Management of hypertension in Australian general practice

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Contents

Abstract

Hypertension affects 6 million Australians and is the most common condition seen in primary care. In 2015, elevated blood pressure was responsible for 5.8% of Australia's total burden of disease and is one of the most prevalent risk factors for cardiovascular disease. In addition to lifestyle modification, effective antihypertensive therapy is available to manage hypertension. Rather than managing patients based on their blood pressure alone, guidelines recommend treating patients according to their absolute cardiovascular disease risk. However, international evidence indicates that adherence to guidelines and medication is poor. In Australia, there has been limited research conducted in general practice to understand the management of hypertension and alignment with guidelines.

Four distinct projects contributed to the main aims of this research: to investigate the management of hypertension in primary care and to inform the design of cost-effective interventions for improving blood pressure control.

The first two projects involved cross-sectional analyses of de-identified electronic health records of 1.2 million patients attending 650 general practices across Australia (MedicineInsight). The first analysis found that the prevalence of hypertension among adults was 39.8% (95% CI: 38.7–40.9), with prevalence increasing with age and greater in males than in females. Furthermore, only 54.9% (95% CI 54.2–55.5) of patients with a diagnosis of hypertension had controlled blood pressure (BP <140/90mmHg). According to guidelines, patients aged 45–74 years are eligible for cardiovascular disease risk assessment. The second analysis found that only 51.0% (95% CI: 48.0–53.9) of these eligible patients had data recorded in their medical records to calculate their risk. Prescribing of antihypertensives was similar across all cardiovascular disease risk categories –

low risk=63.3% (95% CI: 61.9–64.8); moderate risk=61.8% (95% CI: 60.2–63.4); high risk=57.4% (95% CI: 55.4–59.4).

An existing cost model was adapted to use population and electronic health record data to estimate the health and financial costs of uncontrolled hypertension through increased cardiovascular disease risk. Cost analysis demonstrated a potential reduction of 25,845 cardiovascular events over 5 years with an associated cost saving of AUD 179 (in 2019–20) million with improved BP control.

Poor medication adherence is a critical contributing factor to inadequate blood pressure control. Therefore, a systematic scoping review of interventions using behavioural economic concepts to improve medication adherence in patients with chronic conditions was conducted. The review highlighted the importance of targeting non-adherent patients, understanding their reasons for non-adherence, and providing reminders and feedback to patients and physicians as critical factors in improving medication adherence.

This thesis highlights that blood pressure control in primary care remains poor, and compliance with hypertension management guidelines is suboptimal. With substantial costs attributed to uncontrolled blood pressure, investments in interventions to address poor blood pressure control are essential. The findings from the systematic scoping review provide a foundation for designing interventions to improve adherence to blood pressure medications. In addition, the findings on prevalence and costs provide the basis for early economic evaluations to inform the expected value of alternative intervention options.

Manuscripts contributing to the thesis

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Roseleur J, Gonzalez-Chica DA, Karnon J, Stocks NP. Predicted cardiovascular disease risk and prescribing of antihypertensive therapy among patients with hypertension in Australia using MedicineInsight. *Journal of Human Hypertension*. 2023;37(5):370-8. (Chapter 4.3)

Roseleur J, Harvey G, Stocks N, Karnon J. Behavioral economic insights to improve medication adherence in adults with chronic conditions: a scoping review protocol. *JBI Database of Systematic Reviews and Implementation Reports*. 2019;17(9):1915-23. (Chapter 7.3)

Roseleur J, Harvey G, Stocks N, Karnon J. Behavioral economic insights to improve medication adherence in adults with chronic conditions: a scoping review. *The Patient - Patient-Centered Outcomes Research*. 2019;12(6):571-92. (Chapter 7.5)

Roseleur J, Gonzalez-Chica DA, Harvey G, Stocks N, Karnon J. The cost of uncontrolled blood pressure in Australian general practice: a modelling study using electronic health records (MedicineInsight). *Pharmacoeconomics. 2023;41(5):573-87. (*Chapter 5.3)

Declaration

I certify that this work contains no material which has been accepted for the award of any other degree or diploma in my name in any university or other tertiary institution and, to the best of my knowledge and belief, contains no material previously published or written by another person, except where due reference has been made in the text. In addition, I certify that no part of this work will, in the future, be used in a submission in my name for any other degree or diploma in any university or other tertiary institution without the prior approval of the University of Adelaide and where applicable, any partner institution responsible for the joint award of this degree.

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My next administrative role was as the Grants, Operations and Development manager, a.k.a. GOD, at the Centre for Health Policy at Wits University. My incredibly supportive manager, Professor Jane Goudge, firmly set me on the path to a PhD by encouraging me to complete a Master of Public Health. Thank you for the push, Jane! I also wish to sincerely thank Associate Professor Nicola Christofides for your mentorship and convincing me that I could do a PhD. Your advice and ongoing support were invaluable.

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Abbreviations

ACVDR	Absolute cardiovascular disease risk
AR-DRG	Australian refined diagnostic related group
ATC	Anatomical Therapeutic Chemical
BEACH	Bettering the Evaluation and Care of Health
BP	Blood pressure
CHD	Coronary heart disease
CKD	Chronic kidney disease
CVD	Cardiovascular disease
DALYs	Disability-adjusted life years
DBP	Diastolic blood pressure
EHR	Electronic health record
EMR	Electronic medical record
GP	General practitioner
HF	Heart failure
HBPRCA	High Blood Pressure Research Council of Australia
ICD-10	International Classification of Diseases (version 10)
IHD	Ischaemic heart disease
IHPA	Independent Hospital Pricing Authority
IRSAD	Index of Relative Socio-Economic Advantage and Disadvantage
MBS	Medicare Benefits Schedule
MI	Myocardial infarction
NHS	National Health Survey
NPS	National Prescribing Service
NVDPA	National Vascular Disease Prevention Alliance
PAD	Peripheral artery disease

PHN	Primary health network
PIP	Practice Incentives Program
QI	Quality Improvement
SBP	Systolic blood pressure
TIA	Transient ischaemic attack
UA	Unstable angina

Part I

Introduction

Chapter 1

Background

1.1 Hypertension

Hypertension, or high blood pressure (BP), is defined as a BP greater than 140/90mmHg in Australia and Europe, and a BP greater than 130/80mmHg in the United States [1-3]. In 2010, an estimated 1.4 billion people globally had hypertension [4], with the prevalence of hypertension increasing due to an aging population and increasing exposure to lifestyle risk factors [4]. These lifestyle risk factors, such as unhealthy diets and lack of exercise, lead to overweight and obesity which increase the risk of developing hypertension [5, 6]. In Australia, national surveys have estimated that approximately 31–44% of adults have hypertension [7-10].

Hypertension is one of the most prevalent risk factors for cardiovascular disease (CVD) [11]. A Global Burden of Disease study estimated that systolic BP levels of 140mmHg or higher were associated with 7.8 million deaths (14.0% of all deaths) and 143 million disability-adjusted life years (DALYs) in 2015 [12]. Of these deaths and DALYs associated with high BP, ischaemic heart disease accounted for 3.6 million deaths (40.1% of all ischaemic heart disease deaths) and 62 million DALYs, haemorrhagic stroke for 1.4 million deaths (42.5% of haemorrhagic stroke deaths) and 30 million DALYs, ischaemic stroke for 1.1 million deaths (38.1% of ischaemic stroke deaths) and 18 million DALYs, and chronic kidney disease for 550,000 deaths (44.8% of chronic kidney disease deaths) and 12 million DALYs [12]. Other CVDs such as rheumatic heart disease, hypertensive heart disease, cardiomyopathy and myocarditis, atrial fibrillation and flutter, aortic aneurysm,

peripheral vascular disease, endocarditis, and other cardiovascular and circulatory diseases accounted for the remaining deaths and DALYs associated with high BP [12].

In Australia, elevated BP was responsible for 5.8% of the total burden of disease in 2015 [13]. In addition, high BP was associated with 38.0% of the burden of CVD, 34.1% of the burden of kidney disease, and 1.8% of the burden of neurological disease through high BP's association with dementia [13].

The global financial burden of poor BP control was estimated to be USD 372 billion in 2010, representing about 10% of the world's overall health care expenditure [14]. Evidence on the cost of hypertension in Australia is limited. However, CVD cost the health system AUD 11.8 billion in 2018–19 [15], and as 38.0% of CVD burden is attributed to high BP, the health system cost of hypertension can be estimated to be at least AUD 4.5 billion in 2018–19. Furthermore, a study on the productivity losses from hypertension over the working lifetime of the Australian population estimated the loss in gross domestic product to be AUD 137.2 billion [16].

1.1.1 Blood pressure control

Hypertension can be treated with lifestyle modification such as improved diet, increased physical activity, smoking cessation and reduced alcohol consumption. If these lifestyle interventions are unsuccessful, efficacious medications are available to treat hypertension [17]. Despite this, BP control remains poor. In 2010, fewer than half (46.5%; 95% CI: 41.9–51.1) of adults with hypertension were aware of their condition, and only 36.9% (95% CI: 33.8–40.0) were treated with antihypertensive medication [4]. Among those who reported receiving treatment, only 37.1% (95% CI: 33.6–40.5) achieved BP control (defined as systolic BP <140mmHg and diastolic BP <90mmHg) [4].

These findings are broadly aligned with the concept known as the "Rule of Halves," which originated in the 1970s and 1980s and revealed substantial gaps in hypertension management [18-20]. It highlighted that roughly half of the hypertensive population went undiagnosed, and among those diagnosed, only half

received appropriate treatment. Furthermore, even among those receiving treatment, only half achieved adequate BP control, and among those with controlled BP, only half maintained consistent control over time. While progress has been made in hypertension management, it is important to note that these improvements vary across countries, and significant global disparities persist [4]. In Australia, Carrington and colleagues found that 50% of participants who self-reported receiving antihypertensive medication had BP greater than 140/90mmHg [10], whereas Carnagarin and colleagues reported that 59.9% of adults who participated in the May Measurement Month 2017 survey had controlled BP [9]. Both these studies relied on convenience samples of self-selected participants. In contrast, the findings from the National Health Survey, using a representative sample of the Australian population, were considerably lower, with the Australian Institute of Health and Welfare reporting that only 32% of participants had their BP controlled [21].

Poor BP control places patients at increased risk of CVD and all-cause and CVD mortality. A US cohort study of almost 14,000 individuals who participated in the Third National Examination and Nutritional Health Survey found that untreated patients had a 77% increase in CVD mortality risk compared with patients without hypertension (defined as patients not taking antihypertensive medication and with a BP <140mmHg) [22]. Furthermore, those who received antihypertensive treatment but whose BP remained uncontrolled were twice as likely to die from CVD as those without hypertension. In contrast, patients with treated and controlled BP had similar risks to patients without hypertension [22].

Even modest improvements in BP control have benefits for patients. For example, a meta-analysis of the main antihypertensive drug classes found that reducing systolic BP by 10mmHg or diastolic BP by 5mmHg reduced the incidence of stroke by a third and the number of coronary heart disease events by a quarter [23]. A recent meta-analysis of individual participant-level data for 345,000 patients supports this finding [24]. The meta-analysis found a 10% reduction in the risk of a major cardiovascular event for each 5mmHg reduction in systolic BP across all baseline systolic BP readings ranging from 120mmHg to above 170mmHg.

1.2 Hypertension in primary care

Primary care is often the first point of contact for individuals in matters of personal health. Primary care provides a whole-of-person approach to health "along the continuum from health promotion and disease prevention to treatment, rehabilitation and palliative care" [25, p2]. In Australia, general practice is central to the provision of primary health care and the most-used component of the primary care system [26].

Hypertension is the most common condition seen in primary care globally [27] and in Australia [28]. Although it could be expected that patients under the management of their general practitioner (GP) would have better rates of BP control than the general population, international studies in primary care, mainly from Europe, found that control rates varied considerably [29-37]. For example, Qvarnstrom and colleagues [34] assessed BP control in a Swedish primary care setting and found that only 27% of patients aged 30 years or older with a diagnosis of hypertension had a BP below 140/90mmHg. In contrast, an Italian study of almost 1 million patients found that, of those patients with a diagnosis of hypertension, 60.6% had achieved BP control [37]. This study was an update of an earlier analysis of the same database in 2005 in which only 43.2% of patients had achieved BP control [38], demonstrating the improvement that can be achieved from implementing a multidimensional program to improve BP control. This program, entitled "Objective 70%", aimed to achieve BP control in 70% of treated patients, and included encouraging lifestyle changes through education and communication, promotion of home BP monitoring, actions to improve adherence to antihypertensive medication, and prescribing combination therapy, including single-pill options [37, 39].

Studies on hypertension management in Australian general practice are limited. Previous studies in Australia have focused on the prevalence of isolated systolic hypertension in the elderly [40], trends in BP levels of all patients over time [41], management of severe hypertension in general practice [42], hypertension management among groups with specific conditions [43] and prescription of

physical activity for hypertension management [44]. A brief description of each study follows.

In 1998, Howes and colleagues [40] investigated the prevalence of systolic hypertension in elderly patients by requesting GPs to screen 100 consecutive patients aged 60 years and older. Of the almost 39,000 patients screened, half of patients were normotensive (BP <140mmHg). Of those with elevated BP, a third had borderline isolated systolic hypertension, 8.6% had isolated systolic hypertension, 8.2% had mild hypertension and 2.3% had moderate or severe hypertension [40].

Carrington and colleagues [41] sought to assess trends in average BP recorded across all adult patients and undertook a retrospective analysis of general practice electronic heath records from 2005 to 2010 for patients with a recorded BP. The analysis of approximately half a million patients found that average BP remained constant between 2005 and 2010, as did the proportion of patients with a recorded elevated BP (approximately 25%). Furthermore, the study found that of those patients on antihypertensive treatment, up to half had uncontrolled BP [41].

Whereas Carrington and colleagues [41] analysed data for all patients with a recorded BP, Gallego et al [42] limited their investigation to patients with severe hypertension (BP ≥180/110mmHg). Analysis of electronic health records identified 7,500 patients with at least one BP measurement of severe hypertension between March 2008 and March 2009. Despite a large proportion of patients having at least one follow-up visit, and three-quarters of patients either initiated on treatment or prescribed additional antihypertensive therapy, the study found that less than half of patients achieved BP control within 1 year (BP <140/90mmHg) [42].

As hypertension often co-exists with chronic kidney disease (CKD) and is associated with more rapid progression of CKD, Khanam and colleagues [43] investigated BP control among patients with CKD and hypertension and explored factors associated with BP control, particularly continuity of care in general practice. Using a large national dataset of electronic health records called MedicineInsight, the management of 37,000 patients was examined. Overall, 46.7% of patients had achieved a target BP. In this study, target BP was defined as a BP ≤130/80mmHg for patients with diabetes, CVD or albuminuria, and as a BP ≤140/90mmHg for others.

BP control was lower in those with diabetes, CVD or albuminuria (38.2%) than in those without these conditions (61.5%). Continuity of care was found to be positively associated with BP control - patients receiving care from the same GP increased their likelihood of achieving BP control by 22% [43].

In addition to pharmacological therapy, guidelines recommend providing lifestyle advice for the prevention and management of hypertension [1]. Consequently, Smith et al. [44] examined the physical activity prescribing practices of GPs for patients with high BP and the characteristics of patients most likely to receive them. Participating GPs were requested to report their management of 10-20 consecutive patients with high BP. The study found that only about 40% of patients received a prescription for physical activity, with a higher likelihood in younger patients (≤55 years), in patients with fasting glucose in the diabetes range and in those with a history of CVD. In contrast, more than half of patients received a prescription for antihypertensive medications alone [44].

Australian studies that identify factors influencing BP control and prescribing patterns for hypertension management are limited. One Australian cohort study explored whether medication, clinical and lifestyle factors were associated with BP control in patients at risk of heart failure [45]. The cohort consisted of individuals aged 60 years or older with a history of CVD or renal impairment recruited between 2007 and 2010. The study found that in those taking antihypertensive medication, age, male sex and waist circumference was associated with uncontrolled BP, whereas BP control was better in those with self-reported ischaemic heart disease, atrial fibrillation and eGFR ≤60mL/min/1.73 m^2, an indication of CKD.

The international evidence investigating factors that may be associated with BP control is wide-ranging. A brief overview of some of these factors are presented.

Most studies report that males are less likely to achieve BP control [46-55]. However, a study by Borghi and colleagues [56] including patients being treated for the primary prevention of CVD in 12 European countries found that female sex was associated with uncontrolled hypertension. The authors provide no discussion on these findings.

Moreover, the majority of studies found older age to be associated with poor BP control [46, 48, 49, 51, 54, 57-59]. Once again, Borghi and colleagues [56] found the opposite association, with age being negatively associated with uncontrolled hypertension. The authors suggest that this finding may be confounded by indication. For example, older patients may be receiving more aggressive treatment, resulting in better BP control [56].

The association of socioeconomic status variables with BP control is mixed. Some studies have found a positive association with income [48, 54, 60-62], education [54, 61, 62], occupation [54, 62] or a composite of income and education [55], whereas others have found no association with education [60, 63] or occupation [63].

Similarly, findings related to the number of prescribed antihypertensive medications is also mixed. Whereas some studies have found that the likelihood of achieving BP control increases with adding additional classes of antihypertensive drugs [48, 54, 64], others have found that patients prescribed more medications have poorer BP control [49, 57, 65], and others still have found no clear association [53]. These conflicting results may be due to confounding. Patients on more classes of medication may be those who have more difficult to treat hypertension.

Identifying factors associated with BP control in Australia, such as patient characteristics or prescribing patterns, may provide opportunities to intervene, either by targeting interventions at population groups at higher risk, for example older males, or by changing practice in hypertension management, such as support for treatment intensification by GPs.

1.2.1 Guideline-recommended management

Traditionally, hypertension guidelines have relied exclusively on BP levels to guide treatment initiation and intensity [66]. However, epidemiological studies have established that multiple risk factors contribute to the overall risk of CVD and that small increases in several of these factors may have a greater effect on overall risk than the significant elevation of a single risk factor such as BP [67-70]. Furthermore, meta-analyses of individual patient data by the Blood Pressure Lowering Treatment

Trialists' Collaboration confirmed that the absolute benefits of BP-lowering drugs are proportional to baseline cardiovascular risk [71]. Therefore, guidelines now recommend that the management of patients with hypertension should also consider the individual's absolute CVD risk [1-3].

In Australia, the Heart Foundation guidelines recommend calculating the absolute risk of a primary cardiovascular event over the next 5 years by applying the Australian National Vascular Disease Prevention Alliance (NVDPA) risk assessment and risk management algorithm [1]. This algorithm includes the Framingham CVD risk equation [72]. The risk assessment applies to adults aged 45–74 years without a known history of CVD. In Aboriginal and Torres Strait Islander peoples, adults between 35 and 74 years are eligible [1, 73]. Risk assessment is not recommended in patients with existing CVD as CVD risk assessment is aimed at primary prevention [1].

Once CVD risk has been assessed, guidelines recommend that antihypertensive therapy be started for patients at low CVD risk with persistent BP ≥160/100mmHg and for patients at moderate CVD risk with persistent BP ≥140/90mmHg or with a family history of CVD [1]. Patients at high risk of CVD should also receive antihypertensive treatment, irrespective of BP levels [1]. As 50-70% of patients will not achieve BP targets with monotherapy, guidelines recommend the addition of a second medication from a different class of antihypertensives if target BP has not been reached after 3 months. A third drug class may be added once the maximum dose of both classes has been reached [1]. Lifestyle modification advice is recommended for all patients [1].

In summary, hypertension is a highly prevalent condition, both globally and in Australia. Despite the availability of effective treatments, BP control remains poor, resulting in considerable health and financial impacts. Even though hypertension is largely managed in primary care, evidence on the management of hypertension in Australian general practice is limited. Gaps in current knowledge include:

- the prevalence of BP control, which will provide an estimate of the capacity for improvement of interventions, an important determinant of cost-effectiveness,

- the factors associated with BP control in patients attending general practice, which may identify areas for targeted interventions, potentially improving the cost-effectiveness of interventions over generic interventions, and
- compliance with guideline-recommended management, which may also identify targets for interventions to support the design of cost-effective interventions.

This thesis therefore aims to address these gaps and investigate the management of hypertension in primary care to inform interventions to improve BP control, thereby reducing the burden associated with uncontrolled hypertension.

Chapter 2

Research aims and thesis outline

This research aimed to investigate the management of hypertension in Australian general practice to inform the design of cost-effective interventions to improve blood pressure (BP) control.

Specifically, four areas were explored:

- the prevalence of diagnosed hypertension, BP control, and the factors associated with BP control (Chapter 3)
- the use of cardiovascular disease (CVD) risk assessment in patients with a diagnosis of hypertension, and whether CVD risk is associated with prescribing of antihypertensive therapies (Chapter 4)
- the health and financial cost of uncontrolled BP in general practice (Chapter 5)
- potential interventions to improve BP control, specifically through improving medication adherence (Chapters 6 and 7).

A description of the primary population of interest for the thesis is defined below, followed by details of the primary data source used in the studies presented in chapters 3, 4 and 5. Lastly, an overview of the thesis structure is outlined.

2.1 Population

The population of interest for this thesis was patients with a diagnosis of hypertension who attend general practice. This population was selected to identify the population for which general practitioners (GPs) are aware of their patient's condition. All adult patients (18 years and older) were included in the first study (Chapter 3).

Guidelines recommend managing patients according to their absolute CVD risk rather than only using BP levels. Moreover, CVD risk assessment is recommended for adults aged between 45 and 74, and between 35 and 74 for Aboriginal and Torres Strait Islander adults. Therefore, for the second (Chapter 4) and third (Chapter 5) studies, the dataset was limited to patients with a diagnosis of hypertension aged between 45 and 74 years (between 35 and 74 for Aboriginal and Torres Strait Islander adults). Furthermore, patients with a history of CVD were excluded as the assessment of CVD risk is aimed at primary prevention.

2.2 Electronic health records

The first three studies used data from MedicineInsight, an extensive database of de-identified general practice electronic health records. MedicineInsight was created in 2011 and is managed by NPS MedicineWise, a not-for-profit organisation, with support from the Australian Government Department of Health and Aged Care. MedicineInsight aims to support quality improvement in Australian primary care and the post-market surveillance of medications [74]. As of October 2018, MedicineInsight included data from patients attending over 2,700 GPs and 660 general practices across all states and territories (8.2% of all general practices in the country) [74]. All Australian states and territories are represented within MedicineInsight, and practices varying in size and type of services offered are included. Patients in the database are comparable but not representative of the general population as measured by sociodemographic variables and clinical conditions [74].

MedicineInsight collects patient demographics, provider information, diagnoses, reasons for encounters, medications prescribed and reasons for prescription, immunisations and allergies, laboratory test orders and results, and clinical measurements (e.g. weight, height, BP). Progress notes and information captured in the past medical history module are not extracted to ensure patient anonymity. However, patients within each practice receive a unique identifying number and are tracked over time, allowing the development of a longitudinal database to generate a partial clinical history [74].

MedicineInsight applies selection criteria to maximise the suitability of the data for research purposes. Therefore, only general practices established for at least 2 years before data extraction, with no gaps of more than 6 weeks in the previous 2 years and a consistent number of transactions over the same period, were included [74]. MedicineInsight has been widely used to investigate the prevalence and management of diverse acute and chronic conditions, trends in prescribing and investigations, and health prevention activities [43, 75-87]. Recently, Havard and colleagues examined the validity of MedicineInsight extraction algorithms for five common chronic conditions – anxiety, asthma, depression, osteoporosis and type 2 diabetes – against the original electronic health record in five general practices. All the evaluated algorithms had excellent positive predictive value, negative predictive value and specificity (above 0.9). The asthma and osteoporosis algorithms also had excellent sensitivity, while the algorithms for anxiety, depression and type 2 diabetes yielded sensitivities of between 0.85 and 0.89 [88].

Four research projects were conducted and are presented as follows:

Part II comprises two studies focusing on managing hypertension in Australian general practice. Chapter 3 presents a study estimating the prevalence of hypertension and uncontrolled BP in general practice. Logistic regression was used to assess the association of hypertension control and patient sociodemographic variables, time since diagnosis or the number of prescribed antihypertensive medications. Guidelines recommend managing patients according to their CVD risk, and CVD risk assessment is recommended for patients aged between 45 and 74

years without a history of CVD. Therefore, the study described in Chapter 4 evaluated whether a higher proportion of patients with diagnosed hypertension aged between 45 and 74 years with no history of CVD had sufficient data in their electronic health records to calculate their CVD risk compared with patients without a diagnosis of hypertension. Again, logistic regression was used to assess the proportions of patients prescribed antihypertensives according to CVD risk status (low, moderate, high, or high risk clinically) or those with insufficient data to calculate CVD risk.

Part III estimates the cost of uncontrolled hypertension in patients attending general practice. Chapter 5 details the adaptation of an existing model, using population data and data from electronic health records (MedicineInsight) to estimate CVD risk. CVD risk was then used to determine the number of expected CVD events and associated costs for acute hospitalisation under current BP control levels and different levels of BP control to estimate potential savings from improved BP control.

Part IV includes two chapters exploring interventions to improve BP control. Chapter 6 provides an overview of the factors contributing to inadequate BP control and summarises the evidence on medication adherence. Chapter 7 presents the systematic scoping review of the available evidence on behavioural economic interventions to improve medication adherence in high-income settings. As applying behavioural economic insights to health is a relatively new field, restricting the study inclusion criteria to hypertension would have limited the literature from which to draw conclusions. Therefore, the systematic scoping review was not limited to hypertension but included studies on all chronic conditions requiring long-term medication adherence. This chapter includes both the protocol and the review.

Part V concludes this thesis by summarising the main findings and providing recommendations for future research.

Reflections on the PhD journey

When commencing this PhD, the initial research focus was on medication adherence, as international evidence highlighted that only half of patients adhered to their medication by the end of the first year. This led to the systematic scoping review on interventions informed by behavioural economics to address medication adherence. However, no accessible data sources were available to investigate medication adherence in Australia. Rather, general practice electronic health records allowed the investigation of prescribing practices, but not patient adherence. Given that patient adherence is not possible without prescribing, the research focus was modified to explore the management of hypertension in general practice. Consequently, rather than being part of the earlier chapters, the systematic scoping review concludes this thesis.

Part II

Management of Hypertension

in General Practice

Chapter 3

Prevalence of blood pressure control

3.1 Preface

This chapter, published in the *Journal of Hypertension*, presents a cross-sectional analysis of MedicineInsight, an extensive general practice database, to investigate the prevalence of diagnosed hypertension, hypertension control and factors associated with hypertension control. Specifically, the study explored whether hypertension control is influenced by patients' sociodemographic variables, time since diagnosis or the number of prescribed medications.

3.2 Statement of authorship

Title of paper: Blood pressure control in Australian general practice: analysis using general practice records of 1.2 million patients from the MedicineInsight database

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Name of principal author (Candidate): Jacqueline Roseleur

Contribution to the paper: Conception and design, analysis and interpretation of data, drafted the article and critical revisions, and acted as corresponding author.

Overall percentage: 85%

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signed: . . . . . Date: 09/12/2022

Co-author contributions

By signing the statement of authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of co-author: David Gonzalez-Chica

Contribution to the paper: Conception and design, analysis and interpretation of data, and revised it critically for important clinical and intellectual content.

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Name of co-author: Carla De Oliveira Bernardo

Contribution to the paper: Conception and design, analysis and interpretation of data, and revised it critically for important intellectual content.

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3.3 Publication

3.3.1 Abstract

Background

Hypertension is mostly managed in primary care. This study investigated the prevalence of diagnosed hypertension in Australian general practice and whether hypertension control is influenced by sociodemographic characteristics, duration since diagnosis, or prescription of antihypertensive medications.

Methods

Cross-sectional study using a large national database of electronic medical records of patients attending general practice in 2017 (MedicineInsight).

Results

Of 1.2 million 'regular' patients (one or more consultations per year in every year from 2015-2017), 39.8% had a diagnosis of hypertension (95% CI 38.7–40.9). Of these, 85.3% had their blood pressure recorded in 2017, and 54.9% (95% CI 54.2–55.5) had controlled hypertension (<140/90 mmHg). Blood pressure control was lower in females (54.1%) compared with males (55.7%) and in the oldest age group (52.0%), with no differences by socioeconomic status. Hypertension control was lower among 'regular' patients recently diagnosed (6-12 months = 48.6% controlled) relative to those >12 months since diagnosis (1-2 years = 53.6%; 3-5 years 55.5%; >5 years = 55.0%). Among recently diagnosed 'regular' patients, 59.2% had no record of being prescribed antihypertensive therapy in the last six months of the study, of which 44.3% had controlled hypertension. For those diagnosed >5 years ago, 37.4% had no record of being prescribed antihypertensives, and 56% had normal blood pressure levels.

Conclusions

Although the prevalence of hypertension varied by sociodemographics, there were no differences in blood pressure assessment or control by socioeconomic status.

Hypertension control remains a challenge in primary care, and electronic medical records provide an opportunity to assess hypertension management.

Keywords

Systolic pressure; diastolic pressure; blood pressure; computerized medical records; general practice; hypertension

3.3.2 Introduction

Hypertension is the most prevalent risk factor for cardiovascular disease and the largest contributor to morbidity and mortality globally [11]. In 2010, approximately 1.4 billion people worldwide had hypertension, of which only 46.5% were aware of their condition, and 36.9% received treatment [4]. Nonetheless, it is estimated that only 37.1% of all patients treated for hypertension achieve blood pressure (BP) control. In Australia, national surveys have estimated that approximately 31-44% of adults have hypertension [7, 9, 10, 21], but more than half of those treated remain uncontrolled [4], with considerable health and economic consequences [16].

As a highly prevalent chronic condition, hypertension is mostly managed in primary care and is the most common health condition seen by a general practitioner/primary care physician (GP) in Australia [28]. Multiple guidelines advise lifestyle modifications as the first-line strategy for the prevention and treatment of hypertension [1-3]. Pharmacological treatment is recommended for patients with diagnosed hypertension unable to achieve BP control through lifestyle modifications [1-3].

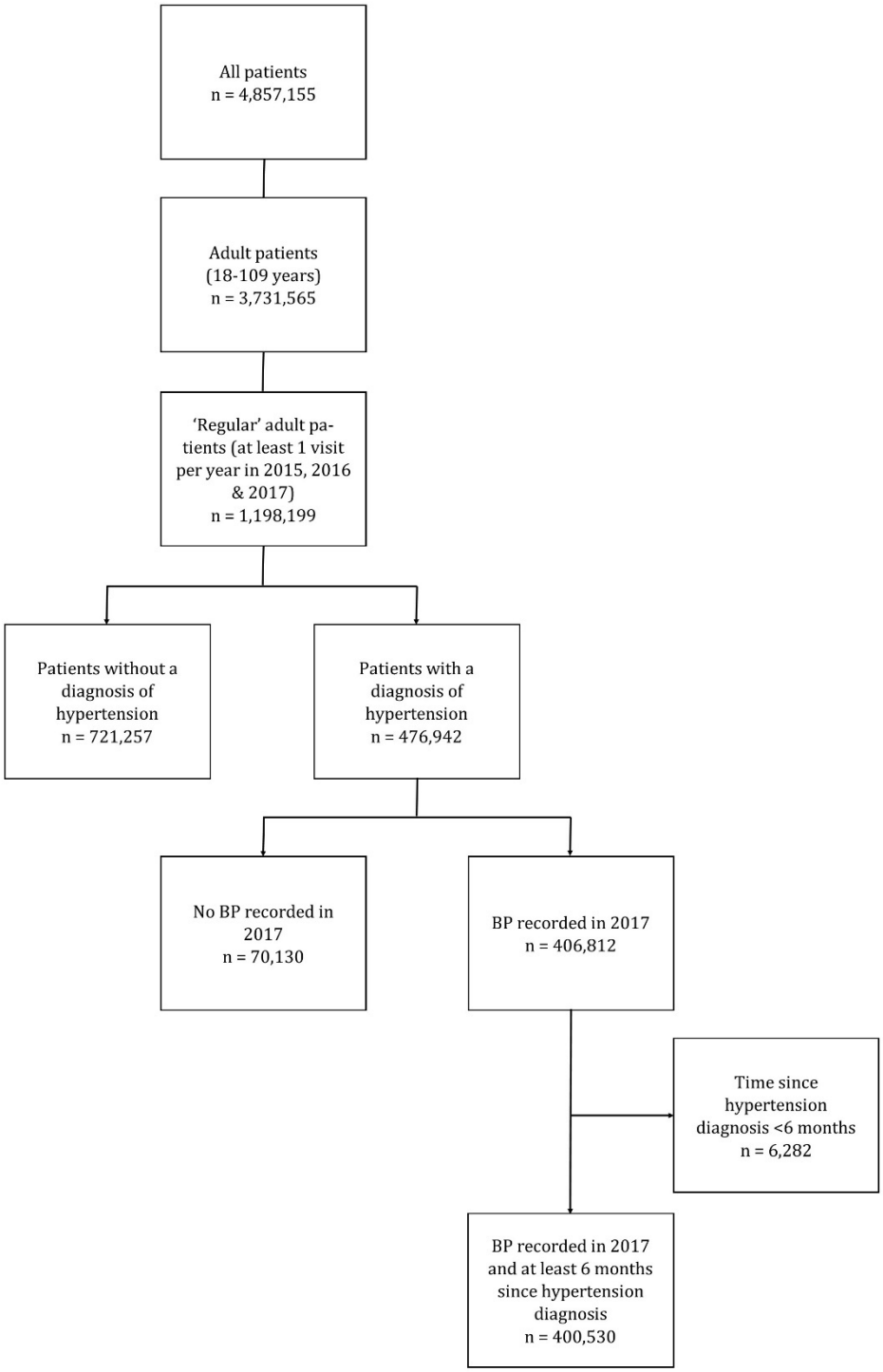
Studies on hypertension management and control in primary care are limited [29, 30, 32-38, 47, 89] with a majority of these studies undertaken in Europe. Previous studies in Australia have focused on trends in BP levels of all patients over time [41], management of severe hypertension in general practice [42], prescription of physical activity for hypertension management [44] and hypertension management among groups with specific conditions [43], Studies that identify factors influencing BP control, prescribing patterns for hypertension management, or if those with a recent or past diagnosis are managed differently, are lacking.

Answering these questions require longitudinal data with appropriate reporting of diagnosis, BP measurements and prescribed medications. Studies based on electronic medical records (EMRs) provide an opportunity to address these methodological issues [90]. MedicineInsight, a large general practice database, has been widely used for the investigation of diverse chronic and acute conditions, diagnostic procedures and management in Australia [76, 80, 81, 84, 91].

The first aim of this study was to investigate the prevalence of diagnosed hypertension and BP recording in Australian general practice and their distribution according to sociodemographic characteristics. The second aim was to explore whether, in a country with a universal health care system and profile similar to other high-income settings [92], hypertension control is influenced by the sociodemographic variables of patients, time since diagnosis, or the number of prescribed medications.

3.3.3 Methods

This is a cross-sectional analysis of a large Australian database including EMRs of all 'regular' patients that visited a practice contributing data to MedicineInsight between 1st January and 31st December 2017. A 'regular' patient was defined as a patient with at least one consultation per year from 2015 to 2017 [93]. Regular patients, therefore, had at least three visits across three years (Figure 1). This study was reported according to REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement reporting guidelines [93].



BP: blood pressure

Figure 1 Identification of 'regular' adult patients with hypertension with a blood pressure measure recorded in 2017.

Data source

MedicineInsight was created in 2011 and is managed by NPS MedicineWise with support from the Australian Government Department of Health. De-identified EMRs from over 650 general practices across Australia (8.2% of all general practices in the country) and over 2700 GPs are included in the dataset [74]. All Australian states and territories are represented within MedicineInsight, and practices varying in size and type of services offered are included.

Details of the data collection process have been published elsewhere [74, 81]. In summary, patients' EMRs are extracted monthly from each practice, de-identified and securely transferred to NPS MedicineWise. Data collected by MedicineInsight include patient demographics, diagnoses, reasons for encounters, medicines prescribed and reasons for prescriptions, allergies and immunizations, pathology test orders and results, and clinical measurements (e.g. weight, height, BP). To ensure patient anonymity, progress notes and information captured in the past medical history module are not extracted. However, patients within each practice receive a unique identifying number and are tracked over time, allowing the development of a longitudinal database to generate a partial clinical history. Patients in the database are comparable, but not representative, to the general population as measured by sociodemographic variables and clinical conditions [74].

To improve data quality, only general practices established for at least two years before data extraction, with no gaps of more than six weeks in the previous two years and a consistent number of transactions over the same period were included (n=532 practices). The final sample consisted of 1,198,199 adults aged 18 years or older in 2015, with at least one annual consultation between 2015 and 2017 (Figure 1).

Hypertension diagnosis

Different sub-sets of the MedicineInsight database were used to identify either the diagnosis of hypertension (i.e. diagnosis, encounter, prescription), prescribed medications (script), or BP measurements (observation). As medical doctors can use either systematized medical coding vocabularies to report arterial hypertension (e.g. systolic, diastolic, essential hypertension) or free-text in the completion of the

diagnosis, synonyms and misspellings of 'hypertension' were considered. These terms were defined based on available literature [94, 95], previous algorithms used for extracting data from the same database [81] and in consultation with two clinicians (NS, DG). Conditions suggesting transient hypertension (e.g. white coat, gestational) or other types of hypertension (e.g. ocular, pulmonary, intracranial) were not classified as hypertension. The list of terms and algorithms for data extraction are available from the authors upon request.

The full EMR of all eligible patients (i.e. 46% of individuals had EMR available going back further than the launch of MedicineInsight in 2011) [81] was searched to classify patients as having hypertension or not. Five variables were extracted from the database: 1) hypertension recorded as a condition in the diagnosis dataset; 2) hypertension recorded as a reason for encounter in the encounter dataset; 3) hypertension recorded as the reason for a prescription in the prescription dataset; 4) prescription of antihypertensive therapy according to the specific Anatomical Therapeutic Chemical Classification System codes (ATC C02, C03, C07, C08, C09) (see online-only data supplement for medicine names); and 5) elevated BPs (i.e. ≥ 140/80 mmHg).

Based on these variables, patients were considered to have hypertension if any of the following criteria were met using the entire medical record:

i) hypertension was recorded on at least two different occasions either in the diagnosis, encounter reason or prescription reason datasets;

ii) hypertension was recorded once in any of diagnosis, encounter reason or prescription reason datasets plus either:

- two or more antihypertensive therapy scripts on different occasions, or
- two or more elevated BPs on different occasions, or
- one script preceded by an elevated BP;

iii) one script preceded by an elevated BP plus either:

- one or more antihypertensive therapy scripts on different occasions.
- one or more elevated BPs on different occasions, or

The inclusion of an elevated BP reading preceding the prescription of antihypertensive therapy was performed to minimize false positives (i.e. patients taking antihypertensive medication for conditions other than hypertension) [94, 95]. Patients with elevated BP but not any other indicator of hypertension (i.e. hypertension not recorded in the diagnosis, encounter reason or prescription reason datasets; no antihypertensive therapy scripts) were classified as not having hypertension, as they could represent 'white coat' hypertension [1]. The figure in the online-only data supplement presents the number of patients in each of the diagnosis criteria.

Hypertension management

The time since first recorded diagnosis was calculated from the first date of hypertension diagnosis (i.e. earliest recorded date of hypertension noted in the records or script for antihypertensive therapy) and the end of the study period. This variable was categorized as <6 months, 6-12 months, 1-2 years, 3-5 years, or >5 years.

The prescription history of the last six months of the study was examined (July to December 2017) to calculate the number of classes of antihypertensive drugs recorded as having been prescribed in the past six months (none, 1, 2, or ≥3 classes of antihypertensives). This period was defined considering patients tend to receive written prescriptions that are sufficient for 6 months of treatment [1]. Antihypertensive medications included alpha-blockers (ATC C02), diuretics (ATC C03), beta-blockers (ATC C07), calcium channel blockers (ATC C08), angiotensin-converting enzyme inhibitors and angiotensin receptor blockers (ATC C09).

Hypertension control

To determine the proportion of patients with controlled hypertension, we created a subset of patients including only those with: 1) a BP reading in 2017 (including both systolic and diastolic BP measures); and 2) time since diagnosis of at least six

months (i.e. guidelines recommend hypertension control should be achieved within six months of hypertension diagnosis) [1] (Figure 1).

Systolic BP (SBP) recorded measurements lower than 60 or greater than 250 mmHg, or diastolic BP (DBP) recorded measurements lower than 40 or greater than 120 mmHg were considered clinically invalid and recoded as missing (n=11,888 or 0.12% of all BP measures) [41]. The last available BP recorded was used to define hypertension control. Patients with hypertension were "controlled" when they had: 1) a SBP below 140 mmHg; and 2) a DBP below 90 mmHg. The same definition was used for patients with diabetes, following recommendations from the current Australian hypertension guidelines [1].

Moreover, patients with uncontrolled hypertension were classified according to the severity of their blood pressure recordings: grade 1, SBP 140-159 mmHg or DBP 90-99 mmHg; grade 2 SBP 160-179 mmHg or DBP 100-109 mmHg; and grade 3, SBP ≥180 mmHg or DBP ≥110 mmHg [1].

Covariates

Patient sociodemographic characteristics included sex (male/female), age (categorized as 20-39, 40-59, 60-79 or ≥80 years), and socioeconomic status in quintiles, as measured by the Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD). IRSAD is a macroeconomic measure of relative advantage and disadvantage developed by the Australian Bureau of Statistics that summarizes information about the social and economic conditions of households within an area (i.e. income, education, employment, occupation and housing characteristics) and is based on residential postcodes. A higher IRSAD score indicates a person resides in a more advantaged area (e.g. more families with high-income or people in highly-skilled occupations, and few families with low incomes or in unskilled occupations) [96].

Statistical analysis

All analyses were performed in STATA 15.0 (StataCorp, College Station, Texas, USA), considering the clusters (general practices) and conditioned to the individual's probability of being in the sample using the inverse of each individuals' average

annual number of consultations (1/average number of consultations per year) [81, 93].

The prevalence of 'regular' patients with hypertension and those with controlled hypertension were expressed as proportions (%) with their corresponding 95% confidence intervals (95% CI). Differences in the proportion of controlled hypertension across categories of the investigated sociodemographic, time since diagnosis and number of classes of antihypertensive therapy prescribed were investigated using chi-squared tests for heterogeneity. Crude results are presented unless otherwise stated.

The association of hypertension control and the number of classes of antihypertensive therapy prescribed in the last six months was assessed using multiple logistic regression adjusted for gender, age and IRSAD. The analysis was stratified by the time since diagnosis (6-12 months, 1-2 years, 3-5 years, and >5 years). Marginal adjusted probabilities of hypertension control in each category were estimated and presented with their respective 95% CI.

The Human Research Ethics Committee of the University of Adelaide exempted this study of an ethical review, as it used existing and non-identifiable data. Access to the data for this study was approved by the MedicineInsight Data Governance Committee (project 2016–007).

3.3.4 Results

Hypertension prevalence

The mean age of the 1.2 million 'regular' adult patients attending a practice within MedicineInsight in 2017 was 54.3 years (SD 18.3), and 59.1% were females. Table 1 shows the prevalence of hypertension was 39.8% (95% CI 38.7%–40.9%; n=476,942). Hypertension was more frequent in males (48.7%), increased with age, but showed an inverse-trend relationship with socioeconomic status (hypertension decreased with increasing socioeconomic status). Table 1 also shows that 85.3% of all adults with diagnosed hypertension (95% CI 84.4%–86.2%; n=406,812) had

their BP measured and recorded in 2017. BP recording was less frequent among those aged 20-39 years but did not vary according to sex or IRSAD quintiles.

Blood pressure control

Table 2 shows that patients with hypertension that had their BP recorded in 2017 and were managed for at least six months (n=400,530) did not differ from the total sample with hypertension and BP recorded (n=406,812). Overall, of those patients with hypertension managed for at least six months, 54.9% had their BP controlled (95% CI 54.2%–55.5%). The mean SBP and DBP for patients with controlled hypertension were 125.1 [SD 9.9] and 73.7 [SD 9.0] mmHg, respectively. The corresponding values for those with uncontrolled hypertension were 149.3 [SD 12.0] and 83.2 [SD 11.2] mmHg (data not shown). Of those with uncontrolled hypertension, 77.5% had grade 1 (140-159/90-99 mmHg), 19.4% grade 2 (160-179/100-109 mmHg) and 3.1% grade 3 hypertension (≥180/110 mmHg).

Table 2 presents the proportion of patients with controlled hypertension in patients with recorded hypertension in 2017 by sociodemographic characteristics and time since diagnosis. BP control was slightly lower in females compared with males or among those aged ≥80 years, but there were no differences by socioeconomic status. The average time since first hypertension diagnosis was 7.2 years (SD=4.1), with over 90% of patients with a diagnosis of hypertension of three or more years and 2.4% for 6-12 months. Hypertension control was between 8% and 12% lower among patients recently diagnosed (6-12 months) relative to those with a longer time since diagnosis.

Table 1 Prevalence of diagnosed hypertension and blood pressure recording in 2017 according to sociodemographic variables

	Total sample	Adults with hypertension (n=476,942)			
				BP recorded in 2017* (n=406,812)	
		Yes		Yes	
	N (%)	N (%)	95% CI	N (%)	95% CI
Overall	1,198,199 (100.0%)	476,942 (39.8%)	[38.7-40.9]	406,812 (85.3%)	[84.4-86.2]
Sex					
Male	490,109 (40.9%)	232,533 (48.7%)	[47.5-49.9]	198,092 (85.7%)	[84.8-86.6]
Female	708,090 (59.1%)	244,409 (33.8%)	[32.7-34.9]	208,720 (84.9%)	[83.9-85.8]
Age group					
20-39	299,124 (25.0%)	15,510 (6.1%)	[5.8-6.3]	11,516 (76.9%)	[74.9-78.9]
40-59	398,568 (33.3%)	117,165 (31.0%)	[30.4-31.7]	96,500 (84.3%)	[83.1-85.4]
60-79	394,841 (33.0%)	255,310 (61.2%)	[60.5-62.0]	221,989 (86.7%)	[85.9-87.5]
>=80	105,666 (8.8%)	88,957 (78.2%)	[77.3-79.2]	76,807 (84.2%)	[83.2-85.2]
IRSAD Quintile					
Highest	284,656 (23.8%)	95,018 (35.6%)	[34.1-37.1]	80,056 (85.0%)	[83.6-86.4]
2nd upper	218,496 (18.2%)	78,741 (36.6%)	[34.9-38.2]	67,056 (85.3%)	[83.9-86.7]
Intermediate	267,958 (22.4%)	111,226 (40.9%)	[39.2-42.6]	95,105 (85.4%)	[84.1-86.6]

	Total sample	Adults with hypertension (n=476,942)			
				BP recorded in 2017* (n=406,812)	
		Yes		Yes	
	N (%)	N (%)	95% CI	N (%)	95% CI
2nd lower	212,938 (17.8%)	92,053 (41.9%)	[40.1-43.8]	78,949 (85.5%)	[83.7-87.3]
Lowest	214,151 (17.9%)	99,904 (44.9%)	[42.9-46.8]	85,646 (85.3%)	[83.9-86.8]

BP: blood pressure; CI: confidence interval

*Adult patients with a diagnosis of hypertension who had their BP recorded in 2017

Crude results presented. Absolute numbers (N) in each category represent 'observed' data (i.e. total number of patients in that category), while percentages and 95% CI were estimated considering the clusters (general practices) and the individual's probability of being in the sample

Table 2 Prevalence of hypertension control* according to sociodemographic characteristics and time since diagnosis

	Patients with hypertension and BP recorded in 2017	Patients with hypertension, BP recorded in 2017 and hypertension management ≥ 6 months		
		Yes	Proportion with controlled blood pressure* (<140/90mmHg)	
	N (%)	N (%)	Yes N (%)	95% CI
Overall	406,812 (100.0%)	400,530 (100%)	219,725 (54.9%)	[54.2-55.5]
Sex				
Male	198,092 (48.7%)	195,159 (48.7%)	107,924 (55.7%)	[55.0-56.4]
Female	208,720 (51.3%)	205,371 (51.3%)	111,801 (54.1%)	[53.4-54.8]
Age categories				
20-39	11,516 (2.8%)	10,898 (2.7%)	5,927 (55.7%)	[54.5-56.8]
40-59	96,500 (23.7%)	94,041 (23.5%)	50,482 (55.0%)	[54.3-55.7]
60-79	221,989 (54.6%)	219,339 (54.8%)	122,501 (55.7%)	[55.0-56.5]
>=80	76,807 (18.9%)	76,252 (19.0%)	40,815 (52.0%)	[51.1-52.9]
IRSAD Quintile				
Highest	80,056 (19.7%	78,604 (19.6%)	43,565 (55.9%)	[55.0-56.9]
2nd upper	67,056 (16.5%)	65,910 (16.5%)	36,373 (55.3%)	[54.0-56.5]
Intermediate	95,105 (23.4%)	93,762 (23.4%)	50,950 (54.3%)	[53.2-55.4]

	Patients with hypertension and BP recorded in 2017	**Patients with hypertension, BP recorded in 2017 and hypertension management ≥ 6 months**		
			Proportion with controlled blood pressure* (<140/90mmHg)	
	N (%)	**Yes N (%)**	**Yes N (%)**	**95% CI**
2nd lower	78,949 (19.4%)	77,741 (19.4%)	42,422 (54.4%)	[53.1-55.7]
Lowest	85,645 (21.1%)	84,513 (21.1%)	46,415 (54.6%)	[53.3-55.9]
Time since first recorded diagnosis				
<6 months	6,282 (1.5%)	-	-	-
6-12 months	9,466 (2.3%)	9,466 (2.4%)	4,467 (48.6%)	[47.4-49.8]
1-2 years	26,321 (6.5%)	26,321 (6.6%)	13,936 (53.6%)	[52.9-54.4]
3-5 years	110,471 (27.2%)	110,471 (27.6%)	61,080 (55.5%)	[54.7-56.2]
>5 years	254,272 (62.5%)	254,272 (63.5%)	140,242 (55.0%)	[54.2-55.7]

BP - blood pressure; CI – confidence interval

* The denominator is the total number of adult patients with a diagnosis of hypertension who had their BP recorded in 2017 and time since diagnosis ≥6 months (n=400,530 or 84.0% of all patients with hypertension).

Crude results presented. Absolute numbers (N) in each category represent 'observed' data (i.e. total number of patients in that category), while percentages and 95% CI were estimated considering the clusters (general practices) and the individual's probability of being in the sample.

Medications and hypertension control

The proportion of patients with a record of being prescribed any antihypertensive medication increased from 40.8% among those with a hypertension diagnosis of 6-12 months to 62.6% among those diagnosed more than five years ago (Figure 2). At the same time, having a record of being prescribed three or more classes of antihypertensive medications was seven times more likely among those with the longest duration since hypertension diagnosis (13.6%) compared to those with the shortest time since hypertension diagnosis (1.9%).

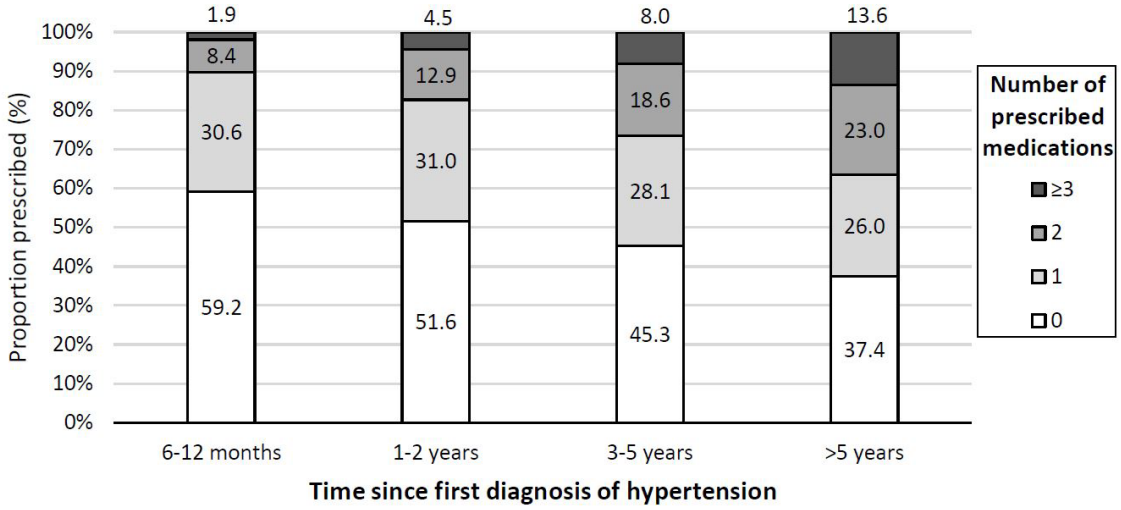


Figure 2 Proportion of patients with a record of prescribed antihypertensive medication, stratified by the time since diagnosis**.**

The denominator is the total number of adult patients with a diagnosis of hypertension who had their BP measured in 2017 and duration of HT management ≥6 months (n=400,530 or 84.0% of all patients with hypertension)

Figure 3 presents hypertension control by the number of classes of antihypertensives recorded as having been prescribed, stratified according to the time since diagnosis. In general, the prevalence of hypertension control ranged between 50% and 56% independent of the time since diagnosis or the number of classes of antihypertensives prescribed. Those with 6-12 months since diagnosis and no record of being prescribed antihypertensive medication were the only group of patients with a lower prevalence of hypertension control (44.3%). Table S2 in the

online-only data supplement presents the class of antihypertensive medications prescribed to patients.

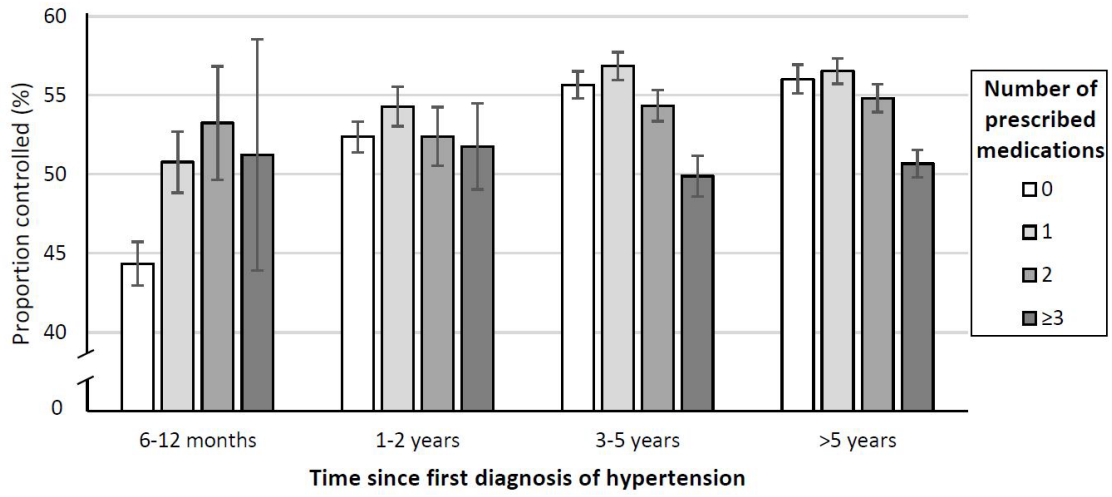


Figure 3 Prevalence of hypertension control according to the number of classes of antihypertensives recorded as having been prescribed, stratified by the time since diagnosis.

The denominator is the total number of adult patients with a diagnosis of hypertension who had their BP measured in 2017 and duration of HT management ≥6 months (n=400,530 or 84.0% of all patients with hypertension). Error bars indicate the 95% confidence interval. Results adjusted for age, sex and socioeconomic status.

3.3.5 Discussion

Three findings can be highlighted in this study. First, the prevalence of hypertension among adults attending general practice was slightly higher than estimates from the community based National Health Survey (NHS) in Australia. Second, even though these patients visited a general practice every year, had regular BP checks, and 59.0% had a record of having received a prescription for antihypertensive therapy, only a little more than half had their BP controlled according to Australian guidelines current at the time. Third, patients with a recent hypertension diagnosis (6-12 months) who had no record of being prescribed antihypertensive medication were less likely to have their BP controlled than those on antihypertensive medication, or than those with a longer duration since their hypertension diagnosis. Moreover, having received two or more classes of antihypertensive drugs in the last

six months did not provide any substantial benefit for hypertension control than those prescribed one class only.

Almost 40% of adult patients in our study were identified as having hypertension. That number is slightly higher than the 34% reported in the NHS in 2017-18. However, only 13.6% of adults investigated in that survey self-reported a medical diagnosis of hypertension, with the remaining estimated from BP measures, suggesting most people with hypertension in Australia are unaware of their condition or their diagnosis [7, 21]. Only a small number of Australian studies using general practice data are available for comparison. The Bettering the Evaluation and Care of Health (BEACH) study reported a prevalence of hypertension of 26.6% using actively collected data from 8,333 patients performed by 290 general practices across Australia during clinical encounters between 2008-09. BEACH provided a unique estimate for individuals of all ages (14% aged <15 years), hindering comparisons with our findings [97]. Nonetheless, the prevalence of hypertension in BEACH and our study is ~2.9 times more frequent than the estimated NHS self-reported prevalence of hypertension in 2007 - which reported a prevalence of 9.4% - (compared to BEACH) and 2017 (compared to MedicineInsight) [7, 98]. Therefore, our findings based on MedicineInsight data seems an accurate representation of the burden of hypertension in Australian general practice compared with active data collection performed by general practitioners (GPs) during face-to-face clinical encounters (BEACH). International estimates of the prevalence of hypertension using primary care data range from 11% to 55%, and both, BEACH and MedicineInsight findings are within that range [34, 35, 37, 47].

Discrepancies between EMR data and survey estimates may be the consequence of disease-specific biases (e.g. recall bias in surveys), misclassification due to disease definitions, and the prevalence of the investigated condition [99, 100]. When comparing administrative and survey data, the literature reports agreement of 74% for positive hypertension diagnosis with a Kappa of 0.66 [100]. People visiting a GP are more likely to have their BP checked, which could also explain these discrepancies. Furthermore, our denominator differs to that used in a population survey.

Australian guidelines recommend BP should be assessed at least every 2 years from the age of 18 years [1]. However, a recent study investigating a random sample of 2,384 adults in South Australia showed that 88% had their BP measured in the last 12 months during a consultation with their GP (up to 95% among those at risk or with CVD) [101]. These numbers are similar to our figures using MedicineInsight, as 85% of those with hypertension had their BP recorded in 2017, with a higher frequency among middle-aged or older adults. BP assessment did not vary according to sex nor socioeconomic status, suggesting this is a universal care procedure performed by GPs, which may support hypertension diagnosis and management.

Our finding that just over half of patients with hypertension had their BP controlled lies within the range reported by other international studies using general practice data (27% to 65%) [29, 32-37]. In Australia, a study using BEACH data from 2006-07 (n=2,618 patients) reported 59% of patients who had been prescribed antihypertensive medication achieved BP control [102]. Some of these studies defined hypertension control using different definitions for diabetic patients and proteinuria status [29, 32-34, 36, 102]. Australian studies using our criteria for hypertension control (≤140/90 mmHg for all patients) reported BP control ranged between 50% and 55% [41, 44]. These figures are consistent with data from the Australian NHS, which found that 56% of females and 59% of males receiving medication for hypertension had their BP controlled [4].

In our study, hypertension control was slightly lower in the oldest age group. This may reflect reluctance from GPs to achieve targets to avoid adverse events (e.g. hypotension, falls), acceptance that older people have higher BP levels or that it is more challenging to control, or because of the coexistence of other chronic conditions affecting BP control [32, 103]. In fact, we identified that the longer the diagnosis of hypertension, the more classes of antihypertensive therapy are prescribed to maintain the same level of control (i.e. GPs only added new medications to those who are not controlled), which is consistent with the literature [104].

Hypertension guidelines recommend lifestyles changes as the primary non-pharmacological measure to achieve BP control, especially among those with newly

diagnosed hypertension. This would explain why six out of ten patients with recent hypertension diagnosis but only a third of those diagnosed more than five years ago had no records of being prescribed antihypertensive therapy. However, our findings suggest that delaying pharmacological management among new cases appears to delay hypertension control which is consistent with findings from sub-studies of large clinical trials [105]. On the other hand, patients with a long history of hypertension diagnosis but not prescribed antihypertensive therapy in the last six months achieved similar rates of hypertension control to those prescribed antihypertensive therapy.

In recent years there has been a growing interest in the use of two-drug combinations as the first step for antihypertensive treatment [106]. Although we did not explore whether different classes of antihypertensive therapy were prescribed sequentially or concomitantly, our data suggest there was no advantage related to the prescription of two classes of antihypertensive therapy compared to just one among recently diagnosed hypertension cases. In a recent British study using EMR and propensity score matching, the rate of BP control among those started on a two-drug therapy (n=2,807) was 17% higher than among those on monotherapy (n=5,614) [107]. However, despite a median duration of four months on these regimens, none of the two groups achieved more than 50% of hypertension control (40.4% and 35.4%, respectively).

The main strengths of this study are the large sample of patients across Australian general practice, the use of multiple strategies to improve data quality and how the results reflect what is really happening in the community in terms of prescribing and BP control. However, the limitations and potential biases of using EMRs for research purposes need to be acknowledged [90, 108]. The accuracy and completeness of data in MedicineInsight may vary by clinician and clinical information system used in each general practice. This may have led to the underestimation of the prevalence of hypertension. However, the use of multiple criteria to identify patients with hypertension likely ameliorated the underestimation [90]. MedicineInsight patients are uniquely recorded within a practice but are recorded as a different patient if they move between practices. As hypertension is a chronic condition, we assumed that patients would mostly visit

the same general practice to manage their condition and to minimize bias we included only 'regular' patients (i.e. at least one consultation per year between 2015-2017). Individual indicators of socioeconomic status (e.g. education level or household income) are unavailable in MedicineInsight, and IRSAD was used as a macro-economic indicator, which is susceptible to ecological fallacy [96]. In any case, it is unlikely that this limitation introduced bias in our results. Finally, we have not examined how different levels of high blood pressure influence decisions about medication use. Conceivably those patients with very high blood pressures will be more likely to be commenced on antihypertensives and less likely to achieve control, at least initially. Furthermore, we have not been able to examine the interplay between side effects, patient compliance and therapeutic inertia.

Despite the limitations, databases of EMRs such as MedicineInsight provide a new tool for monitoring hypertension prevalence and control in Australian general practice. This is particularly important since the largest Australian study of general practice (BEACH) was defunded in 2016 [109]. Italy implemented a multi-dimensional strategy targeted at the general population, outpatients and high-risk individuals to improve BP control to 70%. Using EMR data, researchers were able to monitor the effectiveness of this strategy over time [37, 38]. MedicineInsight may provide a similar opportunity to monitor BP control rates in Australia.

This large cross-sectional study, using electronic health records of patients attending general practice, highlights that hypertension control continues to be a challenge in Australian primary care. Despite hypertension being a condition that can be treated with lifestyle modifications and for which effective affordable medication is available, just over half had their BP controlled. Continued efforts are required to support doctors and patients in the management of hypertension and avoid the deleterious consequences of poor control.

Acknowledgements

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Disclosures

Benjamin Geisler is employed by Wing Tech Inc. who has consulted for Medtronic, a maker of renal denervation systems. The remaining authors report no conflicts of interest.

3.3.6 Online supplementary material

Table S1 Classes of Antihypertensive Therapy

ATC C02: Alpha Blockers

Methyldopa, Clonidine, Guanfacine, Moxonidine, Prazosin, Hydralazine, Minoxidil, Ambrisentan, Bosentan, Epoprostenol, Iloprost, Macitentan, Riociguat, Sildenafil, Tadalafil

ATC C03: Diuretics

Hydrochlorothiazide, Chlortalidone, Indapamide, Furosemide (Frusemide), Etacrynic Acid, Eplerenone, Spironolactone, Tolvaptan

ATC C07: Beta Blockers

Oxprenolol, Pindolol, Propranolol, Atenolol, Bisoprolol, Metoprolol, Nebivolol, Carvedilol, Labetalol

ATC C08: Calcium Channel Blockers

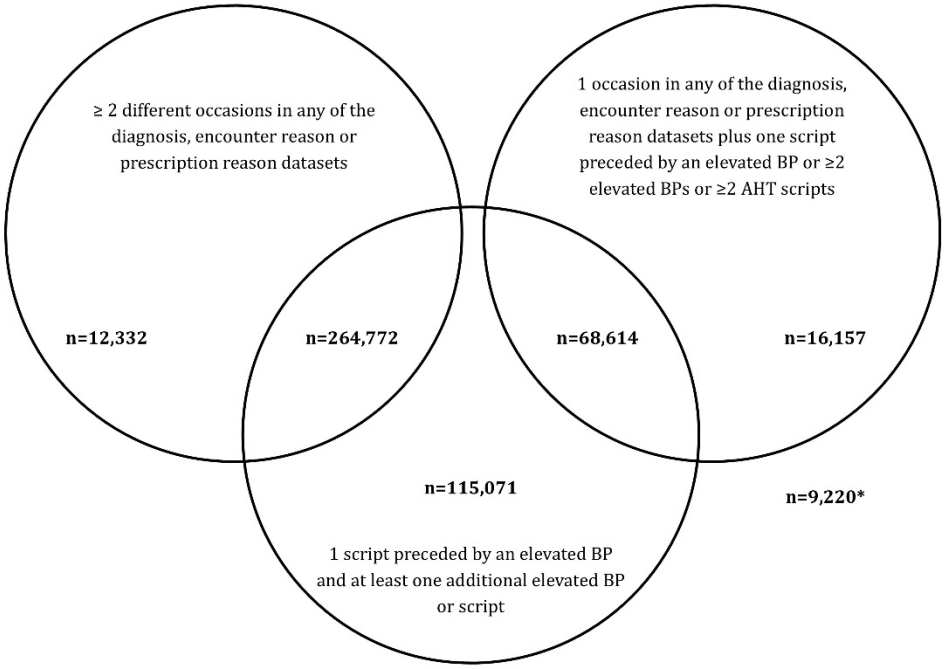
Amlodipine, Felodipinem, Lercanidipine, Nifedipine, Verapamil, Diltiazem

ATC C09A: Angiotensin-converting enzyme (ACE) inhibitors

Captopril, Enalapril, Fosinopril, Lisinopril, Perindopril, Quinapril, Ramipril, Trandolapril

ATC C09B: Angiotensin Receptor Blockers

Candesartan, Eprosartan, Irbesartan, Losartan, Olmesartan, Telmisartan, Valsartan



* 9,220 individuals did not meet the diagnosis criteria. The two top circles are mutually exclusive and therefore no overlap exists.

Figure S1 Criteria for diagnosis of hypertension

Table S2 Class of antihypertensive medication prescribed

Class of antihypertensive therapy	% of patients prescribed
ACE inhibitors	33.6
Angiotensin II receptor blockers	47.4
Calcium channel blockers	35.2
Diuretics	31.9
Beta blockers	20.9
Alpha blockers	8.7

Chapter 4

Cardiovascular disease risk of patients with hypertension

4.1 Preface

As guidelines recommend that hypertension be managed in combination with an assessment of a patient's absolute cardiovascular disease (CVD) risk, this chapter details the management of patients with hypertension according to their CVD risk, with findings published in the *Journal of Human Hypertension*. A cross-sectional analysis of MedicineInsight was conducted. Whereas the previous study (Chapter 3) included all adult patients, this study was limited to patients aged between 45 and 74 years (between 35 and 74 years for Aboriginal and Torres Strait Islander adults) as this is the population for which CVD risk assessment is recommended and in which the CVD risk algorithm has been validated. Furthermore, patients with a history of CVD were excluded as the assessment of absolute CVD risk is aimed at primary prevention.

4.2 Statement of authorship

Title of paper: Predicted cardiovascular disease risk and prescribing of antihypertensive therapy among patients with hypertension in Australia using MedicineInsight

Publication status: Published

Publication details: Roseleur J, Gonzalez-Chica DA, Karnon J, Stocks NP. Predicted cardiovascular disease risk and prescribing of antihypertensive therapy among patients with hypertension in Australia using MedicineInsight. *Journal of Human Hypertension*. 2023;37(5):370-8.

Name of principal author (Candidate): Jacqueline Roseleur

Contribution to the paper: Conception and design, analysis and interpretation of data, drafted the article and critical revisions, and acted as corresponding author.

Overall percentage: 85%

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signed: . . . . . Date: 09/12/2022

Co-author contributions

By signing the statement of authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of co-author: David Gonzalez-Chica

Contribution to the paper: Conception and design, analysis and interpretation of data, and revised it critically for important clinical and intellectual content.

Signed: . . . . . Date: 09/12/2022

Name of co-author: Jonathan Karnon

Contribution to the paper: Conception and design, interpretation of data, and revised it critically for important intellectual content.

Signed: . . . . . Date: 09/12/2022

Name of co-author: Nigel Stocks

Contribution to the paper: Conception and design, interpretation of data, and revised it critically for important clinical and intellectual content.

Signed: . . . . . Date: 09/12/2022

4.3 Publication

Journal of Human Hypertension www.nature.com/jhh

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Predicted cardiovascular disease risk and prescribing of antihypertensive therapy among patients with hypertension in Australia using MedicineInsight

Jacqueline Roseleur[1,2,3]✉, David A. Gonzalez-Chica[2,4], Jonathan Karnon[3] and Nigel P. Stocks[2]

Hypertension guidelines recommend that absolute cardiovascular disease (CVD) risk guide the management of hypertensive patients. This study aimed to assess the proportion of patients with diagnosed hypertension with sufficient data to calculate absolute CVD risk and determine whether CVD risk is associated with prescribing of antihypertensive therapies. This was a cross-sectional study using a large national database of electronic medical records of patients attending general practice in 2018 (MedicineInsight). Of 571,492 patients aged 45–74 years without a history of CVD, 251,733 [40.6% (95% CI: 39.8–41.2)] had a recorded hypertension diagnosis. The proportion of patients with sufficient recorded data available to calculate CVD risk was higher for patients diagnosed with hypertension [51.0% (95% CI: 48.0–53.9)] than for patients without a diagnosis of hypertension [38.7% (95% CI: 36.5–41.0)]. Of those patients with sufficient data to calculate CVD risk, 29.3% (95% CI: 28.1–30.6) were at high risk clinically, 6.0% (95% CI: 5.8–6.3) were at high risk based on their CVD risk score, 12.8% (95% CI: 12.5–13.2) at moderate risk and 51.8% (95% CI: 50.8–52.9) at low risk. The overall prevalence of antihypertensive therapy was 60.9% (95% CI: 59.3–62.5). Prescribing was slightly lower in patients at high risk based on their CVD risk score [57.4% (95% CI: 55.4–59.4)] compared with those at low [63.3% (95% CI: 61.9–64.8)] or moderate risk [61.8% (95% CI: 60.2–63.4)] or at high risk clinically [64.1% (95% CI: 61.9–66.3)]. Guideline adherence is suboptimal, and many patients miss out on treatments that may prevent future CVD events.

Journal of Human Hypertension; https://doi.org/10.1038/s41371-022-00691-z

INTRODUCTION

Traditionally, hypertension guidelines have relied exclusively on blood pressure (BP) levels to guide treatment initiation and intensity [1]. However, cardiovascular disease (CVD) risk factors tend to cluster together, particularly in patients with hypertension. Moreover, antihypertensive treatment according to CVD risk is more effective [2] and cost-effective [3] than using BP levels alone. Therefore, guidelines now recommend that management and prevention of hypertension should also consider absolute CVD risk [4–6].

In Australia, the Heart Foundation recommends calculating the absolute risk of a primary CVD event over the next 5 years by applying the Australian National Vascular Disease Prevention Alliance (NVDPA) risk assessment and risk management algorithm [4], which includes the Framingham CVD risk equation [7]. The risk assessment applies to adults aged 45 and 74 years without a known history of CVD. In Aboriginal and Torres Strait Islander peoples, adults aged between 35 and 74 years are eligible [4, 8]. Patients at low or moderate CVD risk should be prescribed lifestyle therapy and, depending on BP levels, treated with an antihypertensive agent. Patients at high absolute CVD risk should always be managed with antihypertensives [4].

Existing evidence suggests that between 41 and 96% of physicians use a CVD risk calculator to assess absolute CVD risk [9–12]. These studies investigated absolute CVD risk assessment in all eligible patients, not only those with hypertension. As hypertension is already considered a risk factor for CVD [4], it is expected that a high proportion of patients with hypertension would have their absolute CVD risk assessed.

Studies evaluating the CVD risk profile of patients with hypertension in primary care are limited [13–15]. A study in Spain aimed to define the CVD risk profile of patients diagnosed with hypertension in primary and specialist care [15]. Even though physicians were required to undertake a complete medical history and a physical examination as part of the data collection process, 22% of patients had insufficient data to calculate CVD risk. Similarly, a more recent Swiss study requiring general practitioners (GPs) to record demographic and clinical data and conduct laboratory screening for lipid and plasma glucose levels, found that 13% of patients had missing data for determining dyslipidaemia status [13]. In Korea, Kim et al. assessed the CVD risk profile using measures collected as part of the study and the prescribing of antihypertensive therapy in patients with hypertension [14]. The authors reported no missing data and found that

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treatment with antihypertensive therapy did not differ by CVD risk status.

Evidence from real-world primary care settings where GPs are not prompted to collect data as part of a study is lacking. However, electronic health records (EHRs) provide an opportunity to evaluate real-world practice of CVD risk assessment in patients diagnosed with hypertension and subsequent prescribing patterns [16]. Therefore, this study aimed to (1) assess whether a higher proportion of patients with diagnosed hypertension aged 45–74 years and regularly attending Australian general practice have sufficient data in their EHR to calculate absolute CVD risk compared with patients without a diagnosis of hypertension, (2) determine whether a higher CVD risk is associated with more frequent prescribing of antihypertensive therapies among patients with hypertension aged 45–74, and (3) assess whether these findings vary according to age and sex.

METHODS

This study is a cross-sectional analysis of MedicineInsight, a large Australian general practice database of EHR. This study was reported according to REporting of studies Conducted using Observational Routinely-collected health Data Statement reporting guidelines [17].

Data source

As at October 2018, MedicineInsight included data from patients attending over 2700 GPs and 660 general practices across all states and territories (8.2% of all Australian practices) [18] and has been widely used to investigate diverse acute and chronic conditions [19–21]. Patients in the database are comparable, but not representative, to the general population as measured by sociodemographic variables and clinical conditions [18]. Details of the data collection process are published elsewhere [18]. In summary, de-identified EHRs from patients are collected monthly and include diagnoses, reasons for encounters, prescriptions, immunisations, clinical measurements (e.g. BP, pulse, weight), laboratory test orders and results and patient sociodemographic information. Patients within each practice receive a unique identification number that allows the patient to be followed over time. Extraction algorithms for identifying chronic condition diagnoses have recently been validated [22].

Study population

This study includes all patients aged between 45 and 74 years, or between 35 and 74 years for Aboriginal and Torres Strait Islander people, without CVD recorded in their EHR (i.e. ischaemic heart disease, heart failure, stroke, peripheral artery disease and aortic disease) who regularly attended one of these practices (i.e. at least three visits between 2016 and 2018) [23]. The methods used to identify patients diagnosed with hypertension have been described elsewhere [24]. Briefly, GPs can record clinical data (diagnosis, reason for encounter, reason for prescription) with either pre-coded terms or free-text. Misspellings, abbreviations, synonyms or spelling variations are common, and we consequently used a range of terms for "hypertension" to account for these variations. All available data in the patient's EHR was reviewed to identify those with hypertension diagnosis. Almost 70% of patients had data available since 2011. Patients were considered to have hypertension if (1) the condition was recorded as a diagnosis, reason for encounter or reason for prescription (Supplementary File), or (2) if the patient received a prescription for antihypertensive therapy preceded by an elevated BP (i.e. BP higher than 140/90 mmHg). By including an elevated BP, we aimed to reduce misclassification of patients taking antihypertensive therapy for conditions other than hypertension (e.g. heart failure, myocardial infarction). Antihypertensive medications included angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (Anatomical Therapeutic Chemical (ATC) C09), beta-blockers (ATC C07), calcium channel blockers (ATC C08), diuretics (ATC C03) and alpha-blockers (ATC C02).

Data and variables

Cardiovascular risk. First, we estimated whether patients had available recorded information on the different risk factors to enable CVD risk calculation, irrespective of whether they had hypertension or not. We used the most recent measures recorded (i.e. systolic BP, total cholesterol, HDL cholesterol, albumin:creatinine ratio and estimated glomerular filtration rate). As guidelines recommend CVD risk be reviewed at least every 2 years [8], measures recorded in 2015 were also considered to accommodate patients who last visited their GP in 2017. Hence, measures between 2015 and 2018 were included. Where smoking status was not recorded, patients were assumed to be non-smokers. A comparison of the proportion of patients recorded as smokers with data reported in the National Drug Strategy Household Survey found similar proportions for all age groups by sex [25]. As left ventricular hypertrophy is challenging to identify in the EHR, we assumed left ventricular hypertrophy was absent for all patients.

Thereafter, for patients with a diagnosis of hypertension, we followed the recommendations of the National Heart Foundation of Australia guidelines [4] and classified patients with the following conditions as clinically at high risk of CVD: (1) people with diabetes and over 60 years of age, (2) those with diabetes and microalbuminuria (albumin:creatinine ratio >3.5 for females and >2.5 for males), (3) patients with moderate or severe chronic kidney disease [estimated glomerular filtration rate below 45 ml/min/1.73 m^2 or persistent proteinuria (albumin:creatinine ratio >35 mg/mmol in females and >25 mg/mmol in males—two positive measurements, 3 months apart)], (4) systolic BP above 180 mmHg, (5) diastolic BP above 110 mmHg, (6) familial hypercholesterolaemia or (7) total cholesterol level exceeding 7.5 mmol/l [4, 8]. Patients were considered to have diabetes when the patient record had either a diagnosis, encounter reason or prescription reason of diabetes, or they were prescribed antidiabetic medication (ATC A10; except for those with a diagnosis of polycystic ovarian syndrome). Similarly, patients were considered to have familial hypercholesterolaemia when the patient record had either a diagnosis, encounter reason or prescription reason of familial hypercholesterolaemia.

Next, for those patients with diagnosed hypertension who were not at high risk clinically and with sufficient variables available, we calculated the absolute risk of a primary CVD event over the next 5 years by applying the Australian NVDPA risk assessment and risk management algorithm [4, 8]. The absolute CVD risk was categorised as low (<10%), moderate (10–15%), or high (>15%). The NVDPA algorithm underestimates risk in Aboriginal and Torres Strait Islander patients and recommends adding 5% to the calculated risk score [4, 26]. By using that approach, 706 out of 1578 and 317 out of 317 Aboriginal and Torres Strait Islander patients were reclassified from low to moderate risk and from moderate to high risk, respectively.

Therefore, except for those with insufficient data for CVD risk score calculation, patients were classified in one of four groups: (1) low CVD risk, (2) moderate CVD risk, (3) high CVD risk (based on the NVDPA algorithm), or (4) clinically at high risk of CVD.

Outcome: guideline-recommended therapy. According to current guidelines, patients at low or moderate CVD risk should be prescribed lifestyle therapy and, depending on BP levels (e.g. BP persistently ≥160/90 mmHg), an antihypertensive agent. In contrast, patients at high CVD risk should be treated with an antihypertensive agent irrespective of their BP levels [4]. To assess compliance with these recommendations, the history of antihypertensive prescription in the last 6 months (July to December 2018) was examined. For comparison, we also examined the prescription history of patients with insufficient data available for CVD risk calculation. We also considered alternative prescribing investigation periods [12 months (January to December 2018) and 24 months (January 2017 to December 2018)] to explore changes in prescribing patterns over time.

Covariates. Patient sociodemographic characteristics included sex (male/female), 5-year age groups, remoteness (major cities, inner regional and outer regional/remote and very remote) and socioeconomic status in quintiles, as measured by the Index of Relative Socioeconomic Advantage and Disadvantage (IRSAD). Age in 2018 was calculated using the patient's year of birth. IRSAD is a macroeconomic indicator of relative advantage and disadvantage developed by the Australian Bureau of Statistics that summarises information about households' social and economic conditions within an area (i.e. income, education, employment, occupation and housing characteristics) and is based on residential postcodes [27].

Statistical methods

All analyses were performed in STATA 16.0 (StataCorp, College Station, Texas, USA), using practices as clusters and conditioned on the number of consultations to minimise selection bias (i.e. the likelihood of receiving medical treatments or diagnosis increase with the number of visits to the practice) [28].

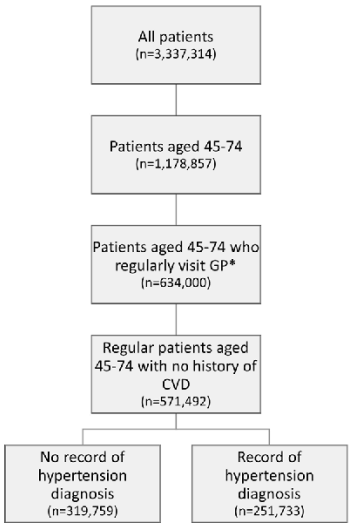

Fig. 1 Flow diagram describing the derivation of the study cohort. *Regular attendance defined as at least three visits in two consecutive years between 2016 and 2018.

The sociodemographic and cardiovascular risk characteristics were presented by sex and age group and expressed as proportions (%), with their corresponding 95% confidence intervals (95% CIs). We present crude results unless otherwise stated.

The proportions of patients prescribed antihypertensives according to CVD risk status (low, moderate, high, or high risk clinically) or those with insufficient data to calculate CVD risk was assessed using logistic regression adjusted for age, IRSAD and remoteness, and was presented separately for males and females.

The Human Research Ethics Committee of the University of Adelaide exempted this study for ethical review, as it used existing and non-identifiable data. Access to the data for this study was approved by the MedicineInsight Data Governance Committee (project 2016-007).

RESULTS

Hypertension diagnosis and data availability

The sample included 571,492 regular patients without a history of CVD and aged 45–74 years [mean age 58.8 years (SD 8.6), 57.7% female], including 12,129 Aboriginal and Torres Strait Islander people aged 35–74 years. Of these, 251,733 [40.6% (95% CI: 39.8–41.2)] had a recorded diagnosis of hypertension [mean age 62.3 years (SD 8.0), 47.9% female]. Figure 1 describes the derivation of the study cohort.

The proportion of patients with sufficient recorded data available to calculate CVD risk was higher for patients diagnosed with hypertension [51.0% (95% CI: 48.0–53.9)] than for patients without a diagnosis of hypertension [38.7% (95% CI: 36.5–41.0)]. This finding was consistent for males and females across all age groups (Fig. 2).

Characteristics of patients diagnosed with hypertension

In those with a hypertension diagnosis, there were no differences according to age, sex, or Indigenous status between those with sufficient ($n = 128,836$) or insufficient ($n = 122,897$) data to calculate their CVD risk (Table 1). However, a higher proportion of patients with sufficient data were from regional/remote/very remote areas (18.2% vs. 10.7%), the lowest IRSAD quintile (21.9% vs. 16.4%), had a diagnosis of diabetes (23.7% vs. 18.9%) or chronic kidney disease (3.0% vs. 2.4%) than those with insufficient data.

Supplementary Table 1 shows the socioeconomic characteristics and cardiovascular risk factors by age group and sex for those with diagnosed hypertension. More males were current smokers (13.4% vs. 11.0%, $p < 0.001$) or had diabetes (23.1% vs. 19.7%, $p < 0.001$) than females. The mean systolic and diastolic BP for males and females were similar [137.9 (SD 15.3)/81.5 (SD 10.3) mmHg and 136.2 (SD 16.4)/81.0 (SD 10.5) mmHg, respectively]. The mean total cholesterol for males and females was 4.9 (SD 1.1) mmol/l and 5.3 (SD 1.1) mmol/l, respectively and the mean HDL cholesterol was 1.3 (SD 0.4) mmol/l for males and 1.6 (SD 0.4) mmol/l for females.

Hypertension and cardiovascular disease risk

Apart from those patients with hypertension and sufficient data to calculate their CVD risk ($n = 128,836$), another 17,819 patients with hypertension were identified as clinically at high risk of CVD [4] despite having insufficient data for risk estimation. These patients were included in the sample for further analyses. Therefore, of all these patients with hypertension ($n = 146,655$), 29.3% (95% CI: 28.1–30.6) were at high risk clinically, 6.0% (95% CI: 5.8–6.3) were at high risk based on their CVD risk score, 12.8% (95% CI: 12.5–13.2) at moderate risk and 51.8% (95% CI: 50.8–52.9) at low risk. Figure 3 shows that similar proportions of males [30.1% (95% CI: 28.8–31.5)] and females [28.5% (95% CI: 27.2–29.7)] were at high risk clinically. However, based on the CVD risk calculation, a larger proportion of males than females were at high risk (10.6% vs. 1.4%, $p < 0.001$) or moderate risk (20.1% vs. 5.5%, $p < 0.001$). This difference was larger in older age groups (Fig. 3).

Prescribing of guideline-recommended therapy

The overall prevalence of antihypertensive therapy in males and females was 61.3% (95% CI: 59.7–62.9) and 60.5% (95% CI: 58.9–62.1), respectively. Figure 4A presents the proportion of patients prescribed an antihypertensive therapy in the last 6 months by CVD risk and sex. Overall, prescribing was slightly lower in patients at high risk based on their CVD risk score [57.4% (95% CI: 55.4–59.4)] compared with those at low [63.3% (95% CI: 61.9–64.8)] or moderate risk [61.8% (95% CI: 60.2–63.4)] or at high risk clinically [64.1% (95% CI: 61.9–66.3)], and this pattern was similar for males and females. For comparison, Fig. 4A also shows prescribing of antihypertensive therapy for patients with hypertension but with insufficient data to calculate CVD risk. Prescribing for these patients was similar to those at high risk based on their CVD risk score, with 58.5% (95% CI: 56.6–60.5) for males and 57.6% (95% CI: 55.6–59.6) for females.

When the prescribing investigation periods were extended to 12 and 24 months (Fig. 4B, C), higher proportions of patients in all risk categories were prescribed antihypertensive therapy. However, the prevalence of antihypertensive prescriptions was similar across all CVD risk categories.

DISCUSSION

Two main findings can be highlighted in this study. First, CVD risk calculation was only possible in half of the patients with hypertension, and neither age, sex, smoking status, nor BP grade influenced data availability. Second, our findings indicate that GP prescribing of antihypertensive therapy was not solely guided by absolute CVD risk.

CVD risk assessment

Despite the recommendation by Heart Foundation guidelines that management of hypertension be based on absolute CVD risk, two Australian studies have found that GPs still base their treatment and management of hypertension on BP as a single risk factor [29, 30]. Jansen et al. [30] conducted an experimental study in 2012 with 144 GPs to understand the use of individual risk factors and absolute CVD risk in making decisions about patient management. GPs stated that they would prescribe BP medication for 93% of the cases with high absolute CVD risk and 83% of the cases with lower absolute risk. More recently, Chapman et al. [29] conducted interviews and focus group discussions with 18 GPs on

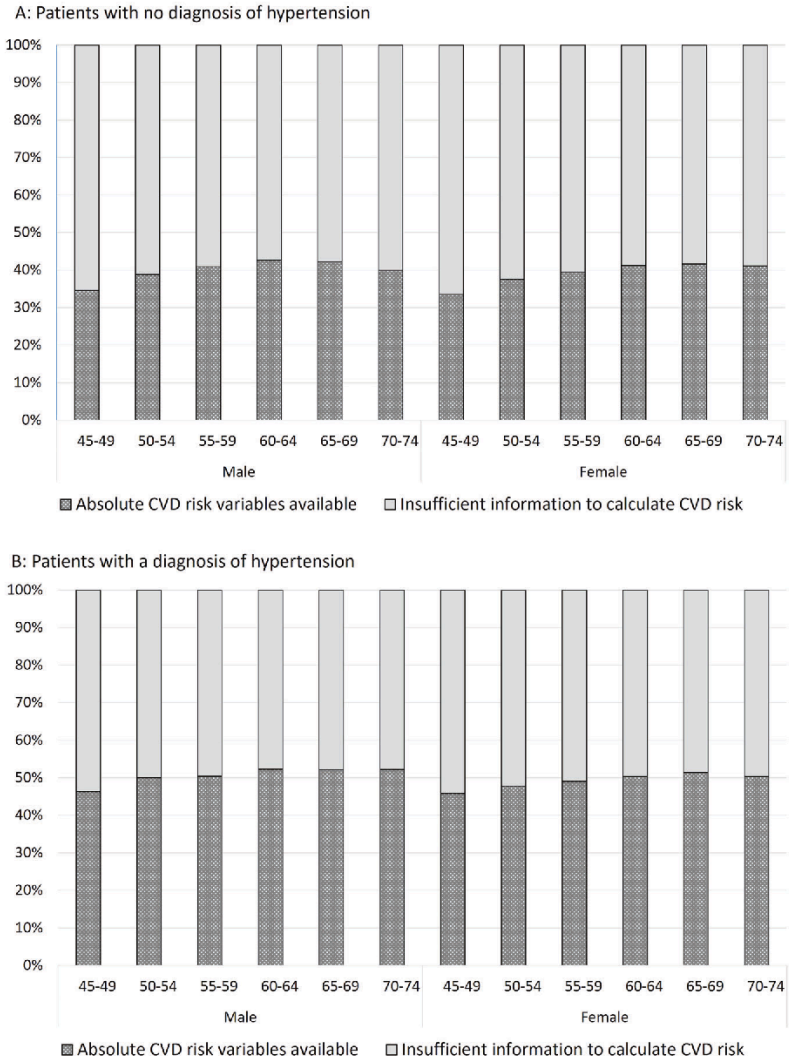

Fig. 2 Data availability for CVD risk calculation. Distribution of the availability of data to calculate absolute risk of a primary CVD event over the next 5 years for patients without a history of cardiovascular disease aged between 45 and 74 by age group and sex for patients (**A**) with no diagnosis of hypertension ($n = 319,719$) and (**B**) patients with a diagnosis of hypertension ($n = 251,733$).

determining the role of BP in the management of absolute CVD risk. They found that when GPs were provided with absolute CVD risk data, all GPs tended to use single risk factor management strategies. Our study, which explored the EHRs of more than 570,000 regular patients, supports these findings. We found that CVD risk calculation was only possible in half of the patients with hypertension, indicating that absolute CVD risk was unavailable to guide the management of patients. This proportion was higher than those without a hypertension diagnosis (51.0% vs. 38.7%), but still suboptimal.

Surveys of GPs report high levels of awareness of CVD risk calculators (92–96%) [12, 31], but considerable variation in the use of CVD risk calculators (41–96%) [9–12, 31]. Among those who reported using these calculators, use was inconsistent. In the US, only 19% of physicians reported always or nearly always using CVD risk when considering primary prevention [12]. In Australia, half of GPs reported assessing CVD risk in more than 80% of their patients [31]. These findings are supported by studies analysing EHRs that found varying rates of missing data to calculate CVD risk. For example, estimates for missing cholesterol data ranged from 31 to 78% [32–34], which is consistent with the findings of our study that almost 50% of patients did not have a cholesterol measure recorded in their EHR.

In Australia, patients aged 45–49 years with at least one identifiable risk factor (lifestyle, biomedical or family history) are eligible for a Medicare-funded health check. This programme aims to prevent or delay the onset of chronic disease and includes undertaking examinations and investigations as clinically required [8]. Furthermore, the Royal Australian College of General Practitioners Guidelines for Preventative Activities in General Practice recommends assessing lipid levels from 45 years [35]. In our study, only 46% of patients aged 45–49 with diagnosed hypertension had sufficient data to calculate CVD risk, despite hypertension being a biomedical risk factor for chronic disease and the existence of a government-funded programme that promotes preventive activities in that age group. This finding suggests that

Table 1. Characteristics of patients aged 45–74 years with a diagnosis of hypertension and no history of CVD with sufficient and insufficient data to calculate absolute CVD risk ($n = 251,733$).

	Sufficient data to calculate CVD risk ($n = 128,836$)		Insufficient data to calculate CVD risk ($n = 122,897$)	
Characteristic	**%**	**95% CI**	**%**	**95% CI**
Age (Mean, SD)	62.0 (8.0)		61.6 (8.2)	
Sex				
Female	49.9	[49.3–50.5]	51.2	[50.5–52.0]
IRSAD quintile				
Highest	20.3	[17.1–24.0]	22.4	[18.7–26.5]
2nd upper	16.8	[14.7–19.1]	17.4	[15.0–20.0]
Intermediate	23.1	[20.0–26.5]	24.3	[20.6–28.4]
2nd lower	17.0	[14.4–20.1]	18.9	[15.8–22.3]
Lowest	21.9	[18.1–26.3]	16.4	[13.2–20.3]
Not recorded	0.9	[0.6–1.2]	0.7	[0.5–0.9]
Remoteness				
Major cities	53.3	[47.7–58.8]	60.0	[54.3–65.5]
Inner regional	27.9	[23.4–32.9]	28.8	[24.0–34.1]
Outer regional/remote/very remote	18.2	[14.2–23.2]	10.7	[8.2–13.9]
Not recorded	0.6	[0.4–0.8]	0.4	[0.3–0.5]
Indigenous status				
Neither Aboriginal nor Torres Strait Islander	80.7	[77.6–83.4]	81.9	[79.2–84.4]
Aboriginal and/or Torres Strait Islander	2.2	[1.8–2.7]	2.0	[1.7–2.2]
Not stated	17.2	[14.4–20.3]	16.1	[13.6–18.9]
Smoking status				
Non smoker	51.4	[50.5–52.3]	50.7	[49.8–51.7]
Smoker	11.8	[11.3–12.4]	12.5	[12.0–13.1]
Ex smoker	32.8	[32.1–33.5]	30.5	[29.7–31.3]
Not recorded	4.0	[3.5–4.5]	6.2	[5.5–7.1]
Blood pressure grade[a]				
Controlled	52.8	[52.0–53.6]	49.4	[48.6–50.1]
Grade 1	36.5	[36.0–37.1]	36.8	[36.2–37.3]
Grade 2	9.0	[8.7–9.3]	9.6	[9.3–9.9]
Grade 3	1.6	[1.5–1.7]	1.8	[1.7–2.0]
Not recorded	0.0	[0.0–0.0]	2.5	[2.0–3.0]
Diabetes	23.7	[22.9–24.5]	18.9	[18.4–19.5]
Chronic kidney disease[a,b]	3.0	[2.7–3.3]	2.4	[2.2–2.7]
Familial hypercholesterolaemia	0.2	[0.2–0.2]	0.1	[0.1–0.1]

Crude results presented. Percentages and 95% CI were estimated considering the clusters (general practices) and the individual's probability of being in the sample.

[a]Only measures recorded between 2015 and 2018 were used.

[b]Patients with record of a diagnosis of chronic kidney disease or an estimated glomerular filtration rate <45 ml/min/1.73 m^2 or persistent proteinuria.

compliance with preventive recommendations is suboptimal, even when a funding mechanism is available. To address the underuse of CVD risk assessment, the Australian Government introduced additional funding in 2019 to fund CVD risk assessment and ongoing management for all patients aged 30 years and older [36]. Further studies are necessary to investigate the impact of this measure.

Prescribing of guideline-recommended therapy

Our study found that GP prescribing of antihypertensive therapy was not guided solely by absolute CVD risk. Approximately the same proportion (~61%) of patients diagnosed with hypertension in all risk groups, including patients with insufficient data available for CVD risk assessment, had been prescribed an antihypertensive drug in the last 6 months of the study. This pattern was similar for males and females. We are only aware of one other study investigating the prescribing patterns by CVD risk in a population with diagnosed hypertension [14]. This Korean study also found no difference in recorded prescribing patterns across risk groups. Australian studies have investigated prescribing by CVD risk in the general population, rather than in those with diagnosed hypertension [37, 38]. Using data from a national survey, Banks et al. found that individuals at high CVD risk were more likely to be taking antihypertensive therapy than those at low CVD risk [37]. As our study included only patients diagnosed with hypertension who regularly visited their GP, we cannot compare our findings to national survey data, which included individuals who may be different to those who regularly consult with their GP. The

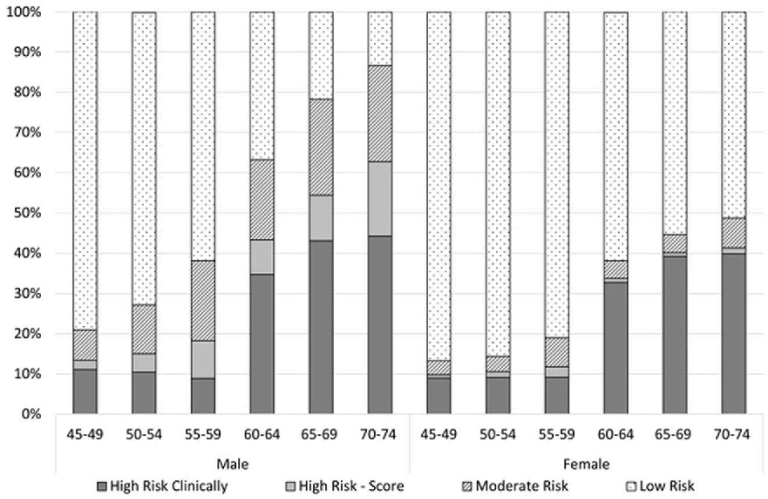

Fig. 3 Distribution of absolute risk of a primary CVD event over the next 5 years for patients with a diagnosis of hypertension aged 45–74, no history of CVD and sufficient details to calculate risk if not at high risk clinically, by age group and sex ($n = 146{,}655$).

Australian Hypertension and Absolute Risk Study (AusHEART) study described the CVD risk and prescribing patterns of patients aged 55 years or older attending general practice [38]. This study calculated the absolute CVD risk of patients using the Framingham risk equations and three different guideline adjustments, including the NVDPA. Prescribing of antihypertensive therapy by CVD risk increased with higher risk levels. However, prescribing data were only presented for risk categories calculated using the National Heart Foundation 2004 guidelines. These guidelines categorise a higher proportion of patients as high risk than the NVDPA, once again limiting our ability to make comparisons.

The prescribing of antihypertensive medications in our study did not vary by absolute CVD risk, even when we investigated longer prescribing periods. These results reflect undertreatment of high-risk patients and potential overtreatment of low-risk patients for CVD risk reduction. According to the Australian guidelines [4], all patients at high risk should be prescribed antihypertensive therapy to reduce their CVD risk. In our study, ~77% of patients with hypertension at high CVD risk and without a prescription of antihypertensive therapy were above target BP levels [i.e. 140/90 mmHg; mean BP in this group 148.0/83.9 mmHg (SD 13.6/9.7); data not shown in tables]. On the other hand, 41% of those at low CVD risk and not managed with antihypertensives had BP levels above the threshold. Clinical inertia (i.e. failure to initiate or escalate treatment when indicated) is often cited as a reason for patients not receiving prescriptions for guideline-recommended therapy [39]. However, debates around inappropriate therapeutic inertia and appropriate inaction continue [40]. Lebeau et al. recently undertook a consensus study to create operational definitions for appropriate inaction and inappropriate inertia in managing patients with hypertension in primary care [40]. Appropriate inaction was defined as not initiating or intensifying treatment for a patient for whom BP goals defined by guidelines have not been achieved and when at least one of the following conditions occurs: (1) elevated BP has not been confirmed by self-measurement or ambulatory BP monitoring, (2) there is a legitimate reservation regarding the reliability of the measurements, (3) there is an adherence concern regarding pharmacological therapy, (4) there is a specific iatrogenic risk, specifically for orthostatic hypotension in the elderly, (5) there is another medical priority more critical and more urgent, and (6) access to treatment is challenging. This definition addresses some of the limitations of previous clinical inertia definitions by recognising the complexity of the GP-patient relationship. Whether appropriate inaction explains our findings is uncertain and would require further research.

Strengths and limitations

Our study is the first in Australia to evaluate the cardiovascular risk profile of patients diagnosed with hypertension and included a large sample of patients across Australian general practice. A limitation of MedicineInsight is the inability to track patients across different practices. This limitation may have resulted in underestimating the proportion of patients with available data to calculate CVD risk. However, the median number of annual visits between 2016 and 2018 ranged from six for those with insufficient data to eight for those clinically at high risk. Therefore, most patients visited the same practice every 2 months on average, enabling enough opportunities to have their CVD risk assessed. Another limitation of MedicineInsight is that progress notes are not extracted, and these may contain information related to CVD risk factors. However, it is unlikely that this limitation would change our results. A recent validation study found accuracy close to 90% between algorithms for chronic conditions using the same fields as our study compared to the original EHR, which included the progress notes [22]. The Framingham CVD risk equation is intended for treatment-naive individuals and will underestimate risk in those receiving treatment. As we used the most recent BP and cholesterol measures to calculate CVD risk, those classified as low or moderate absolute CVD risk may have had a higher baseline risk before medication initiation.

CONCLUSIONS

Patients with hypertension are at increased risk of CVD. Despite guidelines recommending the use of absolute CVD risk in the management of hypertension, only half of patients have sufficient data to calculate CVD risk. For hypertensive patients aged 45–74 who regularly visit their GP, with a calculated high or moderate CVD risk, 40% were not prescribed antihypertensive therapies, despite three-quarters of them having BP levels above the threshold. Therefore, many patients miss out on guideline-promoted treatments that minimise BP complications and reduce the risk of future CVD events.

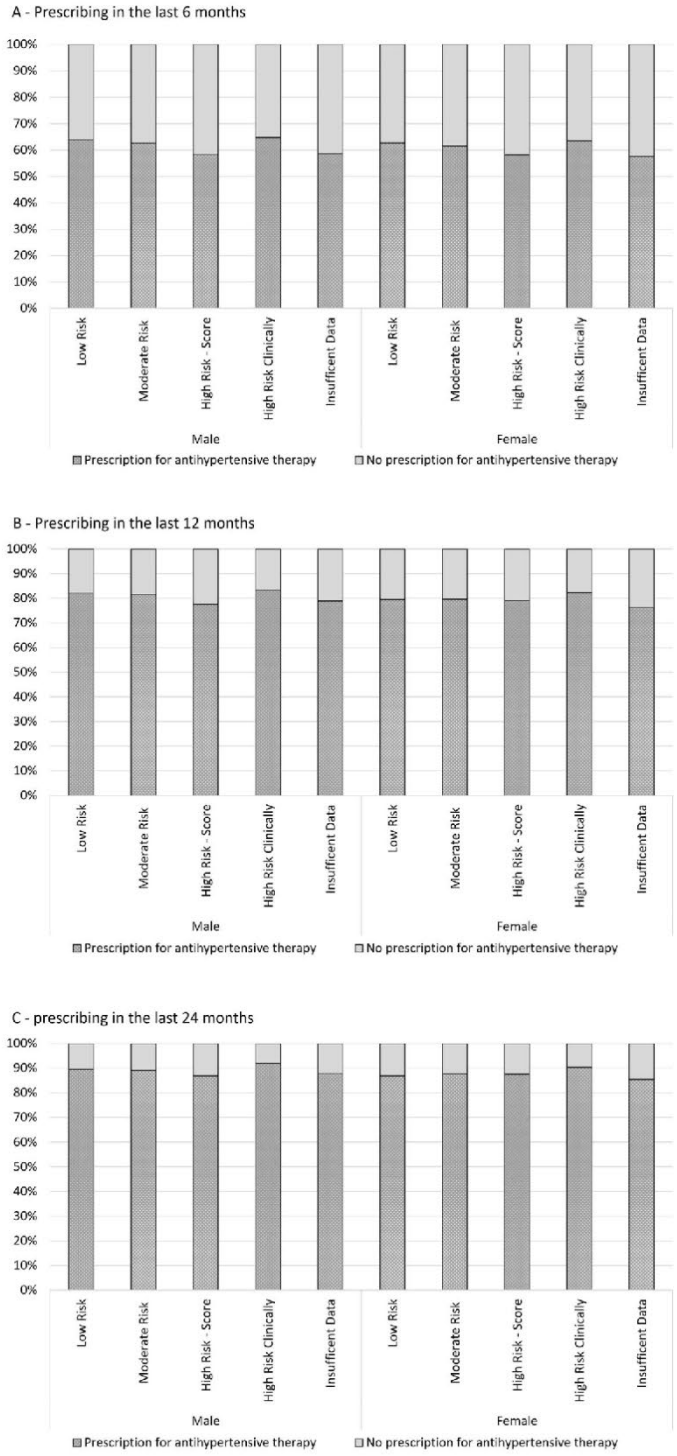

Fig. 4 Antihypertensive therapy prescribing by CVD risk. Prescribing of antihypertensive therapy by absolute risk of a primary CVD event over the next 5 years and those with insufficient data to calculate CVD risk, and sex, in the past 6 months (**A**), 12 months (**B**) and 24 months (**C**) for patients aged 45–74 years ($n = 251{,}733$).

SUMMARY TABLE

What is known on this topic

- Cardiovascular disease (CVD) risk factors tend to cluster together, particularly in patients with hypertension.
- Guidelines therefore recommend that the management of hypertension should be guided by absolute CVD risk, rather than blood pressure alone.
- Electronic health records provide an opportunity to evaluate real-world practice of CVD risk assessment and subsequent prescribing patterns.

What this study adds

- CVD risk calculation was only possible in half of patients with a diagnosis of hypertension.
- GP prescribing of antihypertensive therapy was not solely guided by absolute CVD risk.
- Many patients miss out on guideline-promoted treatments that minimise BP complications and reduce the risk of future CVD events.

DATA AVAILABILITY

Data may be obtained from MedicineInsight and are not publicly available. Third parties may express an interest in the information collected through MedicineInsight. The provision of information in these instances undergoes a formal approval process and is guided by the MedicineInsight independent external Data Governance Committee. This Committee includes general practitioners, consumer advocates, privacy experts and researchers.

REFERENCES

1. Karmali KN, Lloyd-Jones DM. Global risk assessment to guide blood pressure management in cardiovascular disease prevention. Hypertension. 2017;69:e2–9.
2. Muntner P, Whelton PK. Using predicted cardiovascular disease risk in conjunction with blood pressure to guide antihypertensive medication treatment. J Am Coll Cardiol 2017;69:2446–56.
3. Cadilhac DA, Carter R, Thrift AG, Dewey HM. Organized blood pressure control programs to prevent stroke in Australia: would they be cost-effective? Stroke. 2012;43:1370–5.
4. National Heart Foundation of Australia. Guideline for the diagnosis and management of hypertension in adults—2016. Melbourne: National Heart Foundation of Australia; 2016.
5. Whelton PK, Carey RM, Aronow WS, Casey DE Jr, Collins KJ, Dennison Himmelfarb C, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: Executive Summary: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018;71:1269–324.
6. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. J Hypertens. 2018;36:1953–2041.
7. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. Am Heart J. 1991;121:293–8.
8. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. National Stroke Foundation; Canberra, Australia, 2012.
9. Ban JW, Perera R, Stevens R. GPs' familiarity with and use of cardiovascular clinical prediction rules: a UK survey study. BJGP Open. 2020;4:bjgpopen20X101081.
10. Dallongeville J, Banegas JR, Tubach F, Guallar E, Borghi C, De Backer G, et al. Survey of physicians' practices in the control of cardiovascular risk factors: the EURIKA study. Eur J Prev Cardiol. 2012;19:541–50.
11. Gupta R, Stocks NP, Broadbent J. Cardiovascular risk assessment in Australian general practice. Aust Fam Physician. 2009;38:364–8.
12. Shillinglaw B, Viera AJ, Edwards T, Simpson R, Sheridan SL. Use of global coronary heart disease risk assessment in practice: a cross-sectional survey of a sample of U.S. physicians. BMC Health Serv Res. 2012;12:20.
13. Handschin A, Brighenti-Zogg S, Mundwiler J, Giezendanner S, Gregoriano C, Martina B, et al. Cardiovascular risk stratification in primary care patients with arterial hypertension: results from the Swiss Hypertension Cohort Study (HccH). Eur J Prev Cardiol. 2019;26:1843–51.
14. Kim KI, Lee YS, Park CG. Impact of global risk assessment on the evaluation of hypertensive patients treated by primary care physicians in Korea (a Nation-Wide, Multi-Center, Observational, Cross-Sectional, Epidemiologic Study to Evaluate the Proportion of Cardiovascular Risk Factors in Korean hypertensive patients: WONDER study). Hypertens Res. 2014;37:665–71.
15. Barrios V, Escobar C, Calderon A, Echarri R, Gonzalez-Pedel V, Ruilope LM, et al. Cardiovascular risk profile and risk stratification of the hypertensive population attended by general practitioners and specialists in Spain. The CONTROLRISK study. J Hum Hypertens. 2007;21:479–85.
16. Muller S. Electronic medical records: the way forward for primary care research? Fam Pr. 2014;31:127–9.
17. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, et al. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Med. 2015;12:e1001885.
18. Busingye D, Gianacas C, Pollack A, Chidwick K, Merrifield A, Norman S, et al. Data resource profile: MedicineInsight, an Australian national primary health care database. Int J Epidemiol. 2019;48:1741–h.
19. Bezabhe WM, Bereznicki LR, Radford J, Wimmer BC, Salahudeen MS, Garrahy E, et al. Stroke risk reassessment and oral anticoagulant initiation in primary care patients with atrial fibrillation: a ten-year follow-up. Eur J Clin Invest 2021;51:e13489.
20. Begum M, Gonzalez-Chica D, Bernardo C, Woods A, Stocks N. Trends in the prescription of drugs used for insomnia in Australian general practice, 2011-2018. Br J Gen Pract. 2021;71:e877–e886.
21. Frank O, De Oliveira Bernardo C, Gonzalez-Chica DA, Macartney K, Menzies R, Stocks N. Pneumococcal vaccination uptake among patients aged 65 years or over in Australian general practice. Hum Vaccin Immunother. 2020;16:965–71.
22. Havard A, Manski-Nankervis JA, Thistlethwaite J, Daniels B, Myton R, Tu K, et al. Validity of algorithms for identifying five chronic conditions in MedicineInsight, an Australian national general practice database. BMC Health Serv Res. 2021;21:551.
23. The Royal Australian College of General Practitioners. Standards for general practices. 5th ed. Victoria: RACGP; 2020.
24. Roseleur J, Gonzalez-Chica DA, Bernardo CO, Geisler BP, Karnon J, Stocks NP. Blood pressure control in Australian general practice: analysis using general practice records of 1.2 million patients from the MedicineInsight database. J Hypertens. 2021;39:1134–42.
25. Australian Institute of Health and Welfare. National Drug Strategy Household Survey 2019. Canberra: AIHW; 2020.
26. Hua X, McDermott R, Lung T, Wenitong M, Tran-Duy A, Li M, et al. Validation and recalibration of the Framingham cardiovascular disease risk models in an Australian Indigenous cohort. Eur J Prev Cardiol. 2017;24:1660–9.
27. Australian Bureau of Statistics. Census of population and housing: socio-economic indexes for areas (SEIFA). 2011.
28. Goldstein BA, Bhavsar NA, Phelan M, Pencina MJ. Controlling for informed presence bias due to the number of health encounters in an electronic health record. Am J Epidemiol 2016;184:847–55.
29. Chapman N, McWhirter RE, Jose KA, Schultz MG, Ezzy D, Nelson MR, et al. General practitioners maintain a focus on blood pressure management rather than absolute cardiovascular disease risk management. J Eval Clin Pract. 2021;27:1353–60.
30. Jansen J, Bonner C, McKinn S, Irwig L, Glasziou P, Doust J, et al. General practitioners' use of absolute risk versus individual risk factors in cardiovascular disease prevention: an experimental study. BMJ Open. 2014;4:e004812.
31. Greaves K, Smith A, Agostino J, Kunarajah K, Stanton T, Korda R. Cross-sectional survey describing general practitioners' absolute cardiovascular disease risk assessment practices and their relationship to knowledge, attitudes and beliefs about cardiovascular disease risk in Queensland, Australia. BMJ Open. 2020;10:e033859.
32. Cykert S, DeWalt DA, Weiner BJ, Pignone M, Fine J, Kim JI. A population approach using cholesterol imputation to identify adults with high cardiovascular risk: a report from AHRQ's EvidenceNow initiative. J Am Med Inform Assoc. 2019;26:155–8.
33. Jonnagaddala J, Liaw ST, Ray P, Kumar M, Chang NW, Dai HJ. Coronary artery disease risk assessment from unstructured electronic health records using text mining. J Biomed Inf. 2015;58:S203–10.
34. Petersen I, Welch CA, Nazareth I, Walters K, Marston L, Morris RW, et al. Health indicator recording in UK primary care electronic health records: key implications for handling missing data. Clin Epidemiol. 2019;11:157–67.
35. The Royal Australian College of General Practitioners. Guidelines for preventive activities in general practice. East Melbourne, Vic: RACGP; 2016.
36. Department of Health. Fact sheet: new MBS items for heart health check in. Australian Government; 2019.

37. Banks E, Crouch SR, Korda RJ, Stavreski B, Page K, Thurber KA, et al. Absolute risk of cardiovascular disease events, and blood pressure- and lipid-lowering therapy in Australia. Med J Aust. 2016;204:320.
38. Heeley EL, Peiris DP, Patel AA, Cass A, Weekes A, Morgan C, et al. Cardiovascular risk perception and evidence—practice gaps in Australian general practice (the AusHEART study). Med J Aust. 2010;192:254–9.
39. Okonofua EC, Simpson KN, Jesri A, Rehman SU, Durkalski VL, Egan BM. Therapeutic inertia is an impediment to achieving the Healthy People 2010 blood pressure control goals. Hypertension. 2006;47:345–51.
40. Lebeau JP, Biogeau J, Carre M, Mercier A, Aubin-Auger I, Rusch E, et al. Consensus study to define appropriate inaction and inappropriate inertia in the management of patients with hypertension in primary care. BMJ Open. 2018;8:e020599.

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AUTHOR CONTRIBUTIONS
JR, DGC, JK and NS contributed to the conception of the study. JR and DGC contributed to the design of the study. JR performed the statistical analysis and prepared the manuscript. All authors contributed to critically revising the text and provided intellectual contributions to strengthen the manuscript. All authors approved the final version for publication.

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COMPETING INTERESTS
The authors declare no competing interests.

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4.3.1 Online supplementary material

Table S1 Terms used to identify a diagnosis of hypertension in the electronic health record

Coded as diagnosis of hypertension if the diagnosis, reason for encounter or reason for prescription fields contained the following terms:

HYPERTE* | HYPERTANSION | HYPETENSION | HPT | HTN | HIGH BLOOD PRESS* | BLOOD PRESSURE HIGH | HIGH DIASTOLIC BP | DIASTOLIC BP HIGH | ^ DIASTOLIC BP | HIGH DBP | HIGH SYSTOLIC BP | SYSTOLIC BP HIGH | ^ SYSTOLIC BP | HIGH SBP | HIGH SYS BP | BP HIGH | BP-HIGH | HIGHT BP | HBP | ^BP | HIGH BP | BP TOO HIGH | BP TOOOO HIGH | BP CHECK - HIGH | BP CHECK - STILL HIGH | BP CHECK, HIGH | CHECK BP, HIGH | BP REVIEW - STILL HIGH | BP STILL HIGH | BP STILL TOO HIGH | BP RETURNING UP HIGH

Coded as diagnosis of hypertension if the diagnosis, reason for encounter or reason for prescription fields stated the following:

HYPERT | HT

Excluded if the diagnosis, reason for encounter or reason for prescription fields contained the following terms indicating hypertension other than essential or primary hypertension:

OCULAR | OCCULAR | OPHTHALMIC | PORTAL | COAT | COLLAR | BORDER | HOUR | 24 HR | 24HR | HBPM | TIGHTNESS | PREGNANCY | GESTATIONAL | PARTUM | PULMONARY | PUMONARY | IDIOPATHIC | INTRACRANIAL | INTRA CRANIAL |INTRA-CRANIAL | INTRACANAL | INTRACRINIAL | CRANIAL | VENOUS HYPERT* | RENOVASCULAR

Excluded if the diagnosis, reason for encounter or reason for prescription fields contained the following terms indicating that hypertension referred to family history:

FAMIL* & HISTORY | FAM HIST | FH | FHX | PARENT | MOTHER | MUM| FATHER | DAD | PATERNAL | MATERNAL | HUSBAND | WIFE | DAUGHTER | BROTHER | SISTER

Excluded if the diagnosis, reason for encounter or reason for prescription fields contained the following terms indicating uncertainty around the diagnosis of hypertension:

?HTN | ?HPT | ? HYPERTENSION | ?HYPERTENSION |FEAR (OF) | PREVENTIVE CARE – HYPERTENSION | HYPERTENSION - PREVENTIVE CARE | RISK OF HYPERTENSION | RULE OUT HYPERTENSION | SUSPECTED HYPERTENSION | POSSIBLE HYPERTENSION | POSSIBLE HTN | POSSIBLY HYPERTENSION | NO HYPERTENSION | POSSIBLE EARLY HY | HYPERTENSION FOR INVESTIG | PRE HYPERTEN | PRE-HYPERTEN | LABILE

** Stata code is available from the first author upon request**

Table S2 Characteristics of patients with diagnosed hypertension and no history of cardiovascular disease aged between 45–74 by age group and sex (n=251,733)

	Males											
	Age group (years)											
	45-49 (n=11,191)		**50-54 (n=11,460)**		**55-59 (n=24,152)**		**60-64 (n=24,045)**		**65-69 (n=26,023)**		**70-74 (n=25,566)**	
Characteristic	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
IRSAD quintile												
Highest	23.1	[19.8-26.8]	23.1	[19.9-26.6]	22.1	[19.0-25.6]	21.8	[18.6-25.3]	20.9	[17.7-24.4]	20.7	[17.5-24.5]
2nd upper	19.0	[16.6-21.6]	18.8	[16.5-21.2]	18.1	[16.0-20.4]	16.9	[14.9-19.1]	16.4	[14.4-18.6]	16.0	[13.9-18.3]
Intermediate	23.7	[20.7-26.9]	22.9	[20.0-26.1]	23.3	[20.4-26.5]	24.0	[21.0-27.3]	23.2	[20.1-26.7]	23.9	[20.4-27.8]
2nd lower	16.4	[14.0-19.1]	17.3	[14.8-20.2]	17.7	[15.2-20.6]	17.9	[15.4-20.8]	18.5	[15.8-21.5]	18.7	[15.9-21.9]
Lowest	17.0	[14.0-20.6]	17.1	[14.2-20.5]	17.8	[14.8-21.2]	18.5	[15.4-22.1]	20.2	[16.9-24.0]	19.9	[16.5-23.9]
Not recorded	0.8	[0.5-1.2]	0.8	[0.6-1.2]	0.9	[0.7-1.3]	0.9	[0.6-1.2]	0.8	[0.6-1.1]	0.8	[0.6-1.1]
Remoteness												
Major Cities	62.0	[56.9-66.8]	60.1	[55.1-65.0]	57.7	[52.8-62.6]	55.8	[50.8-60.6]	53.8	[48.8-58.8]	53.4	[48.2-58.6]
Inner Regional	23.3	[19.6-27.4]	24.5	[20.7-28.9]	26.7	[22.8-31.1]	28.2	[24.1-32.6]	30.1	[25.8-34.8]	30.9	[26.4-35.9]
Outer Regional/ Remote/Very Remote	14.2	[11.1-18.2]	14.9	[11.8-18.7]	15.0	[11.9-18.6]	15.5	[12.4-19.3]	15.6	[12.5-19.2]	15.1	[12.0-18.9]
Not recorded	0.5	[0.3-0.8]	0.4	[0.3-0.6]	0.6	[0.4-0.8]	0.6	[0.4-0.8]	0.5	[0.4-0.7]	0.5	[0.4-0.7]

	Males											
	Age group (years)											
	45-49 (n=11,191)		50-54 (n=11,460)		55-59 (n=24,152)		60-64 (n=24,045)		65-69 (n=26,023)		70-74 (n=25,566)	
Characteristic	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Indigenous status												
Neither Aboriginal nor Torres Strait Islander	77.0	[74.2-79.6]	79.2	[76.4-81.8]	79.8	[77.2-82.3]	80.0	[77.2-82.5]	81.7	[79.2-84.1]	82.7	[80.1-85.1]
Aboriginal and/or Torres Strait Islander	6.0	[4.9-7.3]	2.5	[2.0-3.0]	2.0	[1.6-2.4]	1.8	[1.5-2.1]	1.2	[1.0-1.4]	0.8	[0.6-0.9]
Not stated	17.0	[14.5-19.8]	18.3	[15.7-21.2]	18.2	[15.7-20.9]	18.2	[15.7-21.1]	17.1	[14.8-19.7]	16.5	[14.1-19.2]
Smoking status												
Non smoker	47.3	[46.0-48.6]	46.8	[45.5-48.1]	44.9	[43.9-45.9]	44.5	[43.5-45.5]	45.5	[44.5-46.5]	44.8	[43.8-45.7]
Smoker	21.1	[19.9-22.4]	19.6	[18.6-20.6]	17.0	[16.2-17.8]	13.6	[12.9-14.3]	9.4	[8.8-9.9]	6.8	[6.4-7.3]
Ex smoker	27.4	[26.4-28.4]	29.4	[28.4-30.5]	33.5	[32.6-34.3]	37.3	[36.3-38.3]	39.4	[38.5-40.3]	42.7	[41.7-43.7]
Not recorded	4.2	[3.6-5.0]	4.2	[3.6-4.9]	4.6	[4.0-5.3]	4.7	[4.1-5.3]	5.7	[5.0-6.5]	5.8	[5.0-6.6]
Systolic blood pressure*												
<140mmHg (Controlled)	54.8	[53.7-55.9]	55.7	[54.4-56.9]	54.3	[53.4-55.2]	53.5	[52.6-54.5]	54.2	[53.3-55.1]	54.3	[53.4-55.3]
140-159mmHg (Grade 1)	36.6	[35.6-37.6]	34.8	[33.7-35.9]	35.6	[34.9-36.4]	36.2	[35.4-37.0]	35.8	[35.1-36.5]	35.6	[34.9-36.4]
160-179mmHg (Grade 2)	6.2	[5.7-6.8]	7.3	[6.7-7.9]	7.6	[7.2-8.0]	7.9	[7.4-8.3]	7.4	[7.0-7.8]	7.5	[7.1-8.0]
≥180mmHg (Grade 3)	1.0	[0.8-1.3]	1.1	[0.9-1.3]	1.1	[1.0-1.3]	1.1	[1.0-1.2]	1.2	[1.1-1.4]	1.1	[1.0-1.3]
Not recorded	1.3	[1.0-1.6]	1.2	[0.9-1.5]	1.3	[1.0-1.6]	1.3	[1.1-1.6]	1.4	[1.1-1.7]	1.4	[1.1-1.8]

	Males											
	Age group (years)											
	45-49 (n=11,191)		50-54 (n=11,460)		55-59 (n=24,152)		60-64 (n=24,045)		65-69 (n=26,023)		70-74 (n=25,566)	
Characteristic	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Diastolic blood pressure*												
<90mmHg (Controlled)	61.8	[60.6-62.9]	65.9	[64.7-67.0]	71.0	[70.1-71.9]	77.9	[77.1-78.7]	84.0	[83.3-84.7]	88.5	[87.8-89.1]
90-99mmHg (Grade 1)	26.8	[25.9-27.7]	24.3	[23.3-25.2]	21.7	[21.0-22.4]	16.7	[16.0-17.4]	12.1	[11.6-12.7]	8.5	[8.0-9.0]
100-140mmHg (Grade 2)	8.2	[7.6-8.8]	7.0	[6.4-7.6]	5.1	[4.8-5.5]	3.5	[3.2-3.8]	2.1	[1.9-2.4]	1.4	[1.2-1.5]
>140mmHg (Grade 3)	1.9	[1.7-2.3]	1.7	[1.4-2.0]	0.9	[0.7-1.0]	0.6	[0.5-0.7]	0.4	[0.3-0.5]	0.3	[0.2-0.3]
Not recorded	1.3	[1.0-1.6]	1.2	[0.9-1.5]	1.3	[1.0-1.6]	1.3	[1.1-1.6]	1.4	[1.1-1.7]	1.4	[1.1-1.8]
Total cholesterol*												
<4.0mmol/L	5.5	[4.9-6.1]	6.7	[6.1-7.4]	8.1	[7.5-8.8]	9.9	[9.2-10.7]	12.3	[11.5-13.2]	14.6	[13.6-15.6]
4.0-7.5 mmol/L	43.3	[40.5-46.2]	45.1	[42.3-47.9]	44.3	[41.7-47.0]	44.5	[41.9-47.1]	41.9	[39.4-44.5]	40.0	[37.4-42.6]
>7.5 mmol/L	1.1	[0.9-1.4]	1.2	[1.0-1.5]	0.9	[0.7-1.0]	0.5	[0.4-0.7]	0.4	[0.4-0.5]	0.3	[0.2-0.3]
Not recorded	50.1	[46.9-53.3]	47.0	[43.8-50.2]	46.7	[43.6-49.9]	45.0	[41.8-48.3]	45.3	[42.1-48.6]	45.2	[41.8-48.6]
High density lipoprotein cholesterol*												
≥1.0 mmol/L	37.2	[34.8-39.6]	40.7	[38.2-43.3]	42.4	[39.9-44.9]	44.4	[41.8-47.0]	44.2	[41.6-46.9]	44.8	[42.0-47.6]
<1.0 mmol/L	9.6	[8.7-10.5]	9.7	[9.0-10.6]	8.7	[8.0-9.4]	8.5	[7.8-9.1]	8.5	[7.9-9.3]	8.1	[7.5-8.8]
Not recorded	53.3	[50.3-56.2]	49.5	[46.5-52.6]	49.0	[46.0-52.0]	47.2	[44.1-50.2]	47.3	[44.1-50.4]	47.1	[43.9-50.4]

	Males											
	Age group (years)											
	45-49 (n=11,191)		**50-54 (n=11,460)**		**55-59 (n=24,152)**		**60-64 (n=24,045)**		**65-69 (n=26,023)**		**70-74 (n=25,566)**	
Characteristic	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Diabetes	18.2	[17.3-19.2]	19.0	[18.0-20.0]	20.9	[20.2-21.7]	23.3	[22.5-24.1]	25.7	[24.9-26.4]	26.7	[25.9-27.5]
Chronic kidney disease*†	1.6	[1.4-1.9]	1.7	[1.4-2.0]	1.9	[1.6-2.1]	2.3	[2.0-2.6]	3.4	[3.1-3.8]	4.9	[4.4-5.3]
Familial hypercholesterolaemia	0.3	[0.2-0.4]	0.2	[0.1-0.3]	0.1	[0.1-0.2]	0.1	[0.1-0.2]	0.1	[0.1-0.1]	0.0	[0.0-0.1]
	Females											
	Age group (years)											
	45-49 (n=10,692)		**50-54 (n=11,288)**		**55-59 (n=23,927)**		**60-64 (n=24,399)**		**65-69 (n=28,752)**		**70-74 (n=30,238)**	
Characteristic	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
IRSAD quintile												
Highest	21.7	[18.5-25.3]	21.6	[18.5-25.0]	21.0	[18.0-24.5]	20.6	[17.5-24.1]	20.6	[17.5-24.2]	21.0	[17.8-24.6]
2nd upper	17.8	[15.6-20.3]	17.8	[15.7-20.1]	17.5	[15.4-19.8]	17.0	[15.0-19.2]	15.8	[13.8-18.1]	16.7	[14.5-19.2]
Intermediate	23.4	[20.4-26.7]	23.7	[20.8-26.9]	23.8	[20.8-27.1]	23.6	[20.5-26.9]	23.9	[20.8-27.4]	24.1	[20.7-28.0]
2nd lower	18.0	[15.3-21.0]	17.0	[14.6-19.8]	17.8	[15.2-20.6]	18.1	[15.5-21.0]	18.3	[15.6-21.3]	18.0	[15.3-21.2]
Lowest	18.4	[15.2-22.0]	19.0	[15.8-22.7]	19.1	[16.1-22.6]	20.0	[16.8-23.7]	20.5	[17.2-24.4]	19.6	[16.2-23.4]
Not recorded	0.7	[0.6-1.0]	0.9	[0.7-1.3]	0.8	[0.6-1.0]	0.6	[0.5-0.9]	0.8	[0.6-1.0]	0.6	[0.4-0.8]

	Females											
	Age group (years)											
	45-49 (n=10,692)		50-54 (n=11,288)		55-59 (n=23,927)		60-64 (n=24,399)		65-69 (n=28,752)		70-74 (n=30,238)	
Characteristic	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Remoteness												
Major Cities	59.8	[54.7-64.7]	59.4	[54.3-64.3]	57.7	[52.7-62.6]	56.7	[51.7-61.6]	55.2	[50.1-60.2]	56.2	[50.9-61.3]
Inner Regional	25.6	[21.7-30.0]	26.1	[22.1-30.5]	27.6	[23.5-32.1]	28.7	[24.5-33.3]	30.2	[25.8-35.0]	30.3	[25.7-35.3]
Outer Regional/Remote/ Very Remote	14.1	[11.0-17.8]	13.9	[10.9-17.6]	14.3	[11.3-17.8]	14.2	[11.3-17.8]	14.0	[11.1-17.5]	13.2	[10.4-16.5]
Not recorded	0.5	[0.4-0.7]	0.5	[0.4-0.8]	0.5	[0.4-0.6]	0.4	[0.3-0.6]	0.5	[0.4-0.7]	0.4	[0.3-0.6]
Indigenous status												
Neither Aboriginal nor Torres Strait Islander	78.0	[75.4-80.5]	81.1	[78.4-83.5]	81.4	[78.9-83.7]	82.0	[79.5-84.2]	82.9	[80.4-85.2]	83.8	[81.1-86.1]
Aboriginal and/or Torres Strait Islander	6.9	[5.8-8.2]	3.1	[2.5-3.8]	2.5	[2.1-3.0]	1.8	[1.5-2.1]	1.4	[1.2-1.6]	0.9	[0.7-1.1]
Not stated	15.1	[12.7-17.8]	15.8	[13.4-18.6]	16.1	[13.8-18.6]	16.2	[14.0-18.7]	15.7	[13.4-18.3]	15.3	[13.0-18.0]
Smoking status												
Non smoker	54.1	[52.7-55.6]	53.1	[51.7-54.5]	53.1	[51.9-54.2]	56.0	[54.9-57.0]	59.9	[58.9-60.9]	59.6	[58.6-60.5]
Smoker	16.9	[15.8-18.0]	16.6	[15.6-17.7]	14.7	[13.9-15.5]	11.1	[10.5-11.8]	8.1	[7.7-8.6]	6.2	[5.8-6.5]
Ex smoker	24.3	[23.3-25.4]	26.0	[25.0-27.1]	27.3	[26.5-28.2]	27.9	[27.0-28.7]	26.7	[25.9-27.6]	28.3	[27.5-29.2]
Not recorded	4.6	[4.0-5.4]	4.2	[3.6-4.9]	5.0	[4.3-5.7]	5.0	[4.4-5.7]	5.2	[4.6-5.9]	6.0	[5.3-6.7]

	Females											
	Age group (years)											
	45-49 (n=10,692)		50-54 (n=11,288)		55-59 (n=23,927)		60-64 (n=24,399)		65-69 (n=28,752)		70-74 (n=30,238)	
Characteristic	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Systolic blood pressure*												
<140mmHg (Controlled)	65.1	[63.9-66.2]	63.5	[62.4-64.6]	61.4	[60.6-62.3]	59.1	[58.3-60.0]	56.7	[55.8-57.6]	54.7	[53.8-55.6]
140-159mmHg (Grade 1)	27.0	[26.0-28.0]	28.1	[27.1-29.1]	29.7	[29.0-30.4]	31.0	[30.3-31.7]	32.9	[32.2-33.6]	33.9	[33.2-34.6]
160-179mmHg (Grade 2)	6.1	[5.6-6.6]	6.5	[6.0-7.0]	6.7	[6.3-7.1]	7.5	[7.1-8.0]	8.0	[7.6-8.4]	8.5	[8.1-8.9]
≥180mmHg (Grade 3)	0.8	[0.7-1.1]	1.0	[0.8-1.2]	1.0	[0.9-1.2]	1.2	[1.1-1.4]	1.3	[1.2-1.5]	1.5	[1.4-1.7]
Not recorded	1.0	[0.8-1.3]	1.0	[0.8-1.3]	1.1	[0.9-1.4]	1.1	[0.9-1.3]	1.0	[0.8-1.3]	1.3	[1.1-1.7]
Diastolic blood pressure*												
<90mmHg (Controlled)	62.2	[61.0-63.4]	67.0	[65.8-68.2]	72.2	[71.2-73.1]	79.1	[78.3-79.8]	83.8	[83.1-84.5]	87.0	[86.4-87.6]
90-99mmHg (Grade 1)	26.9	[25.9-27.9]	24.1	[23.1-25.1]	21.0	[20.3-21.8]	16.0	[15.4-16.6]	12.4	[11.9-13.0]	9.8	[9.3-10.2]
100-140mmHg (Grade 2)	8.1	[7.5-8.7]	6.5	[5.9-7.1]	4.8	[4.4-5.1]	3.3	[3.0-3.6]	2.3	[2.1-2.5]	1.5	[1.4-1.7]
>140mmHg (Grade 3)	1.8	[1.6-2.2]	1.5	[1.2-1.7]	0.9	[0.8-1.1]	0.6	[0.5-0.7]	0.4	[0.3-0.5]	0.3	[0.3-0.4]
Not recorded	1.0	[0.8-1.3]	1.0	[0.8-1.3]	1.1	[0.9-1.4]	1.1	[0.9-1.3]	1.0	[0.8-1.3]	1.3	[1.1-1.7]

	Females											
	Age group (years)											
	45-49 (n=10,692)		50-54 (n=11,288)		55-59 (n=23,927)		60-64 (n=24,399)		65-69 (n=28,752)		70-74 (n=30,238)	
Characteristic	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI	%	95% CI
Total cholesterol*												
<4.0mmol/L	4.4	[3.9-4.9]	4.1	[3.7-4.6]	4.1	[3.7-4.5]	5.2	[4.7-5.7]	6.4	[5.8-6.9]	7.4	[6.9-8.0]
4.0-7.5 mmol/L	45.2	[42.3-48.1]	46.0	[43.1-48.9]	46.6	[43.8-49.4]	46.7	[43.9-49.5]	46.3	[43.6-49.0]	45.1	[42.3-47.9]
>7.5 mmol/L	1.0	[0.8-1.2]	1.2	[1.0-1.5]	1.6	[1.5-1.9]	1.4	[1.2-1.5]	1.4	[1.2-1.6]	1.0	[0.8-1.1]
Not recorded	49.4	[46.2-52.6]	48.6	[45.5-51.8]	47.7	[44.5-50.8]	46.8	[43.6-50.0]	46.0	[42.8-49.2]	46.6	[43.3-49.8]
High density lipoprotein cholesterol*												
≥1.0 mmol/L	42.1	[39.5-44.8]	45.1	[42.3-48.0]	47.1	[44.3-50.0]	48.9	[45.9-51.8]	49.8	[46.8-52.8]	49.1	[46.0-52.1]
<1.0 mmol/L	4.1	[3.5-4.8]	3.1	[2.6-3.5]	2.4	[2.1-2.7]	2.0	[1.7-2.2]	2.0	[1.8-2.3]	1.9	[1.7-2.1]
Not recorded	53.8	[50.8-56.7]	51.8	[48.8-54.8]	50.5	[47.5-53.5]	49.2	[46.1-52.2]	48.1	[45.1-51.3]	49.0	[45.9-52.2]
Diabetes	17.6	[16.6-18.6]	17.2	[16.3-18.2]	18.2	[17.5-19.0]	19.6	[18.8-20.4]	21.1	[20.3-21.9]	21.3	[20.5-22.1]
Chronic kidney disease*†	1.3	[1.1-1.7]	1.3	[1.1-1.5]	1.5	[1.3-1.7]	2.0	[1.8-2.3]	3.0	[2.7-3.3]	4.6	[4.2-5.1]
Familial hypercholesterolaemia	0.1	[0.1-0.2]	0.2	[0.1-0.3]	0.2	[0.1-0.3]	0.2	[0.1-0.2]	0.2	[0.1-0.3]	0.1	[0.1-0.2]

Crude results presented. Percentages and 95% CI were estimated considering the clusters (general practices) and the individual's probability of being in the sample. *Only measures recorded between 2015 and 2018 were used. †Patients with record of a diagnosis of chronic kidney disease or an estimated glomerular filtration rate <45 ml/min/1.73 m^2 or persistent proteinuria.

Part III

Cost of Hypertension

in General Practice

Chapter 5

Cost of uncontrolled hypertension in general practice

5.1 Preface

This chapter, published in *PharmacoEconomics,* describes the evaluation of the health and financial costs of uncontrolled blood pressure (BP) in all Australians aged between 45 and 74 years without a history of cardiovascular disease (CVD) attending general practice. As the CVD risk algorithm estimates the risk of experiencing a CVD event over the next 5 years, the model estimates the costs of uncontrolled BP and potential savings from improved BP control over a 5-year period. Financial costs were restricted to costs associated with acute hospitalisation for primary CVD events.

5.2 Statement of authorship

Title of paper: The cost of uncontrolled blood pressure in Australian general practice: a modelling study using electronic health records (MedicineInsight)

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Name of principal author (Candidate): Jacqueline Roseleur

Contribution to the paper: Conception and design, analysis and interpretation of data, drafted the article and critical revisions, and acted as corresponding author.

Overall percentage: 85%

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signed: . . . . . Date: 09/12/2022

Co-author contributions

By signing the statement of authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

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5.3 Publication

5.3.1 Abstract

Background

Hypertension is the most common condition seen in Australian general practice. Despite hypertension being amenable to lifestyle modifications and pharmacological treatment, only around half of these patients have controlled blood pressure levels (BP <140/90mmHg), placing them at increased risk of cardiovascular disease (CVD).

Objective

To estimate the health and acute hospitalisation costs of uncontrolled hypertension among patients attending general practice.

Methods

We used population data and electronic health records from 634,000 patients aged 45–74 years who regularly attended an Australian general practice between 2016 and 2018 (MedicineInsight database). An existing worksheet-based costing model was adapted to calculate the potential cost savings for acute hospitalisation of primary CVD events by reducing the risk of a cardiovascular event over the next 5 years through improved systolic blood pressure (SBP) control. The model estimated the number of expected CVD events and associated acute hospital costs under current levels of SBP and compared this estimate with the expected number of CVD events and costs under different levels of SBP control.

Results

The model estimated that across all Australians aged 45-74 years who visit their general practitioner (n=8.67 million), 261,858 CVD events can be expected over the next five years at current SBP levels (mean 137.8mmHg, SD=12.3mmHg), with a cost of AUD 1,813 million (in 2019-2020). By reducing the SBP of all patients with a SBP greater than 139mmHg to 139 mmHg, 25,845 CVD events could be avoided with an associated

reduction in acute hospital costs of AUD 179 million. If SBP is lowered further to 129mmHg for all those with SBP greater than 129 mmHg, 56,169 CVD events could be avoided with potential cost savings of AUD 389 million. Sensitivity analyses indicate that potential cost savings range from AUD 46 million to AUD 1,406 million and AUD 117 million to AUD 2,009 million for the two scenarios, respectively. Cost savings by practice range from AUD 16,479 for small practices to AUD 82,493 for large practices.

Conclusions

The aggregate cost effects of poor BP control in primary care are high, but cost implications at the individual practice level are modest. The potential cost savings improve the potential to design cost-effective interventions, but such interventions may be best targeted at a population-level rather than at individual practices.

Key points

- Only half of patients with hypertension have their blood pressure controlled, increasing their risk of cardiovascular disease.
- In this study, we estimated the health and financial costs of uncontrolled hypertension among Australians aged 45–74 who visit their general practitioner.
- By improving blood pressure control, 25,845 cardiovascular events, costing AUD 179 million in acute hospitalisation, can be avoided over the next 5 years.

5.3.2 Introduction

Globally, approximately one-third of adults aged 30–79 years have hypertension [110]. These adults are at increased risk of cardiovascular disease (CVD), with hypertension responsible for over 10 million deaths in 2019 [111]. The global financial burden of suboptimal blood pressure (BP) control was estimated to be USD 372 billion in 2010, representing about 10% of the world's overall health care expenditure [14].

In Australia, elevated BP accounted for 5.8% of the total burden of disease in 2015 [13], and CVD cost the health system AUD 11.8 billion in 2018–19 [15].

Furthermore, the loss in gross domestic product from hypertension over the working lifetime of the Australian population was estimated to be AUD 137.2 billion [16].

Hypertension is largely managed in primary care and is the most common condition seen by a general practitioner (GP) in Australia [28]. Despite hypertension being amenable to lifestyle modifications and pharmacological treatment, only around half of the patients attending general practice have controlled hypertension (BP <140/90mmHg) [112]. Poor BP control puts patients at increased risk of CVD and all-cause and CVD mortality. A US cohort study found that patients who received antihypertensive treatment but remained uncontrolled were twice as likely to die from CVD than those without hypertension. In contrast, treated and controlled patients had similar risks to patients without hypertension [22].

Primary care workers, particularly GPs, have a vital role in supporting patients to achieve recommended BP targets [113]. There has been a recognition that hypertension management according to CVD risk is more effective and cost-effective than relying exclusively on BP levels [114, 115]. Therefore, Australian guidelines recommend that GPs conduct a CVD risk assessment for patients aged between 45 and 74 years without a history of CVD. Subsequently, management decisions to treat hypertension should be guided by a patient's risk of a primary CVD event over the next 5 years [1, 73].

A range of possible interventions could improve BP management in primary care. However, with constraints on health care budgets, decision-makers need information on the potential impact interventions may have on patients and the health system. These include the health costs experienced by patients due to the morbidity and mortality from CVD events and the associated financial costs borne by the health system. Therefore, this study aimed to estimate the financial and health costs of uncontrolled hypertension for patients attending general practice.

5.3.3 Methods

This study used population data and data from MedicineInsight [74], a large and comprehensive Australian general practice electronic health record (EHR) database,

to populate a model and calculate the potential cost savings for acute hospitalisation from improved BP control in patients diagnosed with hypertension.

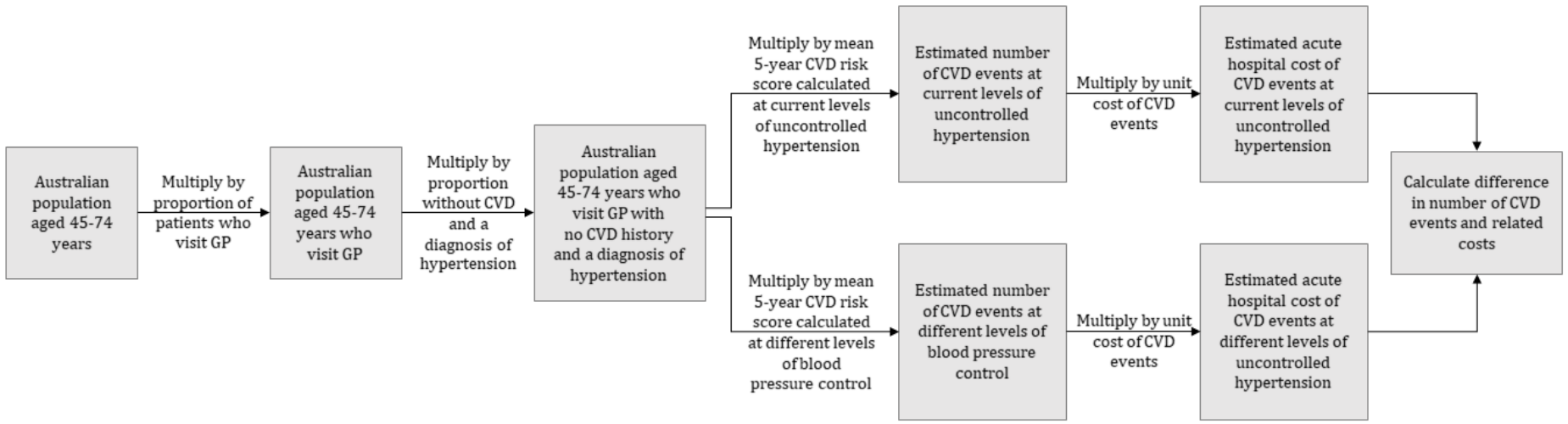
Model structure

We adapted an existing model [116] to calculate the potential cost savings for acute hospitalisation by reducing the risk of a cardiovascular event over the next 5 years through improved systolic blood pressure (SBP) control. The model estimated the number of expected CVD events and associated costs under current levels of BP control. Next, the model estimated the number of expected CVD events and associated costs under different levels of BP control. Comparing these estimates, the model estimated the potential reduction in CVD events and associated costs from improving BP control. The structure of the model is shown in Figure 1.

We modelled two scenarios in all patients diagnosed with hypertension attending general practice. We assumed all patients above a specified BP target achieved the target BP level as follows: 1) for patients with an SBP ≥140mmHg, we recalculated their CVD risk assuming an SBP of 139mmHg, and 2) for patients with an SBP ≥130mmHg, we recalculated their CVD risk assuming an SBP of 129mmHg:

1. Potential risk reduction (SBP=139mmHg) = $\text{CVDRisk}_{\text{Uncontrolled}} - \text{CVDRisk}_{\text{Controlled(139mmHg)}}$
2. Potential risk reduction (SBP=129mmHg) = $\text{CVDRisk}_{\text{Uncontrolled}} - \text{CVDRisk}_{\text{Controlled(129mmHg)}}$

In addition, we estimated the costs of uncontrolled BP at the practice level by practice size (i.e. the number of regular patients attending the practice). Practices were divided into quartiles based on practice size.



CVD: cardiovascular disease; GP: general practitioner

Figure 1 Model structure

Model population

As the Australian National Vascular Disease Prevention Alliance (NVDPA) risk assessment algorithm assesses a patient's risk of developing CVD [73], this study focused on Australian individuals aged between 45 and 74 years without a history of CVD. In addition, we only included those patients who visit their GP in the model. This criterion was used to represent a population who already have contact with their primary care providers, thereby providing opportunities for GPs and primary care nurses to engage patients in lifestyle and pharmacological interventions to reduce BP and CVD risk.

Model inputs

Population statistics and estimates using individual patient data from MedicineInsight were used to derive model inputs. Separate sex and age (in 5-year age groups) cohorts of the Australian population aged 45–74 years were constructed based on the 2021 Australian population data [117]. Data on the proportion of patients who visit their GP by age and sex were drawn from the Patient Experiences in Australia survey [118]. We used the results of the 2018–2019 survey, as data from 2019–2020 and 2020–2021 reflect changes in attendance due to the Covid-19 pandemic.

As of October 2018, MedicineInsight included de-identified data from patients attending over 2,700 GPs and 660 general practices across all states and territories (8.2% of all Australian practices) [74]. Patients in the database are comparable to but not representative of the general population as measured by sociodemographic variables and clinical conditions [74]. Details of the data collection process are published elsewhere [74]. In summary, data from patients' EHRs are collected monthly and include diagnoses, reasons for encounters, prescriptions, immunisations, clinical measurements (e.g. BP, pulse, weight), laboratory test orders and results, and patient sociodemographic information. Patients within each practice receive a unique identification number that allows the patient to be followed over time. We identified 634,000 patients aged 45–74 years who attended an Australian general practice at least three times in any two consecutive years between 2016 and 2018 [119] and almost 70% of patients had data available since

2011. Extraction algorithms for identifying chronic condition diagnoses have been validated [88].

Prevalence of existing CVD and hypertension

Using MedicineInsight, we then estimated the proportion of patients without a history of CVD by identifying patients without CVD recorded in their EHR (i.e. ischaemic heart disease, heart failure, stroke, peripheral artery disease or aortic disease). All available data in the patient's EHR was reviewed to identify those without a history of CVD.

We then identified patients with a diagnosis of hypertension. The methods used to identify patients diagnosed with hypertension are described in detail elsewhere [112, 120]. Briefly, patients were considered to have hypertension if 1) the condition was recorded as a diagnosis, reason for encounter or reason for prescription, or 2) if the patient received a prescription for antihypertensive therapy preceded by an elevated BP (i.e. BP higher than 140/90mmHg). By including an elevated BP, we aimed to reduce the misclassification of patients taking antihypertensive therapy for conditions other than hypertension (e.g. heart failure, myocardial infarction) [95]. Antihypertensive medications included angiotensin-converting enzyme inhibitors and angiotensin II receptor blockers (Anatomical Therapeutic Chemical [ATC] C09), beta-blockers (ATC C07), calcium channel blockers (ATC C08), diuretics (ATC C03) and alpha-blockers (ATC C02).

CVD risk

First, we determined whether patients had recorded information available on the different risk factors required to calculate their CVD risk. For SBP, we only considered values recorded between 2017 and 2018 and calculated the mean of the measures in this period. For patients with only one SBP recorded, this value was used (7.0% of sample). The mean number of SBP values recorded was 6.1 (SD 5.0) and the median was 5 with an interquartile range of 3-8. As cholesterol tests are performed less frequently than BP readings, we included the most recent reported result for total and HDL cholesterol between 2015 and 2018. Where smoking status was not recorded, patients were assumed to be non-smokers (3.7% of sample) [120]. As left ventricular hypertrophy is challenging to identify in the EHR, we

assumed left ventricular hypertrophy was absent for all patients. Patients were considered to have diabetes when the patient record had "diabetes" as a diagnosis, encounter reason or prescription reason, or were prescribed antidiabetic medications (ATC A10; except for those with a diagnosis of polycystic ovarian syndrome).

Thereafter, for those patients with diagnosed hypertension and with enough information available in their EHR to calculate CVD risk, we calculated the risk of a primary CVD event over the next 5 years by applying the Australian NVDPA risk assessment and risk management algorithm (Table 1) [1, 73].

Next, we recalculated the risk of a primary CVD event over the next 5 years under the two scenarios described above: 1) for patients with an SBP ≥140mmHg, we recalculated their CVD risk assuming an SBP of 139mmHg, and 2) for patients with an SBP ≥130mmHg, we recalculated their CVD risk assuming an SBP of 129mmHg. We assumed a relative risk reduction of 0.80 (95% CI 0.77-0.83) in CVD events for every 10mmHg reduction in SBP based on a meta-analysis of 613,815 patients enrolled in randomised controlled trials [121].

The calculated CVD risk was then allocated to the following conditions to reflect the conditions included in the Framingham risk score: unstable angina (UA), myocardial infarction (MI), stroke, transient ischaemic attack (TIA), heart failure (HF), peripheral artery disease (PAD) and coronary heart disease (CHD) death [122]. After that, using data from the National Hospital Morbidity Database [123] and CHD deaths reported by the Australian Institute of Health and Welfare [124], we calculated the proportions of UA, MI, stroke, TIA, HF, PAD and CHD deaths out of all CVD hospitalisation episodes and CHD deaths in a year using the following formula, as illustrated for UA as a proportion of all events – P(UA) [125]:

$$P(UA) = \frac{No.UA}{No.(UA + MI + stroke + TIA + HF + PAD + CHD\ death)}$$

The ICD-10 codes used for each condition are presented in Table 2.

Costs

The costs associated with a CVD event include hospital costs for each condition specified above. These were estimated using the Australian Refined Diagnosis Related Groups (AR-DRG) and 2018–2019 Independent Hospital Pricing Authority (IHPA) data (Table 2) [126]. We calculated a weighted average cost for each condition using the number of separations for each complexity level to account for different complexity levels. In the base case, we assumed CHD death did not incur costs. Costs were adjusted to reflect 2019–2020 costs using the consumer price index for health (Table 1) [127].

Table 1 Model inputs

Variable	Description	Values	Source
Population	45-49 years	Male: 813,286; Female: 831,373	ABS [117]
	50-54 years	Male: 782,401; Female: 822,505	
	55-59 years	Male: 752,387; Female: 786,368	
	60-64 years	Male: 708,837; Female: 750,995	
	65-69 years	Male: 617,423; Female: 660,622	
	70-74 years	Male: 554,506; Female: 583,878	
Proportion of patients who visited their GP at least once in a year	45-49 years	Male: 77.6%; Female: 87.1%	ABS [118]
	50-54 years	Male: 77.6%; Female: 87.1%	
	55-59 years	Male: 86.7%; Female: 90.1%	
	60-64 years	Male: 86.7%; Female: 90.1%	
	65-69 years	Male: 92.7%; Female: 94.2%	
	70-74 years	Male: 92.7%; Female: 94.2%	
Proportion of patients without a history of CVD	45-49 years	Male: 96.1%; Female: 98.3% SA: Male: 92.2%; Female: 94.3%	Medicine Insight
	50-54 years	Male: 93.3%; Female: 97.5% SA: Male: 89.5%; Female: 93.6%	
	55-59 years	Male: 89.9%; Female: 95.7% SA: Male: 85.4%; Female: 90.9%	
	60-64 years	Male: 85.1%; Female: 93.7% SA: Male: 80.8%; Female: 89.1%	
	65-69 years	Male: 79.7%; Female: 90.8% SA: Male: 74.9%; Female: 85.3%	
	70-74 years	Male: 74.0%; Female: 86.1% SA: Male: 69.6%; Female: 80.9%	
Proportion of patients	45-49 years	Male: 29.4%; Female: 17.7% SA: Male: 31.8%; Female: 19.9%	Medicine Insight

Variable	Description		Values	Source
with a diagnosis of hypertension in those without a history of CVD	50-54 years		Male: 38.5%; Female: 25.5% SA: Male: 41.0%; Female: 28.1%	
	55-59 years		Male: 48.0%; Female: 34.1% SA: Male: 50.6%; Female: 36.9%	
	60-64 years		Male: 57.4%; Female: 43.7% SA: Male: 60.0%; Female: 47.0%	
	65-69 years		Male: 64.0%; Female: 52.6% SA: Male: 66.6%; Female: 56.5%	
	70-74 years		Male: 69.1%; Female: 62.4% SA: Male: 71.7%; Female: 66.4%	
Relative risk per 10mmHg SBP reduction			0.80 (0.77-0.83)	[121]
Mean 5-year CVD risk	45-49 years	Male	Current SBP: 5.6%; SBP=139mmHg: 5.0%; SBP=129mmHg: 4.4%	Medicine Insight
		Female	Current SBP: 3.4%; SBP=139mmHg: 3.1%; SBP=129mmHg: 2.7%	
	50-54 years	Male	Current SBP: 7.4%; SBP=139mmHg: 6.6%; SBP=129mmHg: 5.7%	
		Female	Current SBP: 4.3%; SBP=139mmHg: 3.9%; SBP=129mmHg: 3.5%	
	55-59 years	Male	Current SBP: 9.4%; SBP=139mmHg: 8.4%; SBP=129mmHg: 7.3%	
		Female	Current SBP: 5.4%; SBP=139mmHg: 5.0%; SBP=129mmHg: 4.4%	
	60-64 years	Male	Current SBP: 11.6%; SBP=139mmHg: 10.4%; SBP=129mmHg: 9.0%	
		Female	Current SBP: 6.7%; SBP=139mmHg: 6.0%; SBP=129mmHg: 5.3%	
	65-69 years	Male	Current SBP: 13.7%; SBP=139mmHg: 12.4%; SBP=129mmHg: 10.7%	
		Female	Current SBP: 7.9%; SBP=139mmHg: 7.1%; SBP=129mmHg: 6.2%	
	70-74 years	Male	Current SBP: 15.7%; SBP=139mmHg: 14.2%; SBP=129mmHg: 12.4%	
		Female	Current SBP: 9.1%; SBP=139mmHg: 8.1%; SBP=129mmHg: 7.0%	

Variable	Description		Values	Source
CVD events allocation	45-49 years	Male	UA: 8.3%; MI: 40.4%; Stroke: 22.7%; TIA: 5.0%; HF: 11.2%; PAD: 8.3%; CHD Death: 4.1%	AIHW [123, 124]
		Female	UA: 7.6%; MI: 23.6%; Stroke: 37.2%; TIA: 7.5%; HF: 11.8%; PAD: 10.7%; CHD Death: 1.6%	
	50-54 years	Male	UA: 9.8%; MI: 38.2%; Stroke: 22.9%; TIA: 4.5%; HF: 10.2%; PAD: 10.4%; CHD Death: 4.1%	
		Female	UA: 9.4%; MI: 25.6%; Stroke: 32.8%; TIA: 9.1%; HF: 11.2%; PAD: 10.0%; CHD Death: 1.8%	
	55-59 years	Male	UA: 9.5%; MI: 35.6%; Stroke: 22.3%; TIA: 5.3%; HF: 10.2%; PAD: 12.3%; CHD Death: 4.9%	
		Female	UA: 9.4%; MI: 27.3%; Stroke: 29.2%; TIA: 9.3%; HF: 11.7%; PAD: 10.3%; CHD Death: 2.7%	
	60-64 years	Male	UA: 8.8%; MI: 31.7%; Stroke: 23.6%; TIA: 5.4%; HF: 11.8%; PAD: 14.3%; CHD Death: 4.4%	
		Female	UA: 9.0%; MI: 25.7%; Stroke: 25.5%; TIA: 9.6%; HF: 15.6%; PAD: 12.1%; CHD Death: 2.5%	
	65-69 years	Male	UA: 8.6%; MI: 26.9%; Stroke: 24.1%; TIA: 5.3%; HF: 14.2%; PAD: 15.6%; CHD Death: 5.3%	
		Female	UA: 8.4%; MI: 22.0%; Stroke: 27.8%; TIA: 9.2%; HF: 17.5%; PAD: 12.0%; CHD Death: 3.1%	
	70-74 years	Male	UA: 7.3%; MI: 22.3%; Stroke: 25.1%; TIA: 5.7%; HF: 18.5%; PAD: 16.7%; CHD Death: 4.4%	
		Female	UA: 6.9%; MI: 19.5%; Stroke: 28.3%; TIA: 8.0%; HF: 22.5%; PAD: 12.2%; CHD Death: 2.7%	
Hospitalis-ation cost per event	Base Case		UA: $2,964; MI: $9,762; Stroke: $10,118; TIA: $3,408; HF: $3,244; PAD: $5,317; CHD death: $0	IHPA [126]
	Sensitivity Analysis		UA: $9,155; MI: $16,410; Stroke: $12,754; TIA: $4,992; HF: $15,520; PAD: $13,827; CHD death: $16,410	[128-130]

ABS: Australian Bureau of Statistics; AIHW: Australian Institute of Health and Welfare; CHD: coronary heart disease; CVD: cardiovascular disease; GP: general practitioner; HF: heart failure; IHPA: Independent Hospital Pricing Authority; MI: myocardial infarction; PAD: peripheral artery disease; SA: sensitivity analysis; SBP: systolic blood pressure; TIA: transient ischaemic attack; UA: unstable angina

Table 2 ICD-10 codes and AR-DRG codes used to calculate the event allocation and costs for each condition

Condition	ICD-10 codes	AR-DRG codes
Unstable angina	I20.0 - Unstable angina	F72A - Unstable Angina, Major Complexity F72B - Unstable Angina, Minor Complexity
Myocardial infarction	I21 - Acute myocardial infarction	F10A - Interventional Coronary Procedures, Admitted for AMI, Major Complexity F10B - Interventional Coronary Procedures, Admitted for AMI, Minor Complexity F41A - Circulatory Disorders, Adm for AMI W Invasive Cardiac Inves Int, Major Comp F41B - Circulatory Disorders, Adm for AMI W Invasive Cardiac Inves Int, Minor Comp F60A - Circulatory Dsrd, Adm for AMI W/O Invas Card Inves Intervention F60B - Circulatory Dsrd, Adm for AMI W/O Invas Card Inves Intervention, Transf <5 Days
Stroke	I60 - Subarachnoid haemorrhage I61 - Intracerebral haemorrhage I62 - Other nontraumatic intracranial haemorrhage I63 - Cerebral infarction I64 - Stroke, not specified as haemorrhage or infarction	B70A - Stroke and Other Cerebrovascular Disorders, Major Complexity B70B - Stroke and Other Cerebrovascular Disorders, Intermediate Complexity B70C - Stroke and Other Cerebrovascular Disorders, Minor Complexity B70D - Stroke and Other Cerebrovascular Disorders, Transferred <5 Days
Transient ischaemic attack	G45 - Transient cerebral ischaemic attacks and related syndromes	B69A - TIA and Precerebral Occlusion, Major Complexity B69B - TIA and Precerebral Occlusion, Minor Complexity
Heart Failure	I50 - Heart failure	F62A - Heart Failure and Shock, Major Complexity F62B - Heart Failure and Shock, Minor Complexity F62C - Heart Failure and Shock, Transferred <5 Days
Peripheral Artery Disease	I70 - Atherosclerosis I71 - Aortic aneurysm and dissection I72 - Other aneurysm and dissection	F65A - Peripheral Vascular Disorders, Major Complexity F65B - Peripheral Vascular Disorders, Minor Complexity

Condition	ICD-10 codes	AR-DRG codes
	I74 - Arterial embolism and thrombosis	

W: with; W/O: without; Adm: admitted; AMI: acute myocardial infarction; Card: cardiac; Dsrd: disorder; Int: intervention; Invas: invasive; Inves: investigative; TIA: transient ischaemic attack; Transf: transferred

Statistical methods

Analyses of MedicineInsight data to describe the patient population (prevalence of CVD, prevalence of hypertension and proportion with enough information for CVD risk calculation) were performed in STATA 16.1 (StataCorp, College Station, Texas, USA) using practices as clusters and conditioned on the number of consultations to minimise selection bias (i.e. the likelihood of receiving medical treatments or diagnosis increase with the number of visits to the practice) [131]. Excel was used for the costing model.

The Human Research Ethics Committee of the University of Adelaide exempted this study from ethical review as it used existing and non-identifiable data. Access to the data for this study was approved by the MedicineInsight Data Governance Committee (project 2016-007).

Sensitivity analysis

We undertook univariate and multivariate sensitivity analyses. In the univariate sensitivity analyses, rather than using the mean of all BPs recorded between 2017 and 2018, we used the lowest BP and the highest BP recorded between 2017 and 2018. We also applied the upper and lower confidence intervals for the relative risk reduction. The proportion of patients without a history of CVD may have been overestimated and the proportion of patients with a diagnosis of hypertension may have been underestimate if these conditions were not recorded in the electronic health record. We therefore also undertook a sensitivity analysis where we decreased the proportion of patients without a history of CVD based on data published by the Australian Institute of Health and Welfare [124] (i.e. decrease of 4%, 5% and 6% in age groups 45-54, 55-64 and 65-74 respectively). In the base case, we assumed that patients with an uncertain hypertension status did not have a

diagnosis of hypertension, whereas in the sensitivity analysis, these patients were assumed to have a diagnosis of hypertension (see Table 1). In the multivariate sensitivity analyses, we combined the two univariate sensitivity analyses for the BP and relative risk reduction to generate best- and worst-case scenarios.

Furthermore, we searched the literature for Australian cost estimates for each condition to determine the possible range of potential cost savings. Then, we re-ran the model using these cost estimates. To account for the underestimated costs related to CHD death in the base case, we also assumed that CHD deaths attracted the same cost as a myocardial infarction (Table 1).

5.3.4 Results

MedicineInsight sample

The original sample included 634,000 patients aged 45–74 years (mean age 59.3 years, SD 8.6; 55.7% female). Of these, 94.4% (95% CI: 94.2–94.6) of women and 87.1% (95% CI: 86.7–87.4) of men did not have a history of CVD recorded. Confidence intervals are narrow due to the large sample size. The proportion of patients considered to have a diagnosis of hypertension amongst those without a history of CVD was 35.6% (95% CI: 34.8–36.3) for women and 47.4% (95% CI: 46.6–48.2) for men. The sample of patients with hypertension without a history of CVD consisted of 251,733 individuals (mean SBP 138.0mmHg, SD=12.5mmHg; 44.3% with an SBP above 139mmHg in males, 40.0% in females; 76.2% with an SBP above 129mmHg in males, 71.1% in females). Of these, 48.3% (95% CI: 45.5–51.2) of women and 49.5% (95% CI: 46.6–52.3) of men had enough data to calculate their CVD risk (mean SBP 137.8mmHg, SD=12.3mmHg; 45.7% with an SBP above 139mmHg in males, 41.0% in females; 79.6% with an SBP above 129mmHg in males, 73.8% in females). Figure 2 shows the number of patients used to estimate each variable.

CVD events and costs

The results for the expected number of CVD events and related costs over a 5-year period across Australians aged 45–74 years who visit their GP (N=8.7 million

people) using the baseline (current) SBP levels and the two SBP control scenarios are presented in Table 3. At current SBP levels, 261,858 CVD events are expected to occur over a 5-year period (i.e. incidence of CVD among Australians aged 45–74 years visiting a GP of 3.0%), with a cost of AUD 1,813 million for acute hospitalisation. Under a scenario where SBP is lowered to 139mmHg for all patients with an SBP above 139mmHg, 25,845 CVD events could be avoided (i.e. incidence of CVD of 2.7%), with an associated reduction in costs of AUD 179 million. If SBP is lowered further to 129mmHg for all patients with an SBP above 129mmHg, 56,169 CVD events could be avoided (i.e. incidence of CVD of 2.4%), with potential cost savings of AUD 389 million.

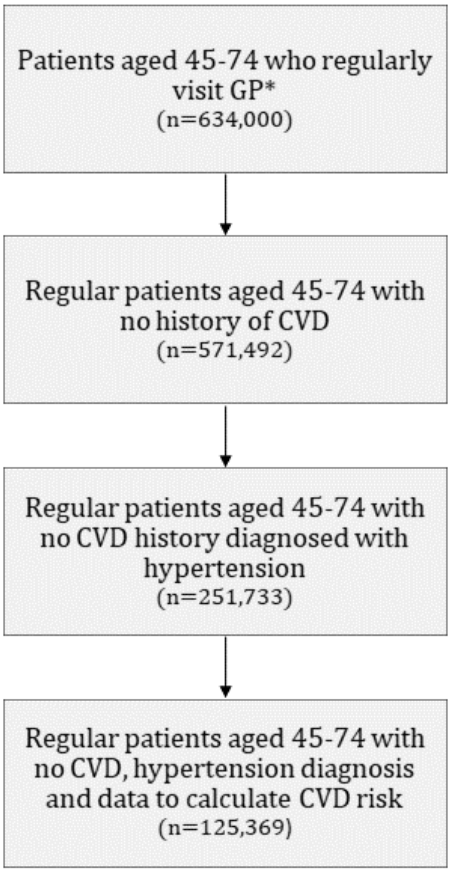
In the sensitivity analyses, applying the lowest and highest recorded baseline BP levels decreased and increased the expected costs by 20.4% (to AUD 1.443 million) and 23.4% (to AUD 2,238 million), respectively. Applying the upper and lower 95% confidence intervals around the mean relative risk decreased and increased the expected costs savings in the scenario where SBP is lowered to 139mmHg for patients with an SBP above 139mmHg by 13.8% (to AUD 154 million) and 13.4% (to AUD 203 million), respectively. Combining the two univariate sensitivity analyses to generate best- and worst-case scenarios resulted in cost savings of AUD 46 million and AUD 714 million, respectively.

In the scenario where SBP is lowered to 129mmHg for patients with an SBP above 129mmHg, applying the upper and lower 95% confidence intervals around the mean relative risk decreased and increased the expected cost savings by 13.4% (to AUD 337 million) and 12.8% (to AUD 439 million), respectively. Combining the two univariate sensitivity analyses to generate best- and worst-case scenarios resulted in cost savings of AUD 117 million and AUD 1,020 million, respectively.

In the sensitivity analysis of the alternative costs estimates, the potential cost savings could increase to AUD 353 million and AUD 767 million for the two base case scenarios, respectively. Combining the alternative costs and the best-case scenario resulted in cost savings of AUD 1,406 million and AUD 2,009 million for the 139mmHg and 129mmHg SBP control scenarios, respectively. The results from additional sensitivity analyses are presented in Table 4.

Results by age and sex for the principal analyses are presented in Table 5. The potential reduction in CVD events increases with age as the proportion of patients with SBP above target levels also increases. As the proportion of men aged 70–74 with SBP above target is slightly lower than those aged 65–69 (45.6% vs 46.2%), the expected reduction in CVD events and costs is also lower.

Table 6 presents the potential reduction in CVD events and costs by practice size. Under a scenario where SBP is lowered to 139mmHg for all patients with an SBP above 139mmHg, small practices with an average of 705 (interquartile range [IQR]: 539–881) patients could avoid two CVD events over a 5-year period with a cost reduction of AUD 16,479, whereas a large practice with an average of 2,921 (IQR: 2,589–3,735) patients could avoid 12 CVD events with a cost saving of AUD 82,493. These cost savings increase to AUD 32,492 and AUD 162,657, respectively, in the sensitivity analysis using the alternative costs.



*Regular attendance defined as at least three visits in any two consecutive years between 2016 and 2018.

Figure 2 Flow diagram of patients used to estimate model parameters

Table 3 Potential reduction in the number of CVD events and costs under two BP control scenarios over a 5-year period in patients with a diagnosis of hypertension

Scenario	**Expected CVD Events**	**Expected Reduction in CVD Events**	**Expected CVD Costs Base Case AUD Million**	**Expected Reduction in CVD Costs Base Case AUD Million**
Current SBP	261,858	-	1,813	-
SBP control to 139mmHg	236,013	25,845	1,634	179
SBP control to 129mmHg	205,689	56,169	1,424	389

Table 4 Sensitivity analyses of results under two BP control scenarios over a 5-year period in patients with a diagnosis of hypertension

	Expected Reduction in CVD Costs AUD Million	
	SBP control to 139mmHg	**SBP control to 129mmHg**
Base case using mean SBP	179	389
Univariate sensitivity analyses		
Lower proportion of patients without CVD	169	368
Higher proportion of patients with hypertension diagnosis	189	411
Applying the lower 95% CI relative risk	203	439
Applying the upper 95% CI relative risk	154	337
Using the lowest recorded SBP	53	135
Using the highest recorded SBP	639	920
Alternative costs	353	767
Multivariate sensitivity analysis		
Lowest SBP + applying the upper 95% CI relative risk	46	117
Highest SBP + applying the lower 95% CI relative risk	713	1,020
Highest SBP + applying the lower 95% CI relative risk + alternative costs	1,406	2,009

Table 5 Potential reduction in the number of CVD events and costs under two BP control scenarios over a 5-year period by age and sex in patients with a diagnosis of hypertension

	Expected CVD events at baseline	Expected reduction in CVD events		Expected CVD costs at baseline AUD million	Expected reduction in CVD costs AUD million	
		SBP control to 139mmHg	SBP control to 129mmHg		SBP control to 139mmHg	SBP control to 129mmHg
Males						
45-49	9,918	952	2,126	74	7	16
50-54	16,021	1,626	3,527	118	12	26
55-59	26,388	2,721	5,864	189	19	42
60-64	34,843	3,558	7,730	246	25	54
65-69	40,121	4,038	8,749	272	27	59
70-74	41,380	3,961	8,813	274	26	58
Females						
45-49	4,233	353	777	32	3	6
50-54	7,680	660	1,466	56	5	11
55-59	12,578	1,094	2,419	90	8	17
60-64	18,466	1,754	3,777	126	12	26
65-69	23,467	2,327	4,989	158	16	34
70-74	26,762	2,799	5,930	177	18	39

Table 6 Potential reduction in the number of CVD events and costs under two BP control scenarios over a 5-year period by practice size in patients with a diagnosis of hypertension

Practice size	Average number of patients seen by practice median (IQR)	Expected CVD events at baseline	Expected reduction in CVD events		Expected CVD costs at baseline AUD	Expected reduction in CVD costs AUD Base case		Expected reduction in CVD costs AUD Sensitivity analysis*	
			SBP control to 139mmHg	SBP control to 129mmHg		SBP control to 139mmHg	SBP control to 129mmHg	SBP control to 139mmHg	SBP control to 129mmHg
Quartile 1	705 (539-881)	26	2	5	179,473	16,479	36,751	32,492	72,465
Quartile 2	1,248 (1,121-1,416)	45	5	10	314,423	31,455	67,628	62,022	133,345
Quartile 3	1,979 (1,700-2,105)	70	7	15	482,647	49,737	106,281	98,069	209,561
Quartile 4	2,921 (2,589-3,735)	117	12	26	811,717	82,493	178,850	162,657	352,650

*In the sensitivity analysis, alternative cost estimates from the literature were used to estimate the potential reduction in costs.

5.3.5 Discussion

This study estimated that failure to achieve BP targets of 139mmHg results in 25,845 unnecessary CVD events over a 5-year period and excess costs of AUD 179 million across those patients aged 45–74 years attending general practice. Almost two-thirds of the excess costs occurred in males. Compared with females, the prevalence of hypertension was higher in males, and males had a higher mean 5-year CVD risk. Furthermore, approximately 50% of the excess costs occurred in those aged between 65 and 74 years, as a greater proportion of older patients have a hypertension diagnosis than younger patients. These findings suggest that these patient groups may be appropriate targets for interventions to improve BP control.

The estimated cost savings almost doubled to AUD 353 million over 5 years when using the alternative cost data in the sensitivity analysis. Even under the alternative scenario, these estimates underestimate the financial burden of CVD as they only include the costs incurred during the hospitalisation of the primary event. Approximately 15% of acute myocardial infarction survivors will experience a second myocardial infarction within 7 years [132], and 12% of patients will develop heart failure within 1 year [133]. Post-care and rehabilitation costs also contribute substantially to the financial burden of CVD. In addition to these health system costs, patients, their families and carers incur substantial costs related to productivity losses, out-of-pocket expenses and informal care costs [16, 134]. On the other hand, those patients who avoid a CVD death will incur additional health costs. Using the annual average per person cost of AUD 109 reported by the Australian Institute for Health and Welfare [135], the patients who avoid a CVD death will incur hospital costs of AUD 557,006 over 5 years; equal to 0.3% of the potential costs savings from controlling SBP to 139mmHg.

Comparisons with other data sources such as national data reported by the Australian Institute for Health and Welfare and Global Burden of Disease studies are difficult as these sources include costs related to all CVD events, including secondary CVD. Furthermore, not all patients with CVD have a hypertension diagnosis. Our study was specifically aimed at estimating the costs incurred by patients with a diagnosis of hypertension, attending general practice and with no history of CVD.

However, we have attempted to compare our findings and present these comparisons in the supplementary material. Our findings are more consistent with AIHW estimates than with GBD estimates as our methods aligned more closely with those used by AIHW.

Given the potential to improve care and reduce the health system costs associated with uncontrolled BP, a range of actions, such as pay-for-performance (P4P), practice facilitation and multifaceted interventions, may be feasible and effective at a practice level.

Pay-for-performance schemes are widespread in health care. However, the evidence on the effectiveness of these schemes remains inconclusive [136-138]. The evidence suggests that pay-for-performance schemes with the following design features are more effective: 1) measuring process indicators that are easy to track, 2) targeting incentives at individual clinicians or small groups, 3) payments conditional on providers' absolute performance rather than relative to other providers' performance, 4) designing the program collaboratively with providers, and 5) incentives that are sufficiently large [136, 137]. In addition, when implementing pay-for-performance schemes, it is essential to consider whether pay-for-performance will reduce or exacerbate inequalities and have unintended consequences such as risk selection, spill-over effects, negative impacts on intrinsic motivation and gaming [136, 139, 140]. Australia implemented an opt-in program (Practice Incentives Program [PIP]) to encourage quality improvement in general practice through the Quality Improvement (QI) Incentive in August 2019 [141]. The program consists of 10 measures, one of which reports on the proportion of patients aged 45–74 years without a CVD diagnosis with risk factors recorded to enable CVD risk assessment. The first annual report monitoring the program found that between October 2020 and July 2021, the proportion of patients with necessary risk factors recorded increased from 44.9% to 48.5% [142]. Identifying patients at increased CVD risk allows for risk stratification, leading to greater efficiency by targeting those individuals at highest risk [143]. A systematic review of evaluations of the Quality and Outcomes Framework implemented in the United Kingdom (UK) found that performance increased in the first year following the implementation of the Quality and Outcomes Framework but returned to pre-intervention rates in

subsequent years [144]. Future monitoring is required to determine whether increases found in the first year will be sustained in Australia.

A systematic review of facilitation interventions found that primary care practices are almost three times more likely to adopt evidence-based guidelines through practice facilitation [145]. Facilitation entails visits by someone external to the practice to help implement changes, for example, using techniques such as audit and feedback, goal setting and consensus building [145]. Interventions with greater effects had fewer practices per facilitator, higher intensity interventions and interventions tailored to the practice context [145]. A more recent review found that implementing practice facilitation increased BP control by an average of 9.0% [146].

Facilitation is often a critical component of multifaceted interventions [147]. This is because the successful translation of research evidence into health systems depends on the evidence's veracity, the context or environment in which the research is to be implemented, and how the research is implemented [148]. Therefore, the implementation of interventions must address multiple factors simultaneously to be successful [149]. For example, in the case of improving BP control, change needs to occur at both the clinician level (e.g. initiating or intensifying antihypertensive therapy, providing patient support) and at the patient level (e.g. medication adherence and self-management strategies). A systematic review of 100 articles reporting 121 comparisons concluded that "multilevel, multicomponent implementation strategies with and without team-based care are most effective for BP control among patients with hypertension" [150, p.118]. For example, through developing and implementing a system-level, multifaceted quality improvement program for hypertension, the Kaiser Permanente Northern California integrated managed care consortium improved BP control rates from 44% to 80% over 8 years [151].

Even when interventions are effective, investment to implement interventions depends on economic considerations. The evidence on the cost-effectiveness of primary care interventions to improve hypertension in Australia is limited [152, 153]. The potential cost savings identified in our study from improving BP control makes it worthwhile investigating the effectiveness and cost-effectiveness of primary care interventions to improve BP control and the feasibility and

sustainability of these interventions. Exploring these interventions in the Australian system is crucial, which differs from other contexts. For example, in contrast to the UK health system where patients register with a practice, in Australia, patients can move between practices at any time.

Despite the significant health and financial burden of uncontrolled BP across all patients aged 45–74 attending general practice, the cost savings for the health system by practice are modest. Potential cost savings range from an average of AUD 16,479 for a small practice to AUD 82,493 for a large practice over 5 years. Furthermore, these saving are based on all patients achieving BP control, which is an unlikely achievement. Consequently, the cost-effectiveness of interventions will likely differ by practice size. For example, low-resource interventions such as treatment intensification [154] may be feasible for smaller practices. In contrast, resource-intensive interventions, for example, those delivered by nurses [155], may not be feasible for small practices. Primary Health Networks (PHN), independent organisations that coordinate primary health care in a region, could support the implementation of more resource-intensive facilitation-based interventions across multiple practices, improving the cost-effectiveness through economies of scale [156]. Furthermore, these health system cost savings will need to be invested into general practice to compensate GPs for the additional time and resources required to improve BP control levels in an environment of competing demands.

Strengths and limitations

Our study is one of the first to estimate the acute hospital costs of uncontrolled BP using an extensive and comprehensive EHR database. In contrast to other studies where values for risk prediction were assumed, the large number of patients with available data in this study enabled a more accurate estimation of the risk of experiencing a cardiovascular event. However, this study has several limitations. First, only half of the patients with a hypertension diagnosis had enough data to calculate their CVD risk. However, the mean SBP and proportion of patients with uncontrolled SBP were similar when comparing patients with and without enough information recorded for CVD risk calculation. Second, CVD risk should be assessed prior to the initiation of treatment. As we used the most recent measures for patients, we likely underestimated the CVD risk of patients who had initiated

treatment and, therefore, the associated costs. We did account for this in terms of BP measures by using the maximum BP recorded between 2017 and 2018 in the sensitivity analysis, although were unable to do so for cholesterol measures. Moreover, for patients considered to be at high risk clinically (e.g. those over 60 years with diabetes), we used the calculated CVD risk with no adjustment for additional risk, thereby underestimating their CVD risk. However, as we were interested in the reduction in risk from improved BP control, this should not have a material impact on our findings. Third, our model did not account for competing risks where some of the baseline population will die of other causes in the five years, thereby reducing CVD expenditure. This is likely to only have a minor effect on the results. Fourth, this study only considered the costs of acute hospitalisation for primary cardiovascular events. Despite hospital costs accounting for the majority of health spending [135], it does not represent the total cost of uncontrolled BP. However, taken together with existing evidence on the productivity losses experienced by patients [16], our study provides an estimate of the magnitude of the costs associated with uncontrolled BP.

5.3.6 Conclusion

There has been a call to action by the High Blood Pressure Research Council of Australia (HBPRCA) for a national commitment to improve BP control, with a focus on "the implementation and scaling up of proven strategies to improve BP management and control across the life course" [113, p.62]. The Australian Department of Health and Aged Care is investing AUD 229 million over 10 years to improve heart health and reduce stroke in Australia through the Medical Research Future Fund (MRFF) Cardiovascular Health Mission Roadmap [157]. This analysis should help decision-makers better understand the clinical and economic importance of improving BP control in primary care and provides a starting point to investigate further the potential impacts of interventions targeted at improving BP control and reducing CVD risk.

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Author contributions

JR and JK conceived the study. JR performed the analysis with support from JK. The first draft of the manuscript was written by JR and all authors provided critical feedback and commented on previous versions of the manuscript. All authors read and approved the final manuscript.

Consent to participate and consent for publication

This study uses existing and non-identifiable data collected by MedicineInsight. The data custodian, MedicineInsight, has provided consent for publication.

Conflict of interest

J Roseleur, DA Gonzalez-Chica, G Harvey, NP Stocks and J Karnon declare that they have no conflicts of interest.

Data Availability Statement

Data may be obtained from MedicineInsight and are not publicly available. Third parties may express an interest in the information collected through MedicineInsight. The provision of information in these instances undergoes a formal approval process and is guided by the MedicineInsight independent external Data Governance Committee. This Committee includes general practitioners, consumer advocates, privacy experts and researchers.

5.3.7 Online supplementary material

Comparison of predicted event rates with independent data

We have compared our findings with those reported for incident ischaemic heart disease (IHD) reported by the Global Burden of Disease (GBD) study [158]. We have also compared our findings with those reported by the Australian Institute of Health and Welfare (AIHW) who report data for myocardial infarction and unstable angina [159]. To calculate the burden of cardiovascular disease (CVD) attributable to hypertension, we have used the estimate from AIHW that 38.0% of the burden of CVD is attributable to hypertension [13]. Table 1 shows the comparisons of our data with the hypertension attributable CVD events using GBD and AIHW data.

Table 1: Comparison of predicted event rates with GBD and AIHW data

		Point estimate	Lower estimate	Upper estimate
GBD for 45-74 both sexes for incident IHD* in 2019		84,856	62,223	110,065
For 5 years		424,279	311,117	550,327
HTN burden	38%	161,226	118,225	209,124
AIHW for 25+ both sexes in 2018^		58,700		
For 5 years		293,500		
HTN burden	38%	111,530		
Costing study - all Australians		81,729	65,307	100,560

*IHD includes ICD10 codes I20-I25.9. ^This estimate reflects acute coronary events which include myocardial infarction and unstable angina. No data presented on the split between the two conditions. AIHW: Australian Institute of Health and Welfare; GBD: Global Burden of Disease; IHD: ischaemic heart disease.

GBD estimates are double the costing study estimates. The AIHW estimates are 36% higher than the costing study. However, AIHW estimates include all patients aged 25 and older and includes unstable angina - no information is provided on the split between the two conditions - so it is not unreasonable that the AIHW estimates are higher than the costing study. The GBD estimates for IHD include ICD10 codes

I20 to I25.9 [160], whereas the codes used for this study only included acute myocardial infarction (ICD10 code I21). We would therefore argue that comparisons with AIHW are more meaningful, than those with GBD.

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Part IV

Improving Blood Pressure Control

Chapter 6

Factors contributing to inadequate blood pressure control

There are several reasons for poor blood pressure (BP) control, including health system barriers and provider-related and patient-related factors. Health system barriers include the availability, accessibility and acceptability of care, and affordability of medications [161-163], whereas provider-related barriers include competing interests, information overload, lack of knowledge of treatment guidelines and clinical inertia [162, 164]. In contrast, patient factors include poor medication adherence, patients' beliefs about hypertension and its treatment, stress, anxiety and depression, low health literacy, comorbidities, patient motivation, coping, and lack of social support [161, 162, 164]. The most critical factors are clinical inertia and poor medication adherence [162, 165].

Chapter 4 showed that clinical inertia related to treatment initiation might play less of a role in poor BP control in Australia, as most patients (approximately 90%) were prescribed antihypertensive medication in the past 2 years. However, only about 60% of patients had received a prescription for antihypertensive therapy in the last 6 months of the study period. This suggests that prescribing practices may be influenced by factors other than clinical inertia, such as patient factors and, specifically, medication adherence [162, 166-168].

6.1 Medication adherence

The World Health Organization has defined adherence as the "extent to which a person's behaviour – taking medication, following a diet, and/or executing lifestyle changes, corresponds with agreed recommendations from a health care provider" [169, p.3]. Medication adherence can be measured through either direct or indirect methods. Direct methods include direct observation of patients ingesting medication, as is often used in tuberculosis treatment [170], or measuring either the drug or a metabolite in patient urine or blood specimens. Indirect methods include self-administered questionnaires, pill counts, electronic medication monitoring systems and pharmacy databases [171], with pharmacy databases the most widely used method. Several methods exist to measure adherence using pharmacy dispensing records, with the most frequently used being the medication possession ratio (MPR) and proportion of days covered (PDC) [172]. The MPR is calculated by dividing the number of days of supplied medication by either a refill interval or a fixed period (e.g. 1 year). The limitation of MPR is that when patients fill their prescriptions early, this "extra" fill during the measurement period may result in an MPR exceeding 100% if not capped [173]. PDC calculations adjust the numerator using time arrays to adjust for any time overlaps and can, therefore, not exceed 100% [172, 173]. In the case of hypertension, an MPR of greater than 80% is considered good adherence [174].

Non-adherence may exist at different stages of the treatment continuum. Patients may not initiate treatment by failing to fill their prescription (initiation stage), they may fail to implement the correct dose by either missing doses or taking more or less than the prescribed dose (implementation stage), or they may discontinue treatment early (discontinuation stage) [175]. Persistence describes the time between initiation of the treatment and the last dose before discontinuation [175]. Non-adherence behaviour can be intentional or unintentional [176, 177]. Intentional non-adherence involves an active decision by the patient to either alter doses or not take the medication at all. In contrast, unintentional non-adherence includes more passive actions such as forgetfulness or the inability to follow instructions due to cognitive or physical limitations [176, 177]. Patients can exhibit

both intentional and unintentional behaviours simultaneously, and unintentional non-adherence may lead to future intentional non-adherence [178].

Rates of primary non-adherence for antihypertensive therapy, defined as the failure to initiate treatment, were estimated at 12.4% (95% CI: 9.5–15.3) in a meta-analysis of 24 studies [179]. The rates for individual studies ranged from 2.0% to 33.5%, meaning that one-third of patients may not fill their first prescription. Even for those who initiate treatment, adherence is poor. Using dispensing records to assess adherence, a meta-analysis of 26 studies with a total sample size of 1,522,203 patients, found that only 48.5% (95% CI: 47.7-49.2) of patients were adherent to antihypertensive medications at 1 year of follow-up [180]. Vrijens and colleagues [181] used an alternative measure, namely electronically compiled dosing histories measured by a medication event monitor, to evaluate medication persistence at 12 months. The monitors automatically record the date and time of each opening of the medication container. The study, which included 4783 patients who had participated in phase IV clinical studies in Switzerland between 1989-2006, also found that almost half of patients had stopped taking their medication by the end of one year. Patients who do not adhere to their prescribed therapy have poorer outcomes than those who adhere [182]. Increasing adherence by only one additional tablet per week could reduce the risk of stroke by approximately 8% and the risk of death by 7% [183].

6.2 Barriers to medication adherence

Many studies have attempted to identify factors associated with medication non-adherence, which is a complex issue. To reflect this complexity and to dispel the common belief that patients are predominantly responsible for non-adherence, the World Health Organization developed the Multidimensional Adherence Model to organise barriers to medication adherence into five dimensions, all of which contribute to non-adherence. These dimensions are the health care team and system-related factors, social and economic factors, and condition-, therapy- and patient-related factors [169].

Health care team and system factors include out-of-pocket costs for medication [184-186], insufficient financial reimbursement or incentives for health care providers to provide recommended care [161], the quality of the patient–provider relationship [184, 185, 187], inconsistency in treatment guidelines [188] and disagreement with clinical recommendations [161], lack of resources such as insufficient consultation time and staff shortages [161], and lack of social support. Social support was defined as routine contact between the patient and the health care provider through follow-up appointments, text messages or phone calls [179]. In Australia, 6% of patients indicated that they either delayed or avoided filling a prescription due to cost [189].

Social and economic factors include demographic characteristics of patients such as sex, age and race [180, 184] as well as socioeconomic factors such as income, education, employment and family structure [190]. Health lifestyles theory posits that health behaviours are a consequence of the interplay between life choices (agency) and life chances (structure). Both life choices and life chances are influenced by structural variables, such as social class, age, sex, ethnicity/race, living conditions and personal safety. An individual's agency may either be constrained or expanded by life chances, the structurally determined chances available to individuals conferred by their social position [191, 192]. A recent systematic review of systematic reviews identified that belonging to a minority ethnic group had a negative impact on adherence, whereas higher socioeconomic position was associated with better adherence [193]. The evidence on the effect of employment and education is less certain [193].

Therapy-related factors include the complexity of the medical regimen [187], drug side effects [161, 185, 186] and the class of prescribed medication [180, 184, 194]. The association with the class of medication could be due to the properties of the drug class, or the cost or market availability of the drug [194, 195]. However, none of these factors were found to have a strong effect on adherence in a systematic review of systematic reviews [193].

Condition-related factors include the severity of the disease [184] and comorbidities such as depression [180, 193, 196, 197]. Robust evidence exists for the negative impact of depression on adherence [193]. Furthermore, low physical

and mental health-related quality of life in older adults is associated with low medication adherence [198].

Patient-related factors include the patient's knowledge, beliefs, attitudes, perceptions and expectations about their disease and treatment [169]. Concern about potential adverse effects rather than actual effects has been reported as a reason for non-adherence [197]. A systematic review on patient and health care provider barriers to hypertension control found that forgetfulness was the most commonly reported patient barrier to medication adherence [161]. Self-efficacy, defined as a person's belief in their ability to achieve a particular behaviour [199], has also been found to influence medication adherence [200, 201].

6.3 Interventions to improve medication adherence

Several systematic reviews in recent years have investigated interventions to improve medication adherence more generally [202-206] and specifically for patients with hypertension [150, 207-211]. The most effective strategies were multilevel, multicomponent strategies [206], often involving team-based care [150, 207]. Effective patient-level strategies involved health coaching, home BP monitoring or special packaging of medications [150, 207, 210]. These interventions require health care personnel to monitor and coach patients closely or need equipment such as home-based BP machines. These resource requirements may not be feasible at a population level in terms of cost-effectiveness or scalability [212], especially as the effects of interventions on medication adherence are moderate [207].

This raises the question of whether less resource-intensive interventions can be identified to improve medication adherence. Nudges, a type of intervention informed by behavioural economics, have been found to be cost-effective tools in several policy areas, including improving college enrolment, energy conservation and vaccination rates [213].

6.4 Behavioural economics in health care

Behavioural economics is a relatively new field that aims to understand and affect human behaviour [214]. Whereas neoclassical economics assumes that individuals are rational and make decisions based on consistent preferences and sufficient information, behavioural economics, which combines psychology with economics, identifies several systematic cognitive biases that influence individual decision-making and behaviours [215]. One such bias, present bias, disproportionately weights present costs and benefits relative to future costs and benefits [216]. Present bias can be illustrated in patients with asymptomatic disorders, such as hypertension, requiring long-term adherence to medication. The cost of taking medication is in the present and is weighted more than the potential benefits of the medication, which are often far in the future [215]. Interventions using financial incentives to offset the immediate costs of inconvenient or onerous behaviours have increased medication adherence [217]. However, these interventions are costly, especially for highly prevalent conditions such as hypertension.

Drawing on additional behavioural economic insights, lottery-based interventions have been used to increase physical activity in overweight and obese adults [218] and improve medication adherence to warfarin in the United States [219, 220]. Two behavioural economic concepts were used in these interventions. In the first concept, regret aversion, individuals incorporate the anticipated regret they may feel from a particular uncertain outcome into the decision-making process to avoid regret [221]. In the second concept, the certainty effect, people tend to overestimate small probabilities and underestimate large probabilities [222]. In the medication intervention, instead of each participant receiving a daily financial incentive for taking their medication, participants were entered into a lottery with a 2 in 5 chance to win a small amount and a 1 in 100 chance to win a larger amount if they took their medication as prescribed. Participants who won the lottery but had not taken their medication were informed that they would have been paid had they taken their medication. A lottery-based intervention costs considerably less than the payment of financial incentives to all participants.

Several other behavioural economic insights have been used to encourage healthy behaviours. One such concept is loss aversion, where the psychological pain of a loss is larger than the pleasure of a gain of equal value [222]. This concept has been used in commitment contracts to improve smoking cessation rates [223] and weight loss [224]. These interventions involve participants depositing their own funds into an account that can only be accessed once the specified goal has been reached, for instance, a urine test at 6 months which is negative for nicotine. If the goal is not reached, the funds are forfeited, for example, donated to a charity.

In summary, medication adherence is an important factor contributing to poor BP control, with almost 50% of patients with hypertension no longer adhering to their treatment within 1 year. Extensive literature on interventions to improve medication adherence concludes that the most effective strategies are multilevel, multicomponent strategies. However, the effects of these resource-intensive interventions on medication adherence are modest. The relatively new field of behavioural economics may provide new, less resource-intensive opportunities to improve medication adherence, thereby reducing the burden of uncontrolled hypertension. Chapter 7 therefore evaluates the evidence for interventions informed by insights from behavioural economics to improve medication adherence.

Chapter 7

Behavioural economic interventions to improve medication adherence

7.1 Preface

This chapter presents the scoping review of the available evidence on behavioural economic interventions to improve medication adherence in high-income settings. Both the protocol for the review, published in *JBI Database of Systematic Reviews and Implementation Reports,* and the final review, published in *The Patient – Patient-Centered Outcomes Research,* are included in this chapter. As applying behavioural economic insights to health is a relatively new field, restricting the study inclusion criteria to hypertension would have limited the literature from which to draw conclusions. Therefore, this review was not limited to hypertension but included studies on all chronic conditions requiring long-term medication adherence.

This study summarises the range of behavioural economic interventions evaluated in various conditions, including financial and non-financial interventions. It also highlights the variation in outcomes for different interventions and population groups, illustrating the complexity of addressing medication adherence.

This is the first systematic scoping review of interventions informed by behavioural economics to improve medication adherence.

7.2 Statement of authorship: protocol

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Name of principal author (Candidate): Jacqueline Roseleur

Contribution to the paper: Conception and design, drafted the article and critical revisions, and acted as corresponding author.

Overall percentage: 85%

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signed: . . . . . Date: 09/12/2022

Co-author contributions

By signing the statement of authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of co-author: Gillian Harvey

Contribution to the paper: Conception and design and revised it critically for important intellectual content.

Signed: . . . . . Date: 09/12/2022

Name of co-author: Nigel Stocks

Contribution to the paper: Conception and design and revised it critically for important intellectual content.

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Name of co-author: Jonathan Karnon

Contribution to the paper: Conception and design and revised it critically for important intellectual content.

Signed: . . . . . Date: 09/12/2022

7.3 Publication: protocol

7.3.1 Abstract

Objective

The objective of this review is to map the evidence on the use of behavioral economic insights to improve medication adherence in adults with chronic conditions.

Introduction

Medication non-adherence is a barrier to effectively managing chronic conditions, leading to poorer patient outcomes and placing an additional financial burden on healthcare systems. As the population ages and the prevalence of chronic disease increases, new ways to influence patient behavior are needed. Approaches that use insights from behavioral economics may help improve medication adherence, thus reducing morbidity, mortality and financial costs of unmanaged chronic diseases.

Inclusion criteria

Eligible studies will include adults taking medication for a chronic condition. All interventions relevant to high-income settings using insights from behavioral economics to improve medication adherence in adults will be considered. Contexts may include, but are not limited to, primary health care, corporate wellness programs and health insurance schemes. Any study design published in English will be considered. Studies in facilities where medication is administered to patients will be excluded.

Methods

PubMed, Embase, Scopus, PsycINFO, EconLit and CINAHL will be searched from database inception to present. Gray literature will be searched using Google Scholar, OpenGrey and the Grey Literature Report. One reviewer will review titles, and then two reviewers will independently review abstracts to identify eligible studies. One reviewer will extract data on study characteristics, study design and study outcomes. A second reviewer will validate 25% of the extracted information. The

results of the data extraction will be presented in a table, and a narrative summary will be presented.

Keywords

Behavioral economics; chronic conditions; medication adherence

7.3.2 Introduction

Medication non-adherence has been identified as a major barrier to effectively managing chronic conditions [169]. The consequences of non-adherence include poorer outcomes for patients [182], higher rates of hospitalization [225, 226] and increased mortality [227], even for patients only taking placebos [228], This increase in morbidity and mortality due to non-adherence places an additional financial burden on healthcare systems [229].

Nonadherence may exist at different stages of the treatment continuum. Patients may not initiate treatment by failing to fill their prescription; they may fail to implement the correct dose by either missing doses or taking more or less than the prescribed dose; or they may discontinue treatment early [175]. Non-adherence behavior can be intentional or unintentional [176, 177]. Intentional non-adherence involves an active decision by the patient to either alter doses or not take the medication at all whereas unintentional non-adherence includes more passive actions such as forgetfulness or the inability to follow instructions due to cognitive or physical limitations [176, 177]. Patients can exhibit both intentional and unintentional behaviors simultaneously [178].

Rates of primary non-adherence, defined as the failure to initiate treatment, is estimated at between 6% and 35% [230-237]. This means that up to one third of patients do not fill their first prescription. Primary reasons for lack of initiation include perceptions around need, affordability and concerns about the risks and benefits of medication [238]. Even if patients fill their first prescription, a Canadian study found that between 6 and 14% of patients taking statins fail to fill their second prescription [239]. Within one year, approximately 50% of patients prescribed antihypertensive therapy were non-adherent [181] and by 24 months 43% of patients with cardiovascular disease were non-adherent [240].

A number of reviews have investigated barriers to medication adherence including at the patient, provider, and health system levels [184, 185, 197, 241-243]. In addition, there exists extensive review literature on interventions to improve medication adherence in general [202, 204, 205], for specific diseases or risk factors, such as hypertension [207-211], diabetes [244-247], and cardiovascular disease [248-252], and for specific target groups, such as older adults [253-255], patients with adherence problems [256] and underrepresented adults [257, 258]. A systematic review in 2013 on the cost-effectiveness of medication adherence interventions was only able to identify 14 eligible studies [259]. The findings from these studies were mixed, with only four studies showing incremental cost-effectiveness ratios below stated willingness-to-pay thresholds. The authors also found that the reason many of the studies were unable to show cost-effectiveness, was that the interventions themselves were ineffective at improving medication adherence.

A potentially cost-effective addition to medication adherence interventions could come from behavioral economic insights. Whereas neoclassical economics assumes that individuals are rational and make decisions based on consistent preferences and sufficient information, behavioral economics identifies a number of systematic cognitive biases that influence individual decision making and behaviors [215]. One such bias, present-bias, disproportionately weights present costs and benefits relative to future costs and benefits [216]. This can be illustrated in patients with asymptomatic disorders, such as hypertension, requiring long-term adherence to medication. The financial costs and the inconvenience of taking medication is in the present and is weighted more than the potential benefits of the medication, which are often far in the future [215]. Interventions using financial incentives to offset the immediate costs of inconvenient or onerous behaviors have been used to increase physical activity [218, 260-263] and improve medication adherence [220, 264]. One study aimed to increase physical activity by offering financial incentives though a lottery system [218]. The financial incentives offset the immediate costs of exercising, and the lottery system takes advantage of another behavioral economic concept, prospect theory, to improve the impact of the financial incentives. Prospect theory states that people tend to overweigh small probabilities when deciding between alternative options that involve uncertainty and risk [222]. Another bias

associated with prospect theory, loss aversion, describes the concept where individuals experience greater pain when losing something, than pleasure from gaining the same thing [265]. Recognition of this bias has been used in interventions to increase weight loss, at least in the short-term [224, 263]. One study included a deposit contract as one of the three weight loss plans being tested [224]. The deposit contract required participants to invest their own money, which was forfeited if they failed to meet their weight loss goals.

Many of the therapies for managing chronic diseases are highly effective. For these therapies to achieve their potential impact, especially as the population ages and the prevalence of chronic disease increases, exploring new ways to influence patient behavior is needed [200, 266]. Approaches using insights from behavioral economics may provide new opportunities to improve medication adherence, thereby reducing the burden, both in terms of morbidity and mortality and additional healthcare costs, of unmanaged chronic diseases. A scoping review on the use of behavioral economic interventions for the prevention and treatment of type II diabetes found 15 studies that used one of three types of behavioral economic interventions – financial incentives, choice architecture adjustments and commitments devices [267]. The authors concluded that these studies showed some potential for improving patient behaviors in relation to diabetes. A broader perspective will be taken in this study, including additional behavioral economic concepts and a wider range of chronic conditions requiring long-term medication adherence. The objective of this review therefore is to map the available evidence to provide an overview of the use of behavioral economic insights to improve medication adherence in adults with chronic conditions in a high-income setting.

A preliminary search was conducted in August 2018 for scoping and systematic reviews on this topic in the following databases: JBI Database of Systematic Reviews and Implementation Reports, Cochrane Database of Systematic Reviews, PubMed, Epistemonikos and The Cumulative Index to Nursing and Allied Health Literature (CINAHL). No similar studies were found.

Review questions

The following are our four research questions, which will be used to inform the development of an intervention in a high-income setting:

i. Which behavioral economic insights have been investigated to improve medication adherence for adult patients with chronic conditions?

ii. Which patient populations, outcomes and diseases have been studied?

iii. Which research methods have been used in the studies on this subject?

iv. How effective are interventions that draw on behavioral economic insights in improving medication adherence for adult patients with chronic conditions?

Inclusion criteria

As a scoping review takes a broader view of an issue, the Population, Concept and Context (PCC) framework has been used [268].

Population

All adults taking medication for the treatment of a chronic condition will be included in this scoping review. Studies in hospitals, prisons, aged-care homes and other facilities where medication is administered to patients will be excluded. Chronic conditions will include both diseases and risk factors requiring long-term medication adherence, including cardiovascular diseases, hypertension, type II diabetes mellitus, HIV and chronic kidney disease. Mental health conditions will also be included.

Concept

All interventions relevant to high income settings using insights from behavioral economics to improve medication adherence in adults will be included, such as interventions to address decision errors relating to present-bias, prospect theory (poor understanding of probabilities), loss aversion and social influences/norms. All study designs published in English, including experimental, quasi-experimental and non-experimental studies will be included. No limits will be placed on the source of

evidence as this approach will lead to greater sensitivity in the search, which is preferred for scoping reviews [269].

Context

All relevant high-income contexts will be considered for inclusion. These may include but not limited to primary health care (general practice facilities, community clinics, pharmacies), companies with corporate wellness programs and health insurance schemes.

Types of studies

As this is a scoping review, all study types including observational studies, pilot studies and randomized trials will be included. Opinion papers and letters will be excluded.

7.3.3 Methods

Study design

A scoping review will be undertaken for this study to provide a synthesis of the current available evidence on the use of interventions that draw on insights from behavioral economics to improve medication adherence in adults with chronic conditions. The purpose of scoping reviews is to provide a broad overview of a particular area of interest, identifying the key concepts, research gaps and summarizing and disseminating research findings [270]. As this study aims to describe a broad range of patients, diseases, research methodologies and behavioral economic interventions to improve medication adherence for chronic conditions, a scoping review is an appropriate methodology [268]. The Joanna Briggs Institute of Reviewers' Manual will be used to conduct this study [269]. As the development of the PRISMA statement for scoping reviews (PRISMA-ScR) is still underway, the PRISMA statement for reporting health care interventions will be used [271, 272].

Information sources and search strategy

The research team includes a general practice expert (NS) who provided advice on the chronic conditions to be included. Thereafter, a three-step search strategy was

undertaken [273]. After an initial search of two databases, the text words and index terms of relevant articles were identified and included in the final search strategy. This search strategy was peer reviewed by an information specialist using the Peer Review of Electronic Search Strategies (PRESS) checklist [274]. The following databases will be searched for citations published in English: PubMed, EMBASE, SCOPUS, PsycINFO, EconLit and the Cumulative Index to Nursing and Allied Health Literature (CINAHL) from database inception to present. Grey literature will be searched using Google Scholar, Open-Grey (www.opengrey.eu) and the Grey Literature Report (www.greylit.org). Forward and backward citation searching of relevant articles will be done. No time limit will be placed on the search strategy. The final search strategy for PubMed is presented in Appendix I. Search strategies for the other databases used are available from the corresponding author.

Study selection

The citations will be imported into Endnote V8.2 (Clarivate Analytics, PA, USA), where duplicates will be removed. Duplicates not detected by EndNote will be removed manually. The remaining citations will be imported into Rayyan [275]. As many of the behavioral economic terms have multiple uses in other research areas and a large number of results is expected, one reviewer will review titles only. Thereafter, two reviewers will independently review abstracts using a questionnaire with inclusion criteria to identify eligible studies. The full-text articles will be reviewed by two reviewers for articles where the title and abstract contain insufficient information to determine eligibility. If the full-text article is still unclear on the study eligibility criteria, study authors will be contacted for further information. Where disagreements exist among reviewers, the article will be discussed between the two reviewers to reach consensus. If there is continued disagreement, a third reviewer will be requested to make a final decision. The reasons for excluding studies at the full-text level will be recorded and reported in the review.

Data extraction

One reviewer will extract data on study characteristics, study design and study outcomes using Microsoft Excel (2013). The extraction form will be trialed on a

sample of five studies to ensure all relevant details are captured. Study characteristics will include authorship, year study was conducted, year and journal of publication, funding source, geographical region and type of article. Study design will include type of study, aim of the study, type of behavioral economic insight used, intervention, comparator, study population, sample size, patient care setting, patient characteristics, disease, type of medication, duration of the intervention, follow-up period and statistical methods used. Study outcomes will include how medication adherence was measured, and the key findings of the study. A second reviewer will validate 25% of the extracted information. Any disagreements will be resolved through discussion until consensus is reached.

Methodological quality appraisal

Methodological quality assessment and risk of bias will not be undertaken for this study, which is consistent with scoping review guidance [268].

Data synthesis

The results of the data extraction will be presented in a table that outlines the first author, geographical location, year of publication, study population, study design, type(s) of interventions, comparator(s), participant characteristics (average age, race, ethnicity and gender) and characteristics of the intervention (strategy, details of the intervention, duration and primary outcomes). Descriptive statistics will be used to provide a summary of the characteristics of the studies, including the year of publication, geographical locations, funding sources, duration of the study, disease and setting of the study. These categorical data will be summarized using percentages and frequencies. A narrative summary of the studies will be prepared considering the nature of the intervention, the population, study design features and the study results. In addition, the narrative summary will also consider the nature of the disease area targeted, i.e. is the condition a physical or a mental condition, is the disease symptomatic or asymptomatic and the proximity or risk of adverse consequences.

Ethics and dissemination

As this scoping review uses data available in the public domain, no ethics application is required. The results from this study will be disseminated at conferences and published in a peer-reviewed journal.

Contributors

JR conceived and designed the study and drafted the protocol. JK, GH & NS helped to design the study and edit the protocol. All authors read and approved the final protocol prior to its submission.

Conflict of interest

The authors declare no conflict of interest.

Acknowledgments

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7.3.4 Appendix

PubMed search strategy

#	TERM	SEARCH TERMS
1	Adherence	"Medication Adherence"[Mesh] OR (adherence[Title/Abstract] OR complian*[Title/Abstract] OR nonadherence[Title/Abstract] OR non-adherence [Title/Abstract] OR adherent[Title/Abstract] OR non-adherent[Title/Abstract] OR nonadherent[Title/Abstract] OR non-complian*[Title/Abstract] OR noncomplian*[Title/Abstract] OR concordan*[Title/Abstract] OR nonconcordan*[Title/Abstract] OR persistence [Title/Abstract] OR non-persistence[Title/Abstract] OR "Self-Management"[Mesh] OR self-management[Title/Abstract] or self-care[Title/Abstract])
2	Medication	"Prescription Drugs"[Mesh] OR medicine*[Title/Abstract] OR medication*[Title/Abstract] OR drug*[Title/Abstract] OR therap*[Title/Abstract] OR treatment*[Title/Abstract] OR pharmaceutical*[Title/Abstract] OR pill*[Title/Abstract] OR tablet*[Title/Abstract]
3	Medication Adherence	#1 AND #2
4	Behavioral Economics	"Economics, Behavioral"[Mesh] OR behavioral economic*[Text Word] OR behavioural economic*[Text Word] OR behavioural economic*[Title/Abstract] OR behavioral economic*[Title/Abstract] OR anchor*[Title/Abstract] OR choice architecture[Title/Abstract] OR confirmation bias*[Title/Abstract] OR default*[Title/Abstract] OR framing[Title/Abstract] OR framed[Title/Abstract] OR priming[Title/Abstract] OR intertemporal choice[Title/Abstract] OR inter-temporal choice[Title/Abstract] OR messenger*[Title/Abstract] OR present bias*[Title/Abstract] OR incentive*[Title/Abstract] OR loss aversion[Title/Abstract] OR endowment effect*[Title/Abstract] OR regret aversion[Title/Abstract] OR reference dependence[Title/Abstract] OR mental accounting[Title/Abstract] OR nudg*[Title/Abstract] OR partitioning[Title/Abstract] OR social norm*[Title/Abstract] OR social proof[Title/Abstract] OR social preference*[Title/Abstract] OR status quo bias*[Title/Abstract] OR inertia[Title/Abstract] OR choice overload[Title/Abstract] OR decision fatigue[Title/Abstract] OR time discount*[Title/Abstract] OR hyperbolic discount*[Title/Abstract] OR time inconsistent

#	TERM	SEARCH TERMS
		preference*[Title/Abstract] OR time inconsistency[Title/Abstract] OR commitment device*[Title/Abstract] OR commitment contract*[Title/Abstract] OR commitment consistency[Title/Abstract] OR precommitment*[Title/Abstract] OR ego effect[Title/Abstract] OR temptation bundl*[Title/Abstract] OR reinforcement*[Title/Abstract] OR gamification[Title/Abstract] OR gaming[Title/Abstract] OR game-based[Title/Abstract] OR libertarian paternalism[Title/Abstract] OR prospect theory[Title/Abstract] OR bounded selfishness[Title/Abstract] OR unbounded selfishness[Title/Abstract] OR bounded rational*[Title/Abstract] OR unbounded rational*[Title/Abstract] OR limited rational*[Title/Abstract] OR bounded willpower[Title/Abstract] OR unbounded willpower[Title/Abstract] OR affect heuristic*[Title/Abstract] OR representativeness heuristic*[Title/Abstract] OR availability heuristic*[Title/Abstract] OR overconfidence[Title/Abstract] OR optimism bias*[Title/Abstract] OR limited attention[Title/Abstract] OR mere-measurement[Title/Abstract] OR question-behaviour effect[Title/Abstract] OR hindsight bias*[Title/Abstract] OR knew-it-all-along effect[Title/Abstract] OR salience[Title/Abstract]
5	Medication Adherence AND Behavioral Economics	#3 AND #4
6	Cardiovascular disease	"Cardiovascular Diseases"[Mesh:noexp] OR cardiovascular disease*[Title/Abstract] OR CVD[Title/Abstract] OR "Heart Diseases"[Mesh] OR heart disease*[Title/Abstract] OR “coronary artery disease*”[Title/Abstract] OR "Dyslipidemias"[Mesh] OR dyslipidemia*[Title/Abstract] OR dyslipidaemia*[Title/Abstract] OR hyperlipidemia*[Title/Abstract] OR hyperlipidaemia*[Title/Abstract] OR hypercholesterolemia*[Title/Abstract] OR hypercholesterolaemia*[Title/Abstract] OR "Arteriosclerosis"[Mesh] OR arteriosclerosis[Title/Abstract] OR arterioscleroses[Title/Abstract] OR atherosclerosis[Title/Abstract] OR atherosclerosis[Title/Abstract]
7	Hypertension	"Hypertension"[Mesh] OR hypertension[Title/Abstract] OR blood pressure*[Title/Abstract] OR diastolic[Title/Abstract]

#	TERM	SEARCH TERMS
		OR systolic[Title/Abstract] OR hypertensive[Title/Abstract] OR antihypertensive[Title/Abstract] OR anti-hypertensive[Title/Abstract]
8	Diabetes Type 2	"Diabetes Mellitus, Type 2"[Mesh] OR diabetes[Title/Abstract] OR diabetic*[Title/Abstract] OR "Hyperglycemia"[Mesh] OR hyperglycemia*[Title/Abstract] OR hyperglycaemia*[Title/Abstract] OR glucose intolerance*[Title/Abstract] OR glucose tolerance*[Title/Abstract]
9	HIV	"HIV"[Mesh] OR Human Immunodeficiency Virus*[Title/Abstract] OR Human Immuno-deficiency Virus*[Title/Abstract] OR HIV[Title/Abstract] OR AIDS[Title/Abstract] OR Acquired Immune Deficiency Syndrome*[Title/Abstract]
10	Chronic Kidney Disease	"Renal Insufficiency, Chronic"[Mesh] OR (chronic kidney disease*[Title/Abstract] OR chronic kidney disorder*[Title/Abstract] OR chronic kidney insufficienc*[Title/Abstract] OR chronic nephropathy*[Title/Abstract] OR chronic renal disease*[Title/Abstract] OR chronic renal failure*[Title/Abstract] OR chronic renal insufficienc*[Title/Abstract] OR kidney chronic failure*[Title/Abstract])
11	Chronic Diseases	"Chronic Disease"[Mesh] OR chronic[Text Word] OR chronic[Title/Abstract]
12	All Diseases	#6 OR #7 OR #8 OR #9 OR #10 OR #11
13	Medication Adherence AND Behavioral Economics AND Chronic Diseases	#5 AND #12

7.4 Statement of authorship: review

Title of paper: Behavioral economic insights to improve medication adherence in adults with chronic conditions: a scoping review

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Name of principal author (Candidate): Jacqueline Roseleur

Contribution to the paper: Conception and design, analysis and interpretation of data, drafted the article and critical revisions, and acted as corresponding author.

Overall percentage: 85%

This paper reports on original research I conducted during the period of my Higher Degree by Research candidature and is not subject to any obligations or contractual agreements with a third party that would constrain its inclusion in this thesis. I am the primary author of this paper.

Signed: . . . . . Date: 09/12/2022

Co-author contributions

By signing the statement of authorship, each author certifies that:

i. the candidate's stated contribution to the publication is accurate (as detailed above);

ii. permission is granted for the candidate to include the publication in the thesis; and

iii. the sum of all co-author contributions is equal to 100% less the candidate's stated contribution.

Name of co-author: Gillian Harvey

Contribution to the paper: Conception and design, interpretation of data, and revised it critically for important intellectual content.

Signed: . . . . . Date: 09/12/2022

Name of co-author: Nigel Stocks

Contribution to the paper: Conception and design, interpretation of data, and revised it critically for important intellectual content.

Signed: . . . . . Date: 09/12/2022

Name of co-author: Jonathan Karnon

Contribution to the paper: Conception and design, interpretation of data, and revised it critically for important intellectual content.

Signed: . . . . . Date: 09/12/2022

7.5 Publication: review

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SYSTEMATIC REVIEW

Behavioral Economic Insights to Improve Medication Adherence in Adults with Chronic Conditions: A Scoping Review

Jacqueline Roseleur[1] · Gillian Harvey[2] · Nigel Stocks[3] · Jonathan Karnon[1,4]

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Abstract

Background and Objective Medication adherence is poor in patients with chronic conditions. Behavioral economic interventions may reduce biases that are associated with poor adherence. The objective of this review is to map the available evidence on behavioral economic interventions to improve medication adherence in adults with chronic conditions in high-income settings.

Methods We conducted a scoping review and reported the study using the Joanna Briggs Institute Reviewers' Manual and the PRISMA Extension for Scoping Review checklist. We searched PubMed, EMBASE, SCOPUS, PsycINFO, EconLit, and CINAHL from database inception to 29 August, 2018 for peer-reviewed studies and included a search of the gray literature. Data on study characteristics, study design, and study outcomes were extracted by one reviewer. Twenty-five percent of the studies were verified by a second reviewer.

Results Thirty-four studies, targeting diabetes mellitus, human immunodeficiency virus, and cardiovascular and renal diseases met our inclusion criteria. All but two studies were from the USA. The majority of interventions used financial incentives, often in conjunction with other behavioral economic concepts. Non-financial interventions included framing, social influences, reinforcement, and feedback. The effectiveness of interventions was mixed.

Conclusions Behavioral economic informed interventions show promise in terms of improving medication adherence. However, there is no single simple intervention. This review highlighted the importance of targeting non-adherent patients, understanding their reasons for non-adherence, providing reminders and feedback to patients and physicians, and measuring clinical outcomes in addition to medication adherence. Further research in settings that differ from the US health system is needed.

Key Points

No simple interventions to improve medication adherence in patients with chronic conditions are available.

Interventions should target non-adherent patients and understand their reasons for non-adherence.

Reminders and feedback on medication-taking behavior should be provided to patients and their healthcare providers to improve adherence to medication.

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1 Background

The burden of chronic diseases is increasing at a rapid rate. Many of these diseases can be managed effectively, with medication an integral part of the treatment regimen. However, medication adherence is low, especially in patients with asymptomatic conditions [1, 2]. Although a large body of evidence exists on interventions to improve medication adherence, current methods to improve medication adherence are complex with limited effectiveness [3].

Interventions informed by insights from behavioral economics have shown some promise in other areas of health, such as smoking cessation [4] and increased physical

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activity [5–7] and may have relevance in influencing medication-taking behavior in patients with chronic diseases. Whereas neoclassical economics assumes that individuals are rational, behavioral economics recognizes that decision making and subsequent behaviors are influenced by cognitive biases—systematic patterns of thinking that deviate from rational thinking [8, 9]. One of these biases, present bias, weights present costs and benefits higher relative to future costs and benefits [10]. For example, hypertensive patients experience the inconvenience and financial costs of taking medication in the present; however, the potential benefits are only experienced far into the future and not everyone benefits [8]. Table 1 provides definitions of key behavioral economic terms.

In a scoping review on behavioral economic interventions focused on prevention and treatment of type 2 diabetes mellitus, Kullgren et al. [11] identified 15 studies that used either financial incentives, choice architecture adjustments (i.e., changing choice environments to influence decisions in a systematic manner), or commitment devices (i.e., allowing people to commit their future selves to actions needed to achieve long-term goals). They concluded that these interventions could address the present-bias preferences that hinder patients' attempts to improve their health. A broader perspective was taken in this study, by including additional behavioral economic concepts and a wider range of chronic conditions requiring long-term medication adherence. The objective of this review therefore was to map the available evidence on the use of behavioral economics to improve medication adherence in adults with chronic conditions in high-income settings [12].

The specific objectives of the review were to [12]:

1. Examine how behavioral economic insights have informed interventions used to address medication adherence for adult patients with chronic conditions;
2. Determine the type of patient populations, outcomes, and diseases that have been studied;
3. Map the research methods used in these studies; and
4. Evaluate the effectiveness of interventions informed by behavioral economics to improve medication adherence for adult patients with chronic conditions.

2 Methods

In August, 2018 we conducted a search according to an a priori published protocol [12]. We conducted and reported the study using the Joanna Briggs Institute Reviewers' Manual and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) Extension for Scoping Review checklist [13, 14].

2.1 Eligibility Criteria

To be included in the review, papers needed to address medication adherence in adults with chronic conditions requiring long-term adherence. Chronic conditions included diseases and risk factors related to human immunodeficiency virus (HIV), cardiovascular diseases, type 2 diabetes, chronic kidney disease, and mental health. Study participants had to self-administer their medication. Only studies in high-income settings were included as results of this review will be used to inform the development of an intervention to be implemented in Australia. Interventions, using any study design, had to use insights from behavioral economics, such as financial incentives, loss aversion, and social influences. Studies on cost sharing were excluded as recent systematic reviews have been published on this form of financial incentive [15, 16]. Reminders were not included in the original search strategy. We considered including this term post-hoc, but as two systematic reviews on reminders have recently been published [17, 18] we opted not to include studies that tested reminders without other behavioral economic concepts.

Table 1 Definitions of behavioral economic terms

Behavioral economic term	Definition
Choice architecture	Changing choice environments to influence decisions in a systematic way
Commitment device	A tool used to allow people to commit their future selves to actions needed to achieve long-term goals
Financial incentives	A monetary reward used to encourage behavior change
Framing	Presenting choices by highlighting either their positive or negative characteristics
Loss aversion	The pain felt from a loss is twice as powerful as the pleasure from a gain
Positive affect/affect heuristic	The way an individual feels influences their decision-making prior to making reflective judgments
Regret aversion	The fear that people have of making a decision they will consider wrong in hindsight
Social influences	The influences that others have on our choices and behaviors

2.2 Information Sources and Search Strategy

We sought to find a wide range of data sources and therefore included peer-reviewed articles, conference abstracts, and gray literature. We undertook a three-step search strategy with the support of an information specialist [19, 20]. The following databases were searched for citations published in English: PubMed, EMBASE, SCOPUS, PsycINFO, EconLit, and CINAHL from database inception to 29 August, 2018. Gray literature sources included Google Scholar, Open-Grey (http://www.opengrey.eu), and the Grey Literature Report (http://www.greylit.org). No time limit was placed on the search. SCOPUS was used for citation tracking and reference lists of included articles were manually searched for relevant articles. The PubMed search strategy is presented in the Electronic Supplementary Material.

2.3 Study Selection Process

After removing duplicates, citations were imported into Rayyan [21]. As some terms used in behavioral economics are also used in other disciplines with different meanings, one reviewer screened titles only to determine relevance (JR). Thereafter, results were imported into Covidence [22] and titles and abstracts were assessed by two reviewers (JR and JK). The full-text articles were obtained for included articles and reviewed by two reviewers (JR and JK). No authors were contacted for additional information.

2.4 Data Extraction

An extraction form was developed and trialed on five studies and discussed amongst all authors to ensure all relevant information was included in the form. Data on study characteristics (e.g., country, funding source, journal), study design (e.g., study type, duration, sample size), patient and intervention characteristics, and study outcomes were extracted by one reviewer. Twenty-five percent of the studies were verified by a second reviewer. Only minor disagreements existed, which were resolved through consensus.

2.5 Methodological Quality Appraisal

Methodological quality assessment and risk of bias were not undertaken for this study, which is consistent with scoping review guidance [13].

2.6 Synthesis of Results

We grouped the studies by disease (i.e., cardiovascular and diabetes, HIV and renal diseases) and summarized the following information in a table: author, year, location, study design, sample size, duration, patient population, strategy, program details, and primary outcomes. We provided a narrative description of the studies.

3 Results

Thirty-four studies met our inclusion criteria; two conference abstracts [23, 24], one PhD dissertation [25], and 31 peer-reviewed journal articles (Fig. 1). All but two studies were from the USA. The studies were published between 2000 and 2018, with 68% ($n=23$) of the studies published in the last 4 years. Almost one-third of the studies were by researchers from one US University [26–36]. No studies from gray literature sources were found.

A range of conditions requiring long-term medication adherence were targeted. These included cardiovascular diseases [23, 26–30, 32, 34, 36–40], hypertension [23–25, 35, 37, 40–45], diabetes [23, 37, 44–46], HIV [47–56], and renal diseases (patients undergoing transplants [31] and hemodialysis [33]). No studies addressed medication adherence in mental health. A range of population groups were included in the interventions. Three studies specifically targeted hypertensive patients from minority groups (African Americans and/or Hispanics) [25, 41, 43] and one study targeted under- or uninsured adult patients with diabetes and/or hypertension [45]. Of the studies that did not specifically target minority groups, 14 included a majority of minority groups [24, 28–30, 33, 35, 42, 46–49, 51, 53, 54, 56]. The remaining studies either did not report on the ethnicity of participants [23, 34, 36, 38, 40, 55] or included a majority of white participants [26, 31, 32, 37, 39, 44, 52]. Forty percent of the HIV studies were targeted at HIV-positive substance users [49, 50, 53, 54].

As our search strategy was purposely broad, we included studies with a range of outcomes, including medication adherence and improved biological measures (e.g., blood pressure, viral load). Medication adherence measures included self-report [24, 25, 33, 35, 40, 42, 45, 54], electronic pill bottles [26–32, 34, 39–41, 46, 47, 49, 50, 52, 53, 55], pill counts [38, 42], ingestible sensors [44], and prescription refill data [23, 35–37, 45]. The majority of studies were randomized trials, with sample sizes ranging from 29 to over 9000. There were four single-arm pilot studies [34, 46, 51, 53], one observational study [23], and one pre-post study [25].

Two-thirds of the studies utilized financial incentives, either as direct financial payments for meeting a specified goal or as a chance to enter into a lottery. Three of the studies that used direct financial incentives did not include any other interventions: one study provided small incentives for setting and achieving condition management goals [23] and two studies paid participants for achieving either viral load

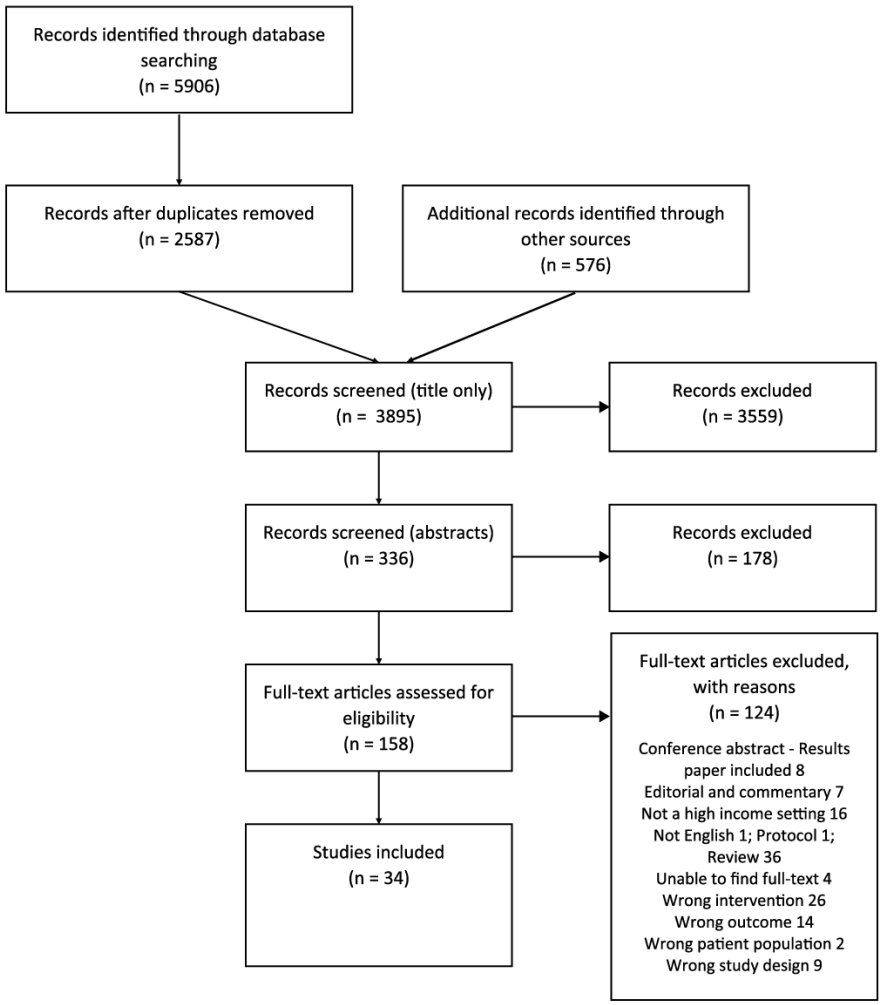

Fig. 1 Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) diagram

measurements below a set threshold [56] or weight loss, improved medication adherence, or increased physical activity goals [45]. The remaining studies combined financial incentives with other interventions such as reminders and reinforcement [42, 46, 48, 53], education [35], commitment contracts [55], and different forms of counseling and support, such as motivational interviewing [51], case management [48], patient navigation [54], cue-dose training [47], and coaching [50].

In the lottery financial incentive studies, participants were entered into lotteries with a higher probability of winning small amounts, and a lower probability of winning larger amounts. Two studies, both in patients taking warfarin, used lotteries alone [29, 34]. The other lottery studies combined lotteries with either reminders and reinforcement [28, 36], feedback [36, 49], counseling [49], social influences [36], or a combination of these [36, 49].

Four studies used both direct financial payments and lotteries. The first study, in addition to the lottery, also tested a guaranteed pay-out incentive to test the concept of loss aversion [40]. In this intervention, participants received money in a virtual account at the onset of the study and had money deducted from the account for each day that a dose was missed. The second study, in addition to the direct and lottery financial incentives, also provided an intervention to identify reasons to stay healthy or live longer to induce positive affect [24]. The third study compared coaching with both types of financial incentives combined with feedback to patients on their biological measures [33] and the last study tested whether direct financial incentives to physicians, lottery incentives to patients, or a combination of the two were more effective than control at reducing low-density lipoprotein cholesterol in patients at high cardiovascular risk [26]. Patients in this study needed to be adherent to their medication, as well as have a reduction in their

low-density lipoprotein cholesterol to be eligible to receive their winnings.

There were 12 studies that did not use financial incentives. Two studies used framing to improve medication adherence [25, 52]. Of these, one used either gain- or loss-framed messaging to encourage adherence [25] whereas the other study tested tailoring messages based on a participant's current psychological state [52]. Another study theorized that improving patients' self-efficacy through positive affect induction and bi-monthly reinforcement telephone calls would improve blood pressure control in African Americans [43]. A Swiss study used reinforcement strategies including newsletters, helplines, and a website to improve adherence to statins [38]. All of the remaining studies used feedback [27, 30, 32, 37, 39, 41, 44] with either reminders [27, 30, 37, 41, 44], reinforcement [41], coaching [37], counseling [39], social influences [27, 30, 32], or a combination of these strategies [27, 32, 37, 41]. Table 2 provides a detailed summary of the included articles, categorized by disease group.

The intervention periods during the studies ranged from less than 1 [46] to 24 months [56]. The most frequent intervention period was 12 months [23, 24, 26, 35–37, 43, 45, 48, 51]. Nine studies had an additional follow-up period ranging from 1 to 12 months [26, 30, 42, 45, 47, 49–51, 54].

Of the randomized trials, 13 studies were found to be effective [24, 26, 30, 31, 39, 41, 42, 44, 48–50, 55, 56]. These studies used financial incentives [24, 26, 42, 48–50, 55, 56], reminders and/or feedback [30, 31, 39, 41, 44, 48, 49], counseling and/or coaching [39, 49, 50], or a combination. Nine studies were ineffective [32, 33, 35, 36, 38, 40, 43, 45, 52] and six were partially effective [27–29, 37, 47, 54]. In the partially effective studies, effects were found only in sub-groups [29, 37], or only one component of an intervention was effective [27, 28], or the effects disappeared during extended follow-up periods [47, 54]. Of the other study types [23, 25, 34, 46, 51, 53], all but one [25] were found to be effective.

4 Discussion

Our scoping review identified 34 studies that used a range of behavioral economic insights to attempt to improve medication adherence in diverse groups of patient populations. Almost two-thirds of interventions utilized financial incentives, either as a direct payment, or as an opportunity to enter a lottery. Many of the financial incentive interventions also included other concepts such as reinforcement, positive affect, social influences, and feedback. The non-financial interventions included framing, reinforcement, positive affect, social influences, counseling, feedback, and reminders.

The outcomes of the interventions were mixed. For example, interventions were mostly effective in patients with HIV groups, but mixed in patients with cardiovascular disease groups. This result could be attributed to the nature of the diseases that are targeted. Many cardiovascular conditions, such as hypertension and hyperlipidemia, are asymptomatic, whereas patients with HIV are more likely to experience symptoms. Evidence for behavioral economic interventions in areas in which a person's condition provides inherent feedback, such as weight loss [57, 58] and smoking cessation [4], is stronger. Inherent feedback may itself be motivating. In our review, interventions that included explicit feedback on medication adherence showed promise; however, this feedback had no influence if it was sent to a medication adherence partner, such as a self-selected family member, friend, or peer [27, 30, 32, 36], but was useful when sent to a healthcare provider [26, 31, 37, 41, 44, 49] who was able to act on this information. This was demonstrated by Asch et al. [26] who showed that shared physician-patient financial incentives were effective at improving medication adherence compared with financial incentives to either patients only or physicians only. Medication intensification by physicians was more likely in patients in the shared physician-patient financial incentives group.

Another study in this review found that even without financial incentives, feedback to providers on patient medication adherence increased the likelihood that providers made therapy adjustments or provided adherence counseling [44]. These findings are consistent with a review on hypertension management that concludes that m-health applications that provide feedback to healthcare providers, and consequently improve patient-provider communication, can be effective tools in improving blood pressure management [59]. In contrast, a recent systematic review found little evidence that feedback to physicians about a patient's medication adherence improved medication adherence or patient outcomes [60]. The review included nine studies where feedback was either the sole intervention or a critical part of a multi-faceted intervention. None of the studies in this scoping review were included in the systematic review as feedback was not a critical component of the intervention. For feedback to be effective, it should be part of a multi-strategy intervention [61].

The effects of other non-financial incentives were similarly mixed. Studies using reminders, either in the form of electronic pill bottles that chimed or lit up when a dose was due or in the form of text messages, were mostly effective. This is consistent with findings from two systematic reviews [17, 18]. Vervloet et al. [18] conclude that reminders were effective in the short term with limited evidence for long-term effectiveness ($\geq$6 months). Two of the studies included in our review exceeded 6 months [37, 48]. However, both

Table 2 Detailed summary of included articles by disease category

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Cardiovascular diseases and diabetes				
Asch (2015), USA [26]	Four-group, multi-center cluster randomized trial; sample size: 1503; 12 months; medium or high risk CVD patients in primary care	Financial incentives for physicians and lottery financial incentives for patients	a) physician incentives: $256 quarterly payments for each enrolled patient meeting the quarterly goal to reduce LDL-C levels from previous quarter's target or to achieve or maintain a specified LDL-C level b) patient incentives: daily lottery - 18 in 100 chance to win $10, 1 in 100 chance to win $100 if adherent the previous day - winnings were paid quarterly if the quarterly LDL-C target was met c) shared physician-patient incentives - combination of physician and patient incentives, with the value halved to equalize total possible payouts across all incentive groups d) control: usual care All participants were compensated for study participation	Mean change in LDL-C (mg/dL (95% CI)) from baseline to 12 months: a) physician incentives: 27.9 (24.9–31.0) b) patient incentives: 25.1 (21.6–28.5) c) shared physician-patient incentives: 33.6 (30.1–37.1) d) control: 25.1 (21.7–28.5)
Boutin-Foster (2016), USA [43]	Two-arm randomized trial; sample size: 177; 12 months; hypertensive African American adults	Improve self-efficacy through positive affect induction, counselling and reinforcement	a) intervention: educational workbook and positive affect and self-affirmation induction protocol (focus on positive thoughts, received unexpected gift cards, counselling based on motivational interviewing) and bi-monthly reinforcement telephone calls b) control: education workbook only All participants developed a behavior contract to identify steps to improve medication adherence	Proportion of patients with BP control at 12 months: a) intervention: 83.7% b) control: 82.2%
Choudhry (2018), USA [37]	Two-arm pragmatic cluster randomized trial; sample size: 4078; 12 months; CVD or diabetic patients in primary care	Coaching, reminders and feedback	a) multicomponent intervention: initial telephone consultation to identify adherence barriers and readiness to modify behaviors and develop a shared plan; feedback to primary care physician; text messages and pillboxes; follow-up consultations; progress reports mailed at 6 and 9 months b) control: usual care	Medication adherence at 12 months by group—overall; hyperlipidemia; hypertension; diabetes: mean % (SD) a) intervention: 46.2 (33.9); 48.2 (33.7); 42.7 (33.4); 39.8 (30.2) b) control: 42.1 (33.8); 44.1 (33.6); 35.9 (33.0); 40.9 (31.0)

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Davidson (2015), USA [41]	Two-arm randomized trial; sample size: 38; 6 months; hypertensive Hispanic and African American adults	Reminders and reinforcement text messages; feedback to providers	a) SMASH intervention: cellular connected electronic medication device provided reminder signals and smartphone messaging reminded patients to take their medication. Culturally-attuned motivational and reinforcement text messages were sent based on medication adherence rates. Nurse managers were alerted if BP remained out of range. b) control: usual care	Percentage of participants with SBP control (< 140 mmHg): baseline; months 1; 3; 6 a) SMASH: 0%; 70.6%; 94.4%; 94.4% b) control: 0%; 15.8%; 55.0%; 41.2%
Frias (2017), USA [44]	Three-arm cluster randomized trial; sample size: 109; 12 weeks; primary care patients with diabetes and hypertension	Feedback to patient and provider; reminders from mobile phone app	a) 4-week intervention: digital medicine offering (DMO) which included digital medicines, wearable sensor patch and mobile device app, with feedback to patients and providers, for 4 weeks b) 12 week intervention: DMO for 12 weeks c) control: usual care All participants were compensated for participation	Mean change in SBP mmHg (SE) from baseline to week 4: a) 4 and 12 week DMO combined: − 21.8 (1.5) b) control: − 12.7 (2.8)
Garza (2016), USA [40]	Three-arm randomized trial; sample size: 36; 90 days; public university employees filling prescriptions at employee pharmacy	Lottery and pre-funded financial incentives	a) Guaranteed pay-out (GPO) incentives: each participant received $30 in a virtual account at the start of the study. For each day that a scheduled dose was missed, $0.50 was deducted from the account. Weekly reports were sent to participants to notify them of the remaining balance b) Lottery incentives: participants entered into weekly lottery to win $50 (1 in 20 chance). Participants could only receive winnings if they achieved 100% adherence over the previous 7 days c) Control: usual care	% days adherent at baseline; intervention; change in measured adherence: mean (SD) a) GPO incentive: 96.4 (6.7); 93.8 (8.5); − 2.6 (5.0) b) lottery incentive: 96.1 (3.9); 96.4 (5.2); 0.3 (5.2) c) control: 97.0 (3.3); 93.8 (8.5); − 3.2 (7.4)

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Jiang (2018), USA [23]	Retrospective observational study; sample size: 2305; 12 months; pharmacy CVD or diabetic patients	Financial incentives	Your Digital Health Advisor, part of Walgreens Balanced Rewards for Healthy Choices program, provided small incentives for setting and achieving lifestyle and condition management goals, including tracking self-monitoring adherence	Dose response relationship between self-monitoring and medication adherence ($Z = -4.68$, $P < 0.001$)
Kessler (2018), USA [27]	Four-arm randomized trial; sample size: 162; 6 months; CVD patients with current statin prescription	Feedback, social influences	a) Partner arm: wireless pill bottle and friend or family member invited to serve as medication adherence partner (MAP) b) alert arm: wireless pill bottle with an automated alert message for missed doses c) Partner + alarm arm: wireless pill bottle and a MAP; automated alert messages to both the participant and the MAP d) Control arm: wireless pill bottle only	6-month average adherence: (SD) a) partner: 43.2% (25.3) b) alert: 52.9% (24.0) c) partner & alert: 54.5% (28.0%) d) control: 36.0% (24.6)
Kimmel (2012), USA [29]	Two-arm randomized trial; sample size: 100; 6 months; patients taking warfarin	Lottery financial incentives	a) Intervention: 1 in 5 chance of a $10 reward and 1 in 100 chance of a $100 reward each day contingent on opening pill box. Patients ineligible due to non-adherence were notified of lottery win. No additional reminders were provided b) Control: usual care	Effect of study arm (lottery vs control) on out-of-range INR (OR (95% CI); p-value) Overall: 0.81 (0.53-1.22); 0.31 INR below range at baseline (n = 18): 0.49 (0.25-0.95); 0.03 INR in-range at baseline (n = 82): 0.99 (0.63-1.58); 1.00

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Kimmel (2016), USA [28]	Four-arm, multi-center, randomized trial; sample size: 270; 6 months; patients in the maintenance phase of warfarin therapy	Lottery financial incentives, reminders	a) Reminder group: electronic medication device with a daily alarm reminder b) Lottery group: daily lottery with 1 in 5 chance of a $10 reward and a 1 in 100 chance of a $100 reward each day contingent on adherence (expected daily value of $3). Reminder alarms were disabled. Payments were made on a monthly basis c) Lottery + reminder group: electronic medication device with a daily alarm reminder and daily lottery d) Control: no lottery and deactivated alarm	Out-of-range INR compared to control (OR (95% CI)); All participants: *P* value = 0.06 a) reminder: 0.64 (0.45–0.93) b) lottery: 0.98 (0.70–1.38) c) lottery + reminder: 0.77 (0.54–1.09)
Kranker (2018), USA [45]	Three-intervention full factorial orthogonal randomized trial; sample size: 570; 12 months; rural vulnerable patients	Financial incentives	Participants randomly assigned to receive 0, 1, 2 or 3 of the following financial incentives: 1. weight loss (WL)—$200 for BMI decrease by at least 3.0 or BMI below 25.0 2. medication adherence (MA)—$70 for taking 90% of prescribed medication 3. physical activity (PA)—$200 for average ≥ 40 minutes per day or $120 for average 20-40 minutes per day	Main and interaction effects of financial incentives: fraction of drug 1 taken; fraction of drug 2 taken MA: 2.4%; 2.6% MA X WL: 0.75%; 0.38% MA X PA: 2.3%; 2.0% MA X WL X PA: 10.4%; 10.4%

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Petry (2015), USA [42]	Two-arm randomized trial; sample size: 29; 12 weeks; hypertensive patients in primary care	Financial incentives, positive messages for adherence	a) Intervention: standard care with 30-min session (same as control group), and cell phone with video capability to record ingestion of medication. Participants earned $0.50 each time they recorded medication ingestion within their dosing window. For each full day of adherence, they earned bonuses. A missed or late recording reset bonuses b) Control: standard care and 30-minute session on improving medication adherence using a structured handout All participants were compensated for study participation	The intervention increased verified ontime medication adherence to > 97% throughout 3 months of treatment, with benefits persisting throughout follow-up
Raiff (2016), USA [46]	Single-arm pilot; sample size: 3; 21–23 days; diabetic patients taking oral medication	Financial incentives, reminders determined by participant	An escalating payment schedule with bonus and reset contingencies was based on daily adherence during set periods (potential earnings $73.50-$84.10). Text messages with previous day's earnings, cumulative earnings to date and possible earnings for that day were sent daily Automated text reminders constructed by the patient were sent if a dose was not taken halfway through their designated time window	Medication adherence: mean percentage of doses taken on time - baseline; intervention DS001: 26.7%; 97.1% DS003: 75%; 97.7% DS006: 66.7%; 85.7%
Reddy (2016), USA [30]	Three-arm randomized trial; sample size: 126; 3 months; veteran patients with a coronary artery disease diagnosis	Reminders and feedback	a) Individual feedback intervention: daily alarm and weekly medication adherence feedback report b) Partner feedback intervention: daily alarm and weekly medication adherence feedback report that was also shared with a medication adherence partner (family member, friend, peer) c) Control: electronic medication device with no alarms or feedback	Medication adherence: baseline; intervention; post-intervention a) individual feedback: 64%; 89%; 60% b) partner feedback: 71%; 86%; 52% c) control: 67%; 67%; 54%

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Reese (2016), USA [32]	Three- and four-arm randomized trials; sample size: 201, 200; 3 months; diabetic patients enrolled in a health care plan	Social influences and feedback	PROMOTE: a) Comparison intervention: weekly messages comparing the individual's statin adherence to that of other participants, with a message of encouragement b) Summary intervention: weekly summaries of that individual's statin adherence c) Control: no messages SUPPORT: a) daily message: daily reports to medication adherence partner (MAP) on medication taking behavior b) weekly message: weekly reports to MAP c) Missed dose message: reports to MAP only if dose was missed 4) Control: no reports	Adherence declined over time in all arms of both studies, including control arms.
Riesen (2008), Switzerland [38]	Multicentre cluster-randomized trial; sample size: 1002; 24 weeks; CVD patients in primary care	Reinforcement	a) Intervention: medication and compliance enhancement tools (starter pack containing a videotape and educational leaflets; newsletters at regular intervals and access to a helpline and website reinforcing initial message in starter pack) b) Control: medication only	Achievement of the 1998 European LDL-C goal (< 3.0 mmol/L) at week 24: a) intervention: 61% b) control: 67%
Russaw (2014), USA [25]	Quasi-experimental; sample size: 91; 1 month; hypertensive African American females	Message framing	Participants received either gain-framed or loss-framed text messages via a cellular phone text message every 2 days for one month	Adherence increased in both groups, but there was no significant difference between the 2 groups

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Shapiro (2014), USA [24]	Two-arm randomized trial; sample size: 207; 12 months; poor hypertensive Latino and African American adults	Financial incentives, lotteries and positive affect	a) Intervention: provision of a home BP monitor, monthly BP checks, "identity" intervention (personalized calendars with pictures of loved ones or activities and goals). $10 at months 1-6, an additional $5 per item if they brought their calendar and BP monitor. Lottery tickets at each visit (expected value: $7/ticket) for recording medication use, measuring BP and improved or normal BP. Payments for SBP and DBP improvement up to normalization of BP b) Control: provision of a home BP monitor and monthly BP checks only. $20 at each of months 1-6 if they returned for BP checks Both groups received $20/visit for BP checks at 9 and 12 months	Mean (SD) BP mmHg: baseline; 6 months a) intervention: 162.3(14.5)/91.6(14.2); 141.9(16.6)/81.1(13.9) b) control: 161.8(14.1)/88.7(12.8); 146.1(18.9)/80.4(15.0) SBP Control: 6 months; 12 months a) intervention: 57.1%; 39.5% b) control: 40.2%; 35.0% Medication adherence in intervention improved relative to control at 6 months
Volpp (2008), USA [34]	Single-arm pilot; sample size: 20; 3 months; patients on warfarin	Lottery financial incentives	Pilot 1: 2 in 5 chance of a $10 reward and 1 in 100 chance of a $100 reward ($5 daily expected value) Pilot 2: 1 in 10 chance of a $10 reward and 1 in 100 chance of a $100 reward ($3 daily expected value) Both: payment of winnings contingent on adherence; patients ineligible due to non-adherence were notified of lottery win; daily reminder chime was provided by the pill monitor	Proportion of out-of-range INRs (baseline; intervention): Pilot 1: 35.0%; 12.2%. Pilot 2: 65.0%. 40.4%. Not sustained post-intervention
Volpp (2015), USA [35]	Four-arm randomized trial; sample size: 337; 12 months; low income or disabled hypertensive adults	Financial incentives	a) Financial incentive (FI): incentive of $8 per medication prescription filled per month b) computerized behavioral intervention (CBI): provided at enrollment and at 6-month follow up c) Both FI and CBI d) Control: usual care	Arms were collapsed to compare subjects with incentive payments with those not receiving incentive payments: Change in BP from enrolment to 12 months: systolic; diastolic (mmHg) a) negative copay: − 13.7; − 6.8 b) Control: − 10; − 4.1

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Volpp (2017), USA [36]	Two-arm, randomized trial; sample size: 1509; 12 months; outpatients after a heart attack with health insurance	Lottery financial incentives, reminders, social support	a) Intervention: (1) up to 4 electronic pill bottles; (2) daily lottery incentives (1 in 5 chance of a $5 reward and a 1 in 100 chance of a $50 reward) based on medication adherence the previous day; (3) the option of enlisting a medication adherence partner; (4) access to social work resources; and (5) a staff engagement advisor to provide close monitoring, feedback, and reinforcement of adherence b) Control: usual care	Time to first readmission for a vascular event or death: Hazard Ratio, 1.04; 95% CI, 0.71–1.52; $P=0.84$
Wu (2012), USA [39]	Three-arm randomized trial; sample size: 82; 9 months; patients with chronic heart failure diagnosis	Counselling, feedback	a) MEMS PLUS: theory-based intervention (4 sessions of individualized teaching and counseling) plus feedback of medication-taking behavior from the MEMS (medication event monitoring system) at two intervention sessions b) MEMS LITE: theory-based intervention only c) Control: usual care	Adherence at baseline; 2 months; 9 months a) MEMS PLUS: 70%; 82%; 74% b) MEMS LITE: 59%; 69%; 65% c) control: 64%; 59%; 36%
HIV				
Alsan (2017), USA [55]	Two-arm pilot randomized trial with nonrandomized control; sample size: 110; 15 months; HIV patients taking ART	Financial incentives and commitment contracts	a) Provider visit incentive (PVI): $30 after attending each provider visit b) Incentive choice arm (IC): choice between provider visit incentive and commitment contract ($30 conditional on attending provider visit and meeting ART adherence threshold) c) Passive control arm (nonrandomized): usual care Incentives were provided for 4 visits only	Adjusted OR of viral suppression at 5th visit: IC vs PVI 1.57 (CI 0.25–9.92; *P* value 0.630); IC vs control 1.44 (CI 0.46–4.49; *P* value 0.52) Adjusted OR of viral suppression at 6th (unanticipated) visit : IC vs PVI 3.38 (CI 0.77–14.84; *P* value 0.107); IC vs control 3.93 (CI 1.19–13.04; *P* value 0.025)

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Cook (2015), USA [52]	Two-arm randomized cross-over trial; sample size: 45; 4 weeks; HIV patients taking ART with no current substance abuse	Tailored messages based on momentary psychological states (framing)	a) AB condition order: messages matched to psychological states were received first for two weeks, then mismatched messages were received for another two weeks b) BA condition order: mismatched messages were received first, then matched messages	Overall there was an increase in adherence, however there was no difference between the matched and mismatched messages
El-Sadr (2017), USA [56]	Two-arm site randomized trial; sample size: 9641; 24 months; HIV patients	Financial incentives	a) Financial incentive: participants received a $70 gift card at each routine quarterly clinic visit if viral load measurement was < 400 copies/mL b) Control: usual care	Mean change in % of patients with viral suppression (baseline-intervention): (SD) a) intervention: 11.5 (11.1) b) control: 3.7 (5.9)
Foster (2014), United Kingdom [51]	Single-arm pilot; sample size: 11; 12 months; adolescents with perinatally-acquired HIV	Financial incentives and motivational interviewing	Intervention: motivational interviewing at baseline and after ART initiation; £25 vouchers for each fall in viral load (VL) at 2 and 4 weeks, £50 when VL < 50 copies/mL, £25 if VL remained suppressed for 3 months, and then at 6 months, and £50 if VL remained < 50 copies/mL at 1 year. All vouchers were also contingent on attending motivational interviewing	Median CD4; median VL; mean CD4 gain Baseline: 30; 12900; NA 12 months: 140; 105; 90 24 months: 75; < 50; 122
Javanbakht (2006), USA [48]	Two-arm randomized trial; sample size: 90; 48 weeks; HIV patients taking ART	Case management, financial incentives and reinforcement	a) Intervention: adherence case management (an education program, individualized planning of regimen, the use of adherence aids and devices, and referrals to psychosocial services as necessary) with financial incentives for decreases in viral load b) Control: usual care	Proportion of patients with ≥ 10-fold (1−log10) decrease in viral load at weeks 12, 24, and 48: a) intervention: 55.3%; 44.7%; 55.3% b) control: 32.6%; 25.6%; 27.9%

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Metsch (2016), USA [54]	Three-arm randomized trial; sample size: 537; 6 months; HIV positive drug users	Financial incentives and navigation support	a) Navigation only: up to 11 sessions with a patient navigator using a strengths-based case management approach to (1) coordinate care with clinicians; (2) review health information; (3) overcome personal or logistical challenges; and (4) provide psychosocial support directly b) Navigation and incentives: as per navigation only arm plus financial incentives for 7 target behaviors including having an active prescription for ART and for viral load reductions and suppression c) Control: usual care	Viral suppression at 12 months: a) navigation only: 41.0% b) navigation + incentives: 43.6% c) control: 38.6%
Moore (2015), USA [53]	Single-arm pilot; sample size: 10; 12 weeks; HIV positive drug users	Cognitive behavioral therapy (CBT), financial incentives and positive messages	Financial incentives for medication adherence and CBT: Escalating continuous payments for weeks 1–6 ($384 possible), followed by tapering, variable interval payments for weeks 7–12 ($150 possible). An automated, positively-framed text message was sent including the amount earned for that day 12 CBT sessions provided over 12 weeks. Participants received payments for session attendance ($260 possible) Participants were compensated for assessments	Medication adherence: Baseline = 80.7% 12 weeks = 93.2%

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Rigsby (2000), USA [47]	Three-arm randomized trial; sample size: 55; 4 weeks; HIV patients	Cue-dose training alone, or with financial incentives	a) Cue-dose training (CD): 4 weekly sessions to support linkage of medication-taking to daily habits and feedback on previous week's adherence b) cue-dose training and cash reinforcement (CD + CR): 4 weekly sessions of cue-dose training and feedback and an escalating financial incentive contingent on adherence c) control: 4 weekly sessions of non-directive inquiries about adherence All participants were compensated for study visits	Mean adherence in the CD + CR group was significantly higher than the control group ($z = 3.5$, $P = 0.0005$), no difference between the CD group and control group. Results were not sustained during follow-up period.
Rosen (2007), USA [49]	Two-arm randomized trial; sample size: 56; 16 weeks; HIV positive drug users	Counselling, lottery financial incentives and feedback	a) Intervention: optional weekly counselling with feedback given on medication-taking behavior; adherence reports to providers; incentives for adherence (cards in a bowl with a chance to win prizes (26.7% chance to earn per $1.00 card, a 7.6% chance for $20.00, and a 0.2% chance of earning $100.00)); counselling for substance abuse and toxicology tests; adherence feedback to providers b) control: optional weekly supportive counselling session ("attention-control" condition) All participants were compensated for study participation	% adherence at baseline, intervention, follow-up: mean (SD) a) intervention: 61 (26), 76 (22), 61 (32) b) control: 59 (29), 44 (27), 46 (27)

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Sorenson (2007), USA [50]	Two-arm randomized trial; sample size: 66; 12 weeks; HIV positive drug users	Coaching and financial incentives	a) Voucher intervention: medication coaching every 2 weeks and vouchers with bonus and reset contingencies for pill bottle openings b) Comparison intervention: medication coaching every 2 weeks only. A fishbowl prize system, not contingent on adherence, was introduced to promote retention in the study Follow up phase: medication coaching continued, but vouchers were discontinued All participants were compensated for study participation	On-time pill bottle openings—baseline; intervention; follow-up (% adherence, SD) a) voucher: 50.1 (17.21); 77.6 (17.49); 66.0 (23.91) b) comparison: 51.9 (19.99); 55.5 (23.09); 53.1 (29.22) No improvements in physical health
Renal diseases				
Reese (2015), USA [33]	Three-arm randomized trial; sample size: 36; 10 weeks; patients receiving chronic hemodialysis in urban hemodialysis centers	Lottery financial incentives and messages to stimulate regret aversion; coaching	a) Financial incentives: participants could receive $10 and an entry into a lottery (1 in 5 chance at $50 reward) for lowering their PO4 below 5.5 mg/dL or 0.5 mg/dL from the previous PO4 value. A note with a message designed to stimulate regret aversion was included for patients who did not qualify b) Coaching: initial in-person interview with a dietician coach; thereafter contact at least 3 times per week offering education and practical suggestions on diet, and methods for remembering to take PO4 binders c) Control: usual care	Median change in PO4 (baseline-final value): IQR a) financial incentives: − 0.60 (− 1.8, 0.70) b) coaching: − 0.80 (− 1.15, 0.2) c) control: − 0.45 (− 1.2, 0.50) *P* value: 0.87

Table 2 (continued)

Author, year, location	Study design, sample size, duration, patient population	Strategy	Program details	Primary outcome
Reese (2017), USA [31]	Three-arm randomized trial; sample size: 120; 6 months; kidney or kidney-pancreas transplant recipients	Automated reminders with or without provider notification	a) Reminders group: a wireless pill bottle lit up and chimed when medication was due and optional additional reminders (texts, phone calls with recorded messages or e-mails with weekly adherence summaries) b) Reminders + notification group: reminders as per reminders group plus notifications to participant's transplant nephrologist and transplantation coordinator if adherence < 90% c) Control: wireless pill bottle only with no alerts	Mean adherence in the last 90 days of trial a) reminders group: 78% b) reminders + notification group: 88% c) control: 55%

studies combined reminders with other interventions, which makes it difficult to disentangle the effects of each component. Reminders, in the form of text messages or smartphone apps, are an effective and potentially low-cost intervention to improving medication adherence [62, 63]. Future research could leverage these technologies to provide more personalized support to patients, tailoring the content of messages to incorporate patient beliefs [64, 65]. In addition, other behavioral economic concepts such as regret aversion could inform the content of messages [66]. Furthermore, newer technologies such as electronic pill bottles and ingestible sensors could be used to only trigger messages when doses have been missed, thereby avoiding alert fatigue [67]. Currently, these technologies are costly to implement, but as with most technologies, costs should decrease over time.

Studies that targeted patients presumed to be non-adherent were more likely to be effective than studies that did not target non-adherent patients. Targeting was generally done through biological measures such as high blood pressure or low CD4 counts. The importance of targeting was also illustrated by the observation of stronger effects in subpopulations with poor baseline adherence in studies that did not specifically target non-adherent patients [29, 56]. Unsurprisingly, studies that had high baseline adherence showed no effect of the intervention on medication adherence or biological measures [32, 38, 40, 53]. The studies in this review that either explicitly identified reasons for non-adherence as part of the intervention [37, 48] or were able to indirectly determine reasons for non-adherence through counseling or coaching [39, 49, 50], including motivational interviewing [51, 54] or cognitive behavioral therapy [53], were able to significantly improve medication adherence. These studies also included financial incentives [49–51, 53, 54], feedback [37, 39], or reinforcement strategies such as positively framed text messages [53]. Because of the complexity of medication adherence and the range of barriers that patients experience [68], in addition to targeting non-adherent patients based on biological measures, future studies should also aim to understand the reasons for non-adherence and tailor interventions accordingly [69].

In those studies that had extended follow-up periods, many of the positive effects found at the end of the intervention period were not sustained [24, 30, 47, 49, 50, 54]. This highlights the issue of the long-term feasibility of interventions, particularly interventions that use financial incentives. One possibility to address this would be a multi-component intervention that provides financial incentives to increase the uptake of other effective components of the intervention for long enough to encourage long-term habit formation. Research on the impact of incentives on habit formation is mixed however and further studies are warranted, particularly in medication adherence [70–72]. Commitment contracts have shown potential at improving adherence both in

medication adherence [55] and for other health behaviors [7, 73, 74] and may be a cost-effective method of sustaining behaviors initiated by financial incentives.

A methodological issue highlighted by this review was the importance of measuring not only medication adherence, but also clinical outcomes. Some studies demonstrated an improvement in medication adherence; however, biological measures did not improve [28, 31, 37, 47, 50]. The authors provided the following reasons for this: (1) small sample size and/or short duration [37, 50]; (2) treatment regimens were not optimized, thus maximum effects from the prescribed regimen had been achieved [47]; (3) the selected biological measures were unable to capture the effects of adherence [31]; and (4) other factors such as diet and drug interactions may have reduced the effects of better adherence [28].

We note that a large number of studies originate from researchers at one university. The results of these studies were mixed and although no methodological appraisal of studies was undertaken, these were randomized studies with large samples sizes. Furthermore, most of the studies were conducted in the USA, and the results may therefore not be transferable to other health systems.

This review has limitations. As behavioral economics is a field that employs concepts and theories from both psychology and economics, it is difficult to define. The authors therefore had to use their own understanding of the field to determine inclusion criteria. The aim of the review was to keep the search broad to be able to inform the development of potential interventions, and this may have resulted in the inclusion of terms that readers may not consider as strictly behavioral economics. As we extracted data, we came across other variations of included terms (e.g., behavioral adherence contracts) that were not included in the original search. A brief search of these terms did not provide additional citations.

5 Conclusions

Behavioral economic informed interventions show promise in terms of improving medication adherence. However, there is no single simple intervention that can improve adherence. Adherence is a complex issue and the findings from this review demonstrate that multi-faceted interventions tailored to patient needs are required. This review highlighted the potential importance of targeting non-adherent patients, understanding their reasons for non-adherence, providing reminders and feedback to patients and physicians, and measuring clinical outcomes in addition to medication adherence. The evidence base needs to be strengthened through research undertaken in different health systems, with study designs able to identify the most effective components of interventions.

Author Contributions JR made substantial contributions to the conception and design, acquisition, analysis, and interpretation of data, and was involved in drafting the final manuscript. GH and NS made substantial contributions to the conception and interpretation of data, and were involved in drafting the final manuscript. JK made substantial contributions to the conception and design, analysis, and interpretation of data, and was involved in drafting the final manuscript. All authors read and approved the final manuscript. JR is the overall guarantor.

Data Availability The data generated or analyzed during this study are included in this published article and the Electronic Supplementary Material.

Compliance with Ethical Standards

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Conflict of interest Jacqueline Roseleur, Gillian Harvey, Nigel Stocks, and Jonathan Karnon have no conflicts of interest that are directly relevant to the content of this article.

Ethics Approval As this scoping review uses data available in the public domain, no ethics application was required.

References

1. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. Am J Med. 2012;125(9):882–7. https://doi.org/10.1016/j.amjmed.2011.12.013.
2. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008;336(7653):1114–7. https://doi.org/10.1136/bmj.39553.670231.25.
3. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, et al. Interventions for enhancing medication adherence. Cochrane Database Syst Rev. 2014. https://doi.org/10.1002/14651858.cd000011.pub4.
4. Halpern SD, French B, Small DS, Saulsgiver K, Harhay MO, Audrain-McGovern J, et al. Randomized trial of four financial-incentive programs for smoking cessation. N Engl J Med. 2015;372(22):2108–17. https://doi.org/10.1056/NEJMoa1414293.
5. Mitchell MS, Goodman JM, Alter DA, John LK, Oh PI, Pakosh MT, et al. Financial incentives for exercise adherence in adults: systematic review and meta-analysis. Am J Prev Med. 2013;45(5):658–67. https://doi.org/10.1016/j.amepre.2013.06.017.
6. Patel MS, Volpp KG, Rosin R, Bellamy SL, Small DS, Fletcher MA, et al. A randomized trial of social comparison feedback and financial incentives to increase physical activity. Am J Health Promot. 2016;30(6):416–24. https://doi.org/10.1177/0890117116658195.
7. van der Swaluw K, Lambooij MS, Mathijssen JJP, Schipper M, Zeelenberg M, Berkhout S, et al. Commitment lotteries promote physical activity among overweight adults: a cluster randomized trial. Ann Behav Med. 2018;52(4):342–51. https://doi.org/10.1093/abm/kax017.

8. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. JAMA. 2007;298(20):2415–7. https://doi.org/10.1001/jama.298.20.2415.
9. Ariely D. Predictably irrational. New York: Harper Collins; 2008.
10. O'Donoghue T, Rabin M. Doing it now or later. Am Econ Rev. 1999;89(1):103–24. https://doi.org/10.1257/aer.89.1.103.
11. Kullgren JT, Hafez D, Fedewa A, Heisler M. A scoping review of behavioral economic interventions for prevention and treatment of type 2 diabetes mellitus. Curr Diabetes Rep. 2017;17(9):73. https://doi.org/10.1007/s11892-017-0894-z.
12. Roseleur J, Harvey G, Stocks N, Karnon J. Behavioral economic insights to improve medication adherence in adults with chronic conditions: a scoping review protocol. JBI Database System Rev Implement Rep. 2019. https://doi.org/10.11124/jbisrir-2017-003971.
13. Peters MD, Godfrey CM, McInerney P, Soares CB, Khalil H, Parker D. Chapter 11: Scoping Reviews. In: Aromataris E, Munn Z (Editors). Joanna Briggs Institute reviewers' manual. The Joanna Briggs Institute, 2017. Available from https://reviewersmanual.joannabriggs.org/
14. Tricco AC, Lillie E, Zarin W, O'Brien KK, Colquhoun H, Levac D, et al. PRISMA Extension for Scoping Reviews (PRISMA-ScR): checklist and explanation. Ann Intern Med. 2018;169(7):467–73. https://doi.org/10.7326/m18-0850.
15. Lee JL, Maciejewski M, Raju S, Shrank WH, Choudhry NK. Value-based insurance design: quality improvement but no cost savings. Health Aff (Millwood). 2013;32(7):1251–7. https://doi.org/10.1377/hlthaff.2012.0902.
16. Sensharma A, Yabroff KR. Do interventions that address patient cost-sharing improve adherence to prescription drugs? A systematic review of recently published studies. Expert Rev Pharmacoecon Outcomes Res. 2019;19(3):263–77. https://doi.org/10.1080/14737167.2019.1567335.
17. Schwebel FJ, Larimer ME. Using text message reminders in health care services: a narrative literature review. Internet Interv. 2018;13:82–104. https://doi.org/10.1016/j.invent.2018.06.002.
18. Vervloet M, Linn AJ, van Weert JC, de Bakker DH, Bouvy ML, van Dijk L. The effectiveness of interventions using electronic reminders to improve adherence to chronic medication: a systematic review of the literature. J Am Med Inf Assoc. 2012;19(5):696–704. https://doi.org/10.1136/amiajnl-2011-000748.
19. Aromataris E, Riitano D. Constructing a search strategy and searching for evidence: a guide to the literature search for a systematic review. Am J Nurs. 2014;114(5):49–56. https://doi.org/10.1097/01.NAJ.0000446779.99522.f6.
20. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS peer review of electronic search strategies: 2015 guideline statement. J Clin Epidemiol. 2016;75:40–6. https://doi.org/10.1016/j.jclinepi.2016.01.021.
21. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan: a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210. https://doi.org/10.1186/s13643-016-0384-4.
22. Covidence systematic review software, Veritas Health Innovation, Melbourne, Australia. Available at https://www.covidence.org
23. Jiang J, Smith-Ray R, Taitel MS, Hou JG, Singh T, Orr G. The association between medication self-monitoring using an incentivized digital health program and claims-based medication adherence. Value Health. 2018;21:S110. https://doi.org/10.1016/j.jval.2018.04.746.
24. Shapiro MF, Shu SB, Goldstein NJ, Fox CR, Villa ES, Flores M, et al. Impact of a behavioral economics intervention on control of hypertension among very poor, predominantly minority adults: a randomized trial. J Gen Intern Med. 2014;29:S116–7.
25. Russaw A, Abrahamson T, Mack, C, Dinuit V, Glivings M, Nnadozie N (2014). Message framing utilization in hypertension research with African American Women, ProQuest Dissertations and Theses.
26. Asch DA, Troxel AB, Stewart WF, Sequist TD, Jones JB, Hirsch AG, et al. Effect of financial incentives to physicians, patients, or both on lipid levels: a randomized clinical trial. JAMA. 2015;314(18):1926–35. https://doi.org/10.1001/jama.2015.14850.
27. Kessler JB, Troxel AB, Asch DA, Mehta SJ, Marcus N, Lim R, et al. Partners and alerts in medication adherence: a randomized clinical trial. J Gen Intern Med. 2018;33(9):1536–42.
28. Kimmel SE, Troxel AB, French B, Loewenstein G, Doshi JA, Hecht TE, et al. A randomized trial of lottery-based incentives and reminders to improve warfarin adherence: the Warfarin Incentives (WIN2) Trial. Pharmacoepidemiol Drug Saf. 2016;25(11):1219–27. https://doi.org/10.1002/pds.4094.
29. Kimmel SE, Troxel AB, Loewenstein G, Brensinger CM, Jaskowiak J, Doshi JA, et al. Randomized trial of lottery-based incentives to improve warfarin adherence. Am Heart J. 2012;164(2):268–74. https://doi.org/10.1016/j.ahj.2012.05.005.
30. Reddy A, Huseman TL, Canamucio A, Marcus SC, Asch DA, Volpp K, et al. Patient and partner feedback reports to improve statin medication adherence: a randomized control trial. J Gen Intern Med. 2017;32(3):256–61. https://doi.org/10.1007/s11606-016-3858-0.
31. Reese PP, Bloom RD, Trofe-Clark J, Mussell A, Leidy D, Levsky S, et al. Automated reminders and physician notification to promote immunosuppression adherence among kidney transplant recipients: a randomized trial. Am J Kidney Dis. 2017;69(3):400–9. https://doi.org/10.1053/j.ajkd.2016.10.017.
32. Reese PP, Kessler JB, Doshi JA, Friedman J, Mussell AS, Carney C, et al. Two randomized controlled pilot trials of social forces to improve statin adherence among patients with diabetes. J Gen Intern Med. 2016;31(4):402–10. https://doi.org/10.1007/s11606-015-3540-y.
33. Reese PP, Mgbako O, Mussell A, Potluri V, Yekta Z, Levsky S, et al. A pilot randomized trial of financial incentives or coaching to lower serum phosphorus in dialysis patients. J Ren Nutr. 2015;25(6):510–7. https://doi.org/10.1053/j.jrn.2015.06.001.
34. Volpp K, Loewenstein G, Troxel A, Doshi J, Price M, Laskin M, et al. A test of financial incentives to improve warfarin adherence. BMC Health Serv Res. 2008;8:272. https://doi.org/10.1186/1472-6963-8-272.
35. Volpp KG, Troxel AB, Long JA, Ibrahim SA, Appleby D, Smith JO, et al. A randomized controlled trial of negative co-payments: the CHORD trial. Am J Manag Care. 2015;21(8):e465–73.
36. Volpp KG, Troxel AB, Mehta SJ, Norton L, Zhu J, Lim R, et al. Effect of electronic reminders, financial incentives, and social support on outcomes after myocardial infarction: the HeartStrong randomized clinical trial. JAMA Intern Med. 2017;177(8):1093–101. https://doi.org/10.1001/jamainternmed.2017.2449.
37. Choudhry NK, Isaac T, Lauffenburger JC, Gopalakrishnan C, Lee M, Vachon A, et al. Effect of a remotely delivered tailored multicomponent approach to enhance medication taking for patients with hyperlipidemia, hypertension, and diabetes: the STIC2IT cluster randomized clinical trial. JAMA Intern Med. 2018;178(9):1182–9. https://doi.org/10.1001/jamainternmed.2018.3189.
38. Riesen WF, Noll G, Dariolo R. Impact of enhanced compliance initiatives on the efficacy of rosuvastatin in reducing low density lipoprotein cholesterol levels in patients with primary hypercholesterolaemia. Swiss Med Wkly. 2008;138(29–30):420–6.
39. Wu JR, Corley DJ, Lennie TA, Moser DK. Effect of a medication-taking behavior feedback theory-based intervention on outcomes in patients with heart failure. J Card Fail. 2012;18(1):1–9. https://doi.org/10.1016/j.cardfail.2011.09.006.
40. Garza KB, Owensby JK, Braxton Lloyd K, Wood EA, Hansen RA. Pilot study to test the effectiveness of different financial

incentives to improve medication adherence. Ann Pharmacother. 2016;50(1):32–8. https://doi.org/10.1177/1060028015609354.
41. Davidson TM, McGillicuddy J, Mueller M, Brunner-Jackson B, Favella A, Anderson A, et al. Evaluation of an mHealth medication regimen self-management program for African American and Hispanic uncontrolled hypertensives. J Pers Med. 2015;5(4):389–405. https://doi.org/10.3390/jpm5040389.
42. Petry NM, Alessi SM, Byrne S, White WB. Reinforcing adherence to antihypertensive medications. J Clin Hypertens (Greenwich). 2015;17(1):33–8. https://doi.org/10.1111/jch.12441.
43. Boutin-Foster C, Offidani E, Kanna B, Ogedegbe G, Ravenell J, Scott E, et al. Results from the trial using motivational interviewing, positive affect, and self-affirmation in African Americans with hypertension (TRIUMPH). Ethn Dis. 2016;26(1):51–60. https://doi.org/10.18865/ed.26.1.51.
44. Frias J, Virdi N, Raja P, Kim Y, Savage G, Osterberg L. Effectiveness of digital medicines to improve clinical outcomes in patients with uncontrolled hypertension and type 2 diabetes: prospective, open-label, cluster-randomized pilot clinical trial. J Med Internet Res. 2017;19(7):e246. https://doi.org/10.2196/jmir.7833.
45. Kranker K. The efficacy of using financial incentives to change unhealthy behaviors among a rural chronically ill and uninsured population. Am J Health Promot. 2018;32(2):301–11. https://doi.org/10.1177/0890117117696621.
46. Raiff BR, Jarvis BP, Dallery J. Text-message reminders plus incentives increase adherence to antidiabetic medication in adults with type 2 diabetes. J Appl Behav Anal. 2016;49(4):947–53. https://doi.org/10.1002/jaba.337.
47. Rigsby MO, Rosen MI, Beauvais JE, Cramer JA, Rainey PM, O'Malley SS, et al. Cue-dose training with monetary reinforcement: pilot study of an antiretroviral adherence intervention. J Gen Intern Med. 2000;15(12):841–7.
48. Javanbakht M, Prosser P, Grimes T, Weinstein M, Farthing C. Efficacy of an individualized adherence support program with contingent reinforcement among nonadherent HIV-positive patients: results from a randomized trial. J Int Assoc Physicians AIDS Care (Chic). 2006;5(4):143–50. https://doi.org/10.1177/1545109706291706.
49. Rosen MI, Dieckhaus K, McMahon TJ, Valdes B, Petry NM, Cramer J, et al. Improved adherence with contingency management. AIDS Patient Care STDS. 2007;21(1):30–40. https://doi.org/10.1089/apc.2006.0028.
50. Sorensen JL, Haug NA, Delucchi KL, Gruber V, Kletter E, Batki SL, et al. Voucher reinforcement improves medication adherence in HIV-positive methadone patients: a randomized trial. Drug Alcohol Depend. 2007;88(1):54–63. https://doi.org/10.1016/j.drugalcdep.2006.09.019.
51. Foster C, McDonald S, Frize G, Ayers S, Fidler S. "Payment by results": financial incentives and motivational interviewing, adherence interventions in young adults with perinatally acquired HIV-1 infection: a pilot program. AIDS Patient Care STDS. 2014;28(1):28–32. https://doi.org/10.1089/apc.2013.0262.
52. Cook PF, Carrington JM, Schmiege SJ, Starr W, Reeder B. A counselor in your pocket: feasibility of mobile health tailored messages to support HIV medication adherence. Patient Prefer Adherence. 2015;9:1353–66. https://doi.org/10.2147/ppa.S88222.
53. Moore BA, Rosen MI, Wang Y, Shen J, Ablondi K, Sullivan A, et al. A remotely-delivered CBT and contingency management therapy for substance using people with HIV. AIDS Behav. 2015;19(Suppl. 2):156–62. https://doi.org/10.1007/s10461-014-0990-x.
54. Metsch LR, Feaster DJ, Gooden L, Matheson T, Stitzer M, Das M, et al. Effect of patient navigation with or without financial incentives on viral suppression among hospitalized patients with HIV infection and substance use: a randomized clinical trial. JAMA. 2016;316(2):156–70. https://doi.org/10.1001/jama.2016.8914.
55. Alsan M, Beshears J, Armstrong WS, Choi JJ, Madrian BC, Nguyen MLT, et al. A commitment contract to achieve virologic suppression in poorly adherent patients with HIV/AIDS. AIDS. 2017;31(12):1765–9. https://doi.org/10.1097/qad.0000000000001543.
56. El-Sadr WM, Donnell D, Beauchamp G, Hall HI, Torian LV, Zingman B, et al. Financial incentives for linkage to care and viral suppression among HIV-positive patients: a randomized clinical trial (HPTN 065). JAMA Intern Med. 2017;177(8):1083–92. https://doi.org/10.1001/jamainternmed.2017.2158.
57. Volpp KG, John LK, Troxel AB, Norton L, Fassbender J, Loewenstein G. Financial incentive-based approaches for weight loss: a randomized trial. JAMA. 2008;300(22):2631–7. https://doi.org/10.1001/jama.2008.804.
58. Kullgren JT, Troxel AB, Loewenstein G, Asch DA, Norton LA, Wesby L, et al. Individual- versus group-based financial incentives for weight loss: a randomized, controlled trial. Ann Intern Med. 2013;158(7):505–14. https://doi.org/10.7326/0003-4819-158-7-201304020-00002.
59. Thangada ND, Garg N, Pandey A, Kumar N. The emerging role of mobile-health applications in the management of hypertension. Curr Cardiol Rep. 2018;20(9):78. https://doi.org/10.1007/s11886-018-1022-7.
60. Zaugg V, Korb-Savoldelli V, Durieux P, Sabatier B. Providing physicians with feedback on medication adherence for people with chronic diseases taking long-term medication. Cochrane Database Syst Rev. 2018. https://doi.org/10.1002/14651858.cd012042.pub2.
61. Conn VS, Ruppar TM, Chase JA, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: systematic review and meta-analysis. Curr Hypertens Rep. 2015;17(12):94. https://doi.org/10.1007/s11906-015-0606-5.
62. Thakkar J, Kurup R, Laba TL, Santo K, Thiagalingam A, Rodgers A, et al. Mobile telephone text messaging for medication adherence in chronic disease: a meta-analysis. JAMA Intern Med. 2016;176(3):340–9. https://doi.org/10.1001/jamainternmed.2015.7667.
63. Orr JA, King RJ. Mobile phone SMS messages can enhance healthy behaviour: a meta-analysis of randomised controlled trials. Health Psychol Rev. 2015;9(4):397–416. https://doi.org/10.1080/17437199.2015.1022847.
64. Petrie KJ, Perry K, Broadbent E, Weinman J. A text message programme designed to modify patients' illness and treatment beliefs improves self-reported adherence to asthma preventer medication. Br J Health Psychol. 2012;17(1):74–84. https://doi.org/10.1111/j.2044-8287.2011.02033.x.
65. Gatwood J, Hohmeier KC, Brooks IM. Beyond the reminder: the next steps in pharmacist-driven, mHealth patient engagement. J Am Pharm Assoc (2003). 2019;59(2S):S21–4. https://doi.org/10.1016/j.japh.2018.10.003.
66. Brewer NT, DeFrank JT, Gilkey MB. Anticipated regret and health behavior: a meta-analysis. Health Psychol. 2016;35(11):1264–75. https://doi.org/10.1037/hea0000294.
67. Amankwaa I, Boateng D, Quansah DY, Akuoko CP, Evans C. Effectiveness of short message services and voice call interventions for antiretroviral therapy adherence and other outcomes: a systematic review and meta-analysis. PLoS One. 2018;13(9):e0204091. https://doi.org/10.1371/journal.pone.0204091.
68. AlGhurair SA, Hughes CA, Simpson SH, Guirguis LM. A systematic review of patient self-reported barriers of adherence to antihypertensive medications using the world health organization multidimensional adherence model. J Clin Hypertens

(Greenwich). 2012;14(12):877–86. https://doi.org/10.1111/j.1751-7176.2012.00699.x.

69. Conn VS, Ruppar TM, Enriquez M, Cooper P. Medication adherence interventions that target subjects with adherence problems: systematic review and meta-analysis. Res Soc Adm Pharm. 2016;12(2):218–46. https://doi.org/10.1016/j.sapharm.2015.06.001.
70. Carrera M, Royer H, Stehr M, Sydnor J. Can financial incentives help people trying to establish new habits? Experimental evidence with new gym members. J Health Econ. 2018;58:202–14. https://doi.org/10.1016/j.jhealeco.2018.02.010.
71. Loewenstein G, Price J, Volpp K. Habit formation in children: evidence from incentives for healthy eating. J Health Econ. 2016;45:47–54. https://doi.org/10.1016/j.jhealeco.2015.11.004.
72. Strohacker K, Galarraga O, Williams DM. The impact of incentives on exercise behavior: a systematic review of randomized controlled trials. Ann Behav Med. 2014;48(1):92–9. https://doi.org/10.1007/s12160-013-9577-4.
73. Kulendran M, King D, Schmidtke KA, Curtis C, Gately P, Darzi A, et al. The use of commitment techniques to support weight loss maintenance in obese adolescents. Psychol Health. 2016;31(11):1332–41. https://doi.org/10.1080/08870446.2016.1204452.
74. Lesser LI, Thompson CA, Luft HS. Association between monetary deposits and weight loss in online commitment contracts. Am J Health Promot. 2018;32(1):198–204. https://doi.org/10.1177/0890117116661157.

7.5.1 Online supplementary material

Table S1 PubMed search strategy

#	TERM	SEARCH TERMS
1	Adherence	"Medication Adherence"[Mesh] OR (adherence[Title/Abstract] OR complian*[Title/Abstract] OR nonadherence[Title/Abstract] OR non-adherence [Title/Abstract] OR adherent[Title/Abstract] OR non-adherent[Title/Abstract] OR nonadherent[Title/Abstract] OR non-complian*[Title/Abstract] OR noncomplian*[Title/Abstract] OR concordan*[Title/Abstract] OR nonconcordan*[Title/Abstract] OR persistence [Title/Abstract] OR non-persistence[Title/Abstract] OR "Self-Management"[Mesh] OR self-management[Title/Abstract] or self-care[Title/Abstract])
2	Medication	"Prescription Drugs"[Mesh] OR medicine*[Title/Abstract] OR medication*[Title/Abstract] OR drug*[Title/Abstract] OR therap*[Title/Abstract] OR treatment*[Title/Abstract] OR pharmaceutical*[Title/Abstract] OR pill*[Title/Abstract] OR tablet*[Title/Abstract]
3	Medication Adherence	#1 AND #2
4	Behavioral Economics	"Economics, Behavioral"[Mesh] OR behavioral economic*[Text Word] OR behavioural economic*[Text Word] OR behavioural economic*[Title/Abstract] OR behavioral economic*[Title/Abstract] OR anchor*[Title/Abstract] OR choice architecture[Title/Abstract] OR confirmation bias*[Title/Abstract] OR default*[Title/Abstract] OR framing[Title/Abstract] OR framed[Title/Abstract] OR priming[Title/Abstract] OR intertemporal choice[Title/Abstract] OR inter-temporal choice[Title/Abstract] OR messenger*[Title/Abstract] OR present bias*[Title/Abstract] OR incentive*[Title/Abstract] OR loss aversion[Title/Abstract] OR endowment effect*[Title/Abstract] OR regret aversion[Title/Abstract] OR reference dependence[Title/Abstract] OR mental accounting[Title/Abstract] OR nudg*[Title/Abstract] OR partitioning[Title/Abstract] OR social norm*[Title/Abstract] OR social proof[Title/Abstract] OR social preference*[Title/Abstract] OR status quo bias*[Title/Abstract] OR inertia[Title/Abstract] OR choice overload[Title/Abstract] OR decision fatigue[Title/Abstract] OR time discount*[Title/Abstract] OR hyperbolic discount*[Title/Abstract] OR time inconsistent

#	TERM	SEARCH TERMS
		preference*[Title/Abstract] OR time inconsistency[Title/Abstract] OR commitment device*[Title/Abstract] OR commitment contract*[Title/Abstract] OR commitment consistency[Title/Abstract] OR precommitment*[Title/Abstract] OR ego effect[Title/Abstract] OR temptation bundl*[Title/Abstract] OR reinforcement*[Title/Abstract] OR gamification[Title/Abstract] OR gaming[Title/Abstract] OR game-based[Title/Abstract] OR libertarian paternalism[Title/Abstract] OR prospect theory[Title/Abstract] OR bounded selfishness[Title/Abstract] OR unbounded selfishness[Title/Abstract] OR bounded rational*[Title/Abstract] OR unbounded rational*[Title/Abstract] OR limited rational*[Title/Abstract] OR bounded willpower[Title/Abstract] OR unbounded willpower[Title/Abstract] OR affect heuristic*[Title/Abstract] OR representativeness heuristic*[Title/Abstract] OR availability heuristic*[Title/Abstract] OR overconfidence[Title/Abstract] OR optimism bias*[Title/Abstract] OR limited attention[Title/Abstract] OR mere-measurement[Title/Abstract] OR question-behaviour effect[Title/Abstract] OR hindsight bias*[Title/Abstract] OR knew-it-all-along effect[Title/Abstract] OR salience[Title/Abstract]
5	Medication Adherence AND Behavioral Economics	#3 AND #4
6	Cardiovascular disease	"Cardiovascular Diseases"[Mesh:noexp] OR cardiovascular disease*[Title/Abstract] OR CVD[Title/Abstract] OR "Heart Diseases"[Mesh] OR heart disease*[Title/Abstract] OR “coronary artery disease*”[Title/Abstract] OR "Dyslipidemias"[Mesh] OR dyslipidemia*[Title/Abstract] OR dyslipidaemia*[Title/Abstract] OR hyperlipidemia*[Title/Abstract] OR hyperlipidaemia*[Title/Abstract] OR hypercholesterolemia*[Title/Abstract] OR hypercholesterolaemia*[Title/Abstract] OR "Arteriosclerosis"[Mesh] OR arteriosclerosis[Title/Abstract] OR arterioscleroses[Title/Abstract] OR atherosclerosis[Title/Abstract] OR atheroscleroses[Title/Abstract]
7	Hypertension	"Hypertension"[Mesh] OR hypertension[Title/Abstract] OR blood pressure*[Title/Abstract] OR diastolic[Title/Abstract]

#	TERM	SEARCH TERMS
		OR systolic[Title/Abstract] OR hypertensive[Title/Abstract] OR antihypertensive[Title/Abstract] OR anti-hypertensive[Title/Abstract]
8	Diabetes Type 2	"Diabetes Mellitus, Type 2"[Mesh] OR diabetes[Title/Abstract] OR diabetic*[Title/Abstract] OR "Hyperglycemia"[Mesh] OR hyperglycemia*[Title/Abstract] OR hyperglycaemia*[Title/Abstract] OR glucose intolerance*[Title/Abstract] OR glucose tolerance*[Title/Abstract]
9	HIV	"HIV"[Mesh] OR Human Immunodeficiency Virus*[Title/Abstract] OR Human Immuno-deficiency Virus*[Title/Abstract] OR HIV[Title/Abstract] OR AIDS[Title/Abstract] OR Acquired Immune Deficiency Syndrome*[Title/Abstract]
10	Chronic Kidney Disease	"Renal Insufficiency, Chronic"[Mesh] OR (chronic kidney disease*[Title/Abstract] OR chronic kidney disorder*[Title/Abstract] OR chronic kidney insufficienc*[Title/Abstract] OR chronic nephropathy*[Title/Abstract] OR chronic renal disease*[Title/Abstract] OR chronic renal failure*[Title/Abstract] OR chronic renal insufficienc*[Title/Abstract] OR kidney chronic failure*[Title/Abstract])
11	Chronic Diseases	"Chronic Disease"[Mesh] OR chronic[Text Word] OR chronic[Title/Abstract]
12	All Diseases	#6 OR #7 OR #8 OR #9 OR #10 OR #11
13	Medication Adherence AND Behavioral Economics AND Chronic Diseases	#5 AND #12

Part V

Conclusions and Recommendations

Chapter 8

Conclusions and recommendations

This research investigated the management of hypertension in general practice, the costs associated with current hypertension control and the evidence on interventions informed by behavioural economics to address medication adherence. The principal findings, contributions and recommendations for further research are presented in this concluding chapter.

The findings from this thesis are expected to inform the design of cost-effective interventions to improve blood pressure (BP) control in Australia by identifying target patient groups for intervention and providing data for early economic evaluations, thereby contributing to improved health outcomes for patients and better efficiency for the health care system.

8.1 Principal findings

Blood pressure control in Australian general practice

Of the approximately 40% of patients diagnosed with hypertension, only 55% had their BP controlled, despite 59% of patients having been prescribed antihypertensive therapy. BP control was slightly lower in females compared with males, and among those aged at least 80 years, but there were no differences by socioeconomic status. In general, the prevalence of hypertension control ranged between 50% and 56% across all groups, independent of the time since diagnosis or the number of classes of antihypertensive medications prescribed. However, patients with a recent hypertension diagnosis (6-12 months) with no record of

being prescribed antihypertensive medications were less likely to have their BP controlled (44% of patients) than those on antihypertensive medication (51%-53%). Patients with a recent diagnosis were also less likely to have controlled BP than those with a longer duration since their hypertension diagnosis.

Management of hypertension in Australian general practice

An assessment of the information recorded in patient electronic health records found that only half of the patients diagnosed with hypertension had enough information recorded to enable absolute cardiovascular disease (CVD) risk calculation. This finding was not influenced by age, sex, smoking status or BP grade. However, the proportion of patients with sufficient recorded data available to calculate CVD risk was higher for patients diagnosed with hypertension than for patients without a diagnosis of hypertension (51% vs 39%). An exploration of prescribing found that prescribing of antihypertensive therapy by general practitioners (GPs) was not guided solely by absolute CVD risk. In patients with a calculated high or moderate CVD risk, 40% were not prescribed antihypertensive therapies, despite three-quarters of them having BP levels above the threshold of 140/90mmHg.

Cost of uncontrolled blood pressure in Australian general practice

Modelling estimated that across all 8.7 million Australians aged between 45 and 74 years who visit their GP, 261,858 CVD events can be expected over the next 5 years at current systolic blood pressure (SBP) levels (mean 137.8mmHg, SD=12.3mmHg), with a cost of AUD 1,813 million. By reducing the SBP of all patients with an SBP greater than 139 mmHg to 139mmHg, 25,845 CVD events could be avoided with an associated reduction in acute hospital costs of AUD 179 million. If SBP is lowered further to 129mmHg for all those with SBP greater than 129 mmHg, 56,169 CVD events could be avoided with potential cost savings of AUD 389 million. The sensitivity analyses indicate that potential cost savings range from AUD 46 million to AUD 1,406 million and AUD 117 million to AUD 2,009 million for the two scenarios, respectively. Despite these significant costs, the cost savings for the health system by practice are modest. Potential cost savings range from an average of AUD 16,479 for a small practice to AUD 82,493 for a large practice over 5 years.

Nevertheless, the limitations of the cost estimates in this study need to be acknowledged. On the one hand, the potential cost savings from improving BP control are underestimated as they only include the acute hospital costs of the primary CVD event. Including the costs related to rehabilitation and secondary CVD events would increase the potential savings, as would including the costs associated with other conditions, such as renal disease and dementia, that are associated with uncontrolled BP. On the other hand, the model assumed that BP control could be achieved for all patients, an unlikely achievement due to the complexity of achieving BP control. Despite these limitations, these estimates highlight the deleterious health and financial consequences of current levels of BP control and the magnitude of the potential gains from improving management of hypertension in general practice.

Interventions for improving medication adherence

A scoping review of the literature found that interventions informed by behavioural economics have demonstrated mostly positive effects and show promise when applied to improving medication adherence. However, no single simple solution exists. Instead, the findings suggest that multifaceted interventions tailored to patient needs are required. At the same time, the review highlights the importance of targeting non-adherent patients, understanding their reasons for non-adherence by using questionnaires or counselling methods which allowed tailoring of interventions to address their individual barriers, providing reminders and feedback to patients and physicians, and measuring clinical outcomes in addition to medication adherence as part of the evaluation of the intervention. Furthermore, as most studies were conducted in the United States, research in different health systems is needed.

8.2 Translation and impact

Chapter 3 has been cited by the High Blood Pressure Research Council of Australia in their call to action published in the *Medical Journal of Australia* [113]. The call to action appealed for a national commitment to improve BP control and used the

findings from the study presented in Chapter 3 to demonstrate that BP control remains poor.

Other work stemming from this thesis includes the use of machine learning to improve the identification of patients at risk of hypertension by using electronic medical records. Preliminary findings were presented by Jacqueline Roseleur at the World Congress of Epidemiology held in September 2021 where she was awarded the early career researcher best oral presentation [276].

Furthermore, the findings from this thesis have informed a proposed body of work by the Discipline of General Practice at the University of Adelaide on improving BP control in general practice through clinical decision support systems.

All the published manuscripts have been cited, with the scoping review presented in Chapter 7 receiving 10 citations at the time of writing.

8.3 Contributions to public health and medicine

The thesis has made contributions with respect to policy and research methods. These contributions are discussed in the next sections.

8.3.1 Policy contributions

This research represents the first in-depth exploration of the management of patients with a diagnosis of hypertension in Australian general practice. The evidence presented in this thesis on the prevalence of BP control, the current management of hypertension, the health and financial costs of uncontrolled BP, and an exploration of potential solutions to improve medication adherence could inform actions to respond to the recent call to action to address uncontrolled hypertension in Australia [113]. The call to action by the High Blood Pressure Research Council of Australia argues that “not only has Australia fallen behind on the number of people with high BP who are aware, treated and controlled, but we also feel that a significant degree of complacency has arisen in both cardiovascular research and the public health agenda regarding the need to improve BP control” [113 p.61]. The authors maintain that the current funding in Australia focuses on the management

of existing CVD rather than on the prevention of CVD by improving awareness, treatment and control of elevated BP [113]. The assertions regarding treatment and control are supported by the findings presented in Chapter 3, which found that BP control rates were low, and Chapter 4, which found that half of patients did not have enough information available to conduct a CVD risk assessment, nor was prescribing guided by CVD risk, thus constraining efforts to improve primary prevention of CVD.

Australian hypertension guidelines have recommended CVD risk assessment since at least 2008 [1, 277]. Despite this recommendation, only half of patients had enough data available to calculate their CVD risk. Furthermore, these findings suggest that there has been little improvement in the past decade [102, 278]. On a positive note, patients with a hypertension diagnosis were more likely to have data available for CVD risk assessment than those without a hypertension diagnosis, suggesting that some GPs are aware of the need to assess CVD risk in patients with hypertension.

Even in patients for whom CVD risk measurement is possible, CVD risk does not appear to influence treatment. The study presented in Chapter 4 found that approximately the same proportion of patients received a prescription for antihypertensive therapy, irrespective of CVD risk. This is particularly concerning in those patients with a calculated high or moderate CVD risk as these patients miss out on guideline-promoted treatments that minimise BP complications and reduce the risk of future CVD events. These patients represent a target population in which better management would have considerable benefits.

The findings from the costing study also provide evidence on the magnitude of the cost of uncontrolled hypertension that can be used as the basis for early economic evaluations to inform the expected value of alternative intervention options. Furthermore, despite the significant health and financial burden of uncontrolled BP across all patients, the costing study has demonstrated that cost savings for the health system by practice is modest. Consequently, practice-level interventions may not be cost-effective in smaller practices, particularly interventions that are resource-intensive, for example, those delivered by nurses. This aligns with a report by the Australian Health Policy Collaboration, which emphasizes the need for national funding to be established and allocated to each

Primary Health Network (PHN) to strengthen the capabilities of general practices. By providing dedicated funding, PHNs can effectively build the necessary infrastructure, resources, and expertise within general practices to deliver high-quality healthcare interventions [279].

The scoping review of interventions informed by behavioural economics to address medication adherence supports the current evidence that no easy solutions exist and that multifaceted interventions tailored to patient needs are required instead. Despite this, behavioural economic interventions continue to draw interest from researchers [280-285] particularly as interventions such as reminders and feedback using framing are potentially low cost [286].

8.3.2 Methodological contributions

From a methodological perspective, this research demonstrates the benefits of using electronic health records in assessing the prevalence of hypertension, BP control and management of hypertension. The findings on the prevalence of hypertension and BP control were similar to health surveys, indicating that electronic health records are a reliable alternative to surveys. Therefore, electronic health records provide an efficient evaluation method with larger cohorts of patients at potentially lower cost. Moreover, analysis of electronic health records provides insights into the management of hypertension, such as prescribing practices, that are more challenging to determine using surveys. Previous Australian studies on the management of hypertension only reported on whether patients had been prescribed antihypertensive medication, but did not report on the number of antihypertensive medications or the classes of antihypertensive therapy prescribed [7, 21, 102] as has been done in the studies presented in Chapters 3 and 4 of this thesis.

Furthermore, rather than relying on either assumed values or data from small surveys in other populations to populate models, electronic health records provide actual values for variables of interest. For example, the original model that was adapted for the study in Chapter 5 used a national health survey for prevalence, and several other studies for the cardiovascular event rates [116]. In the validation

process, the Framingham risk score was used for comparison. However, as no data was available for many of the parameters used in the Framingham risk score (i.e. diabetes, smoking, total and HDL cholesterol), the authors used the same values for all patients. Another study by Mennini and colleagues [287] estimated the total cost of CVD related to hypertension for five European countries. This study also used health survey data to estimate the prevalence of hypertension and only used age, sex and BP to calculate the Framingham risk score due to the unavailability of data. Using electronic health records for 125,369 patients, the study in Chapter 5 was able to estimate the prevalence of patients with a diagnosis of hypertension in the population of interest and calculate their Framingham risk score using their recorded values with fewer assumptions than previous studies. This enabled a more accurate estimate of the health and financial costs of uncontrolled BP, with reduced uncertainty.

In addition, the findings from this thesis can be used as a baseline to use electronic health records to monitor progress over time. For instance, Italy was able to monitor the progress of their "Objective 70%" program through repeated analyses of the same database of electronic health records [37, 38]. In addition to measuring the prevalence of hypertension and BP control, CVD risk measurement should also be monitored. To address the underuse of CVD risk assessment, the Australian Government introduced additional funding in 2019 to fund CVD risk assessment and ongoing management for all patients aged 30 years and older [288]. The data used in this thesis preceded this time and further studies are necessary to investigate the impact of this measure.

The study presented in Chapter 5 demonstrated how risk algorithms and average costs may be used to estimate the cost of uncontrolled BP with only general practice electronic health record datasets. Ideally, for conditions where clinical events require hospitalisation or other services outside of primary care, datasets need to be linked to different sources of electronic health records and other routinely collected data to estimate the resource use and costs associated with clinical events [289]. An example of such a data platform is CALIBER (CArdiovascular disease research using LInked Bespoke studies and Electronic health Records). CALIBER combines primary care data from the UK Clinical Practice

Research Datalink (CPRD), secondary care data from Hospital Episode Statistics, disease registry data from the Myocardial Ischaemia National Audit Project and mortality data from the Office for National Statistics, and has been used to predict lifetime costs of stable coronary artery disease [290]. In the absence of linked datasets such as CALIBER, conditions for which risk prediction scores are available using only data from primary care electronic health records, such as CVD and stroke, can be used to estimate the probability of an event occurring but not costs related to the event. Future investments in creating Australian datasets like CALIBER could improve the modelling of the cost-effectiveness of interventions.

However, despite the use of electronic health records to inform policy and practice in several countries [291-293], the limitations and potential biases of using electronic health records for research must be carefully considered as electronic health records are designed for patient management and not specifically for research purposes [90, 108]. In the case of MedicineInsight, progress notes are not extracted because these data may contain identifiable information. GPs may record information on diagnoses or other relevant information related to CVD risk factors in the progress notes, which may have resulted in an underestimation of CVD risk when using MedicineInsight data. However, it is unlikely that this limitation would change the results. A recent validation study found accuracy close to 90% when algorithms for chronic conditions using the same fields as this thesis were compared with the original electronic health record, which included the progress notes [88]. Moreover, as the electronic health records imported into MedicineInsight allow for free text data entry in most fields, cleaning the database took many months. The free text nature of the data also required assumptions to be made. The availability of clinicians on the research team allowed the assumptions to be informed by clinical practice.

8.4 Recommendations for future research

The studies in this thesis conducted cross-sectional analyses to explore hypertension management. The findings that BP control was not associated with time since diagnosis and the number of classes of antihypertensive medications prescribed suggest that other factors could be associated with poor BP control.

Several recommendations for future research are proposed in the following sections.

8.4.1 Understanding prescribing practices

An exploration of long-term prescribing patterns through longitudinal analysis may provide a better understanding of factors associated with treatment initiation and intensification. For example, how long does it take GPs to intensify treatment by adding additional classes of antihypertensive therapy in patients who are not achieving BP control? These prescribing patterns may be related to patient characteristics, for example, comorbidities, or the prescribed classes and doses of antihypertensive medication. Characteristics of the patient–provider relationship, such as continuity of care [294], may also be an important factor, and the general practice size and funding model may influence this relationship. For example, private practices that charge a gap payment may be able to spend more time with patients. Other factors, such as communication and patient health literacy, may also affect the patient-provider relationship and a patient's willingness to accept lifestyle modification advice and treatment initiation and intensification. However, analysis of electronic health records will need to be supplemented with surveys and interviews to capture these factors.

Although not the primary aim of this thesis, the study in Chapter 4 found that most patients with hypertension (approximately 90%) were prescribed antihypertensive medication in the past 2 years. However, only about 60% of patients had received a prescription for antihypertensive therapy in the last 6 months of the study period. Understanding why GPs stop prescribing is another critical component of improving BP control. Reasons may include patient non-attendance, patients receiving scripts from other health care practitioners or pharmacists dispensing medication without a current prescription. Patient non-attendance can be assessed using MedicineInsight. However, MedicineInsight is unable to track patients who visit other general practices. Alternative data sources are needed to determine whether patients receive prescriptions from other health care providers, such as specialists or GPs at other general practices. One potential source is data from the Pharmaceutical Benefits Scheme (PBS) that captures the

dispensing of medications by all pharmacies and public and private hospitals [295]. For those patients who continue to attend their GP and are not receiving prescriptions from other health care providers, other factors may influence GP prescribing, or lack thereof, such as reducing pill burden in patients with multimorbidity or the elderly [296], responding to or preventing medication side effects experienced by patients [297], aligning health care with an individual's health priorities [298] or medication affordability [103]. Interviews with GPs and patients will be essential to develop an understanding of these reasons. Exploration of this kind may identify the barriers experienced by GPs in the management of hypertension and provide insights into which specific treatment trajectory optimises BP control in patients with hypertension. For example, particular combinations of medications in certain patient populations may be more likely to result in discontinuation. These optimal treatment trajectories could be incorporated into clinical decision support systems to guide management decisions and provide personalised medication advice.

8.4.2 Supporting hypertension management

With the challenges of competing demands in general practice, exploring ways to support hypertension management, including improving CVD risk assessment in eligible patients, requires further attention. The electronic health record is an important tool in general practice and the design of electronic health records can impact clinical decision-making. This creates an opportunity to apply interventions to support decision-making [299]. For example, the electronic health record could be loaded with updated clinical guidelines and include evidence-based prompts and reminders to support patient management and optimise selection of medication [300]. Australian GPs have previously highlighted a preference for intermittent reminders of existing guidelines and protocols [301], and single page summaries on the management of particular groups of patients [302]. Furthermore, the inclusion of prompts and reminders can be informed by behavioural economics through framing or defaults, which have been found to be effective in a recent systematic review on physician behaviour change [303]. For example, single-pill combination therapy could be displayed first when listing antihypertensive medications in the

prescribing module of the electronic health record [304]. Other possible areas to explore include using electronic health records to remind GPs to measure CVD risk factors in eligible patients with missing or outdated information [305], automatically generating pathology requests for these patients or integrating CVD risk assessment in pathology services [306, 307]. PHNs can support the evaluation of these interventions by monitoring established funding mechanisms like the Practice Incentives Program - Quality Improvement (PIP-QI) initiative [279]. For instance, one PIP-QI metric tracks the percentage of patients aged 45-74 without a CVD diagnosis who have recorded risk factors for CVD risk assessment [141]. PHNs can utilize these results not only to monitor the impact of interventions on this metric but also to provide performance feedback to GPs relative to peer groups through social norms feedback. Effective feedback to GPs regarding their performance compared to peers has been shown to improve prescribing practices and may also prove beneficial for CVD risk assessment, especially when the potential consequences of inaction are clearly outlined [308].

In addition to informing treatment decisions by GPs, CVD risk scores can also be useful tools for engaging patients in strategies to reduce their CVD risk, particularly as hypertension is often an asymptomatic condition. A recent randomised trial in an Australian chest pain clinic demonstrated the effectiveness using CVD risk scores to educate and engage patients [309]. Patients presenting to the chest pain clinic without coronary ischaemia were randomised to either usual care or received counselling about their CVD risk score and recommendations to reduce the risk score. After 12 months, patients in the intervention had significantly improved CVD risk scores compared to those receiving usual care [309]. As this intervention was conducted with patients who had experienced chest pain and were likely more motivated to change behaviour and adhere to medications, further research is required to determine the effectiveness within a general practice population. A 2010 systematic review found that providing patients with their CVD risk score can be effective if provided regularly, rather than only at one point in time [310].

8.4.3 Understanding medication adherence in patients

Chapter 7's findings highlighted the complexity of addressing adherence and emphasized the need for multi-faceted interventions that cater to individual patient needs. Therefore, it is crucial for GPs to assess medication adherence in patients and gain a thorough understanding of the reasons behind poor adherence. This knowledge would enable GPs to provide more targeted and effective support to their patients. For example, one option would be to identify patients with uncontrolled BP and an existing prescription for antihypertensive medication in the electronic health records and then send them a link to a medication adherence questionnaire before their next appointment [311, 312]. The GP would then be able to engage with the patient more meaningfully to address concerns or barriers the patient may be experiencing. Challenges relating to pill burden could be addressed through use of single-pill combination therapy [113, 313] whereas patients who forget to take their medication could be referred to smartphone applications that provide reminders [314, 315].

Asking patients about their adherence may also identify preferences for non-pharmacological interventions, as illustrated by a recent Australian study exploring patients' needs and preferences for managing high BP. The study found that common concerns identified by patients pertained to managing high BP without medication, including through exercise and diet [302]. Previous research found that despite GPs reporting that they feel qualified to provide education on lifestyle modifications to manage hypertension, time was identified as a barrier [103]. One possible approach to address the barrier of time would be to use team care arrangements (TCA), which along with GP management plans (GPMP) form part of Medicare's Chronic Disease Management (CDM) program. TCAs allow GPs to refer patients to allied health practitioners (such as dieticians and exercise physiologists) to provide specific and tailored advice on lifestyle changes. However, in most instances, the CDM programme considers hypertension to be a risk factor rather than a chronic condition, despite calls for care planning provisions to be extended to patients at high risk of CVD [279]. This limits the ability of GPs to refer patients to allied health services unless patients have co-existing chronic conditions (for example diabetes, asthma or arthritis) [316]. Economic evaluation of GPs referring

patients to TCAs for hypertension alone could support policy change if found to be cost-effective.

8.4.4 Early economic evaluation

Even small changes will require effort from practices, with activities and implementation strategies needing resources. It is important to consider the funding mechanisms for these interventions. Current activity in general practice is funded through MBS reimbursement. However, the MBS rates have not increased in line with inflation over the past decades, resulting in GPs either charging a gap to patients, or favouring high-volume, low-value care [317, 318]. A recent review of the MBS has recommended that existing fee-for-service models be complemented by a block or blended payment model to support longitudinal, coordinated care for patients with chronic disease [319]. Early economic evaluation could inform the most appropriate funding mechanisms for alternative interventions to improve BP control. Positive developments in funding comprise the inclusion of an MBS item for CVD risk assessment in 2019 [288], and for home BP monitoring to support the diagnosis and management of hypertension in 2021 [320]. Further studies are necessary to investigate the impact of these measures.

Early economic modelling can also be used to support the development and tailoring of interventions; as general practice is a complex system in which to implement interventions [167, 168], the iterative and ongoing process of modelling could be used to represent the complexities of the setting and, where relevant, the intervention. This iterative modelling process can enhance the understanding of the expected effects of interventions and their potential cost-effectiveness [321]. For example, decisions on whether an intervention should be delivered by a GP or nurse could be informed through modelling existing care pathways to determine capacity constraints and inform the design of new models of care [321]. Furthermore, existing funding mechanisms, for example, Medicare Benefits Schedule (MBS) items and other incentives such as the Practice Incentives Program - Quality Improvement (PIP-QI), can be included in the modelling process to gain insight into potential cost-effectiveness of the interventions.

Moreover, as interventions addressing adherence should be targeted at non-adherent patients, as demonstrated in the review presented in Chapter 7, the costs associated with identifying non-adherent patients and further still, the costs associated with identifying barriers to adherence and adapting interventions to respond to these barriers could also be included in the modelling process to determine the impact on cost-effectiveness of these additional resource requirements.

The identification of potential intervention options relevant to Australian general practice could be conducted through stakeholder engagement. The findings from the scoping review using insights from behavioural economics (Chapter 7) can be presented alongside other potential interventions to relevant stakeholders, such as GPs, patients and primary health networks. With input from the stakeholders, the intervention and implementation costs and effects can be estimated and applied to the cost and health effect estimates presented in the costing study (Chapter 5), providing the basis for estimating quality-adjusted life years gained (QALYs).

8.5 Concluding remarks

As the population ages and the prevalence of hypertension continues to increase both globally and in Australia, the financial and health burden associated with uncontrolled hypertension will also continue to increase, further burdening an already resource-constrained health system. Although effective lifestyle and pharmacological interventions are available to reduce elevated BP, analysis of electronic health records have identified that only a little more than half of patients in general practice had their BP controlled according to Australian guidelines. Furthermore, even though guidelines recommend the use of absolute CVD risk in the management of hypertension, only half of patients had sufficient data recorded to calculate CVD risk. Moreover, of those patients with a calculated high or moderate CVD risk, 40% were not prescribed antihypertensive therapies, despite three-quarters of them having uncontrolled BP.

Areas requiring further investigation include the exploration of long-term prescribing patterns through longitudinal analysis to provide a better

understanding of factors associated with treatment initiation and intensification, analysis of alternative data sources to understand why GPs stop prescribing, exploring ways to support hypertension management, including improving CVD risk assessment in eligible patients and assessing medication adherence and reasons for poor adherence to allow GPs to support patients in more specific ways.

With substantial costs attributed to uncontrolled BP, cost-effective investments in interventions to address BP control are essential. The findings from the scoping review provide a foundation for designing interventions to improve adherence to BP medications. In addition, the findings on prevalence and costs provide the basis for early economic evaluations to inform the expected value of alternative intervention options. As evidenced in other settings, better hypertension control is possible [37, 151, 322]. However, this will require a national commitment focused on better awareness and treatment of raised BP [113].

References

1. National Heart Foundation of Australia. Guideline for the diagnosis and management of hypertension in adults – 2016. Melbourne: National Heart Foundation of Australia; 2016.
2. Whelton PK, Carey RM, Aronow WS, Casey DE, Jr., Collins KJ, Dennison Himmelfarb C, DePalma SM, Gidding S, Jamerson KA, Jones DW, MacLaughlin EJ, Muntner P, Ovbiagele B, Smith SC, Jr., Spencer CC, Stafford RS, Taler SJ, Thomas RJ, Williams KA, Sr., et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA guideline for the prevention, detection, evaluation, and management of high blood pressure in adults: executive summary: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. Hypertension. 2018 Jun;71(6):1269-324.
3. Williams B, Mancia G, Spiering W, Agabiti Rosei E, Azizi M, Burnier M, Clement DL, Coca A, de Simone G, Dominiczak A, Kahan T, Mahfoud F, Redon J, Ruilope L, Zanchetti A, Kerins M, Kjeldsen SE, Kreutz R, Laurent S, et al. 2018 ESC/ESH guidelines for the management of arterial hypertension: the Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Journal of Hypertension. 2018 Oct;36(10):1953-2041.
4. Mills KT, Bundy JD, Kelly TN, Reed JE, Kearney PM, Reynolds K, Chen J, He J. Global disparities of hypertension prevalence and control: a systematic analysis of population-based studies from 90 countries. Circulation. 2016 Aug 9;134(6):441-50.

5. Brown CD, Higgins M, Donato KA, Rohde FC, Garrison R, Obarzanek E, Ernst ND, Horan M. Body mass index and the prevalence of hypertension and dyslipidemia. Obesity Research. 2000 Dec;8(9):605-19.

6. Garrison RJ, Kannel WB, Stokes J, 3rd, Castelli WP. Incidence and precursors of hypertension in young adults: the Framingham Offspring Study. Preventive Medicine. 1987 Mar;16(2):235-51.

7. Australian Bureau of Statistics. National Health Survey: first results, 2017–18. ABS cat no 4364055001 2018 Dec 12 [cited 5 Apr 2022]. Available from: https://www.abs.gov.au/ausstats/abs@.nsf/Lookup/by%20Subject/4364.0.55.001~2017-18~Main%20Features~Hypertension%20and%20measured%20high%20blood%20pressure~60

8. Tanamas SK, Magliano DJ, Lynch B, Sethi P, Willenberg L, Polkinghorne KR, Chadban S, Dunstan D, JE S. AusDiab 2012. The Australian Diabetes, Obesity and Lifestyle Study. Melbourne: Baker IDI Heart and Diabetes Institute; 2013.

9. Carnagarin R, Fonseca R, Brockman D, Hering D, Matthews VB, Mihailidou A, Reid C, Lee R, Lambert GW, Burrell LM, Sharman JE, Xia X, Poulter NR, Beaney T, Islam SM, Carrington M, Schlaich MP. May Measurement Month 2017: an analysis of blood pressure screening results from Australia-South-East Asia and Australasia. European Heart Journal Supplements. 2019 Apr;21(Suppl D):D14-D6.

10. Carrington MJ, Jennings GL, Stewart S. Pattern of blood pressure in Australian adults: results from a national blood pressure screening day of 13,825 adults. International Journal of Cardiology. 2010 Dec 3;145(3):461-7.

11. GBD 2015 Risk Factors Collaborators. Global, regional, and national comparative risk assessment of 79 behavioural, environmental and occupational, and metabolic risks or clusters of risks, 1990–2015: a systematic analysis for the Global Burden of Disease Study 2015. The Lancet. 2016 Oct 8;388(10053):1659-724.

12. Forouzanfar MH, Liu P, Roth GA, Ng M, Biryukov S, Marczak L, Alexander L, Estep K, Hassen Abate K, Akinyemiju TF, Ali R, Alvis-Guzman N, Azzopardi P,

Banerjee A, Barnighausen T, Basu A, Bekele T, Bennett DA, Biadgilign S, et al. Global burden of hypertension and systolic blood pressure of at least 110 to 115 mm Hg, 1990–2015. JAMA. 2017 Jan 10;317(2):165-82.

13. Australian Institute of Health and Welfare. Australian Burden of Disease Study: impact and causes of illness and death in Australia 2015. Canberra: AIHW; 2019.

14. Gaziano TA, Bitton A, Anand S, Weinstein MC, International Society of Hypertension. The global cost of nonoptimal blood pressure. Journal of Hypertension. 2009 Jul;27(7):1472-7.

15. Australian Institute of Health and Welfare. Disease expenditure in Australia 2018–19. 2021 Aug 25 [cited 15 Mar 2022]. Available from: https://www.aihw.gov.au/reports/health-welfare-expenditure/disease-expenditure-australia/contents/australian-burden-of-disease-groups

16. Hird TR, Zomer E, Owen AJ, Magliano DJ, Liew D, Ademi Z. Productivity burden of hypertension in Australia. Hypertension. 2019 Apr;73(4):777-84.

17. Neal B, MacMahon S, Chapman N, Blood Pressure Lowering Treatment Trialists Collaboration. Effects of ACE inhibitors, calcium antagonists, and other blood-pressure-lowering drugs: results of prospectively designed overviews of randomised trials. Blood Pressure Lowering Treatment Trialists' Collaboration. The Lancet. 2000 Dec 9;356(9246):1955-64.

18. Smith WC, Lee AJ, Crombie IK, Tunstall-Pedoe H. Control of blood pressure in Scotland: the rule of halves. BMJ. 1990 Apr 14;300(6730):981-3.

19. Wilber JA. The problem of undetected and untreated hypertension in the community. Bulletin of the New York Academy of Medicine. 1973 Jun;49(6):510-20.

20. Wilber JA, Barrow JG. Hypertension – a community problem. The American Journal of Medicine. 1972 1972/05/01/;52(5):653-63.

21. Australian Institute of Health and Welfare. High blood pressure. Cat. no. PHE 250. Canberra: AIHW; 2019.

22. Zhou D, Xi B, Zhao M, Wang L, Veeranki SP. Uncontrolled hypertension increases risk of all-cause and cardiovascular disease mortality in US adults: the NHANES III Linked Mortality Study. Scientific Reports. 2018 Jun 20;8(1):9418.

23. Law MR, Morris JK, Wald NJ. Use of blood pressure lowering drugs in the prevention of cardiovascular disease: meta-analysis of 147 randomised trials in the context of expectations from prospective epidemiological studies. BMJ. 2009 May 19;338:b1665.

24. Rahimi K, Bidel Z, Nazarzadeh M, Copland E, Canoy D, Ramakrishnan R, Pinho-Gomes A-C, Woodward M, Adler A, Agodoa L, Algra A, Asselbergs FW, Beckett NS, Berge E, Black H, Brouwers FPJ, Brown M, Bulpitt CJ, Byington RP, et al. Pharmacological blood pressure lowering for primary and secondary prevention of cardiovascular disease across different levels of blood pressure: an individual participant-level data meta-analysis. The Lancet. 2021 May 1;397(10285):1625-36.

25. World Health Organization, United Nations Children's Fund (UNICEF). A vision for primary health care in the 21st century: towards universal health coverage and the Sustainable Development Goals. Geneva: World Health Organization; 2018.

26. Australian Institute of Health and Welfare. Review and evaluation of Australian information about primary health care: a focus on general practice. Canberra: AIHW; 2008.

27. Finley CR, Chan DS, Garrison S, Korownyk C, Kolber MR, Campbell S, Eurich DT, Lindblad AJ, Vandermeer B, Allan GM. What are the most common conditions in primary care? Systematic review. Canadian Family Physician. 2018 Nov;64(11):832-40.

28. NPS MedicineWise. General practice insights report July 2018–June 2019. Sydney: NPS MedicineWise; 2020.

29. Buckley B, Shanahan E, Colwell N, Turgonyi E, Bramlage P, Perry IJ. Blood pressure control in hypertensive patients in Irish primary care practices. Journal of Clinical Hypertension (Greenwich, Conn). 2009 Aug;11(8):432-40.

30. Holmquist C, Hasselstrom J, Bengtsson Bostrom K, Manhem K, Wettermark B, Hjerpe P, Kahan T. Improved treatment and control of hypertension in Swedish primary care: results from the Swedish primary care cardiovascular database. Journal of Hypertension. 2017 Oct;35(10):2102-8.

31. Li YT, Wang HHX, Liu KQL, Lee GKY, Chan WM, Griffiths SM, Chen RL. Medication adherence and blood pressure control among hypertensive patients with coexisting long-term conditions in primary care settings: a cross-sectional analysis. Medicine (Baltimore). 2016 May;95(20):e3572.

32. Paulsen MS, Andersen M, Thomsen JL, Schroll H, Larsen PV, Lykkegaard J, Jacobsen IA, Larsen ML, Christensen B, Sondergaard J. Multimorbidity and blood pressure control in 37 651 hypertensive patients from Danish general practice. Journal of the American Heart Association. 2012 Dec 31;2(1):e004531.

33. Paulsen MS, Sondergaard J, Reuther L, Larsen PS, Munck AP, Larsen PV, Damsgaard J, Poulsen L, Hansen DG, Jacobsen IA, Larsen ML, Christensen HR, Christensen B, Andersen M. Treatment of 5413 hypertensive patients: a cross-sectional study. Family Practice. 2011 Dec;28(6):599-607.

34. Qvarnstrom M, Wettermark B, Ljungman C, Zarrinkoub R, Hasselstrom J, Manhem K, Sundstrom A, Kahan T. Antihypertensive treatment and control in a large primary care population of 21 167 patients. Journal of Human Hypertension. 2011 Aug;25(8):484-91.

35. Santiago LM, Pereira C, Botas P, Simoes AR, Carvalho R, Pimenta G, Neto G. Hypertensive patients in a general practice setting: comparative analysis between controlled and uncontrolled hypertension. Revista Portuguesa de Cardiologia. 2014 Jul-Aug;33(7-8):419-24.

36. Teh XR, Lim MT, Tong SF, Husin M, Khamis N, Sivasampu S. Quality of hypertension management in public primary care clinics in Malaysia: an update. PLoS One. 2020 Aug 11;15(8):e0237083.

37. Tocci G, Nati G, Cricelli C, Parretti D, Lapi F, Ferrucci A, Borghi C, Volpe M. Prevalence and control of hypertension in the general practice in Italy:

updated analysis of a large database. Journal of Human Hypertension. 2017 Apr;31(4):258-62.

38. Filippi A, Paolini I, Innocenti F, Mazzaglia G, Battaggia A, Brignoli O. Blood pressure control and drug therapy in patients with diagnosed hypertension: a survey in Italian general practice. Journal of Human Hypertension. 2009 Nov;23(11):758-63.

39. Volpe M, Tocci G. Strategies to improve control of blood pressure in hypertension: moving towards a 70% objective. Expert Review of Cardiovascular Therapy. 2013 2013/06/01;11(6):653-6.

40. Howes LG, Reid C, Bendle R, Weaving J. The prevalence of isolated systolic hypertension in patients 60 years of age and over attending Australian general practitioners. Blood Pressure. 1998 May;7(3):139-43.

41. Carrington MJ, Jennings GL, Stewart S. Pressure points in primary care: blood pressure and management of hypertension in 532 050 patients from 2005 to 2010. Journal of Hypertension. 2013 Jun;31(6):1265-71.

42. Gallego B, Runciman WB, Perez-Concha O, Liaw ST, Day RO, Dunn AG, Coiera E. The management of severe hypertension in Australian general practice. BMC Health Services Research. 2013 Oct 14;13:414.

43. Khanam MA, Kitsos A, Stankovich J, Castelino R, Jose M, Peterson GM, Wimmer B, Razi Zaidi T, Radford J. Association of continuity of care with blood pressure control in patients with chronic kidney disease and hypertension. Australian Journal of General Practice. 2019 May;48(5):300-6.

44. Smith BJ, Owen AJ, Liew D, Kelly DJ, Reid CM. Prescription of physical activity in the management of high blood pressure in Australian general practices. Journal of Human Hypertension. 2019 Jan;33(1):50-6.

45. Campbell DJ, McGrady M, Prior DL, Coller JM, Boffa U, Shiel L, Liew D, Wolfe R, Stewart S, Reid CM, Krum H. Most individuals with treated blood pressures above target receive only one or two antihypertensive drug classes. Internal Medicine Journal. 2013 Feb;43(2):137-43.

46. Dave GJ, Bibeau DL, Schulz MR, Aronson RE, Ivanov LL, Black A, Spann L. Predictors of uncontrolled hypertension in the Stroke Belt. Journal of Clinical Hypertension (Greenwich, Conn). 2013 Aug;15(8):562-9.

47. Balijepalli C, Bramlage P, Losch C, Zemmrich C, Humphries KH, Moebus S. Prevalence and control of high blood pressure in primary care: results from the German Metabolic and Cardiovascular Risk Study (GEMCAS). Hypertension Research. 2014 Jun;37(6):580-4.

48. Rowan CG, Flory J, Stempniewicz N, Cuddeback J, Brunelli SM. Stage 2 hypertension: predictors of failure to achieve blood pressure control and the impact of adding one additional antihypertensive class. Pharmacoepidemiology and Drug Safety. 2015 Nov;24(11):1170-9.

49. Farah R, Zeidan RK, Chahine MN, Asmar R, Chahine R, Salameh P, Pathak A, Hosseini H. Predictors of uncontrolled blood pressure in treated hypertensive individuals: first population-based study in Lebanon. Journal of Clinical Hypertension (Greenwich, Conn). 2016 Sep;18(9):871-7.

50. Zavala-Loayza JA, Benziger CP, Cardenas MK, Carrillo-Larco RM, Bernabe-Ortiz A, Gilman RH, Checkley W, Miranda JJ. Characteristics associated with antihypertensive treatment and blood pressure control: a population-based follow-up study in Peru. Global Heart. 2016 Mar;11(1):109-19.

51. Costa Filho FF, Timerman A, Saraiva JFK, Magalhaes CC, Pinto IMF, Oliveira GBF, Mattos AC, Avezum A. Independent predictors of effective blood pressure control in patients with hypertension on drug treatment in Brazil. Journal of Clinical Hypertension (Greenwich, Conn). 2018 Jan;20(1):125-32.

52. Haggart RC, Bartels CM, Smith MA, Johnson HM. Sociodemographics and hypertension control among young adults with incident hypertension: a multidisciplinary group practice observational study. Journal of Hypertension. 2018 Dec;36(12):2425-33.

53. Konig M, Gollasch M, Rosada A, Demuth I, Spira D, Steinhagen-Thiessen E. Antihypertensive treatment patterns and blood pressure control in older adults: results from the Berlin Aging Study II. Drugs and Aging. 2018 Nov;35(11):993-1003.

54. Tapela N, Collister J, Clifton L, Turnbull I, Rahimi K, Hunter DJ. Prevalence and determinants of hypertension control among almost 100 000 treated adults in the UK. Open Heart. 2021;8(1):e001461.

55. Lin SF, Kuo TT, Pan WH, Bai CH. Effects of socioeconomic status on the control of hypertension in patients <65 and ≥65 years of age in Taiwan: a nationwide cross-sectional study. BMJ Open. 2022 Feb 23;12(2):e050041.

56. Borghi C, Tubach F, De Backer G, Dallongeville J, Guallar E, Medina J, Perk J, Roy C, Banegas JR, Rodriguez-Artalejo F, Halcox JP. Lack of control of hypertension in primary cardiovascular disease prevention in Europe: results from the EURIKA study. International Journal of Cardiology. 2016 Sep 1;218:83-8.

57. Greenberg JD, Tiwari A, Rajan M, Miller D, Natarajan S, Pogach L. Determinants of sustained uncontrolled blood pressure in a national cohort of persons with diabetes. American Journal of Hypertension. 2006;19(2):161-9.

58. Degli Esposti E, Di Martino M, Sturani A, Russo P, Dradi C, Falcinelli S, Buda S. Risk factors for uncontrolled hypertension in Italy. Journal of Human Hypertension. 2004 Mar;18(3):207-13.

59. Jahangiry L, Ghanbari J, Abbasalizad Farhangi M, Sarbakhsh P, Ponnet K. Predictors of poor blood pressure control among Iranian hypertensive patients. BMC Research Notes. 2017 Dec 4;10(1):668.

60. Mourtzinis G, Manhem K, Kahan T, Schiöler L, Isufi J, Ljungman C, Andersson T, Hjerpe P. Socioeconomic status affects achievement of blood pressure target in hypertension: contemporary results from the Swedish primary care cardiovascular database. Scandinavian Journal of Primary Health Care. 2021 2021/10/02;39(4):519-26.

61. Paulsen MS, Andersen M, Munck AP, Larsen PV, Hansen DG, Jacobsen IA, Larsen ML, Christensen B, Sondergaard J. Socio-economic status influences blood pressure control despite equal access to care. Family Practice. 2012 Oct;29(5):503-10.

62. Qin Z, Li C, Qi S, Zhou H, Wu J, Wang W, Ye Q, Yang H, Wang C, Hong X. Association of socioeconomic status with hypertension prevalence and control in Nanjing: a cross-sectional study. BMC Public Health. 2022 2022/03/02;22(1):423.

63. Blok S, Haggenburg S, Collard D, Van Der Linden EL, Galenkamp H, Moll van Charante EP, Agyemang C, Van Den Born B-JH. The association between socioeconomic status and prevalence, awareness, treatment and control of hypertension in different ethnic groups: the Healthy Life in an Urban Setting study. Journal of Hypertension. 2022;40(5):897-907.

64. DeVore AD, Sorrentino M, Arnsdorf MF, Ward RP, Bakris GL, Blankstein R. Predictors of hypertension control in a diverse general cardiology practice. Journal of Clinical Hypertension (Greenwich, Conn). 2010 Aug;12(8):570-7.

65. Cheong AT, Tong SF, Sazlina SG, Azah AS, Salmiah MS. Blood pressure control among hypertensive patients with and without diabetes mellitus in six public primary care clinics in Malaysia. Asia-Pacific Journal of Public Health. 2015 Mar;27(2):Np580-9.

66. Karmali KN, Lloyd-Jones DM. Global risk assessment to guide blood pressure management in cardiovascular disease prevention. Hypertension. 2017 Mar;69(3):e2-e9.

67. Neaton JD, Wentworth D. Serum cholesterol, blood pressure, cigarette smoking, and death from coronary heart disease: overall findings and differences by age for 316,099 white men. Archives of Internal Medicine. 1992 Jan;152(1):56-64.

68. O'Donnell MJ, Xavier D, Liu L, Zhang H, Chin SL, Rao-Melacini P, Rangarajan S, Islam S, Pais P, McQueen MJ, Mondo C, Damasceno A, Lopez-Jaramillo P, Hankey GJ, Dans AL, Yusoff K, Truelsen T, Diener HC, Sacco RL, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. The Lancet. 2010 Jul 10;376(9735):112-23.

69. Wilson PW, D'Agostino RB, Levy D, Belanger AM, Silbershatz H, Kannel WB. Prediction of coronary heart disease using risk factor categories. Circulation. 1998 May 12;97(18):1837-47.

70. Yusuf S, Hawken S, Ounpuu S, Dans T, Avezum A, Lanas F, McQueen M, Budaj A, Pais P, Varigos J, Lisheng L, Investigators IS. Effect of potentially modifiable risk factors associated with myocardial infarction in 52 countries (the INTERHEART study): case-control study. The Lancet. 2004 Sep 11-17;364(9438):937-52.

71. Blood Pressure Lowering Treatment Trialists C. Blood pressure-lowering treatment based on cardiovascular risk: a meta-analysis of individual patient data. The Lancet. 2014 Aug 16;384(9943):591-8.

72. Anderson KM, Odell PM, Wilson PW, Kannel WB. Cardiovascular disease risk profiles. American Heart Journal. 1991 Jan;121(1 Pt 2):293-8.

73. National Vascular Disease Prevention Alliance. Guidelines for the management of absolute cardiovascular disease risk. Melbourne National Stroke Foundation; 2012.

74. Busingye D, Gianacas C, Pollack A, Chidwick K, Merrifield A, Norman S, Mullin B, Hayhurst R, Blogg S, Havard A, Stocks N. Data resource profile: MedicineInsight, an Australian national primary health care database. International Journal of Epidemiology. 2019 Dec 1;48(6):1741-h.

75. Begum M, Gonzalez-Chica D, Bernardo C, Woods A, Stocks N. Trends in the prescription of drugs used for insomnia: an open-cohort study in Australian general practice, 2011–2018. British Journal of General Practice. 2021 Nov;71(712):e877-e86.

76. Bernardo CO, Gonzalez-Chica D, Stocks N. Influenza-like illness and antimicrobial prescribing in Australian general practice from 2015 to 2017: a national longitudinal study using the MedicineInsight dataset. BMJ Open. 2019 May 1;9(4):e026396.

77. De Oliveira Bernardo C, Gonzalez-Chica DA, Chilver M, Stocks N. Influenza immunisation coverage from 2015 to 2017: a national study of adult patients from Australian general practice. Vaccine. 2019 Jul 18;37(31):4268-74.

78. De Oliveira Bernardo C, Gonzalez-Chica DA, Stocks N. Impact of funding influenza vaccination on coverage among Australian children: a national study using MedicineInsight, a large general practice database. Human Vaccines & Immunotherapeutics. 2020 Mar 3;16(3):630-5.

79. Frank O, De Oliveira Bernardo C, Gonzalez-Chica DA, Macartney K, Menzies R, Stocks N. Pneumococcal vaccination uptake among patients aged 65 years or over in Australian general practice. Human Vaccines & Immunotherapeutics. 2020 Apr 2;16(4):965-71.

80. Gonzalez-Chica D, Stocks N. Changes to the frequency and appropriateness of vitamin D testing after the introduction of new Medicare criteria for rebates in Australian general practice: evidence from 1.5 million patients in the NPS MedicineInsight database. BMJ Open. 2019 Mar 8;9(3):e024797.

81. Gonzalez-Chica DA, Vanlint S, Hoon E, Stocks N. Epidemiology of arthritis, chronic back pain, gout, osteoporosis, spondyloarthropathies and rheumatoid arthritis among 1.5 million patients in Australian general practice: NPS MedicineWise MedicineInsight dataset. BMC Musculoskeletal Disorders. 2018 Jan 18;19(1):20.

82. Lee CMY, Mnatzaganian G, Woodward M, Chow CK, Sitas F, Robinson S, Huxley RR. Sex disparities in the management of coronary heart disease in general practices in Australia. Heart. 2019 Dec;105(24):1898-904.

83. Manski-Nankervis JE, Thuraisingam S, Sluggett JK, Lau P, Blackberry I, Ilomaki J, Furler J, Bell JS. Prescribing for people with type 2 diabetes and renal impairment in Australian general practice: a national cross sectional study. Primary Care Diabetes. 2019 Apr;13(2):113-21.

84. Radford J, Kitsos A, Stankovich J, Castelino R, Khanam M, Jose M, Peterson G, Saunder T, Wimmer B, Razizaidi T. Epidemiology of chronic kidney disease in Australian general practice: National Prescribing Service MedicineWise MedicineInsight dataset. Nephrology (Carlton). 2019 Oct;24(10):1017-25.

85. Roseleur J, Gonzalez-Chica DA, Emery J, Stocks NP. Skin checks and skin cancer diagnosis in Australian general practice before and during the COVID-

19 pandemic, 2011–2020. British Journal of Dermatology. 2021 Oct;185(4):853-5.

86. Spooner C, Afrazi S, de Oliveira Costa J, Harris MF. Demographic and health profiles of people with severe mental illness in general practice in Australia: a cross-sectional study. Australian Journal of Primary Health. 2022 Jun 2;28(5):408-16.

87. Zheng M, Bernardo CO, Stocks N, Gonzalez-Chica D. Diabetes mellitus diagnosis and screening in Australian general practice: a national study. Journal of Diabetes Research. 2022;2022:1566408.

88. Havard A, Manski-Nankervis JA, Thistlethwaite J, Daniels B, Myton R, Tu K, Chidwick K. Validity of algorithms for identifying five chronic conditions in MedicineInsight, an Australian national general practice database. BMC Health Services Research. 2021 Jun 5;21(1):551.

89. Magvanjav O, Cooper-DeHoff RM, McDonough CW, Gong Y, Hogan WR, Johnson JA. Combination antihypertensive therapy prescribing and blood pressure control in a real-world setting. American Journal of Hypertension. 2020;33(4):316-24.

90. Muller S. Electronic medical records: the way forward for primary care research? Family Practice. 2014 Apr;31(2):127-9.

91. Manski-Nankervis JA, Thuraisingam S, Sluggett JK, Kilov G, Furler J, O'Neal D, Jenkins A. Prescribing of diabetes medications to people with type 2 diabetes and chronic kidney disease: a national cross-sectional study. BMC Family Practice. 2019 Feb 18;20(1):29.

92. The Commonwealth Fund. International Profiles of Health Care Systems. London: The Commonwealth Fund; 2017.

93. Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sorensen HT, von Elm E, Langan SM, Committee RW. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) statement. PLoS Medicine. 2015 Oct;12(10):e1001885.

94. Tu K, Campbell NR, Chen ZL, Cauch-Dudek KJ, McAlister FA. Accuracy of administrative databases in identifying patients with hypertension. Open Medicine. 2007 Apr 14;1(1):e18-26.

95. Peng M, Chen G, Kaplan GG, Lix LM, Drummond N, Lucyk K, Garies S, Lowerison M, Weibe S, Quan H. Methods of defining hypertension in electronic medical records: validation against national survey data. Journal of Public Health. 2016 Sep;38(3):e392-e9.

96. Australian Bureau of Statistics. Census of Population and Housing: Socio-Economic Indexes for Areas (SEIFA). 2011.

97. Harrison C, Britt H, Miller G, Henderson J. Prevalence of chronic conditions in Australia. PLoS One. 2013;8(7):e67494.

98. Australian Bureau of Statistics. National Health Survey: summary of results, 2007–08. Canberra: ABS; 2009.

99. Lujic S, Simpson JM, Zwar N, Hosseinzadeh H, Jorm L. Multimorbidity in Australia: Comparing estimates derived using administrative data sources and survey data. PLoS One. 2017;12(8):e0183817.

100. Muggah E, Graves E, Bennett C, Manuel DG. Ascertainment of chronic diseases using population health data: a comparison of health administrative data and patient self-report. BMC Public Health. 2013 Jan 9;13:16.

101. Gonzalez-Chica DA, Bowden J, Miller C, Longo M, Nelson M, Reid C, Stocks N. Patient-reported GP health assessments rather than individual cardiovascular risk burden are associated with the engagement in lifestyle changes: population-based survey in South Australia. BMC Family Practice. 2019 Dec 13;20(1):173.

102. Webster RJ, Heeley EL, Peiris DP, Bayram C, Cass A, Patel AA. Gaps in cardiovascular disease risk management in Australian general practice. Medical Journal of Australia. 2009 Sep 21;191(6):324-9.

103. Howes F, Hansen E, Williams D, Nelson M. Barriers to diagnosing and managing hypertension – a qualitative study in Australian general practice. Australian Family Physician. 2010 Jul;39(7):511-6.

104. Benetos A, Petrovic M, Strandberg T. Hypertension Management in Older and Frail Older Patients. Circulation Research. 2019 Mar 29;124(7):1045-60.

105. Volpe M, Gallo G, Tocci G. Is early and fast blood pressure control important in hypertension management? International Journal of Cardiology. 2018 Mar 1;254:328-32.

106. Mancia G, Rea F, Corrao G, Grassi G. Two-Drug Combinations as First-Step Antihypertensive Treatment. Circulation Research. 2019 Mar 29;124(7):1113-23.

107. Marinier K, Macouillard P, de Champvallins M, Deltour N, Poulter N, Mancia G. Effectiveness of two-drug therapy versus monotherapy as initial regimen in hypertension: A propensity score-matched cohort study in the UK Clinical Practice Research Datalink. Pharmacoepidemiology and Drug Safety. 2019 Dec;28(12):1572-82.

108. Verheij RA, Curcin V, Delaney BC, McGilchrist MM. Possible Sources of Bias in Primary Care Electronic Health Record Data Use and Reuse. Journal of Medical Internet Research. 2018 May 29;20(5):e185.

109. Staff M, Roberts C, March LM. Using aggregated general practice data to evaluate primary care interventions. Medical Journal of Australia. 2017 Apr 3;206(6):242-3.

110. Zhou B, Carrillo-Larco RM, Danaei G, Riley LM, Paciorek CJ, Stevens GA, Gregg EW, Bennett JE, Solomon B, Singleton RK, Sophiea MK, Iurilli MLC, Lhoste VPF, Cowan MJ, Savin S, Woodward M, Balanova Y, Cifkova R, Damasceno A, et al. Worldwide trends in hypertension prevalence and progress in treatment and control from 1990 to 2019: a pooled analysis of 1201 population-representative studies with 104 million participants. The Lancet. 2021 Sep 11;398(10304):957-80.

111. Murray CJL, Aravkin AY, Zheng P, Abbafati C, Abbas KM, Abbasi-Kangevari M, Abd-Allah F, Abdelalim A, Abdollahi M, Abdollahpour I, Abegaz KH, Abolhassani H, Aboyans V, Abreu LG, Abrigo MRM, Abualhasan A, Abu-Raddad LJ, Abushouk AI, Adabi M, et al. Global burden of 87 risk factors in 204 countries and territories, 1990–2019: a systematic analysis for the

Global Burden of Disease Study 2019. The Lancet. 2020 Oct 17;396(10258):1223-49.

112. Roseleur J, Gonzalez-Chica DA, Bernardo CO, Geisler BP, Karnon J, Stocks NP. Blood pressure control in Australian general practice: analysis using general practice records of 1.2 million patients from the MedicineInsight database. Journal of Hypertension. 2021 Jun 1;39(6):1134-42.

113. Schutte AE, Webster R, Jennings G, Schlaich MP. Uncontrolled blood pressure in Australia: a call to action. Medical Journal of Australia. 2022 Feb 7;216(2):61-3.

114. Cadilhac DA, Carter R, Thrift AG, Dewey HM. Organized blood pressure control programs to prevent stroke in Australia: would they be cost-effective? Stroke. 2012 May;43(5):1370-5.

115. Muntner P, Whelton PK. Using predicted cardiovascular disease risk in conjunction with blood pressure to guide antihypertensive medication treatment. Journal of the American College of Cardiology. 2017 May 16;69(19):2446-56.

116. Lloyd A, Schmieder C, Marchant N. Financial and health costs of uncontrolled blood pressure in the United Kingdom. Pharmacoeconomics. 2003;21(Suppl 1):33-41.

117. Australian Bureau of Statistics. National, state and territory population. 2021 Dec 16 [cited 12 Feb 2022]. Available from: https://www.abs.gov.au/statistics/people/population/national-state-and-territory-population/jun-2021

118. Australian Bureau of Statistics. Patient experiences in Australia: 2018–2019. 2019 Nov 12 [cited 12 Feb 2022]. Available from: https://www.abs.gov.au/statistics/health/health-services/patient-experiences-australia-summary-findings/2018-19#data-download

119. The Royal Australian College of General Practitioners. Standards for general practices, 5th edition. Melbourne: RACGP; 2020.

120. Roseleur J, Gonzalez-Chica DA, Karnon J, Stocks NP. Predicted cardiovascular disease risk and prescribing of antihypertensive therapy among patients with hypertension in Australia using MedicineInsight. Journal of Human Hypertension. 2023 May;37(5):370-8.

121. Ettehad D, Emdin CA, Kiran A, Anderson SG, Callender T, Emberson J, Chalmers J, Rodgers A, Rahimi K. Blood pressure lowering for prevention of cardiovascular disease and death: a systematic review and meta-analysis. The Lancet. 2016 Mar 5;387(10022):957-67.

122. D'Agostino RB, Sr., Vasan RS, Pencina MJ, Wolf PA, Cobain M, Massaro JM, Kannel WB. General cardiovascular risk profile for use in primary care: the Framingham Heart Study. Circulation. 2008 Feb 12;117(6):743-53.

123. Australian Institute of Health and Welfare. National hospital morbidity database. 2020 [cited 5 Feb 2022]. Available from: https://www.aihw.gov.au/reports/hospitals/principal-diagnosis-data-cubes/contents/data-cubes

124. Australian Institute of Health and Welfare. Heart, stroke and vascular disease – Australian facts. 2021 Sep 29 [cited 5 Feb 2022]. Available from: https://www.aihw.gov.au/reports/heart-stroke-vascular-diseases/hsvd-facts/data

125. Si S, Moss J, Karnon J, Stocks N. Cost-effectiveness evaluation of the 45-49 year old health check versus usual care in Australian general practice: A modelling study. PLoS One. 2018;13(11):e0207110.

126. National Hospital Cost Data Collection. NHCDC Round 23 Admitted Acute Cost Weight Table – Version 10.0. 2019 [cited 5 Feb 2022]. Available from: https://www.ihpa.gov.au/what-we-do/nhcdc/public-sector

127. Australian Bureau of Statistics. Consumer Price Index, Australia. 2022 Jan 25 [cited 5 Feb 2022]. Available from: https://www.abs.gov.au/statistics/economy/price-indexes-and-inflation/consumer-price-index-australia/dec-2021

128. Cadilhac DA, Dewey HM, Denisenko S, Bladin CF, Meretoja A. Changes in acute hospital costs after employing clinical facilitators to improve stroke care in Victoria, Australia. BMC Health Services Research. 2019 Jan 18;19(1):41.

129. National Heart Foundation of Australia. Economic cost of acute coronary syndrome in Australia: the cost to governments. Melbourne: National Heart Foundation of Australia; 2018.

130. Smith SL, Norman R, Moxon JV, Velu R, Quigley F, Golledge J. Outcomes and costs of open and endovascular revascularisation for chronic limb ischaemia in an Australian cohort. Heart, Lung and Circulation. 2021 Oct;30(10):1552-61.

131. Goldstein BA, Bhavsar NA, Phelan M, Pencina MJ. Controlling for informed presence bias due to the number of health encounters in an electronic health record. American Journal of Epidemiology. 2016 Dec 1;184(11):847-55.

132. Smolina K, Wright FL, Rayner M, Goldacre MJ. Long-term survival and recurrence after acute myocardial infarction in England, 2004 to 2010. Circulation: Cardiovascular Quality and Outcomes. 2012 Jul 1;5(4):532-40.

133. Kaul P, Ezekowitz JA, Armstrong PW, Leung BK, Savu A, Welsh RC, Quan H, Knudtson ML, McAlister FA. Incidence of heart failure and mortality after acute coronary syndromes. American Heart Journal. 2013 Mar;165(3):379-85 e2.

134. National Heart Foundation of Australia. Economic cost of acute coronary syndrome in Australia: the cost to individuals and their families. Melbourne: National Heart Foundation of Australia; 2018.

135. Australian Institute of Health and Welfare. Health expenditure Australia 2019–20. Canberra: AIHW; 2021.

136. Eijkenaar F, Emmert M, Scheppach M, Schoffski O. Effects of pay for performance in health care: a systematic review of systematic reviews. Health Policy. 2013 May;110(2-3):115-30.

137. Ogundeji YK, Bland JM, Sheldon TA. The effectiveness of payment for performance in health care: a meta-analysis and exploration of variation in outcomes. Health Policy. 2016 Oct;120(10):1141-50.

138. Flodgren G, Eccles MP, Shepperd S, Scott A, Parmelli E, Beyer FR. An overview of reviews evaluating the effectiveness of financial incentives in changing healthcare professional behaviours and patient outcomes. Cochrane Database of Systematic Reviews. 2011 Jul 6;2011(7):CD009255.

139. Wilding A, Munford L, Guthrie B, Kontopantelis E, Sutton M. Family doctor responses to changes in target stringency under financial incentives. Journal of Health Economics. 2022 Jul 2;85:102651.

140. Allen T, Mason T, Whittaker W. Impacts of pay for performance on the quality of primary care. Risk Management and Healthcare Policy. 2014;7:113-20.

141. Australian Government Department of Health. Practice Incentives Program Quality Improvement Incentive Fact Sheet. 2019 [cited 7 Jul 2022]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/46506AF50A4824B6CA25848600113FFF/$File/Practice-Incentives-Program-Quality-Improvement-Incentive-Fact-Sheet-what-practices-need-to-know.pdf

142. Australian Institute of Health and Welfare. Practice Incentives Program Quality Improvement Measures: National report on the first year of data 2020–21. 2021 Aug 27 [cited 7 Jul 2022]. Available from: https://www.aihw.gov.au/reports/primary-health-care/pipqi-measures-national-report-2020-21/contents/pipqi-measures/qim-8-risk-factors-recorded-for-cvd-assessment

143. World Health Organization. HEARTS technical package for cardiovascular disease management in primary health care: risk based CVD management. Geneva: WHO; 2020.

144. Gillam SJ, Siriwardena AN, Steel N. Pay-for-performance in the United Kingdom: impact of the quality and outcomes framework – a systematic review. Annals of Family Medicine. 2012 Sep-Oct;10(5):461-8.

145. Baskerville NB, Liddy C, Hogg W. Systematic review and meta-analysis of practice facilitation within primary care settings. Annals of Family Medicine. 2012 Jan-Feb;10(1):63-74.

146. Wang A, Pollack T, Kadziel LA, Ross SM, McHugh M, Jordan N, Kho AN. Impact of practice facilitation in primary care on chronic disease care processes and outcomes: a systematic review. Journal of General Internal Medicine. 2018 Nov;33(11):1968-77.

147. Harvey G, Kitson A. Translating evidence into healthcare policy and practice: Single versus multi-faceted implementation strategies – is there a simple answer to a complex question? International Journal of Health Policy and Management. 2015 Mar;4(3):123-6.

148. Kitson A, Harvey G, McCormack B. Enabling the implementation of evidence based practice: a conceptual framework. Quality in Health Care. 1998 Sep;7(3):149-58.

149. Bero LA, Grilli R, Grimshaw JM, Harvey E, Oxman AD, Thomson MA. Closing the gap between research and practice: an overview of systematic reviews of interventions to promote the implementation of research findings. BMJ. 1998 Aug 15;317(7156):465-8.

150. Mills KT, Obst KM, Shen W, Molina S, Zhang HJ, He H, Cooper LA, He J. Comparative effectiveness of implementation strategies for blood pressure control in hypertensive patients: a systematic review and meta-analysis. Annals of Internal Medicine. 2018 Jan 16;168(2):110-20.

151. Jaffe MG, Lee GA, Young JD, Sidney S, Go AS. Improved blood pressure control associated with a large-scale hypertension program. JAMA. 2013 Aug 21;310(7):699-705.

152. Howard K, White S, Salkeld G, McDonald S, Craig JC, Chadban S, Cass A. Cost-effectiveness of screening and optimal management for diabetes, hypertension, and chronic kidney disease: a modeled analysis. Value in Health. 2010 Mar-Apr;13(2):196-208.

153. Ong KS, Carter R, Vos T, Kelaher M, Anderson I. Cost-effectiveness of interventions to prevent cardiovascular disease in Australia's indigenous population. Heart, Lung and Circulation. 2014 May;23(5):414-21.

154. Stewart S, Carrington MJ, Swemmer CH, Anderson C, Kurstjens NP, Amerena J, Brown A, Burrell LM, de Looze FJ, Harris M, Hung J, Krum H, Nelson M, Schlaich M, Stocks NP, Jennings GL, Investigators V-BS. Effect of intensive structured care on individual blood pressure targets in primary care: multicentre randomised controlled trial. BMJ. 2012 Nov 20;345:e7156.

155. Stephen C, Halcomb E, Fernandez R, McInnes S, Batterham M, Zwar N. Nurse-led interventions to manage hypertension in general practice: a systematic review and meta-analysis. Journal of Advanced Nursing. 2022 May;78(5):1281-93.

156. Hoomans T, Severens JL. Economic evaluation of implementation strategies in health care. Implementation Science. 2014 Dec 18;9(1):168.

157. Australian Department of Health and Aged Care. MRFF Cardiovascular Health Mission Roadmap. 2021 Oct 1 [cited 2 Aug 2022]. Available from: https://www.health.gov.au/resources/publications/mrff-cardiovascular-health-mission-roadmap

158. Global Burden of Disease Collaborative Network. Global Burden of Disease Study 2019 (GBD 2019) Results. 2020 [cited 5 Dec 2022]. Available from: https://vizhub.healthdata.org/gbd-results/

159. Australian Institute of Health and Welfare. Australia's health 2018. Australia's health series no 16 AUS 221 2018 [cited 5 Dec 2022]. Available from: https://www.aihw.gov.au/getmedia/7ec2ec71-4af4-43cf-bdaf-e4b15a04f11d/aihw-aus-221-chapter-3-6.pdf.aspx

160. GBD 2019 Diseases and Injuries Collaborators. Global burden of 369 diseases and injuries in 204 countries and territories, 1990-2019: a systematic analysis for the Global Burden of Disease Study 2019. Lancet. 2020 Oct 17;396(10258):1204-22.

161. Khatib R, Schwalm JD, Yusuf S, Haynes RB, McKee M, Khan M, Nieuwlaat R. Patient and healthcare provider barriers to hypertension awareness,

treatment and follow up: a systematic review and meta-analysis of qualitative and quantitative studies. PLoS One. 2014;9(1):e84238.

162. Ogedegbe G. Barriers to optimal hypertension control. Journal of Clinical Hypertension (Greenwich, Conn). 2008 Aug;10(8):644-6.

163. Burnier M. Medication adherence and persistence as the cornerstone of effective antihypertensive therapy. American Journal of Hypertension. 2006 Nov;19(11):1190-6.

164. Chow CK, Gupta R. Blood pressure control: a challenge to global health systems. The Lancet. 2019 Aug 24;394(10199):613-5.

165. Burnier M. Drug adherence in hypertension. Pharmacological Research. 2017 Nov;125(Pt B):142-9.

166. Grant R, Adams AS, Trinacty CM, Zhang F, Kleinman K, Soumerai SB, Meigs JB, Ross-Degnan D. Relationship between patient medication adherence and subsequent clinical inertia in type 2 diabetes glycemic management. Diabetes Care. 2007 Apr;30(4):807-12.

167. Heisler M, Hogan MM, Hofer TP, Schmittdiel JA, Pladevall M, Kerr EA. When more is not better: treatment intensification among hypertensive patients with poor medication adherence. Circulation. 2008 Jun 3;117(22):2884-92.

168. Lopez-Simarro F, Moral I, Aguado-Jodar A, Cols-Sagarra C, Mancera-Romero J, Alonso-Fernandez M, Miravet-Jimenez S, Brotons C. [The impact of therapeutic inertia and the degree of the medication adherence on the control goals for patients with diabetes]. Semergen. 2018 Nov - Dec;44(8):579-85.

169. Sabate E. Adherence to longterm therapies: evidence for action. Geneva: World Health Organization; 2003.

170. World Health Organization. Treatment of tuberculosis: guidelines – fourth edition. Geneva: WHO; 2010.

171. Osterberg L, Blaschke T. Adherence to medication. New England Journal of Medicine. 2005 Aug 4;353(5):487-97.

172. Peterson AM, Nau DP, Cramer JA, Benner J, Gwadry-Sridhar F, Nichol M. A checklist for medication compliance and persistence studies using retrospective databases. Value in Health. 2007 Jan-Feb;10(1):3-12.

173. Raebel MA, Schmittdiel J, Karter AJ, Konieczny JL, Steiner JF. Standardizing terminology and definitions of medication adherence and persistence in research employing electronic databases. Medical Care. 2013 Aug;51(8 Suppl 3):S11-21.

174. Ho PM, Bryson CL, Rumsfeld JS. Medication adherence: its importance in cardiovascular outcomes. Circulation. 2009 Jun 16;119(23):3028-35.

175. Vrijens B, De Geest S, Hughes DA, Przemyslaw K, Demonceau J, Ruppar T, Dobbels F, Fargher E, Morrison V, Lewek P, Matyjaszczyk M, Mshelia C, Clyne W, Aronson JK, Urquhart J, Team ABCP. A new taxonomy for describing and defining adherence to medications. British Journal of Clinical Pharmacology. 2012 May;73(5):691-705.

176. Lehane E, McCarthy G. Intentional and unintentional medication non-adherence: a comprehensive framework for clinical research and practice? A discussion paper. International Journal of Nursing Studies. 2007 Nov;44(8):1468-77.

177. Wroe AL. Intentional and unintentional nonadherence: a study of decision making. Journal of Behavioral Medicine. 2002 Aug;25(4):355-72.

178. Gadkari AS, McHorney CA. Unintentional non-adherence to chronic prescription medications: how unintentional is it really? BMC Health Services Research. 2012 Jun 14;12:98.

179. Lemstra M, Nwankwo C, Bird Y, Moraros J. Primary nonadherence to chronic disease medications: a meta-analysis. Patient Preference and Adherence. 2018;12:721-31.

180. Lemstra M, Alsabbagh MW. Proportion and risk indicators of nonadherence to antihypertensive therapy: a meta-analysis. Patient Preference and Adherence. 2014;8:211-8.

181. Vrijens B, Vincze G, Kristanto P, Urquhart J, Burnier M. Adherence to prescribed antihypertensive drug treatments: longitudinal study of electronically compiled dosing histories. BMJ. 2008 May 17;336(7653):1114-7.

182. DiMatteo MR, Giordani PJ, Lepper HS, Croghan TW. Patient adherence and medical treatment outcomes: a meta-analysis. Medical Care. 2002 Sep;40(9):794-811.

183. Bailey JE, Wan JY, Tang J, Ghani MA, Cushman WC. Antihypertensive medication adherence, ambulatory visits, and risk of stroke and death. Journal of General Internal Medicine. 2010 Jun;25(6):495-503.

184. Zeber JE, Manias E, Williams AF, Hutchins D, Udezi WA, Roberts CS, Peterson AM, Group IMAGRPW. A systematic literature review of psychosocial and behavioral factors associated with initial medication adherence: a report of the ISPOR Medication Adherence & Persistence Special Interest Group. Value in Health. 2013 Jul-Aug;16(5):891-900.

185. van der Laan DM, Elders PJM, Boons C, Beckeringh JJ, Nijpels G, Hugtenburg JG. Factors associated with antihypertensive medication non-adherence: a systematic review. Journal of Human Hypertension. 2017 Nov;31(11):687-94.

186. Marshall IJ, Wolfe CD, McKevitt C. Lay perspectives on hypertension and drug adherence: systematic review of qualitative research. BMJ. 2012 Jul 9;345:e3953.

187. Gellad WF, Grenard JL, Marcum ZA. A systematic review of barriers to medication adherence in the elderly: looking beyond cost and regimen complexity. American Journal of Geriatric Pharmacotherapy. 2011 Feb;9(1):11-23.

188. Alhawassi TM, Krass I, Pont LG. Prevalence, prescribing and barriers to effective management of hypertension in older populations: a narrative review. Journal of Pharmaceutical Policy and Practice. 2015;8:24.

189. Australian Bureau of Statistics. Patient experiences in Australia: 2021–2022. 2022 Nov 18 [cited 19 Nov 2022]. Available from: http://www.abs.gov.au/ausstats/abs@.nsf/mf/4839.0

190. Alsabbagh MH, Lemstra M, Eurich D, Lix LM, Wilson TW, Watson E, Blackburn DF. Socioeconomic status and nonadherence to antihypertensive drugs: a systematic review and meta-analysis. Value in Health. 2014 Mar;17(2):288-96.

191. Cockerham WC. Health lifestyle theory and the convergence of agency and structure. Journal of Health and Social Behavior. 2005 Mar;46(1):51-67.

192. Cockerham WC, D. Wolfe J, Bauldry S. Health lifestyles in late middle age. Research on Aging. 2019 2020/01/01;42(1):34-46.

193. Gast A, Mathes T. Medication adherence influencing factors–an (updated) overview of systematic reviews. Systematic Reviews. 2019 2019/05/10;8(1):112.

194. Kronish IM, Woodward M, Sergie Z, Ogedegbe G, Falzon L, Mann DM. Meta-analysis: impact of drug class on adherence to antihypertensives. Circulation. 2011 Apr 19;123(15):1611-21.

195. Evans CD, Eurich DT, Lu X, Remillard AJ, Shevchuk YM, Blackburn D. The association between market availability and adherence to antihypertensive medications: an observational study. American Journal of Hypertension. 2013 Feb;26(2):180-90.

196. Eze-Nliam CM, Thombs BD, Lima BB, Smith CG, Ziegelstein RC. The association of depression with adherence to antihypertensive medications: a systematic review. Journal of Hypertension. 2010 Sep;28(9):1785-95.

197. Devine F, Edwards T, Feldman SR. Barriers to treatment: describing them from a different perspective. Patient Preference and Adherence. 2018;12:129-33.

198. Holt EW, Muntner P, Joyce CJ, Webber L, Krousel-Wood MA. Health-related quality of life and antihypertensive medication adherence among older adults. Age and Ageing. 2010 Jul;39(4):481-7.

199. Bandura A. Self-efficacy: toward a unifying theory of behavioral change. Psychological Review. 1977 Mar;84(2):191-215.

200. Holmes EA, Hughes DA, Morrison VL. Predicting adherence to medications using health psychology theories: a systematic review of 20 years of empirical research. Value in Health. 2014 Dec;17(8):863-76.

201. Nafradi L, Nakamoto K, Schulz PJ. Is patient empowerment the key to promote adherence? A systematic review of the relationship between self-efficacy, health locus of control and medication adherence. PLoS One. 2017;12(10):e0186458.

202. Nieuwlaat R, Wilczynski N, Navarro T, Hobson N, Jeffery R, Keepanasseril A, Agoritsas T, Mistry N, Iorio A, Jack S, Sivaramalingam B, Iserman E, Mustafa RA, Jedraszewski D, Cotoi C, Haynes RB. Interventions for enhancing medication adherence. Cochrane Database of Systematic Reviews. 2014 Nov 20;2014(11):CD000011.

203. Conn VS, Hafdahl AR, Cooper PS, Ruppar TM, Mehr DR, Russell CL. Interventions to improve medication adherence among older adults: meta-analysis of adherence outcomes among randomized controlled trials. Gerontologist. 2009 Aug;49(4):447-62.

204. Conn VS, Ruppar TM, Enriquez M, Cooper PS, Chan KC. Healthcare provider targeted interventions to improve medication adherence: systematic review and meta-analysis. International Journal of Clinical Practice. 2015 Aug;69(8):889-99.

205. Viswanathan M, Golin CE, Jones CD, Ashok M, Blalock SJ, Wines RC, Coker-Schwimmer EJ, Rosen DL, Sista P, Lohr KN. Interventions to improve adherence to self-administered medications for chronic diseases in the United States: a systematic review. Annals of Internal Medicine. 2012 Dec 4;157(11):785-95.

206. Kripalani S, Yao X, Haynes RB. Interventions to enhance medication adherence in chronic medical conditions: a systematic review. Archives of Internal Medicine. 2007 Mar 26;167(6):540-50.

207. Conn VS, Ruppar TM, Chase JA, Enriquez M, Cooper PS. Interventions to improve medication adherence in hypertensive patients: systematic review and meta-analysis. Current Hypertension Reports. 2015 Dec;17(12):94.

208. Morrissey EC, Durand H, Nieuwlaat R, Navarro T, Haynes RB, Walsh JC, Molloy GJ. Effectiveness and content analysis of interventions to enhance medication adherence and blood pressure control in hypertension: a systematic review and meta-analysis. Psychology & Health. 2017 Oct;32(10):1195-232.

209. Ogedegbe G, Schoenthaler A. A systematic review of the effects of home blood pressure monitoring on medication adherence. Journal of Clinical Hypertension (Greenwich, Conn). 2006 Mar;8(3):174-80.

210. Fletcher BR, Hartmann-Boyce J, Hinton L, McManus RJ. The effect of self-monitoring of blood pressure on medication adherence and lifestyle factors: a systematic review and meta-analysis. American Journal of Hypertension. 2015 Oct;28(10):1209-21.

211. Gwadry-Sridhar FH, Manias E, Lal L, Salas M, Hughes DA, Ratzki-Leewing A, Grubisic M. Impact of interventions on medication adherence and blood pressure control in patients with essential hypertension: a systematic review by the ISPOR Medication Adherence and Persistence Special Interest Group. Value in Health. 2013 Jul-Aug;16(5):863-71.

212. Choudhry NK, Kronish IM, Vongpatanasin W, Ferdinand KC, Pavlik VN, Egan BM, Schoenthaler A, Houston Miller N, Hyman DJ, American Heart Association Council on H, Council on C, Stroke N, Council on Clinical C. Medication adherence and blood pressure control: a scientific statement from the American Heart Association. Hypertension. 2022 Jan;79(1):e1-e14.

213. Benartzi S, Beshears J, Milkman KL, Sunstein CR, Thaler RH, Shankar M, Tucker-Ray W, Congdon WJ, Galing S. Should governments invest more in nudging? Psychological Science. 2017;28(8):1041-55.

214. Volpp KG, Asch DA. Make the healthy choice the easy choice: using behavioral economics to advance a culture of health. QJM. 2017 May 1;110(5):271-5.

215. Loewenstein G, Brennan T, Volpp KG. Asymmetric paternalism to improve health behaviors. JAMA. 2007 Nov 28;298(20):2415-7.

216. O'Donoghue T, Rabin M. Doing it now or later. American Economic Review. 1999;89(1):103-24.

217. Petry NM, Rash CJ, Byrne S, Ashraf S, White WB. Financial reinforcers for improving medication adherence: findings from a meta-analysis. American Journal of Medicine. 2012 Sep;125(9):888-96.

218. Patel MS, Volpp KG, Rosin R, Bellamy SL, Small DS, Heuer J, Sproat S, Hyson C, Haff N, Lee SM, Wesby L, Hoffer K, Shuttleworth D, Taylor DH, Hilbert V, Zhu J, Yang L, Wang X, Asch DA. A randomized, controlled trial of lottery-based financial incentives to increase physical activity among overweight and obese adults. American Journal of Health Promotion. 2018 Sep;32(7):1568-75.

219. Kimmel SE, Troxel AB, French B, Loewenstein G, Doshi JA, Hecht TE, Laskin M, Brensinger CM, Meussner C, Volpp K. A randomized trial of lottery-based incentives and reminders to improve warfarin adherence: the Warfarin Incentives (WIN2) Trial. Pharmacoepidemiology and Drug Safety. 2016 Nov;25(11):1219-27.

220. Kimmel SE, Troxel AB, Loewenstein G, Brensinger CM, Jaskowiak J, Doshi JA, Laskin M, Volpp K. Randomized trial of lottery-based incentives to improve warfarin adherence. American Heart Journal. 2012 Aug;164(2):268-74.

221. Connolly T, Butler D. Regret in economic and psychological theories of choice. Journal of Behavioral Decision Making. 2006;19(2):139-54.

222. Kahneman D, Tversky A. Prospect Theory: an analysis of decision under risk. Econometrica. 1979;47(2):263-91.

223. Giné X, Karlan D, Zinman J. Put your money where your butt is: a commitment contract for smoking cessation. American Economic Journal: Applied Economics. 2010;2(4):213-35.

224. Volpp KG, John LK, Troxel AB, Norton L, Fassbender J, Loewenstein G. Financial incentive-based approaches for weight loss: a randomized trial. JAMA. 2008 Dec 10;300(22):2631-7.

225. Dragomir A, Cote R, Roy L, Blais L, Lalonde L, Berard A, Perreault S. Impact of adherence to antihypertensive agents on clinical outcomes and hospitalization costs. Medical Care. 2010 May;48(5):418-25.

226. Sokol MC, McGuigan KA, Verbrugge RR, Epstein RS. Impact of medication adherence on hospitalization risk and healthcare cost. Medical Care. 2005 Jun;43(6):521-30.

227. Kim S, Shin DW, Yun JM, Hwang Y, Park SK, Ko YJ, Cho B. Medication adherence and the risk of cardiovascular mortality and hospitalization among patients with newly prescribed antihypertensive medications. Hypertension. 2016 Mar;67(3):506-12.

228. Simpson SH, Eurich DT, Majumdar SR, Padwal RS, Tsuyuki RT, Varney J, Johnson JA. A meta-analysis of the association between adherence to drug therapy and mortality. BMJ. 2006 Jul 1;333(7557):15.

229. Cutler RL, Fernandez-Llimos F, Frommer M, Benrimoj C, Garcia-Cardenas V. Economic impact of medication non-adherence by disease groups: a systematic review. BMJ Open. 2018 Jan 21;8(1):e016982.

230. da Costa FA, Pedro AR, Teixeira I, Braganca F, da Silva JA, Cabrita J. Primary non-adherence in Portugal: findings and implications. International Journal of Clinical Pharmacy. 2015 Aug;37(4):626-35.

231. Fischer MA, Choudhry NK, Brill G, Avorn J, Schneeweiss S, Hutchins D, Liberman JN, Brennan TA, Shrank WH. Trouble getting started: predictors of primary medication nonadherence. American Journal of Medicine. 2011 Nov;124(11):1081 e9-22.

232. Fischer MA, Stedman MR, Lii J, Vogeli C, Shrank WH, Brookhart MA, Weissman JS. Primary medication non-adherence: analysis of 195,930 electronic prescriptions. Journal of General Internal Medicine. 2010 Apr;25(4):284-90.

233. Pottegard A, Christensen R, Houji A, Christiansen CB, Paulsen MS, Thomsen JL, Hallas J. Primary non-adherence in general practice: a Danish register study. European Journal of Clinical Pharmacology. 2014 Jun;70(6):757-63.

234. Reynolds K, Muntner P, Cheetham TC, Harrison TN, Morisky DE, Silverman S, Gold DT, Vansomphone SS, Wei R, O'Malley CD. Primary non-adherence to bisphosphonates in an integrated healthcare setting. Osteoporosis International. 2013 Sep;24(9):2509-17.

235. Shin J, McCombs JS, Sanchez RJ, Udall M, Deminski MC, Cheetham TC. Primary nonadherence to medications in an integrated healthcare setting. American Journal of Managed Care. 2012 Aug;18(8):426-34.

236. Thengilsdottir G, Pottegard A, Linnet K, Halldorsson M, Almarsdottir AB, Gardarsdottir H. Do patients initiate therapy? Primary non-adherence to statins and antidepressants in Iceland. International Journal of Clinical Practice. 2015 May;69(5):597-603.

237. Jensen ML, Jorgensen ME, Hansen EH, Aagaard L, Carstensen B. Long-term patterns of adherence to medication therapy among patients with type 2 diabetes mellitus in Denmark: The importance of initiation. PLoS One. 2017;12(6):e0179546.

238. Gadkari AS, McHorney CA. Medication nonfulfillment rates and reasons: narrative systematic review. Current Medical Research and Opinion. 2010 Mar;26(3):683-705.

239. Lemstra M, Blackburn D. Nonadherence to statin therapy: discontinuation after a single fill. Canadian Journal of Cardiology. 2012 Sep-Oct;28(5):567-73.

240. Naderi SH, Bestwick JP, Wald DS. Adherence to drugs that prevent cardiovascular disease: meta-analysis on 376,162 patients. American Journal of Medicine. 2012 Sep;125(9):882-7 e1.

241. Banerjee A, Khandelwal S, Nambiar L, Saxena M, Peck V, Moniruzzaman M, Faria Neto JR, Quinto KC, Smyth A, Leong D, Werba JP. Health system barriers and facilitators to medication adherence for the secondary prevention of cardiovascular disease: a systematic review. Open Heart. 2016;3(2):e000438.

242. Yap AF, Thirumoorthy T, Kwan YH. Systematic review of the barriers affecting medication adherence in older adults. Geriatr Gerontol Int. 2016 Oct;16(10):1093-101.

243. Jaam M, Awaisu A, Ibrahim MI, Kheir N. Synthesizing and appraising the quality of the evidence on factors associated with medication adherence in diabetes: A systematic review of systematic reviews. Value Health Reg Issues. 2017 Sep;13:82-91.

244. Capoccia K, Odegard PS, Letassy N. Medication adherence with diabetes medication: A systematic review of the literature. Diabetes Educator. 2016 Feb;42(1):34-71.

245. Antoine SL, Pieper D, Mathes T, Eikermann M. Improving the adherence of type 2 diabetes mellitus patients with pharmacy care: a systematic review of randomized controlled trials. BMC Endocrine Disorders. 2014 Jul 7;14:53.

246. Lun Gan JK, Brammer JD, Creedy DK. Effectiveness of educational interventions to promote oral hypoglycaemic adherence in adults with Type 2 diabetes: a systematic review. JBI Libr Syst Rev. 2011;9(9):269-312.

247. Vignon Zomahoun HT, de Bruin M, Guillaumie L, Moisan J, Gregoire JP, Perez N, Vezina-Im LA, Guenette L. Effectiveness and content analysis of interventions to enhance oral antidiabetic drug adherence in adults with type 2 diabetes: Systematic review and meta-analysis. Value in Health. 2015 Jun;18(4):530-40.

248. Fuller RH, Perel P, Navarro-Ruan T, Nieuwlaat R, Haynes RB, Huffman MD. Improving medication adherence in patients with cardiovascular disease: a systematic review. Heart. 2018 Mar 23.

249. Rash JA, Campbell DJ, Tonelli M, Campbell TS. A systematic review of interventions to improve adherence to statin medication: What do we know about what works? Preventive Medicine. 2016 Sep;90:155-69.

250. Njie GJ, Finnie RK, Acharya SD, Jacob V, Proia KK, Hopkins DP, Pronk NP, Goetzel RZ, Kottke TE, Rask KJ, Lackland DT, Braun LT. Reducing medication costs to prevent cardiovascular disease: A community guide systematic review. Preventing Chronic Disease. 2015 Nov 25;12:E208.

251. Gandapur Y, Kianoush S, Kelli HM, Misra S, Urrea B, Blaha MJ, Graham G, Marvel FA, Martin SS. The role of mHealth for improving medication

adherence in patients with cardiovascular disease: a systematic review. Eur Heart J Qual Care Clin Outcomes. 2016 Oct 1;2(4):237-44.

252. Adler AJ, Martin N, Mariani J, Tajer CD, Owolabi OO, Free C, Serrano NC, Casas JP, Perel P. Mobile phone text messaging to improve medication adherence in secondary prevention of cardiovascular disease. Cochrane Database Syst Rev. 2017 Apr 29;4:CD011851.

253. Costa E, Giardini A, Savin M, Menditto E, Lehane E, Laosa O, Pecorelli S, Monaco A, Marengoni A. Interventional tools to improve medication adherence: review of literature. Patient Prefer Adherence. 2015;9:1303-14.

254. Marcum ZA, Hanlon JT, Murray MD. Improving medication adherence and health outcomes in older adults: An evidence-based review of randomized controlled trials. Drugs and Aging. 2017 Mar;34(3):191-201.

255. Patton DE, Hughes CM, Cadogan CA, Ryan CA. Theory-based interventions to improve medication adherence in older adults prescribed polypharmacy: A systematic review. Drugs and Aging. 2017 Feb;34(2):97-113.

256. Conn VS, Ruppar TM, Enriquez M, Cooper P. Medication adherence interventions that target subjects with adherence problems: Systematic review and meta-analysis. Research in Social & Administrative Pharmacy. 2016 Mar-Apr;12(2):218-46.

257. Conn VS, Enriquez M, Ruppar TM, Chan KC. Cultural relevance in medication adherence interventions with underrepresented adults: systematic review and meta-analysis of outcomes. Preventive Medicine. 2014 Dec;69:239-47.

258. Ruppar TM, Dunbar-Jacob JM, Mehr DR, Lewis L, Conn VS. Medication adherence interventions among hypertensive black adults: a systematic review and meta-analysis. Journal of Hypertension. 2017 Jun;35(6):1145-54.

259. Oberje EJ, de Kinderen RJ, Evers SM, van Woerkum CM, de Bruin M. Cost effectiveness of medication adherence-enhancing interventions: a systematic review of trial-based economic evaluations. Pharmacoeconomics. 2013 Dec;31(12):1155-68.

260. Mitchell MS, Goodman JM, Alter DA, John LK, Oh PI, Pakosh MT, Faulkner GE. Financial incentives for exercise adherence in adults: systematic review and meta-analysis. American Journal of Preventive Medicine. 2013 Nov;45(5):658-67.

261. Patel MS, Asch DA, Rosin R, Small DS, Bellamy SL, Eberbach K, Walters KJ, Haff N, Lee SM, Wesby L, Hoffer K, Shuttleworth D, Taylor DH, Hilbert V, Zhu J, Yang L, Wang X, Volpp KG. Individual versus team-based financial incentives to increase physical activity: A randomized, controlled trial. Journal of General Internal Medicine. 2016 Jul;31(7):746-54.

262. Patel MS, Volpp KG, Rosin R, Bellamy SL, Small DS, Fletcher MA, Osman-Koss R, Brady JL, Haff N, Lee SM, Wesby L, Hoffer K, Shuttleworth D, Taylor DH, Hilbert V, Zhu J, Yang L, Wang X, Asch DA. A randomized trial of social comparison feedback and financial incentives to increase physical activity. American Journal of Health Promotion. 2016 Jul;30(6):416-24.

263. Patel MS, Asch DA, Rosin R, Small DS, Bellamy SL, Heuer J, Sproat S, Hyson C, Haff N, Lee SM, Wesby L, Hoffer K, Shuttleworth D, Taylor DH, Hilbert V, Zhu J, Yang L, Wang X, Volpp KG. Framing financial incentives to increase physical activity among overweight and obese adults: A randomized, controlled trial. Annals of Internal Medicine. 2016 Mar 15;164(6):385-94.

264. Volpp K, Loewenstein G, Troxel A, Doshi J, Price M, Laskin M, Kimmel S. A test of financial incentives to improve warfarin adherence. BMC Health Services Research. 2008 Dec 23;8:272.

265. Tversky A, Kahneman D. Loss aversion in riskless choice: A reference-dependent model. The Quarterly Journal of Economics. 1991;106(4):1039-61.

266. Asch DA, Volpp KG. Reimagining halfway technologies with behavioral science. Annals of Internal Medicine. 2017 Oct 3;167(7):505-6.

267. Kullgren JT, Hafez D, Fedewa A, Heisler M. A scoping review of behavioral economic interventions for prevention and treatment of type 2 diabetes mellitus. Current Diabetes Reports. 2017 Sep;17(9):73.

268. Peters MD, Godfrey CM, Khalil H, McInerney P, Parker D, Soares CB. Guidance for conducting systematic scoping reviews. Int J Evid Based Healthc. 2015 Sep;13(3):141-6.

269. Peters MD, Godfrey CM, McInerney P, Soares CB, Khalil H, Parker D. Chapter 11: Scoping Reviews. In: Aromataris E, Munn Z, editors. Joanna Briggs Institute Reviewer's Manual. Adelaide, South Australia: The Joanna Briggs Institute; 2017.

270. Arksey H, O'Malley L. Scoping studies: towards a methodological framework. International Journal of Social Research Methodology. 2005 2005/02/01;8(1):19-32.

271. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JPA, Clarke M, Devereaux PJ, Kleijnen J, Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. Journal of Clinical Epidemiology. 2009 2009/10/01/;62(10):e1-e34.

272. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). Extensions in development. 2018. Available from: http://www.prisma-statement.org/Extensions/InDevelopment.aspx

273. Aromataris E, Riitano D. Constructing a search strategy and searching for evidence. A guide to the literature search for a systematic review. American Journal of Nursing. 2014 May;114(5):49-56.

274. McGowan J, Sampson M, Salzwedel DM, Cogo E, Foerster V, Lefebvre C. PRESS Peer Review of Electronic Search Strategies: 2015 guideline statement. Journal of Clinical Epidemiology. 2016 2016/07/01/;75:40-6.

275. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan-a web and mobile app for systematic reviews. Syst Rev. 2016 Dec 5;5(1):210.

276. World Congress of Epidemiology [@WEpi2021]. Co-chair of the ECR sub-committee of #WCEpi2021 announced the ECR and Best Poster awards, for those scoring highest on abstracts. Twitter 6 Sep 2021 [viewed 26 Nov 2022]. Available from: https://twitter.com/WEpi2021/status/1434832658815598597

277. National Heart Foundation of Australia. Guide to management of hypertension 2008. Quick reference guide for health professionals. Updated December 20102010.

278. Imms A, Quinn S, Nelson M. General practitioners' use of cardiovascular risk calculators. Australian Family Physician. 2010 Jan-Feb;39(1-2):57-60.

279. Dunbar J, Duggan M, Fetherston H, Knight A, McNamara K, Banks E, Booth K, Bunker S, Burgess P, Colagiuri S, Dawda P, Ford D, Greenland R, Grenfell R, Knight S, Morgan M. Heart Health: the first step to getting Australia's health on track. Melbourne: AHPC; 2017.

280. Hare AJ, Patel MS, Volpp K, Adusumalli S. The role of behavioral economics in improving cardiovascular health behaviors and outcomes. Current Cardiology Reports. 2021;23(11).

281. Belizan M, Alonso JP, Nejamis A, Caporale J, Copo MG, Sánchez M, Rubinstein A, Irazola V. Barriers to hypertension and diabetes management in primary health care in Argentina: qualitative research based on a behavioral economics approach. Translational Behavioral Medicine. 2020;10(3):741-50.

282. Waddell KJ, Shah PD, Adusumalli S, Patel MS. Using behavioral economics and technology to improve outcomes in cardio-oncology. JACC: CardioOncology. 2020;2(1):84-96.

283. Patton SR, Cushing CC, Lansing AH. Applying behavioral economics theories to interventions for persons with diabetes. Current Diabetes Reports. 2022;22(5):219-26.

284. Roy Paladhi U, Katz DA, Farquhar C, Thirumurthy H. Using behavioral economics to support PrEP adherence for HIV prevention. Current HIV/AIDS Reports. 2022;19(5):409-14.

285. Woodbury MJ, Cohen JM, Merola JF, Perez-Chada LM. Leveraging behavioral economics to promote treatment adherence: a primer for the practicing dermatologist. Journal of the American Academy of Dermatology. 2022;87(5):1075-80.

286. McLean S, Gee M, Booth A, Salway S, Nancarrow S, Cobb M, Bhanbhro S. Health Services and Delivery Research. Targeting the use of reminders and notifications for uptake by populations (TURNUP): a systematic review and evidence synthesis. Southampton (UK): NIHR Journals Library; 2014.

287. Mennini FS, Marcellusi A, von der Schulenburg JM, Gray A, Levy P, Sciattella P, Soro M, Staffiero G, Zeidler J, Maggioni A, Schmieder RE. Cost of poor adherence to anti-hypertensive therapy in five European countries. European Journal of Health Economics. 2015 Jan;16(1):65-72.

288. Australian Department of Health. New MBS items for Heart Health Check (fact sheet). 2019 Mar 27 [cited 15 Nov 2021]. Available from: http://www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/2E3497ACC7C00A68CA2583CA00171F72/$File/Factsheet%20-%20Heart%20Health%20Check.pdf

289. Hazra NC, Rudisill C, Gulliford MC. Developing the role of electronic health records in economic evaluation. European Journal of Health Economics. 2019;20(8):1117-21.

290. Asaria M, Walker S, Palmer S, Gale CP, Shah AD, Abrams KR, Crowther M, Manca A, Timmis A, Hemingway H, Sculpher M. Using electronic health records to predict costs and outcomes in stable coronary artery disease. Heart. 2016;102(10):755.

291. Culliford D, Maskell J, Judge A, Cooper C, Prieto-Alhambra D, Arden NK. Future projections of total hip and knee arthroplasty in the UK: results from the UK Clinical Practice Research Datalink. Osteoarthritis and Cartilage. 2015 Apr;23(4):594-600.

292. Maret-Ouda J, Tao W, Wahlin K, Lagergren J. Nordic registry-based cohort studies: possibilities and pitfalls when combining Nordic registry data. Scandinavian Journal of Public Health. 2017 Jul;45(17_suppl):14-9.

293. Willems IAT, Gorgels WJMJ, Oude Voshaar RC, Mulder J, Lucassen PLBJ. Tolerance to benzodiazepines among long-term users in primary care. Family Practice. 2013;30(4):404-10.

294. Low KJ, Pelter MA, Deamer RL, Burchette RJ. Identification and evaluation of risk factors in patients with continuously uncontrolled hypertension. Journal of Clinical Hypertension (Greenwich, Conn). 2015 Apr;17(4):281-9.

295. Mellish L, Karanges EA, Litchfield MJ, Schaffer AL, Blanch B, Daniels BJ, Segrave A, Pearson S-A. The Australian Pharmaceutical Benefits Scheme data collection: a practical guide for researchers. BMC Research Notes. 2015 2015/11/02;8(1):634.

296. Sheppard JP, Payne RA. Deprescribing antihypertensives in patients with multimorbidity. Prescriber. 2020 2020/10/01;31(10):16-9.

297. Doust J, Bonner C, Bell K. Future directions in cardiovascular disease risk prediction. Australian Journal for General Practitioners. 2020 07/22;49:488-94.

298. Tinetti ME, Naik AD, Dindo L, Costello DM, Esterson J, Geda M, Rosen J, Hernandez-Bigos K, Smith CD, Ouellet GM, Kang G, Lee Y, Blaum C. Association of patient priorities-aligned decision-making with patient outcomes and ambulatory health care burden among older adults with multiple chronic conditions: a nonrandomized clinical trial. JAMA Intern Med. 2019 Oct 7;179(12):1688-97.

299. Patel MS, Volpp KG, Asch DA. Nudge units to improve the delivery of health care. New England Journal of Medicine. 2018 Jan 18;378(3):214-6.

300. Schiffrin EL, Campbell NR, Feldman RD, Kaczorowski J, Lewanczuk R, Padwal R, Tobe SW. Hypertension in Canada: past, present, and future. Annals of Global Health. 2016 Mar-Apr;82(2):288-99.

301. Howes F, Hansen E, Nelson M. Management of hypertension in general practice – a qualitative needs assessment of Australian GPs. Australian Family Physician. 2012 May;41(5):317-23.

302. Chapman N, Marques FZ, Picone DS, Adji A, Broughton BRS, Dinh QN, Gabb G, Lambert GW, Mihailidou AS, Nelson MR, Stowasser M, Schlaich M, Schultz MG, Mynard JP, Climie RE. Content and delivery preferences for information to support the management of high blood pressure. Journal of Human Hypertension. 2022 2022/08/10.

303. Wang SY, Groene O. The effectiveness of behavioral economics-informed interventions on physician behavioral change: a systematic literature review. PLoS One. 2020;15(6):e0234149.

304. Patel MS, Day S, Small DS, Howell JT, 3rd, Lautenbach GL, Nierman EH, Volpp KG. Using default options within the electronic health record to increase the prescribing of generic-equivalent medications: a quasi-experimental study. Annals of Internal Medicine. 2014 Nov 18;161(10 Suppl):S44-52.

305. Frank OR. Clinical software packages can be improved to help general practitioners increase the provision of preventive care. Australian Journal of Primary Health. 2022;28(3):204-6.

306. Chapman N, Fonseca R, Murfett L, Beazley K, McWhirter RE, Schultz MG, Nelson MR, Sharman JE. Integration of absolute cardiovascular disease risk assessment into routine blood cholesterol testing at pathology services. Family Practice. 2020 Oct 19;37(5):675-81.

307. Chapman N, Picone DS, Climie RE, Schultz MG, Nelson MR, Sharman JE. Blood pressure during blood collection and the implication for absolute cardiovascular risk assessment. Pulse of the Montana State Nurses Association. 2020;8(1-2):40-6.

308. Zeng Y, Shi L, Liu C, Li W, Li J, Yang S, Yang X, Huang Q, Yang L. Effects of social norm feedback on antibiotic prescribing and its characteristics in behaviour change techniques: a mixed-methods systematic review. The Lancet Infectious Diseases. 2023;23(5):e175-e84.

309. Black JA, Campbell JA, Parker S, Sharman JE, Nelson MR, Otahal P, Hamilton G, Marwick T. Absolute risk assessment for guiding cardiovascular risk management in a chest pain clinic. Medical Journal of Australia. 2021;214(6):266-71.

310. Sheridan SL, Viera AJ, Krantz MJ, Ice CL, Steinman LE, Peters KE, Kopin LA, Lungelow D. The effect of giving global coronary risk information to adults: a systematic review. Archives of Internal Medicine. 2010 Feb 8;170(3):230-9.

311. Bailey SC, Oramasionwu CU, Infanzon AC, Pfaff ER, Annis IE, Reuland DS. An electronic health record-based strategy to systematically assess medication

use among primary care patients with multidrug regimens: feasibility study. JMIR Research Protocols. 2017 Aug 10;6(8):e157.

312. Frank O, Aylward P, Stocks N. Development of pre-consultation prevention summary and reminder sheets for patients: preliminary study of acceptability and sustainability. Australian Family Physician. 2014 May;43(5):310-4.

313. Chow CK, Atkins ER, Hillis GS, Nelson MR, Reid CM, Schlaich MP, Hay P, Rogers K, Billot L, Burke M, Chalmers J, Neal B, Patel A, Usherwood T, Webster R, Rodgers A, Hung A, Edison A, Abraham AE, et al. Initial treatment with a single pill containing quadruple combination of quarter doses of blood pressure medicines versus standard dose monotherapy in patients with hypertension (QUARTET): a phase 3, randomised, double-blind, active-controlled trial. The Lancet. 2021;398(10305):1043-52.

314. Santo K, Singleton A, Rogers K, Thiagalingam A, Chalmers J, Chow CK, Redfern J. Medication reminder applications to improve adherence in coronary heart disease: a randomised clinical trial. Heart. 2019;105(4):323-9.

315. Kassavou A, A'Court CE, Chauhan J, Brimicombe JD, Bhattacharya D, Naughton F, Hardeman W, Mascolo C, Sutton S. Assessing the acceptability of a text messaging service and smartphone app to support patient adherence to medications prescribed for high blood pressure: a pilot study. Pilot and Feasibility Studies. 2020 2020/09/21;6(1):134.

316. Australian Department of Health and Aged Care. Questions and Answers on the Chronic Disease Management (CDM) items. 2014 Mar 14 [cited 26 Nov 22]. Available from: https://www1.health.gov.au/internet/main/publishing.nsf/Content/mbsprimarycare-chronicdiseasemanagement-qanda

317. Woodley M. Should bulk-billing rates be used as a measure of healthcare success? 2021 Jun 7 [cited 26 Oct 2022]. Available from: https://www1.racgp.org.au/newsgp/professional/should-bulk-billing-rates-be-used-as-a-measure-of

318. The Royal Australian College of General Practitioners. Primary health care 10–year plan [RACGP submission to the Department of Health]. Melbourne: RACGP; 2021.

319. Medicare Benefits Schedule Review Taskforce. An MBS for the 21st century recommendations, learnings and ideas for the future: final report to the Minister for Health. Canberra: Department of Health; 2020.

320. Australian Department of Health. New Medical Benefits Schedule (MBS) item for diagnosis of hypertension through ambulatory blood pressure monitoring 2022 Jan 10 [cited 1 Oct 2022]. Available from: www.mbsonline.gov.au/internet/mbsonline/publishing.nsf/Content/E85CF435BA6315B8CA25875900779856/$File/QRG-Ambulatory-Blood-Pressure-Monitoring13.01.22.pdf

321. Partington A, Karnon J. It's not the model, it's the way you use it: exploratory early health economics amid complexity; Comment on "Problems and promises of health technologies: the role of early health economic modelling". International Journal of Health Policy and Management. 2021;10(1):36-8.

322. Padwal RS, Bienek A, McAlister FA, Campbell NR, Outcomes Research Task Force of the Canadian Hypertension Education Program. Epidemiology of hypertension in Canada: an update. Canadian Journal of Cardiology. 2016 May;32(5):687-94.