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PHARMACOEPIDEMIOLOGY

How does prescribing for antihypertensive products stack up against guideline recommendations? An Australian population-based study (2006–2014)

Correspondence Andrea L. Schaffer, Centre for Big Data Research in Health, University of New South Wales, Sydney, NSW 2052, Australia. Tel.: +61 2 9385 8895; Fax: +61 2 9385 3880; E-mail: andrea.schaffer@student.unsw.edu.au

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Andrea L. Schaffer[1], Sallie-Anne Pearson[1] and Nicholas A. Buckley[2]

[1]Centre for Big Data Research in Health, University of New South Wales, Sydney, NSW, 2052, Australia, and [2]Blackburn Building (D06), University of Sydney, Sydney, NSW, 2006, Australia

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AIMS

We describe choice of first-line antihypertensive drug therapy and uptake of fixed-dose combinations (FDCs) in Australia, and investigate the impact of initiation on FDCs and other non-recommended first-line therapies on treatment discontinuation.

METHOD

This was a population-based retrospective cohort study using a random 10% sample of persons dispensed an Australian Pharmaceutical Benefits Scheme listed medicine from 1 July 2005 to 30 June 2014. The primary outcomes were adherence to Australian recommendations at initiation of antihypertensive therapy, discontinuation of initial therapy and discontinuation of any therapy in the first year after initiation.

RESULTS

In our sample of 55 937 persons initiating therapy, 42.0% did so outside Australian recommendations, including not initiating on recommended monotherapy (26.3%) and not initiating on the lowest recommended dose (30.6%). Only 1.7% of individuals who were dispensed an FDC established therapy on the free combination regimen (as recommended) prior to switching. After adjusting for covariates, persons initiating on non-recommended monotherapy (OR = 2.64, 95% CI 2.47–2.83) or FDCs of two or more antihypertensives (OR = 1.42, 95% CI 1.30–1.55), were more likely to discontinue all antihypertensive drug treatment in the first year compared to persons initiating on recommended monotherapy.

CONCLUSION

More than half of antihypertensive initiators conformed to Australian guidelines. Initiation on FDCs and other non-recommended treatments was associated with lower persistence on antihypertensive therapy in the first year. Long-term effectiveness and outcomes may be enhanced by initiating with low dose monotherapy.

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WHAT IS ALREADY KNOWN ABOUT THIS SUBJECT

- Use of FDCs to treat hypertension has been increasing.
- In Australia, there is little evidence about how use of antihypertensives, in particular FDCs, follows guidelines.
- While there is evidence that the use of FDCs increases persistence compared to the equivalent free combination, little is known about how initiating on FDCs compares to recommended monotherapy.

WHAT THIS STUDY ADDS

- In Australia the choice of first-line antihypertensive agent follows guidelines for most individuals.
- FDCs are being used outside guideline recommendations and often involve higher doses than monotherapy.
- Initiation on an FDC and non-recommended monotherapy was associated with lower persistence on any antihypertensive therapy in the first year.

Introduction

Worldwide, antihypertensive medications are used by 29% of men and 41% of women [1]. Treating hypertension is complex, as patients often require multiple medicines to control their blood pressure [2–4]. Moreover, there are a large number of available antihypertensive agents with differing efficacy, side effects and cost; prescribing physicians must account for these multiple factors, as well as a patient's comorbid conditions and other prescribed medicines, when determining the best line of treatment [5]. A large proportion of those initiated on antihypertensive drugs discontinue their medication [6, 7]. Thus, a key determinant of real world effectiveness is persistence.

Fixed-dose combination (FDC) products for the treatment of hypertension consist of a single pill containing the active ingredients of two or three antihypertensives with different mechanisms of action. While they reduce pill burden, the lack of dose flexibility with FDCs can be problematic, and create difficulty with identifying the cause of adverse effects [8, 9]. Additionally, while FDCs can reduce out-of-pocket costs for patients [10, 11], they often incur higher costs for third-party payers than the subsidy of the individual components [12].

Many international guidelines [13–15] suggest that individuals with severe hypertension should initiate on combination therapy. In contrast, Australian guidelines only recommend initiation on a single antihypertensive, adding in a second component, followed by upward titration of doses if blood pressure is not adequately controlled [16]. The guidelines additionally recommend that patients be stabilized on both of the individual antihypertensives prior to switching to an FDC. There is support for the use of FDCs as first-line therapy [17, 18], with those continuing on therapy having better blood pressure control than those initiating with monotherapy [19, 20]. While one meta-analysis did not find a persistence benefit for FDCs compared to free combination therapy [21], more recent observational studies have found that initiation on an FDC is associated with greater persistence [22–25], but few studies have compared initiation on an FDC to monotherapy. The current literature suggests that initiating on an FDC is associated with greater persistence than diuretic monotherapy, but worse persistence than other types of monotherapy [26–28].

International and Australian studies report that the use of combination therapy is increasing [17, 29, 30]. Therefore, the objective of this study is to investigate antihypertensive use in Australia, and how real world use compares to Australian guideline recommendations. Specifically, we focus on three aspects of the guidelines: (1) first-line therapy; (2) uptake of FDCs; and (3) how deviation from recommendations affects discontinuation in the first year.

Methods

Australian guidelines

The guidelines were published in 2008 and updated in 2010 and include recommendations for diagnosis of hypertension, evaluating patients with hypertension, lifestyle modification and drug treatment [16]. We focused on drug treatment guidelines, which recommend initiation on monotherapy with an angiotensin-converting-enzyme (ACE) inhibitor, angiotensin-II receptor blocker (ARB), calcium channel blocker, or thiazide diuretic (in individuals ≥65 years only); this differs from UK guidelines, which recommend initiation on calcium channel blocker monotherapy in individuals ≥55 years [31]. The guidelines also provide specific advice for individuals with comorbid or associated conditions. Australian guidelines do not recommend initiation on an FDC, in contrast to North American guidelines that recommend their use as first-line therapy in certain individuals [13, 14]. The recommendations remained consistent during the entire study period.

Data source and study population

In Australia, all citizens and permanent residents are entitled to subsidized access to prescribed medicines through the Pharmaceutical Benefits Scheme (PBS). We used PBS dispensing records from 1 July 2005 to 30 June 2014 for a 10% random sample of persons dispensed a PBS-listed medicine. This is a standard dataset provided by the Department of Human Services for analytical use and is selected based on the last digit of each individual's randomly assigned unique identifier. This dataset captures all dispensed PBS-listed medicines attracting a government subsidy, which occurs when the price of the medicine is above the PBS co-payment threshold. While many commonly dispensed antihypertensives fall below the general co-payment and would not be captured in the data, certain individuals ('concessional beneficiaries') are eligible for a reduced co-payment. This population consists primarily of individuals ≥65 years and/or with low incomes and represent the majority of

individuals prescribed antihypertensives. We included only long-term concessional beneficiaries (e.g. individuals dispensed only medicines attracting a reduced co-payment during the entire study period), as we would have complete capture of dispensed medicines in this population for the entire study period. Individuals had to have at least one dispensing record for any medicine during the run-in period prior to initiation. To protect the privacy of persons in this dataset, all dates of dispensing are offset randomly by +14 or −14 days; the direction of the offset is the same for all records for each individual.

Our cohort consisted of all persons initiating antihypertensives. As it is common for people to reinitiate on antihypertensives after periods of non-use, and prior antihypertensive therapy is likely to influence subsequent treatment, to ensure that the cohort consisted primarily of persons naïve to antihypertensives, we used a three-year run-in period without evidence of a dispensing for an antihypertensive to define incident use.

Antihypertensive medicines

We classified medicines using the WHO's Anatomic Therapeutic Classification and included all individual and combination medicines listed on the PBS with a primary indication for the treatment of arterial hypertension, including: C03 – Diuretics (hydrochlorothiazide, chlorthalidone, indapamide), C07 – Beta-blockers (oxprenolol, atenolol, metoprolol tartrate, labetalol), C08 – Calcium channel blockers (felodipine, amlodipine, nifedipine, lercanidipine, verapamil, diltiazem) and C09 – Agents acting on the renin-angiotensin system (ramipril, enalapril, perindopril, captopril, fosinopril, quinapril, trandolapril, lisinopril, valsartan, eprosartan, candesartan, irbesartan, olmesartan, telmisartan, losartan). We excluded C02 (antihypertensives) as medicines in this class are more commonly used to treat conditions other than hypertension in Australia. The PBS-listed FDCs of two or more antihypertensives include: an ACE inhibitor/ARB combined with a diuretic (fosinopril/hydrochlorothiazide, candesartan/hydrochlorothiazide, perindopril/hydrochlorothiazide, quinapril/hydrochlorothiazide, eprosartan/ hydrochlorothiazide, telmisartan/hydrochlorothiazide, irbesartan/hydrochlorothiazide, olmesartan/hydrochlorothiazide, valsartan/hydrochlorothiazide); an ACE inhibitor/ARB combined with a calcium channel blocker (ramipril/felodipine, trandolapril/verapamil, lercanidipine/enalapril, perindopril/amlodipine); and an ARB combined with a calcium channel blocker and a diuretic (valsartan/amlodipine/hydrochlorothiazide, olmesartan/amlodipine/hydrochlorothiazide). We also included FDCs of an antihypertensive and a medicine where the primary indication was not hypertension, specifically hydrochlorothiazide combined with a potassium-sparing diuretic (amiloride, triamterene) and amlodipine combined with atorvastatin. All antihypertensives dispensed within the first seven days of initiation were considered to be part of the first-line therapy.

To determine whether prescribing of first-line therapy adhered to the guidelines, we classified antihypertensives into the following groups: ACE inhibitors, ARBs, thiazide diuretics (including thiazide-like diuretics), beta-blockers and calcium channel blockers. To describe the first year of treatment, we further classified first-line treatment into: ACE inhibitor/ARB monotherapy, thiazide diuretic monotherapy, beta-blocker monotherapy, calcium channel blocker monotherapy, antihypertensive FDC only, other FDC only and multiple antihypertensive medicines.

Measures

We identified individuals dispensed medicines for the treatment of several health conditions the year prior to initiation, including those for which there were recommended prescribing practices in the guidelines: angina (C01DA – organic nitrates), depression (N06A – depression, excluding lithium), diabetes (A10 – drugs used in diabetes), gastro-oesophageal reflux disease (GORD) (A02BC – proton pump inhibitors), gout (M04 – antigout preparations), heart failure (spironolactone, eplerenone, frusemide, digoxin, ethacrynic acid, carvedilol, bisoprolol, metoprolol succinate), hyperlipidaemia (C10 – lipid modifying agents), and obstructive airway disease (R03 – drugs for obstructive airway disease).

Given the absence of daily dose information, we assumed that individuals were taking one or two tablets per day, in accordance with recommendations for each specific medicine, to determine total days' supply. We defined discontinuation as a period of 60 days or more past the last day of use (as defined by total days' supply) without any dispensing. We identified individuals who were still using the same antihypertensive(s) that they initiated on at the end of the first year, without discontinuing, switching to a different antihypertensive or adding another antihypertensive during the entire year. We also calculated the dose for each medicine at initiation.

We identified all individuals who were ever dispensed an antihypertensive FDC in the first year of treatment, calculated the time to initiation, and determined whether they had been dispensed either of the individual medicines, or medicines from the same class(es), prior to initiation.

Statistical analysis

Using logistic regression, we determined the predictors of initiating on each class of antihypertensives (in comparison to all other antihypertensive classes), and predictors of discontinuation in the first year. All models were adjusted for year of initiation, sex, age at initiation, the number of medicines dispensed in the year prior to initiation, and having been dispensed medicines for the management of angina, depression, diabetes, GORD, gout, heart failure, hyperlipidaemia and/or obstructive airway disease. The discontinuation model also included measures of concordance with Australian guidelines. Individuals who initiated on FDCs other than a combination of two antihypertensives were excluded from this model. All analyses were performed with SAS version 9.3 (SAS Institute Inc., Cary, NC, USA) and Stata version 12 (Statacorp, College Station, TX, USA).

Ethics and data access approval

This study has ethics approval from the New South Wales Population and Health Services Ethics committee (2013/11/

494). Data access was approved by the Australian Department of Human Services External Request Evaluation Committee.

Results

Choice of first-line therapy

Over the study period, 55 937 people initiated antihypertensive therapy. The median age was 67 years (interquartile range (IQR), 54–75), and 56.6% were female (Table 1). ACE inhibitors (39.1%) followed by ARBs (29.9%) were the most common antihypertensive classes initiated. Initiation of therapy using a thiazide diuretic (9.9%) was least common. The majority of people dispensed ACE inhibitors (88.0%) and ARBs (85.0%) initiated on monotherapy.

Five per cent (n = 2804) of individuals initiated on an antihypertensive FDC, most commonly an ACE inhibitor/ARB in combination with a diuretic (71.4%), followed by an ACE inhibitor/ARB in combination with a calcium channel blocker (26.8%), and a triple combination of an ARB, a calcium channel

Table 1

Characteristics of antihypertensive initiators [n (%)] by choice of first-line therapy

	ACE inhibitors (n = 21 862)	ARBs (n = 16 710)	Thiazide diuretics (n = 5548)	Beta-blockers (n = 9479)	Calcium channel blockers (n = 8085)	Total (n = 55 937)
Age						
18–49 years	3553 (16.3)	3001 (18.0)	1322 (23.8)	2143 (22.6)	1708 (21.1)	10 531 (18.8)
50–59 years	2969 (13.6)	2550 (15.3)	785 (14.2)	1049 (11.1)	1018 (12.6)	7470 (13.4)
60–69 years	5857 (26.8)	4968 (29.7)	1379 (24.9)	2156 (22.8)	2037 (25.2)	14 869 (26.6)
70–79 years	6316 (28.9)	4523 (27.1)	1409 (25.4)	2585 (27.3)	2226 (27.5)	15 635 (28.0)
80+ years	3167 (14.5)	1668 (10.0)	653 (11.8)	1546 (16.3)	1096 (13.6)	7432 (13.3)
Sex						
Male	10 414 (47.6)	7192 (43.0)	1908 (34.4)	4142 (43.7)	3406 (42.1)	24 276 (43.4)
Female	11 448 (52.4)	9518 (57.0)	3640 (65.6)	5337 (56.3)	4679 (57.9)	31 661 (56.6)
Number of medicines dispensed in year prior						
Quartile 1 (1–2)	5669 (25.9)	4736 (28.3)	1361 (24.5)	2212 (23.3)	2033 (25.2)	14 324 (25.6)
Quartile 2 (3–4)	5082 (23.3)	3954 (23.7)	1165 (21.0)	2115 (22.3)	1751 (21.7)	12 749 (22.8)
Quartile 3 (5–7)	5370 (24.6)	3984 (23.8)	1375 (24.8)	2363 (24.9)	1878 (23.2)	13 664 (24.4)
Quartile 4 (≥8)	5741 (26.3)	4036 (24.2)	1647 (29.7)	2789 (29.4)	2423 (30.0)	15 200 (27.2)
Medicines dispensed for treatment of						
Angina	814 (3.7)*	230 (1.4)	66 (1.2)	685 (7.2)*	332 (4.1)*	1941 (3.5)
Depression	4935 (22.6)	3656 (21.9)	1375 (24.8)	2400 (25.3)	1951 (24.1)	13 091 (23.4)
Diabetes	3059 (14.0)*	1500 (9.0)	338 (6.1)	564 (6.0)	559 (6.9)	5514 (9.9)
Gastro-oesophageal reflux disease	6515 (29.8)	4746 (28.4)	1671 (30.1)	3040 (32.1)	2546 (31.5)	16 891 (30.2)
Gout	803 (3.7)	620 (3.7)	145 (2.6)	307 (3.2)	242 (3.0)	1928 (3.5)
Heart failure	1626 (7.4)*	662 (4.0)	379 (6.8)	741 (7.8)*	451 (5.6)	3537 (6.3)
Hyperlipidaemia	6720 (30.7)	4493 (26.9)	1304 (23.5)	2674 (28.2)	2092 (25.9)	15 788 (28.2)
Obstructive airway disease	4225 (19.3)	3202 (19.2)	1237 (22.3)	1575 (16.6)	1897 (23.5)	11 011 (19.7)
Initiated as part of fixed-dose combination						
Antihypertensives combination	1136 (5.2)	2077 (12.4)	2405 (43.3)	0 (0.0)	867 (10.7)	3205 (5.7)
Other combination†	0 (0.0)	0 (0.0)	1307 (23.6)	0 (0.0)	681 (8.4)	1988 (3.5)
Initiated in free combination with another antihypertensive						
	1523 (7.0)	483 (3.0)	126 (2.3)	1403 (14.8)	963 (11.9)	2434 (4.3)

Individuals can appear in more than one column if initiated on multiple antihypertensives. *Possibly dispensed for indication other than hypertension. †Other combinations include hydrochlorothiazide and a potassium-sparing diuretic, and amlodipine and atorvastatin.

blocker and a thiazide diuretic (1.9%), while 4.3% (n = 2434) initiated on multiple medicines.

Consistent with the guidelines, in our multivariable analysis persons dispensed diabetes medicines were more likely to be dispensed ACE inhibitors (OR = 2.15, 95% CI 2.02–2.28) but less likely to be dispensed thiazide diuretics (OR = 0.54, 95% CI 0.48–0.62) (Table S1). Beta-blockers were less commonly used in persons dispensed medicines for diabetes (OR = 0.47, 95% CI 0.43–0.52) and obstructive airway disease (OR = 0.67, 95% CI 0.62–0.71), but more common in persons dispensed medicines to treat angina (OR = 2.54, 95% CI 2.29–2.82) and depression (OR = 1.06, 95% CI 1.00–1.12); the latter combination is considered potentially harmful in the guidelines. Other potentially harmful/beneficial practices are indicated in Table S1.

Overall, 58.1% (n = 32 469) of initiators had no observed deviations from Australian guidelines. The most common deviations were not initiating on monotherapy with an ACE inhibitor, ARB, calcium channel blocker or thiazide diuretic (≥65 years only) (26.3%), and not initiating on the lowest recommended dose (30.6%) (Table 2). Persons who initiated on non-recommended therapies (i.e. non-recommended monotherapy, an FDC or multiple medicines) tended to be younger and also were more likely to initiate on higher doses and a "potentially harmful" comorbidity-antihypertensive combination (Table 3).

Uptake of antihypertensive FDCs

Among persons with at least one year of follow-up (n = 45 954), 13.9% (n = 6399) were dispensed an antihypertensive FDC within the first year. Of these, 40.4% were dispensed the FDC as their first antihypertensive, and a further 25.9% switched to the FDC within the first 90 days. Prior to the FDC, only 1.7% were dispensed both of the medicines in the combination product. A total of 47.5% of persons were dispensed at least one of the individual medicines, while 55.9% were dispensed at least one of the individual medicine classes. Moreover, switching to the FDC resulted in a dose increase for 48.4% of persons who had been dispensed one of the individual medicines prior to the FDC.

Discontinuation

Overall, 33.2% (n = 15 260) of persons were still being dispensed the same antihypertensive(s) they initiated on, without discontinuation, switching or addition of another antihypertensive at the end of the first year. Continuing use of the same initial therapy was highest among those who

Table 2

Number and percentage of initiators according to Australian recommendations

Australian recommendations	*n* (Total)	*n* (%) following recommendation	*n* (%) not following recommendation
For patients with uncomplicated hypertension, begin antihypertensive monotherapy with an ACEI inhibitor/ARB, a calcium channel blocker, or a thiazide diuretic (≥65 years only). Beta-blockers are not recommended in uncomplicated hypertension.	55 937	41 226 (73.7)	14 711 (26.3)
Begin antihypertensive therapy with the lowest recommended dose	55 937	38 813 (69.4)	17 124 (30.6)
For patients with comorbid and associated conditions: The following antihypertensive agents are considered **potentially beneficial**:			
Angina and beta-blockers (except oxprenolol, pindolol), calcium channel blockers, ACE inhibitors	1943	1689 (86.9)	254 (13.1)
Gout and losartan	1928	2 (0.1)	1926 (99.9)
Heart failure and ACE inhibitors, ARBs, thiazide diuretics, beta-blockers	3537	3152 (89.1)	385 (10.9)
Diabetes and ACE inhibitors, ARBs	5514	4539 (82.3)	975 (17.7)
The following antihypertensive agents are considered **potentially harmful**:			
Asthma/COPD and beta-blockers	11 011	9437 (85.7)	1574 (14.3)
Depression and beta-blockers	13 091	10 691 (81.7)	2400 (18.3)
Gout and thiazide diuretics	1928	1783 (92.5)	145 (7.5)
Heart failure and calcium channel blockers	3537	3086 (87.2)	451 (12.8)
Diabetes and beta-blockers, thiazide diuretics	5514	4621 (83.8)	893 (16.2)
For patients who were dispensed a fixed-dose antihypertensive combination:			
Patients should be established on the free combination regimen before switching to a FDC product	6399	108 (1.7)	6291 (98.3)

Table 3

Characteristics of antihypertensive initiators [*n* (%)] by concordance with guidelines

		Not recommended therapies		
	Recommended monotherapy	**Monotherapy**	**Fixed-dose combination**	**Multiple medicines**
Age				
18–49 years	6819 (16.5)	2126 (28.0)	629 (22.5)	434 (17.8)
50–59 years	5416 (13.1)	962 (12.7)	503 (18.0)	315 (13.0)
60–69 years	11 292 (27.4)	1714 (22.6)	787 (28.2)	610 (25.1)
70–79 years	12 003 (29.1)	1836 (24.2)	646 (23.2)	674 (27.7)
80+ years	5694 (13.8)	948 (12.5)	226 (8.1)	400 (16.4)
Sex				
Male	18 180 (44.1)	2983 (39.3)	1295 (46.4)	1243 (51.1)
Female	23 044 (55.9)	4603 (60.7)	1496 (53.6)	1190 (48.9)
Number of medicines dispensed in year prior				
Quartile 1 (1–2)	10 491 (25.5)	1909 (25.2)	827 (29.6)	687 (28.2)
Quartile 2 (3–4)	9375 (22.7)	1754 (23.1)	635 (22.8)	560 (23.0)
Quartile 3 (5–7)	10 085 (24.5)	1902 (25.1)	666 (23.9)	541 (22.2)
Quartile 4 (≥8)	11 273 (27.4)	2021 (26.6)	663 (23.8)	645 (26.5)
Medicines dispensed for treatment of:				
Angina	1733 (4.2)	3 (0.0)	22 (0.8)	155 (6.4)
Depression	9378 (22.8)	2063 (27.2)	614 (22.0)	510 (21.0)
Diabetes	4556 (11.1)	373 (4.9)	228 (8.2)	222 (9.1)
Gastro-oesophageal reflux disease	12 577 (30.5)	2271 (29.9)	759 (27.2)	724 (29.8)
Gout	1508 (3.7)	212 (2.8)	91 (3.3)	80 (3.3)
Heart failure	3091 (7.5)	37 (0.5)	138 (4.9)	162 (6.7)
Hyperlipidaemia	11 985 (29.1)	1867 (24.6)	700 (25.1)	665 (27.3)
Obstructive airway disease	9378 (22.8)	2063 (27.2)	614 (22.0)	510 (21.0)
Initiated on lowest recommended dose	32 938 (79.9)	3479 (45.9)	1289 (46.2)	494 (20.3)
Initiating on a 'potentially harmful' comorbidity-antihypertensive combination	952 (2.3)	2776 (36.6)	235 (8.4)	624 (25.7)
Year of initiation				
2008/09	8488 (20.6)	1393 (18.4)	529 (19.0)	562 (23.1)
2009/10	7167 (17.4)	1294 (17.1)	455 (16.3)	458 (18.8)
2010/11	6802 (16.5)	1299 (17.1)	453 (16.2)	380 (15.6)
2011/12	6518 (16.5)	1121 (14.8)	437 (15.7)	318 (13.1)
2012/13	6239 (15.1)	1289 (17.0)	438 (15.7)	323 (13.3)
2013/14	6010 (14.6)	1190 (15.7)	479 (17.2)	392 (16.1)

initiated on ACE inhibitor/ARB monotherapy (40.9%) and lowest among those who initiated on multiple medicines (13.5%) (Table 4).

Forty-seven per cent (n = 21 599) of individuals discontinued all antihypertensive treatment in the first year, including 23.6% who had only one antihypertensive

Table 4

Use of antihypertensives in first year after initiation [*n* (%)] by first-line therapy in individuals with one year of follow-up (*n* = 45 954)

	Monotherapy				FDC only			
	ACE inhibitor/ ARB (*n* = 27 632)	**Thiazide diuretic (*n* = 1486)**	**Beta-blockers (*n* = 6478)**	**Calcium channel blocker (*n* = 4538)**	**Antihypertensive combination (*n* = 2266)**	**Other combination* (*n* = 1626)**	**Multiple medicines (*n* = 1928)**	**Total (*n* = 45 954)**
Discontinuation of all antihypertensive therapy								
After first dispensing	4334 (15.7)	676 (45.5)	2625 (40.5)	1371 (30.2)	636 (28.1)	826 (50.8)	376 (19.5)	10 844 (23.6)
At any time	10 354 (37.5)	967 (65.1)	4482 (69.2)	2562 (56.5)	1243 (54.9)	1131 (69.6)	860 (44.6)	21 599 (47.0)
Continuous antihypertensive therapy								
No change in therapy from initiation	11 289 (40.9)	287 (19.3)	1213 (18.7)	1192 (26.3)	662 (29.2)	357 (22.0)	261 (13.5)	15 260 (33.2)
Switching to or addition of another antihypertensive(s)	5989 (21.7)	232 (15.6)	783 (12.1)	784 (17.3)	361 (15.9)	138 (8.5)	809 (42.0)	9096 (19.8)
Uptake of antihypertensive fixed-dose combination								
	3146 (11.4)	114 (7.7)	144 (2.2)	256 (5.6)	2266 (100.0)	38 (2.3)	435 (22.5)	6399 (13.9)

*Other combinations include hydrochlorothiazide and a potassium-sparing diuretic, and amlodipine and atorvastatin.

dispensing (or one co-dispensing for those initiated on multiple medicines). Initiation on ACE inhibitor/ARB monotherapy was associated with the lowest rate of discontinuation of all treatment (37.5%), while over half of individuals who initiated on all other monotherapies as well as an FDC discontinued their use (Table 4).

Time to discontinuing first-line therapy according to adherence to guidelines is shown in Figure 1. In our multivariable analysis, compared to individuals who initiated on the recommended monotherapy, those who initiated on the non-recommended monotherapy (i.e. beta-blockers and thiazide diuretics in individuals <65 years) were more likely to change from the treatment they initiated on (OR = 2.01, 95% CI 1.86–2.17) (Table 5) and discontinue all treatment (OR = 2.64, 95% CI 2.47–2.83) (Table 5). Individuals who initiated on an antihypertensive FDC were also more likely to change from their initial treatment (OR = 1.20, 95% CI 1.09–1.32) as well as discontinue all antihypertensive treatment (OR = 1.42, 95% CI 1.30–1.55).

While persons initiating on multiple antihypertensives were more likely to change from their initial treatment, they were less likely to discontinue all antihypertensive treatment (OR = 0.81, 95% CI 0.73–0.89) (Table 5). Initiating on greater than the lowest recommended dose was also associated with a greater risk of discontinuing all treatment (OR = 1.62, 95% CI 1.55–1.70).

Discussion

This is one of the few population-based studies of antihypertensive initiation in Australia. When compared to Australian guidelines, we observed deviations from recommendations for first-line therapy in 42% of individuals who initiated antihypertensive treatment. Contrary to recommendations, over half of people dispensed an FDC were not previously dispensed either of the medicines that formed part of the FDC. We also observed high rates of treatment discontinuation in the first year, which was greater in individuals initiating on the non-recommended monotherapy, FDCs or a higher than recommended dose.

The main strength of this study is that it is population-based and has complete capture of dispensing for our population. We also used a long run-in period to reduce the misclassification of incident users. Given that prolonged periods of discontinuation are common in persons treated with antihypertensives [32], this approach ensures that the choice of first-line therapy was not influenced by previous treatment; it is in these treatment-naïve patients that following recommendations is most important. The main limitation of our study is the lack of diagnostic information. We have assumed that the individuals in our sample were dispensed antihypertensives for the treatment of hypertension, but for some individuals they may have been dispensed for other indications, particularly beta-blockers which are used to treat various cardiac conditions other than hypertension. Our data also lack clinical information that would allow us to determine the appropriateness of prescribing by identifying individuals with severe hypertension and relevant comorbidities. Further, the differences observed between choices of therapy may reflect underlying differences between the treatment populations beyond the factors for which we adjusted.

Our finding of high rates of discontinuation, particularly after the first dispensing, is similar to a Canadian study (1994–2002) that found that 50% discontinued in the first year and 20% discontinued after the first fill [6] and a German study (2000–2001) that found that 16% received only one prescription [7]. We also found that initiating on a higher dose and a potentially harmful comorbidity-antihypertensive combination, both of which increase the risk of adverse effects, was associated with increased discontinuation of all drug therapy, as was a younger age, male sex and an increased pill burden. Interestingly, initiating on multiple medicines was associated with an increased risk of discontinuing all therapy, but a decreased risk after adjusting for dose, suggesting that the greater risk for patients initiating on multiple medicines was attributable to being given higher than recommended doses.

Overall initiation on an FDC in our sample was lower than the findings of a US study (2007–2010) [33], but similar to the figures reported in a Canadian study (1999–2010) [27]. This may reflect different national recommendations; during the time period of our study, the American Heart Association [34], and the Seventh Joint National Committee (JNC) [35] both recommended initiation with combination therapy for individuals with severe hypertension, while in Australia initiation with an FDC is not recommended. Few studies have compared persistence in initiators of an FDC to monotherapy; similar to our findings, an observational study from Canada found that persistence on therapy was lower among individuals who initiated on an FDC compared to ACE inhibitor, ARB or calcium channel blocker monotherapy, the main recommended first-line therapies in Australia [27].

While for most individuals the choice of first-line antihypertensive is consistent with current recommendations, we have found that FDCs are being used outside Australian guidelines and that this practice is reducing long-term treatment persistence. Initiating on FDCs without prior therapy has been associated with greater discontinuation [36]. These findings are concerning as more and more FDCs are being

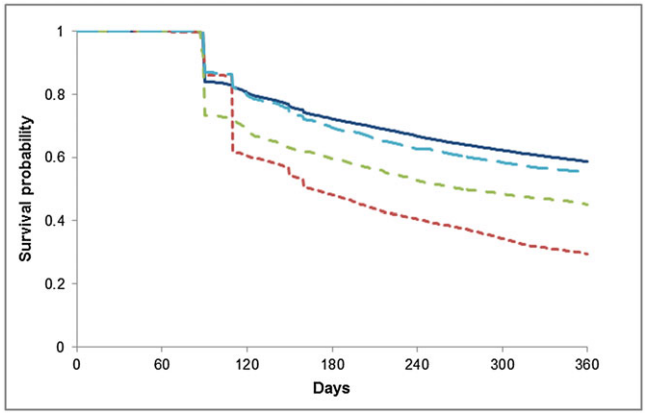

Figure 1

Time to discontinuation by first-line therapy and adherence to Australian guidelines. Monotherapy (recommended), Fixed-dosed combination, Monotherapy (not recommended), Multiple Medicines

Table 5

Logistic regression of discontinuation among 45 954 initiators with at least one year of follow-up

	Discontinuation of initial therapy				Discontinuation of all antihypertensive therapy			
	Unadjusted		Adjusted†		Unadjusted		Adjusted†	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
First-line therapy								
Monotherapy (recommended)	1.00 (Ref)	<0.001	1.00 (Ref)	<0.001	1.00 (Ref)	<0.001	1.00 (Ref)	<0.001
Monotherapy (not recommended)†	2.71 (2.54–2.91)		2.01 (1.86–2.17)		3.37 (3.18–3.58)		2.64 (2.47–2.83)	
Fixed-dose combination (antihypertensives)	1.48 (1.34–1.62)		1.20 (1.09–1.32)		1.73 (1.59–1.88)		1.42 (1.30–1.55)	
Multiple antihypertensives	3.90 (3.42–4.46)		2.70 (2.36–3.10)		1.15 (1.04–1.26)		0.81 (0.73–0.89)	
Not initiating on lowest recommended dose*	2.15 (2.05–2.26)	<0.001	1.70 (1.61–1.79)	<0.001	1.92 (1.85–2.01)	<0.001	1.62 (1.55–1.70)	<0.001
Initiating on a "potentially harmful" comorbidity-antihypertensive combination	2.27 (2.08–2.47)	<0.001	1.26 (1.14–1.40)	<0.001	2.18 (2.03–2.34)	<0.001	1.13 (1.04–1.24)	0.006
Year of initiation								
2008/09	0.99 (0.93–1.05)	0.18	1.01 (0.94–1.07)	0.37	0.96 (0.90–1.01)	0.04	0.99 (0.94–1.06)	0.19
2009/10	1.04 (0.97–1.11)		1.04 (0.98–1.11)		1.02 (0.96–1.09)		1.04 (0.98–1.11)	
2010/11	1.00 (0.94–1.07)		1.01 (0.94–1.08)		1.04 (0.98–1.10)		1.05 (0.98–1.12)	
2011/12	0.96 (0.90–1.02)		0.98 (0.91–1.04)		0.97 (0.91–1.03)		0.99 (0.93–1.06)	
2012/13	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
Age								
18–49 years	2.08 (1.96–2.22)	<0.001	1.89 (1.77–2.02)	<0.001	2.97 (2.80–3.14)	<0.001	2.72 (2.56–2.89)	<0.001
50–59 years	1.22 (1.15–1.31)		1.19 (1.11–1.27)		1.47 (1.38–1.56)		1.43 (1.34–1.52)	
60–69 years	1.00 (Ref)		1.00 (Ref)		1.00 (Ref)		1.00 (Ref)	
70–79 years	1.04 (0.99–1.09)		1.05 (1.00–1.11)		0.99 (0.94–1.04)		1.00 (0.95–1.06)	
80+ years	1.17 (1.10–1.25)		1.15 (1.08–1.24)		1.28 (1.20–1.37)		1.27 (1.18–1.35)	
Sex								
Male	1.00 (Ref)	0.54	1.00 (Ref)	0.84	1.00 (Ref)	0.37	1.00 (Ref)	<0.001
Female	1.01 (0.97–1.05)		1.00 (0.96–1.05)		0.98 (0.95–1.02)		0.93 (0.90–0.97)	
Number of medicines dispensed in year prior								
Quartile 1 (1–2)	1.00 (Ref)	0.009	1.00 (Ref)	<0.001	1.00 (Ref)	<0.001	1.00 (Ref)	<0.001

(*continues*)

Table 5

(Continued)

	Discontinuation of initial therapy				Discontinuation of all antihypertensive therapy			
	Unadjusted		Adjusted†		Unadjusted		Adjusted†	
	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value	OR (95% CI)	*P*-value
Quartile 2 (3–4)	0.95 (0.90–1.01)		1.01 (0.95–1.07)		0.94 (0.89–0.99)		0.99 (0.94–1.05)	
Quartile 3 (5–7)	0.92 (0.87–0.97)		1.01 (0.95–1.07)		0.95 (0.90–1.00)		1.04 (0.98–1.10)	
Quartile 4 (≥8)	0.99 (0.94–1.05)		1.13 (1.05–1.22)		1.06 (1.00–1.11)		1.21 (1.13–1.30)	
Medicines dispensed for treatment of:								
Angina	1.16 (1.03–1.29)	0.01	1.27 (1.13–1.43)	<0.001	1.04 (0.93–1.15)	0.52	1.25 (1.13–1.40)	<0.001
Depression	1.04 (0.99–1.09)	0.10	0.91 (0.87–0.96)	<0.001	1.14 (1.09–1.20)	<0.001	0.94 (0.90–0.99)	0.02
Diabetes	0.81 (0.76–0.87)	<0.001	0.87 (0.82–0.94)	<0.001	0.92 (0.86–0.97)	0.006	0.98 (0.91–1.05)	0.49
Gastro-oesophageal reflux disease	0.97 (0.92–1.01)	0.10	1.00 (0.95–1.05)	0.89	0.93 (0.89–0.97)	<0.001	0.96 (0.92–1.01)	0.11
Gout	0.85 (0.77–0.95)	0.003	0.89 (0.80–0.99)	0.04	0.83 (0.74–0.92)	<0.001	0.86 (0.77–0.96)	0.007
Heart failure	0.86 (0.79–0.93)	<0.001	0.90 (0.82–0.98)	0.02	0.93 (0.85–1.00)	0.06	1.06 (0.97–1.16)	0.18
Hyperlipidaemia	0.75 (0.72–0.78)	<0.001	0.82 (0.78–0.86)	<0.001	0.74 (0.71–0.77)	<0.001	0.84 (0.80–0.88)	<0.001
Obstructive airway disease	1.02 (0.97–1.07)	0.51	0.99 (0.94–1.05)	0.80	1.02 (0.98–1.07)	0.32	0.99 (0.94–1.04)	0.66

*Adjusted for all variables in the table. †Beta-blockers without any indication for their use, or thiazide diuretics in <65 years.

introduced to the market. Treatment for hypertension is often life-long, and adherence and persistence to antihypertensive therapy is generally poor [37]. Given that there are currently few effective interventions for improving medication adherence [38], prescribing physicians should engage in treatment strategies that support optimal adherence.

While it is generally argued that FDC might support continuing drug therapy, evidence to support this assertion, and in particular that initiation on FDC will support long-term therapy and improve health outcomes is largely lacking. Used appropriately, FDCs have a role in individuals who require multiple agents to control their blood pressure, and are an attractive long-term option due to their reduced cost. However, more research is needed to determine which FDC initiation strategies optimize long-term persistence. Starting off on the right foot with antihypertensive therapy is essential to achieving maximum potential health benefits.

Competing Interests

All authors have completed the Unified Competing Interest form at http://www.icmje.org/coi_disclosure.pdf (available on request from the corresponding author) and declare: AS and SP had support from the National Health and Medical Research Council for the submitted work; AS, SP and NB had no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; AS, SP and NB had no other relationships or activities that could appear to have influenced the submitted work.

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Contributors

All authors contributed to the conception and design of the study and the interpretation of the data. AS drafted the manuscript; SP and NB revised it critically. All authors gave approval to the final version. Nicholas A. Buckley was the principal investigator.

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Supporting Information

Additional Supporting Information may be found in the online version of this article at the publisher's web-site:

http://onlinelibrary.wiley.com/doi/10.1111/bcp.13043/suppinfo.

Table S1 Multivariable analysis of initiation on each antihypertensive class as compared to all other classe