness and safety in cardiovascular disease management: a systematic review. *Pharmaceuticals (Basel)*. 2025;**18**:493.