Patient adherence to treatment with statins for the prevention of cardiovascular disease

Author: Anne Hinchliffe, Consultant in Pharmaceutical Public Health

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Purpose and Summary of Document:
The evidence for statins in primary and secondary prevention of cardiovascular disease is unequivocal. However, poor adherence is a barrier to patients obtaining maximum benefit from treatment. This paper summarises the evidence assessing the magnitude and impact of non-adherence with statins. The key findings are:

- Adherence in the real world is substantially lower than that seen in clinical trials
- In several studies adherence rates of less than 50% were observed
- Patients receiving statins for secondary prevention are more likely to adhere to therapy than those receiving them for primary prevention
- Adherence with statins declines over time
- A significant proportion of patients stop taking their statin within two years of initiation
- Patients with high adherence are less likely to be hospitalised than those with lower adherence
- Interventions to support adherence need to be identified and implemented
1 Background
The statins are a class of medicine which work by inhibiting 3 hydroxy-3-methylglutaryl co A reductase, an enzyme involved in cholesterol synthesis.\(^1\) They include:

- Simvastatin
- Pravastatin
- Fluvastatin
- Atorvastatin
- Rosuvastatin

Over the past 15 years a number of large randomised clinical trials have provided robust evidence supporting the use of statins to reduce the risk of vascular events in at risk patients. The National Institute for Health and Clinical Excellence (NICE) recommend the use of statins for the prevention of cardiovascular events\(^2\), and indeed these drugs are prescribed widely within NHS Wales. However, there is also increasing evidence that adherence with statins is poor.

2 Purpose
To identify and summarise the published evidence in relation to non-adherence and discontinuation with statins.

3 Method
This paper presents a rapid review of the evidence and is not a systematic review. The databases Medline and Embase were searched for relevant papers using the search terms; hydroxymethylglutaryl co A reductase inhibitors, anticholesteremic agents, medication adherence, compliance and concordance. Papers from 1990 to December 2010 were included.

Papers were collated under the following headings:

- Discontinuation in the clinical trial setting
- Adherence and discontinuation in non-trial settings
  - primary prevention
  - secondary prevention
- Interventions to support adherence
4 Results

The results are summarised briefly in each sub-section. For further information about the research studies please see the relevant tables and references.

4.1 Discontinuation in the clinical trial setting

Insull reported the proportion of patients who continued to take their statin following recruitment into three secondary prevention trials, 4S’s, LIPID and CARE. Continuation rates were good ranging from 88% to 96% around 5 years post initiation.

The only primary prevention study for which continuation rates were found was the West of Scotland Coronary Prevention Study (WoSCoPS). After one year 84.5% patients remained in the study and this fell to 70.4% at five years.

Further information is provided in Table 1.

Generally, adherence to medication is better when a patient is enrolled in a clinical trial compared with a ‘real-life’ situation. This improved adherence in the trial setting is clearly observed with statins.
### Table 1: Discontinuation in the clinical trial setting

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Population</th>
<th>Setting</th>
<th>Trial</th>
<th>Drug</th>
<th>Adherence</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>2.</td>
<td>National Institute for Health and Clinical Excellence. <em>Statins for the prevention of cardiovascular events in patients at increased risk of developing cardiovascular disease or those with established cardiovascular disease.</em> TA094. London: NICE; 2006.</td>
<td></td>
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<td></td>
<td></td>
<td>Statement: “Compliance with treatment remained high at 85% to 95% after 3 to 4 years in secondary prevention studies”</td>
</tr>
<tr>
<td>3.</td>
<td>Insull W. <em>The problem of compliance to cholesterol altering therapy.</em> <em>J Intern Med</em> 1997: 241; 317-25</td>
<td>N=2221 &amp; N=4007 &amp; N=3302 &amp; N=2081</td>
<td>4S &amp; LIPID &amp; WoSCoPS &amp; CARE</td>
<td>Simvastatin &amp; Pravastatin &amp; Pravastatin &amp; Pravastatin</td>
<td>10.4% discontinuation at 5.4 years &amp; 12% discontinuation at 4.0 years &amp; 29.6% discontinuation at 4.9 years &amp; 6.0% discontinuation at 5.0 years</td>
<td>Secondary prevention &amp; Secondary prevention &amp; Primary prevention &amp; Secondary prevention</td>
</tr>
<tr>
<td>4.</td>
<td>Shepherd J et al. <em>Prevention of coronary heart disease with pravastatin in men with hypercholesterolemia.</em> <em>NEJM</em> 1995: 333; 1301-7.</td>
<td>6595 men, 45-64 years</td>
<td>Scotland</td>
<td>WoSCoPS</td>
<td>Pravastatin</td>
<td>Patients who had not withdrawn from study Year 1 84.5% Year 2 80.6% Year 3 77.3% Year 4 75.3% Year 5 70.4%</td>
</tr>
</tbody>
</table>
4.2  **Adherence and discontinuation in non-trial settings**

Whilst there is no common measure of adherence, one used in a number of studies is proportion of days covered (PDC). PDC is a ratio of the amount of medication required for the patient to take the prescribed dose compared with the amount actually prescribed or dispensed over a given period. There is a distinct difference between having a prescription dispensed and taking the medicine as required and as such PDC is likely to over estimate adherence.

4.2.1  Secondary prevention

Six studies reported adherence and/or discontinuation rates with statins prescribed for secondary prevention.\textsuperscript{5-10} Adherence varied from 36% to 75% but caution is needed comparing rates between studies due to the different definitions of adherence used and the time periods over which adherence was measured. In both primary and secondary prevention studies, adherence is seen to decline significantly over time.

Two studies reported discontinuation rates and these varied from 27% after one year to 63% after two years.\textsuperscript{6,10}

Further information is provided in Table 2.
### Table 2: Adherence and discontinuation rates with statins prescribed for secondary prevention

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Population</th>
<th>Design</th>
<th>Setting</th>
<th>Measure of adherence</th>
<th>Adherence</th>
<th>Discontinuation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>5.</td>
<td>Maggioni AP et al. Use and misuse of statins after an acute coronary syndrome (ACS): analysis of a prescription database of a community setting of more than 2,000,000 subjects. Slide presentation. ESC Congress 2010 Aug 28-Sep 01 Stockholm, Sweden.</td>
<td>Patients discharged after acute coronary syndrome between Jan 2007 and June 2007 n=3549</td>
<td>Retrospective cohort study using the ARNO observatory database</td>
<td>PDC = 100%</td>
<td>67% achieved PDC =100% over the first year</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6.</td>
<td>Chodick G et al. Long-term persistence with statin treatment in a not-for-profit health maintenance organization: a population-based retrospective cohort study in Israel. Clin Ther 2008: 30; 2167-79</td>
<td>Patients initiated on a statin between 1998 and 2006 n= 93, 866</td>
<td>Retrospective cohort study</td>
<td>PDC ≥80% adherent, 20% to &lt;80% partially adherent, &lt;20% non adherent</td>
<td>From initiation to discontinuation. Mean PDC 59% Proportion of cohort who were non-adherent (PDC &lt;20%) 23%</td>
<td>63% patients discontinued therapy by 2 years</td>
<td>See also results for primary prevention from same study</td>
</tr>
<tr>
<td>7.</td>
<td>Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002: 288; 462-7</td>
<td>Patients ≥ 66 years, initiated on a statin between 1994 and 1998 Acute coronary syndrome (ACS) n=22,379; coronary artery disease (CAD) n=36,106;</td>
<td>Retrospective cohort study</td>
<td>Follow up 2 years after initiation of a statin Patients were considered adherent if they had a statin prescription dispensed</td>
<td>Proportion of patients receiving statin prescriptions continuously over 2 years ACS 40%; CAD 36%</td>
<td>Max. prescription period 100 days, therefore 120 days allowed a 20 day grace period</td>
<td>See also results for primary prevention from same study</td>
</tr>
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</table>
### Literature review: Patient adherence with statins

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Population</th>
<th>Design</th>
<th>Setting</th>
<th>Measure of adherence</th>
<th>Adherence</th>
<th>Discontinuation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>8.</td>
<td>Blackburn DF et al. Adherence to statins, beta-blockers and angiotension-converting enzyme inhibitors following a first cardiovascular event: A retrospective cohort study. <em>Can J Cardiol</em> 2005; 21; 485-8</td>
<td>1221 patients, started on a statin within 1 year of their first cardiovascular event, between 1994 and 2001</td>
<td>Retrospective cohort study using linked administrative databases</td>
<td>Saskatchewan, Canada</td>
<td>Patient was considered adherent if PDC ≥80%</td>
<td>At year 1, 62% patients were adherent (PDC ≥80%)</td>
<td>The risk of any cause death was lower in patients with a PDC ≥80% compared with those with a PDC ≤80% [HR= 0.44; 95% CI 0.30- 0.64]</td>
</tr>
<tr>
<td>9.</td>
<td>McGinnis BD et al. Statin adherence and mortality in patients enrolled in a secondary prevention program. <em>Am J Manag Care</em> 2009; 15; 689-95</td>
<td>Patients initiated on a statin for secondary prevention between 2000 and 2005 n=2201</td>
<td>Retrospective cohort study Followed up to Dec 2006, 2007 and 2008</td>
<td>USA</td>
<td>PDC</td>
<td>75% over 3 years</td>
<td>The risk of any cause death was lower in patients with a PDC ≥80% compared with those with a PDC ≤80% [HR= 0.44; 95% CI 0.30- 0.64]</td>
</tr>
<tr>
<td>10.</td>
<td>Kulkarni SP et al. Long-term adherence with cardiovascular drug regimens. <em>Am Heart J</em> 2006: 151; 185-91</td>
<td>729 patients with coronary artery disease undergoing cardiac catheterization between 1998 and 2001, prescribed a statin at discharge</td>
<td>Cohort</td>
<td>USA</td>
<td>Self-reported medicine regimen at 12 months compared with medication on hospital discharge</td>
<td>27% patients discontinued statins within the first year</td>
<td></td>
</tr>
</tbody>
</table>
4.2.2 Primary prevention

Generally, adherence rates were lower in studies where the statin was prescribed for primary prevention, but comparisons are difficult due to differences in adherence measures between studies.

Jackevicius et al.\(^7\) found only 25% patients had collected sufficient medication to comply with their prescribed dose over the first two years and Perreault et al.\(^{12}\) noted a decrease in the proportion of patients achieving high adherence (PDC ≥ 80%) from 74% during the first year to 53% the following year.

One study\(^6\) measured discontinuation rates and this reported 77% patients stopped taking their statin within two years of starting.

For further information see Table 3

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Table 3: Adherence and discontinuation rates with statins prescribed for primary prevention

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Population</th>
<th>Design</th>
<th>Setting</th>
<th>Measure of adherence</th>
<th>Adherence</th>
<th>Discontinuation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>11. Corrao G. et al.</td>
<td>Patients ≥ 18 years, newly prescribed statins for primary prevention of CVD n=90,832</td>
<td>Retrospective cohort study</td>
<td>Italy</td>
<td>PDC</td>
<td>High adherence PDC ≥ 75%; intermediate 51% -75%; low 26% -50%; very low ≤ 25%</td>
<td>Of 90,832 patients, 1480 were hospitalisation for IHD. Patients with lower adherence were statistically more likely to be admitted than those who had the highest adherence (PDC ≥ 75%) HR 0.81 (0.71-0.94)</td>
<td></td>
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<tr>
<td>6. Chodick G et al.</td>
<td>Patients initiated on a statin between 1998 and 2006 n= 136,052</td>
<td>Retrospective cohort study</td>
<td>Not-for-profit health maintenance organisation, Israel</td>
<td>PDC</td>
<td>PDC &gt;80% adherent, 20% to &lt;80% partially adherent, &lt;20% non adherent</td>
<td>From initiation to discontinuation, mean PDC 45%. Proportion of cohort who were non-adherent (PDC &lt;20%) 37%</td>
<td>See also results for secondary prevention from same study</td>
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<td>Ref.</td>
<td>Population</td>
<td>Design</td>
<td>Setting</td>
<td>Measure of adherence</td>
<td>Adherence</td>
<td>Discontinuation</td>
<td>Comments</td>
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<td><strong>North America</strong></td>
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<tr>
<td>7.</td>
<td>Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. <em>JAMA</em> 2002: 288; 462-7</td>
<td>Patients ≥ 66 years, initiated on a statin between 1994 and 1998 n=85,020</td>
<td>Retrospective cohort study</td>
<td>Canada</td>
<td>Follow up 2 years after initiation of a statin</td>
<td>Proportion of patients receiving statin prescriptions continuously over 2 years, 25%</td>
<td>Max. prescription period 100 days, therefore 120 days allowed a 20 day grace period. See also results for secondary prevention from same study</td>
</tr>
<tr>
<td>12.</td>
<td>Perreault S et al. Impact of better adherence to statin agents in the primary prevention of coronary artery disease. <em>Eur J Clin Pharmacol</em> 2009: 65; 1013-24</td>
<td>115,290 patients, aged 45 to 85 years, without indication of CVD, and newly treated with statins between 1999 and 2004</td>
<td>Retrospective cohort study using the Regie de l’assurance maladie du Quebec databases</td>
<td>Canada</td>
<td>PDC ≥ 80%</td>
<td>74% patients had PDC ≥ 80% during the first year, and this fell to 53% after 1 year of follow up</td>
<td>Patients with high adherence to statins (PDC ≥ 80%) showed a risk reduction of 18% (RR: 0.82 (95% CI: 0.77-0.87)) in the incidence of coronary artery disease compared to an adherence level of &lt;20%</td>
</tr>
</tbody>
</table>
4.2.3 Primary or secondary prevention

Several studies\textsuperscript{13-19} studied adherence with statins without recording the indication for which the statin was prescribed.

Amongst studies reporting adherence as the proportion of the population achieving PDC \( \geq 80\% \), rates varied from 32\% to 71\% with adherence declining over time. Three studies\textsuperscript{13, 16, 18} recorded persistence with treatment which ranged from 73\% to 35\% at one year. In one study the proportion of patients continuing treatment fell from 73\% at one year to 44\% at 10 years.\textsuperscript{13}

For further information see Table 4
Table 4: Adherence and discontinuation rates with statins – indication unknown

<table>
<thead>
<tr>
<th>Ref.</th>
<th>Population</th>
<th>Design</th>
<th>Setting</th>
<th>Measure of adherence</th>
<th>Adherence</th>
<th>Discontinuation</th>
<th>Comments</th>
</tr>
</thead>
</table>
| 13.       | Helin-Salmivaara A et al.  
Long-term persistence with statin therapy: a nationwide register study in Finland.  
_Clin Ther_ 2008: 30; 2228-40 | New users of statins in 1995, n=18,072 | Finland         | PDC                  | 71% patients were adherent (PDC ≥ 80%) | Patients were considered to have discontinued treatment if the gap between consecutive prescriptions was >270 days  
1 year persistence 73%  
10 year persistence 44%  
13% stopped after the first prescription | Patients who had at least one prescription for another cardiovascular medication were more likely to continue statin therapy up to the 5th year |
| 14.       | Evans CD et al.  
Retrospective observational assessment of statin adherence among subjects patronizing different types of community pharmacies in Canada.  
_J Manag Care Pharm_ 2009: 15; 476-84 | Patients initiated on a statin between Jan 1 2000 and Dec 31 2005 n=8,699 | Retrospective cohort study using the Saskatchewan Drug Plan and Extended Benefits database | PDC ≥ 80% | In the first year, 52% patients achieved PDC ≥ 80% , by year 3 only 43% achieved this level of adherence |                                                                                     |
| 15.       | Benner JS et al.  
Long-term persistence in use of statin therapy in elderly patients.  
_JAMA_ 2002: 288; 455-61 | Patients ≥ 65 years initiated on statin treatment between 1990 and 1998 | Retrospective cohort study, New Jersey Medicaid and Pharmaceutical Assistance to the Aged and Disabled programs | PDC | Mean PDC during first quarter, 79%; second quarter 56%, and after 120 months 42%PDC ≥ 80%, at 3 months 60%; at 6 months 43%; at 120 months 32% | Significant decrease in adherence between 3 and 6 months after initiation |
<table>
<thead>
<tr>
<th>Ref.</th>
<th>Population</th>
<th>Design</th>
<th>Setting</th>
<th>Measure of adherence</th>
<th>Adherence</th>
<th>Discontinuation</th>
<th>Comments</th>
</tr>
</thead>
<tbody>
<tr>
<td>16.</td>
<td>Sung JCY et al. Factors affecting patient compliance with antihyperlipidemic medications in an HMO population. <em>Am J Manag Care</em> 1998: 4; 1421-30</td>
<td>Patients on antihyperlipidemic medications n=772</td>
<td>Retrospective cohort study</td>
<td>Health maintenance organisation, California, USA</td>
<td>PDC ≥ 90% based on pharmacy claims data between April 1993 (or when the drug was started if later) and Feb 1995</td>
<td>37% patients were adherent (PDC ≥90%)</td>
<td>38% patients discontinued their antihyperlipidemic medications at some time during the study</td>
</tr>
<tr>
<td>17.</td>
<td>Aubert RE et al. Is there a relationship between early statin compliance and a reduction in healthcare utilization? <em>Am J Manag Care</em> 2010: 16; 459-66</td>
<td>Patients started on a statin between July 2001 and June 2002 n= 10,227</td>
<td>Retrospective cohort study using an integrated pharmacy and medical claims database</td>
<td>USA</td>
<td>PDC ≥80% during first 2 years of treatment</td>
<td>34% patients were adherent (PDC ≥80%)</td>
<td>In year 3 adherent patients had significantly fewer hospitalisations (16% vs 19%, p&lt;0.01) and lower medical costs compared with non-adherent patients ($4040 vs. $4908 per patient excluding the cost of statin therapy)</td>
</tr>
<tr>
<td>Ref.</td>
<td>Population</td>
<td>Design</td>
<td>Setting</td>
<td>Measure of adherence</td>
<td>Adherence</td>
<td>Discontinuation</td>
<td>Comments</td>
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<tr>
<td>18.</td>
<td>Huser MA, Evans TS, Berger V. Medication adherence trends with statins. <em>Adv Ther</em> 2005; 22; 163-71</td>
<td>140 patients newly initiated on a statin</td>
<td>Retrospective analysis using pharmacy records</td>
<td>USA</td>
<td>PDC</td>
<td>PDC 56% to 64% between patient groups</td>
<td>Persistence at 12 months 35%</td>
</tr>
<tr>
<td>19.</td>
<td>Mann DM et al. Predictors of nonadherence to statins: A systematic review and meta-analysis. <em>Ann Pharmacother</em> 2010: 44; 1410-21</td>
<td>Publications from MEDLINE, EMBASE and PsycINFO</td>
<td>Literature review</td>
<td>22 cohort studies met the inclusion criteria</td>
<td></td>
<td></td>
<td>Adherence was reduced in the following groups: Older people (&gt;70 years); younger people (&lt;50 years); women; patients with lower income. A history of CVD or a diagnosis of hypertension or diabetes was associated with better adherence</td>
</tr>
</tbody>
</table>
4.3 Impact of poor adherence on health outcomes

Evidence from clinical randomised controlled trials demonstrates that patients with established cardiovascular disease or those at high risk of developing CVD benefit from treatment with statins. It would therefore seem reasonable to assume that if patients don’t adhere to treatment their health outcomes will be worse.

In the current review, four studies\textsuperscript{11,12,17,20} reported the impact of adherence on health outcomes. All four found improved outcomes in patients who were more adherent to treatment.

An Italian study\textsuperscript{11} included over 90,000 primary prevention patients of which 1480 were hospitalised for ischaemic heart disease (IHD). Patients with poorer adherence PDC $<75\%$ were more likely to be admitted than those with high adherence $\geq75\%$ (HR 0.81, 95\% CI 0.71-0.94).

Perreault et al.\textsuperscript{12} followed-up 115,290 patients in Canada prescribed a statin for primary prevention. Those with high adherence (PDC $\geq80\%$) showed a risk reduction of 18\% [RR 0.82, 95\%CI 0.77-0.87] in the incidence of coronary artery disease compared to patients with poor adherence (PDC $<20\%$).

Two studies were conducted in the USA. One\textsuperscript{17} followed up patients for three years post initiation with a statin and linked adherence during the first two years with hospitalisations during the third. Adherent patients (PDC $\geq80\%$) had fewer hospitalisations (16\% vs 19\%, $p<0.01$) and lower medical costs than patients with poorer adherence. The other\textsuperscript{20} compared hospitalisation rates and healthcare costs with different levels of adherence in patients with each of the following conditions, diabetes, hypertension, hypercholesterolemia and chronic health failure. For all four conditions, patients who maintained $\geq80\%$ adherence were significantly less likely to be hospitalised compared with patients with lower levels of adherence.

4.4 Interventions to improve adherence with statins

A 2010 Cochrane update review\textsuperscript{21} was found summarising the evidence for interventions to improve adherence with lipid-lowering drugs. A pragmatic decision not to search further for original papers was taken.

Eleven randomised controlled trials met the inclusion criteria for the review, which covered the use of lipid lowering medication in adults for both primary and secondary prevention of CVD. The studies included interventions that caused a change in adherence ranging from -3\% to 25\%. The most promising category of interventions focused on patient re-
enforcement and reminding. Four studies were included in this category and these showed improved adherence ranging from 6% to 24%. Simplification of the drug regimen and patient information and education were also shown to be beneficial.

In 2009 NICE published a clinical guideline on medicines adherence. The guideline recognised that a number of factors influence adherence and therefore it would not be improved with a simple, single intervention. Good communication and involving the patient in the decision making process, to the extent he/she wants to be involved were advocated, as was assessing patient adherence and offering support to improve adherence. The evidence for specific interventions to improve adherence was equivocal and therefore NICE recommended a range of possible interventions with the intervention chosen being tailored to the specific difficulties the patient was experiencing.

5 Summary

Despite some variation in the way adherence is measured and differences in the magnitude of the problem, the studies consistently showed:

- Adherence in the real world is substantially worse than that seen in clinical trials
- Patients receiving statins for secondary prevention are more likely to adhere to therapy than those receiving them for primary prevention
- Adherence with statins declines over time
- A significant proportion of patients stop taking their statin within two years of initiation
- Patients with high adherence are less likely to be hospitalised than those with lower adherence
- Additionally, a Cochrane review found limited evidence for interventions to improve adherence with statins
6 References


7. Jackevicius CA, Mamdani M, Tu JV. Adherence with statin therapy in elderly patients with and without acute coronary syndromes. JAMA 2002: 288; 462-7


11. Corrao G. et al. Results of a retrospective database analysis of adherence to statin therapy and risk of nonfatal ischaemic heart disease in daily clinical practice in Italy. *Clin Ther* 2010: 32; 300-10


