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Long-term persistence and adherence to blood pressure lowering agents among older Australians

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Key words:

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Key points:

- Long-term persistence and adherence to blood pressure lowering (BPL) medications in older Australians is generally poor
- The risk of discontinuation and poor adherence is high in the first six to twelve months since initiation
- Re-initiation rates are high among users who discontinued blood pressure lowering medications

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- Compared to other blood pressure lowering agents, long-term persistence on fixed dose combination drugs is the best
- Interventions to enhance compliance to BPL agents, especially in the first year of initiation, are needed

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Abstract

Objectives: Poor adherence and persistence to blood pressure lowering (BPL) medications leads to increased risk of morbidity and mortality. The aim of this study was to investigate the long-term adherence, persistence and re-initiation of BPL agents among older Australians (aged ≥ 65 years).

Methods: We utilised the Pharmaceutical Benefits Scheme data covering a 10% random sample of Australians. We identified 31,088 older Australians (mean age 75.4 years; 56% females) with newly initiated BPL therapy from 2008 to 2016. Adherence was assessed using the proportion of days covered (PDC) at six-monthly intervals. Discontinuation was defined as ≥ 90 days without BPL coverage. Cox regression was applied to compare time to discontinuation of BPL agents across different BPL agents and among various sub-groups.

Results: Over a mean follow-up of 3.8 years, 40-70% of older Australians prescribed a BPL agent discontinued it. The median time to discontinuation ranged from 159 to 373 days. Persistence with fixed dose combinations was best (68%, 58% and 41% at 6, 12 and 36 months, respectively), followed by angiotensin II receptor blockers (69%, 58% and 40%), beta-blockers (67%, 54% and 36%), angiotensin converting enzyme inhibitors (62%, 51% and 34%), calcium channel blockers (57%, 47% and 31%) and diuretics (59%, 41% and 23%). Among those who discontinued, 30-50% re-initiated, with median days to re-initiation ranging from 177 to 302 days. Only 21-42% of the study population maintained 'good' adherence ($PDC \geq 0.8$) to BPLs over three years.

Conclusion: Compliance to BPL agents is poor among older Australians. Interventions to enhance adherence and persistence to BPL agents are needed.

Word count: 255

Introduction

Strong epidemiological and clinical trial evidence supports the use of blood pressure lowering (BPL) agents to control blood pressure (BP), thereby lowering the risk of cardiovascular disease (CVD). A recent meta-regression analysis showed that for every 10 mmHg reduction in systolic blood pressure (SBP) achieved with BPL agents, there is a 20% lower risk of CVD and a 13% lower risk of all-cause mortality (1). This effect is observed regardless of baseline BP levels (1). Other systematic reviews focusing on subgroups of patients with different morbidities have consistently demonstrated similar beneficial effects of BPL agents (2, 3). However, adherence is key. A recent cohort study reported that 'good' adherence to BPL agents, as measured by 'proportion of days covered' (PDC) with medications ≥ 0.8 , was associated with a 56% reduction in CVD over 6 years compared to 'poor' adherence (4).

The prevalence and burden of high blood pressure increases with age, exceeding 60% among those aged ≥ 65 years (5-7). It is the most common reason for general practice encounters (56%) in older Australians (8), and responsible for the most important attributable risk for stroke and coronary heart disease (9). Despite strong evidence of the efficacy of BPL agents, the attainment of treated BP targets in clinical practice is not optimal. According to 2015 national statistics, 42-47% Australians aged ≥ 65 years had uncontrolled/unmanaged high blood pressure ($\geq 140/90$ mmHg) (6). Poor adherence and persistence to medications is one of the major contributors to the inadequate control of BP (10-12). Therefore, in clinical practice, the challenges are to understand the patterns of patients' poor adherence and persistence to BPL agents and to improve the situation, especially populations at high absolute risk for CVD (13). The most commonly dispensed BPL agent categories are angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-receptor blockers (BBs), calcium channel blockers (CCBs) and (low-dose) diuretics. Use of these agents is frequently indicated by co-morbidities, but all may be used in uncomplicated hypertension (14-16).

A few studies have investigated patients' compliance to BPL agents by categories (17-21), most of which reported adherence and persistence in a fixed time period (one or two years). The results are heterogeneous, given the different contexts of BPL utilisation across countries and eras. Importantly, the patterns of long-term persistence and adherence to BPL agents, including re-initiation after discontinuation, remains largely unexplored. Therefore in the present study, we aimed to examine the long-term adherence and persistence to BPL agents, as well as re-initiation after discontinuation, among older Australians (aged ≥ 65 years).

Methods

Data source

We utilised national dispensing claims data from the Australian Pharmaceutical Benefit Scheme (PBS) provided by the Commonwealth Department of Human Services. This dataset included all medicines dispensed for a 10% randomly selected Australian population eligible for PBS-subsidised medications from March 2005. For the present study, we extracted data from 2006 to 2016. From the dataset, we obtained information on persons' demographic characteristics, medication item codes, prescribers and the dispensing date. The dataset was provided in a non-identifiable state, but retained unique encrypted identifiers to allow for tracking of individuals over time. We restricted our analyses to 'long-term concession' individuals, whose medication dispensing were likely to be comprehensively captured (22). 'Long-term concession' individuals comprise Australians who contribute a low co-payment ('out-of-pocket' expenses) for their medications, and hence have at least 90% of their medications subsidised via the PBS (23).

Using the World Health Organisation Anatomical Therapeutic Chemical (ATC) classification codes, we included medications catalogued under C02 (other antihypertensives), C03 (diuretics), C07 (beta-blockers (BBs)), C08 (calcium channel blockers (CCBs)), C09A (angiotensin converting enzyme inhibitors (ACEIs)), C09C (angiotensin II receptor blockers (ARBs)) and C09B/C09D (fixed dose combinations (FDCs) that contained either ACEIs or ARBs).

Eligible participants

Study subjects were:

- 1) aged ≥ 65 years and 'long-term concession' individuals
- 2) had no BPL dispensing for at least two consecutive years from 2006 to 2016 (wash-out period)
- 3) had at least two dispensing records of any BPL agent following the two-year wash-out period from 2008 to 2016

Study indicators

The duration of use (coverage per drug dispensed) for each BPL agent (at ATC5 level) was determined using the waiting time distribution (WTD) method (24). Consistent with Australian

literature, we used the 75th percentile of the WTD per BPL agent to represent duration of use (25, 26). By applying the Rx-Risk-V tool, we derived indicators for ten pre-existing chronic conditions based on the dispensing records 12 months prior to the first dispensing of BPL agents (27, 28). The ten chronic conditions were diabetes, dyslipidaemia, osteoporosis, chronic pain, cardiac disease (angina or arrhythmia), autoimmune disease (hyperthyroidism, gout or steroid disease), conditions requiring anti-platelet or anti-coagulant therapy, respiratory disease, gastrointestinal disease and mental health disease (depression, anxiety, dementia, epilepsy or psychosis).

Persistence or discontinuation to medication was determined by the gaps between continuous records of dispensing. We defined discontinuation as a medication non-possession gap exceeding 90 days between dispensings. Given the divergent follow-up period per dispensing BPL category, the risks of discontinuation were calculated per person-year. Re-initiation of BPL agents comprised dispensing of the same category of BPL agents after discontinuation. The gaps (days) between the date of coverage from the preceding dispensing and re-initiation dispensing were summarised by BPL categories.

We used the proportion of days covered (PDC) method to measure adherence to medications (29). We calculated the cumulative PDC at six-month intervals until three years post initiation of a BPL agent. Within the defined time periods, we calculated the total days of BPL coverage. PDCs were calculated by dividing the total days of BPL coverage by the number of days during the respective follow-up period. We used a PDC cut-off of 0.8 to define ‘good’ adherence to BPL agents (30).

Statistical methods

Descriptive analyses and Kaplan-Meier curves were used to summarise the persistence and adherence to BPL agents at different time points. Cox regression analyses were applied to compare users’ persistence to BPL agents by drug category with age included as a time-dependent variable. The regression models were adjusted for sex, initial prescriber (general practitioners (GPs) or other health professionals), the initial category of BPL agent, the dispensing sequence of BPL categories and whether people had one or more pre-existing chronic conditions. The adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were reported. Data analyses were performed using STATA version 15.

Ethics

The study received approval from the Monash University Human Research Ethics Committee.

Results

We identified 78,883 BPL naïve individuals who were alive and had no record of BPL dispensing for two consecutive years from 2008 to 2016 (Supplementary Table 1). Of the BPL naïve individuals, 39% (n=31,088) had at least two episodes of BPL dispensing, thus forming the study cohort (Figure 1 and Supplementary Table 2). The mean follow-up period was 3.8 years (standard deviation 2.5 years). Over the study period, 16% of the study cohort died (n=4,982). The characteristics of the study cohort are summarised in Supplementary Table 2.

Figure 1: cohort identification

Almost one third of study participants started with ACEIs (31%), followed by ARBs (22%), BBs (16%), diuretics (15%) and CCBs (9%) (Figure 1). The temporal trends of BPL initiation are summarised in supplementary Figure 1. Diuretics as initial BPL agents dropped from 18% in 2008 to 12% in 2016, whereas the use of ACEIs as initial BPL agents increased from 30% in 2008 to 34% in 2016 (Supplementary Figure 1). The overall discontinuation rates ranged from 31 (ARBs/FDCs) to 69 (other anti-hypertensives) per 100 person-years across different categories of BPL agents (Table 1). Median days to discontinuation ranged from 159 for ‘other anti-hypertensives’ (C02) to 373 for ARBs. However, a high proportion of discontinued users reinitiated their initial BPL agent (Table 1). Re-initiation ranged from 31% for other anti-hypertensives (C02) to 49% for BBs, with median days to re-initiation ranging from 177 (BBs) to 302 (diuretics) (Table 1).

Table 1: Characteristics of BPL dispensing by ATC sub-categories

Life table analyses showed better persistence to FDCs (68%, 58% and 41% at 6, 12 and 36 months, respectively) and ARBs (69%, 58% and 40%), followed by BBs (67%, 54% and 36%), ACEIs (62%, 51% and 34%) and CCBs (57%, 47% and 30%). Diuretics (59%, 41% and 23%) and other anti-hypertensives (52%, 37% and 18%) were the least persistent categories (Figure 2).

Levels of ‘good’ adherence ($PDC \geq 0.8$) at six-monthly intervals for three years are summarised in Figure 3. At six months, 50-60% of users maintained good adherence to the majority of BPL categories. At 12 months, increasing variance in adherence occurred across the different BPL categories, with good adherence ranging from 34% of patients for other anti-hypertensives to 51% of patients for FDCs. Beyond 12 months, adherence steadily decreased across all BPL categories. At three years, 21-42% of users had good adherence to BPL agents.

Figure 2: KM curve of first non-persistence by BPL categories

Figure 3: Time to good adherence ($PDC \geq 0.8$) by BPL categories

The Cox regression model showed that compared to ACEIs (reference category), FDCs (aHR: 0.78, 95% CI: 0.75, 0.81) and ARBs (aHR: 0.80, 95% CI: 0.77, 0.83) had the lowest hazard ('risk') of discontinuation, followed by BBs (aHR: 0.86, 95% CI: 0.83, 0.89). Compared to ACEIs, the risk of discontinuation was higher for CCBs (aHR: 1.09, 95% CI: 1.05, 1.14), diuretics (aHR: 1.10, 95% CI: 1.07, 1.14) and highest for other anti-hypertensives (aHR: 1.29, 95% CI 1.22, 1.37) (Table 2).

BPL discontinuation increased with age at initiation and if treatment was initiated by GPs (aHR: 1.04, 95% CI: 1.02, 1.06), but we found no gender differences (aHR: 0.99, 95% CI: 0.97, 1.01). The dispensing sequence of BPL categories did not have a significant impact on discontinuations. However, compared to diuretics, people who started therapy with ACEIs had better persistence (aHR: 0.93, 95% CI: 0.89, 0.96), whereas discontinuations were highest among those who started with FDCs (aHR: 1.26, 95% CI: 1.19, 1.33). BPL discontinuation was also higher among those with pre-existing diabetes, gastrointestinal disease, autoimmune disease and chronic pain, but lower among those with dyslipidaemia or who were on concurrent anti-platelet or anti-coagulant therapy (Table 2).

Table 2: Adjusted hazard ratios from Cox regression model for discontinuation of blood pressure lowering agents

Discussion

We found poor long-term persistence and adherence to BPL agents among older Australians, among whom 60-70% discontinued over a mean of 3.8 years follow-up, and 'good' adherence ($PDC \geq 0.8$) dropped to 21-42% by three years. The majority of discontinuations occurred within the 6-12 month period following initiation. Among discontinued users, 30-50% re-initiated their initial BPL agent and the majority of re-initiations occurred within one year. In terms of long-term persistence across categories of BPL agents, the ranking (highest to lowest) was FDCs, ARBs, BBs, ACEIs, CCBs, diuretics and other anti-hypertensives.

ACEIs and ARBs were the most dispensed BPL agents among older Australians, followed by diuretics, BBs, CCBs, FDCs and other anti-hypertensives. ACEIs were the most common initiating BPL agents. This is reflective of national clinical guidelines for CVD management, in which ACEI/ARB are recommended as first-line pharmacotherapy for most cardiovascular conditions (14-16).

Consistent with the literature, we found low short- and long-term persistence and poor adherence to all BPL agents. This is possibly due to the lack of symptoms of hypertension and the preventive nature of BPL use among people with no indications for other cardiovascular comorbidities or risk factors (21). Reflective of this hypothesis, we found improved persistence to BPL agents among those with dyslipidaemia or who were on anti-platelet or anti-coagulant therapy, which indicated existing or high risks of cardiovascular disease.

For most BPL categories, discontinuation and poor adherence were more likely to occur within the first six months of initiation. Also, it appears that once users complied with BPL agents in the first year, the majority would maintain good adherence in the long-term. This is largely consistent with existing literature on BPL agents (17-21) and statins (22). We also found high re-initiation (30-50%) after discontinuation from all BPL categories, with the majority of people restarting within one year from discontinuation. This suggests that a large portion of BPL discontinuations were not due to medical reasons (e.g. adverse events or switching to other BPL agents). Therefore, it is crucial to reinforce adherence and persistence to BPL agents, especially in the first year since initiation. A number of studies have proposed promising interventions to improve medical adherence in older populations, including providing feedback and reminders (31), reducing the pill burden (32), improving health literacy (33), motivational interviewing (34) and multi-facet interventions (34, 35).

Consistent with the literature (17-21), we found worse long-term persistence and adherence to diuretics (C03) compared to other commonly used BPL categories. We also observed a declining use of diuretics as initiating BPL agents in older Australians from 2008 to 2016 (from 18% to 12%). These are likely to be related to the recommendation of cautious use of diuretics among patients with multi-morbidity and polypharmacy, particularly in older adults (36), and also possibly the lack of high quality evidence supporting thiazides as first-line therapy for hypertension in older adults (37). Correspondingly, the latest Australian hypertension guidelines weakened the recommendation of low-dose diuretics as first line anti-hypertensive medications (38).

Of all BPL categories, persistence to FDCs was best. This accords with a systematic review which reported a 24% reduction in discontinuation to FDC agents in the management of hypertension (39). Polypharmacy and complex treatment regimens are known determinants of poor compliance to medications. FDCs are proven to improve persistence and adherence by reducing pill burden (39). However, use of FDCs remained relatively low in older Australians, with only 21% of our study

cohort having dispensing of FDCs. This is consistent with the recommendation of conservative use of FDC in older patients due to increased risks of BPL-induced adverse events (40).

Unlike other studies (21, 41), we did not restrict our analysis to initial BPL categories. Instead, we included all BPL dispensing records from eligible individuals, which means one may have up to seven BPL categories dispensed within the study period. Therefore, in the regression analysis, we adjusted for initial BPL categories and the dispensing sequence of BPL categories. We did not find associations between dispensing sequence and persistence to BPL agents. However, we noted associations between initial BPL categories and subsequent persistence to BPL agents. While ACEIs as initial BPL agents was associated with lower risk of discontinuation to subsequent BPL agents, FDCs as initial BPL agents increased the risk of discontinuation. This is likely related to the indications for BPL dispensing and that FDCs as initial BPL agents was generally contrary to guidelines, especially in the older population.

Several limitations to our study warrant mention. First, 'long-term concession' people may not be representative of all Australians aged ≥ 65 years. A recent study investigating the differences between concession card holders and general beneficiaries among population aged 45 years and above, concluded that concession card holders were on average older, less educated and had more risk factors/morbidity conditions (42). Concession card holders also had higher level of adherence to statins than general beneficiaries (42). Therefore, our study is likely to have underestimated the level of poor adherence and persistence to BPLs in older Australians. Yet, the differences may not be substantial because the proportion of concession card holders is higher in older population than the younger age groups. Secondly, we were unable to ascertain the clinical indications and doses from the PBS data because these are not recorded. Instead, we applied the WTD method and used the 75th percentile to determine duration of use per dispensing. This method has been validated and applied in similar studies (25, 26). Thirdly, since the objective of our analysis was to compare long-term persistence and adherence for different categories of BPL agents, and because we did not have information on the indications for prescribing, we did not examine inter-category replacement. Therefore, discontinuation or poor adherence to BPL agents may not have indicated discontinuation of BPL therapy altogether. Fourthly, we did not have hospitalisation records, and PBS data is not captured from all hospitals. Therefore, we may have overestimated the treatment gap or under-estimated adherence among persons who were hospitalised. However, this is expected to affect only the few long-term hospital admissions, and the effect will be minimal for the majority of admissions with normal length of stays. Finally, we did not have data for the reasons for discontinuations or poor adherence to BPL agents.

Conclusion

Compliance to BPL agents is poor among older Australians. Persistence and adherence differed by BPL categories. Interventions to enhance compliance to BPL agents, especially in the first year of initiation, are needed.

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Declaration of originality

There has been no proceeding publications or conference presentations on this manuscript.

Conflict of interest

The authors declare no conflict of interest

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Table 1: Characteristics of blood pressure lowering agents dispensed by ATC sub-categories

	Total	Discontinuation		Re-initiation*	Days until discontinuation Median (25 th , 75 th percentiles)	Days until Re-initiation
		Number	Rate per 100 Person-Years (95% CI)			
Diuretics (C03)	10,405	6,908	62.5 (61.0, 63.9)	3,309 (47.9%)	182 (115, 442)	302 (151, 730)
BBs (C07)	10,353	6,121	37.6 (36.7, 38.6)	3,001 (49.0%)	273 (105, 788)	177 (115, 409)
CCBs (C08)	7,766	5,139	46.9 (45.6, 48.2)	1,769 (34.4%)	195 (55, 698)	226 (131, 567)
ACEIs (C09A)	14,568	9,423	40.0 (39.2, 40.8)	3,146 (33.4%)	246 (74, 858)	219 (131, 546)
ARBs (C09C)	12,162	7,424	31.2 (30.4, 31.9)	3,209 (43.2%)	373 (92, 1135)	210 (129, 517)
FDC (C09B;C09D)	6,584	3,798	32.2 (31.2, 33.2)	1,434 (37.8%)	346 (86, 1011)	197 (127, 449)
Anti-hypertensives (C02)	2,596	2,003	69.3 (66.3, 72.4)	626 (31.3%)	159 (101, 478)	196 (126, 396)

*denominators are number of discontinued users in specific categories of blood pressure lowering agents;

BB, beta blockers; CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; FDC, fixed dose combinations.

Table 2: Adjusted hazard ratios from Cox regression model for discontinuation of blood pressure lowering agents.

Lowering agents.		HR	95% CI		P value
BPL categories					
	Diuretics (C03)	1.10	1.07	1.14	<0.01
	BBs (C07)	0.86	0.83	0.89	<0.01
	CCBs (C08)	1.09	1.05	1.14	<0.01
	ACEIs (C09A)	1.00			
	ARBs (C09C)	0.80	0.77	0.83	<0.01
	FDCs (C09B;C09D)	0.78	0.75	0.81	<0.01
	Other anti-hypertensives (C02)	1.29	1.22	1.37	<0.01
Age		1.00	1.00	1.00	0.02
Sex					
	Female	1.00			
	Male	0.99	0.97	1.01	0.23
Prescriber					
	specialists/others	1.00			
	GP	1.04	1.02	1.06	<0.01
Initiating BPL agent					
	Diuretics (C03)	1.00			
	BBs (C07)	1.04	1.00	1.08	0.08
	CCBs (C08)	0.98	0.94	1.03	0.44
	ACEIs (C09A)	0.93	0.89	0.96	<0.01
	ARBs (C09C)	0.99	0.95	1.02	0.44
	FDCs (C09B;C09D)	1.26	1.19	1.33	<0.01
	Other anti-hypertensives (C02)	1.06	1.00	1.13	0.05
Sequence of dispensing					
	1	1.00			
	2	1.01	0.98	1.03	0.57
	3	0.99	0.96	1.02	0.46
	4	1.00	0.96	1.05	0.91
	5	0.99	0.92	1.08	0.88
	6	1.11	0.96	1.29	0.16
	7	0.75	0.48	1.16	0.19
Comorbid conditions*					
	Mental health disease	1.01	0.99	1.04	0.24
	Dyslipidaemia	0.97	0.95	0.99	0.00
	Diabetes	1.05	1.02	1.09	0.00
	Antiplatelet or anti-coagulant therapy	0.94	0.92	0.97	0.00
	Cardiac disease	0.98	0.95	1.02	0.38
	Respiratory disease	0.99	0.96	1.02	0.57
	Gastrointestinal disease	1.06	1.04	1.08	0.00
	Autoimmune disease	1.05	1.02	1.08	0.00
	Osteoporosis	1.03	1.00	1.06	0.07
	Chronic pain	1.06	1.04	1.08	0.00
Year of 1 st BPL dispensing					
	2008	1.00			
	2009	1.01	0.97	1.05	0.71
	2010	0.97	0.93	1.01	0.13
	2011	0.96	0.92	1.00	0.06
	2012	0.94	0.90	0.98	0.01
	2013	0.95	0.91	1.00	0.03
	2014	0.96	0.91	1.00	0.05
	2015	0.92	0.88	0.96	0.00
	2016	0.53	0.49	0.56	0.00

*the reference group is absence of indicated comorbidity; BPL: blood pressure lowering; HR: hazard ratio; CI: confidence interval. BB, beta blockers; CCB, calcium channel blockers; ACEI, angiotensin converting enzyme

Figure 1: cohort identification

BPL: blood pressure lowering; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; BBs: beta-blockers; CCB: calcium channel blockers; FDC: fixed dose combinations.

Figure 2: Kaplan-Meier curves of first non-persistence by categories of blood pressure lowering agents

ACEIs: Angiotensin converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; BBs: beta-blockers; CCB: calcium channel blockers; FDC: fixed dose combinations

Figure 3: Time to good adherence ($PDC \geq 0.8$) by categories of blood pressure lowering agents

ACEIs: Angiotensin converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; BBs: beta-blockers; CCB: calcium channel blockers; FDC: fixed dose combinations

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Key words:

blood pressure lowering medication; adherence; persistence; older population; Australia

Key points:

- Long-term persistence and adherence to blood pressure lowering (BPL) medications in older Australians is generally poor
- The risk of discontinuation and poor adherence is high in the first six to twelve months since initiation
- Re-initiation rates are high among users who discontinued blood pressure lowering medications
- Compared to other blood pressure lowering agents, long-term persistence on fixed dose combination drugs is the best
- Interventions to enhance compliance to BPL agents, especially in the first year of initiation, are needed

Word count: 2,726

Abstract

Objectives: Poor adherence and persistence to blood pressure lowering (BPL) medications leads to increased risk of morbidity and mortality. The aim of this study was to investigate the long-term adherence, persistence and re-initiation of BPL agents among older Australians (aged ≥ 65 years).

Methods: We utilised the Pharmaceutical Benefits Scheme data covering a 10% random sample of Australians. We identified 31,088 older Australians (mean age 75.4 years; 56% females) with newly initiated BPL therapy from 2008 to 2016. Adherence was assessed using the proportion of days covered (PDC) at six-monthly intervals. Discontinuation was defined as ≥ 90 days without BPL coverage. Cox regression was applied to compare time to discontinuation of BPL agents across different BPL agents and among various sub-groups.

Results: Over a mean follow-up of 3.8 years, 40-70% of older Australians prescribed a BPL agent discontinued it. The median time to discontinuation ranged from 159 to 373 days. Persistence with fixed dose combinations was best (68%, 58% and 41% at 6, 12 and 36 months, respectively), followed by angiotensin II receptor blockers (69%, 58% and 40%), beta-blockers (67%, 54% and 36%), angiotensin converting enzyme inhibitors (62%, 51% and 34%), calcium channel blockers (57%, 47% and 31%) and diuretics (59%, 41% and 23%). Among those who discontinued, 30-50% re-initiated, with median days to re-initiation ranging from 177 to 302 days. Only 21-42% of the study population maintained 'good' adherence ($PDC \geq 0.8$) to BPLs over three years.

Conclusion: Compliance to BPL agents is poor among older Australians. Interventions to enhance adherence and persistence to BPL agents are needed.

Word count: 255

Introduction

Strong epidemiological and clinical trial evidence supports the use of blood pressure lowering (BPL) agents to control blood pressure (BP), thereby lowering the risk of cardiovascular disease (CVD). A recent meta-regression analysis showed that for every 10 mmHg reduction in systolic blood pressure (SBP) achieved with BPL agents, there is a 20% lower risk of CVD and a 13% lower risk of all-cause mortality (1). This effect is observed regardless of baseline BP levels (1). Other systematic reviews focusing on subgroups of patients with different morbidities have consistently demonstrated similar beneficial effects of BPL agents (2, 3). However, adherence is key. A recent cohort study reported that 'good' adherence to BPL agents, as measured by 'proportion of days covered' (PDC) with medications ≥ 0.8 , was associated with a 56% reduction in CVD over 6 years compared to 'poor' adherence (4).

The prevalence and burden of high blood pressure increases with age, exceeding 60% among those aged ≥ 65 years (5-7). It is the most common reason for general practice encounters (56%) in older Australians (8), and responsible for the most important attributable risk for stroke and coronary heart disease (9). Despite strong evidence of the efficacy of BPL agents, the attainment of treated BP targets in clinical practice is not optimal. According to 2015 national statistics, 42-47% Australians aged ≥ 65 years had uncontrolled/unmanaged high blood pressure ($\geq 140/90$ mmHg) (6). Poor adherence and persistence to medications is one of the major contributors to the inadequate control of BP (10-12). Therefore, in clinical practice, the challenges are to understand the patterns of patients' poor adherence and persistence to BPL agents and to improve the situation, especially populations at high absolute risk for CVD (13). The most commonly dispensed BPL agent categories are angiotensin converting enzyme inhibitors (ACEIs), angiotensin II receptor blockers (ARBs), beta-receptor blockers (BBs), calcium channel blockers (CCBs) and (low-dose) diuretics. Use of these agents is frequently indicated by co-morbidities, but all may be used in uncomplicated hypertension (14-16).

A few studies have investigated patients' compliance to BPL agents by categories (17-21), most of which reported adherence and persistence in a fixed time period (one or two years). The results are heterogeneous, given the different contexts of BPL utilisation across countries and eras. Importantly, the patterns of long-term persistence and adherence to BPL agents, including re-initiation after discontinuation, remains largely unexplored. Therefore in the present study, we aimed to examine the long-term adherence and persistence to BPL agents, as well as re-initiation after discontinuation, among older Australians (aged ≥ 65 years).

Methods

Data source

We utilised national dispensing claims data from the Australian Pharmaceutical Benefit Scheme (PBS) provided by the Commonwealth Department of Human Services. This dataset included all medicines dispensed for a 10% randomly selected Australian population eligible for PBS-subsidised medications from March 2005. For the present study, we extracted data from 2006 to 2016. From the dataset, we obtained information on persons' demographic characteristics, medication item codes, prescribers and the dispensing date. The dataset was provided in a non-identifiable state, but retained unique encrypted identifiers to allow for tracking of individuals over time. We restricted our analyses to 'long-term concession' individuals, whose medication dispensing were likely to be comprehensively captured (22). 'Long-term concession' individuals comprise Australians who contribute a low co-payment ('out-of-pocket' expenses) for their medications, and hence have at least 90% of their medications subsidised via the PBS (23).

Using the World Health Organisation Anatomical Therapeutic Chemical (ATC) classification codes, we included medications catalogued under C02 (other antihypertensives), C03 (diuretics), C07 (beta-blockers (BBs)), C08 (calcium channel blockers (CCBs)), C09A (angiotensin converting enzyme inhibitors (ACEIs)), C09C (angiotensin II receptor blockers (ARBs)) and C09B/C09D (fixed dose combinations (FDCs) that contained either ACEIs or ARBs).

Eligible participants

Study subjects were:

- 1) aged ≥ 65 years and 'long-term concession' individuals
- 2) had no BPL dispensing for at least two consecutive years from 2006 to 2016 (wash-out period)
- 3) had at least two dispensing records of any BPL agent following the two-year wash-out period from 2008 to 2016

Study indicators

The duration of use (coverage per drug dispensed) for each BPL agent (at ATC5 level) was determined using the waiting time distribution (WTD) method (24). Consistent with Australian literature, we used the 75th percentile of the WTD per BPL agent to represent duration of use (25, 26). By applying the Rx-Risk-V tool, we derived indicators for ten pre-existing chronic conditions based on the dispensing records 12 months prior to the first dispensing of BPL agents (27, 28). The ten chronic conditions were diabetes, dyslipidaemia, osteoporosis, chronic pain, cardiac disease (angina or arrhythmia), autoimmune disease (hyperthyroidism, gout or steroid disease), conditions requiring anti-platelet or anti-coagulant therapy, respiratory disease, gastrointestinal disease and mental health disease (depression, anxiety, dementia, epilepsy or psychosis).

Persistence or discontinuation to medication was determined by the gaps between continuous records of dispensing. We defined discontinuation as a medication non-possession gap exceeding 90 days between dispensings. Given the divergent follow-up period per dispensing BPL category, the risks of discontinuation were calculated per person-year. Re-initiation of BPL agents comprised dispensing of the same category of BPL agents after discontinuation. The gaps (days) between the date of coverage from the preceding dispensing and re-initiation dispensing were summarised by BPL categories.

We used the proportion of days covered (PDC) method to measure adherence to medications (29). We calculated the cumulative PDC at six-month intervals until three years post initiation of a BPL agent. Within the defined time periods, we calculated the total days of BPL coverage. PDCs were calculated by dividing the total days of BPL coverage by the number of days during the respective follow-up period. We used a PDC cut-off of 0.8 to define 'good' adherence to BPL agents (30).

Statistical methods

Descriptive analyses and Kaplan-Meier curves were used to summarise the persistence and adherence to BPL agents at different time points. Cox regression analyses were applied to compare users' persistence to BPL agents by drug category with age included as a time-dependent variable. The regression models were adjusted for sex, initial prescriber (general practitioners (GPs) or other health professionals), the initial category of BPL agent, the dispensing sequence of BPL categories and whether people had one or more pre-existing chronic conditions. The adjusted hazard ratios (aHRs) with 95% confidence intervals (CIs) were reported. Data analyses were performed using STATA version 15.

Ethics

The study received approval from the Monash University Human Research Ethics Committee.

Results

We identified 78,883 BPL naïve individuals who were alive and had no record of BPL dispensing for two consecutive years from 2008 to 2016 (Supplementary Table 1). Of the BPL naïve individuals, 39% (n=31,088) had at least two episodes of BPL dispensing, thus forming the study cohort (Figure 1 and Supplementary Table 2). The mean follow-up period was 3.8 years (standard deviation 2.5 years). Over the study period, 16% of the study cohort died (n=4,982). The characteristics of the study cohort are summarised in Supplementary Table 2.

Figure 1: cohort identification

Almost one third of study participants started with ACEIs (31%), followed by ARBs (22%), BBs (16%), diuretics (15%) and CCBs (9%) (Figure 1). The temporal trends of BPL initiation are summarised in supplementary Figure 1. Diuretics as initial BPL agents dropped from 18% in 2008 to 12% in 2016,

whereas the use of ACEIs as initial BPL agents increased from 30% in 2008 to 34% in 2016 (Supplementary Figure 1). The overall discontinuation rates ranged from 31 (ARBs/FDCs) to 69 (other anti-hypertensives) per 100 person-years across different categories of BPL agents (Table 1). Median days to discontinuation ranged from 159 for ‘other anti-hypertensives’ (C02) to 373 for ARBs. However, a high proportion of discontinued users reinitiated their initial BPL agent (Table 1). Re-initiation ranged from 31% for other anti-hypertensives (C02) to 49% for BBs, with median days to re-initiation ranging from 177 (BBs) to 302 (diuretics) (Table 1).

Table 1: Characteristics of BPL dispensing by ATC sub-categories

Life table analyses showed better persistence to FDCs (68%, 58% and 41% at 6, 12 and 36 months, respectively) and ARBs (69%, 58% and 40%), followed by BBs (67%, 54% and 36%), ACEIs (62%, 51% and 34%) and CCBs (57%, 47% and 30%). Diuretics (59%, 41% and 23%) and other anti-hypertensives (52%, 37% and 18%) were the least persistent categories (Figure 2).

Levels of ‘good’ adherence ($PDC \geq 0.8$) at six-monthly intervals for three years are summarised in Figure 3. At six months, 50-60% of users maintained good adherence to the majority of BPL categories. At 12 months, increasing variance in adherence occurred across the different BPL categories, with good adherence ranging from 34% of patients for other anti-hypertensives to 51% of patients for FDCs. Beyond 12 months, adherence steadily decreased across all BPL categories. At three years, 21-42% of users had good adherence to BPL agents.

Figure 2: KM curve of first non-persistence by BPL categories

Figure 3: Time to good adherence ($PDC \geq 0.8$) by BPL categories

The Cox regression model showed that compared to ACEIs (reference category), FDCs (aHR: 0.78, 95% CI: 0.75, 0.81) and ARBs (aHR: 0.80, 95% CI: 0.77, 0.83) had the lowest hazard (‘risk’) of discontinuation, followed by BBs (aHR: 0.86, 95% CI: 0.83, 0.89). Compared to ACEIs, the risk of discontinuation was higher for CCBs (aHR: 1.09, 95% CI: 1.05, 1.14), diuretics (aHR: 1.10, 95% CI: 1.07, 1.14) and highest for other anti-hypertensives (aHR: 1.29, 95% CI: 1.22, 1.37) (Table 2).

BPL discontinuation increased with age at initiation and if treatment was initiated by GPs (aHR: 1.04, 95% CI: 1.02, 1.06), but we found no gender differences (aHR: 0.99, 95% CI: 0.97, 1.01). The dispensing sequence of BPL categories did not have a significant impact on discontinuations.

However, compared to diuretics, people who started therapy with ACEIs had better persistence (aHR: 0.93, 95% CI: 0.89, 0.96), whereas discontinuations were highest among those who started with FDCs (aHR: 1.26, 95% CI: 1.19, 1.33). BPL discontinuation was also higher among those with pre-existing diabetes, gastrointestinal disease, autoimmune disease and chronic pain, but lower among those with dyslipidaemia or who were on concurrent anti-platelet or anti-coagulant therapy (Table 2).

Table 2: Adjusted hazard ratios from Cox regression model for discontinuation of blood pressure lowering agents

Discussion

We found poor long-term persistence and adherence to BPL agents among older Australians, among whom 60-70% discontinued over a mean of 3.8 years follow-up, and 'good' adherence ($PDC \geq 0.8$) dropped to 21-42% by three years. The majority of discontinuations occurred within the 6-12 month period following initiation. Among discontinued users, 30-50% re-initiated their initial BPL agent and the majority of re-initiations occurred within one year. In terms of long-term persistence across categories of BPL agents, the ranking (highest to lowest) was FDCs, ARBs, BBs, ACEIs, CCBs, diuretics and other anti-hypertensives.

ACEIs and ARBs were the most dispensed BPL agents among older Australians, followed by diuretics, BBs, CCBs, FDCs and other anti-hypertensives. ACEIs were the most common initiating BPL agents. This is reflective of national clinical guidelines for CVD management, in which ACEI/ARB are recommended as first-line pharmacotherapy for most cardiovascular conditions (14-16).

Consistent with the literature, we found low short- and long-term persistence and poor adherence to all BPL agents. This is possibly due to the lack of symptoms of hypertension and the preventive nature of BPL use among people with no indications for other cardiovascular comorbidities or risk factors (21). Reflective of this hypothesis, we found improved persistence to BPL agents among those with dyslipidaemia or who were on anti-platelet or anti-coagulant therapy, which indicated existing or high risks of cardiovascular disease.

For most BPL categories, discontinuation and poor adherence were more likely to occur within the first six months of initiation. Also, it appears that once users complied with BPL agents in the first year, the majority would maintain good adherence in the long-term. This is largely consistent with existing literature on BPL agents (17-21) and statins (22). We also found high re-initiation (30-50%) after discontinuation from all BPL categories, with the majority of people restarting within one year from discontinuation. This suggests that a large portion of BPL discontinuations were not due to medical reasons (e.g. adverse events or switching to other BPL agents). Therefore, it is crucial to reinforce adherence and persistence to BPL agents, especially in the first year since initiation. A number of studies have proposed promising interventions to improve medical adherence in older populations, including providing feedback and reminders (31), reducing the pill burden (32), improving health literacy (33), motivational interviewing (34) and multi-facet interventions (34, 35).

Consistent with the literature (17-21), we found worse long-term persistence and adherence to diuretics (C03) compared to other commonly used BPL categories. We also observed a declining use of diuretics as initiating BPL agents in older Australians from 2008 to 2016 (from 18% to 12%). These are likely to be related to the recommendation of cautious use of diuretics among patients with multi-morbidity

and polypharmacy, particularly in older adults (36), and also possibly the lack of high quality evidence supporting thiazides as first-line therapy for hypertension in older adults (37). Correspondingly, the latest Australian hypertension guidelines weakened the recommendation of low-dose diuretics as first line anti-hypertensive medications (38).

Of all BPL categories, persistence to FDCs was best. This accords with a systematic review which reported a 24% reduction in discontinuation to FDC agents in the management of hypertension (39). Polypharmacy and complex treatment regimens are known determinants of poor compliance to medications. FDCs are proven to improve persistence and adherence by reducing pill burden (39). However, use of FDCs remained relatively low in older Australians, with only 21% of our study cohort having dispensing of FDCs. This is consistent with the recommendation of conservative use of FDC in older patients due to increased risks of BPL-induced adverse events (40).

Unlike other studies (21, 41), we did not restrict our analysis to initial BPL categories. Instead, we included all BPL dispensing records from eligible individuals, which means one may have up to seven BPL categories dispensed within the study period. Therefore, in the regression analysis, we adjusted for initial BPL categories and the dispensing sequence of BPL categories. We did not find associations between dispensing sequence and persistence to BPL agents. However, we noted associations between initial BPL categories and subsequent persistence to BPL agents. While ACEIs as initial BPL agents was associated with lower risk of discontinuation to subsequent BPL agents, FDCs as initial BPL agents increased the risk of discontinuation. This is likely related to the indications for BPL dispensing and that FDCs as initial BPL agents was generally contrary to guidelines, especially in the older population.

Several limitations to our study warrant mention. First, 'long-term concession' people may not be representative of all Australians aged ≥ 65 years. A recent study investigating the differences between concession card holders and general beneficiaries among population aged 45 years and above, concluded that concession card holders were on average older, less educated and had more risk factors/morbidity conditions (42). Concession card holders also had higher level of adherence to statins than general beneficiaries (42). Therefore, our study is likely to have underestimated the level of poor adherence and persistence to BPLs in older Australians. Yet, the differences may not be substantial because the proportion of concession card holders is higher in older population than the younger age groups. Secondly, we were unable to ascertain the clinical indications and doses from the PBS data because these are not recorded. Instead, we applied the WTD method and used the 75th percentile to determine duration of use per dispensing. This method has been validated and applied in similar studies (25, 26). Thirdly, since the objective of our analysis was to compare long-term persistence and adherence for different categories of BPL agents, and because we did not have information on the indications for prescribing, we did not examine inter-category replacement. Therefore, discontinuation or poor adherence to BPL agents may not have indicated discontinuation of BPL therapy altogether. Fourthly, we did not have hospitalisation records, and PBS data is not captured from all hospitals. Therefore, we may have

overestimated the treatment gap or under-estimated adherence among persons who were hospitalised. However, this is expected to affect only the few long-term hospital admissions, and the effect will be minimal for the majority of admissions with normal length of stays. Finally, we did not have data for the reasons for discontinuations or poor adherence to BPL agents.

Conclusion

Compliance to BPL agents is poor among older Australians. Persistence and adherence differed by BPL categories. Interventions to enhance compliance to BPL agents, especially in the first year of initiation, are needed.

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Declaration of originality

There has been no proceeding publications or conference presentations on this manuscript.

Conflict of interest

The authors declare no conflict of interest

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Table 1: Characteristics of blood pressure lowering agents dispensed by ATC sub-categories

	Total	Discontinuation		Re-initiation*	Days until discontinuation	Days until Re-initiation
		Number	Rate per 100 Person-Years (95% CI)		Median (25 th , 75 th percentiles)	Median (25 th , 75 th percentiles)
Diuretics (C03)	10,405	6,908	62.5 (61.0, 63.9)	3,309 (47.9%)	182 (115, 442)	302 (151, 730)
BBs (C07)	10,353	6,121	37.6 (36.7, 38.6)	3,001 (49.0%)	273 (105, 788)	177 (115, 409)
CCBs (C08)	7,766	5,139	46.9 (45.6, 48.2)	1,769 (34.4%)	195 (55, 698)	226 (131, 567)
ACEIs (C09A)	14,568	9,423	40.0 (39.2, 40.8)	3,146 (33.4%)	246 (74, 858)	219 (131, 546)
ARBs (C09C)	12,162	7,424	31.2 (30.4, 31.9)	3,209 (43.2%)	373 (92, 1135)	210 (129, 517)
FDC (C09B;C09D)	6,584	3,798	32.2 (31.2, 33.2)	1,434 (37.8%)	346 (86, 1011)	197 (127, 449)
Anti-hypertensives (C02)	2,596	2,003	69.3 (66.3, 72.4)	626 (31.3%)	159 (101, 478)	196 (126, 396)

*denominators are number of discontinued users in specific categories of blood pressure lowering agents;

BB, beta blockers; CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; FDC, fixed dose combinations.

Table 2: Adjusted hazard ratios from Cox regression model for discontinuation of blood pressure lowering agents.

Lowering agents.		HR	95% CI		P value
BPL categories					
	Diuretics (C03)	1.10	1.07	1.14	<0.01
	BBs (C07)	0.86	0.83	0.89	<0.01
	CCBs (C08)	1.09	1.05	1.14	<0.01
	ACEIs (C09A)	1.00			
	ARBs (C09C)	0.80	0.77	0.83	<0.01
	FDCs (C09B;C09D)	0.78	0.75	0.81	<0.01
	Other anti-hypertensives (C02)	1.29	1.22	1.37	<0.01
Age		1.00	1.00	1.00	0.02
Sex					
	Female	1.00			
	Male	0.99	0.97	1.01	0.23
Prescriber					
	specialists/others	1.00			
	GP	1.04	1.02	1.06	<0.01
Initiating BPL agent					
	Diuretics (C03)	1.00			
	BBs (C07)	1.04	1.00	1.08	0.08
	CCBs (C08)	0.98	0.94	1.03	0.44
	ACEIs (C09A)	0.93	0.89	0.96	<0.01
	ARBs (C09C)	0.99	0.95	1.02	0.44
	FDCs (C09B;C09D)	1.26	1.19	1.33	<0.01
	Other anti-hypertensives (C02)	1.06	1.00	1.13	0.05
Sequence of dispensing					
	1	1.00			
	2	1.01	0.98	1.03	0.57
	3	0.99	0.96	1.02	0.46
	4	1.00	0.96	1.05	0.91
	5	0.99	0.92	1.08	0.88
	6	1.11	0.96	1.29	0.16
	7	0.75	0.48	1.16	0.19
Comorbid conditions*					
	Mental health disease	1.01	0.99	1.04	0.24
	Dyslipidaemia	0.97	0.95	0.99	0.00
	Diabetes	1.05	1.02	1.09	0.00
	Antiplatelet or anti-coagulant therapy	0.94	0.92	0.97	0.00
	Cardiac disease	0.98	0.95	1.02	0.38
	Respiratory disease	0.99	0.96	1.02	0.57
	Gastrointestinal disease	1.06	1.04	1.08	0.00
	Autoimmune disease	1.05	1.02	1.08	0.00
	Osteoporosis	1.03	1.00	1.06	0.07
	Chronic pain	1.06	1.04	1.08	0.00
Year of 1 st BPL dispensing					
	2008	1.00			
	2009	1.01	0.97	1.05	0.71
	2010	0.97	0.93	1.01	0.13
	2011	0.96	0.92	1.00	0.06
	2012	0.94	0.90	0.98	0.01
	2013	0.95	0.91	1.00	0.03
	2014	0.96	0.91	1.00	0.05
	2015	0.92	0.88	0.96	0.00
	2016	0.53	0.49	0.56	0.00

*the reference group is absence of indicated comorbidity; BPL: blood pressure lowering; HR: hazard ratio; CI: confidence interval. BB, beta blockers; CCB, calcium channel blockers; ACEI, angiotensin converting enzyme inhibitors; ARB, angiotensin II receptor blockers; FDC, fixed dose combinations.

Figure 1: cohort identification

BPL: blood pressure lowering; ACEIs: Angiotensin converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; BBs: beta-blockers; CCB: calcium channel blockers; FDC: fixed dose combinations.

Figure 2: Kaplan-Meier curves of first non-persistence by categories of blood pressure lowering agents

ACEIs: Angiotensin converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; BBs: beta-blockers; CCB: calcium channel blockers; FDC: fixed dose combinations

Figure 3: Time to good adherence ($PDC \geq 0.8$) by categories of blood pressure lowering agents

ACEIs: Angiotensin converting enzyme inhibitors; ARBs: angiotensin II receptor blockers; BBs: beta-blockers; CCB: calcium channel blockers; FDC: fixed dose combinations

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