Title

Psychological distress and medication use for secondary prevention of cardiovascular events:
Evidence from a large-scale population-based cohort study

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INTRODUCTION

Cardiovascular diseases (CVD), including ischaemic heart disease and stroke, are major contributors to the disease burden and are leading causes of death in Australia and other high income countries.[1] Present in up to one-third of all patients following a major CVD event are symptoms of depression and anxiety – collectively referred to as psychological distress.[2, 3]

In addition to reducing quality of life,[4] psychological distress is also associated with poorer prognosis following an acute CVD event. Patients who experience distress have a two-fold increase in rates of secondary CVD events,[5] higher hospital re-admission rates and greater health care costs,[6] and more than a 50% increase in the risk of all-cause mortality [7] compared to patients who do not experience distress. Contributors to the poorer outcomes observed in patients with compared to those without distress remain unclear but are thought to reflect, in part, more severe disease and lower adoption of secondary prevention behaviours among patients with higher compared to lower levels of distress.[8]

Appropriate treatment, including treatment with medications to prevent secondary CVD events, is one of the most important predictors of long term prognosis for patients with CVD. Given the known benefits of drug therapies for cardiac patients, current Australian guidelines for the management of coronary heart disease and stroke recommend all patients be treated with combined blood pressure- and lipid-lowering medications unless contraindicated.[9, 10] Yet, optimal use these medications remains low, with less than half of Australians with broadly-defined CVD taking both medications.[11] Use of these preventive medications is likely to be even lower among patients with psychological distress, potentially contributing to the poorer outcomes seen in this patient group, but evidence is currently limited.

Previous studies have shown that patients with psychological distress are less likely to follow medical recommendations than those without distress,[12, 13] including recommendations to follow medication regimens to manage chronic disease.[14] For example, one study reported that the odds of self-reported full or partial continuation with medications which prevent secondary CVD events were 50% lower among people who report psychological distress.[15] Similarly, another reported that the odds of not taking medication as prescribed, forgetting to take medication and deciding to skip medication were approximately two times higher among distressed compared to non-distressed patients.[16] Most research examining the associations between distress and medication use are based on self-reported medication adherence. However, risks of poor CVD outcomes are generally more strongly related to medication use measured with dispensing rather than self-reported

use,[17] yet the extent to which variation in medication use according to psychological distress is evident in dispensing data has not yet been investigated.

The aim of this paper was to quantify variation in use of blood pressure- and lipid-lowering medication in relation to level of psychological distress using questionnaire data linked to hospitalisation, death and pharmaceutical dispensing data, in Australians with a history of myocardial infarction (MI), angina, ischaemic stroke or transient ischaemic attack (TIA).

METHODS

Data came from The Sax Institute's 45 and Up Study, a large-scale cohort study of more than 266,000 men and women living in New South Wales (NSW) Australia, aged 45 years and over.[18] Participants were randomly sampled from the Department of Human Services (formerly Medicare Australia) enrolment database — a virtually complete list of Australian citizens and permanent residents as well as some temporary residents and refugees — and mailed an invitation to join the study. People aged over 80 years and residents of rural and remote areas were oversampled. All participants were sent a baseline questionnaire between January 2006 and December 2009, at which time they gave consent for follow-up and linkage of their information to administrative databases. The overall response rate was 18%, a number equivalent to approximately 10% of the NSW population aged 45 years.

Baseline questionnaire data were linked to four separate administrative databases: the NSW Admitted Patient Data Collection; the Pharmaceutical Benefits Scheme database, supplied by Department of Human Services; the NSW Registry of Births, Deaths and Marriages; and the National Death Index. The Admitted Patient Data Collection database contains all hospitalisations in NSW from 1 July 2001 to 31 December 2016 and includes admission and discharge dates, and diagnostic codes, coded using International Statistical Classification of Disease and Related Health Problems, Tenth Revision, Australian Modification (ICD-10-AM). The Pharmaceutical Benefits Scheme database contains information on community-based prescription medications subsidised by the Australian Government from 2004 to 31 December 2016, however it does not include medications issued in hospital, over-the-counter medications and private prescriptions,[19] an unknown but likely small proportion of medications. Date of death (obtained from the NSW Registry of Births, Deaths and Marriages and National Death Index contains a record of all deaths occurring in Australia) was used to exclude participants who died during the study period. Linkage of the 45 and Up cohort data to the Pharmaceutical Benefits Scheme database was done by the Sax Institute using a unique identifier

that was provided by Department of Human Services; linkage to Admitted Patient Data Collection and NSW Registry of Births, Deaths and Marriages was performed by the Centre for Health Record Linkage,[20] and the Australian Institute of Health and Welfare linked data to the National Death Index using probabilistic linkage methods.

Study sample

We included participants who were discharged from hospital following a major CVD event up to six years prior to completing the baseline questionnaire and who had a valid Kessler 10 (K10) score at the baseline questionnaire (the exposure of interest). Up to six years was chosen because it was the maximum time period for which hospital data were available for the majority of participants prior to the baseline questionnaire. Major CVD was defined as an admission with myocardial infarction (MI, ICD-10-AM: I21, I22), angina (I20), ischaemic stroke (I63) or TIA (G45) in any of the 50 diagnosis fields.

The study period was defined as three months (91 days) after completion of the baseline questionnaire. Over this time, complete dispensing records were only available for people who held a valid healthcare concession-card (Pensioner Concession Card, a Commonwealth Seniors Health Care or a Health Care Card). Hence, we restricted our analyses to participants who were concession-card holders, defined having at least one concessional and no non-concessional Pharmaceutical Benefits Scheme claims, during the three months following baseline. Respondents were excluded if they (i) joined by volunteering through contacting the study helpline, (ii) had linkage errors, (iii) reported having a Department of Veteran Affairs (DVA) White or Gold card at baseline (medications for these people are captured with a different administrative dataset) or (iv) died within the study period.

Exposure

The exposure variable was psychological distress, measured with the K10 on the baseline questionnaire. The K10 measures frequency of non-specific symptoms of distress, such as “nervous”, “hopeless”, “worthless” and “depressed”.[21] Scores range from 10-50 and high scores can be used to indicate the increasing likelihood of the presence of a common mental disorder, including mood and anxiety disorders.[22] There are no universally agreed cut points for the K10. For this study, we used cut points consistent with the Australian Bureau of Statistics[23]: low (10-<12; reference category), mild (12-<16), moderate (16-<22) and high (22-50) psychological distress.

Outcomes

We measured two outcomes. The first was use of both blood pressure- and lipid-lowering medication during the study period, defined as at least two dispensings of both medications. The second outcome was use of neither blood pressure- nor lipid-lowering medication during the study period, defined as <2 dispensing of both medications. Given that use was assessed over a three-month period up to six years after the initial major CVD admission, these outcomes likely capture longer-term continuation with these medications. 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); and combination blood pressure- and lipid-lowering medication (C10BX). Lipid lowering medications included medications with ATC codes beginning with C10.

Other variables

We also measured characteristics considered potential confounding variables between distress and medication use. Personal characteristics included: sex (male, female); age (based on date of birth) at time of the baseline questionnaire (45-54, 55-64, 65-74, 75-84, ≥85 years); country of birth (Australia/New Zealand, other); region of residence (major cities, inner regional, regional/remote Australia); highest level of education (no qualifications, certificate/ diploma/ trade, university degree); and annual household income (AUD:<20,000, 20,000-<40,000, ≥40,000). Health characteristics included: self-reported diabetes, assessed on the baseline questionnaire (yes or no); time since discharge from most recent CVD event (in years: <1, 1-2, 3-4, 5-<6); and CVD diagnosis at time of most recent CVD hospitalisation (MI, angina, stroke/TIA, mixed diagnosis). If participants had more than one diagnosis, they were classified according to their primary diagnosis; those with no primary diagnosis and secondary diagnosis of more than one type of CVD were classified as having a mixed diagnosis.

Statistical approach

Modified Poisson regression was used to estimate relative risks (RR) describing the association between psychological distress and medication use. This approach uses Poisson regression applied to binomial data, with correction for underestimated variance estimates (which increases as outcomes become more common) using robust standard errors [24, 25].

For both outcomes, two models were used: Model 1 was adjusted for age and sex; Model 2 was adjusted for additional personal (country of birth, region of residence, education and income) and health characteristics (self-reported diabetes, time since most recent discharge for a major CVD

event and CVD diagnosis at time of most recent CVD hospitalisation). Tests for linear trend were also performed by including psychological distress as an ordinal variable. Missing data on covariates were included in the analysis as separate categories.

We performed eight supplementary analyses to further investigate the association between psychological distress and medication use. First, using the likelihood ratio test, we examined whether the association varied in relation to time since most recent CVD admission. Second, in order to assess whether any observed associations were due to respondents with higher distress being in poorer physical health, we further adjusted for factors indicative of physical health, including: number of additional medications dispensed in the three months following baseline (other than blood pressure- and lipid-lowering medications); physical disability (assessed with the MOS-PF in categories: none [MOS PF score: 100], minor [90-99], moderate [60-89] or severe [0-59] disability); and the Charlson index (number of admissions for selected conditions in categories [0, 1, ≥ 2]). Third, results were re-estimated stratified by type of most recent major CVD diagnosis. For this analyses, we excluded respondents with a mixed diagnosis because of small numbers. Fourth, we examined the association between psychological distress and use of at least one (blood pressure- and/or lipid-lowering) medication. Fifth, we examine whether any observed variation was due to patients being readmitted to hospital during the study period (medications in hospitals are not captured with the Pharmaceutical Benefits Scheme dataset) by excluding these patients. Sixth, the analysis was restricted to participants who were admitted with a primary CVD diagnosis. Seventh, among participants who initially used both medications and who survived 12-months following baseline, we examined whether longer-term continuation with both medications varied in relation to distress. Continued use was defined as having $\geq 80\%$ days covered by lipid- and blood pressure-lowering medications during the 12-month period. In the final set of analyses, results were re-estimated stratified by sex.

Data were accessed through the Secure Unified Research Environment and all analyses were conducted using Stata version 14.1. The 45 and Up Study was approved by the University of New South Wales Human Research Ethics Committee (HREC). Ethics approval for this study was obtained from the Australian National University Human Ethics Committee (2010/513) and the NSW Population and Health Services Research Ethics Committee (HREC/10/CIPHS/33; CI NSW Study Reference 2010/05/234).

RESULTS

After excluding study volunteers (n=1616), respondents aged <45 years (n=6) and people with linkage errors (n=187), there were 264,890 potentially eligible individuals. Among these respondents, 19,457 people were hospitalised with MI, angina or stroke/TIA sometime in the six years prior to baseline, including 10,308 who were concessional beneficiaries. Of these, 7776 (75.4%) had a valid K10 score. We further excluded 133 (1.7%) DVA card holders and 45 (0.6%) respondents who died within the study period, leaving a final sample of 7598 participants, including 34.0% with low distress, 35.4% with mild, 18.3% with moderate and 12.3% with high distress.

Overall, respondents with higher levels of distress tended to be younger, with lower levels of education and income, much higher levels of physical disability and more additional medications dispensed three months following the baseline questionnaire. There were no differences in time since most recent CVD event or CVD type by level of psychological distress (Table 1).

Table 1. Sample characteristics in relation to level of psychological distress

	Low distress	Mild distress	Moderate distress	High distress	Total
Total, %(n)	34.0 (2586)	35.4 (2690)	18.3 (1388)	12.3 (934)	100 (7598)
SOCIODEMOGRAPHIC					
Males, %(n)	67.9 (1756)	64.5 (1734)	59.1 (820)	58.0 (542)	63.9 (4852)
Median age (IQR)	74 (68-80)	74 (68-80)	73 (66-80)	69 (61-77)	73 (67-80)
Age, %(n)					
45-54	1.0 (25)	2.0 (54)	4.3 (59)	10.8 (101)	3.2 (239)
55-64	9.5 (246)	12.5 (335)	19.3 (268)	27.9 (261)	14.6 (1110)
65-74	44.3 (1145)	40.3 (1084)	34.2 (474)	29.4 (275)	39.2 (2978)
75-84	38.8 (1004)	38.0 (1021)	33.0 (458)	24.2 (226)	35.7 (2709)
85+	6.4 (166)	7.3 (196)	9.3 (129)	7.6 (71)	7.4 (562)
Country of birth, %(n)					
Australian/New Zealand	77.8 (1992)	78.8 (2100)	75.4 (1036)	72.3 (666)	77.0 (5794)
Other	22.2 (569)	21.2 (565)	24.6 (338)	27.7 (255)	23.0 (1727)
Region of residence, %(n)					
Major cities	53.1 (1355)	52.2 (1387)	54.9 (750)	55.5 (514)	53.4 (4006)
Inner regional	36.4 (930)	38.2 (1015)	35.3 (482)	32.6 (302)	36.4 (2729)
Regional/ remote	10.5 (267)	9.6 (256)	9.9 (135)	11.9 (110)	10.2 (768)
SOCIOECONOMIC					
Education, %(n)					
No qualification	16.4 (413)	19.1 (505)	25.2 (341)	31.3 (284)	20.8 (1543)
Certificate/diploma/trade	70.8 (1782)	69.2 (1829)	66.0 (893)	60.0 (545)	68.0 (5049)
University degree	12.8 (323)	11.7 (308)	8.8 (119)	8.7 (79)	11.2 (829)
Annual household income, %(n)					
<\$20,000	47.7 (936)	53.3 (1094)	58.9 (623)	71.4 (503)	54.6 (3156)
\$20,000-<\$40,000	35.4 (696)	33.3 (684)	29.5 (312)	21.3 (150)	31.9 (1842)
≥40,000	16.9 (332)	13.4 (274)	11.6 (123)	7.4 (52)	13.5 (781)
HEALTH					
Median years since CVD event (IQR)	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)	2 (1-4)
Time since CVD event, %(n)					
<1 year	11.5 (298)	11.9 (321)	13.8 (191)	18.0 (168)	12.9 (978)
1-2 years	40.3 (1041)	40.7 (1094)	39.3 (545)	41.0 (383)	40.3 (3063)
3-4 years	31.0 (802)	30.4 (818)	31.7 (440)	27.1 (253)	30.4 (2313)
5-<6years	17.2 (445)	17.0 (457)	15.3 (212)	13.9 (130)	16.4 (1244)
CVD type %(n)					
MI	25.3 (655)	23.6 (635)	21.5 (299)	20.7 (193)	23.5 (1782)
Angina	56.0 (1447)	58.3 (1569)	59.4 (825)	57.6 (538)	57.6 (4379)
Stroke/TIA	17.3 (446)	16.7 (448)	17.6 (244)	19.8 (185)	17.4 (1323)
Mixed diagnosis	1.5 (38)	1.4 (38)	1.4 (20)	1.9 (18)	1.5 (114)
Self-reported diabetes	17.8 (459)	21.6 (580)	25.2 (350)	27.8 (260)	21.7 (1649)
Physical disability %(n)					
None	13.2 (290)	5.6 (131)	3.1 (37)	2.6 (21)	7.3 (479)
Minor	30.6 (674)	17.8 (416)	9.4 (114)	7.0 (57)	19.2 (1261)
Moderate	36.8 (809)	39.1 (916)	31.3 (379)	19.8 (162)	34.5 (2266)
Severe	19.4 (427)	37.6 (880)	56.3 (682)	70.7 (578)	39.1 (2567)
No. additional medications dispensed, %(n)					
0-4	64.3 (1662)	51.7 (1391)	40.9 (568)	36.9 (345)	52.2 (3966)
5-7	22.9 (591)	27.8 (748)	30.3 (421)	24.4 (228)	26.2 (1988)
8 or more	12.9 (333)	20.5 (551)	28.8 (399)	38.7 (361)	21.6 (1644)

Note: missing values, n(%): income: 1819 (23.8%); country of birth: 77 (1.0%); region of residence: 95 (1.3%); education: 177 (2.3%); physical disability: 1644 (21.6%). There were no missing values on age, sex, self-reported diabetes status, time since most recent CVD event, CVD type, or number of additional medications dispensed.

Two-thirds (63.4%) of participants used both blood pressure- and lipid-lowering medications including 65.0% of those with low, 65.5% mild, 60.6% moderate and 57.1% high psychological distress (Table 2). After adjusting for age and sex, the proportion using both medications was lower among those with higher compared to low distress levels of distress—the RRs of using both medications were 1.02 (95%CI: 0.98-1.06), 0.96 (0.91-1.01) and 0.93 (0.87-0.99) for mild, moderate and high distress respectively ($p(\text{trend})=0.010$) (Figure 1). Results were largely unchanged and a linear trend remained after accounting additionally for country of birth, region of residence, education, income, time since most recent CVD admission and diabetes ($p(\text{trend})=0.001$).

Table 2. Use of blood pressure- and lipid- lowering medication in the three months following the baseline questionnaire, according to level of psychological distress.

	None %(n)	Blood pressure- lowering medications only %(n)	Lipid-lowering medications only %(n)	Both lipid- and blood pressure- lowering medications %(n)
Psychological distress				
Low distress	7.6 (197)	13.8 (358)	13.6 (351)	65.0 (1680)
Mild distress	7.7 (206)	12.1 (325)	14.8 (397)	65.5 (1762)
Moderate distress	10.8 (150)	11.0 (153)	17.6 (244)	60.6 (841)
High distress	15.1 (141)	11.0 (103)	16.8 (157)	57.1 (533)
Total	9.1 (694)	12.4 (939)	15.1 (1149)	63.4 (4816)

Note: Percentages given as row percent.

Figure 1. Relative risks (RR) and 95% confidence intervals (CIs) of using blood pressure- and lipid-medication in the three months following baseline in relation to level of psychological distress.

Around one-in-ten (9.1%) participants were using neither medication (92% of these respondents were never dispensed both medications). Proportions using neither medication ranged from 8% of those with low and mild levels of distress to 15% of those with high psychological distress (Table 2). After adjusting for age and sex, the risk of using neither medication was higher in those with higher levels of distress: the RRs for mild, moderate and high compared to low distress were 0.96 (0.80-1.16), 1.22 (0.99-1.50) and 1.52 (1.22-1.89), respectively ($p(\text{trend}) < 0.001$) (Figure 2). After accounting for personal and health characteristics (Model 2), RRs were 0.99 (0.82-1.19) for mild, 1.30 (1.06-1.59) for moderate and 1.60 (1.28-1.98) for high compared to low distress ($p(\text{trend}) < 0.001$).

Figure 2. Relative risks (RR) and 95% confidence intervals (CIs) of using neither blood pressure- nor lipid- lowering medication in the three months following baseline in relation to level of psychological distress.

Supplementary analyses

There was no evidence that the association between psychological distress and medication use varied by time since most recent CVD admission (Model 2: both medications: $p=0.685$; neither medication $p=0.499$). The overall patterns of association between psychological distress and use of blood pressure- and lipid-lowering medications were similar when controlling for number of additional medications dispensed in the three-month period (Tables S1-S2), level of physical disability (Tables S3-S4) and Charlson index (Tables S5-S6). When stratified by type of most recent CVD diagnosis (Tables S7-S8), relative to the full sample, the proportion of respondents using both medications was higher among those admitted with MI (ranging from 70.6% with low distress to 60.6% with high distress) and lower in those admitted with stroke/TIA (ranging from 51.0% with low distress to 39.1% with high distress) but the RRs were broadly similar. When the outcome was changed to using at least one medication, the overall proportion of respondents using medication increased (>80%) but use remained lower for respondents with higher levels of distress (Table S9). Results were not materially different when excluding respondents who were readmitted to hospital within three months of completing the baseline questionnaire (Tables S10-S11), or those with a secondary CVD diagnosis (Tables S12-S13). Among those who were initially using both medications, there was no distress-related variation in 12-month continuation with medications (Table S14).

In sex stratified analyses, 66.1% of men (including 66.7% with low and 62.7% with high distress) and 58.6% of women (61.2% low and 49.2% high distress) were using both blood pressure- and lipid lowering medications. Proportions using neither medication were 7.7% for men (ranging from 6.7% with low distress to 12.2% with high distress) and 11.7% of women (9.6% of low distress and 19.1% with high distress) were using neither medication (Table S15). In men and women, proportions using both medications were lower (Model 2 $p(\text{trend})$: men=0.055; women=0.004, Table S16) and proportions using neither medication was higher among those with higher levels of distress (model 2 $p(\text{trend})$: men and women=0.002, Table S17).

DISCUSSION

Use of medications recommended to prevent secondary CVD events was lower in people with higher levels of distress. Around two-thirds of respondents who had a major CVD were using guideline-recommended blood pressure- and lipid-lowering medications three months following the baseline

questionnaire. However, patients with higher psychological distress were less likely to be using both medications and more likely to be using neither medication.

By its nature, data on psychological distress is virtually always self-reported. To our knowledge this is the first study to use such data linked to independent pharmaceutical dispensing data to look at guideline-recommended medication use in people who have had a CVD event. Our findings are consistent with previous findings using self-reported measures of medication use. Previous studies have demonstrated that depression and anxiety are associated with lower self-reported adherence to CVD medications following hospitalisation for a CVD event.[16, 26-28] Lower CVD medication use is associated with symptoms of depression [15, 29, 30] and anxiety,[31] diagnoses of these conditions [16, 26, 32] and use of a variety of CVD medications, including blood pressure- [32] and lipid-lowering medications,[26] and aspirin.[29] The dose-response association between use of guideline-recommended medications and levels of distress is also consistent with other findings, with one study reporting that that proportions self-reporting medication non adherence were 15.3%, 39.6% and 54.5% for patients with no, mild or severe depressive symptoms.[28] The point estimates observed in this study were somewhat weaker relative to previous findings. While small [26, 30] or even no differences [33, 34] have been previously reported, previous research describing mental health related variation in medication use has shown that effect sizes are generally smaller when using dispensing data compared to self-reported measures of medication use [14].

Reasons for the lower use of guideline-recommended medications among respondents with higher psychological distress remain unclear, including whether the variation is appropriate, reflecting differences in patient preferences or clinical characteristics, or whether the findings reflect unmet need of those with distress. Blood pressure-and lipid-lowering medications are recommended for all patients following an acute coronary event or stroke unless contraindicated, however it is unclear whether patients in this study had been prescribed these medications. We adjusted for a broad range of factors, including CVD type, physical disability and number of additional medications. However, residual confounding cannot be ruled out, particularly as measurement of many covariates were self-reported and some adjustment variables (mainly income) included missing data which were coded as a separate category.

Findings from previous studies examining variation in self-reported medication adherence indicate that lower use of guideline-recommended medications following a major CVD event may reflect differences in distressed patient thoughts and behaviours. Symptoms of depression and anxiety are associated with forgetting, skipping and reducing the dosage of medications [35], fear of potential adverse reactions and reporting that treatment was not effective and wanting to save money on medications.[36] Other studies have argued that lower medication use may reflect less optimism

about the future, lower commitment to self-care and even impaired cognitive function for patients who experience symptoms of distress relative to those who do not experience these symptoms.[37] If patients are initially prescribed these medications, not using the recommended medications might be a reflection of the longer-term experience of these factors, ultimately leading to discontinuation. Furthermore, changes in depressive symptoms are associated with changes in self-reported medication adherence, such that worsening of symptoms predicts greater non-adherence [29]. These findings, together with the evidence that patients who experience depression and anxiety are less likely to engage in a range of secondary prevention measures (e.g. quitting smoking and increasing physical activity),[15] suggest that patients who experience distress may need additional support to optimise their use of secondary prevention medications.

Strengths and limitations

By linking data from administrative databases to questionnaire data we were able to quantify preventative CVD medication dispensing in relation to symptoms of psychological distress and control for a number of important sociodemographic and health characteristics. While all those dispensed such medicines must have received a prescription for them, information on whether respondents had been prescribed but not dispensed these medications was not available. Clinical data, such as blood pressure measurements, were also not available so it was not possible to ascertain if contraindications were present. Private prescriptions are not captured on the Pharmaceutical Benefits Scheme database, resulting in a potential underestimate of the total proportion of our study participants who were receiving guideline-recommended medication. While this is an unknown proportion of prescriptions, it is unlikely to be substantial or to vary according to level of distress. The 45 and Up study had a response rate of 18%, is sampled from the general population and captures an array of population groups. This study was restricted to 45 and Up Study respondents who were concession-card holders who are generally older, of lower socioeconomic status and in poorer health compared to the general population. While the absolute proportions of respondents receiving medications may not be generalizable to the broader Australian population, relative measures of association are likely to be generalizable, assuming no confounding or effect medication.[38, 39]

Conclusions

Appropriate use of medications to prevent secondary CVD events is one of the most important predictors of long term prognosis among cardiac patients. This study reinforces the importance of recognising that patients who experience symptoms of depression and anxiety are at greater risk of

not using guideline-recommended medication following a CVD event and may need additional support to optimise their use of secondary prevention medications. Our findings highlight the ongoing opportunity to prevent secondary CVD events among patients with higher levels of psychological distress and improve secondary prevention of CVD at the population-level.

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Conflict of interest

The authors report they have no conflicts of interest

Author contributions

JW, led the design of the study, interpretation of the findings and writing of the manuscript. EP conducted the analyses. All authors contributed to the design of the study, interpretation of findings, and provided input on the manuscript.

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FIGURE CAPTIONS

Figure 1. Relative risks (RR) and 95% confidence intervals (CIs) of using blood pressure- and lipid-medication in the three months following baseline in relation to level of psychological distress.

Notes: Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes. Model 2 is plotted.

Figure 2. Relative risks (RR) and 95% confidence intervals (CIs) of using neither blood pressure- nor lipid- lowering medication in the three months following baseline in relation to level of psychological distress. Notes: Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes. Model 2 is plotted.

SUPPLEMENTARY TABLES

Table S1. Relative risks (RR) and 95% confidence intervals (CIs) of using blood pressure- and lipid-lowering medication in the three months following baseline in relation to level of psychological distress with additional adjustment for number of medications dispensed over the three-month period.

	No. using both medications / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)	Model 3 RR (95%CI)
Psychological distress				
Low distress	1680/2586 (65.0)	1.00	1.00	1.00
Mild distress	1762/2690 (65.5)	1.02 (0.98-1.06)	1.01 (0.97-1.05)	0.99 (0.96-1.03)
Moderate distress	841/1388 (60.6)	0.96 (0.91-1.01)	0.95 (0.90-1.00)	0.92 (0.88-0.97)
High distress	533/934 (57.1)	0.93 (0.87-0.99)	0.91 (0.86-0.97)	0.88 (0.83-0.94)
Test for trend		0.010	0.001	<0.001

Notes: Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes; Model 3 is further adjusted for number of additional medications dispensed in the three-month period.

Table S2. Relative risks (RR) and 95% confidence intervals (CIs) of using neither blood pressure- nor lipid- lowering medication in the three months following baseline in relation to level of psychological distress with additional adjustment for number of medications dispensed over the three-month period.

	No. using neither medication / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)	Model 3 RR (95%CI)
Psychological distress				
Low distress	197/2586 (7.6)	1.00	1.00	1.00
Mild distress	206/2690 (7.7)	0.96 (0.80-1.16)	0.99 (0.82-1.19)	1.04 (0.86-1.25)
Moderate distress	150/1388 (10.8)	1.22 (0.99-1.5)	1.30 (1.06-1.59)	1.43 (1.17-1.76)
High distress	141/934 (15.1)	1.52 (1.22-1.89)	1.60 (1.28-1.98)	1.83 (1.47-2.29)
Test for trend		<0.001	<0.001	<0.001

Notes: Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes; Model 3 is further adjusted for number of additional medications dispensed in the three-month period.

Table S3. Relative risks (RR) and 95% confidence intervals (CIs) of using blood pressure- and lipid-lowering medication in the three months following baseline in relation to level of psychological distress with additional adjustment for physical disability

	No. using both medications / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)	Model 3 RR (95%CI)
Psychological distress				
Low distress	1680/2586 (65.0)	1.00	1.00	1.00
Mild distress	1762/2690 (65.5)	1.02 (0.98-1.06)	1.01 (0.97-1.05)	0.99 (0.96-1.03)
Moderate distress	841/1388 (60.6)	0.96 (0.91-1.01)	0.95 (0.90-1.00)	0.93 (0.88-0.98)
High distress	533/934 (57.1)	0.93 (0.87-0.99)	0.91 (0.86-0.97)	0.89 (0.83-0.95)
Test for trend		0.001	0.010	<0.001

Notes: Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes; Model 3 is further adjusted for physical disability.

Table S4. Relative risks (RR) and 95% confidence intervals (CIs) of using neither blood pressure- nor lipid- lowering medication in the three months following baseline in relation to level of psychological distress with additional adjustment for physical disability

	No. using neither medication / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)	Model 3 RR (95%CI)
Psychological distress				
Low distress	197/2586 (7.6)	1.00	1.00	1.00
Mild distress	206/2690 (7.7)	0.96 (0.80-1.16)	0.99 (0.82-1.19)	1.05 (0.87-1.26)
Moderate distress	150/1388 (10.8)	1.22 (0.99-1.5)	1.30 (1.06-1.59)	1.41 (1.14-1.75)
High distress	141/934 (15.1)	1.52 (1.22-1.89)	1.60 (1.28-1.98)	1.77 (1.40-2.22)
Test for trend		<0.001	<0.001	<0.001

Notes: Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes; Model 3 is further adjusted for physical disability.

Table S5. Relative risks (RR) and 95% confidence intervals (CIs) of using blood pressure- and lipid-lowering medication in the three months following baseline in relation to level of psychological distress with additional adjustment for the Charlson index

	No. using both medications / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)	Model 3 RR (95%CI)
Psychological distress				
Low distress	1680/2586 (65.0)	1.00	1.00	1.00
Mild distress	1762/2690 (65.5)	1.02 (0.98-1.06)	1.01 (0.97-1.05)	1.01 (0.97-1.05)
Moderate distress	841/1388 (60.6)	0.96 (0.91-1.01)	0.95 (0.90-1.00)	0.94 (0.89-0.99)
High distress	533/934 (57.1)	0.93 (0.87-0.99)	0.91 (0.86-0.97)	0.90 (0.84-0.96)
Test for trend		0.001	0.010	<0.001

Notes: Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes; Model 3 is further adjusted for the Charlson index.

Table S6. Relative risks (RR) and 95% confidence intervals (CIs) of using neither blood pressure- nor lipid- lowering medication in the three months following baseline in relation to level of psychological distress with additional adjustment for the Charlson index

	No. using neither medication / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)	Model 3 RR (95%CI)
Psychological distress				
Low distress	197/2586 (7.6)	1.00	1.00	1.00
Mild distress	206/2690 (7.7)	0.96 (0.80-1.16)	0.99 (0.82-1.19)	0.99 (0.82-1.19)
Moderate distress	150/1388 (10.8)	1.22 (0.99-1.5)	1.30 (1.06-1.59)	1.32 (1.08-1.62)
High distress	141/934 (15.1)	1.52 (1.22-1.89)	1.60 (1.28-1.98)	1.64 (1.32-2.04)
Test for trend		<0.001	<0.001	<0.001

Notes: Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes; Model 3 is further adjusted for the Charlson index.

Table S7. Relative risks and 95% confidence intervals of using both blood pressure- and lipid-lowering medication in the three months following the baseline questionnaire for respondents with MI, angina or ischaemic stroke/ TIA in relation to level of psychological distress.

	No. using both medications/ no. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
MI (n=1782)			
Low distress	463/ 655 (70.7)	1.00	1.00
Mild distress	450/ 635 (70.9)	1.02 (0.95-1.09)	1.01 (0.94-1.08)
Moderate distress	203/ 299 (67.9)	0.99 (0.91-1.09)	0.98 (0.89-1.08)
High distress	116/ 193 (60.1)	0.89 (0.79-1.01)	0.87 (0.77-0.99)
Test for trend		0.15	0.07
Angina (n=4,379)			
Low distress	957/ 1447 (66.1)	1.00	1.00
Mild distress	1044/ 1569 (66.5)	1.01 (0.96-1.07)	1.00 (0.95-1.05)
Moderate distress	512/ 825 (62.1)	0.97 (0.91-1.03)	0.94 (0.88-1.00)
High distress	325/ 538 (60.4)	0.96 (0.89-1.04)	0.94 (0.86-1.01)
Test for trend		0.22	0.026
Stroke/ TIA (n=1323)			
Low distress	233/ 446 (52.2)	1.00	1.00
Mild distress	245/ 448 (54.7)	1.05 (0.93-1.19)	1.04 (0.92-1.18)
Moderate distress	114/ 244 (46.7)	0.92 (0.78-1.08)	0.90 (0.77-1.05)
High distress	77/ 185 (41.6)	0.85 (0.70-1.03)	0.82 (0.67-1.00)
Test for trend		0.006	0.025

Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes.

Table S8. Relative risks and 95% confidence intervals of using neither blood pressure- nor lipid-lowering medication in the three months following the baseline questionnaire for respondents with MI, angina or ischaemic stroke/ TIA in relation to level of psychological distress.

	No. using neither medication/ no. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
MI (n=1782)			
Low distress	39/ 655 (6.0)	1.00	1.00
Mild distress	36/ 635 (5.7)	0.87 (0.56-1.35)	0.86 (0.55-1.34)
Moderate distress	26/ 299 (8.7)	1.12 (0.69-1.82)	1.13 (0.69-1.83)
High distress	20/ 193 (10.4)	1.32 (0.75-2.32)	1.38 (0.78-2.45)
Test for trend		0.33	0.27
Angina (n=4,379)			
Low distress	108/ 1447 (7.5)	1.00	1.00
Mild distress	115/ 1569 (7.3)	0.94 (0.73-1.21)	0.99 (0.77-1.27)
Moderate distress	77/ 825 (9.3)	1.06 (0.80-1.41)	1.16 (0.87-1.55)
High distress	71/ 538 (13.2)	1.26 (0.93-1.70)	1.41 (1.04-1.90)
Test for trend		0.15	0.026
Stroke/ TIA (n=1323)			
Low distress	47/ 446 (10.5)	1.00	1.00
Mild distress	51/ 448 (11.4)	1.08 (0.74-1.56)	1.10 (0.75-1.60)
Moderate distress	44/ 244 (18.0)	1.64 (1.12-2.39)	1.78 (1.22-2.61)
High distress	49/ 185 (26.5)	2.22 (1.52-3.25)	2.34 (1.60-3.43)
Test for trend		<0.001	<0.001

Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes.

Table S9. Relative risks (RR) and 95% confidence intervals (CIs) of using blood pressure- and/ or lipid-lowering medication in the three months following baseline in relation to level of psychological distress.

	No. using blood pressure- and/ or lipid- lowering medications / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
Psychological distress			
Low distress	2389/2586 (92.4)	1.00	1
Mild distress	2484/2690 (92.3)	1.00 (0.99-1.02)	1.00 (0.99-1.02)
Moderate distress	1238/1388 (89.2)	0.98 (0.96-1.00)	0.98 (0.96-1.00)
High distress	793/934 (84.9)	0.95 (0.92-0.98)	0.94 (0.91-0.97)
Test for trend		<0.001	<0.001

Notes: Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes.

Table S10. Relative risks (RR) and 95% confidence intervals (CIs) of using blood pressure- and lipid-lowering medication in the three months following baseline in relation to level of psychological distress, excluding respondents who were readmitted to hospital within three months of baseline.

	No. using both medications / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
Psychological distress			
Low distress	1421/2181 (65.2)	1.00	1.00
Mild distress	1447/2188 (66.1)	1.02 (0.98-1.07)	1.01 (0.97-1.06)
Moderate distress	663/1076 (61.6)	0.98 (0.92-1.03)	0.96 (0.91-1.02)
High distress	412/713 (57.8)	0.94 (0.87-1.01)	0.93 (0.86-1.00)
Test for trend		0.07	0.027

Notes: Estimates are based on 6158 participants. Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes.

Table S11. Relative risks (RR) and 95% confidence intervals (CIs) of using neither blood pressure- nor lipid- lowering medication in the three months following baseline in relation to level of psychological distress, excluding respondents who were readmitted to hospital within three months of baseline.

	No. using neither medication / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
Psychological distress			
Low distress	167/2181 (7.7)	1.00	1.00
Mild distress	156/2188 (7.1)	0.90 (0.73-1.10)	0.92 (0.75-1.14)
Moderate distress	106/1076 (9.9)	1.08 (0.86-1.37)	1.15 (0.91-1.46)
High distress	101/713 (14.2)	1.37 (1.07-1.76)	1.43 (1.12-1.83)
Test for trend		0.018	0.005

Notes: Estimates are based on 6158 participants. Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes.

Table S12. Relative risks (RR) and 95% confidence intervals (CIs) of using blood pressure- and lipid-lowering medication in the three months following baseline in relation to level of psychological distress, restricted to participants who were admitted with a primary diagnosis of CVD.

	No. using both medications / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
Psychological distress			
Low distress	1540/2327 (66.2)	1.00	1.00
Mild distress	1588/2388 (66.5)	1.01 (0.97-1.06)	1.01 (0.97-1.05)
Moderate distress	756/1212 (62.4)	0.97 (0.92-1.02)	0.96 (0.91-1.01)
High distress	479/815 (58.8)	0.94 (0.88-1.00)	0.92 (0.86-0.98)
Test for trend		0.040	0.007

Notes: Estimates are based on 6742 participants. Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes.

Table S13. Relative risks (RR) and 95% confidence intervals (CIs) of using neither blood pressure- nor lipid- lowering medication in the three months following baseline in relation to level of psychological distress, restricted to participants who were admitted with a primary diagnosis of CVD.

	No. using both medications / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
Psychological distress			
Low distress	167/2327 (7.2)	1.00	1.00
Mild distress	173/2388 (7.2)	0.97 (0.79-1.19)	0.99 (0.81-1.22)
Moderate distress	120/1212 (9.9)	1.19 (0.94-1.49)	1.27 (1.02-1.60)
High distress	116/815 (14.2)	1.52 (1.19-1.93)	1.63 (1.28-2.07)
Test for trend		0.001	<0.001

Notes: Estimates are based on 6742 participants. Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes.

Table S14. Relative risks (RR) and 95% confidence intervals (CIs) of continuing to use blood pressure- and lipid- lowering medication in the 12-months following baseline in relation to level of psychological distress

	No. continuing to use both medications / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
Psychological distress			
Low distress	1035/1656 (62.5)	1.00	1.00
Mild distress	1099/ 1727 (63.6)	1.02 (0.97-1.08)	1.02 (0.97-1.08)
Moderate distress	490/822 (59.6)	0.97 (0.90-1.04)	0.97 (0.90-1.03)
High distress	302/ 516 (58.5)	0.95 (0.88-1.04)	0.95 (0.88-1.04)
Test for trend		0.19	0.18

Notes: Estimates are based on 4721 participants who used both medications in the three months following baseline who survived the 12-month period. Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes.

Table 15. Use of blood pressure- and lipid- lowering medication in the three months following the baseline questionnaire according to level of psychological distress, stratified by sex.

	None %(n)	Blood pressure- lowering medications only %(n)	Lipid-lowering medications only %(n)	Both blood pressure- and lipid- lowering medications %(n)
Men				
Psychological distress				
Low distress	6.7 (117)	15.6 (274)	11.0 (193)	66.7 (1172)
Mild distress	6.6 (114)	13.4 (233)	11.5 (199)	68.5 (1188)
Moderate distress	9.4 (77)	13.3 (109)	15.4 (126)	62.0 (508)
High distress	12.2 (66)	11.6 (63)	13.5 (73)	62.7 (340)
Total	7.7 (374)	14.0 (679)	12.2 (591)	66.1 (3208)
Women				
Psychological distress				
Low distress	9.6 (80)	10.1 (84)	19.0 (158)	61.2 (508)
Mild distress	9.6 (92)	9.6 (92)	20.7 (198)	60.0 (574)
Moderate distress	12.9 (73)	7.8 (44)	20.8 (118)	58.6 (333)
High distress	19.1 (75)	10.2 (40)	21.4 (84)	49.2 (193)
Total	11.7 (320)	9.5 (260)	20.3 (558)	58.6 (1608)

Note: Estimates are based on 4852 men and 2746 women. Percentages given as row percent.

Table S16. Relative risks (RR) and 95% confidence intervals (CIs) of using blood pressure- and lipid-lowering medication in the three months following baseline in relation to level of psychological distress, by sex.

	No. using both medications / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
Men			
Psychological distress			
Low distress	1172/1756 (66.7)	1.00	1.00
Mild distress	1188/1734 (68.5)	1.03 (0.99-1.08)	1.02 (0.98-1.07)
Moderate distress	508/820 (62.0)	0.94 (0.88-1.00)	0.93 (0.88-0.99)
High distress	340/542 (62.7)	0.97 (0.90-1.04)	0.96 (0.89-1.03)
Test for trend		0.10	0.055
Women			
Psychological distress			
Low distress	508/830 (61.2)	1.00	1.00
Mild distress	574/956 (60.0)	0.99 (0.92-1.06)	0.97 (0.90-1.05)
Moderate distress	333/568 (58.6)	0.99 (0.91-1.08)	0.96 (0.88-1.04)
High distress	193/392 (49.2)	0.86 (0.77-0.97)	0.83 (0.74-0.93)
Test for trend		0.034	0.004

Notes: Estimates are based on 4852 men and 2746 women. Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes; Model 3 is further adjusted for number of additional medications dispensed in the three-month period.

Table S17. Relative risks (RR) and 95% confidence intervals (CIs) of using neither blood pressure- nor lipid- lowering medication in the three months following baseline in relation to level of psychological distress, by sex.

	No. using neither medication / No. participants (%)	Model 1 RR (95%CI)	Model 2 RR (95%CI)
Men			
Psychological distress			
Low distress	117/1756 (6.7)	1.00	1.00
Mild distress	114/1734 (6.6)	0.96 (0.75-1.23)	0.97 (0.75-1.24)
Moderate distress	77/820 (9.4)	1.28 (0.97-1.69)	1.32 (1.00-1.73)
High distress	66/542 (12.2)	1.51 (1.12-2.05)	1.57 (1.16-2.13)
Test for trend		0.004	0.002
Women			
Psychological distress			
Low distress	80/830 (9.6)	1.00	1.00
Mild distress	92/956 (9.6)	0.97 (0.73-1.29)	1.01 (0.76-1.34)
Moderate distress	73/568 (12.9)	1.17 (0.86-1.59)	1.29 (0.95-1.75)
High distress	75/392 (19.1)	1.54 (1.12-2.12)	1.62 (1.18-2.24)
Test for trend		0.008	0.002

Notes: Estimates are based on 4852 men and 2746 women. Model 1 is adjusted for age and sex; model 2 is further adjusted for country of birth, region of residence, education, income, time since most recent CVD discharge and diabetes; Model 3 is further adjusted for number of additional medications dispensed in the three-month period.