

# Persistence with a single pill versus two pills of amlodipine and atorvastatin: the Australian experience, 2006–2010

Leon A Simons, Michael Ortiz and Gordon Calcino

Persistence with long-term medication in hypertension or dyslipidaemia (hypercholesterolaemia) in the community is known to be unsatisfactory.<sup>1–8</sup> Out of 49 000 patients in Australia who were initiated on antihypertensive therapy in 2004–2006, 19% failed to collect the first repeat prescription at 1 month and 50% had discontinued therapy within 20 months.<sup>8</sup> Overall tablet burden and dosing frequency are predictors of poor compliance,<sup>9,10</sup> and this has stimulated the development of single-pill, fixed-dose combinations administered once daily. We analysed Medicare Australia Pharmaceutical Benefits Scheme (PBS) claims over the period December 2006–March 2010 for a single-pill, fixed-dose combination of amlodipine (a calcium channel blocker [CCB]) and atorvastatin (a statin). It is prescribed for the management of hypertension and dyslipidaemia together. Using these data as a broad surrogate of persistence, we derived a picture of persistence in Australian patients prescribed amlodipine and atorvastatin together (AA) in one pill, in comparison with those prescribed the separate components as two-pill, dual-drug therapy.

## METHODS

### Participants and study design

We analysed PBS prescription claims for two periods, April 2005–March 2010 and December 2006–March 2010. For the April 2005–March 2010 period, we examined two-pill prescriptions for amlodipine and atorvastatin, and for the December 2006–March 2010 period, we examined the single-pill AA combination of the same drugs.

This was based on a 10% sample of the Australian population, using a random number selection algorithm of encrypted (de-identified) Medicare numbers. All strengths of amlodipine are priced below the general patient copayment threshold and are not recorded by Medicare (ie, they are priced below the standard charge for non-concessional patients). Hence, the study was restricted to patients classified as long-term concessional patients, a group who had exclusively received concessional medica-

## ABSTRACT

**Objective:** To study patient persistence on therapy for hypertension and dyslipidaemia using a single-pill combination compared with a two-pill approach.

**Design and setting:** Post-hoc observational assessment of Pharmaceutical Benefits Scheme claim records covering the period April 2005 to March 2010.

**Participants:** A 10% random sample of Australian long-term concession card holders was analysed. The patients studied had commenced on either amlodipine and atorvastatin as two individual pills, or a single pill containing both amlodipine and atorvastatin (AA), with neither combined approach having been dispensed to them in the previous 6 months.

**Main outcome measures:** The proportions of patients failing to fill their first repeat prescription after 1 month or failing to persist with treatment at 12 months, and the median persistence time (MPT) were measured.

**Results:** Of 4146 patients prescribed the AA single pill, 11% failed to fill the first repeat prescription and 33% had ceased treatment by 12 months (MPT, 35 months). Of 6204 patients prescribed amlodipine and atorvastatin as two pills, 23% failed to fill the first repeat prescriptions and 59% had ceased treatment by 12 months (MPT, 7 months). In a multivariate model, cessation of single-pill therapy increased by 165% if there was no prior therapy, but only increased by 48%–55% if there was no prior therapy with a calcium channel blocker or statin. MPT on the single pill was 8 months in those without prior antihypertensive therapy, but was  $\geq 37$  months in those with any prior antihypertensive therapy.

**Conclusion:** A single-pill combination drug is associated with superior long-term persistence compared with two-pill therapy in the management of hypertension and dyslipidaemia.

MJA 2011; 195: 134–137

tion over the previous 5 years. They are estimated to represent around 65% of all patients receiving these drugs (Maxine Robinson, committee secretary, Drug Utilisation Sub-Committee of the Pharmaceutical Benefits Advisory Committee, personal communication, April 2009).

### Outcome measures

We analysed our data using four groups of patients, which were those who had:

- *initiated* two-pill, dual-drug therapy or single-pill therapy (had no prescriptions issued for that option in the previous 6 months)
- *ceased* two-pill or single-pill therapy (had no prescription refills for 3 consecutive months (ie, therapy had lapsed for at least 2 months)
- *switched* from two-pill to single-pill therapy (these patients were censored [discontinued from our dataset] from the month of switching)

- *been treated before* (had used amlodipine, other CCBs, atorvastatin, other statins or other antihypertensive drugs in the 3 months before initiation).

### Statistical analysis

Using the Kaplan–Meier technique, we generated persistence curves for the treatment groups. Persistence curves were compared pairwise, using proportional hazard models (ie, time to event, with the outcome being cessation of the nominated treatment). There was a progressive catchment of patients over time, therefore the duration of follow-up was variable and all patients were censored at 31 March 2010. The group initiated on single-pill AA treatment was used as the reference group, with reporting of hazard ratios and log rank statistics.

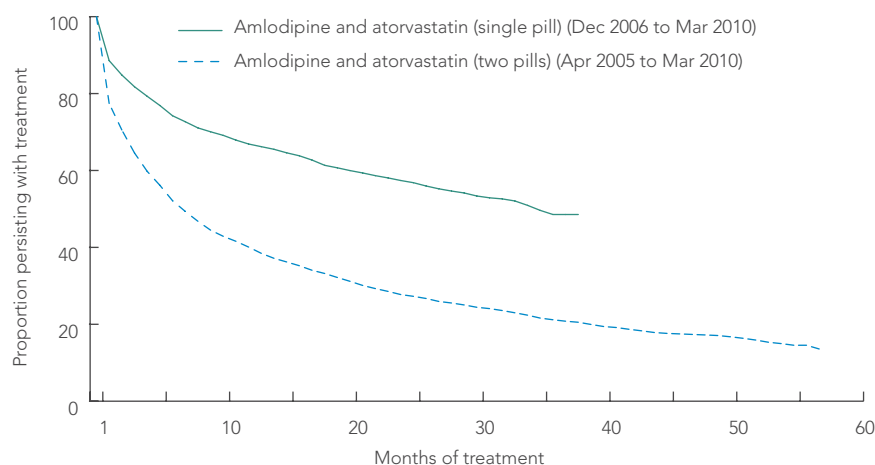
A stepwise multivariate model was used to adjust single-pill AA treatment persistence for potential confounding by other key variables. The key assumption of constant

### 1 Characteristics of patients and their prior treatments at study entry\*

	Amlodipine and atorvastatin (two-pill therapy) (n = 6204)	AA (single-pill therapy) (n = 4146)	P
Male	2858 (46%)	1921 (46%)	ns
Prescriptions from general practitioner	4589 (74%)	3789 (91%)	
Prescriptions from specialist	1615 (26%)	357 (9%)	< 0.0001
Age distribution (years)			
< 50	239 (4%)	165 (4%)	
50–59	510 (8%)	352 (8%)	
60–69	1591 (26%)	1139 (27%)	
70–79	2602 (42%)	1732 (42%)	
≥ 80	1262 (20%)	758 (18%)	ns
Mean age, years (SD)	71.2 (10.3)	70.7 (10.3)	< 0.007
Treatment during previous 3 months			
Amlodipine only	1814 (29%)	751 (18%)	< 0.0001
Atorvastatin only	3063 (49%)	993 (24%)	< 0.0001
Neither of above	918 (15%)	1358 (33%)	< 0.0001
Amlodipine and atorvastatin	409 (7%)	1044 (25%)	na
Other statins	523 (8%)	982 (24%)	< 0.0001
Other calcium channel blockers	562 (8%)	633 (15%)	< 0.0001
Antihypertensive drugs previously being used			
Nil	665 (11%)	472 (11%)	ns
1	1397 (23%)	826 (20%)	< 0.002
2	2007 (32%)	1195 (29%)	< 0.0001
≥ 3	2135 (34%)	1653 (40%)	< 0.0001

AA = amlodipine+atorvastatin. ns = not significant. na = not applicable. \* Data are frequency except age. Frequencies are contrasted by  $\chi^2$ , age by t test. ◆

### 2 Persistence curves for AA single-pill therapy versus amlodipine and atorvastatin two-pill therapy\*



AA = amlodipine+atorvastatin. \* Patients using two-pill amlodipine and atorvastatin therapy were censored (discontinued from our dataset) if they switched to single-pill amlodipine and atorvastatin. ◆

proportional hazard over time was supported by parallel persistence curves. A power calculation was performed for the hazard ratios from the Kaplan–Meier curves.

If a minimum of 2000 patients entered this two-treatment parallel-design study, the study could detect a significant treatment difference if the hazard ratio was 1.19 with

power of 90%, assuming a two-sided 5% significance level. This is based on the assumption of a 24-month accrual period, 12-month follow-up period and 12-month median survival time. The sample from the PBS database exceeded this 2000-patient sample-size minimum.

Patient identities remained anonymous during this investigation and ethics approval was obtained from the Medicare External Request Evaluation Committee.

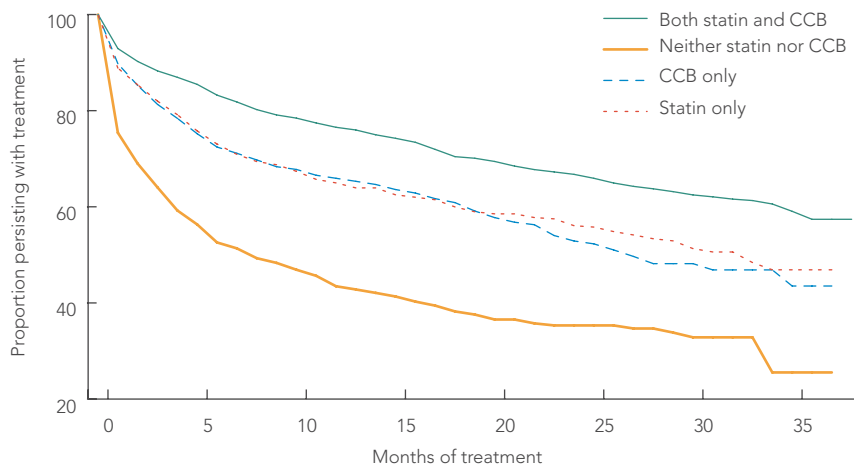
### RESULTS

The PBS database generated information on 6204 patients who were prescribed amlodipine and atorvastatin as two-pill therapy, and on 4146 patients who were prescribed AA as single-pill therapy. Their demographic features by selected prior treatments are summarised in Box 1.

Persistence curves for those initiated on single-pill AA or dual-pill amlodipine and atorvastatin are shown in Box 2. Apparent persistence was far superior in those initiated on single-pill AA. Median persistence time (MPT) on single-pill AA was 35 months (95% CI, 33 to ≥ 38 months), and was only 7 months (95% CI, 6–8 months) on amlodipine and atorvastatin. Patients switching from amlodipine and atorvastatin to single-pill AA were censored at that point, and this would slightly overestimate the extent of cessation on two-pill therapy. The hazard ratio for cessation of amlodipine and atorvastatin (two pills) versus AA (one pill) was 2.17 (95% CI, 2.05–2.13;  $P < 0.0001$ ), that is, a 117% higher rate of cessation. Since much of the persistence data for amlodipine and atorvastatin preceded that for single-pill AA by 20 months in real time, the respective proportions of patients failing to collect their first repeat prescription after 1 month was highly informative: 23% for the two-pill combination and only 11% for the single-pill prescription. The corresponding proportions of patients failing to persist with treatment at 12 months were 59% and 33%.

Persistence with single-pill AA treatment varied according to the treatment used in the 3 months before initiation (see Box 3). The MPT was only 8 months (95% CI, 6–11 months) in those having used neither a CCB nor a statin, 32 months (95% CI, 28 to ≥ 38 months) in those using a statin only, 27 months (95% CI, 23 to ≥ 38 months) in those using a CCB only, and ≥ 38 months (confidence intervals could not be derived) in those using both a CCB and a statin. The corresponding proportions of patients failing to collect their first repeat prescription at

### 3 Persistence curves for AA single-pill therapy, according to prior therapy



AA = amlodipine+atorvastatin. CCB = calcium channel blocker.

1 month were 25%, 11%, 10% and 7%. The corresponding proportions of patients failing to persist with treatment at 12 months were 57%, 35%, 34% and 23%.

The MPT using the single pill was only 8 months (95% CI, 6–12 months) in those not previously using any antihypertensive drugs, compared with  $\geq 37$  months (95% CI, 29 to  $\geq 38$  months) in those using one or more antihypertensive drugs. The MPT on single-pill AA varied with age. This was 17 months (95% CI, 6–30 months) in those aged < 50 years, 28 months (95% CI, 19 to  $\geq 38$  months) in those 50–59 years, 36 months (95% CI, 34 to  $\geq 38$  months) in those aged 60–69 years,  $\geq 38$  months (95% CI, 35 to  $\geq 38$  months) in those aged 70–79 years, and 25 months (95% CI, 18–32 months) in those aged  $\geq 80$  years.

Findings from the stepwise multivariate model of AA, single-pill cessation are presented in Box 4. Taking prior CCB and statin therapy as a reference group, if neither a CCB nor a statin were used in prior therapy, treatment cessation on single-pill AA increased by 165% (95% CI, 127%–210%;  $P < 0.0001$ ). If a CCB only or a statin only had been used in prior therapy, cessation on single-pill AA increased by 55% (95% CI, 31%–83%;  $P < 0.0001$ ) and 48% (95% CI, 29%–70%;  $P < 0.0001$ ), respectively. Taking the use of two antihypertensive drugs as a reference group, in those naive to prior antihypertensive therapy, cessation of single-pill AA increased by 38% (95% CI, 18%–62%;  $P < 0.001$ ), while in patients using three or more antihypertensive agents prior to treatment, cessation of single-pill AA increased by 15% (95% CI, 2%–29%;  $P < 0.02$ ). Females were 13% (95% CI, 2%–25%;  $P < 0.02$ ) more

likely to cease single-pill AA treatment than males. Cessation of single-pill AA treatment was significantly greater in younger age groups, but this was significant only in the univariate model.

### DISCUSSION

We confirmed that long-term persistence with a single-pill combined formulation in the management of hypertension and dyslipidaemia in the Australian population is far superior to that observed when patients have used the separate component drugs. Since patients in the amlodipine and atorvastatin group were censored if they switched to single-pill AA treatment, the switch being a logical clinical step, this will have slightly understated the apparent persistence in the two-pill group. If patients had not been censored at the point of switch, their apparent excess cessation, compared with single-pill AA, would have been reduced from 117% to 110%. Furthermore, the proportion failing to collect the first repeat prescription was twofold greater in the two-pill group. Our findings confirm the thrust of conclusions from United States health maintenance and managed care organisations.<sup>11-13</sup>

By examination of treatment in the 3 months before initiation, we have been able to identify which patients are more likely to

### 4 Stepwise multivariate analysis of patients discontinuing AA single-pill therapy\*

	Univariate HR (95% CI)	P	Multivariate HR (95% CI)	P
Female	1.18 (1.07–1.31)	< 0.002	1.13 (1.02–1.25)	< 0.02
Male	1.00		1.00	
Specialist treatment	1.10 (0.92–1.31)	ns		
GP treatment	1.00			
Age (years)				
< 50	1.76 (1.39–2.22)	< 0.0001		
50–69	1.33 (1.11–1.59)	< 0.002		
60–69	1.05 (0.93–1.19)	ns		
70–79	1.00			
$\geq 80$	1.38 (1.21–1.58)	< 0.0001	1.36 (1.20–1.54)	< 0.0001
Treatment in previous 3 months				
Statin only <sup>†</sup>	1.48 (1.30–1.68)	< 0.0001	1.48 (1.29–1.70)	< 0.0001
CCB only <sup>†</sup>	1.53 (1.29–1.81)	< 0.0001	1.55 (1.31–1.83)	< 0.0001
Neither CCB nor statin <sup>†</sup>	2.78 (2.44–3.16)	< 0.0001	2.65 (2.27–3.10)	< 0.0001
CCB and statin <sup>†</sup>	1.00		1.00	
Antihypertensive drugs previously used				
Nil	2.22 (1.90–2.59)	< 0.0001	1.38 (1.18–1.62)	< 0.0001
1	1.21 (1.04–1.40)	< 0.02		
2	1.00			
$\geq 3$	1.04 (0.92–1.18)	ns	1.15 (1.02–1.29)	< 0.02

AA = amlodipine + atorvastatin as a single pill. HR = hazard ratio. GP = general practitioner. ns = not significant. CCB = calcium channel blocker. \* In the stepwise approach, only items of statistical significance remain in the final model. <sup>†</sup> The statistics on prior statin or CCB therapy relate to the curves in Box 3.

persist with treatment. Patients appear to be more likely to persist on a single, combination pill if they have used one or both components previously, or if they have received any antihypertensive therapy, as noted by others.<sup>12</sup> In univariate analysis, poorer persistence was noted on the single pill in the youngest and oldest subgroups, consistent with a pattern we previously reported in patients newly treated with antihypertensive drugs.<sup>8</sup>

Other contributors to poor persistence include the cost of medication and the risk of adverse events.<sup>10</sup> The former is perhaps less relevant in our study as the patients paid only a nominal amount for medication. Adverse events with antihypertensive drugs do contribute to poor persistence.<sup>14</sup>

There were some limitations in our approach. There was an absence of medical histories; we had no information on the degree of blood pressure and cholesterol control; only concession card holders were studied (yet they still represented around 65% of Australian patients using these medications); and we did not adjust for any temporal effects in the data.

It must follow that poor persistence will impact on the clinical outcomes. Cardiovascular disease outcomes in the second Australian National Blood Pressure Study were 20%–23% higher in patients reporting poor compliance with their medication.<sup>15</sup> It has been calculated that hypertensive patients taking antihypertensive and statin therapy at real-world adherence levels can be expected to receive about 50% of the potential benefit seen in clinical trials.<sup>16</sup> In a recent US study using similar drugs, those on a single-pill regimen were more adherent and showed a lower cardiovascular event rate. Incidence rates per 100 person-years were 1.39 on a single pill, 2.21 on a two-pill regimen; and 2.26 in the non-adherent group on any therapy.<sup>17</sup>

What can be done to improve persistence? Drugs with fewer side effects, more convenient once-daily dosing schedules, a greater number of single-pill combination products and better patient education are potential solutions. Ultimately, better persistence and better control of hypertension, dyslipidaemia and other chronic diseases or risk factors will rest on a partnership between health professionals and the individual patient.

## ACKNOWLEDGEMENTS

Raw data for the study were supplied by Medicare Australia. Leon Simons contributed his time in an

honorary capacity. Michael Ortiz is an employee of Abbott Products. Gordon Calcino is an independent contractor. The manufacturer of the amlodipine and atorvastatin single pill had no involvement in any aspect of this study or report.

## COMPETING INTERESTS

None relevant to this article declared (ICMJE disclosure forms completed).

## AUTHOR DETAILS

**Leon A Simons**, MD, FRACP, Associate Professor of Medicine, Lipid Department<sup>1</sup>

**Michael Ortiz**, BPharm, PhD, Conjoint Associate Professor, Clinical School, Pricing and Reimbursement Manager<sup>1,2</sup>

**Gordon Calcino**, BA, GradDipMedStats, Director<sup>3</sup>

<sup>1</sup> St Vincent's Hospital, University of New South Wales, Sydney, NSW.

<sup>2</sup> Abbott Products, Sydney, NSW.

<sup>3</sup> HI Connections, Canberra, ACT.

**Correspondence:** l.simons@unsw.edu.au

## REFERENCES

- 1 Simons LA, Levis G, Simons J. Apparent discontinuation rates in patients prescribed lipid-lowering drugs. *Med J Aust* 1996; 164: 208-211.
- 2 Caro JJ, Salas M, Speckman JI, et al. Persistence with treatment for hypertension in actual practice. *CMAJ* 1999; 160: 31-37.
- 3 Simons LA, Simons J, Mcmanus P, Dudley J. Discontinuation rates for use of statins are high. *BMJ* 2000; 321: 1084.
- 4 Benner JS, Glynn RJ, Mogun H, et al. Long-term persistence in use of statin therapy in elderly patients. *JAMA* 2002; 288: 455-461.
- 5 Degli Espositi E, Sturani A, Di Martino M, et al. Long-term persistence with antihypertensive drugs in new patients. *J Hum Hypertens* 2002; 16: 439-444.
- 6 Osterberg L, Blaschke T. Adherence to medication. *N Engl J Med* 2005; 353: 487-497.

7 Elliott WJ, Plauschinat CA, Skrepnek GH, Gause D. Persistence, adherence, and risk of discontinuation with commonly prescribed antihypertensive drug monotherapies. *J Am Board Fam Med* 2007; 20: 72-80.

8 Simons LA, Ortiz M, Calcino G. Persistence with antihypertensive medication: Australia-wide experience, 2004–2006. *Med J Aust* 2008; 188: 224-227.

9 Kirtsis DN, Giral P, Bruckert E, Turpin G. Factors associated with low compliance with lipid-lowering drugs in hyperlipidemic patients. *J Clin Pharm Ther* 2000; 25: 445-451.

10 Chapman RH, Benner JS, Petrilla AA, et al. Predictors of adherence with antihypertensive and lipid-lowering therapy. *Arch Intern Med* 2005; 165: 1147-1152.

11 Bangalore S, Kamalakkannan G, Parkar S, Messerli FH. Fixed-dose combinations improve medication compliance: a meta-analysis. *Am J Med* 2007; 120: 713-719.

12 Hussein MA, Chapman RH, Benner JS, et al. Does a single-pill antihypertensive/lipid-lowering regimen improve adherence in US managed care enrollees? *Am J Cardiovasc Drugs* 2010; 10: 193-202.

13 Gupta AK, Arshad S, Poulter NR. Compliance, safety, and effectiveness of fixed-dose combinations of antihypertensive agents: a meta-analysis. *Hypertension* 2010; 55: 399-407.

14 After the diagnosis: adherence and persistence with hypertension therapy. *Am J Manag Care* 2005; 11 (13 Suppl): S395-S399.

15 Nelson MR, Reid CM, Ryan P, et al. Self-reported adherence with medication and cardiovascular disease outcomes in the second Australian National Blood Pressure Study (ANBP2). *Med J Aust* 2006; 185: 487-489.

16 Cherry SB, Benner JS, Hussein MA, et al. The clinical and economic burden of nonadherence with antihypertensive and lipid-lowering therapy in hypertensive patients. *Value Health* 2009; 12: 489-497.

17 Chapman RH, Yeaw J, Roberts CS. Association between adherence to calcium-channel blocker and statin medications and likelihood of cardiovascular events among US managed care enrollees. *BMC Cardiovasc Disord* 2010; 10: 29.

(Received 4 Nov 2010, accepted 10 May 2011) □