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ORIGINAL ARTICLE

Long-term persistence with single-pill, fixed-dose combination therapy versus two pills of amlodipine and perindopril for hypertension: Australian experience

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ABSTRACT

Objective: To study treatment persistence and mortality using a single-pill, fixed-dose combination tablet compared with a two-pill combination for hypertension.

Research design and methods: We analyzed Australian Pharmaceutical Benefit Scheme records 2011–2014 in a 10% random sample of concessional patients prescribed concomitant amlodipine and perindopril – either as a single-pill, fixed-dose combination tablet ($n = 9340$) or as two-pill combination therapy ($n = 3093$). Main outcome measures were: (a) proportions failing to continue amlodipine + perindopril over time, (b) proportions failing to continue any subsequent calcium channel and angiotensin inhibition therapy over time and (c) proportions dying.

Results: After 12 months, 34% of single-pill and 57% of two-pill users discontinued amlodipine + perindopril, median persistence time 42 months versus 7 months; 28% and 47% respectively discontinued any calcium channel–angiotensin inhibition therapy. After 48 months, 8% of single-pill and 18% of two-pill users had died. In a multivariate model adjusted for age, gender, duration and intensity of prior hypertension therapy, initial dose of amlodipine and perindopril, diabetes, hyperlipidemia, and complexity of care, the hazard ratio for risk of discontinuation over 42 months in the two-pill versus single-pill amlodipine + perindopril group was 1.94 (95% CI 1.83–2.06). The hazard ratio for discontinuation in two-pill versus single-pill users of any calcium channel–angiotensin inhibition therapy was 1.86 (1.74–1.99). The adjusted hazard ratio for risk of death over 48 months was 1.83 (1.55–2.16), but the mortality outcome may be an overestimate due to residual confounding.

Conclusions: Use of a single-pill, fixed-dose combination in hypertension is associated with superior persistence and reduced mortality compared with use of two pills, suggesting a higher priority for the use of fixed-dose combinations.

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Hypertension therapy; persistence; fixed-dose combinations; mortality

Introduction

Long-term patient persistence with medication for chronic asymptomatic conditions such hypertension or hypercholesterolemia is known to be unsatisfactory[1–5]. Of 49,000 patients in Australia initiated to hypertension therapy in 2004–2006, 50% had discontinued therapy within 20 months[3]. Overall tablet burden and dosing frequency, amongst other factors, are predictors of poor compliance[6], and this has stimulated the use of once daily single-pill fixed-dose combination products for a number of clinical indications. Previous reports highlight superior persistence with single-pill approaches to therapy[7–9].

A single-pill, fixed-dose combination tablet of amlodipine + perindopril, respectively a calcium channel blocker and an inhibitor of angiotensin converting enzyme (ACE), has become one of the most commonly prescribed products in Australia for hypertension. In this report we have analyzed long-term persistence and mortality Australia-wide using this single-pill compared with a two-pill combination of the same drugs. We have also analyzed overall persistence if patients subsequently switched to other drugs offering calcium channel and angiotensin inhibition.

Methods

Data source

Analysis was performed on Pharmaceutical Benefits Scheme (PBS) pharmacy payment claims in a 10% random sample of the Australian population, the data being drawn from de-identified records held by Medicare Australia via the Department of Human Services. All Australian citizens have a unique identifying number and we received data from every citizen whose number ended in a single but undisclosed digit.

Data was available for the period January 2005 through March 2015. The single-pill, fixed-dose combination tablet of amlodipine + perindopril was subsidized by the PBS only from June 2010. Hence, we analyzed persistence and mortality over the period January 2011 through December 2014. Analysis was restricted to patients who had received all their

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PBS prescriptions on a concessional and heavily subsidized basis. Patients were eligible for concessional supply of drugs by virtue of advancing age, financial circumstances and co-morbidity, but this concessional group represented around two thirds of the Australian population. The restriction to concessional patients was necessary because some non-concessional prescriptions are not recorded by the PBS. The PBS administrative database does not provide information on medical history, but limited diagnostic information could be inferred from relevant concomitant medication data.

Definition of one-pill and two-pill groups

There is an expectation that some patients using two-pill combination therapy amlodipine and perindopril will switch to a one-pill fixed-dose combination after a titration period. Therefore, the analysis separated patients into one-pill or two-pill mutually exclusive groups. Patients receiving a fixed-dose combination at any point in the time window were included in the "one-pill group", and persistence was assessed from the date of the first one-pill dose, or from the date of the first two-pill combination, whichever came first.

Conversely, patients in the "two-pill group" would have not received a single-pill, fixed-dose combination of these drugs in the time window. Patients were deemed to belong to the two-pill group when the use of amlodipine and perindopril overlapped. If one or both components were stopped, then patients were deemed to have ceased therapy.

Outcome measures

Patients were deemed to be persistent as long as they filled relevant prescriptions at least once every 6 months. Once a gap of six consecutive months occurred, discontinuation was deemed to have occurred on the date of last purchase before this gap.

Patients switching over to similar treatments were counted as continuing, but their persistence episode was still counted from the first purchase of amlodipine and perindopril. Similar therapy would be another combination of calcium channel blocker, ACE inhibitor and angiotensin receptor blocker, defined as calcium channel and angiotensin inhibition. Thus, we are able to study persistence exclusively with amlodipine + perindopril, but finally with any other calcium channel and angiotensin inhibition.

Mortality assessment

The PBS data provides year of death only. A proxy for date of death was generated using the date of last purchase of any PBS-listed product. If no product was purchased in the notified year of death, the date of death was arbitrarily assumed to be 1 January. The time to death started from commencement of the persistence analysis until the inferred date of death. All patients were censored at 31 December 2014 unless they were recorded as dying.

Persistence and mortality analyses, statistical methods

Patients who purchased only one prescription in either the single-pill or two-pill groups and who thus had only one day follow-up were removed from all persistence analyses, but not from mortality analysis. Persistence with medication was defined as time from first prescription of amlodipine + perindopril until discontinuation, or until censored on the last day of follow-up or inferred death. Using the Kaplan–Meier survival method, we generated monthly persistence and daily mortality/survival curves for the two treatment groups. Main outcome measures were: (a) proportions failing to continue amlodipine + perindopril over time, (b) proportions failing to continue any subsequent calcium channel and angiotensin inhibition therapy over time and (c) proportions who died.

Multivariate Cox proportional hazards models were used to adjust persistence and mortality for potential confounding by available key variables: age at study entry, gender, duration and intensity of prior hypertension therapy, initial dose of amlodipine and perindopril, overall medication burden (a surrogate for complexity of care), diabetes and hyperlipidemia.

Power calculation, ethics approval

A power calculation was performed for the hazard ratios from the Kaplan–Meier persistence curves. A sample size of 691 patients will be sufficient to detect a clinically significant difference in persistence between the two arms of therapy if the hazard ratio was 1.10 with power of 80%, assuming a two-sided 5% significance level. A sample size of 2101 patients will be sufficient to detect a clinically significant difference in mortality if the hazard ratio was 1.10 with power of 80%, assuming a two-sided 5% significance level. Patient identities remained anonymous during this investigation and ethics approval was obtained from the External Request Evaluation Committee of the Australian Department of Human Services.

Results

The database yielded 9340 patients in the single-pill group and 3093 in the two-pill group, representative of a total of 124,330 patients nationally. Demographic and key clinical details are summarized in Table 1. There were important differences between the two groups. The two-pill group included fewer men, were older, more entered the analysis on the higher 10 mg dose of amlodipine and fewer entered at the higher 10 mg dose of perindopril. This group also manifested a greater pre-study duration and intensity of hypertension therapy, had more evidence of diabetes and hyperlipidemia, and had a greater prescription burden throughout the study, indicating a higher degree of complexity of care. This suggests that members of the two-pill group were "sicker".

The persistence curves for the single- and two-pill groups are shown in Figure 1. As described in the *Methods* section, a small proportion of patients were excluded from analysis of

Table 1. Demographic and key clinical details in the two groups.

	Single-pill group $n = 9340$	Two-pill group $n = 3093$
Mean age (95% CI) at study entry, years	67.8 (67.6–68.1)	71.5 (71.0–71.9)*
Male gender	4577 (49%)	1418 (46%)†
Amlodipine high dose at entry (10 mg)	1869 (20%)	769 (25%)*
Perindopril high dose at entry (8–10 mg)	5109 (55%)	1224 (40%)*
Pre-study hypertension therapy:		
Nil Rx	877 (9%)	151 (5%)*
1–3 years	2732 (29%)	732 (24%)
4+ years	5731 (61%)	2210 (71%)
Drugs for hypertension over 1 year pre-study:		
0 classes	1037 (11%)	180 (6%)*
1–2 classes	6960 (75%)	2168 (70%)
3+ classes	1343 (14%)	745 (24%)
Prescription volume in study:		
0–19/year	4730 (51%)	1098 (36%)*
20–49/year	3429 (37%)	1301 (42%)
50+/year	1181 (13%)	694 (22%)
ATC 3 drug count over 1 year pre-study:		
0–3	2501 (27%)	478 (16%)*
4–6	3081 (33%)	836 (27%)
7–9	2219 (24%)	860 (28%)
10+	1539 (17%)	919 (30%)
Diabetes	1512 (16%)	632 (20%)*
Hyperlipidemia	4029 (43%)	1583 (51%)*

Continuous variables contrasted with *t*-test, frequencies contrasted with χ^2: *$p < .001$, †$p = .002$. Prescription volume in study, one measure of complexity of care, excludes medication for hypertension. ATC 3 drug count refers to the Anatomical Therapeutic Chemical classification system pharmacologic subgroup, another measure of complexity of care. Clinical diagnoses were inferred from relevant concomitant medication data.

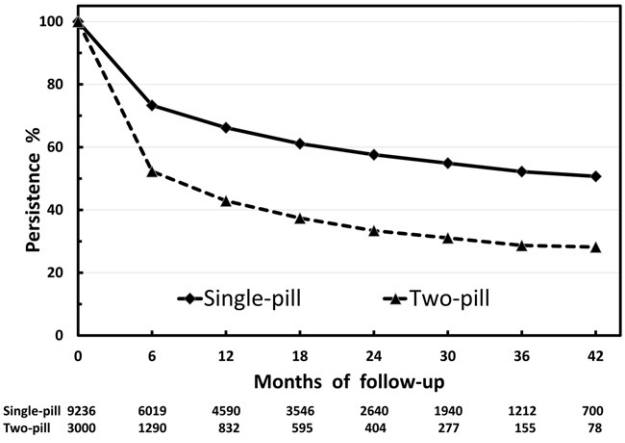

Figure 1. Persistence curves for patients allocated to single-pill and two-pill therapy. Sample numbers at time points are shown.

persistence when only one prescription was purchased and only one day of follow-up was available. After 12 months, 34% of single-pill and 57% of two-pill users had discontinued amlodipine + perindopril. Median persistence time for the single-pill group was 42 months (95% CI 33 to ≥43), but only 7 months in the two-pill group (95% CI 5–9). The unadjusted univariate hazard ratio for discontinuation in the two-pill versus single-pill group was 1.99 (95% CI 1.88–2.10). In a multivariate model adjusted for potential confounding variables listed in Table 1, the hazard ratio for risk of discontinuation was minimally changed, 1.94 (95% CI 1.83–2.06).

After allowance for switching medication and exclusion of the small proportion receiving only a single prescription, persistence curves on any subsequent calcium channel and angiotensin inhibition, based on the original group allocations, are shown in Figure 2. After 12 months, 28% of single-pill and 47% of two-pill users had discontinued any calcium channel and angiotensin inhibition. Median persistence time for the single-pill group was >48 months, but was only 15 months in the two-pill group (95% CI 13–17). The unadjusted univariate hazard ratio for discontinuation in the two-pill versus single-pill group was 1.86 (95% CI 1.75–1.98), and was little changed in the multivariate model, 1.86 (95% CI 1.74–1.99).

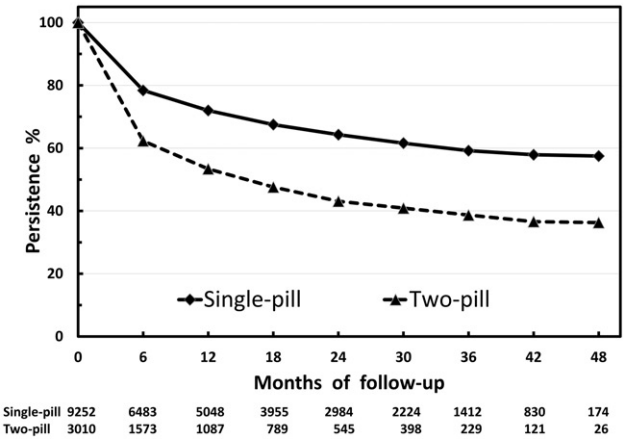

Figure 2. Persistence curves on any calcium channel and angiotensin inhibition, based on original single-pill and two-pill allocations. Sample numbers at time points are shown.

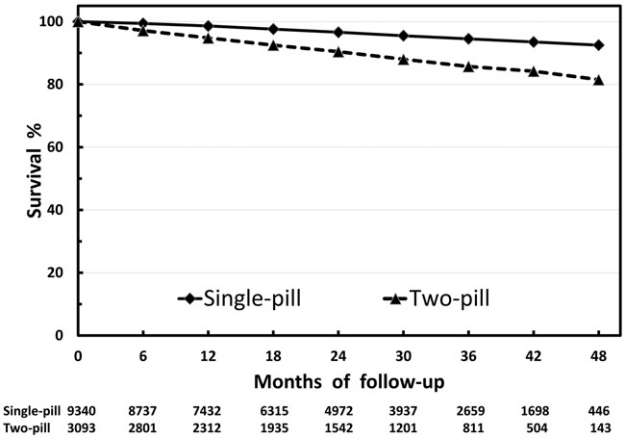

Figure 3. Mortality survival curves based on the original single-pill and two-pill allocations. Sample numbers at time points are shown.

Mortality survival curves based on the original group allocations (but with no exclusions) are shown in Figure 3. After 48 months, 8% of single-pill users and 18% of two-pill users had died. In the unadjusted univariate model, the hazard ratio for risk of death in the two-pill versus single-pill group was 2.81 (95% CI 2.42–3.26). In the multivariate model adjusted for potential confounding variables in Table 1, the hazard ratio for risk of death was markedly reduced, 1.83 (95% CI 1.55–2.16).

There were other findings of note in the multivariate models. Females in the two-pill group were 14% (95% CI 9–19) more likely to cease treatment than males; those aged 60–69 years were 13% (95% CI 6–19) more likely to cease than those under 60 years; those on high dose amlodipine (10 mg)

were 14% (95% CI 8–19) more likely to cease than those on 5 mg. Males were 47% (95% CI 26–71) more likely to die than females; those on high dose amlodipine (10 mg) were 20% (95% CI 1–42) more likely to die than those on 5 mg.

Discussion

We have evaluated long-term persistence in patients using single-pill, fixed-dose combination versus two-pill therapy with amlodipine + perindopril in "real world" circumstances, and confirmed superior persistence in the former group. In the multivariate model, those on two-pill therapy were 94% more likely to discontinue than those on single-pill therapy over 42 months. After allowance for switching to alternate calcium channel and angiotensin inhibition, members of the original two-pill group were still 86% more likely to discontinue than those in the original one-pill group. The actual cessation rates we have reported are disturbing whatever therapy is offered. In a controlled trial, cardiovascular disease outcomes were reported to be 23% higher in patients noted to be poorly compliant with medication for hypertension[10].

The current findings confirm the results of previous studies, showing that patients receiving single-pill, fixed-dose combinations have superior persistence compared with those taking the individual components[11–15]. One study in particular showed similar results to our own when using amlodipine + perindopril, but with only 12 months of follow-up[15].

The difference in mortality over 48 months in the two-pill group versus the one-pill group was impressive, 18% versus 8% mortality. We acknowledge that this was not a randomized comparison and Table 1 indicates differences between the respective groups, suggesting that the two-pill group were "sicker" and likely to experience higher mortality. Adjusting for potential confounders reduced the hazard ratio for mortality from 2.81 to 1.83. This very large difference in mortality between the respective groups was unexpected and is likely to be an overestimate, possibly due to residual confounding by other unmeasured variables. An association between cessation of therapy and increased mortality was previously observed when calcium channel blocker blockers were combined with ACE inhibitors or angiotensin receptor blockers, resulting in a 15% increase in mortality over 4 years[16].

Factors related to medication persistence and adherence in chronic disease states have been reviewed[1,6]. Barriers to good adherence have been identified at the patient level and include co-morbidity, lack of information and education, financial reasons, having other priorities and the actual tablet burden and frequency. Physicians may contribute to the problem through use of complex regimens, inadequate provision of education to patients and through insufficient support. There are also societal factors of increasing importance, notably misinformation distributed through electronic and print media. A partial solution might arise through a more collaborative relationship between patient, physician and other health professionals, but this continues to be challenging.

There are some limitations with the present study. We have only assessed patients initially allocated to the specific combination of amlodipine + perindopril, but this is the most commonly prescribed fixed-dose product for hypertension in Australia. However, we have made allowance for patients switching to similar combination therapy. This was a retrospective, observational study and patients were not randomized to the respective groups. Differences between the groups at baseline were noted and potential confounding has been addressed in the multivariate models. While this may not have been fully adequate in the mortality analysis, the hazard ratios for persistence were not materially impacted by adjustment for available confounders. Hence, the persistence outcome is likely to be a genuine effect. While we have analyzed only concessional patients, they would represent around 65% of relevant patients who might have been eligible for this study. PBS administrative records do not provide clinical details, information on blood pressure control, or the reasons for discontinuation.

Conclusions

Use of a single-pill, fixed-dose combination in hypertension is associated with superior persistence and reduced mortality compared with use of two pills of the individual drugs. This finding, while not unique, suggests that fixed-dose combinations should be given higher priority in the management of moderate to severe hypertension.

Transparency

Declaration of funding

This study was supported by a research grant from Servier Laboratories (Australia) Pty Ltd, a company that markets perindopril and related products.

Author contributions: All authors contributed equally to study design, interpretation and manuscript preparation. E.C. conducted data extraction and analysis.

Declaration of financial/other relationships

L.A.S. has disclosed that he is a consultant to Servier Laboratories (Australia) and other pharmaceutical companies. E.C. and M.O. have disclosed that they are paid consultants to the study.

CMRO peer reviewers on this manuscript have no relevant financial or other relationships to disclose.

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