THE ECONOMIC CONSEQUENCES OF NON-ADHERENCE TO LIPID-LOWERING THERAPY – RESULTS FROM THE ANGLO-SCANDINAVIAN-CARDIAC OUTCOMES TRIAL (ASCOT)

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**THE ECONOMIC CONSEQUENCES OF NON-ADHERENCE TO LIPID-
LOWERING THERAPY – RESULTS FROM THE ANGLO-SCANDINAVIAN-
CARDIAC OUTCOMES TRIAL (ASCOT)**

Peter Lindgren^{1,2}, Jennifer Eriksson¹, Martin Buxton³, Thomas Kahan⁴, Neil R Poulter⁵,
Björn Dahlöf⁶, Peter S Sever⁵, Hans Wedel⁷, Bengt Jönsson⁸ on behalf of the ASCOT
trial investigators

¹i3 Innovus, Stockholm, Sweden

²Division of cardiovascular epidemiology, Institute of Environmental Medicine,
Karolinska Institutet, Stockholm, Sweden

³Brunel University, Uxbridge, UK

⁴Department of Clinical Sciences, Danderyd Hospital, Karolinska Institutet, Stockholm,
Sweden

⁵Imperial College, London, UK

⁶Sahlgrenska University Hospital/Östra, Göteborg, Sweden

⁷Nordic School of Public Health, Göteborg, Sweden

⁸Centre for Health Economics, Stockholm School of Economics, Stockholm, Sweden

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Address for correspondence:

Peter Lindgren

i3 Innovus

Klarabergsviadukten 90D

111 64 Stockholm

Sweden

Peter.lindgren@i3innovus.com

Fax: + 48 8 545 28 542

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Abstract

Background

Adherence to lipid lowering therapy in clinical practice is less than ideal. Analysis of registry data has indicated that this is associated with poor outcomes. The objective of the present analysis was to assess the impact of high adherence to drug (defined as >80% of days covered), compared to low adherence to drug (<50% of days covered) in terms of risk of events and long-term economic consequences.

Design

Open-label follow-up of a randomized placebo-controlled trial in hypertensive patients.

Methods

Cox proportional hazards and Poisson regression models were used to assess the hazard ratio of patients with high adherence compared to low adherence while controlling for cardiovascular risk. A Markov model was used to predict the long term costs and health outcomes associated with poor adherence during the follow-up period.

Results

Both statistical models indicated that high adherence is associated with improved prognosis (Cox model: 0.75; 95% CI: 0.56-0.98, Poisson model hazard ratio: 0.73, 95% CI 0.58-0.98). Discounted at 3.5% per year, the Markov model predicts that as a consequence of higher adherence during the follow-up period, costs would be higher (£1,689 per patient compared to £1,323 per patient) due to higher drug costs, but the

projected survival and quality-adjusted survival (QALY) would also be longer (10.83 compared to 10.81 life years and 8.13 compared to 8.11 QALYs).

Conclusion

Given the higher risk of cardiovascular events associated with low adherence shown here, measures to improve adherence are an important part of the prevention of cardiovascular disease.

Key-words (3 -10): Hydroxymethylglutaryl-CoA reductase inhibitors, atorvastatin, medication adherence, primary prevention, economics, hypertension

What's known?

- Adherence to statin therapy in clinical practice is less than ideal.
- Registry studies indicate an association between low adherence to statin therapy and cardiovascular outcomes.

What's new?

- There is a significant reduction of events in patients in primary prevention who are adherent.
- This reduction is predicted to lead to health gains and somewhat lower costs of hospitalizations.

Introduction

The clinical benefits of statin therapy have been extensively demonstrated in a range of clinical trials and best evidence suggests that a “lower the better” policy is probably best clinical practice, at least in secondary prevention. [1-6] Consequently, proper control of cholesterol is an important therapeutic goal in both primary and secondary prevention of cardiovascular disease. [7] In spite of this, several studies indicate that adherence to lipid lowering therapy is less than ideal, with estimates of the proportion of patients remaining on treatment after 1 year ranging between 25% and 90%, with a downward trend over time. [8-13]

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Poor adherence to therapy have important clinical consequences: Registry data have shown an association between all-cause mortality and low adherence to statin therapy. [14] A similar pattern has been observed for the use of cardioprotective medications in diabetic patients. [15] In primary prevention, studies have indicated increased risk of coronary heart disease (CHD) and congestive heart failure (CHF) in patients with poor adherence. [16, 17] In economic terms, poor adherence could lead to lower cost of drug if patients do not fill their prescriptions, but also higher costs associated with a higher risk of cardiovascular events. In a retrospective population based registry study conducted in the US, Sokol and colleagues investigated the association between adherence to statin therapy among 2,981 patients stratified into five groups defined by medical possession ratio. The investigators found a statistical significant reduction in total health care costs (defined as drug costs and cost of hospitalizations for any cause) with increased adherence. [18] To our knowledge, this is the only study considering the economic

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aspects of poor adherence to statin therapy based on observational data as opposed to assumptions regarding the effect of poor adherence.

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The Anglo-Scandinavian Cardiac Outcomes Trial (ASCOT) was a multicentre randomised trial in which two antihypertensive treatment strategies for the reduction of CHD was investigated in 19,257 patients with no prior or current history of CHD. In the blood pressure-lowering arm of ASCOT (ASCOT-BPLA) a newer regimen of antihypertensive drugs based on the calcium channel blocker amlodipine, adding the angiotensin-converting enzyme inhibitor perindopril as required to reach blood pressure targets (amlodipine-based), was compared with an older regimen based on the beta-blocker atenolol, adding the diuretic bendroflumethiazide with potassium as required (atenolol-based). In addition, in a 2x2 factorial design, the trial included a double-blind lipid-lowering arm (ASCOT-LLA) - a comparison of atorvastatin to placebo in 10,305 patients. This part of the trial was closed early (after a median follow-up of 3.3 years) after a recommendation by the data safety monitoring board on the grounds that atorvastatin had resulted in a highly significant reduction in the primary endpoint (non-fatal myocardial infarction, MI, and fatal CHD) as well as a reduction in the number of strokes. [1] The blood-pressure lowering arm was also stopped prematurely on the ground of higher efficacy of the amlodipine-based therapy after a median follow-up of 5.5 years. [19] After the early termination of the lipid-lowering arm, the choice to remain on drug or discontinue was left at the discretion of the treating physician and patient. Data were however continuously collected as part of the ongoing blood-pressure lowering arm. At the end of follow-up, patients originally randomized to atorvastatin had

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a 36% lower risk of the primary end-point in spite of crossing between treatments, potentially due to carry-over benefits. [20]

The objectives of our study were two-fold: First to study the association between adherence and cardiovascular outcomes during the follow-up after the closure of the lipid lowering arm, and second to quantify the long-term economic consequences and health outcomes linked to reduced adherence.

Methods

Patients

The design and inclusion criteria of ASCOT-LLA have been described in detail previously. [21] The trial included men and women aged between 40 and 79 years, with either untreated hypertension (systolic blood pressure >160 mm Hg and/or diastolic blood pressure >100 mm Hg) or treated hypertension with systolic blood pressure >140 mm Hg and/or diastolic blood pressure >90 mm Hg and who, while not being treated with a statin or fibrate, had a total cholesterol concentration of 6.5 mmol/L or less. Patients were also required to have at least three of the following risk factors: male sex, age 55 years or older, microalbuminuria or proteinuria, current smoker, a ratio of plasma total cholesterol to HDL-cholesterol of 6 or higher, a family history of early CHD, left ventricular hypertrophy, other specified abnormalities on electrocardiogram, type 2 diabetes, peripheral arterial disease, previous stroke or transient ischaemic attack.

In order to assess the impact of low adherence on total cardiovascular events and procedures (including fatal CHD, silent and non-silent MI, fatal and non-fatal stroke, fatal and non-fatal heart failure, stable and unstable angina, peripheral artery disease, life-threatening arrhythmias and revascularisation procedures such as coronary artery by-pass grafting, CABG, and percutaneous coronary interventions, PCI), patients randomized to atorvastatin without events before the closure of the lipid-lowering arm were included in this analysis.

The impact of low adherence on cardiovascular events

The number of days on drug (start and stop dates) were collected as part of the case report forms of the trial. Based on this information, adherence was defined as the proportion of days covered (PDC), with high adherence defined as PDC >80% and low adherence as PDC <50%.

To control for underlying cardiovascular risk, ~~we created a risk score~~ by fitting a logistic regression model to the patient level data in the placebo arm of the trial, and included male sex, ~~older~~ age (>60 years), current smoker, systolic and diastolic blood pressure, total cholesterol, LDL cholesterol and HDL cholesterol, history of cerebrovascular disease, diabetes, left ventricular hypertrophy and blood pressure regimen. ~~This was then used to assign a risk score to each patient in our study sample based on their risk factor profile.~~

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Two statistical models were used to assess the impact of adherence on cardiovascular events: A Cox proportional hazards model and a Poisson regression model. Both models included cardiovascular risk (based on the risk score described above), accumulated adherence, and current age of the patients. The Poisson model also included time since the entry in the follow-up. We were primarily interested in investigating high adherence compared to low, but in order not to lose patients, accumulated adherence (based on PDC) was divided into three groups (less than 50%, between 50 and 80% and above 80%) with the lowest groups used as the reference group in the regressions.

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The impact of low adherence on health economic endpoints

To assess the long-term impact of poor adherence we used a Markov model based on the ASCOT patient-level data. This model has been described in detail elsewhere. [22]

Briefly, the model consists of five health states describing the health of the patient: Event free, MI, revascularization, stroke and death. Only the first MI, revascularization and stroke are explicitly included in the model although costs from subsequent events were included when attributing cost to each health state. Each year, the risk of moving between the health states is governed by transition probabilities derived using survival analysis from the trial data, taking age, gender, blood pressure lowering regime and the use of atorvastatin into account. Survival following events was assumed to be the same irrespective of current treatment.

Costs in the model (expressed in 2007 £) were based on the resource consumption following an event in the trial. For atorvastatin, we used the listed price of 0.64 £ per day

with the total cost in the two arms depending on the actual observed adherence. Each health state is also associated with utility weights to predict the number of quality adjusted life years (QALY) associated with the different treatments. Utility weights for the health states were based on a previously published substudy of ASCOT patients using the EQ-5D to assess the health following events, converting responses to utility weights using social valuations from the UK. [23]

To assess the impact of adherence, we used the model to compare a group of patients with high adherence (PDC >80%) during the open-label follow-up to a groups of patients with low adherence (PDC <50%) by adjusting the risks with the relative risk observed in the Poisson model described above. We assumed that patients would receive an amlodipine-based antihypertensive therapy and therefore have the underlying risk as patients with amlodipine in combination with atorvastatin, as this has previously been indicated to be cost-effective in comparison to an atenolol-based strategy. [24] At the end of follow-up, patients in both arms of the model were assumed to have the same risk as those of amlodipine-treated patients alone, and the model is run until all patients are dead.

To assess the impact of parameter uncertainty on the results, a probabilistic sensitivity analysis (PSA) as undertaken where each model input parameter was drawn from its underlying distribution. For transition probabilities, costs and utility weights, the empirical distributions were used (estimated by bootstrapping from the original patient level data). The relative risk associated with high adherence was assumed to be log-normal and the proportion of patients on drug in the high and low adherence arms were

assumed to be beta-distributed. One-way sensitivity analysis of key model inputs was also conducted.

The analyses were performed from the perspective of the UK NHS, with costs and outcomes discounted at a rate of 3.5% per annum in accordance with the recommendations made by NICE. [25]

Results

In total, 4671 patients were included in the study with a median of 2.4 years of follow-up. Table 1 shows the demographic characteristics at baseline for patients with high and low adherence (548 patients fell into the middle group, data not shown for these). The groups are fairly similar in their characteristics, with no marked pattern of higher risk patients in one group or the other.

<Table 1>

As can be seen in table 2, patients with high adherence have a significantly lower risk of cardiovascular events than patients with low adherence. There is also a numerically lower risk for the limited number of patients with medium adherence (PDC 50 – 80%), although this was not statistically significant. The Cox proportional hazards model and Poisson regression model show very similar results.

<Table 2>

The Markov model predicts that 1 first event per 100 treated patients is avoided by high adherence. 43% of the events would be MI or fatal CHD, 29% revascularisation procedures and 28% stroke. In table 3, the projected long-term effects of low adherence predicted by the model are presented. 10% of the treatment cost in the high adherence group is offset by savings due to fewer events.

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<Table 3>

Figure 1 shows the results from the PSA based on 1,000 replications in the form of a cost-effectiveness scatter plot. In the vast majority of the simulations, high adherence is associated with positive long term outcomes.

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<Figure 1>

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Figure 2 shows a tornado diagram of the results from the one-way sensitivity analyses.

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Results are most sensitive to the relative risk associated with high adherence. Results are also sensitive to assumptions on the cost of drug in the low adherence arm. The upper bound in the analysis represent a situation where costs are only incurred for days where the drug was consumed (on average 7% of days), while the upper bound would indicate a situation where drug costs are incurred for the entire period, representing wastage of drug for all days where it is not consumed. A situation between these extremes would represent a situation where some, but not all, of the prescriptions are filled by the patient.

Changes to the start age of the patient (which could be seen as a proxy for risk), the discount rate applied, and changes to utility decrement caused by and costs associated with events has relatively small impact.

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Discussion

Our study shows that patients with greater than 80% adherence to lipid lowering drug therapy have a 25% reduction of cardiovascular events compared to patients with low adherence. During the WOSCOPS trial, patients with a compliance of greater than 75% had a 38% risk reduction of the primary end point compared to patients with lower compliance. [26] One potential explanation for our results being slightly lower is that we looked at a group of patients who had been on treatment for 3.3 years (median) already, and there may be a protective carry-over effect from this treatment. [20]

Based on the findings in a meta-analysis of clinical trial data where patients with good adherence to placebo had better survival than those with poor adherence, a healthy adherer effect has been proposed. [27] This would imply that patients with generally good health would be more likely to take the drug, and therefore introduce a bias when measuring the effect of adherence. In our analysis, we control for underlying cardiovascular risk, and so a healthy adherer effect is unlikely to explain our findings.

The use of 80% of days covered as a cut-off for cost-effectiveness is of course arbitrary, and does not constitute a magic boundary. It is however consistent with much of the published literature on adherence. [28]

When extrapolating over a longer timeframe, our model predicts that 10% of the cost of drug is saved through reduction in other health care costs in patients with high adherence.

The avoided events are also predicted to lead to an improved quality-adjusted survival of

0.02 QALYs. Compared to the findings of Sokol and colleagues where a reduction of total costs was observed, our results may seem small [18] One explanatory factor is that

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the cost associated with e.g. hospitalizations in the US is generally considerably higher compared to the UK, which leads to higher savings from each avoided event. The main reason however, can be found in the underlying absolute risk of cardiovascular disease:

The ASCOT-LLA population is a primary prevention population treated intensively with

antihypertensive agents and having cholesterol levels 6.5 mmol/L and below, meaning

that they have a lower underlying risk of events. Furthermore, in our analysis we consider

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only patients who did not suffer an event during the blinded part of the trial, thus diluting

the risk of events even further. Considering a cost-effectiveness perspective, the cost to

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gain a QALY from high adherence would be £ 19,000, which is below the threshold

value of £ 20,000 – 30,000 per QALY employed by NICE. [25] High adherence would

therefore be perceived as being of good value to society – even in this relative low risk

group of patients. Compared to our previous analysis of amlodipine plus atorvastatin

versus amlodipine alone, the cost per QALY is higher in this analysis. The reason may

once again lie in the suggested carry-over effect, and the fact that patients with low-

adherence still have some protection from their previous treatment. [20] By multiplying the number of days on drug with a daily cost, we also assumed a very low costs in the low adherence group. In practice, poor adherence would manifest itself not only as patients not filling their prescription, but also in patients filling their prescriptions and then not taking the drug, leading to wastage. If patients filled prescriptions for 25% of the days under study, the ICER would be reduced to £ 15,000 per QALY. If patients were to fill all prescriptions and take the medication to the extent reported here (7.3% of the time), persuading them to take the drug to the same extent as in the high adherence groups would lead to overall savings, albeit modest ones (£ 36 per patient).

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In our analysis, patients were still in the active follow up stage of ASCOT-BPLA. This adds strength to our analysis as data were collected in a controlled fashion, but it also adds some complications when extrapolating results. In the extrapolation presented here, the impact of non-adherence to the antihypertensive therapies was not considered. It could be argued that patients with a low adherence to statin also would have low adherence to other drugs. This needs to be taken into account when considering potential measures to improve adherence as the actions taken could have beneficial impact on blood pressure lowering as well.

There are to date very few studies based on the observed effect of poor adherence to statin therapy. Our results indicate that there is a significant reduction of events in patients who are adherent, and that this translates into long-term benefits. An important area of future research would be to investigate what measures to improve adherence

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would be cost-effective. Based on the thresholds employed by NICE, there seems to be some room to take action. This will be particularly true when the price of the drug falls after ~~the patent expires~~.

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Author contributions

PL was responsible for the concept/design of this substudy, data analysis and interpretation, and drafted the article. JE participated in data analysis and critical revision of the article. MB, TK, NP, BD, PS, HW and BJ provided input on the study concept and critically revised the manuscript. NP, BD, PS and HW formed the executive committee of the ASCOT trial.

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Table 1: Baseline characteristics for Atorvastatin patients with low (<50%) or high (>80%) adherence to atorvastatin during ASCOT-LLA extended follow-up

	High adherence to Atorvastatin n=2415	Low adherence to Atorvastatin n=1708
Demographics and clinical characteristics		
Woman	403 (16.7%)	359 (21.0%)
Age (years)		
≤60.0	871 (36.1%)	617 (36.1%)
>60.0	1544 (63.9%)	1091 (63.9%)
Mean (SD)	63.0 (8.2)	63.3 (9.0)
Current smoker	755 (31.3%)	613 (35.9%)
Obesity ¹	830 (34.4%)	537 (31.4%)
Creatinine > 120 micromol/L	148 (6.1%)	106 (6.2%)
Very high blood pressure ²	193 (8.0%)	164 (9.6%)
Medical history		
Previous stroke / TIA	236 (9.8%)	173 (10.1%)
Diabetes	674 (27.9%)	357 (20.9%)
LVH (according to ECG or echocardiography)	369 (15.3%)	223 (13.1%)
ECG abnormalities other than LVH	358 (14.8%)	245 (14.3%)
Peripheral vascular disease	133 (5.5%)	87 (5.1%)
Other relevant cardiovascular disease	91 (3.8%)	62 (3.6%)
Mean (SD) number of risk factors	3.7 (0.9)	3.6 (0.9)
Drug therapy		
Previous antihypertensive treatments (number of drugs)		
None	372 (15.4%)	394 (23.1%)
1	1120 (46.4%)	759 (44.4%)
≥2	923 (38.2%)	555 (32.5%)
Lipid-lowering therapy	39 (1.6%)	6 (0.4%)
Aspirin use	500 (20.7%)	252 (14.8%)

¹ BMI > 30, ² SBP > 190 or DBP > 120 mm Hg

Table 2: Hazard ratios (95% confidence interval) on the risk of cardiovascular events and procedures during the open-label follow-up of ASCOT-LLA

	Cox proportional hazards model	Poisson model
Cardiovascular risk (in %)	1.06 (1.03-1.09)**	1.06 (1.03-1.09)**
Accumulated adherence 50%-80%	0.73 (0.46-1.14)	0.71 (0.46-1.12)
Accumulated adherence >80%	0.75 (0.57-0.98)*	0.73 (0.56-0.96)*
Current age	1.03 (1.02-1.05)**	1.03 (1.02-1.05)**
Time since entry in follow-up	na	0.91 (0.75-1.10)
*p < 0.05; **p<0.001		

Table 3: Predicted per-patient long-term costs (£) and health outcomes

	High adherence	Low adherence	Difference
Cost of lipid lowering	427	33	353
Other health care costs	1,252	1,290	-38
Total cost	1,689	1,323	366
Predicted life years	10.83	10.81	0.02
Predicted QALY	8.13	8.11	0.02

Figure 1: Cost-effectiveness scatter plot of the probabilistic sensitivity analysis comparing the net difference in costs and effects between the high adherence and low-adherence groups.

Legend

Each dot represent the net cost and QALY from one simulation where all model inputs are drawn from their underlying distribution, thus giving an estimate of the joint parameter uncertainty in the model.

Figure 2: Tornado diagram with results from sensitivity analyses on key model inputs.

Legend

RR of events: The relative risk of events in the high adherence group. Drug cost: The proportion of days patients in the low-adherence group accrue drug costs. Start age: The starting age of the cohort. Discount rate: The yearly discount rate applied to costs and effects. Utility from events: A modification to the utility reduction caused by events. Costs from events: A modification to the cost of events.