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# Original article

# Prevalence, management and control of hypertension in older adults on admission to hospital



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#### ABSTRACT

*Introduction:* The aim of this study was to explore the prevalence and management of hypertension among older adults on admission to hospital and to assess the choice of antihypertensive pharmacotherapy in light of relevant comorbid conditions using the national treatment guideline.

*Materials and methods:* A retrospective cross sectional study of 503 patients aged 65 years or older admitted to a large metropolitan teaching hospital in Sydney Australia was conducted. The main outcome measures were prevalence of hypertension, blood pressure (BP) control, antihypertensive medication use and the appropriateness of antihypertensive medications.

*Results:* Sixty-nine percent (n = 347) of the study population had a documented diagnosis of hypertension and of these, approximately one third were at target BP levels on admission to hospital. Some concerns regarding choice of antihypertensive noted with 51% of those with comorbid diabetes and 30% of those with comorbid heart failure receiving a potentially inappropriate antihypertensive agent.

*Conclusions:* Despite the use of antihypertensive pharmacotherapy, many older adults do not have optimal BP control and are not reaching target BP levels. New strategies to improve blood pressure control in older populations especially targeting women, those with a past history of myocardial infarction and those on multiple antihypertensive medications are needed.

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# 1. Introduction

Hypertension is a major risk factor for cardiovascular disease and carries a high health burden in terms of morbidity and mortality. The prevalence of hypertension increases with age, and it is estimated that older adults over the age of 65 years account for 70% of all adult hypertension in developed countries (Logan, 2011; Pimenta and Oparil, 2012). While the prevalence of hyper-

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tension in older adults is high, there is robust evidence regarding the benefits of good blood pressure (BP) control within this population, in terms of reduced mortality and morbidity (Wing et al., 2003; Bulpitt et al., 2011; Dahlöf et al., 1991; Alhawassi et al., 2015). A recent Cochrane review examining 15 clinical trials looking specifically at pharmacotherapy for hypertension in older patients found that treating those aged 60 years or older with mild to moderate hypertension reduced both all cause mortality and cardiovascular morbidity and mortality in older people (Musini et al., 2009).

Notwithstanding the benefits of managing hypertension and the ongoing discussion about what constitutes optimal hypertension management in older patients there is a paucity of data regarding actual management of hypertension in older populations in practice. Few studies have examined current prevalence or management for hypertension in older patients, and those that have been conducted often pre-date the current evidence regarding the benefits of managing hypertension in older adult population

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(Cranney et al., 1999; Fotherby et al., 1992). In the studies that have been conducted, there is some indication that management of older patients may be suboptimal. Studies in both Europe and the United States (US) have reported considerable under treatment of older patients with hypertension (Primatesta and Poulter, 2004; Lochner et al., 2012).

Transitions of care, such as hospitalization, allow for a review of chronic conditions and medications. Medication review and/or reconciliation on admission to hospital provide a complete medication history for each individual (Watt and Colquhoun, 2009). Therefore, taking the best possible medication history during the admission procedure not only provides valuable information for clinical decision-making throughout the admission, but also provides insight into the management of conditions and prescribed medications prior to hospitalization. The aim of this study was to explore the prevalence and management of hypertension among older adults on admission to hospital and to assess the choice of antihypertensive pharmacotherapy in light of relevant comorbid conditions using the national treatment guideline.

# 2. Methods

# 2.1. Patient selection and data collection

Patients aged 65 years and over, admitted to the Royal North Shore Hospital in Sydney Australia. between January 1st 2010 and December 31st 2010 were eligible for inclusion in the study. The Royal North Shore Hospital is a 600 bed tertiary metropolitan hospital located in northern Sydney, Australia. To allow for adequate medical documentation, only admissions with duration of at least 48 h were included in the sample. Patients admitted outside the study period, those for whom the medical records could not be accessed and those aged less than 65 years of age were excluded.

There were 5815 admissions during the study period which met the inclusion criteria, to reach our required sample size of 503 admissions a systematic sampling frame of every 9th admission was used. A systematic sampling frame of every 9th admission throughout the study period was used to ensure that admissions were distributed evenly throughout the year and overcome any potential seasonal clustering. Seasonal variation in cardiovascular disease has been well documented (Khan and Halder, 2014; Marti-Soler et al., 2014). Systematic sampling, also known as interval random sampling, is an economical probability sampling method in which a random selection is made for the first participant and then subsequent participants are selected using a fixed interval until the required sample size is reached (Daniel, 2012). Systematic sampling ensures the sample is spread across the entire population, or in this case, across the entire calendar year, minimizing potential seasonal variation (Daniel, 2012). For patients with multiple admissions during the study period, only the first admission in the study year was included in the study and the next consecutive admission included where relevant.

# 2.2. Study design and covariates

This was a retrospective cross sectional study using medical record audit data. Data were extracted from the medical records by a single trained researcher using a pre-defined case record form. Data collected included demographic information, medical history including documented information on relevant comorbidities, prescribed medications on admission, BP control on admission and documented hypertension diagnosis of either current or with a documented history. Comorbidities were defined as those documented in the medical record using the Charlson Comorbidity Index to calculate age adjusted Comorbidity Burden. Documented diagnoses of renal disease and chronic kidney disease were defined as chronic renal disease for the purposes of this research.

#### 2.3. Blood pressure control

Patients were considered to be at target BP control if they met the current Australian National Guideline for the Management of Hypertension (National Foundation of Australia, 2008). Comorbidities (chronic kidney disease, diabetes, peripheral arterial disease, Stroke and transient ischaemic attacks) were taken into consideration for BP targets as specified by the guidelines.

# 2.4. Antihypertensive medications

Details of antihypertensive medication use on admission, prior to any changes being made by the hospital medical team, were collected. Antihypertensive medications were defined as those medications recommended for the management of hypertension according to the current National Guideline for the Management of Hypertension (National Foundation of Australia, 2008). Medicines were coded according to the World Health Organization Anatomic Therapeutic Chemical (ATC) classification system (WHO Collaborating Centre for Drug Statistics Methodology, 2017). Antihypertensive medications included Angiotensin Converting Enzyme Inhibitors (ACEI) and Angiotensin II Receptor Blockers (ARB, ATC C09), Calcium Channel Blockers (CCB, ATC C08), Beta-Blockers (BB, ATC C07) with the exception of sotalol (C07AA07), thiazide and thiazide-like diuretics (ATC C03A, C03B and C03E) including and other antihypertensives (ATC C02), namely methyldopa, moxonidine, prazosin, terazosin, clonidine and hydralazine. Fixed-dose combination products were considered as two separate medications.

#### 2.5. Choice of antihypertensive agent and comorbid conditions

Choice of therapy was explored by examining the association between antihypertensive medication and related comorbidities. Related comorbidities were those mentioned in the National guideline current at the time the study was conducted (National Foundation of Australia, 2008). The proportion of patients receiving one or more antihypertensive therapies recommended in the current treatment guideline as potentially beneficial for each relevant comorbid condition was determined as was the proportion patients receiving one or more antihypertensive medications considered potentially harmful as per the current guideline.

#### 2.6. Statistical analysis and sample size calculation

Data were entered into a custom-designed Microsoft Access database and analyzed using the Statistical Package for the Social Sciences (SPSS) software (IBM SPSS Statistics version 20). Univariate analyses using the Student's t-test, Mann Whitney U test or Pearsons chi-squared test were used to assess difference in demographics and disease characteristics between patients with and without a documented diagnosis of hypertension. A two-tailed probability value of <0.05 was considered to be statistically significant for all analyses.

Based on previous work, the prevalence of hypertension in the study population was estimated to be between 60 and 70% (Egan et al., 2010). To determine the point prevalence within a 2% margin of error assuming a confidence level of 95% a sample size of 322–368 was required.

#### Table 1

Cohort characteristics.

	Documented diagnosis of hypertension (N = 347)	No documented diagnosis of hypertension (N = 156)	P value <b>0.004</b>	
Median age (IQR)	81.4 (74.9-87.0)	78.7 (72.6-84.4)		
Number of women (%)	209 (60.2) 86 (55.1)		0.284	
Number at target BP on admission (%)	189 (54.5) 102 (65.4)		<0.001	
Median systolic BP mmHg	142 (124–160) 133 (118–148)		<0.001	
Median diastolic BP mmHg	75 (66–83)	72 (64–82)	0.028	
Number at target blood pressure (%)	116 (33.4%)	84 (53.8%)	< 0.001	
Number living in own home (%)	288 (83.0)	127 (81.4)	0.730	
Number considered frail (%)	163 (47.0)	70 (44.9)	0.630	
Number of current smokers (%)	22 (6.3)	12 (7.7)	0.569	
Median BMI (IQR)	25 (22-29)	23.0 (21.0-26.0)	0.060	
Median comorbidity burden (Age adjusted CCI (IQR))	6.0 (5-8)	6.0 (5.0-7.0)	0.368	
Relevant cardiovascular comorbidities (Number (%))				
Heart failure	45 (13.0)	15 (9.6)	0.303	
Chronic renal disease	68 (19.6)	17 (10.9)	0.020	
Atrial fibrillation	84 (24.2)	24 (15.4)	0.026	
Past history of MI	100 (28.8)	21 (13.5)	<0.001	
Angina	48 (13.8)	11 (7.1)	0.035	
Diabetes	60 (17.3)	13 (8.3)	0.009	
Other comorbidities (Number, (%))				
Depression	48 (13.8)	21 (13.5)	1.000	
Dementia	33 (9.5)	20 (12.8)	0.274	
Asthma	34 (9.8)	16 (10.3)	0.873	
Chronic obstructive pulmonary disease	34 (9.8)	20 (12.8)	0.350	
Admission type (Number (%))				
Surgical	99 (28.5)	46 (29.5)		
Medical	112 (32.2)	59 (37.8)		
Geriatric	31 (8.9)	12 (7.7)		
Cardiology	83 (23.9)	26 (16.7)		
Other	22 (6.3)	13 (8.3)		
Median number of medications on admission (IQR)	8 (5-10)	5 (3-8)	< 0.001	
Number using each antihypertensive medication class (%				
Any antihypertensive medication	315 (90.2)	30 (19.2)		
ACEI	129 (37.2)	9 (5.8)	<0.001	
ARB	135 (38.9)	3 (1.9)	<0.001	
BB	107 (30.8)	14 (9.0)	<0.001	
CCB	122 (35.2)	7 (4.5)	<0.001	
Thiazide and thiazide-like diuretic	69 (19.9)	1 (0.6)	<0.001	
Other antihypertensive	20 (5.8)	1 (0.6)	0.004	

Note: IQR = interquartile rang, BP = blood pressure, BMI = body mass index, CCI = Charlson comorbidity index, MI = myocardial infarction, ACEI = angiotensin-converting enzyme inhibitors, ARB = angiotensin II receptor blockers, BB = beta blockers, CCB = calcium channel blockers.

\* Methyldopa, moxonidine, prazosin, terazosin, clonidine and hydralazine.

# 2.7. Ethical approval

Ethical approval for this study was granted by the Northern Sydney Central Coast Health (NSCCH) Human Research Ethics Committee (HREC) protocol number (1105-147M). Due to the retrospective nature of the study design, the ethical approval granted included a waiver of the need for informed consent from study cohort participants.

# 3. Results

# 3.1. Prevalence of hypertension

The study cohort consisted of 503 patients aged  $\geq$ 65 years admitted to the hospital during 2010. Of these, 69.0% (n = 347) had a documented diagnosis of hypertension. Patients with a documented diagnosis of hypertension were significantly older than those without hypertension (Table 1). Patients with hypertension had higher systolic and diastolic BP on admission and were more likely to have a co-existing documented disease, atrial fibrillation, and a past history of myocardial infarction (MI), angina or diabetes (Table 1). There was no difference in the prevalence of non-cardiovascular comorbidities between patients with and without hypertension.

# 3.2. Hypertension and target blood pressure control

One third of all patients with a documented diagnosis of hypertension (33.4%) were at target BP on admission to hospital taking relevant comorbidities into consideration (Table 1). Most patients (66.6%) had been diagnosed with hypertension for longer than six months. Information regarding BP control prior to hospitalization was available for only 16.4% of patients and of these, 30% (n = 17) were reported to be at their target BP.

#### 3.3. Antihypertensive pharmacotherapy

While antihypertensive agents may be used for a number of cardiovascular conditions in addition to hypertension, patients with documented hypertension were significantly more likely to use an antihypertensive agent than those without (Table 1).

The median number of antihypertensive agents per patient was 2.0 (IQR 1.0-2.0). No association between blood pressure control on hospital admission and the number of antihypertensive agents used prior to admission was observed. (Table 2). The majority of patients with a documented diagnosis of hypertension were using one or more antihypertensive medications, 38% (n = 131/347) were using monotherapy and 51% used multiple antihypertensive agents. Of those using multiple agents, 31% (n = 107/347) used

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#### Table 2

Number of antihypertensive medications used prior to current admission by patients with documented history of hypertension (n = 347).

Number of antihypertensive agents	Percentage of patients at target BP (n = 189) (%)	Percentage of patients NOT at target BP (n = 149) (%)
0 (n = 34)	23.53	76.5
1 (n = 129)	38.0	62.0
2 (n = 111)	41.4	58.6
≥3 (n = 73)	34.2	65.8

two agents and 20% (n = 70/347) used three or more antihyperten-

sive agents prior to their admission. Slightly over one quarter of patients (n = 57/216, 26.4%) with documented hypertension using

multiple agents were using a fixed-dose combination. The most

common fixed-dose combination was irbesartan/hydrochlorothia zide (n = 22) followed by telmisartan/hydrochlorothiazide (n = 8) and perindopril/indapamide (n = 8). Using a fixed-dose combination antihypertensive agent was not associated with being at target blood pressure control ( $\chi^2$  = 0.798, p = 0.372). Eleven percent (n = 39) of patients were not using any antihypertensive agents.

Angiotensin II receptor blockers were the most commonly used medication type, followed closely by ACEI and CCB. Almost three quarters (72.0%) of patients were using either an ACEI (37.2%) or an ARB (38.9%), with a small percentage using both (4%).

#### 3.4. Choice of antihypertensive agent and comorbid conditions

In general, the majority of patients were receiving antihypertensive treatment in accordance with the guidelines taking

#### Table 3

Choice of antihypertensive agent in hypertension patients with documented comorbid conditions. Choices recommended the National treatment guidelines for each comorbidity are highlighted in green, those that are considered poor choices and recommended to be used with caution or contraindicated in the National Guideline are highlighted in red.

	At least one medication recommended in the national guideline n (%)	At least one medication NOT recommended in the national guideline n (%)	ACE or ARB <sup>§</sup> n (%)	BB <sup>§</sup> n (%)	CCB <sup>§</sup> n (%)	Thiazide <sup>§§</sup> n (%)	Other antihypertensives <sup>§</sup> n (%)
Angina (n=48)	45 (93.8%)	NA	37 (77.1%)	13 (27.1%)	24 (50%)	12 (25.0%)	6 (12.5%)
Atrial Fibrillation (n=71)	65 (91.5%)	NA	53 (74.6%)	21 (29.6%)	27 (38.0%)	10 (14.1%)	4 (5.6%)
Asthma/COPD (n=34)	NA	10 (14.9%)	45 (67.2%)	10 (14.9%)	25 (37.3%)	18 (26.9%)	5 (7.5%)
Depression (n=49)	NA	7 (14.3%)	30 (61.2%)	7 (14.3%)	20 (40.8%)	10 (20.4%)	0
Gout (n=26)	22 (84.6%)	2 (7.7%)	22 (84.6%)	8 (30.8%)	9 (34.6%)	2 (7.7%)	0
Heart Failure (n=49)	38 (77.6%)	15 (30.6%)	34 (69.4%)	16 (32.7%)	15 (30.6%)	7 (14.3%)	3 (6.1%)
Myocardial infarction (n=100)	89 (89.0%)	NA	74 (74.0%)	36 (36.0%)	31 (31.0%)	11 (11.0%)	8 (8.0%)
Chronic renal disease (n=68)	47 (69.1%)	NA	47 (69.1%)	16 (23.5%)	26 (38.2%)	15 (22.1%)	5 (7.4%)
Cerebrovascular disease (n=71)	53 (74.6%)	NA	51 (71.8%)	11 (15.5%)	29 (40.8%)	12 (16.9%)	3 (4.2%)
Diabetes (n=60)	50 (83.3%)	31 (51.7%)	50 (83.3%)	18 (30.0%)	25 (41.7%)	16 (26.7%)	6 (10.0%)

Note: Percentages for each comorbidity do not sum to 100% as patients may use multiple agents.

§ Including combination products.

<sup>§§</sup> Methyldopa, moxonidine, prazosin, terazosin, clonidine and hydralazine.

relevant comorbid condition into account (Table 3). Those with comorbid angina or atrial fibrillation were most likely to receive one or more antihypertensive medications considered in the guide-line as potentially beneficial, while those with chronic kidney disease were least likely to receive guideline recommended treatment. Almost 50% of patients with diabetes received one or more antihypertensive medications considered in the guidelines to be potentially harmful, namely beta blockers (30%) or thiazide diuretics (27%). Almost one third of patients (30%) with comorbid heart failure were currently using calcium channel blockers, all of which were considered potentially harmful in the treatment guideline.

#### 4. Discussion

This study has shown that, notwithstanding the emergence of a robust body of evidence supporting the importance and clinical benefit of treating hypertension in older persons over the past decade, considerable gaps remain in the uptake of evidence into clinical practice. Over two thirds of older adults presenting to hospital in this study had a documented diagnosis of hypertension and despite the majority of the study population receiving antihypertensive pharmacotherapy, just over half were at their BP target as defined by the current National Guideline for the Management of Hypertension on admission to hospital and once relevant comorbidities were taken into consideration a high proportion were receiving antihypertensives medicines that were considered potentially harmful according to the guidelines current at the time of the study.

#### 4.1. Prevalence of hypertension in older populations

In this study, two thirds or older adults presenting to hospital had a history of hypertension. Given that participants in this study were identified on hospital presentation it could be expected that the prevalence in our population is higher than that reported elsewhere however this does not appear to be the case. Similar prevalence for hypertension, between 60% and 70% have been reported for hypertension in older community dwelling populations internationally (Ma et al., 2015; Polsinelli et al., 2017). A longitudinal study by Egan et al. using the The National Health and Nutrition Examination Survey (NHANEs) data showed that the prevalence of hypertension among those aged over 60 years has remained consistently between 60 and 70% since 2008 (Egan et al., 2010).

#### 4.2. Blood pressure control

Blood pressure control in this study was slightly higher than previously reported in other studies, however the majority of data regarding current practices in the management of hypertension comes from the general population rather than from older populations. Data from the Framingham cohort, where two thirds were aged over 60 years, reported that 48% of participants were at target BP (Lloyd-Jones et al., 2005) while a community-based study in the US found that 43% of participants were at target levels (McAlister et al., 2011). However, the mean age of subjects in both these studies was much younger than those included in our sample. There may be some indication that BP control in older persons is improving over time with 55% of our sample at target BP compared to 19% in a 2000/2001 study that used data from the Health Survey for England to look at BP control in those aged 65 years and older (Primatesta and Poulter, 2004). This observed improvement in BP control in older adults concurs with results from recent studies, which showed a noticeable trend to improvement in hypertension management. However, the BP control rate is not yet optimal in a significant proportion of older patients with hypertension (McAlister et al., 2011; Pont and Alhawassi, 2016; Alhawassi et al., 2015).

#### 4.3. Antihypertensive medications

In our cohort almost all individuals were using at least one antihypertensive agent, with less than one quarter of the cohort receiving monotherapy. Blood pressure control did not increase significantly with increasing number of antihypertensive agents most likely reflecting the need for more intensive pharmacotherapy among those with the most difficult to control blood pressure. Management of optimal BP control and management of hypertension in the older adults remains challenging (Pont and Alhawassi, 2016). A review of international treatment guidelines supporting management of hypertension demonstrated the lack of guidance for managing hypertension among older persons (Alhawassi et al., 2015). While considerable evidence exists regarding the efficacy of pharmacotherapy for older populations with hypertension there is a lack of guidance optimal management in daily practice.

#### 4.4. Choice of antihypertensive agent and comorbid conditions

Taking relevant comorbidities into consideration, the majority of the older patients in this cohort were receiving potentially beneficial antihypertensive treatment consistent with that recommended in the guideline current at the time of the study. However when potentially harmful antihypertensive choices were considered in light of relevant comorbidities, over half of all patients with diabetes were receiving an antihypertensive, namely a beta-blocker or thiazide, considered potentially harmful in the treatment guidelines. It should be noted that both beta blockers and thiazide diuretics are recommended for use with caution rather than contraindicated in the guideline, and the guidelines recommend that thiazide diuretics may be considered beneficial in the management of type 2 diabetes when used in combination with an ACE inhibitor. Furthermore, the current guideline at the time the study was conducted was revised in 2016 with changes to the recommended pharmacotherapy for relevant comorbidities. In the 2016 National guideline, the use of calcium channel blockers in hypertension patients with co-existing heart failure and the use of beta blockers in those with type 1 or 2 diabetes remains a relative contraindication, suggesting these agents should be used with caution among older persons with hypertension (National Heat Foundation of Australia, 2016).

It should be noted that there are often considerable differences in recommendations included in treatment guidelines (Oxman et al., 2008). A systematic review of treatment guidelines for the management of hypertension reported significant disagreement in terms of which agents should be utilized for older populations (Alhawassi et al., 2015). Thiazide diuretics and calcium channel blockers were recommended as first line therapy for older adults in the majority of guidelines, with a number specifically recommending dihydropyridine calcium channel blockers (Alhawassi et al., 2015). Similar differences regarding choice of optimal pharmacotherapy for hypertension with relevant comorbid conditions is likely to exist, thus choice of therapy should not only take the medical evidence into consideration, such as clinical guidelines, but also on physician clinical judgment and patient preferences to ensure that each individual receives optimal pharmacotherapy taking their individual clinical context into consideration (Hoffmann et al., 2014).

An important consideration in the use of multiple antihypertensive agents in older patients is the potential for cumulative adverse effects associated with the concurrent use of multiple agents. While there is strong evidence to support the use of pharmacotherapy to manage BP in older population, pharmacokinetic and dynamic changes associated with ageing increase the risk of adverse drug reactions and make older persons more vulnerable to the adverse effects associated with antihypertensive medications. Antihypertensive medications have been associated with a number of adverse effects in older people including postural hypotension, increased risk of falls, electrolyte disturbances and deterioration in renal function (Pimenta and Oparil, 2012). Use of high anti-hypertensive doses or concomitant use of multiple agents may increase these risks and further work exploring and quantifying the risk of adverse outcomes associated with antihypertensive pharmacotherapy is needed.

# 4.5. Study limitations

One limitation in our study was the identification of participants with hypertension. As we were interested in the choice of pharmacotherapy being used for the management of hypertension, participants in this study were considered to have hypertension if they had a documented diagnosis of pre-existing hypertension in their medical record. This may overestimate the prevalence of hypertension. The Australian National Blood Pressure (ANBP) study demonstrated that a significant proportion of older adults remained normotensive following withdrawal of their antihypertensive therapy, suggesting that the initial diagnostic methodology for hypertension in general practice may be unreliable for some older patients (Nelson et al., 2003). Similarly we relied on documentation of comorbid conditions in the medical record, which may be affected by differences in clinical practice at the time of diagnosis. These may further impacted by differences in clinical documentation. A second limitation of our study is that blood pressure control was assessed on admission to hospital and may not necessarily reflect long-term blood pressure control. Acute anxiety, such as that which may be experienced during hospitalization is associated with short-term increases in blood pressure and may mean that our results over estimate the extent of sub optimal blood pressure control in our older population (Byrd and Brook, 2014). However the importance of understanding blood pressure control in older persons presenting to hospital should not be underestimated. Previous work in the same cohort found that 70% of the cohort was not at target BP prior to hospitalization (Alhawassi et al., 2015). The same research reported that hospitalization was associated with considerable change to antihypertensive medication regimens, even when the primary reason for admission is non-cardiovascular (Alhawassi et al., 2015). Finally, data extraction was undertaken by a single researcher to ensure consistency throughout the study but, common to all retrospective studies reliant on health record data, data quality and availability was dependent on the quality of documentation by the health care team at the time of care.

# 5. Conclusions

The results of this study show that older patients with a history of hypertension are receiving antihypertensive pharmacotherapy, but just over half were at target BP levels according to the current national guideline highlighting a clear evidence-practice gap. Balancing the benefits of antihypertensive pharmacotherapy against increased risk potential medication related harms among older persons remains challenging.

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#### **Conflict of interest**

The authors report no conflicts of interest relevant to this research.

#### **Author contribution**

TA contributed to study conception and design, data collection, analysis and interpretation, drafting and critical revision of the manuscript. IK contributed to study conception and design, data analysis and interpretation, and critical revision of the manuscript. LP contributed to study conception and design, data analysis and interpretation, drafting and critical revision of the manuscript.

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