

**TITLE** Secondary preventive medication use in a prevalent population-based cohort of acute coronary syndrome survivors

**Running Head** Medication use after acute coronary syndrome

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#### **ABSTRACT**

**Aim** Describe the dispensing patterns for guideline-recommended medications during 2008 in people with acute coronary syndrome (ACS) and how dispensing varies by gender and time since last ACS hospitalisation.

**Method** A descriptive cohort spanning 20 years of people alive post ACS in 2008. We extracted all ACS hospitalisations and deaths in Western Australia (1989-2008), and all person-linked Pharmaceutical Benefits Scheme claims nationally for 2008. Participants were 23,642 men and women (36.8%), alive and aged 65-89 years in mid-2008 who were hospitalised for ACS between 1989 and 2008. Main outcome was the proportion of the study cohort (in 2008) dispensed guideline-recommended cardiovascular medications in that year. Adjusted odds ratios estimating the association between type (and number) of guideline-recommended medications and time since last ACS hospitalisation.

**Results** Medications most commonly dispensed in 2008 were statins (79.6% of study cohort), then angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers (ACEi/ARBs) (71.1%), aspirin or clopidogrel (59.4%) and  $\beta$ -blockers (54.6%). Only 51.8% of the cohort was dispensed 3 or more of these drug types in 2008. Women with ACS were 18% less likely to be dispensed statins (adjusted Odds Ratio (OR) = 0.82; 95% CI 0.76-0.88). Overall, for each incremental year since last ACS admission there was an 8% increased odds (adjusted OR=1.08; 95% CI 1.07-1.08) of being dispensed fewer of the recommended drug regimen in 2008.

**Conclusion** Longer time since last ACS admission was associated with dispensing fewer medications types and combinations in 2008. Interventions are warranted to improve dispensing long-term and any apparent gender inequality in the drug class filled.

*Words 250*

**MeSH-compliant keywords:** acute coronary syndrome, pharmacoepidemiology, prevention & control, evidence-based practice, gender

## INTRODUCTION

The global non-fatal burden of acute a coronary syndrome (ACS) is rising as more patients survive an attack [1]. Enhancing the prescription and dispensing of secondary prevention treatments are likely to have the greatest potential for the reducing both death and recurrent events [2]. The use of secondary preventive drugs following non-fatal ACS improves prognosis and is universally advocated. Meta-analyses [3-9] of randomised clinical trials have reported that following ACS, the use of  $\beta$ -blockers, angiotensin-converting enzyme inhibitors (ACEi) or angiotensin-receptor blockers (ARB), statins, and dual antiplatelet medications are associated with reductions in adverse cardiovascular events. Despite the availability of guidelines [10-13] and substantial government subsidies for these medications, gaps in prescription and dispensing persist in Australia and elsewhere [14-17].

In Australia, studies show that even at hospital discharge a substantial proportion of eligible patients are not prescribed all of the recommended medications [18, 19]. A recent bi-national Snapshot of 2,299 people with confirmed ACS found that only 65% were prescribed sufficient preventive drugs (4-5 of the following: lipid lowering, aspirin, antiplatelet,  $\beta$ -blocker, ACEi/ARB) at discharge.<sup>16</sup> A retrospective investigation of another cohort with a diagnosis of myocardial infarction (MI) between 2005 and 2007 found aspirin and statins were prescribed at discharge in 86% to 88% of people, followed by ACEi/ARBs (75%),  $\beta$ -blockers (73%) and clopidogrel (69%) [19]. These percentages were similar to those in the aforementioned Snapshot, aside from ACEi/ARBs which were prescribed to 65% of those with ACS in the more recent study [18].

Following discharge from hospital, there is limited evidence regarding the long-term regimen of secondary preventive cardiovascular medications in Australia. One study of 9,635 Australian Veterans with ischaemic heart disease reported high persistence (continuance of the treatment for the prescribed duration) to cardiovascular medications over a 6.5 year period, particularly for lipid-lowering drugs, antiplatelets and ACEi/ARBs [14]. Whether or not these patterns of preventive medication persistence are also present in the broader community is unanswered.

This study describes the dispensing patterns for guideline-recommended medications during 2008 in a cohort of people alive post ACS. We investigated whether differences in dispensing exist between males and females, and how type and number of medications dispensed during 2008 varies by time since last ACS admission.

## METHODS

### Data sources

A cohort of people alive post ACS in 2008 was identified and characterised from administrative health records, linked using highly accurate probabilistic matching methods previously described [20]. Record linkage permitted person-specific hospital admissions, dispensed medications and mortality to be investigated. Details of the Hospital Morbidity Data Collection (HMDC), Mortality Register and PBS databases used in this study have been described in our study protocol [21].

### Study population

The study included all people alive aged 65-89 years on 30 June 2008 with a discharge diagnosis of ACS from Western Australian (WA) hospital during a 20-year period ending on 30 June 2008 (the 'study year') and assumed to be living in WA at the time. International Classification of Diseases version 9-Clinical Modification and 10-Australian Modification (ICD-9-CM and ICD-10-AM) codes were used to identify all hospitalisations for ACS where either MI (ICD-9 410, ICD-10 I21-22) or unstable angina (ICD-9 411.1, ICD-10 I20.0) were recorded in the principal discharge diagnosis field. Details of the final study cohort are shown in Figure 1.

### Dispensed Medications

In Australia, expensive medicines are subsidised by the government through the PBS to make them more affordable, with patients paying a specified co-payment. All government-subsidised drugs dispensed from community pharmacies in Australia for which a claim is made to Medicare Australia are recorded in the national PBS database. Cheaper medications whose cost is below the patient co-payment are paid in full by the patient and not recorded in the PBS database. However, patients aged  $\geq 65$  years are eligible for government concession cards which greatly reduces the co-payment for the commonly prescribed secondary preventive medications for cardiovascular disease thereby generating a

PBS record. The age restriction of the study cohort to a minimum of 65 years was designed to address this limitation of the PBS data. An estimated 90-95% of the Australian population aged 65 years or more hold a concession card [22].

All medications listed on the PBS schedule have an associated PBS item code that identifies the drug and the product strength (different brands of the drug have the same code). Additionally, the PBS database includes the Anatomical Therapeutic Chemical (ATC) classification code [23] for each medication. After cross-checking with PBS item codes, ATC codes were used for identifying the medications of interest given their consistent use over time and ability to capture the known PBS item code. The medications of interest and associated ATC codes are shown in Supplementary table 1. A medication was regarded as dispensed if there was at least one prescription claim for that medication during 2008. We identified any dispensing during the entire calendar period for 2008 to account for any seasonal variations that might impact dispensing patterns. A category of 'no PBS record of any type' was used in the multivariable analysis to adjust for seniors likely to have missing drug data.

Low-dose aspirin is listed on the PBS schedule. However, aspirin use is difficult to assess from the PBS database because of its availability over-the-counter from community pharmacies and supermarkets. This availability of aspirin at low cost without requirement of a prescription means that use of aspirin for secondary prevention is underestimated using PBS records [16, 17]. While the PBS-derived prevalence of aspirin or clopidogrel use is described in ACS survivors for this study (table 1), aspirin was excluded from subsequent analyses. Dispensing of clopidogrel, particularly in 2008, was used to represent the antiplatelet drug group although this is likely to indicate dual antiplatelet therapy as PBS restricts prescription of clopidogrel to use with aspirin (except in aspirin intolerant patients) for reduction of atherothrombotic events in ACS with or without coronary stenting.

### Statistical analyses

Characteristics of ACS survivors (Table 1) were compared using descriptive statistics. T-tests were used to test for crude differences in mean age by gender. The chi-squared test was used to assess gender-specific differences in type and number of medications dispensed.

The association between 'time (years) since most recent ACS hospital admission' and type of drug(s) dispensed during 2008 (Figure 2) was tested using logistic regression. Covariates in logistic regression models included: age (at 30 June 2008), gender, coronary revascularisation procedure (coronary bypass, stenting and angioplasty) each with a 20-year look-back from 30 June 2008, and Charlson comorbidity score (adapted from the Dartmouth-Manitoba algorithm [24]) within 5 years prior to 30 June 2008.

Logistic regression was used to confirm whether significant associations remained for gender after adjustment for covariates identified *a priori*: age (at 30 June 2008), coronary bypass, stenting, angioplasty, and Charlson comorbidity score all with their attendant 20-year lookbacks (Table 2). Gender differences in median time from the most recent ACS admission to 30 June 2008 were tested using the Wilcoxon-Mann-Whitney test.

Odds ratios (OR) for 'time since most recent ACS hospital admission' and number of medication types (0-3 medications, excluding clopidogrel) dispensed in 2008 (table 3) were estimated using ordinal logistic regression, with and without the aforementioned covariates. Since logistic regression for an ordinal outcome requires proportional odds between increments of medication numbers dispensed, this was tested using binary outcomes (0-1, 1-2, 2-3 medication types dispensed). We found no significant variations between increments and therefore, for simplicity, we report the overall (ordinal) OR estimate instead of the multiple two-way comparisons.

## RESULTS

Of the 23,642 people in the study cohort, males comprised 63% and were, on average, younger than women (Table 1). More than half (57.2%) of the cohort had a prior MI. Males were more likely than females to have had been revascularised ( $p < 0.0001$ ) prior to 30 June 2008 (table 1). The median number of years since last ACS admission was also significantly higher ( $p < 0.0001$ ) in males (Table 1). A total of 2373 (10.0%) had no identifiable record of having any of the four medication types dispensed during 2008.

## Medications dispensed by study cohort in 2008

The most commonly dispensed medications in 2008 in the study cohort were statins, with 79.6% of survivors filling a script in 2008, followed by ACEi/ARBs (71.1%), aspirin or clopidogrel (59.4%) and  $\beta$ -blockers (54.6%) (Table 1). Males were more likely to have been dispensed statins than females (82% vs 75.5%,  $p<0.0001$ ).

Gender was associated with the odds of being dispensed some medication types (Table 2). The odds of females post ACS being dispensed statins in 2008 were 18% less than for men (adjusted OR=0.82; 95% CI 0.76-0.88), adjusting for age, prior revascularisation, Charlson comorbidity score and years since most recent ACS admission. Decreased odds were also observed for women being dispensed clopidogrel in 2008 compared to men (adjusted OR=0.91; 95% CI 0.85-0.97). No gender differences were observed for  $\beta$ -blockers or ACEi/ARB. Patients who had a prior coronary revascularisation procedure compared to those who did not were more likely to be dispensed each of the secondary prevention medications in 2008.

Time since last ACS admission showed an inverse relationship with the proportion of study cohort being dispensed a secondary preventive medication (Table 2, Figure 2). Clopidogrel showed the largest drop in dispensing during 2008 for each year since last ACS admission (OR=0.84; 95% CI 0.83-0.84), followed by  $\beta$ -blockers (OR=0.93; 95% CI 0.93-0.94), statins (OR=0.94; 95% CI 0.93-0.94) and ACEi/ARBs (OR=0.95; 95% CI 0.94-0.95). Steady patterns of decline since last ACS admission were apparent for all medications, apart from clopidogrel which decreased rapidly thereafter levelling out by seven years (Figure 2).

## Number of medication types dispensed by study cohort in 2008

Almost 90% of people alive post ACS were dispensed one or more of the four guideline-recommended medications ( $\beta$ -blockers, statins, ACEi/ARBS and clopidogrel) in 2008 (Table 1). Only 51.8% were dispensed three or more and 18.2% all four medication types in that year. Since clopidogrel was recommended for relatively short-term use in ACS survivors (up to 12 months), we excluded clopidogrel from analyses investigating multiple drug types dispensed since last ACS admission (Table 3, Figure 3). Some 89.6% of the study cohort in 2008 were dispensed one or more of the three long-term recommended medications ( $\beta$ -blockers, statins and ACEi/ARBS), with a majority (74.8%) being dispensed two or three medications and 41.0% dispensed all three. In the subset where ACS was within one year prior to 2008, 85.1% were dispensed multiple medications types during 2008. This compares with 78.1% if their last ACS admission was five years prior (2003), and 65.6% if ten years prior (Figure 3). For comparison, supplementary Figure 1 describes differences in number of medication type's dispensed (including clopidogrel) in relation to time since most recent ACS admission.

A number of factors were associated with the odds of being dispensed multiple medication types during 2008 (Table 3). Previous revascularisation was associated with being dispensed greater numbers of medication types. Women had greater odds of being dispensed fewer medication types (adjusted OR=1.06; 95% CI 1.01-1.12). Increasing number of years since last ACS admission was associated with the number of medication types that were dispensed in 2008, with an overall 8% increased odds per year (adjusted OR=1.08; 95% CI 1.07-1.08) of being dispensed a lower number of medication types in 2008 (Table 3).

## DISCUSSION

In our 2008 cohort of 23,642 people alive post ACS aged 65-89 years we identified robust dispensed levels of statins, ACEi/ARBs,  $\beta$ -blockers and clopidogrel+aspirin at 5years and beyond. Excluding clopidogrel, around three-quarters of the entire cohort were dispensed two or three of the other secondary prevention drug types that are recommended for long-term cardiovascular risk reduction. Gender was an independent predictor of less dispensing of both individual drugs (statins and clopidogrel) but also medication combinations. Further, coronary revascularisation was a driver of greater preventive medication dispensing.

The strengths of this study lay in the 20-year follow-up (including death), the unselected ACS population and full capture of pharmacy dispensing post event. Differences in dispensing individual medications and medication

combinations are unlikely explained by cost as the vast majority of people were concession card holders with fixed co-payments regardless of medication type or number and a universal safety net of A\$290/annum (or US\$305 in 2008). Being an observational study imposes some limitations, including an inability to determine whether dispensed medications were used in the recommended manner. Dosage information and reasons for non-dispensing of recommended medications were also unavailable. This precludes us from determining whether gaps in dispensing indicate contra-indications and medication side-effects, inadequate prescribing practices of recommended medications, whether individuals are not filling their scripts, or other unknown reasons. The use of low-dose aspirin for secondary prevention is incomplete thereby compromising the assessment of 'any' or 'dual' antiplatelet therapy over time. As this was a retrospective analysis, the results may also be affected by a survivor bias.

### **Individual preventive drug classes**

The most commonly dispensed drug types in 2008 were statins, followed by ACEi/ARBs,  $\beta$ -blockers and clopidogrel. However, only 51.8% of the study cohort were dispensed three or more of these drug types in 2008. The percentage of each drug type dispensed varied with time since last ACS admission. Predictably, clopidogrel dispensing showed the steepest decline initially in relation to time since last ACS admission. This most likely reflects guideline recommendations and the void of evidence for its continuation with aspirin beyond 12 months post-ACS with or without coronary stenting [25]. Conversely, the apparent influence of time since most recent ACS admission on reduced dispensing of  $\beta$ -blockers, ACEi/ARBs and statins in 2008 was more moderate and similar for medication types other than clopidogrel. This likely relates to recommendations for these to be used indefinitely [8-11]. Similarities in the proportion of MI patients taking such preventive medications have been reported previously in a large meta-analysis [14].

### **Combined preventive drug classes**

The numbers of people dispensed multiple medication types, excluding the time-limited drug clopidogrel, also varied by time since last ACS admission. During 2008, the numbers dispensed 2-3 medication types proximal to one, five and 10 years post-ACS fell from 850/1000 to 656/1000. Few studies report on multiple medication continuance following acute MI and of those that do follow-up it is usually for less than one year. An exception is the secondary analysis of the recent randomised MI FREEE Trial [26]. In a restricted analyses, 2,365 (574/1000) acute MI-survivors filled all prescriptions for statin,  $\beta$ -blockers and ACEi/ARB out to 40 months.

### **Predictors of filling medication prescription**

Differences in the dispensing of both individual medications and medication combinations by gender were evident. In particular, compared to men, women were dispensed significantly fewer statin (82% versus 75%; respectively) prescriptions whereas no such differences existed with dispensing  $\beta$ -blockers or ACEi/ARBs. The findings persisted even after adjustment for a number of confounders, including age and coronary revascularisation. The gender disparity for statin is particularly striking since, previous observational study of MI survivors in WA, optimal all-cause survival for females was associated with drug combinations including statins ( $\beta$ -blockers and statins, with or without ACEi/ARBs) [27]. Other studies have reported lower statin use in females compared to males [28, 29] despite their comparable benefit in reduced cardiovascular events for both sexes [30, 31]. Among the potential reasons for this discrepancy are physicians applying a higher threshold for statin treatment in women [32, 33], gender-specific side effects from lipid-lowering drugs, such as increased risk for statin-associated myopathy [34] and lower extremity pain [35], and an adverse cardiovascular risk profile compared with men [28].

Receipt of prior coronary revascularisation being associated with greater medication persistence is indirectly supported by a secondary analysis of the randomised MI FREEE study [26]. This finding may relate to receipt of pre-discharge medication counselling and prioritisation by the physician(s), the patient or both for continuance with the prescribed medications following a major heart procedure [36].

The sustained prescription and dispensing of guideline advocated drugs following ACS is considered among the major therapeutic options to reduce subsequent mortality and non-fatal ischaemic events. A greater number of major ischemic cardiovascular events are likely to be prevented by more complete coverage with guideline-recommended medication combinations in comparison with individual drugs; particularly in women.

In summary, around three-quarters of people alive post ACS aged 65-89 years were dispensed two or three of the guideline recommended cardiovascular medications (excluding clopidogrel) during 2008. Time since last ACS admission was associated with being dispensed fewer medication types in 2008, and was inferior in women than men. Women were also less likely to be dispensed a statin during 2008 than men. Specific reasons for this should be investigated and interventions for improving long-term use of  $\beta$ -blockers, statins and ACEi/ARBs (particularly in combination) should be considered. Our findings are more likely generalizable to seniors with heavily subsidized access to these cardio-protective medications used to treat ACS.

**Ethics** – Ethics approvals for the study were obtained from the following: (i) Department of Health WA HREC #2014/11 on 21/10/2014; (ii) Western Australian Aboriginal Health Ethics Committee #572 on 19/06/2014; and (iii) and The UWA HREO RA/4/1/1130 on 03 February 2016.

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*Words 2992*

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**Table 1 Characteristics of acute coronary syndrome (ACS) survivor cohort**

Characteristics	Male n (%)	Female n (%)	Total n (%)	Crude p-value* for gender difference
Total numbers of people, %	14,947 (63)	8,695 (37)	23,642	
Mean years of age (SD)	75.4 (6.5)	77.9 (6.7)	76.4 (6.7)	<0.0001
Age groups, %				<0.0001
65-69 years	25.3	15.8	21.8	
70-74	24.8	18.9	22.6	
75-79	23.0	23.1	23.0	
80-84	17.8	24.3	20.2	
85-89	9.2	17.9	12.4	
Dispensed drug types during 2008, %				
β-blockers	54.4	54.9	54.6	0.4093
Statins	82.0	75.5	79.6	<0.0001
ACEi/ARBs	71.3	70.9	71.1	0.4746
Aspirin	39.9	40.9	40.2	0.1281
Clopidogrel	33.3	32.0	32.8	0.0328
Aspirin or clopidogrel	59.0	59.9	59.4	0.2195
Number of long-term maintenance drug types dispensed in 2008, %^				
0 drugs	9.9	10.3	10.0	0.3399
1	11.0	13.1	11.8	<0.0001
2	25.9	27.2	26.4	0.0249
3	34.6	31.8	33.6	<0.0001
4	18.6	17.6	18.2	0.0522
Prior angioplasty, %	14.7	10.3	13.1	<0.0001
Prior stenting, %	36.6	29.0	33.8	<0.0001
Prior coronary bypass surgery, %	30.9	17.7	26.1	<0.0001
Charlson comorbidity score mean (SD)	1.4 (2.1)	1.5 (2.1)	1.4 (2.1)	0.1015
Median years since <i>last</i> ACS admission	5.5	4.6	5.2	<0.0001
Median years since <i>first</i> ACS admission	6.6	5.7	6.2	<0.0001
Mean (SD) years since <i>last</i> ACS admission	6.7 (5.2)	5.9 (5.0)	6.4 (5.2)	<0.0001
Mean (SD) years since <i>first</i> ACS admission	7.5 (5.4)	6.7 (5.1)	7.2 (5.3)	<0.0001

\* Gender differences were tested using chi square test (for categorical variables), T-test (mean age, Charlson), Wilcoxon-Mann-Whitney test (median age). ^ Long-term secondary preventive drugs (β-blockers, ACEi/ARB= angiotensin-converting enzyme inhibitors/angiotensin-receptor blockers, statins, clopidogrel). SD=standard deviation, ACS=acute coronary syndrome

**Table 2 Adjusted odds ratios (ORs) from logistic regression models for being dispensed each drug type in 2008 in the ACS survivor cohort**

Covariate	Adjusted ORs* (95% CI)			
	$\beta$ -blockers	Statins	ACE i/ARBs	Clopidogrel
Age in 2008	1.00 (1.00-1.01)	0.97 (0.96-0.98)	0.99 (0.99-1.00)	1.01 (1.01-1.02)
Gender	1.00 (0.94-1.06)	0.82 (0.76-0.88)	1.04 (0.98-1.11)	0.91 (0.85-0.97)
Prior angioplasty	1.15 (1.06-1.25)	1.90 (1.69-2.13)	1.12 (1.02-1.21)	1.34 (1.22-1.47)
Prior stenting	1.30 (1.23-1.39)	2.42 (2.22-2.64)	1.51 (1.41-1.62)	3.13 (2.93-3.34)
Prior coronary bypass surgery	1.12 (1.05-1.19)	2.45 (2.24-2.67)	1.52 (1.41-1.62)	1.02 (0.95-1.10)
Charlson comorbidity score	1.05 (1.03-1.06)	1.01 (0.99-1.03)	1.10 (1.08-1.11)	1.08 (1.06-1.09)
Years since last ACS admission	0.93 (0.93-0.94)	0.94 (0.93-0.94)	0.95 (0.94-0.95)	0.84 (0.83-0.84)

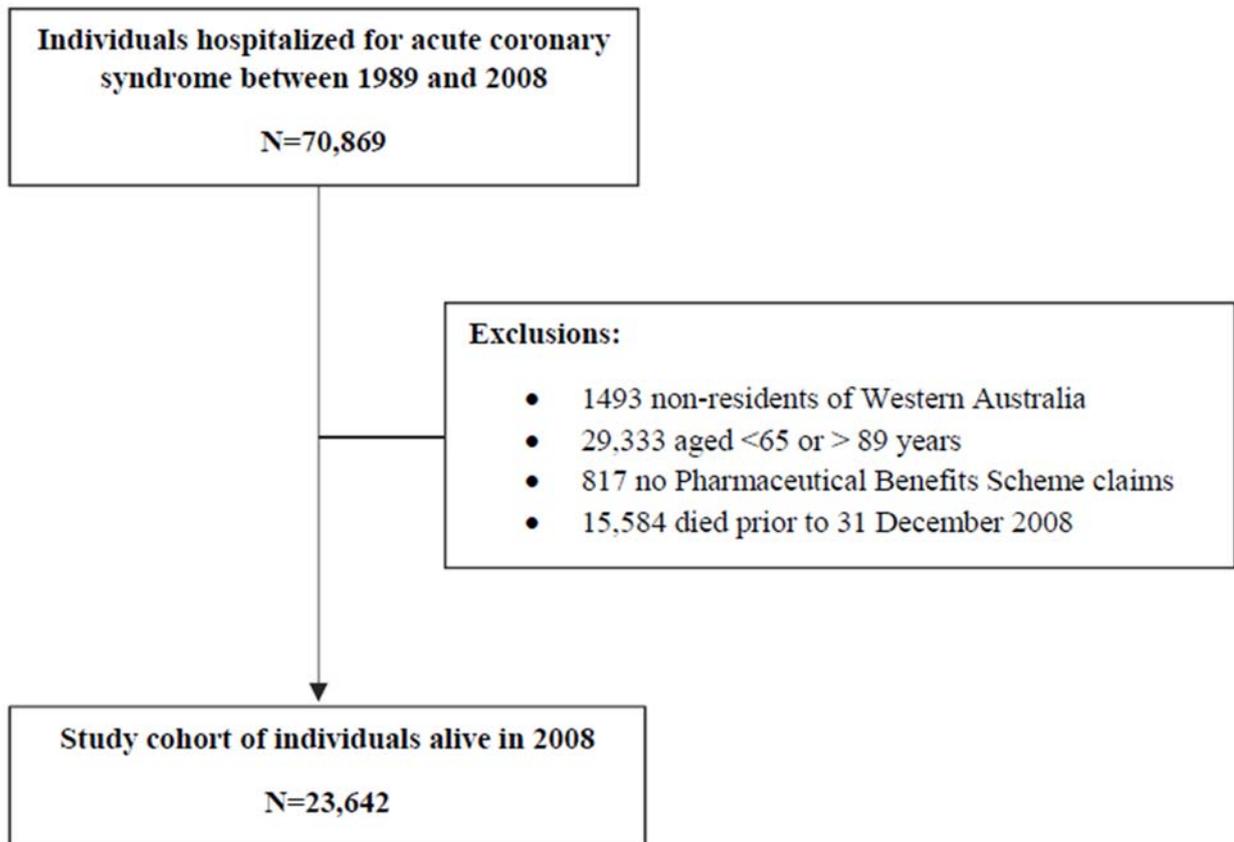
\* Covariates in adjusted models: age in 2008 (continuous), gender (reference=female), prior stenting (reference=yes), prior angioplasty (reference=yes), prior coronary bypass (reference=yes), Charlson score (continuous), years since last ACS admission (continuous), angiotensin-converting enzyme inhibitors=ACEi, angiotensin-receptor blockers=ARB, ACS=acute coronary syndrome

**Table 3 Odds ratios (ORs) from ordinal logistic regression models for being dispensed fewer of three drug types (statins, angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers,  $\beta$ -blockers) in 2008 in the acute coronary syndrome survivor cohort**

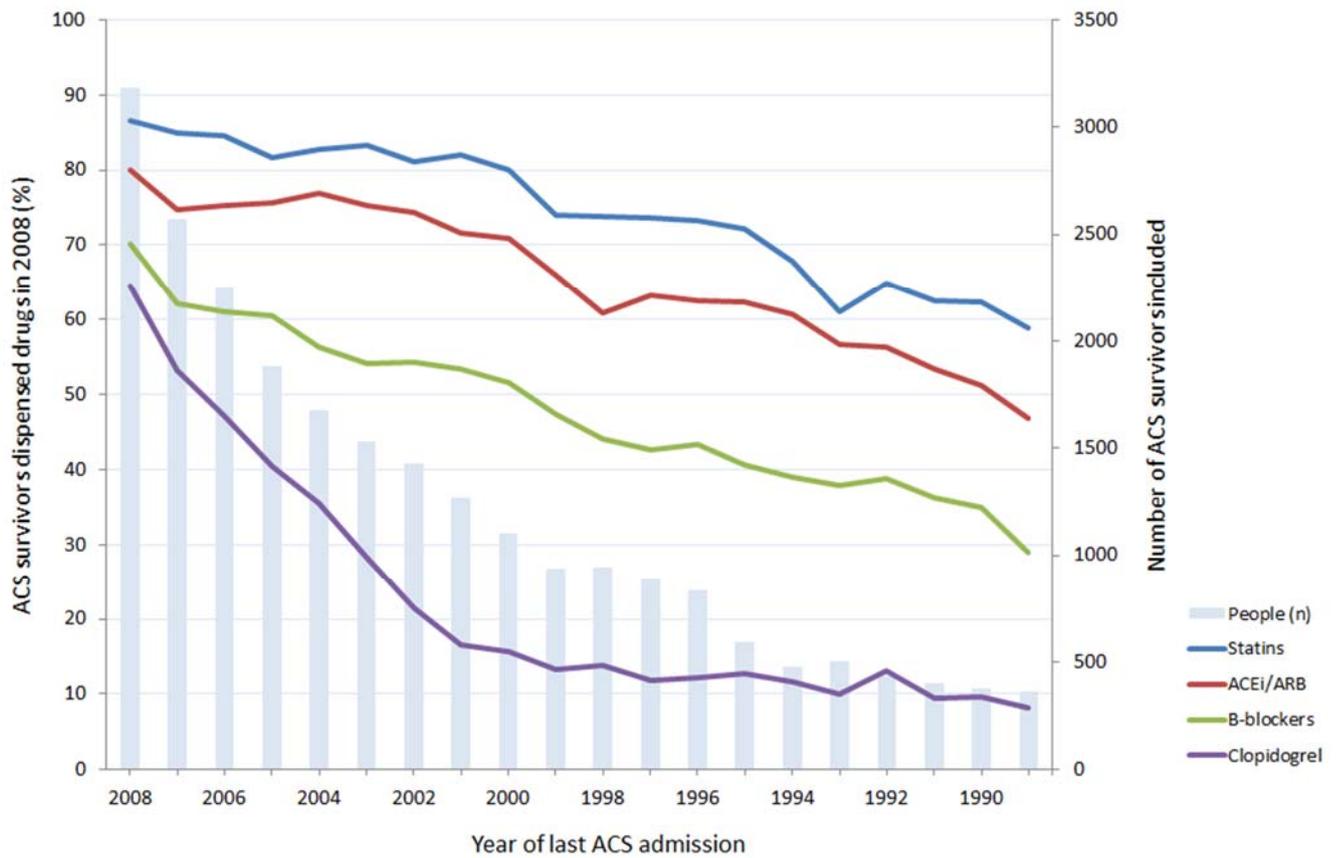
<b>Covariate</b>	<b>crude OR (95% CI)</b>	<b>adjusted OR (95% CI)*</b>
Age	1.02 (1.01-1.02)	1.01 (1.01-1.02)
Female	1.14 (1.09-1.20)	1.06 (1.01-1.12)
Prior angioplasty	0.81 (0.75-0.86)	0.80 (0.74-0.86)
Prior stenting	0.50 (0.48-0.53)	0.61 (0.58-0.65)
Prior coronary bypass surgery	0.74 (0.70-0.78)	0.66 (0.63-0.70)
Charlson comorbidity score	0.92 (0.90-0.93)	0.94 (0.93-0.96)
Years since last ACS admission	1.09 (1.09-1.10)	1.08 (1.07-1.08)

\* Covariates in adjusted model: age in 2008 (continuous), gender (reference = male), prior angioplasty (reference = no prior angioplasty), prior stenting (reference = no prior stenting), prior coronary bypass (reference =no prior coronary bypass), Charlson score (continuous), years since last ACS admission (continuous), ACS = acute coronary admission, CI = confidence level.

**Figure 1** Flow chart of original cohort and exclusions

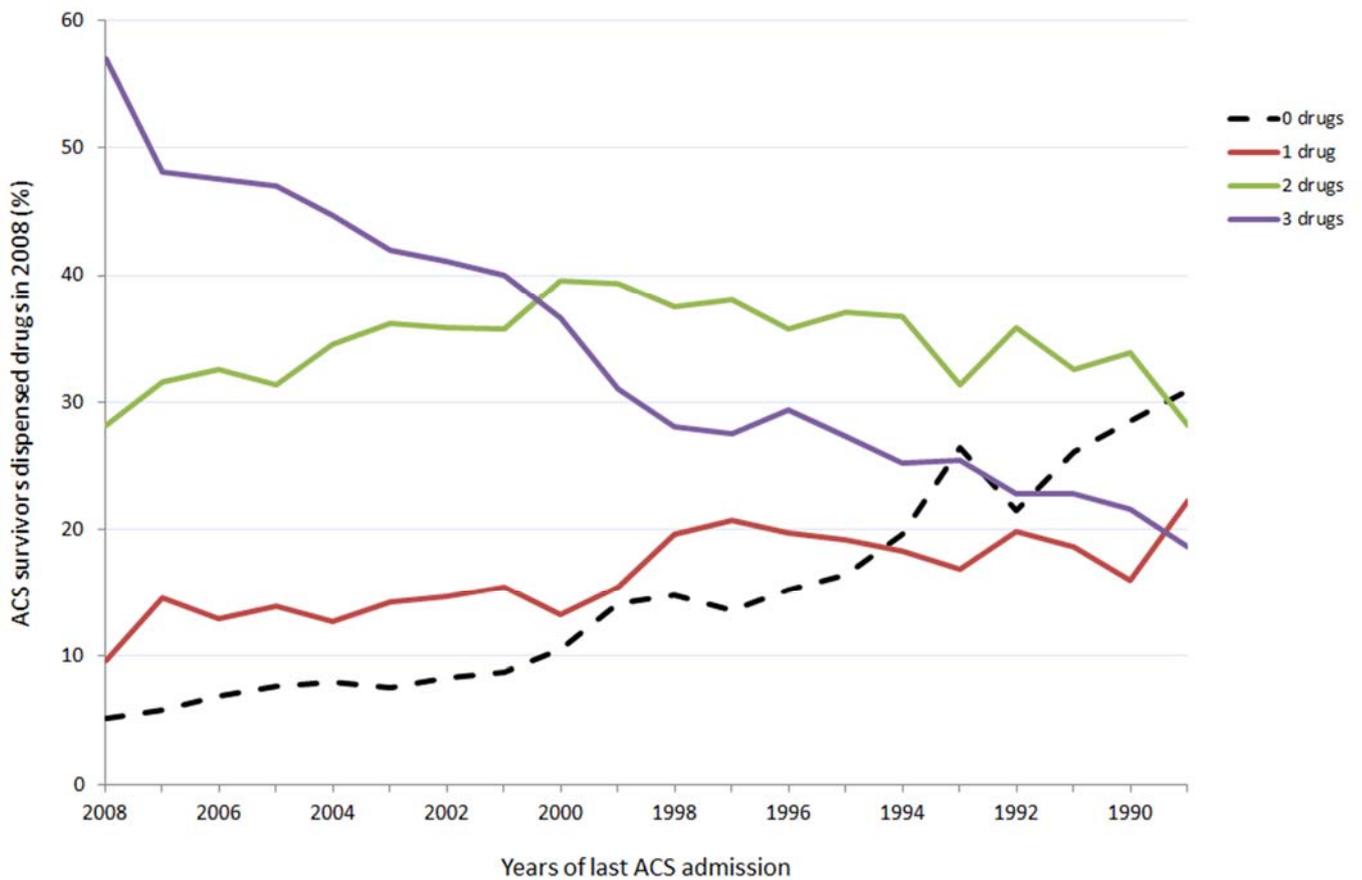


**Figure 2 Drugs dispensed to acute coronary syndrome (ACS) survivors (%) in 2008 versus year of last ACS admission**



The time since last ACS admission ranges from 0 for 2008 to 20 years for 1989 (which is the start of the 20-year look-back period from 2008). ACEi=angiotensin-converting enzyme inhibitors; ARB=angiotensin-receptor blockers

**Figure 3** Number of long-term maintenance drug types (0-3) dispensed in 2008 to acute coronary syndrome (ACS) survivors (%) versus year of last ACS admission



The time since last ACS admission ranges from 0 for 2008 to 20 years for 1989 (which is the start of the 20-year look-back period from 2008). The drug class permutations included in the plots are statins,  $\beta$ -blockers and angiotensin-converting enzyme inhibitors or angiotensin-receptor blockers.