Leon A Simons
Michael Ortiz
Gordon Calcino

Long term persistence with statin therapy

Experience in Australia 2006–2010

Background

Long term persistence on statin drugs has been shown to be unsatisfactory, however, there is little recent Australian data. This study examines current persistence Australia-wide in patients who have been newly prescribed a statin drug.

Method

We conducted a longitudinal assessment of Pharmaceutical Benefit Scheme claim records dating from April 2005 to March 2010. Main outcome measures were the proportion of patients who were not filling a first repeat prescription at 1 month, and median persistence time during follow up.

Results

For 77 867 patients initiated to statin, 86% of prescriptions came from general practitioners. Forty-three percent of patients discontinued statin within 6 months, 23% failed to collect their first repeat at 1 month, and median persistence time was only 11 months. In those aged 65–74 years, median persistence time was 19 months but only 3–6 months for those less than 55 years.

Discussion

Unsatisfactory long term persistence on statin therapy has changed little over the past 10 years. There may be an opportunity for early intervention within 3–4 weeks of initiation to improve persistence, as valuable resources are being wasted and an opportunity for disease prevention missed.

Keywords: hydroxymethylglutaryl-CoA reductase inhibitors; medication adherence

Therapy with hydroxymethylglutaryl-CoA (HMG-CoA) reductase inhibitor drugs, better known as 'statins', has become an essential part of cardiovascular disease prevention and therapy.[1,2] Yet it is recognised that statin treatment, in conjunction with therapy of other chronic asymptomatic conditions, is associated with unsatisfactory long term persistence.[3] In 1996,we reported that 40% of Sydney (New South Wales) residents who had been newly prescribed lipid lowering drugs had discontinued this therapy within 6 months.[4] In 1999, we accessed Australia-wide Pharmaceutical Benefits Scheme (PBS) claim records and reported that 30% of patients newly prescribed lipid lowering drugs, mainly statins, had discontinued therapy within 6 months.[5] More recently we reported that 35% of Australian patients newly prescribed antihypertensive drugs had also discontinued therapy within 6 months.[6]

The matter of poor long term persistence with therapy in hypercholesterolaemia has been recognised as a worldwide phenomenon.[7–13] Overall tablet burden and dosing frequency, and to some extent financial considerations, are known predictors of poor compliance.[14–17]

Pharmaceutical companies have offered patients compliance or loyalty programs, but there is little objective evidence that these programs improve persistence. Programs in community pharmacy have employed regular follow up and behavioural change principles, and some improvement in persistence has been noted.[18,19] A recent Cochrane review found that even the most effective interventions, such as combinations of more convenient care, education, counselling, reminders, self monitoring, and mailed communications did not lead to major improvements in compliance.[20]

Recent Australian data on persistence with statin drugs has not been reported and persistence may have changed since the report in 1999. In the present report we have analysed Medicare Australia PBS claim data from 2006–2010 for patients newly prescribed any statin drug.

Method

Data source

The analysis was performed on PBS claims for relevant prescriptions between April 2005 and March 2010, a 5 year period, in a 10% random sample of the Australian population. Data was drawn from de-identified records held by Medicare Australia. Some statin drugs are priced below the 'general patient co-payment threshold' and are not recorded. Therefore, the study was restricted to patients classified as 'long term concessional' – estimated to represent around 65% of all patients receiving these drugs[21] – an approach used in previous studies.[6]

Persistence analyses

We applied the following patient definitions:

- initiation of any statin drug, including single pill combination drugs – no prescription for any statin in the previous 6 months
- cessation of statin therapy – no prescription refills for 3 consecutive months (ie. therapy lapse for at least 2 months)
- those switching between statin drugs were considered as continuing therapy
- concurrent treatment with clopidogrel in the 12 months previous up to 2 months after

initiation – used as a very crude surrogate for the presence of coronary artery disease.

Using the Kaplan Meier technique, we generated persistence curves for statins overall and for individual statins. Persistence curves were compared pairwise using proportional hazard models (ie. time to event, the outcome being cessation of 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. A multivariate model was used to adjust statin persistence for potential confounding by other key variables. A *p* value <0.05 in a two-sided test was accepted as significant.

Patient identities remained anonymous during this investigation and ethics approval was obtained from the Medicare Australia Ethics Committee.

Table 1. Demographic features of patients at time of initiation of a statin

All statins	n=77867	Proportion of sample
Atorvastatin	41579	53%
Fluvastatin	235	0.3%
Pravastatin	4250	5.0%
Rosuvastatin	14020	18%
Simvastatin	16044	21%
Vytorin™*	546	0.7%
Caduet™**	1214	2.0%
Age group		
<45 years	5205	7%
45–54 years	7939	10%
55–64 years	15657	20%
65–74 years	26447	34%
>74 years	22619	29%
Other demographics		
Male	34052	44%
Female	43815	56%
GP prescriber	66594	86%
Specialist prescriber	11273	14%

* Vytorin (simvastatin/ezetimibe) is the registered trademark of Merck Sharp & Dohme (Australia) Pty Ltd

** Caduet (atorvastatin/amlodipine is the registered trademark of Pfizer Australia Pty Ltd

Note: The statin distribution includes 21 patients who met the criteria but who were returning to statin after >6 months cessation

Results

The database generated information on 77 867 patients newly prescribed a statin drug. Their demographic features are summarised in *Table 1*. Gender was almost evenly distributed, while 86% of initial prescriptions came from GPs, who in some cases may have been continuing an initial hospital discharge prescription. Almost two-thirds of the group were aged 65 years and over. The majority of prescriptions were written for atorvastatin, simvastatin and rosuvastatin.

The persistence curve for patients prescribed any statin (allowing for switching between statins) is presented in *Figure 1*. Forty-three percent of patients had discontinued all statin therapy within 6 months, 23% failed to collect the first repeat prescription at 1 month, while median persistence time (95% CI) on any statin was 11 (11–11) months (95% confidence intervals were extremely narrow because of the very large sample size and the minimum reporting interval of 1 month).

Persistence data by statin initially prescribed and by demographic features are presented in *Table 2*. These findings allow for switching between individual statin drugs. Persistence with fluvastatin, pravastatin, simvastatin or a combination tablet of simvastatin and ezetimibe (Vytorin™) appeared to be inferior to overall behaviour. Persistence with rosuvastatin or a combination tablet of atorvastatin and amlodipine (Caduet™) appeared to be superior to overall behaviour. The hazard ratios in *Table 2* allow a more valid statistical comparison between

Table 2. Persistence data for any statin by statin initially prescribed and by demographic features

	Failed to collect first repeat prescription at 1 month (95% CI)	Median persistence time in months (95% CI)	Hazard ratio (95% CI)	*p* value
All statins	**23% (22–23)**	**11 (11–11)**	**–**	**–**
Atorvastatin	23% (22–23)	11 (11–11)	1.20 (1.17–1.23)	<0.0001
Fluvastatin	32% (26–38)	5 (3–9)	1.53 (1.31–1.79)	<0.0001
Pravastatin	27% (26–29)	6 (6–7)	1.45 (1.38–1.51)	<0.0001
Rosuvastatin	19% (18–19)	19 (18–21)	1.00	–
Simvastatin	26% (25–26)	8 (8–9)	1.32 (1.28–1.36)	<0.0001
Vytorin™	33% (29–37)	5 (4–6)	1.61 (1.45–1.79)	<0.0001
Caduet™	15% (14–18)	30 (24–37+)	0.85 (0.78–0.93)	<0.0001
Demographics				
<45 years	37% (36–38)	3 (3–4)	2.02 (1.95–2.09)	<0.0001
45–54 years	27% (26–28)	6 (6–7)	1.50 (1.45–1.55)	<0.0001
55–64 years	24% (23–24)	10 (9–11)	1.22 (1.18–1.25)	<0.0001
65–74 years	19% (19–20)	19 (18–20)	1.00	–
>74 years	21% (21–22)	12 (11–12)	1.21 (1.19–1.24)	<0.0001
Male	23% (23–23)	10 (10–11)	1.02 (0.99–1.03)	NS
Female	22% (22–23)	11 (11–12)	1.00	–
GP prescriber	23% (23–24)	10 (9–10)	1.21 (1.18–1.25)	<0.0001
Specialist prescriber	19% (18–20)	19 (18–21)	1.00	–

Note: Reference groups for pairwise comparisons were: rosuvastatin for statin; 65–74 years for age; female for gender; specialist for prescriber

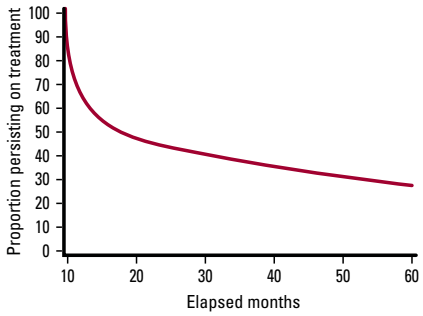

Figure 1. Persistence curve for patients initiated on any statin

individual persistence curves. Using rosuvastatin as the reference group, the overall cessation rate on atorvastatin was 20% increased; simvastatin 32% increased; pravastatin 45% increased; fluvastatin 53% increased; and simvastatin/ezetimide 61% increased; while cessation on atorvastatin/amlodipine was 15% reduced.

Median persistence time appeared to be longest in those aged 65–74 years and shortest in the younger age groups. Using 65–74 years as a reference, the overall cessation rate in those less than 45 years was 102% increased; 45–54 years 50% increased; 55–64 years 22% increased and >74 years 21% increased. These findings were similar in a multivariate model (100%, 49%, 21% and 22% increased respectively).

There was no material gender difference in persistence, but the rate of cessation was 21% increased if statins were GP initiated (20% increased in a multivariate model).

While the absence of clopidogrel concurrent use may not be truly informative (n=69 747), there were 7474 patients using clopidogrel as defined. Using the latter group as a crude surrogate for cases of secondary prevention, 33% had discontinued all statin therapy by 6 months, 15% failed to collect the first repeat at 1 month and median persistence time was 23 (22–26) months.

Discussion

We have confirmed that long term persistence with statin drugs in Australia is still unsatisfactory and that this situation has changed very little since the 1990s.[4,5] The problem has been highlighted around the world,[7,10,12,13] and the findings are not unique to statin drugs.[3] Similarly, unsatisfactory persistence has been reported in patients newly prescribed antihypertensive drugs.[6,22]

It must follow that poor persistence will impact on clinical outcomes. It has been calculated that hypertensive patients taking antihypertensive and statin therapy at real world adherence levels might receive only about 50% of the potential benefit seen in clinical trials![23] Cardiovascular disease outcomes in the Second Australian National Blood Pressure Study were 20–23% higher in patients reporting poor compliance with their medication.[24]

By examination of patients with concurrent use of clopidogrel, we have derived a very crude surrogate for secondary prevention. While this group comprised only 9.6% of the overall sample, 33% had discontinued statins within 6 months compared with 43% in the overall sample. Median persistence time in this group was double that observed in the total sample. This contrast bears some similarity to the findings in GP versus specialist prescribers. Although we have no clinical data, one might speculate that specialists were initiating statins in higher risk, more motivated patients.

Contributors to poor persistence include the overall tablet burden, cost of medication, the risk of adverse events, and apathy.[10,15–17] All patients were concession card holders, many on multiple medications, and they may have been at relative social disadvantage. Therefore, financial burden may have contributed in some part to poor persistence, even if only a nominal amount was paid for medication. Adverse events with statins do occur, albeit at a relatively low rate,[25] but these are probably not frequent enough to account for such a high cessation rate. The better persistence with the single pill fixed dose combination of atorvastatin/amlodipine which minimises the tablet burden, is noted and this is an emerging trend in drug delivery.[26] Rather surprisingly, persistence with the single pill fixed dose combination of simvastatin/ezetimide had poorer persistence.

This study has strengths and limitations. We have examined patients in a real world situation and the case numbers are very large. There has been allowance made for switching between statins through avoiding censoring at the point of switch. Cessation in this report genuinely means cessation, including of any similar therapy.

It is intriguing that patients initiated to a statin associated with less cholesterol reduction at maximum doses (eg. fluvastatin or pravastatin) have much higher rates of cessation and are not switched to another statin.

Limitations include:

- the absence of medical history
- no information on the degree of cholesterol control
- no strong definition of secondary prevention
- possible mortality in the oldest patients
- the inclusion of only concession card holders (however, these represented around 65% of patients in Australia using these medications).

In 1996 we undertook qualitative research in randomly selected patients who had discontinued statins.[4] Four key opinions were expressed:

- they were not convinced that drug therapy reduced cardiovascular risk or was truly safe in the longer term
- their GP and/or pharmacists expressed conflicting opinions about the worth of treatment
- their GP and/or pharmacist failed to satisfy them with the information given about treatment, and
- they had a poor recall of what information was actually made available.

While research has not been conducted to update these opinions, it is likely that some of these ideas still prevail, despite increasing knowledge and awareness.

While no ideal methods of intervention are available,[20] what can be done to improve persistence? Potential solutions include drugs with fewer adverse effects, more convenient once daily dose schedules, a greater number of single pill combinations products and better patient education. As most initiations or continuation of statins (and antihypertensive therapy) occur in general practice, there is a challenge here for GPs (and other physicians) to address the problem through very early intervention.

Given that almost one-quarter of patients do not fill the first repeat prescription for a statin, we suggest that GPs should schedule a follow up visit with blood tests 3–4 weeks after initiation, before a patient has the chance to discontinue. Other reminder mechanisms provided by practice staff may also be helpful.

Community pharmacists will also continue to play a role. If poor persistence continues unabated, it means wasting valuable resources and missing an opportunity for disease prevention.

Implications for general practice

- Statin therapy is most often initiated or continued by GPs.
- Long term persistence on statins remains unsatisfactory and has changed little over the past 10 years.
- Early intervention is essential.
- A follow up visit should be scheduled 3–4 weeks after initiation.
- Further educational materials should be provided.
- Reminder mechanisms with the help of practice staff should be employed.

Authors

Leon A Simons MD, FRACP, is Associate Professor of Medicine and Director, University of New South Wales, St Vincent's Hospital, New South Wales. l.simons@unsw.edu.au

Michael Ortiz BPharm, PhD, is Pricing and Reimbursement Manager, Abbott Products Pty Ltd, and Conjoint Senior Lecturer, St Vincent's Clinical School, University of New South Wales

Gordon Calcino BA, GradDipMedStats, is Director, HI Connections Pty Ltd, Woden, Australian Capital Territory.

Conflict of interest: Leon Simons contributed his time in an honorary capacity, Michael Ortiz is an employee of Abbott Products Pty Ltd, for whom Gordon Calcino is an independent contractor. Abbott Products do not manufacture or market statin drugs in Australia. There was no input to this study from any pharmaceutical manufacturer beyond that already stated. Raw data for the study was supplied by Medicare Australia.

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correspondence **afp@racgp.org.au**