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Application of a risk-guided strategy to secondary prevention of coronary heart disease: analysis from a state-wide data linkage in Queensland, Australia

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ABSTRACT

Objective This study sought whether higher risk patients with coronary heart disease (CHD) benefit more from intensive disease management.

Design Longitudinal cohort study.

Setting State-wide public hospitals (Queensland, Australia).

Participants This longitudinal study included 20 426 patients hospitalised in 2010 with CHD as the principal diagnosis. Patients were followed-up for 5 years.

Primary and secondary outcomes and measures The primary outcome was days alive and out of hospital (DAOH) within 5 years of hospital discharge. Secondary outcomes included all-cause readmission and all-cause mortality. A previously developed and validated risk score (PEGASUS-TIMI54) was used to estimate the risk of secondary events. Data on sociodemography, comorbidity, interventions and medications were also collected.

Results High-risk patients (n=6573, risk score ≥6) had fewer DAOH (Δ=−142 days (95% CI: −152 to −131)), and were more likely to readmit or die (all p<0.001) than their low-risk counterparts (n=13 367, risk score <6). Compared with patients who were never prescribed a medication, those who consumed maximal dose of betablockers (Δ=39 days (95% CI: 11 to 67)), angiotensin-converting enzyme inhibitors/angiotensin receptor blockers (Δ=74 days (95% CI: 49 to 99)) or statins (Δ=109 days (95% CI: 90 to 128)) had significantly greater DAOH. Patients who received percutaneous coronary intervention (Δ=99 days (95% CI: 81 to 116)) or coronary artery bypass grafting (Δ=120 days (95% CI: 92 to 148)) also had significantly greater DAOH than those who did not. The effect sizes of these therapies were significantly greater in high-risk patients, compared with low-risk patients (interaction p<0.001). Analysis of secondary outcomes also found significant interaction between both medical and interventional therapies with readmission and death, implicating greater benefits for high-risk patients.

Conclusions CHD patients can be effectively risk-stratified, and use of this information for a risk-guided strategy to prioritise high-risk patients may maximise benefits from additional resources spent on intensive disease management.

Strengths and limitations of this study

⇒ Inclusion of a state-wide sample of all hospitalised patients with coronary heart disease, thereby avoiding any selection bias.
⇒ Use of a primary outcome (days alive and out of hospital) that accounts for time to readmissions, frequency of readmissions and duration of each readmission, as well as survival.
⇒ Provision of a comprehensive data set of all medications taken over the 5 years of follow-up, by linkage to the national Pharmaceutical Benefits Scheme.
⇒ Unable to be certain that patients took the medications that they purchased—although it seems unlikely that patients would purchase more medications if the remaining had not been finished.
⇒ Data describe patient course in the first half of the last decade, but although medical therapy has somewhat evolved since then, the degree of change has been small, and the focus of the study on risk and treatment benefit is unlikely to have changed.

INTRODUCTION

Despite substantial reductions in related mortality over recent decades, coronary heart disease (CHD) remains the greatest cause of morbidity and mortality worldwide.[1] In Australia, CHD accounts for 12% of all deaths, almost one in two cardiovascular deaths and a third of all hospitalisations due to cardiovascular disease.[2] Despite effective guideline-based treatment, patients with established CHD are at risk of having a secondary adverse event.[3] Such secondary events substantially increase mortality risks, reduce the quality of life and lead to greater healthcare costs and burden.[4]

An increasing number of expensive therapies are able to reduce CHD risk, including proprotein convertase subtilisin/kexin type 9 inhibitors, sodium-glucose transport protein 2 inhibitors, glucagon-like peptide-1 receptor inhibitors and canakinumab.[5 6] Adherence to

therapy in secondary prevention is often suboptimal,[7] and can be improved by disease management programmes. The efficiency of these additional interventions could be optimised by targeting them at patients at the highest risk who may be most likely to benefit. However, the approach to risk assessment in secondary prevention is variable. In many guidelines, all patients are categorised as being at increased risk following an acute coronary event, and managed similarly.[8] The current European guidelines recognise that risks are not distributed equally and recommend risk assessment in secondary prevention, but provided no advice on how to manage the high-risk patients differently.[9] While a number of risk calculators have been developed for this purpose,[10] risk assessment is not conducted routinely in secondary prevention of CHD. We hypothesised that CHD patients with high risk may benefit more from intensive interventions to reduce adverse outcomes. This study sought to apply a previously developed and validated secondary cardiovascular event risk score to predict readmission and death in CHD patients after hospital discharge, and test whether higher risk patients benefit more from intensive disease management.

METHODS

Study population

This data linkage study included all patients (n=20 426) from all public hospitals in Queensland (Australia) in 2010 who were hospitalised with CHD as the principal diagnosis.

The Australian Institute of Health and Welfare provided linked data from the Queensland Hospital Admitted Patient Data Collection, Emergency Department Information System, Registrar of General Deaths, Medicare Benefits Schedule and Pharmaceutical Benefits Scheme. The 10th revision of the International Statistical Classification of Diseases and Related Health Problems (ICD-10) was used to identify all CHD-related diagnoses (I20.X–I25.X). Because our primary interest was postdischarge outcomes, we excluded 486 patients who did not survive the index admission. Therefore, our final analysis included 19 940 patients, all of whom were followed for 5 years.

Primary outcome

Primary outcome was days alive and out of hospital (DAOH) over 5 years of hospital discharge. DAOH incorporates both readmission and death and gives greater weights to death, particularly those that occur early after hospital discharge. A definition of DAOH has been previously described.[11] Briefly, DAOH was calculated by subtracting total days spent in hospital over the follow-up period from total length of follow-up (5 years). If a patient died within 5 years of hospital discharge, their total length of follow-up was the number of days from the first discharge to the date of death.

Secondary outcomes

Secondary outcomes included all-cause readmission and all-cause death.

Risk stratification

A previously developed and validated risk score of secondary coronary events in CHD (PEGASUS-TIMI54) was used to estimate risks.[12] PEGASUS-TIMI54 was selected because our study had collected the variables that are required for risk estimation. This point-based score (values ranging between 0 and 13 points) included age (0–2 points), renal dysfunction (0–2 points), presence of prior acute myocardial infarction (0–4 points), severity of CHD (0–3 points) and the presence of diabetes mellitus (0–2 points). Any patients with a score ≥6, who were reported having approximately 3–4 times higher risks of a secondary event than those with a score <6, were classified as high-risk.[12]

Interventional therapies

Data on percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) were collected through a linkage to the Medicare Benefits Schedule.

Medical therapies

Data on all medications purchased by a patient were collected through a linkage to the Pharmaceutical Benefits Scheme. This study focused on cardioprotective effects of beta-blockers, angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB) and statins (online supplemental table 1). An average fraction of maximal dose for these medications was calculated as the ratio of the average dose over the follow-up period to the maximal dose of the respective medication (online supplemental table 1). This fraction ranged from 0% (among patients who never took a medication throughout the follow-up period) to 100% (among those who reached the maximal dose of the respective medication at the beginning of follow-up and maintained that dose throughout the follow-up period). This parameter reflected how well patients were up-titrated in cardioprotective therapies after being discharged from the index admission, and was used for all analysis throughout this study.

Statistical analysis

Linear regression was used to analyse the study primary outcome (DAOH). Because DAOH was skewed, a Box-Cox transformation was performed to determine the best method for transforming this data. DAOH was then appropriately transformed according to findings from the Box-Cox analysis (by taking logarithm for example) prior to the estimation of means or associations using linear regression. The results were then back-transformed to their original units, as reported in this study.[13] Cox proportional hazards regression was used for the analysis of time from hospital discharge to death. An extension of the Cox regression model (the Andersen and Gill model) was used to analyse time to recurrent events (repeated readmissions or death).[14]

Table 1 Patients' baseline characteristics

		Low risk (n=13367)	High risk (n=6573)	P value
Demography	Male	63%	66%	<0.001
	Age at index admission (year)	65±10	65±11	0.08
	Index of relative socioeconomic disadvantage	965.7±68.7	973.1±70.5	0.43
Comorbidities	Hypertension	40%	54%	<0.001
	Diabetes	4%	24%	<0.001
	Atrial fibrillation	6%	12%	<0.001
	Heart failure	4%	11%	<0.001
	Chronic kidney disease	<1%	9%	<0.001
	Chronic pulmonary disease	2%	4%	<0.001
	Peripheral vascular disease	1%	3%	<0.001
	Cerebrovascular disease	<1%	1%	<0.001
	Charlson comorbidity index	1.2±0.6	2.6±1.0	<0.001
Interventions	PCI	12%	12%	0.53
	CABG	5%	4%	0.004
Beta-blockers	Average fraction of maximal dose (%)	19±21	25±22	<0.001
	No beta-blockers	55%	43%	<0.001
ACEi/ARB	Average fraction of maximal dose (%)	23±20	27±23	<0.001
	No ACEI	50%	39%	<0.001
Statins	Average fraction of maximal dose (%)	37±35	47±32	<0.001
	No statins	19%	12%	<0.001

Data are shown as either percentage (%) or mean±SD.
ACEi, angiotensin converting enzyme inhibitors; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; PCI, percutaneous coronary intervention.

A competing-risk regression model (the Fine and Gray method) was used to analyse time to the first readmission, with death as a competing risk.[15] For the associations of medications (betablockers, ACEi/ARB and statins) with study outcomes, the effect sizes (ie, β and HRs) reported in this study reflect the difference between patients who reached maximal dose of the respective medication at the beginning of follow-up (ie, 100% of maximal dose) and those who never took the medication over the follow-up period (0% of maximal dose). For the associations with interventions (PCI and CABG), the effect sizes reported in this study reflect the difference between who received the respective intervention during the study period and those who did not. All analyses were adjusted for age, sex and socioeconomic status based on residential postcodes from the Australian Bureau of Statistics Index of Relative Socioeconomic Disadvantage.[16] All analyses were performed using STATA V.17 (Statacorp, College Station, Texas, USA).

Patient and public involvement

No patient involved.

RESULTS

Patients' baseline characteristics

Patients' baseline characteristics are shown in table 1. Of the 19940 patients who survived the index admission, 6573 patients (33%) were classified as high-risk for a secondary event and 13367 patients as low-risk. Patients from both groups had similar age at the index admission, with a higher proportion of males in the high-risk group. All comorbidities were significantly higher among patients in the high-risk group, compared with their counterparts in the low-risk group. While a higher proportion of men was observed in the high-risk group, there was no statistical difference between the two groups of patients in relation to age at onset and residential socioeconomic status.

Of the 19940 patients included in our study, 60% (n=11911) were diagnosed with acute coronary syndrome during their index admission. In general, patients with acute coronary syndrome had greater predicted PEGASUS-TIMI54 risk scores (6.5±2.4) than those without (4.4±1.2, p<0.001).

Interventional and medical therapies

While the rate of PCI during the index admission was similar among patients in low-risk and high-risk groups, CABG was performed slightly more often for those with lower risks (table 1). Of the three cardioprotective medications included in this study, patients were most likely prescribed and best up-titrated with statins, followed by ACEi/ARB and beta-blockers. Patients in the high-risk group were better up-titrated for all medications than those in the low-risk group.

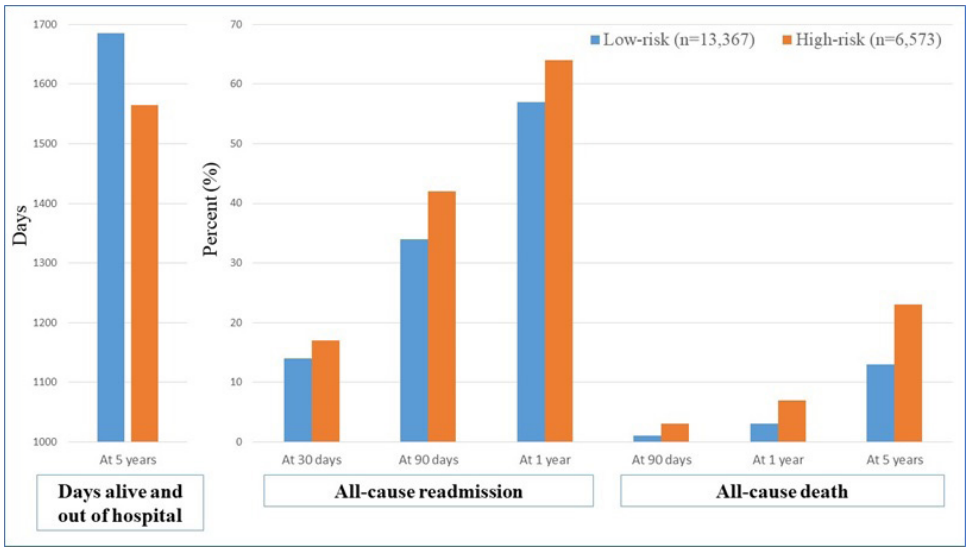

Figure 1 Patients' outcomes, stratified by levels of predicted risk.

There were very weak correlations between average fraction dose of betablockers and ACEi/ARB (r=0.15, p<0.001), betablockers and statins (r=0.04, p<0.001) and ACEi/ARB and statins (r=0.02, p<0.001). Patients who received PCI were better up-titrated in betablockers (Δ=7.7% of maximal dose, p<0.001), ACEi/ARB (Δ=8.7%, p<0.001) and statins (Δ=4.5%, p<0.001). Those who underwent CABG were also better up-titrated in betablockers (Δ=4.3%, p<0.001), ACEi/ARB (Δ=6.6%, p<0.001) and statins (Δ=5.1%, p<0.001).

Adverse outcomes by level of predicted risk

As presented in figure 1, high-risk patients had fewer DAOH within 5 years after hospital discharge, higher readmission rates and higher death rates, compared with their counterparts in the low-risk group (all p<0.001).

Associations of intensive management with post-discharge outcomes in CHD

Findings from figure 2 show that both medical and interventional therapies were associated with higher DAOH within 5 years of hospital discharge. In multivariable analysis, CABG, PCI and statins were associated with greatest increases in DAOH.

For secondary outcomes, while beta-blocker, ACEi/ARB and PCI were negatively associated with recurrent readmissions, CABG was positively associated with readmission. After accounting for death as a competing risk, beta-blocker and ACEi/ARB remained negatively associated with an early readmission, and PCI and CABG were positively associated with an early readmission. All

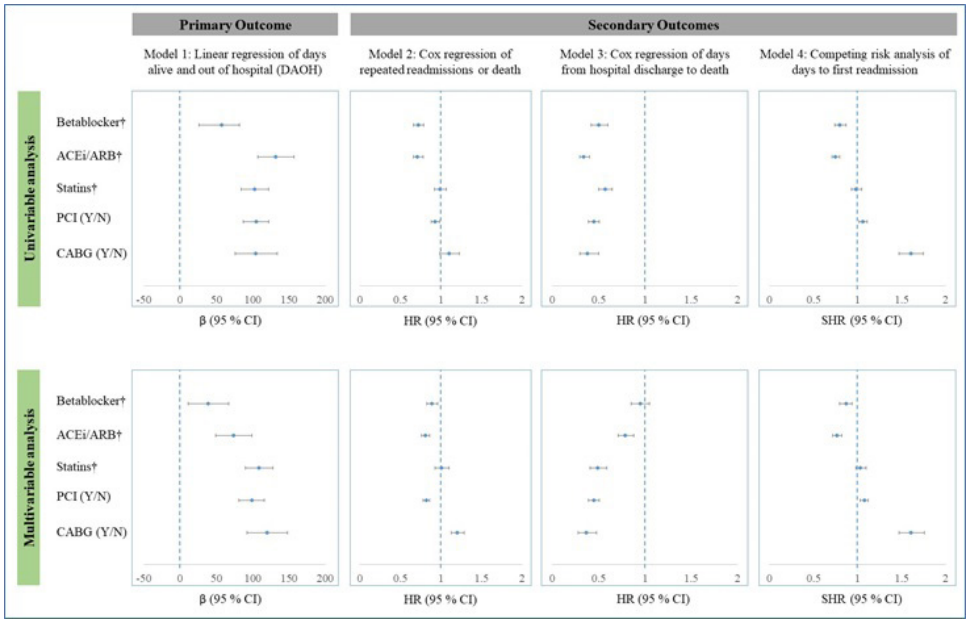

Figure 2 Associations of medications and interventions with study outcomes. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; DAOH, days alive and out of hospital; PCI, percutaneous coronary intervention.

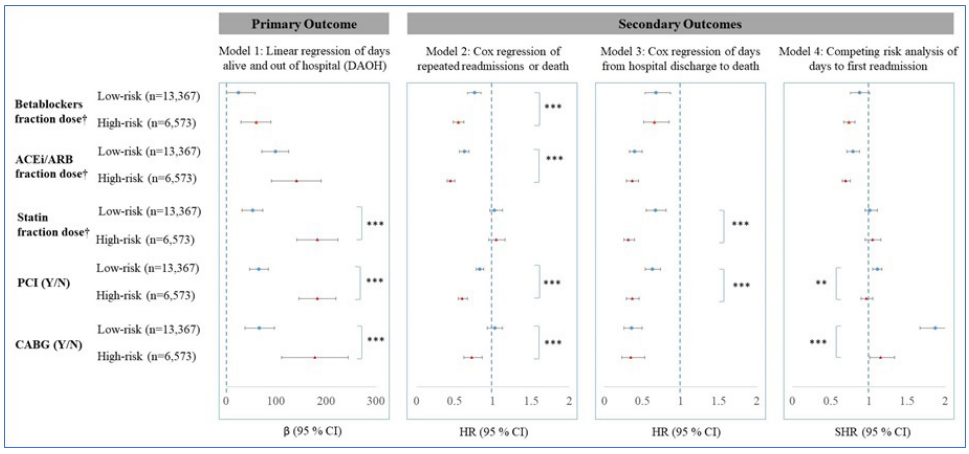

Figure 3 Associations of medication fraction dose and interventions with study outcomes, stratified by levels of predicted risk. ACEi, angiotensin-converting enzyme inhibitors; ARB, angiotensin receptor blockers; CABG, coronary artery bypass grafting; DAOH, days alive and out of hospital; PCI, percutaneous coronary intervention.

medications and interventions were negatively associated with mortality.

Effect sizes of intensive management differed by levels of predicted risk

Findings from figure 3 show stronger effects sizes of all medications and interventions on DAOH among patients with high risk. Statins, PCI and CABG had the greatest differences in effects sizes between the high-risk and low-risk groups. These findings suggest that high-risk patients may benefit more from up-titration of cardioprotective medications and interventions than their lower risk counterparts.

Findings for secondary outcomes were consistent with those of DAOH. Greater effect sizes on reducing readmission were observed in the high-risk patients for most interventional and medical therapies. For mortality, up-titration of statins and PCI were associated with a greater reduction in death in high-risk patients than that in the low-risk group. Only PCI and CABG were associated with greater risks of an early readmission in the low-risk group than that in the high-risk group, after accounting for death as the competing risk.

DISCUSSION

Findings from this study suggest that patients hospitalised with CHD can be effectively risk-stratified using a previously developed and validated risk score, and that high-risk patients may benefit more from intensive management to reduce adverse outcomes. Therefore, a risk-guidance strategy may be feasible and beneficial in secondary prevention of CHD. This does not mean a denial of treatment in patients who are classified as low risk. Instead, our findings implicate that the excess risk in the high-risk group may be treatable. In circumstances where additional investment to ensure treatment-to-target or facilitate early intervention could not be provided widely to all patients, they should prioritise high-risk patients to maximise investment return. This risk-guidance strategy will particularly benefit health systems with limited resources.

Readmission after hospitalisation with CHD

Readmission after hospitalisation with CHD was found to be frequent in our study, consistent with findings from other studies.[17 18] Readmission rate in CHD appeared to be only slightly lower than that in heart failure in Australia.[19] This relatively small difference in readmission rates between CHD and heart failure was also observed in other countries, including the USA.[20] However, the readmission rate observed in our study was higher than that reported from the Australian and New Zealand population of the Global Registry of Acute Coronary Syndrome (GRACE).[21] This discrepancy was probably due to two reasons. First, our study included both planned and unplanned readmissions because it was impossible to differentiate them in such a large sample of patients. The readmission rate in our study was very similar to a statewide readmission rate from a Victorian Admitted Episodes Data set (Australia), which confirms the validity of our data. Second, the GRACE report only included readmissions due to cardiovascular causes as opposed to the all-cause readmissions reported in this study. CHD patients often have multiple comorbidities, and approximately 50% of their readmissions are due to non-cardiovascular causes.[22]

Implications of designating high-risk patients

Findings from this study have shown that CHD patients can be effectively risk-stratified using a previously developed and validated risk score. Patients classified as high-risk were more likely to readmit or die and had fewer DAOH. The findings of this analysis support the contention that the risk calculator identifies 'treatable risk'. That is, CHD patients with higher risk are more likely to provide a return on the investment of additional steps to reduce recurrent events. Likewise, while both medical and interventional therapies appeared to increase DAOH

and improve survival for all CHD patients,[9] these were particularly so in those at highest risk.

A risk-guidance may be feasible in secondary prevention of CHD

Our findings support risk assessment of secondary events in all CHD patients. This may have implications for the selection of patients for new and expensive medical therapies that are able to reduce CHD risks.[5 6] Disease management programmes have been reported to reduce readmission and mortality risks among cardiovascular patients.[23 24] However, these programmes—usually led by cardiac nurses or other health professionals—are expensive. Many hospitals have attempted to apply disease management programmes to all patients, but had to abandon them soon after their trials because of financial constraints.[25] Long-term sustainability of these programmes requires a risk stratification to identify high-risk patients who are most likely to benefit from the intervention. Findings from this study are consistent with our recent findings from a randomised controlled trial that risk-guidance is feasible and effective in preventing readmission in heart failure, and that heart failure patients with higher risks are likely to benefit more from an intensive disease management programme.[23] A risk-guidance strategy will improve quality of care and especially benefit clinical practice in resource-constrained environments by guiding the allocation of limited resources and optimising returns on these investments.

In this study, the PEGASUS-TIMI54 was used as a means to demonstrate our hypothesis regarding the use of a risk-guidance strategy in secondary prevention of CHD. We selected this risk score because of its relatively simple scoring system and that our study had collected the variables required for risk estimation. The findings from this study could not determine if PEGASUS-TIMI54 is superior to other previously developed risk scores[10] for the purpose of risk stratification. A further study is required to compare the discrimination and predictability to determine the optimal risk score for use in clinical practice. In the meantime, physicians might consider selecting a validated risk score that is most feasible for their practice.

Strengths and limitations

Our study has a number of unique strengths. First, we included a state-wide sample of all hospitalised patients with CHD, thereby avoiding any selection bias. Second, our 5-year follow-up period was sufficient for collecting data on both readmission and death and calculating meaningful DAOH. This has allowed analysis of both soft and hard endpoints and a competing risk analysis. Third, our primary outcome (DAOH) incorporated both readmission and death, and reflected patient's quality of life. Our recurrent events analysis accounted for time to readmissions, frequency of readmissions and duration of each readmission—all of which influence patient's mortality risks and hospital expenditure, and are often overlooked when using a binary outcome. Fourth, the linkage to the Pharmaceutical Benefits Scheme provided a comprehensive data set of all medications taken by our patients over the 5 years of follow-up—which otherwise would be almost impossible to collect for a study of this scale.

The inclusion of both planned and unplanned readmissions was a limitation of this study. This might have partly explained the positive association of CABG with an early readmission in our study. However, this limitation did not influence our primary findings regarding additional benefits on readmission and survival from intensive management among the high-risk patients. Second, our data describe patient course in the first half of the last decade, but although medical therapy has somewhat evolved since then, the degree of change has been small, and the focus of the study on risk and treatment benefit is unlikely to have changed. Third, we cannot be absolutely certain that patients took the medications that they purchased. However, it was unlikely for patients to purchase more medications if the remaining had not been finished. Fourth, the selection of a risk score for use in this study was based on feasibility. We could not collect all necessary predictors to enable a performance comparison among currently available risk scores. We have previously reported that non-clinical factors are important drivers of readmissions, and failure to incorporate these factors into a predictive model may lead to a lower discriminatory power in predicting readmission.[26] PEGASUS-TIMI54 only included clinical factors[12] and may not be the most efficient algorithm for a risk-guidance strategy. This limitation may have underestimated the additional benefits of intensive management in high-risk patients that we reported in this study. Finally, lack of data on cardiac function was another limitation to be considered. This data, if available, would have enabled a sensitivity analysis to gain more insights into any differences among patients with reduced and preserved left ventricular ejection fraction, and allowed investigation of the possible causal pathways.

Conclusions

CHD patients can be effectively stratified in the secondary prevention. Findings from this study suggest that a risk-guidance to prioritise high-risk patients may maximise benefits and optimise investment returns on any additional resources spent on intensive disease management, and thereby saving costs and increasing quality of care. Such a strategy can be made feasible by routine risk assessment in patients hospitalised with CHD.

Contributors QLH: codesigned study, performed analysis, wrote initial draft, guarantor. SN and JB: gathered data, assisted analysis, revised initial draft. PAS: resourced data set, revised initial draft. TM: designed and supervised study, revised initial draft.

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Competing interests None declared.

Patient and public involvement Patients and/or the public were not involved in the design, or conduct, or reporting or dissemination plans of this research.

Patient consent for publication Not required.

Ethics approval This study complied with the Declaration of Helsinki. The research protocol was approved by the Human Research Ethics Committee of the Australian Institute of Health and Welfare (Eo2017-3-362, 18 July 2017), which approved waver of consent for this linkage study.

Provenance and peer review Not commissioned; externally peer reviewed.

Data availability statement Data are available upon reasonable request. Investigators seeking to share data should contact the corresponding author.

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Supplementary Table 1. Commonly used cardio-protective medications and their maximum dose

		Max dose
Beta-blockers	Bisoprolol	10mg
	Nebivolol	10mg
	Metoprolol succinate	200mg
	Metoprolol tartrate	180mg
	Carvedilol	100mg
	Atenolol	100mg
	Sotalol	320mg
	Propranolol	320mg
	Labetalol	2400mg
	Oxprenolol	320mg
	Pindolol	60mg
ACEI/ARB	Ramipril	10mg
	perindopril	16mg
	Lisinopril	40mg
	Irbesartan	300mg
	Valsartan	320mg
	Telmisartan	80mg
	Losartan	100mg
	Candesartan	32mg
Statins	Simvastatin	80mg
	Atorvastatin	80mg
	Rosuvastatin	40mg
	Fluvastatin	80mg
	Lovastatin	80mg
	Pitavastatin	4mg
	Pravastatin	80mg