



Differences between men and women in the use of preventive medications following a major cardiovascular event: Australian prospective cohort study

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ABSTRACT

Most cardiovascular disease (CVD) events can be prevented with appropriate risk management. Existing evidence suggests women are less likely than men to receive guideline-recommended medications, however data on sex-differences in preventive medication use following a CVD event are lacking. Relative risks (RRs) comparing use of blood pressure- and lipid-lowering medications in men and women at 3-, 6-, 9- and 12-months following hospitalisation for myocardial infarction (MI) or stroke from 2012 to 2017 were quantified using linked data from 8,278 participants enrolled in the Australian 45 and Up Study. Overall, 51% of women and 58% of men were using both blood-pressure- and lipid-lowering medications three months after a MI or stroke event, decreasing to 48% and 53%, respectively, at 12 months after an event. Adjusting for potential confounders, women were 9% less likely than men (RR = 0.91 [95% CI: 0.87, 0.95]) to be using both medications and 19% more likely (RR = 1.19 [95% CI: 1.07, 1.32]) to use neither medication three months after a MI or stroke event. At the 12-month mark, women were 8% less likely (RR = 0.92 [95% CI: 0.88, 0.97]) to be using both medications and 14% more likely (RR = 1.14 [95% CI: 1.03, 1.26]) to use neither medication. Women were consistently less likely to use both preventive medications and more likely to use neither medication at each follow-up time point. Overall, there were major shortfalls in basic preventive medication use post-CVD event and sex disparities are likely to further jeopardise efforts to reduce CVD events in the community.

1. Introduction

Globally, cardiovascular disease (CVD) is the leading cause of death, and a leading cause of morbidity (GBD 2017 Causes of Death Collaborators 2018; GBD 2017 Disease and Injury Incidence and Prevalence Collaborators 2018). Absolute numbers of CVD events and deaths are higher in women due to a greater number of women living to older ages (Mosca et al., 2011). Secondary CVD events can be prevented by controlling risk factors such as blood pressure and cholesterol. Blood pressure- and lipid-lowering medications and antithrombotics are recommended for all people who have had a myocardial infarction (MI) or ischaemic stroke event (Chew et al., 2016; National Heart Foundation of Australia and the Cardiac Society of Australia and New Zealand, 2012; Stroke Foundation, 2019). International evidence suggests that fewer women than men receive blood pressure- and lipid-lowering

medications for CVD (Shah et al., 2016; Simpson et al., 2005) and women are less likely to adhere to statin use compared to men (Goldstein et al., 2016; Lewey et al., 2013).

Data from Australia show that following a MI or acute coronary syndrome (ACS) event (MI or unstable angina), men are more likely than women to receive (Hay et al., 2020; Hyun et al., 2021; Khan et al., 2018) and continue to use (Hyun et al., 2021) recommended preventive medications. Compared with over half (50.3% [95% CI: 39.8–60.8%]) of Australian men, only 34.1% (22.7–45.5%) of Australian women with self-reported broadly defined CVD reported using both blood pressure- and lipid-lowering medications (Banks et al., 2016). Similar differences in preventive medication use between men and women with pre-existing CVD have been found within primary care populations (Driscoll et al., 2011; Hyun et al., 2017; Lee et al., 2019). Evidence to date has focused on medication use at a single point in time, often prescription at hospital

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discharge (Hay et al., 2020; Khan et al., 2018; Redfern et al., 2014), or relies on self-report data (Hyun et al., 2021). We are lacking large-scale general population data about the longer term use of preventive medications in men and women following a CVD event. Given that medication use declines over time, data on medication use after an event is needed to help disentangle sex-differences in prescribing, initial use and adherence.

The aim of this study was to quantify differences between Australian men and women in use of blood pressure- and lipid-lowering medications during the first year following a MI or stroke event using linked dispensing and hospital record data.

2. Methods

2.1. Study population

We used data from participants in the Sax Institute's 45 and Up Study, a population-based cohort involving 267,153 men and women from New South Wales (NSW), Australia. The Study is described in detail elsewhere (45 and Up Study Collaborators et al., 2008). Participants in the Study were randomly sampled from the Services Australia (formerly the Australian Government Department of Human Services) Medicare enrolment database, which provides near complete coverage of the population. They joined the study by completing a questionnaire distributed from January 2006 to December 2008 and giving signed consent for follow-up and linkage of their information to a range of health databases.

Baseline questionnaire data were linked to hospital data from the NSW Admitted Patient Data Collection (APDC), date of death from the NSW Registry of Births, Deaths and Marriages and the National Death Index, and medication dispensing data from the Pharmaceutical Benefits Scheme (PBS). Linked data were available up until 31 December 2017 across all datasets. Data from the baseline 45 and Up questionnaire, hospitalisations and deaths were linked probabilistically by the Centre for Health Record linkage using personal information (including full name, date of birth, sex and address), with false positive rates documented at < 0.5% (Centre for Health Record Linkage, 2020). The Sax Institute linked the baseline 45 and Up questionnaire data and the PBS data, supplied by Services Australia, using a confidential unique identifier.

Participants were included in the study if they had a hospital admission for MI (International Statistical Classification of Diseases and Related Health Problems, Tenth Revision [ICD-10] codes I21 and I22) or stroke (ischaemic stroke or transient ischaemic attack [TIA; ICD-10 codes I63 and G45]) recorded as principal diagnosis in the APDC, on or after 1 July 2012. This is the date from which complete PBS medication dispensing data for prescriptions were available. We followed participants from their index event date (first recorded hospital discharge for MI or stroke) for up to 12 months, date of death or end of follow up (31 December 2017), which ever was the earliest.

We excluded participants who self-reported holding a Department of Veteran's Affairs white or gold card on the baseline questionnaire, as these people have access to subsidised medications under a separate Australian Government program. We further excluded participants who died or reached the end of follow-up within 3 months of the index event date.

2.2. Exposures and outcomes

The main exposure was sex, male or female, ascertained from the Services Australia Medicare enrolment database. The outcome was medication use over time, defined as: (i) use of both a blood pressure- and lipid-lowering medication, measured at 3-, 6-, 9- and 12-months following the index event; and (ii) no use of either blood pressure- or lipid-lowering medications at each of these time points. Medication use was assessed independently at each time point such that participants

could move between different user categories (use of both medications, use of a single medication, or use of neither medication) over time. At the time of follow-up, recommended blood pressure-lowering medications following MI included angiotensin-converting-enzyme (ACE) inhibitors and beta-blockers (Aroney et al., 2006). Following stroke, recommended blood-pressure lowering medications included most antihypertensive agents with the exception of beta-blockers (National Stroke Foundation, 2010). Statins were the recommended lipid-lowering medication following both CVD events. For this study, we defined blood pressure-lowering medications as: antihypertensive medications (Anatomical Therapeutic Chemical [ATC] classification codes: C02A, C02B, C02C, C02D, C02k, C02L); beta blocking agents (C07A, C07B, C07C, C07D, C07F); calcium channel blockers (C08C, C08D, C08E, C08G); agents acting on the renin-angiotensin system (C09A, C09B, C09C, C09D); diuretics (C03); and combination blood pressure- and lipid-lowering medication (C10BX). Lipid lowering medications included medications with ATC codes beginning with C10. A full list of ATC codes is provided in Appendix A1. Although also recommended for MI and stroke patients, we did not measure antithrombotic medication use in our analysis as some of these medications are available over the counter and would not be captured consistently in the PBS dataset. Since dispensing of a medication does not necessarily equate with use, we defined medication 'users' as having at least two dispensings of lipid-lowering medication and two dispensings of a blood pressure-lowering medication within the follow-up period. Further information on how medication use at each time point was ascertained, including accounting for potential stockpiling of medication, is detailed in Appendix A2.

2.3. Covariates

Other covariates included age at hospital admission (45–54, 55–64, 65–74, 75–84, 85 years or older), education (no qualifications, certificate/diploma/trade or university degree), region of residence (major cities, inner regional, or outer regional/remote), type of CVD event (MI or stroke) and history of prior CVD (yes/no). In Australia, the amount a person pays out-of-pocket per medication varies by whether they hold a concession card, with general beneficiaries (i.e. those without a concession card) generally paying more per medication than those who hold a concession card. To account for differences in use of medication due to out-of-pocket costs, patient concession status (concessional beneficiary, general beneficiary or mixed) was also included as a covariate. Details on definitions and data sources are provided in Appendix A3.

2.4. Statistical analyses

We used modified Poisson regression with robust standard errors to estimate relative risks (RRs) and 95% confidence intervals (CI) at each time point for the outcomes in women compared to men, adjusting for the covariates described above. Modified Poisson regression is appropriate for estimating RR for common outcomes, while odds ratios from logistic regression tend to overestimate RR (Zou, 2004). Missing values for covariates were included in the analyses as separate categories. At each time point, only participants with follow-up data were included in the denominator. Four sensitivity analyses were conducted to test assumptions of the study design: (i) restricting participants to those with a full 12-months of follow-up following the index event; (ii) restricting participants to those without prior CVD (identified in hospitalisation data or from self-report); (iii) defining medication users as those with at least one rather than two dispensings of blood pressure- and lipid-lowering medications over the 12-month study period; and (iv) additional adjustment for prior use of CVD medications, defined as at least one dispensing of each a lipid- and blood pressure-lowering medication in the three months prior to the index CVD event.

2.5. Ethics

Ethics approval for the 45 and Up Study was provided by the University of New South Wales Human Research Ethics Committee (HREC). Ethics approval for this analysis was provided by the NSW Population and Health Services Research Ethics Committee (Cancer Institute Ref 2012/05/389, AU RED Ref HREC/12/CIPHS/31), and the Australian National University HREC (2012/504).

3. Results

There were 8278 participants with a hospital admission for MI or stroke included in the analysis. Sixty percent of participants were male and the mean age was 76 years (standard deviation [SD]: 10.5) for all participants, 75 years (SD: 10.1) for males and 77 years (SD: 10.7) for females. A slightly higher proportion of men than women had a tertiary degree. Men were slightly more likely to be hospitalised with a MI than stroke, while the reverse was true for women (Table 1).

At three months following hospital discharge for a MI or stroke, 13% of men and 16% of women were using neither blood pressure- nor lipid-lowering medications (Table 2). Three months after the index event, 58% of men compared to 51% of women were using both blood pressure- and lipid-lowering medications, decreasing to 53% and 48% at the 12-month mark, respectively (Table 2).

After adjusting for age, education, type of CVD event, history of prior CVD and patient concession status, women were 9% less likely than men (RR = 0.91 [95% CI: 0.87, 0.95]) to be using both blood pressure- and lipid-lowering medications and 19% more likely (RR = 1.19 [95% CI: 1.07, 1.32]) to use neither medication at three months following hospital discharge for a MI or stroke (Table 2). At 12 months after the index event, women were 8% less likely than men (RR = 0.92 [0.88, 0.97]) to be using both medications and 14% more likely (RR = 1.14 [1.03, 1.26]) to use neither medications (Table 2).

Results were similar after restricting to those with at least 12 months of follow-up data, to those without prior CVD, and when including medication users with one or more dispensings of each medication within 12-months (see Appendix B). Results were in the same direction, but RRs were slightly less strong after additional adjustment for medication use in the three months prior to the index CVD event.

4. Discussion

In this large-scale data linkage study in the immediate period following a MI or stroke, women were around 9% less likely than men to

Table 1
Baseline characteristics of the study sample by sex, Australia, 2012–2017.

	Male % (n)	Female % (n)	Total
All participants	60 (4,986)	40 (3,292)	100 (8,278)
Age, years			
45–64	19 (941)	16 (539)	18 (1,480)
65–84	62 (3,070)	56 (1,848)	59 (4,918)
≥85	19 (975)	28 (905)	23 (1,880)
Education			
No school certificate	14 (694)	19 (608)	16 (1,302)
Certificate/diploma/trade	67 (3,256)	68 (2,190)	67 (5,446)
Tertiary	19 (948)	13 (412)	17 (1,360)
CVD type			
MI	53 (2,647)	43 (1,422)	49 (4,069)
Stroke/TIA	47 (2,339)	57 (1,870)	51 (4,209)
Patient concession status			
Concession-only	70 (3,468)	78 (2,523)	73 (5,991)
General-only	21 (1,027)	15 (479)	19 (1,506)
Mixed	9 (437)	7 (239)	8 (676)

Percentages are within sexes for each characteristic and do not include missing values. Number of missing values: education = 170 (2.1%); concession status = 105 (1.3%).

Table 2

Association between sex and the dispensing of combined lipid- and blood pressure-lowering medications at 3-, 6-, 9- and 12-months following hospital admission for myocardial infarction, stroke/transient ischaemic attack, Australia, 2012–2017.

	Neither medication		Both medications	
	% (n)	RR (95% CI) ¹	% (n)	RR (95% CI)
CVD medication dispensed at 3-months following index event (n = 8,278)				
Male	13 (641)	1.00 (ref)	58 (2,873)	1.00 (ref)
Female	16 (536)	1.19 (1.07, 1.32)	51 (1,676)	0.91 (0.87, 0.95)
CVD medication dispensed at 6-months following index event (n = 7,690)				
Male	14 (669)	1.00 (ref)	56 (2,598)	1.00 (ref)
Female	18 (549)	1.21 (1.09, 1.34)	49 (1,512)	0.90 (0.86, 0.94)
CVD medication dispensed at 9-months following index event (n = 7,195)				
Male	16 (675)	1.00 (ref)	55 (2,372)	1.00 (ref)
Female	19 (533)	1.16 (1.05, 1.29)	49 (1,398)	0.91 (0.87, 0.95)
CVD medication dispensed at 12-months following index event (n = 6,703)				
Male	17 (676)	1.00 (ref)	53 (2,154)	1.00 (ref)
Female	19 (518)	1.14 (1.03, 1.26)	48 (1,296)	0.92 (0.88, 0.97)

¹ Analyses adjusted for age, education, type of CVD event, history of prior CVD, and patient concession status.

be using guideline-recommended preventive CVD medications and 19% more likely not to be using any CVD preventive medications. This relationship remained over time, including 12 months after the index event, and after adjusting for a range of potential confounders.

Our findings are broadly consistent with previous studies within Australia. Registry data from 43 public hospitals nationwide showed that women hospitalised for ACS are less likely than men to be prescribed recommended medications at discharge, and follow-up self-report data indicated that women were 16% less likely than men to be using at least 75% of the recommended medications (aspirin, other antiplatelet, lipid-lowering medication, beta-blocker and ACE inhibitor/angiotensin II receptor blocker) at 12 months following hospitalisation (Hyun et al., 2021). Results from a representative Australian cross-sectional sample found that more men (50%) than women (34%) with self-reported CVD were using lipid- and blood pressure-lowering medications, with 19% and 23%, respectively, using neither medication (Banks et al., 2016). These consistent findings, despite the use of different samples and differences in study design, indicate that, in Australia at least, there are likely to be sex-differences in the use of CVD preventive medications.

Such differences might arise through a number of different mechanisms, including differences in prescribing practice. Registry data analysis of over 12,000 patients across 30 Victorian hospitals found that women treated for MI, who had undergone percutaneous coronary intervention and had preserved left ventricular ejection fraction (>44%), had 34–38% lower odds of receiving recommended medications within 30 days of discharge than their male counterparts (Hay et al., 2020). This difference was driven primarily by a difference in lipid-lowering therapy, consistent with another study that found women had 49% lower odds of being prescribed statins at discharge (Khan et al., 2018). Primary care studies show comparable patterns, with women less likely to be prescribed combination medication for existing CVD than men (Hyun et al., 2017; Lee et al., 2019; Simpson et al., 2005; Turnbull et al., 2011). A recent study of 130,926 patient records from 438 primary care sites across Australia (2014 to 2018) showed that only 22% of women compared to 34% of men with coronary heart disease were prescribed all four recommended daily medications (antiplatelet agents, angiotensin-converting enzyme inhibitors or angiotensin II receptor antagonists, beta-blockers and statins), and 21% of women vs. 10% of men were prescribed none of these (Lee et al., 2019). Similar findings have been reported in international studies (Shah et al., 2016; Simpson et al., 2005).

The difference in prescribing pattern observed in these previous studies may be in part due to an interplay of physician- and patient-related factors. This may include a perception – by physicians and

patients – that women are at lower risk of severe outcomes from CVD than men (Mosca et al., 2005). There is evidence that healthcare providers tend to assign women to a lower CVD risk category than men with identical risk factors (Mosca et al., 2005; Turnbull et al., 2011), even in patients with established CVD (Turnbull et al., 2011). Sex differences in medications prescribed following a CVD event have been shown even when women have more co-morbidities such as hypertension, diabetes, chronic kidney disease and previous cerebrovascular diseases, than men (Hay et al., 2020; Hyun et al., 2021; Khan et al., 2018).

Women may also be less likely to adhere to CVD medications following an event. In a multi-country meta-analysis of statins usage, women were found to have 10% higher odds of non-adherence to statins medication (OR 1.10, 95% CI 1.07–1.13) compared with men (Lewey et al., 2013). Certain co-morbidities, such as diabetes, are sometimes reported to be associated with higher levels of medication adherence (Leslie et al., 2019), while other co-morbidities, such as depression, are associated with lower levels of adherence (Gast and Mathes, 2019). A nationwide Australian study found that the strongest predictor of adherence to recommended secondary prevention medications at six months following an ACS event was being discharged with prescriptions for $\geq 75\%$ of indicated medications (OR 10.23, 95% CI 7.89–13.27) (Brieger et al., 2018). Although we did not specifically assess adherence over time, our results suggest that the differences in medication use and non-use between men and women exist in the initial period following an MI or stroke and persist over time.

To our knowledge, this study is the first to quantify sex differences in longer term medication use following a MI or stroke within a general Australian population sample, using pharmacy dispensing rather than self-reported data. Blood pressure- and lipid-lowering medications are recommended for all patients following a MI or ischaemic stroke unless contraindicated. To account for switching between medications which might occur due to adverse events or patient preferences, we focused on broad categories of blood pressure- and lipid-lowering medications rather than reporting on specific medications. This approach also ensured that minor updates to specific types of blood pressure- and lipid-lowering medications recommended within clinical guidelines over the follow up period are unlikely to affect results. A key limitation of dispensing data is that they do not provide information on whether a medication was actually used by the patient. We sought to account for this by requiring at least two dispensings of both medications within 12 months of the index event; sensitivity analyses showed our results were robust to changes in this definition with similar results observed when people with one or more dispensings were considered users. Although we did not include antithrombotic medication usage in our analysis, previous studies show similar sex differences in prescription of antithrombotic medications (Hyun et al., 2021; Lee et al., 2019; Simpson et al., 2005; Turnbull et al., 2011). The data from this study came from the 45 and Up Study which has a response rate of around 18%, comparable to similar international cohort studies. While the absolute proportions of participants using medications may not be generalisable, relative measures of association (i.e. the reported RRs for sex-differences) are likely to be generalisable, assuming limited confounding or effect modification (Mealing et al., 2010; Rothman et al., 2013).

The findings from this paper suggest that there is a disparity in the use of medication after a MI or stroke between men and women; a difference that persists over time with men being more likely than women to use preventive CVD medications. Blood pressure- and lipid-lowering medications are established effective preventive medications that can halve the risk of future CVD events (Yusuf, 2002). Ensuring appropriate preventive treatment of all people with CVD, including women, should be a cornerstone of the approach for reducing CVD within the population.

CRedit authorship contribution statement

Eden Barrett: Writing - original draft, Writing - review & editing.

Ellie Paige: Conceptualisation, Methodology, Formal analysis, Writing - original draft, Writing - review & editing. **Jennifer Welsh:** Conceptualisation, Methodology. **Rosemary Korda:** Conceptualisation, Methodology. **Grace Joshy:** Conceptualisation, Methodology. **Melonie Martin:** Conceptualisation, Methodology, Investigation. **Emily Banks:** Conceptualisation, Methodology.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at <https://doi.org/10.1016/j.pmedr.2021.101342>.

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