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RESEARCH ARTICLE

Missed opportunity: a clinical data linkage study of guideline-directed medical therapy and clinical outcomes of patients discharged with acute coronary syndrome who attended cardiac rehabilitation programs

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Abstract

Background: Although guidelines recommend guideline-directed medical therapy (GDMT) for patients with acute coronary syndrome (ACS), implementation is limited in clinical practice.
Aim: To assess the level of GDMT in ACS patients after discharge who attended cardiac rehabilitation (CR) programs and association with clinical outcomes.
Method: A cross-sectional study was conducted in 13 rural and 10 metropolitan CR programs via all modes of delivery (face-to-face, telephone, or general practice-hybrid) operating in South Australia, Australia. ACS patients were included if they were ≥18 years of age and were referred and attended CR programs with medication details recorded in their hospital discharge summary. GDMT was assessed according to the Australian clinical guidelines for the management of acute coronary syndromes 2016. Prescription of all the four recommended medication classes was considered optimal. Logistic regression and χ^2 test were used for association. Ethical approval was granted by the South Australian Department for Health and Wellbeing Human Research Ethics Committee (Reference No. HREC/15/SAH/63) and the Northern Territory Department of Health Human Research Ethics Committee (Reference No. HREC 2015-2484) which included a waiver of consent per the *National Statement on Ethical Conduct in Human Research* and the study conforms with the *Good Clinical Practice Guidelines*.
Results: Of the 1229 patients included, 74.6% were male and 41.1% had acute myocardial infarction. Only 39.7% of patients received optimal prescription. Prescription of any three or two medication class combinations occurred for 78.3% and 94.1% of patients, respectively. Optimal GDMT was associated with fewer hospital admissions (odds ratio = 0.647, 95% confidence interval 0.424–0.987, p = 0.043) with no significant gender association. Women were less likely to be prescribed angiotensin converting enzyme inhibitors (p = 0.003), angiotensin receptor blockers (p = 0.007), statins (p = 0.005), and any two (p < 0.001) and three combinations (p = 0.023) of medication classes.
Conclusion: GDMT prescription was suboptimal in patients with ACS before attendance at CR. Primary care and CR clinicians have missed an opportunity to implement best practice guideline recommendations, particularly for women.

Keywords: evidence-based prescription, secondary prevention, acute coronary syndrome, mortality, hospital readmission.

INTRODUCTION

Cardiovascular disease (CVD) remains the leading cause of death worldwide, taking the life of 17.9 million people annually.[1] Guideline-directed medical therapy (GDMT) is strongly recommended by guidelines for secondary prevention and has been shown to be effective in improving clinical outcomes and quality of life of patients.[2–4] The effectiveness on better clinical outcomes from medications is dependent on adherence to guideline recommendations by prescribers and the use of the prescribed medications by the patient. Adherence to guideline recommendations for prescription of evidence-based pharmacotherapy is vital for the success of treatment and prevention of secondary CVD.[2]

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International[2] and Australian national[5] guidelines have recommended the use of evidence-based pharmacotherapy for the prevention of secondary cardiovascular risk factors and complications in patients diagnosed with CVD, including acute coronary syndrome (ACS). Guidelines recommend long-term combination of antiplatelet therapy, statins, angiotensin converting enzyme inhibitors (ACEIs)/angiotensin receptor blockers (ARBs), and beta-blockers to be prescribed for patients with ACS for effective secondary prevention. The level of evidence for these recommendations is strong, and adherence to preventative pharmacotherapy and secondary prevention cardiac rehabilitation (CR) programs reduces morbidity, rates of hospital admission, and mortality.[6,7] Cardiac rehabilitation is the sum of interventions necessary to improve the physical, psychological, and social health of patients after an acute cardiovascular event. The Australian Cardiovascular Health and Rehabilitation Association recommends five core components: referral and access to services, assessment and short-term monitoring, recovery and long-term monitoring, lifestyle/behavioural modification and medication adherence, and evaluation and quality improvement.[8] GDMT is the cornerstone for secondary prevention in patients with ACS. Evidence has shown that a reduction of 1 mmol/L of low-density lipoprotein cholesterol (LDL-C) using long-term statin therapy causes about a 20% reduction in the annual risk of a major vascular event.[5] Similarly, the composite endpoint of stroke, coronary revascularisation, myocardial infarction, stroke, or vascular death was reduced by 20% (relative risk [RR] = 0.80, 95% confidence interval [CI] 0.77–0.82) for every 1.0 mmol/L reduction in LDL-C with long-term statin therapy. Beta-blocker therapy in combination with aspirin and statins reduces all-cause mortality by 23%.[5] ACEIs/ARBs also reduce cardiovascular mortality (odds ratio [OR] = 0.82, 95% CI 0.76–0.88, $p < 0.0001$), non-fatal myocardial infarction and stroke with long-term use.[5] Despite the benefit of adhering to the recommendations, studies have shown gaps in translating them into clinical practice, indicating inadequate utilisation of secondary cardiovascular prevention medications[9] where implementation of optimal GDMT ranged from 65% to 71%.[10–12] Although adherence to guideline recommendations has significantly improved in hospital settings, further improvements are suggested for the implementation of best practice recommendations in general and in particular, in elderly patients and some conditions such as unstable angina.[13,14] CVD is still the number one killer for women, but evidence demonstrates it remains underdiagnosed, underprevented, and or undertreated for secondary prevention.[15,16]

The benefit of complying with guideline recommendations is well established, with limited evidence on the implementation of these recommendations into clinical practice, especially in CR program attendees. Moreover, the evidence on the prescription of GDMT in women who attended and completed CR is limited. Therefore, the aim of this study was to assess the level of GDMT and adherence to guideline recommendations in patients with ACS, and to determine association of adherence to guideline-recommended medication prescriptions with patient clinical outcomes (hospital readmission and mortality) and gender. Our hypothesis is that ACS patients prescribed with optimal GDMT will have better clinical outcomes (less mortality and hospital admission risk) compared with those prescribed suboptimal GDMT, and that prescriptions of guideline-recommended medications will be lower in women compared to men.

METHOD

Ethics Statement

Ethical approval was granted by the South Australian Department for Health and Wellbeing Human Research Ethics Committee (Reference No. HREC/15/SAH/63) and the Northern Territory Department of Health Human Research Ethics Committee (Reference No. HREC 2015-2484) which included a waiver of consent per the *National Statement on Ethical Conduct in Human Research* and the study conforms with the *Good Clinical Practice Guidelines*.

Study Design

A retrospective, cross-sectional study with data linkage was conducted.

Setting

All CR programs (13 rural and 10 metropolitan) in South Australia (SA), Australia, that provide services using all modes of delivery (face-to-face, telephone, and a combination of face-to-face and telephone services [hybrid]) through the Country Access to Cardiac Health (CATCH) database were included. The CATCH database is a statewide clinical database operated by the Integrated Cardiac Clinical Network SA (iCCNet SA). It is used and accessed by CR programs operating in country, regional, and metropolitan South Australia to store and enter patient clinical data.[17]

Participants

All patients ≥18 years of age who were referred to CR programs with a diagnosis of ACS after discharged

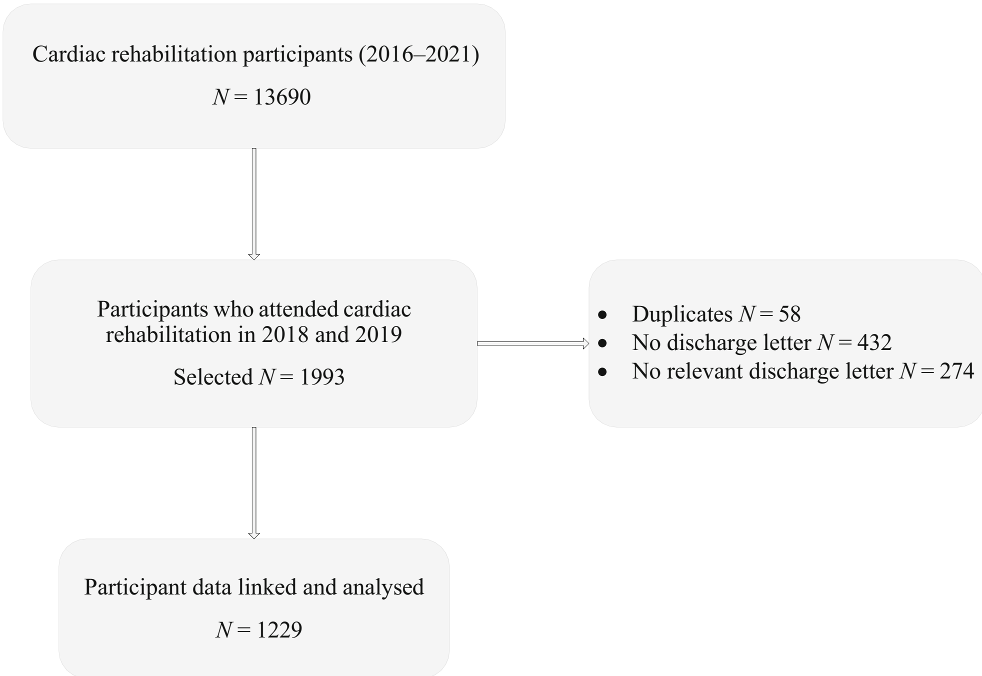

FIGURE 1 Flow diagram of participants included in the study.

from hospital and who attended their CR programs in 2018 and 2019 were selected from all patients who were referred and attended CR programs from 2016–2021. Patients with medication details recorded in the CATCH database were screened and on meeting the inclusion criteria were included in the analysis (Figure 1). As per the data collection template of CATCH, patients who were classified as having ACS[8] listed below were included:

- non-ST elevation myocardial infarction (NSTEMI)
- ST elevation myocardial infarction (STEMI)
- acute myocardial infarction (AMI) with no intervention
- AMI with intervention
- coronary artery bypass grafting (CABG)
- elective intervention: CABG
- elective intervention: post coronary intervention
- post-CABG
- revascularisation procedure (angioplasty/stent)
- stable angina
- unstable angina
- unstable angina with no intervention
- unstable angina with intervention.

Patients who commenced and or completed treatment through private hospitals in South Australia were excluded.

Variables and Outcomes

All program types (country, regional, and metropolitan) were included except programs offered through a private health service. Patients who attended their CR program in 2018 and 2019 were included. Patients' medication details (medication name, dose, frequency, duration, and route of administration when available), principal diagnosis, and secondary comorbidities were accessed and extracted from their CATCH database file. Clinical data including mortality and hospital admission were de-identified and assigned a unique key by South Australian and Northern Territory DataLink (SA NT Datalink) with a follow up duration of 12 months.[18] All data were de-identified, collected, and managed using REDCap (Vanderbilt, Nashville, Tennessee, USA) electronic data capture tools hosted at Flinders University.[19,20] Patient and medication data were linked to the relevant clinical outcomes through the SA NT DataLink process using a unique patient identifier (Patients Specific Linkage Key [PSLK] and CATCH ID) to achieve the outcome of the study. The de-identified data were monitored and audited for accuracy and quality by a data manager. Patient data were linked using a unique identifier and all unmatched data were excluded from the analysis.

The primary outcome of this study was the level of prescription of guideline-recommended medication classes for patients with ACS. GDMT was considered optimal when all of the four recommended medication classes (antiplatelets including either single or dual antiplatelets, statins, beta-blockers, and ACEIs/ARBs) were prescribed as per national guidelines.[5] Correlation of GDMT and clinical outcomes of patients within 12 months, including all-cause and cardiovascular-related mortality and cardiovascular-related hospital readmission, was performed. Gender-specific analysis for prescriptions of GDMT and clinical outcome was conducted considering the other patient factors as constants (age, CR program completion, program types [country, regional, metropolitan], modes of delivery [face-to-face, telephone, or hybrid], program durations, and number of sessions).

Data Sources and Measurements

The details of patients' prescribed medications were extracted from hospital discharge summaries saved in the CATCH database. The prescribed medication classes were compared with the recommendations of the Australian clinical guidelines for the management of acute coronary syndromes 2016.[5] Prescriptions of all the four guideline-recommended medication classes were considered optimal GDMTs. A unique patient identifier (PSLK and CATCH ID) was used to link patient data with the clinical outcomes (mortality and hospital readmission) obtained from the SA NT DataLink process.

Study Size

This study utilised convenience sampling methodology. All patients who were referred and attended CR from 2016–2021 (N = 13 690) were considered. Patients who commenced their CR in 2018 and 2019 (N = 1993) with records of medication details (N = 1229) were included for analysis (Figure 1). The years 2018 and 2019 were selected to consider implementation of the 2016 guideline[5] in practice, i.e. prasugrel was included as one of the approved antiplatelet medications for ACS patients, and also to minimise the impact of the coronavirus disease 2019 (COVID-19) on CR program attendance and completion.

Quantitative Variables

Guideline-recommended medication prescriptions and clinical outcomes (mortality and readmissions) were analysed as quantitative variables.

Statistical Methods

The collected data were cleaned and exported from REDCap into SPSS version 28 (IBM Corp., Armonk, New York, USA). Guideline-recommended medication prescriptions were linked to clinical outcomes (mortality and hospital admission) of patients at 12 months post-discharge from hospital for patients who attended CR programs. GDMT was coded as dichotomous data (optimal = 100%, i.e. prescription of all four recommended classes of medications [antiplatelets, statins, beta-blockers, ACEI/ARBs] and suboptimal <100%, i.e. prescriptions of three or fewer of the recommended classes of medications). Similarly, mortality and hospital admissions were coded as dichotomous (Yes/No). Mortality was classified as cardiovascular--related (as per *International Statistical Classification of Diseases and Related Health Problems*, *Tenth Revision*, *Australian Modification* [ICD-10AM] coding) and all-cause mortality with a follow up of 12 months.

Binary logistic regression was used for association of GDMT and clinical outcomes (mortality and hospital admission). Other factors, including age, gender, CR program completion, program types (country, metropolitan), modes of delivery (face-to-face, telephone, or hybrid), program durations, and number of sessions, were adjusted as confounding factors for the analysis. The chi-square (χ^2) test was used for association of GDMT and clinical outcomes with gender and p-value <0.05 was considered as statistically significant.

RESULTS

Participant Characteristics

Of the total 1993 eligible participants, 432 had no discharge letters and 274 had discharge letters with no medication details. Only 1229 patients were linked to clinical outcomes data and analysed (Figure 1). Of these, the majority were male 917 (74.6%), with 765 (62.2%) patients discharged to their homes. Myocardial infarction (STEMI/NSTEMI) was the main reason for hospital admission with 509 (41.1%) patients and 997 (81.1%) patients completed their CR program. Group sessions via face-to-face consultation was the most common mode of CR delivery with 499 (40.6%) patients attending their program in this way, followed by telephone programs with 432 (35.2%) patients. Most patients lived with others (n = 863, 70.2%) and 630 patients (51.3%) were retired or pensioners when attending their CR program. The number of sessions offered and attended across all CR sites ranged from 1 to 16 (Table S1).

Of the 1229 patients, the most commonly prescribed medications from each of the four recommended classes of medications were: aspirin (n = 1060, 86.2%), atorvastatin (n = 560, 45.6%), metoprolol (n = 526, 42.8%), perindopril (n = 414, 33.7%), and irbesartan (n = 86, 7.0%) (Table S2).

Guideline-directed Medical Therapy

Guideline-recommended medication classes were prescribed to 488 (39.7%) patients. Three and two class combinations were prescribed to 962 (78.3%) and 1156 (94.1%) patients respectively, and 12 patients (1.0%) received none of the recommended medication classes. The most prescribed three medication class combinations were antiplatelet/statin/ACEI or ARB (n = 729, 59.3%), followed by antiplatelet/beta-blocker/ACEI or ARB combinations (n = 528, 43.0%). From two medication class combinations, antiplatelet and statin combination (n = 1013, 82.4%) and antiplatelet (n = 1141, 92.8%) from one medication class were the most prescribed (Figure 2 and Table S3).

Prescriptions of the four recommended classes of medications were significantly associated with hospital admission (OR = 0.647, 95% CI 0.424–0.987, p = 0.043), while no significant association was found with cardiovascular-related or all-cause mortality (Table 1). Although no significant association was observed between clinical outcomes and gender, women were less likely to be prescribed ACEIs (χ^2 = 11.510, p = 0.003), ARBs (χ^2 = 9.876, p = 0.007), statins (χ^2 = 10.68, p = 0.005), antiplatelet and statin combinations (χ^2 = 6.774, p = 0.034), or any two (χ^2 = 16.412, p < 0.001) and three (χ^2 = 7.502, p = 0.023) medication class combinations (Table 2).

DISCUSSION

Guideline-recommended, evidence-based prescription in patients with ACS who attended CR after discharge was suboptimal, with only 39.7% receiving all the recommended medication classes. Those patients prescribed GDMT were 35% less likely to be admitted to hospital compared with those who were not. While no significant association was found between optimal GDMT and clinical outcomes with gender, prescriptions of recommended classes of medications, including statins, ACEIs, ARBs, antiplatelet and statin combinations, and any two and three medication classes prescribed, were significantly lower in women compared to men.

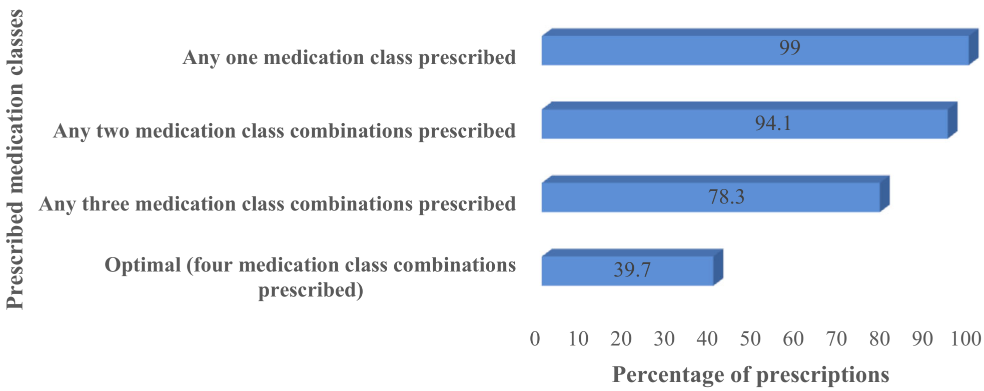

FIGURE 2 Percentage of prescription compliance with guideline recommendations (N = 1229).

TABLE 1 Associations of guideline-directed medical therapy with clinical outcomes

Number of medication classes prescribed	Clinical outcomes	Odds ratio	95% confidence interval	p-value
Prescription of four medication classes	Hospital admission within a year	0.647	0.424–0.987	**0.043**
	Cardiovascular-related mortality	0.641	0.175–2.344	0.501
	All-cause mortality	0.686	0.061–7.744	0.761
Prescription of three medication classes	Hospital admissions within a year	0.695	0.402–1.202	0.193
	All-cause mortality	0.423	0.169–1.057	0.066
Prescription of two medication classes	Hospital admissions within a year	0.528	0.183–1.520	0.236
	All-cause mortality	0.600	0.130–2.765	0.513
Prescription of one medication class	Hospital admissions within a year	2.205	0.435–11.177	0.340
	All-cause mortality	0.287	0.030–2.746	0.279

Bold indicates statistical significance.

TABLE 2 Association of guideline-directed medical therapy and clinical outcomes with gender (male as constant), n = 1229

Factor	Male, N (%)	Female, N (%)	χ^2 value	p-value
Antiplatelet prescription	852 (69)	288 (23)	0.251	0.882
Statin prescription	807 (66)	261 (21)	10.68	**0.005**
Beta-blocker prescription	590 (48)	189 (15)	3.21	0.201
ACEI prescription	450 (37)	120 (10)	11.510	**0.003**
ARB prescription	184 (15)	89 (7)	9.876	**0.007**
ACEI/ARB prescription	628 (51)	207 (17)	2.64	0.267
Antiplatelet and statin and beta-blocker and ACEI/ARB prescription	375 (30)	113 (9)	2.83	0.243
Antiplatelet and statin and beta-blocker prescription	510 (41)	155 (13)	4.55	0.103
Antiplatelet and statin and ACEI/ARB prescription	552 (45)	177 (14)	2.66	0.264
Antiplatelet and beta-blocker and ACEI/ARB prescription	406 (33)	122 (10)	3.342	0.188
Statin and beta-blocker and ACEI/ARB prescription	387 (31)	117 (10)	2.865	0.239
Any three medications prescribed	730 (59)	232 (19)	7.502	**0.023**
Antiplatelet and statin prescription	764 (62)	249 (20)	6.774	**0.034**
Antiplatelet and beta-blocker prescription	556 (45)	176 (14)	3.251	0.197
Antiplatelet and ACEI/ARB prescription	595 (48)	195 (16)	2.413	0.299
Statin and ACEI/ARB prescription	579 (47)	184 (15)	3.412	0.182
Statin and beta-blocker prescription	534 (43)	162 (13)	5.157	0.076
Beta-blocker and ACEI/ARB prescription	422 (34)	128 (10)	3.206	0.201
Any two medications prescribed	865 (70)	291 (24)	16.412	**<0.001**
Cardiovascular-related mortality	15 (1)	4 (0.3)	2.906	0.574
All-cause mortality	33 (3)	8 (0.7)	3.493	0.479
Hospital admission within a year	717 (58)	256 (20)	2.280	0.320

Bold indicates statistical significance. ACEI = angiotensin converting enzyme inhibitor; ARB = angiotensin receptor blocker.

The GDMT (39.7%) result of our study was lower than an Australia and New Zealand study where optimal preventive medication prescription occurred for 65% (n = 2299) of ACS patients[10] and a South Korean study where 75.7% received all five of the recommended medications after discharge with ACS (n = 494).[21] Another Australian study conducted in ACS patients showed four or more of the five recommended medications were prescribed to 77% (n = 754) of patients, as reported by the CONCORDANCE study.[22] This difference could potentially be due to differences in sample size, the source of data as these studies used an electronic medical record while our study used discharge summaries which are more likely to have poor documentation, and variations in the definition of guideline recommendations because all these studies used the list of recommended medications and/or prescriptions of at least three classes of medication while our study used classes of recommended medications. In our study, the low rate of guideline-recommended medication prescription may have led to a non-significant association with mortality and gender. Another study showed a reduction in all-cause mortality associated with GDMT that persisted for up to 12 months post-hospital discharge.[11] This could be due to the difference in sample size (n = 3681 vs n = 1229) and the level of prescriptions of recommended medication classes, where 69% of patients were prescribed optimal therapy[11] while in our study, only 39.7% were prescribed optimal therapy.

The low female attendance (25%) in CR programs in our study was similar to the 2013–2015 audit conducted in South Australia, where of 4286 patients who attended CR programs only 26% (n = 1134) were female.[23] Our study demonstrated that prescription of guideline-recommended medication classes, including statins, ACEIs, and ARBs, was lower in women than in men, which was similar to studies conducted by Alkofide et al.[24] and Zhao et al.[25]

The result of our study indicates the challenge the health system faces to promote optimal GDMT for patients with ACS during hospital stays. Moreover, it highlights the major role of CR and secondary prevention programs in optimising GDMT. Despite the strong recommendation of guidelines in advocating to increase the uptake of effective and proven secondary prevention mechanisms, including recommended medications, access to these services remains low.[26]

A strength of this study is that it included all the 23 (13 rural and regional, and 10 metropolitan) South

Australian CR programs that deliver services through all modes of delivery, indicating the generalisability of the result to all CR program attendees discharged from hospital with ACS. A limitation of this study is the poor data quality reported in patient discharge summaries. This study was solely dependent on the documented medications in the discharge summaries, which might underestimate the extent of real GDMT for patients with ACS. This indicates that patients might have received the recommended medications but these were not comprehensively documented in their discharge summary. In some of the discharge summaries, the handwriting was unreadable (see Figure S1). There were also discharge summaries with no medications recorded, and such records were excluded to reduce potential bias. Lack of data made it challenging to collect and check for patient contraindications of the recommended classes of medications, coexisting comorbidities, renal function status, age, and ethnicity because the documentation was not comprehensive and might underestimate the level of GDMT reported in this study. Another limitation was that this study did not consider the impact of patient adherence to their medication, which might also affect clinical outcomes.

The prescription of guideline-recommended medication classes was suboptimal in ACS patients who were discharged from hospital. Prescription of recommended medication classes was significantly associated with fewer hospital admissions within 12 months. Although no gender association was found with prescription of all the guideline-recommended medication classes and clinical outcomes, prescription of some medication classes was significantly lower in women. These findings present great opportunity to adhere to guideline recommendations in clinical practice to reduce hospital admissions for ACS patients before and during attendance at their CR programs. Hospital pharmacists also have a key role to play in conducting medication reviews before discharging patients to enhance the implementation of guideline recommendations and reduce hospital admissions. Clinicians (primary care and cardiac rehabilitation services) have missed an opportunity before discharge and during CR programs to implement best practice guideline recommendations, particularly for women.

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CONFLICT OF INTEREST STATEMENT

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AUTHORSHIP STATEMENT

Lemlem Gebremedhin Gebremichael: Conceptualisation; data curation; formal analysis; methodology; writing – original draft; writing – review and editing. **Alline Beleigoli:** Conceptualisation; formal analysis; methodology; validation. **Jonathon W. Foote:** Data curation; formal analysis; methodology; validation; writing – review and editing. **Norma B. Bulamu:** Data curation; validation; writing – review and editing. **Joyce S. Ramos:** Data curation; validation; writing – review and editing. **Orathai Suebkinorn:** Validation; writing – review and editing. **Julie Redfern:** Validation; writing – review and editing. **Robyn A. Clark:** Conceptualisation; funding acquisition; project administration; supervision; validation; writing – review and editing.

ETHICS STATEMENT

Ethical approval was granted by the South Australian Department for Health and Wellbeing Human Research Ethics Committee (Reference No. HREC/15/SAH/63) and the Northern Territory Department of Health Human Research Ethics Committee (Reference No. HREC 2015-2484) which included a waiver of consent per the *National Statement on Ethical Conduct in Human Research* and the study conforms with the *Good Clinical Practice Guidelines*.

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OPEN ACCESS STATEMENT

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DATA AVAILABILITY STATEMENT

The data underlying this article cannot be shared publicly due to the Government of South Australia SA Health policy for data linkage privacy. The data will be shared on reasonable request to the corresponding author.

Supporting information

Additional supporting information may be found in the online version of this article:

FIGURE S1 Samples of patient discharge summary.

TABLE S1 Patient demographic and clinical characteristics (N = 1229)

TABLE S2 Commonly prescribed medications (N = 1229)

TABLE S3 Summary of prescription of guideline recommended drug class and combinations (N = 1229)

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