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Compliance with statins in primary care

By Nicola Howell, Robert Trotter, David R. Mottram and Philip H. Rowe

Abstract

Aim

To investigate patient compliance with statin therapy and its effect on health outcomes.

Design

A retrospective cohort study.

Subjects and settings

All patients prescribed a statin, in a large Liverpool GP practice, from 31 December 1991 to 26 January 2003.

Outcome measures

Compliance on cardiovascular mortality indices.

Results

25 per cent of the patients were non-compliant. The incidence of all cause mortality was significantly reduced in the compliant sub-group (P=0.0043, relative risk reduction [RRR] 44%). Compliance with therapy was associated with a significant reduction in CHD mortality (P=0.0088, RRR 56%), and non-cardiovascular mortality (P=0.0055, RRR=63%). Cholesterol monitoring was found to be a statistically significant predictor (P<0.001) of patient compliance. Diabetes patients were the most likely to be receiving this service (P<0.001).

Conclusion

Non-compliance means that the maximal benefits of statin therapy are not being attained in this patient population. Prescribing of statins to patients in whom no benefit is being realised represents a significant cost to the practice. This emphasises the need to implement compliance-enhancing initiatives, such as regular cholesterol monitoring.

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Several landmark clinical trials have been published showing the benefits of statins in the prevention and management of coronary heart disease. LIPID,[1] CARE[2] and 4S[3] show that prolonged treatment with statins significantly reduces morbidity and mortality in patients with pre-existing CHD. WOSCOPS[4] and AFCAPS/TexCAPS[5] demonstrated similar benefits in patients without a history of CHD. The Heart Protection Study (HPS)[6] has provided further evidence of the benefits of statin therapy, irrespective of CHD history or baseline cholesterol.

In the wake of this evidence, the current CHD guidelines[7,8] clearly define the importance of prescribing these drugs to all patients deemed at risk. Consequently statin prescribing by North Liverpool PCT has risen.[9] Statins are not inexpensive drugs, hence this increase in statin prescribing has had a significant impact on the budget. The assumption being made is that the benefits seen in these clinical trials will be conferred upon the local population, that is, the number of clinical coronary events may be reduced by as much as one third.

Simply prescribing these drugs to the patient is insufficient to reap the expected benefits. Patient compliance is an important determinant of benefit from statin therapy and must be ensured if risk reduction is to be achieved. Indeed, the greatest reduction in morbidity/mortality in the WOSCOPS[4] trial was seen in those patients who took more than 75 per cent of their medicines.[10] This highlights non-compliance as one such barrier, which in turn suggests that non-compliance lessens the benefits from providing statin therapy. As the statins all have well defined dose-response curves, the concept that the non-compliant patient who is using a dose below that prescribed can expect proportionally less benefit is supported.

Favourable effects on mortality and morbidity were seen in trials only after one to two years of continuous treatment with statins. It is apparent that for both primary and secondary prevention, compliance with statin therapy is required long term. Any patient failing to persist with therapy for this minimum length of time will have derived no benefit, and will remain at higher risk of a myocardial infarction or other coronary event.

A patient's non-compliance with therapy can take many forms, including the patient stopping therapy altogether, continuing with the medication but failing to take it as prescribed or taking it at an inappropriate time.[11]

Patient compliance with statin therapy is expected to be poor since research shows that patients are less well motivated to comply long term with preventive treatments or those targeting asymptomatic conditions with no immediately apparent benefits.[12,13] A lack of overt symptoms also means that minor side effects associated with the medication are less acceptable.

Recently, three studies[14–16] have been published which suggest that the level of compliance (deemed those taking ≥80 per cent of therapy[17]) outside the clinical trial setting decreases with time and is influenced by many factors such as age, history of CHD, diabetes or hypertension, education and continuing support from a health care professional. They show compliance can drop to less than 50 per cent after two years — a level similar to that seen for other long-term drug regimens.[11] In addition, they confirmed that the benefits expected with statin therapy were only realised in those patients who continuously took over 80 per cent of their medication.

In order that maximal benefits are achieved in the local population, the true level of compliance with statin therapy needs to be identified. The effective application of appropriate compliance enhancing interventions requires a knowledge of the reasons for poor compliance, which sub-groups are most at risk, and the time when compliance is most likely to drop off. Knowledge of the true long-term persistence rates will also allow a more accurate estimation of population level cost and benefit of statin prescribing.

To this aim a retrospective cohort study was conducted, the purpose of which was to investigate true patient compliance with statin therapy in primary care. The influence of other factors on compliance was also assessed, eg, gender, age, history of CHD, diabetes or hypertension. The effects of compliance on the incidence of myocardial infarction, all cause mortality, fatal MI, CHD deaths, all cause cardiovascular deaths and non-cardiovascular deaths were determined.

Methods

Study population A retrospective cohort study was performed, using the electronic medical records in a large (seven partners and three salaried GPs; 12,700 patients) city-based GP practice in Liverpool. The practice used guidelines from Sheffield and New Zealand. At the time of writing, there were 636 patients on the CHD register of whom 98 per cent were on aspirin or clopidogrel,

68 per cent were on a statin and 83 per cent had a blood pressure of 150/90 or below.

A search of the records was conducted to identify those patients of any age and gender who were prescribed a statin (atorvastatin, cerivastatin, fluvastatin, pravastatin or simvastatin) between 31 December 1991 and 26 January 2003.

For each of the subjects so identified, medical records were accessed, and the following data were collected and entered into an Access database:

- Date of birth
- Gender
- Previous MI — if yes, the date of the most recent MI
- History of major vascular disease — yes or no (subjects were identified as suffering major vascular disease, if under the "problems" field a diagnosis of angina, past MI, PVD, CVA/TIA or angioplasty was recorded.)
- Diabetic — yes or no (Either being listed as diabetic under the "problems" field or having insulin or other diabetes medicines on repeat prescription identified Type 1 and Type 2 diabetes patients.)
- Hypertensive — yes or no (Either being listed as hypertensive under the "problems" field or repeated blood pressure measurements of over 140/90.)
- Regular cholesterol monitoring — yes or no (Defined as having had cholesterol levels checked in the past six months, and at least annually before that date.)
- Prophylactic aspirin prescribed — yes or no
- Smoker — yes, no or unclear (A subject was identified as a smoker if currently recorded as being a smoker, or if they had a history of being a smoker. Non-smokers were identified as such if their records stated that they were non-smokers. If a subject could not be identified as either a smoker or a non-smoker, a result of unclear was recorded.)
- BMI — a BMI of >30kg/m² is a contributory risk factor for CHD
- Type and dose of statin prescribed
- Number of days on each statin prescription
- Date of first and last statin prescription issued
- Number of statin prescriptions issued
- If statin therapy was changed at any time, the date of the change was recorded, as was the type and dose of the new statin
- If statin therapy was discontinued — deemed as more than six months lapsing between the date of last prescription issue and the end of the study period (A reason for discontinuation was sought in the medical record.)
- If the patient was classed as "transferred out", a reason for this was sought
- The date the subject registered with the practice was listed in the "summary report"
- Once the first date of statin prescription was identified, the records were searched further to exclude any patients who had received a prescription for a statin in the previous 18 months (This ensured the study was restricted to new users of statin therapy.)

For transferred out subjects, the reasons were: patient's request; GP's request; death; internal transfer — moved to another GP practice within the same health authority; moved to another GP practice in another health authority; other — eg, joined the armed forces; non-responsive to mail from the health authority. For those subjects transferred out due to death, a cause of death was sought from the medical records.

Analysis of results For each eligible subject, the proportion of days covered (PDC) by a statin prescription was calculated by dividing the number of days of statin therapy by the number of days between the first and last statin prescription and multiplying by 100.

On the basis of their PDC the cohort was divided into two groups: PDC≥80 per cent and PDC<80 per cent.

Subjects who had not been issued with a statin prescription in the previous six months were deemed to have discontinued therapy, unless they had been transferred to another cholesterol reducing drug or had been advised to cease therapy by their GP/hospital clinic (as stated in the patient records), eg, due to adverse effects.

A PDC of <80 per cent or non-persistence with therapy was interpreted as non-compliance.[17] Those subjects with a PDC of ≥80 per cent and who were persisting with therapy were deemed compliant. The compliant and non-compliant subgroups were further grouped by gender, smoking status, diabetes and hypertension.

Those patients who suffered an MI or died during the study period were identified. The cause of death for all deceased patients was identified from the following sources: surgery records of death certificates signed by own GP; records held at Royal Liverpool University Hospital Trust, if the patient died while in hospital; Liverpool Register Office.

Statistical methods Patients were divided into compliant and non-compliant subgroups for all analyses.

The following statistical analyses were conducted using Minitab:

Data were summarised as mean (±SD) for continuous variables and number of patients for categorical variables.

Chi-squared analysis was used to determine the significance of any difference between sub-groups.

Student's *t*-test was used to determine the significance of any difference between two population means.

SPSS version 11 was used to construct Kaplan-Meier survival curves and perform log-rank tests for the occurrence of either an MI or death. Deceased patients were split into sub-groups according to cause of death — definite MI, CHD, all cause cardiovascular deaths and all cause non-cardiovascular deaths. Kaplan-Meier survival analysis was used because it takes account of the differing length of time a patient was prescribed a statin, when determining the significance of compliance on the occurrence of an event.

Relative risk reductions (RRR) were calculated in the standard manner.[18] Cox hazard ratios (CHR) and 95 per cent confidence intervals were calculated using SPSS version 11.

Results

Cohort characteristics A total of 1,010 patients were prescribed a statin from the 31 December 1991 to 26 January 2003. Of these, 869 met the inclusion criteria described in the methods. A total of 654 patients were classed as compliant and 215 as non-compliant. There was no statistically significant difference for any characteristic between the compliant and non-compliant groups.

Statin prescription The number of patients in the study population who were prescribed a statin rose throughout the study period, and is still continuing to increase. In this population simvastatin (47.8 per cent) was the most commonly prescribed statin, followed by pravastatin (41.2 per cent). Few patients were prescribed fluvastatin, atorvastatin or cerivastatin.

The mean time from the initiation of therapy to either discontinuation of therapy or the end of the study period was 968 days (SD 852; median 697.5) for compliant patients and 699 days (SD 856; median 425) for non-compliant patients.

Of the study population, 74 patients discontinued statin therapy. All patients were considered as compliant during the first month of therapy. A second statin prescription was not collected by 27 of these patients. After six months only 30 of these patients were still persisting with therapy, reducing to 14 after two years. In the majority of cases (54; 73 per cent) no reason for the discontinuation had been recorded on the patient records. Discontinuation due to side effects was recorded for 10 patients (14 per cent).

Of the persisting patients, 182 had their statin prescription changed during the course of therapy. In two cases, this was due to the withdrawal of cerivastatin from the market. Other reasons for change in therapy were: cholesterol levels unsatisfactory (98; 54 per cent); side effects (25; 14 per cent); advised by the hospital (15; 8 per cent); the patient forgot to take their medicine at night (6; 3 per cent); no reason given (36; 20 per cent).

The side effects responsible for the change in therapy for 25 patients were: gastrointestinal effects (9); muscle pain (7); insomnia (3); creatinine kinase raised (3); dermatological (2); possible adverse drug reaction (1).

Table 1: The influence of variables on compliance

Variable		Percentage of compliant population (number of patients)	Percentage of non-compliant population (number of patients)	Statistical significance *P*=	95% Confidence interval
Gender	Male	51% (333)	43% (93)	0.128	-0.102–0.013
	Female	49% (322)	57% (121)		
Age>60 years		42% (274)	42% (91)	0.825	-0.051–0.064
Major vascular disease		54% (353)	49% (106)	0.234	-0.023–0.092
Diabetes		23% (148)	22% (48)	0.926	-0.065–0.072
Hypertensive		75% (490)	67% (145)	0.075	-0.008–0.127
Cholesterol monitoring		60% (392)	43% (92)	<0.001	0.071–0.188
Smoker		47% (307)	43% (93)	0.291	-0.027–0.089
BMI>30kg/m^2		21% (137)	17% (37)	0.257	-0.027–0.089
Prescription of aspirin		42% (277)	41% (89)	0.805	-0.051–0.065

Table 2: Association of various factors with the receipt of regular cholesterol monitoring

	Number of patients with			
	Cholesterol monitoring	No cholesterol monitoring	*P*=	95% Confidence intervals
Diabetes patients	135	61	<0.001	0.095–0.245
Hypertensive patients	361	274	0.228	0.029–0.122
Patients with BMI>30	98	76	0.275	0.103–0.030
Smoking status	233	167	0.277	-0.030–0.104

Table 3: Summary of cause of death for deceased patients in both subgroups

	Number of patients	
	Compliant n=654	Non-compliant n=215
All cause mortality	24	14
All cardiovascular deaths	16	7
Deaths due to CHD (MI)	8 (5)	6 (4)
Deaths due to stroke	3	1
Non-cardiovascular deaths	8	7

Factors associated with compliance The association of several factors with compliance with statin therapy was investigated. There was no significant association between choice of statin prescribed and compliance (*P*=0.589). Other factors are shown in Table 1.

The only factor associated with a significant enhancement of compliance was cholesterol monitoring. In this study, 43 per cent of the non-compliant sub-group received cholesterol monitoring compared with 60 per cent of the compliant sub-group.

Further analysis (Table 2) shows that, currently, only diabetes patients are significantly more likely to receive regular cholesterol monitoring. Those patients with hypertension, or a BMI >30kg/m^2 were no more likely to receive cholesterol monitoring than those without these conditions. Smokers were also no more likely to receive cholesterol monitoring than non-smokers.

Non-fatal myocardial infarction while on a statin In the study population 12 patients were identified as suffering a non-fatal MI while in receipt of a statin prescription. Kaplan Meier Survival Curves were constructed and a log-rank test analysis was performed to determine the significance of compliance with statin therapy on the incidence of MIs in this population but this was found to be non-significant (*P*=0.643).

Mortality in study population A total of 38 patients in the study population died. There were no significant differences between the compliant and non-compliant patients at the start of therapy. A summary of the cause of death for the deceased patients is presented in Table 3.

Kaplan Meier Survival Curves and log-rank tests were used to determine the association between compliance with statin therapy and the cause of death. Compliance with statin therapy was associated with a significant reduction in all cause mortality (*P*=0.0043; RRR 44 per cent; CHR 2.542 [95 per cent CI 1.310–4.933]) and with a significant reduction in CHD mortality, (*P*=0.0088; RRR 56 per cent; CHR 3.832 [95 per cent CI 1.381–10.633]). Compliance was associated with only a non-significant reduction in all-cardiovascular deaths (*P*=0.1574; RRR 27 per cent; CHR 1.901 [95 per cent CI 0.778–4.641]). Finally, compliance was associated with a significant reduction in non-cardiovascular mortality (*P*=0.0055, RRR 63 per cent; CHR 3.832 [95 per cent CI 1.381–10.633]).

Discussion

Compliance in study population This study found that, in a large GP practice, 25 per cent of the patients prescribed a statin over the study period were non-compliant with therapy. The level of compliance identified in this patient population was similar to that seen in another primary care study.[19] In that study, compliance with pravastatin and cholestyramine was compared. Compliance with pravastatin ranged from 76 per cent (pravastatin 20mg) to 78 per cent (pravastatin 40mg), and was significantly higher than with cholestyramine (44 per cent). In WOSCOPS,[4] 26 per cent of patients were deemed non-compliant at the end of the study period.

Thirty-eight patients in the study population died during the period of analysis. At baseline, only the average age of patients in the compliant sub-group (66 years), compared with the non-compliant sub-group (63 years), showed a difference that approached statistical significance (*P*=0.084). This may have placed the compliant patients at increased risk of a CHD event as risk increases with age.[20] No other differences in baseline characteristic affecting risk of a coronary event were identified. A log-rank test showed that the risk of a fatal CHD event was significantly lower (*P*=0.0043) in those patients compliant with their prescribed therapy. The risk of an event in the non-compliant sub-group was found to be 2.542 (95 per cent CI 1.310–4.933) times greater. This finding confirms the observation in WOSCOPS[4] (a primary prevention study), that the benefits seen in patients receiving pravastatin were significantly reduced in those patients subsequently identified as non-compliant.

All cause cardiovascular mortality (including stroke and atheroma) was also decreased in the patients compliant with therapy, but this reduction did not achieve statistical significance (*P*=0.1574). In WOSCOPS,[4] a 32 per cent reduction in risk of all fatal cardiovascular events was observed.

In contrast with the findings in the major clinical trials,[3,8] this study found mortality of non-cardiovascular cause was significantly reduced in those patients compliant with statin therapy (*P*=0.0055). The risk of dying from a non-cardiovascular cause was found to be 3.832 (95 per cent CI 1.381–10.633) times higher in the non-compliant sub-group. Compliance with medication may be associated with other behaviours beneficial to health that reduce the risk of non-cardiovascular mortality, or statins themselves may have benefits other than those associated with lowering cholesterol levels. Although further research would be required to investigate these possibilities, it is of interest to note that Phase II clinical trials are currently under way investigating the benefits of statins as anticancer agents.[21]

Investigation of possible associations with compliance In order that resources to improve patient compliance can be directed appropriately, knowledge of the factors linked to compliance is required. This study examined the possible association of several factors with non-compliance with statin therapy. Gender, age, diagnosis of major vascular disease, diabetes status, smoking status, having a BMI >30kg/m^2 and concomitant prescription of aspirin were all found to be non-significantly associated with compliance.

The association with a diagnosis of hypertension on compliance approached, but did not attain statistical significance. Further work would be required to determine whether or not there is a link. A possible hypothesis is that because patients are receiving treatment for hypertension they have already got into the habit of taking medicines on a regular basis, hence they find it easier to comply with other therapies.

Regular cholesterol monitoring was found to be highly significantly associated with compliance with therapy. This finding might be explained by evidence from a previous compliance study,[22] which showed that compliance with therapy increases if the patient has regular contact with a health professional, and is kept informed of their progress towards a goal. In addition, the visit for a cholesterol check would provide the patient with another opportunity to discuss any concerns they have regarding their medication. The appointment would also present the nurse with a chance to emphasise the importance of regular medicine taking.

Regular cholesterol monitoring therefore has two benefits — by monitoring lipid levels, the success of the prescribed therapy can be assessed and compliance monitored. This finding questions the argument that the use of cholesterol monitoring is now unnecessary[9] since there is evidence of health benefits in all patients prescribed an appropriate dose of statin.[8]

Analysis of those patients who had received regular cholesterol monitoring showed that diabetes patients were the most likely to be receiving this service. This is possibly because diabetes patients are regularly called into the surgery for checks on their diabetic control. This highlights areas where cholesterol monitoring services need to be targeted, and their potential as a compliance-enhancing initiative.

Other observations Previously, it was recommended that therapy should be initiated at a low dose and titrated upward until the target cholesterol was achieved.[23] The titration method depends upon the use of regular cholesterol monitoring to identify those patients who need their statin dose altering. The observation that only 56 per cent of patients in the study population had their cholesterol checked regularly highlights one of the main failings with this approach.

Failure to achieve target cholesterol levels might also be caused by poor compliance with the prescribed therapy, suggesting that the true level of non-compliance in this population is higher than 25 per cent. A failure to identify poor compliance as the reason target cholesterol levels have not been attained may lead to inappropriate changes to the patients' drug therapy.

Non-persistence with therapy Side effects were cited as the reason for discontinuing therapy in 10 of the 74 patients identified as being non-persistent with therapy. A further 10 patients had expressed no desire to take cholesterol lowering therapy and in the remaining 54 patients no reason was recorded in the medical records. This may suggest that the patients' discontinuation had gone unnoticed by any health care professional. The incomplete nature of the information recorded on the surgery computer highlights an area for possible future improvement.

All these patients were deemed persistent with therapy for the first month, since it was not possible to determine at which point during the initial prescription the patient ceased to take the medication. Only 47 of these patients returned to collect a second prescription, and by six months, just 30 remained persistent with statin therapy. This finding is of particular concern as the major clinical trials[1–5] reported that it takes six to 12 months for a statistically significant benefit from statin treatment to become apparent. Furthermore, it supports the targeting of compliance-enhancing strategies at the first six months of therapy, the assumption being that if a patient continues with therapy for more than six months, they will be more likely to adopt it into their lifestyle, and continue with it long term.

Limitations and assumptions of the study The sample size is relatively small compared with other studies on compliance. As a retrospective study, reliance was placed on the completeness and accuracy of the data entered on the surgery computer. The method used to assess compliance was indirect, therefore no pattern of compliance was attained or reasons for discontinuation of treatment.

Conclusion

This study has shown that the benefits realised from long-term statin therapy are related to patient compliance. This finding highlights a need to introduce compliance-enhancing initiatives, such as regular cholesterol monitoring. These initiatives should be particularly targeted towards all new users of statin therapy.

This paper was accepted for publication on 1 December 2003.

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