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Non-adherence to statins therapy and its impact on cardiac morbidity and mortality: A metanalysis

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Dyslipidemia is a major risk factor for cardiovascular disease, the leading cause of death worldwide. Statins have been shown to significantly reduce morbidity and mortality in patients with coronary artery disease and in patients with hyperlipidemia. However, there is a significant gap between expected and actual benefits; this may be attributed to poor adherence to statin therapy. Literature search was conducted by using Pubmed, Wiley interscience, and EMBASE electronic databases for relevant studies for the meta-analysis. Inclusion criteria in this analysis were randomized controlled trials, retrospective analysis of data from randomized controlled trials, and observational studies. Adherence to statin therapy is suboptimal in both primary and secondary prevention of cardiovascular disease. The aim of this metanalysis was to assess non-adherence rates to statins in patients enrolled in both primary and secondary cardiovascular diseases prevention and to evaluate the impact of statins non-adherence over time on cardiac morbidity and mortality. Causes of non-adherence to statins are shown a discrepancy and include patient factors, practitioner factors and health system factors. Non-adherence is associated with adverse health outcomes and increased costs of health care. Non-adherence to statins is a significant issue for the prevention and treatment of cardiovascular disease. Increased awareness of the causes and solutions for overcoming non-adherence including safer prescribing, improvent in physician-patient alliance and reduction in drug costs, will enhance the cost-effectiveness of the use of statins and significantly improve patient care and outcomes.

Key words: Statins, non-adherence, cardiovascular diseases.

INTRODUCTION

Cardiovascular disease is the leading cause of death in the industrialized world. In developing countries there has also been a commensurate increase in the prevalence of this disease. Hydroxymethyl glutaryl-coenzyme A reductase (HMG_COA reductase) inhibitors (Statins) are the most commonly prescribed medications for decreasing lipid levels. In 2005, 29.7% million individuals in the United States (US) were prescribed statin therapy (http://en.wikipedia.Org/wiki/statin).Largescale,clinicalend-point trials in a wide spectrum of subjects have

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demonstrated the universal efficacy of statins in the prevention of coronary, cerebrovascular and peripheral vascular disease in both primary and secondary prevention settings. In these trials, cholesterol lowering has been in the order of 20- 40%, with a commensurate relative risk reduction in clinical events. Despite their well-established benefits and corresponding recommendations from expert bodies, statins are widely underused in the 'real world' of clinical practice (Alsheikh et al., 2007; Kane and Lipsky, 2000; Hey-Hadavi et al., 2007). Studies also suggest, that patients' adherence to satins therapy is suboptimal and the persistence among those newly prescribed statins is poor. One study found that 40% of elderly patients lacked adequate statin therapy three months after receiving a prescription, and 60% lacked adequate supply after one year (Wolozin et al., 2007). Poor adherence to statin therapy is associated with adverse health outcomes, including higher hospitalization rates and increased non-pharmacy medical costs. Earlier studies have identified patient characteristics associated with statin therapy non-adherence, such as age, sex, comorbidities, and costs (Bates et al., 2009). There is a major gap between the use of statins in clinical trial settings and actual practice (LIPID, 1998). Unfortunately, little is known about suboptimal use of statins and its impact on cardiac morbidity and mortality. Therefore, the aims of this meta-analysis to assess non-adherence rates to statins in patients enrolled in both primary and secondary cardiovascular diseases prevention and to evaluate the impact of statins non-adherence over time on cardiac morbidity and mortality.

PHARMACOLOGY OF STATINS

Statins

The statins (or HMG-CoA reductase inhibitors) are a class of drug used to lower plasma cholesterol level. They lower cholesterol by inhibiting the enzyme HMG-CoA reductase, which is the rate-limiting enzyme of the mevalonate pathway of cholesterol synthesis. Akira Endo and Masao Kuroda of Tokyo, Japan commenced research into inhibitors of HMG-CoA reductase in 1971. This team reasoned that certain microorganisms may produce inhibitors of the enzyme to defend themselves against other organisms, as menalonate is a precursor of many substances required by organisms for the maintenance of their cell wall (ergosterol) or cytoskeleton (isoprenoids) (http://en.wikipedia.Org/wiki/statin). The first agent isolated was mevastatin (ML-236B), a molecule produced by the fungus *Penicillium citrinum.* The pharmaceutical company Merck & Co. showed an interest in the Japanese research in 1976, and isolated lovastatin (mevinolin, MK803), the first commercially marketed statin, from the fungus *Aspergillus terreus* (Ma et al., 1986) (Figure 1).

Mechanism of action

Statins act by competitively inhibiting HMG-CoA reductase, the first committed enzyme of the HMG-CoA reductase pathway (http://en.wikipedia. Org/wiki/statin). Because statins are like HMG-CoA on a molecular level they take the place of HMG-CoA in the enzyme and reduce the rate by which it can produce mevalonate, the next molecule in the cascade that eventually produces cholesterol, as well as several other compounds. This ultimately reduces cholesterol via several mechanisms (Figure 2) (Ma et al., 1986).

Inhibiting cholesterol synthesis

By inhibiting HMG-CoA reductase, statins block the pathway for synthesizing cholesterol in the liver. This is significant because most circulating cholesterol comes from internal manufacture rather than the diet. When the liver can no longer produce cholesterol, levels of cholesterol in the blood will fall. Cholesterol synthesis appears to occur mostly at night, so statins with short half-lives are usually taken at night to maximize their effect. Studies have shown greater LDL and total cholesterol reductions in the short-acting simvastatin taken at night rather than the morning, (Cilla et al., 1996, Ma et al., 1986) but have shown no difference in the long-acting atorvastatin (Ma et al., 1986).

Increasing LDL uptake

Liver cells sense the reduced levels of liver cholesterol and seek to compensate by synthesizing LDL receptors to draw cholesterol out of the circulation. This is accomplished via protease enzymes that cleave a protein called "membrane-bound sterol regulatory element binding protein", which migrates to the nucleus and causes increased production of various other proteins and enzymes, including the LDL receptor. The LDL receptor then relocates to the liver cell membrane and binds to passing LDL and VLDL particles (the "bad cholesterol" linked to disease). LDL and VLDL are drawn out of circulation into the liver where the cholesterol is reprocessed into bile salts. These are excreted, and subsequently recycled mostly by an internal bile salt circulation (Ma et al., 1986).

Other effects

Statins exhibit action beyond lipid-lowering activity in the prevention of atherosclerosis. The ASTEROID (A Study

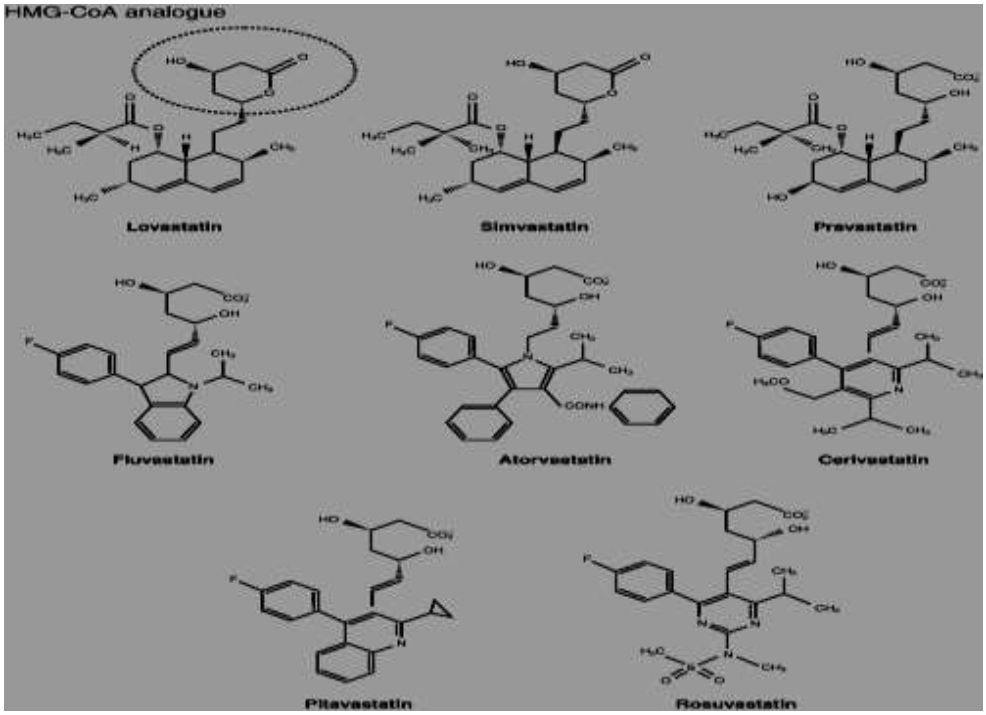

Figure 1. Chemical structures of the statins.
Source: http://en.wikipedia. Org/wiki/statin

to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden) trial showed direct ultrasound evidence of atheroma regression during statin therapy (Nissen et al., 2006). Researchers hypothesize that statins prevent cardiovascular disease via four proposed mechanisms: improve endothelial function, modulate inflammatory responses, maintain plaque stability, and prevent thrombus formation (Furberg, 1999).

Statins may even benefit those without high cholesterol. In 2008 the JUPITER (Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin) study showed fewer stroke, heart attacks, and surgeries even for patients who had no history of high cholesterol or heart disease, but only elevated C-reactive protein levels. There were also 20% fewer deaths (mainly from reduction in cancer deaths) though deaths from cardiovascular causes were not reduced (Shear, 1992). Statins have been linked to a marked reduction in prostate cancer, benign prostate enlargement, incontinence and impotence in older men (Law et al., 2003).

Indications and uses

While statins are effective in decreasing mortality in those who have had previous cardiovascular disease there is not a mortality benefit in those at high-risk but without prior cardiovascular disease (Law et al., 2003). Statins, the most potent cholesterol-lowering agents available, lower LDL cholesterol (so-called "bad cholesterol") by 1.8 mmol/L. This translates in a 60% decrease in the number of cardiac events (heart attack, sudden cardiac death, angina etc), and a 17% reduced risk of stroke (Law et al., 2003). They have less effect than the fibrates or niacin in reducing triglycerides and raising HDL-cholesterol ("good cholesterol"). Professional guidelines generally require that the patient has tried a cholesterol-lowering diet before statin use is considered; statins or other pharmacologic agents may then be recommended for patients who do not meet their lipid-lowering goals through diet and lifestyle approaches. The indications for the prescription of statins have broadened over the years. Initial studies, such as the Scandinavian Simvastatin Survival Study (4S), supported the use of statins in secondary prevention for cardiovascular disease, or as primary prevention only when the risk for cardiovascular disease was significantly raised (Wilson et al., 1998). Indications were broadened considerably by studies such as the Heart Protection Study (HPS), which showed preventative effects of statin use in specific risk groups, such as diabetics. The ASTEROID trial using only a statin at high dose, achieved lower than usual target calculated

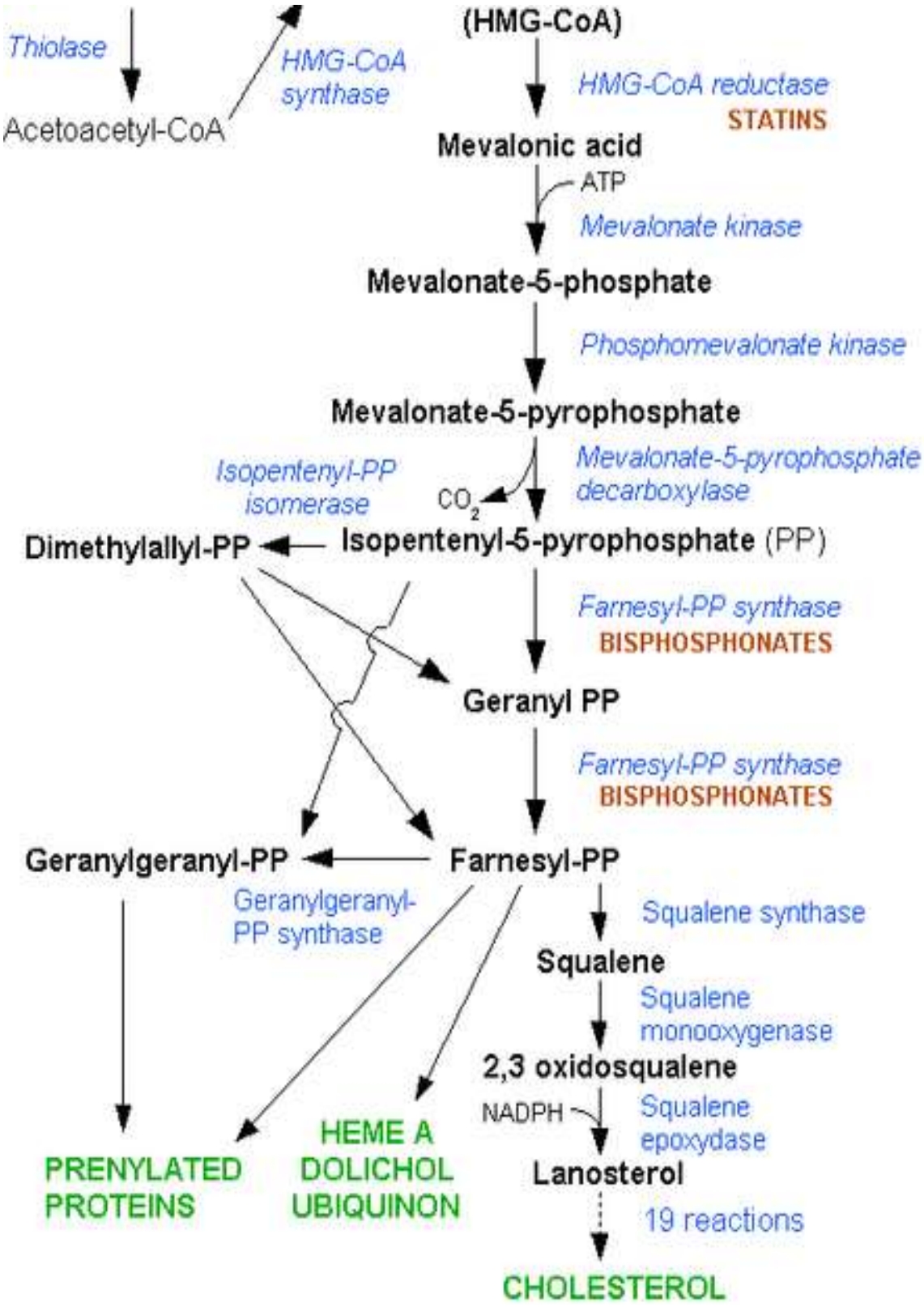

Figure 2. The cholesterol synthesis pathway, which is blocked by statins via inhibiting the rate limiting enzyme HMG-CoA reductase.
Source: http://en.wikipedia. Org/wiki/statin

LDL values and showed disease regression within the coronary arteries using intravascular ultrasonography (Nissen et al., 2006).

Based on clinical trials, the National Cholesterol Education Program guidelines (NCEP), and the increasing focus on aggressively lowering LDL-cholesterol, the statins continue to play an important role in both the primary and secondary prevention of coronary heart disease, myocardial infarction, stroke and peripheral artery disease (Furberg, 1996).

Members

Fermentation-derived and synthetic

The statins are divided into two groups: fermentation-derived (naturally occurring) and synthetic. The synthetic ones include Atorvastatin, Cerivastatin, Fluvastatin Rosuvastatin and Pitavastatin. LDL-lowering potency varies between agents. Cerivastatin is the most potent, followed by (in order of decreasing potency), rosuvastatin, atorvastatin, simvastatin, lovastatin, pravastatin, and Fluvastatin (Ryan, 2015). The relative potency of pitavastatin has not yet been fully established (Shepherd et al., 2008). Some types of statins are naturally occurring such as Lovastatin, Mevastatin, and Simvastatin. They can be found in such foods as oyster mushrooms and red yeast rice (Liu et al., 2006). Randomized controlled trials found them to be effective, but the quality of the trials was low (Amarenco et al., 2006).

Comparative effectiveness

No large-scale comparison exists that examines the relative effectiveness of the various statins against one another for preventing hard cardiovascular outcomes, such as death or myocardial infarction (Amarenco et al., 2006).

An independent analysis has been done to compare atorvastatin, pravastatin and simvastatin, based on their effectiveness against placebos. It found that, at commonly prescribed doses, there are no statistically significant differences amongst statins in reducing cardiovascular morbidity and mortality (Amarenco et al., 2006). The comparative dose efficacy study of atorvastatin versus simvastatin (CURVES) study, which compared the efficacy of different doses of atorvastatin, simvastatin, pravastatin, lovastatin, and fluvastatin for reducing LDL and total cholesterol in patients with hypercholesterolemia, found that atorvastatin was more effective without increasing adverse events (Jones et al., 1998).

Statin equivalence

Statins differ in their ability to reduce cholesterol levels. Doses should be individualized according to patient characteristics such as goal of therapy and response (Jones et al., 1998). After initiation and/or dose changes, lipid levels should be analyzed within 1-3 months and dosage adjusted accordingly, then every 6-12 months afterwards (Dotani et al., 2000, Pan et al., 2004) (Table 1).

Safety

Adverse effects

Statins are generally perceived as well-tolerated. The most common adverse side effects are raised liver enzymes and muscle problems. In clinical trials, reported adverse effects are low; but "higher in studies of real-world use" and more varied. Statins increased the risk of an adverse effect by 39% compared to placebo (odds ratios 1.4); two-thirds of these were myalgia or raised liver enzymes with serious adverse effects like placebo (Abramson and Wright, 2007).

Some patients on statin therapy report myalgias, muscle cramps, or, less frequently, gastrointestinal or other symptoms. Liver enzyme derangements may also occur, typically in about 0.5%, are also seen at similar rates with placebo use and repeated enzyme testing, and generally return to normal either without discontinuance over time or after briefly discontinuing the drug (Abramson and Wright, 2007). Multiple other side-effects occur rarely; typically, also at similar rates with only placebo in the large statin safety/efficacy trials. Two randomized clinical trials found cognitive issues while two did not; recurrence upon reintroduction suggests that these are causally related to statins in some individuals. One Danish study suggested a relation between long term statin use and increased risk of nerve damage or polyneuropathy (Golomb and Evans, 2008), but suggested this side effect is "rare, but it does occur"; other researchers have pointed to studies of the effectiveness of statins in trials involving 50,000 people which have not shown nerve damage as a significant side effect (Silva et al., 2006).

More serious but rare reactions include myositis and myopathy, with the potential for rhabdomyolysis (the pathological breakdown of skeletal muscle) leading to acute renal failure. Coenzyme Q10 (ubiquinone) levels are decreased in statin use; Q10 supplements are sometimes used to treat statin-associated myopathy, though evidence of their effectiveness is currently lacking (Silva et al., 2006). A common variation in the *SLCO1B1* gene, which participates in the absorption of statins, has been shown to significantly increase the risk of myopathy

Table 1. Statin equivalence.

Statin equivalent dosages						
%LDL Reduction (approx.) (%)	**Atorvastatin (mg)**	**Fluvastatin (mg)**	**Lovastatin (mg)**	**Pravastatin (mg)**	**Rosuvastatin (mg)**	**Simvastatin (mg)**
20-Oct	-	20	10	10	-	5
20-30	-	40	20	20	-	10
30-40	10	80	40	40	5	20
40-45	20	-	80	80	10-May	40
46-50	40	-	-	-	20-Oct	80
50-55	80	-	-	-	20	-
56-60%	-	-	-	-	40 mg	-
Starting dose						
Starting dose	10–20	20	10-20	40	10 mg; 5 mg if hypothyroid, >65 yo, Asian;	20 mg
If higher LDL reduction goal	40 mg if >45%	40 mg if >25%	20 mg if >20%	-	20 mg if LDL >190	40 mg if >45%
Optimal timing	Anytime	Evening	With evening meals Anytime	Anytime	Anytime	Evening

Source: “http://en.wikipedia. Org/wiki/statin”

(Julie and steve 2002).

Graham et al. (2004) reviewed records of over 250,000 patients treated from 1998 to 2001 with the statin drugs atorvastatin, cerivastatin, fluvastatin, lovastatin, pravastatin, and simvastatin. The incidence of rhabdomyolyis was 0.44 per 10,000 patients treated with statins other than cerivastatin. However, the risk was over tenfold greater if cerivastatin was used, or if the standard statins (atorvastatin, fluvastatin, lovastatin, pravastatin, simvastatin) were combined with fibrate (fenofibrate or gemfibrozil) treatment. Cerivastatin was withdrawn by its manufacturer in 2001 (Teresa et al., 2006).

All commonly used statins show somewhat similar results, however the newer statins, characterized by longer pharmacological half-lives and more cellular specificity, have had a better ratio of efficacy to lower adverse effect rates. The risk of myopathy is lowest with pravastatin and fluvastatin probably because they are more hydrophillic and as a result have less muscle penetration. Lovastatin induces the expression of gene atrogin-1, which is believed to be responsible in promoting muscle fiber damage (Teresa et al., 2006).

Despite initial concerns that statins might increase the risk of cancer, various studies concluded later that statins have no influence on cancer risk (Teresa et al., 2006). Indeed, a 2005 trial showed that patients taking statins for over 5 years reduced their risk of colorectal cancer by 50%; this effect was not exhibited by fibrates. The trialists warn that the number needed to treat would approximate 5000, making statins unlikely tools for primary prevention. However, in a recent meta-analysis of 23 statin treatment arms with 309,506 person-years of follow-up, there was an inverse relationship between achieved LDL-cholesterol levels and rates of newly diagnosed cancer that the authors claim requires further investigation (Graham et al., 2004).

Drug interactions

Combining any statin with a fibrate, another category of lipid-lowering drugs increases the risks for rhabdomyolysis to almost 6.0 per 10,000 person-years. Most physicians have now abandoned routine monitoring of liver enzymes and creatine kinase, although they still consider this prudent in those on high-dose statins or in those on statin/fibrate combinations, and mandatory in the case of muscle cramps or of deterioration in renal function (Teresa et al., 2006).

Consumption of grapefruit or grapefruit juice inhibits the metabolism of statins. Furanocoumarins in grapefruit juice (that is, bergamottin and dihydroxybergamottin) inhibit the cytochrome P450 enzyme CYP3A4, which is involved in the metabolism of most statins (however it is a major inhibitor of only lovastatin, simvastatin and to a lesser degree atorvastatin) and some other medications (Graham et al., 2004). This increases the levels of the statin, increasing the risk of dose-related adverse effects (including myopathy/rhabdomyolysis). Consequently,

Table 2. Adherence observed during principal randomized controlled trials of statins for primary and secondary prevention of cardiovascular disease.

Trial	Author, year	Definition of adherence	Method of ascertainment	Mean lowering of serum cholesterol concentration (%)	Primary or secondary prevention	Mean age	Observation period (years)	Adherence at end of period (%)
AFCAS/ texCAS	JAMA, 1998	≥75%	Pill counts	19	Primary prevention	58	5.2	99
EXCEL	Shear et al. (1992)	≥75% medication taken	Self report	Not stated	Secondary prevention	54	4	99
CARE	Sacks et al. (1996)	Continuation of therapy	Not stated	20	Secondary prevention	59	Median 5	94
4-S	Conroy et al. (1998)	Continuation of therapy	Not stated	26	Secondary prevention	58	Median 5.4	90
Heart Protection Study	Farmer et al. (2003)	≥80% medication taken	Pill counts	17	Secondary prevention	64	Median 5	82
LIPID	The LIPID Study Group, 1998	Continuation of therapy	Not stated	18	Secondary prevention	62	6.1	81
WOSCOPS	Shepherd et al. (1995)	≥75%	Pill counts	20	Primary prevention	55	Mean 4.9	70

consumption of grapefruit juice is not recommended in patients undergoing therapy with most statins. An alternative, somewhat risky, approach is that some users take grapefruit juice to enhance the effect of lower (hence cheaper) doses of statins. This is not recommended as a result of the increased risk and potential for statin toxicity (Teresa et al., 2006).

MATERIALS AND METHODS

Search strategy

Searches for relevant research reports were conducted using Pubmed, Wiley interscience and EMBASE electronic data bases. The key words used for search were statins, HMG-COA reductase inhibitors, adherence, non-adherence, compliance and concordance. A manual search of the reference lists from retrieved paper was also performed to identify further relevant studies.

Inclusion criteria

Eligible for inclusion criteria in this analysis were randomized controlled trials, retrospective analysis of data from randomized controlled trials, and observational studies evaluating the association between adherence to statins therapy and its effect on cardiovascular diseases.

Data extraction

Parameters extracted from the studies included study design, number of patients, mean age of patients, mean study length, definition of adherence.

Definition of nonadherence

Adherence (synonymous with compliance and concordance) is the ‘extent to which patients follow the recommendations by their healthcare professional’. ‘Adherence is the product of a relationship that is built on respect, active participation, and partnership between patient and health professional, not coercion or manipulation, on the part of either’ (Marquez et al., 1998). Non-adherence is the inverse or reciprocal of adherence. Non-adherence can be subdivided into primary non-adherence (that is, the failure to initiate therapy) and secondary non-adherence (that is, the failure to continue therapy). Secondary non-adherence can further be categorized into failure to take the medication as directed (dose and frequency of regimen) and the premature discontinuation of the medication (Mahler et al., 1999). Most studies cited in this article have used a definition of adherence as a patient taking at least 80% of the prescribed doses, although some studies have used qualitative descriptions of adherence.

RESULTS

Study characteristics

Relevant research papers were identified from the literature search. From these papers studies which satisfied the inclusion criteria were identified and included in a meta-analysis. Table 2 display Adherence observed during principal randomized controlled trials of statins for primary and secondary prevention of cardiovascular

Table 3. Studies of statin adherence in the community setting.

Authors, year	Study design	Operational definition of adherence	Method of ascertainment	Primary or secondary prevention	Mean participant age	Observation period	Adherence at end of period (%)
Ho et al. (2006)	Cohort	Continuation of therapy	Structured telephone interview	Secondary prevention	65	6 months	87
Kotseva et al. (2009)	Cohort	≥80% medication availability	Pharmacy records	Secondary prevention	67	2.4 years	64
Bouchard et al. (2007)	Nested case–control	≥90% prescriptions filled	Data retrieved from healthcare database	Primary prevention	63	1 year	62
Law et al. (2003)	Retrospective cohort study	≥80% medication availability	Pharmacy records	Primary and secondary prevention	58	2 years	58
Bates et al. (2009)	Retrospective cohort study	300/365 minimum daily doses received	Health Authority database	Primary and secondary prevention	≥40	3 years	52
Vinker et al. (2008)	Retrospective cohort study	≥80% prescriptions filled	Pharmacy records	Secondary prevention	58	5 years	49
Benner et al. (2004)	Retrospective cohort study	Continuation of therapy	Pharmacy records	Primary and secondary prevention	60	3 years	21

disease. Adherence to statin therapy in clinical trials (Table 2) tends to be much higher than in every day practice (community settings) (Table 3).

Frequency of non-adherence

Non-adherence to statins is a surprisingly common problem. The exact rate of non-adherence is difficult to determine. However, clinical trial and post marketing data underscore the scale of the problem. In the West of Scotland Coronary Prevention Study (WOSCOPS), 6595 men with moderate hypercholesterolemia were randomized to pravastatin 40 mg a day or placebo. After a mean follow-up of 4.9 years there was a highly statistically significant reduction in coronary events of 31% (Bates et al., 2009). The authors correctly used an intention-to-treat analysis to show this benefit. However, the magnitude of benefit might have been higher, for at the first follow-up visit only approximately 85% of patients were adherent to treatment (WOSCOPS, 1997). A Canadian study of primary prevention cases reported high discontinuation rates for statin usage of 35 and 65% at 6 months and 3 years, respectively (Vinker et al., 2008). Retrospective data from a UK electronic database of 6462 diabetic patient records indicated that adherence to statin therapy was only 87% at 3 months, falling to 61% at 6 months and thereafter remaining stable over a follow-up period of 13 years. Only 50% of patients were fully adherent to the prescribed regimen, with the remainder having some degree of non-adherence (Benner et al., 2002). In an Israeli study of 47,680 Health Management Organisation (HMO) patients there was a high rate of discontinuation at 12 months, with only 61% of patients adherent with 80% of their statin therapy; at 6 years of follow-up this had fallen to just 10% (Vinker et al., 2008). Elderly patients are a group who may be at particular risk of statin non-adherence. There are several reasons for this. These include polypharmacy, susceptibility to drug side effects, cognitive dysfunction, physical disability (poor eyesight, arthritis) and depression. In a retrospective cohort study of 34,501 patients over the age of 65 years enrolled in a Medicaid program, adherence to statin therapy was 79% at 3 months, falling to only 42% at 10 years (Benner et al., 2002). Significantly, after 5 years, only 25% of patients were adherent to prescribed statin therapy at least 80% of the time. Contrary to expectations, adherence to statins is also a significant problem in patients who have suffered a primary coronary event. Ho et al. (2006) retrospectively evaluated 13,596 patients with previous symptomatic myocardial infarction or coronary revascularization. Non-adherence, defined as a patient taking less than 80% of the prescribed medication, was assessed at 180 days for statins, beta blockers and ACE inhibitors: the rate of non-adherence was 26, 28 and 21% respectively. The Global Reduction in Acute Coronary Events (GRACE) investigators followed up acute coronary syndrome patients 6 months after discharge and reported lower rates of non-adherence than other

Table 4. Reasons for medication non-adherence**.**

Categories of Nonadherence	Examples
Health system (Hermans et al., 2010)	Poor quality of provider-patient relationship; poor communication; lack of access to healthcare; lack of continuity of care
Condition (Jackeviticus et al., 2008)	Asymptomatic chronic disease (lack of physical cues); mental health disorders (e.g., depression)
Patient factors (Ho et al., 2006)	Physical impairments (e.g., vision problems or impaired dexterity); cognitive impairment; psychological/behavioral; younger age; nonwhite race
Therapy (Thiebaud et al., 2005)	Complexity of regimen; side effects
Socioeconomic (Jackeviticus et al., 2008, Pletcher et al., 2009, Stranberg et al., 1994, LIPID, 1998)	Low literacy; higher medication costs; poor social support

studies (statins 13%, beta blockers 12%, ACE inhibitors 20%) (Ho et al., 2006). In a separate study, patients who were reviewed within 3 months of initiation of statin therapy were 45% more likely to be adherent than those who were not reviewed (Benner et al., 2004). Stroke patients have also been found to have a relatively high discontinuation rate for statins of 39% at 12 months compared with 17% for antiplatelet agents and 10% for ACE inhibitors. The discontinuation period for statin therapy varies over time. A retrospective cohort study of 239,911 patients who failed to refill a prescription for a statin found that 54% of patients had a period of discontinuation that lasted at least 90 days, with 48% of these patients resuming therapy within1 year and 60% within 2 years (Colivicchi et al., 2007).

Risk factors for statin non-adherence

There are several causes of non-adherence; while some are obvious, some are more subtle and elusive. Identifying the causes of non-adherence is essential for managing patients. The factors that can influence non-adherence to statin therapy are presented in Table 4. In the WOSCoPS study, the predictors of non-adherence to pravastatin were smoking, younger age and the absence of hypertension (WOSCOPS, 1997). In the study by Ho et al. (2006) younger patients, those with depression and those with chronic obstructive pulmonary disease were more likely to be non-adherent to all classes of cardiovascular medications (including statins); there was also a nonsignificant trend towards increased non-adherence in those with dementia (Colivicchi et al., 2007). Whilst the young may be non-adherent owing to lack of concern regarding their health, the elderly are also at risk of non-adherence. In a study from the USA by Benner et al., older age, lower income and depression were predictors of non-adherence to statins. Furthermore, the presence of cardiovascular disease also predicted adherence; patients with a recent myocardial infarction were more likely to be adherent than patients whose prescription was for primary prevention. Jackevicius et al. (2008) reported similar findings in a Canadian study. In this study the significant predictors of non-adherence with statins were younger age, low income status, predischarge counselling, and drug initiation by a cardiologist; diabetics also tended to be non-adherent. A separate study from the USA also suggested that poor literacy was a predictor of statin non-adherence (Pletcher et al., 2009). In a UK study, the predictors of non-adherence among diabetic patients included previous cardiovascular disease and older age (Amarenco et al., 2006). In contrast to the USA data, social disadvantage was not found to predict statin non-adherence in this group of diabetics. Those who had a new event on statin therapy were more likely to become non-adherent, suggestive possibly of disillusionment with the therapy (Vinker et al., 2008). A recently reported study of 6276 Belgian subjects found in a multivariate model that statin adherence as well as a positive patient outlook was significant factors in achieving LDL-C goals. The cost of medications remains a controversial cause of non-adherence. The largest series to evaluate the cost of medicines and adherence found that in 132 studies an increase in cost sharing was associated ‘with lower rates of drug treatment, worse adherence among existing users, and more frequent discontinuation of therapy’ (Hermans et al.,2010). The authors found that for a 10% increase in cost sharing, medication use falls by 2- 6%. Data from a separate HMO study indicated that for a US $10 increase in monthly copayments, there is a 1.8% reduction in statin adherence for those beginning therapy, and a 3% reduction in those continuing therapy (Goldman et al., 2006). Patients’ non-adherent to statin therapy had more hospital visits and higher health care costs, although the cost difference between the groups did not

reach statistical significance. A recent study by Doshi et al. suggested that, for US Veterans Affairs patents, a rise in the copayment from US $2 to $7 was associated with a 7% fall in adherence rates, and a 12% increase in discontinuation rates lasting 90 days or more (Doshi et al., 2009). There are other factors that may lead to statin non-adherence.

In an HMO study, Sung et al. (1998) found that in women, multiple doses of lipid-lowering therapy and overall good health were predictors of medication nonadherence, suggesting that polypharmacy in those without cardiovascular disease may fail owing to patients not realizing the need for therapy. Dormuth et al. (2009) recently reported that those adherent to statins were more likely to undergo screening tests, and were less likely to be involved in accidents, suggesting that patients who are adherent may be more health conscious and more risk averse. Switching statins has also been shown to increase the likelihood of non-adherence (Thiebaud et al., 2005). A study of patients who switched from one statin to another found that 'switchers' were 19% less adherent to their statin than 'non-switchers'. Cost was not considered to be a reason for switching or nonadherence (cost difference between groups US $1.33/month). The reason for switching statins was not elucidated and may have been the same reason for discontinuation (e.g., side effects, lack of perceived benefit, patient perception) (Thiebaud et al., 2005) (Table 4).

Statin adverse effects and non-adherence

The side effects of statins experienced by patients are also an important cause of non-adherence to medication. In this context, the best evidence of statin discontinuation rates was reported in the Prediction of Muscular Risk in Observational Conditions (PRIMO) study (Bates et al., 2009). In this observational study, 7,394 French patients with dyslipidemia were studied to determine the rates and predictors of muscle side effects from statins. Overall 19.8% of subjects discontinued their statin therapy, whilst 16.7% required a dose reduction. Most of the muscle side effects occurred within the first 3 months, like the findings of Colivicchi et al. (2007). Predictors of discontinuation included a personal history of muscle pain on lipid-lowering therapy, unexplained cramps, a raised creatinine kinase, a family history of muscle symptoms with or without lipid-lowering therapy, and hypothyroidism. The more potent longer-acting statins (atorvastatin and simvastatin) had higher rates of discontinuation than the less potent pravastatin and fluvastatin XL. A recent study found that a small percentage of patients were unable to tolerate high doses of simvastatin because of a genetic polymorphism in an anion transporter protein (SLCO1B1) responsible for the hepatic uptake of statins; this impairment presumably led to higher systemic levels of simvastatin and muscle toxicity (SEARCH, 2008). Interestingly, those patients with the genetic polymorphism were able to tolerate lower doses of simvastatin. Finally, no reason may be identified for non-adherence other than disillusionment with 'too many pills. In the Colivicchio et al. stroke study, 72% of patients and their medical practitioners could not identify a medical reason for discontinuing statin therapy other than 'too many pills', with the other 28% discontinued for mild side effects [Colivicchi et al. (2007).

Elevated alanine transaminase or aspartate transaminase levels were more common in patients treated with atorvastatin 80 mg compared with placebo (3.2 versus 0.9%), but specific musculoskeletal or liver abnormalities remained rare (≤ 3%). A similar study involving a pooled analysis of 3145 patients aged ≥ 75 years who received placebo or atorvastatin 10-80 mg in 45 completed randomized trials demonstrated that the rate of adverse events did not increase with higher doses of the drug and was similar in atorvastatin-treated patients and those who received placebo. Thus, currently available evidence suggests that the safety of statin therapy remains similar in older and younger patients, even with intensive lipid lowering (Thiebaud et al., 2005) (Table 5).

Impacts of statin non-adherence on cardiac morbidity and mortality

Health consequences of statin non-adherence

Non-adherence to statins is associated with significant health risks. In the WOSCoPS study adherence was also found to be an independent predictor of adverse cardiovascular outcomes. In those who were adherent to pravastatin less than 75% of the time, the event rates for coronary death or nonfatal myocardial infarction were like placebo, whilst those who were adherent to pravastatin 75% or more of the time had significant reductions in these end points (WOSCoPS, 1997). In a separate nested case-control study of 20,543 primary prevention patients, it was found that non-adherence in the first year of therapy had little impact on the prevalence of nonfatal myocardial infarction; however, in those with adherence rates of less than 90% after 1 year, there was an excess risk of nonfatal myocardial infarction. Similar findings were recently reported in large database analysis, only 55% of patients were adherent to at least 80% of their statin doses. Those exhibiting the highest levels of adherence (> 80%) had a 26% reduction in stroke compared with those who exhibited the lowest rates of adherence (< 20% adherence). Following a coronary event, non-adherence to statins is also associated with excess risk of a recurrent clinical event (Bouchard et al., 2007). In the study by Ho et al. (2006), patients with

Table 5. Adverse events reported in trials comparing different intensities of statin therapy among patients with coronary artery disease.

Variable	PROVE IT-TIMI 22		A TO Z		TNT		IDEAL		REVERSAL		SAGE	
Event	Low n=2063	High n=2099	Low n=2230	High n=2263	Low n=5006	High n=4995	Low n=4449	High n=4439	Low n=327	High n=327	Low n=445	**High n=446**
Adverse event leading to drug discontinuation, no (%) of patients	56(2.7)	69(3.3)	191(8.6)	216(9.5)	265(5.3)	360(7.2)	186(4.2)	426(9.6)	22(6.7)	21(6.4)	46(10.3)	**48(10.8)**
Aminotransferase level elevations, no. (%) of patients	23(1.1)	69(3.3)	8(0.4)	19(0.9)	9(0.2)	60(1.2)	5(0.1)	43(1.0)	5(1.6)	7(2.3)	1(0.2)	**19(4.3)**
Myalgia,no(%)of patients	56(2.7)	69(3.3)	35(1.6)	50(2.2)	234(4.7)	241(4.8)	51(1.1)	97(2.2)	12(3.4)	9(2.8)	12(2.7)	**14(3.1)**
Myopathy (myalgia with creatnine elevation),no.(%) of patients	NR	NR	1(0.04)	9(0.4)	NR	NR	11(0.3)	6(0.1)	NR	NR	NR	**NR**
Rhadomyolysis, no.(%) of patients	**0**	**0**	**0**	**3(0.1)**	**3(0.06)**	**2(0.04)**	**3(0.07)**	**2(0.05)**	**0**	**0**	**0**	**0**

NOTE: PROVE IT_TIMI 22= Pravastatin or Atorvastatin Evaluation and Infection Therapy - Thrombolysis in Myocardial Infarction 22, A-to-Z= Aggrastat to Zocor, TNT= Treating new targets, IDEAL= The Incremental Decrease in Events through Aggressive Lipid Lowering, REVERSAl=Reversal of atherosclerosis with aggressive lipid lowering therapy, SAGE=study assessing goals in elderly, NR=not reported.

lower rates of adherence had higher rates of all-cause mortality (non-adherence with statins OR 1.82; 95% CI 1.61- 2.06), cardiovascular hospitalizations (non-adherence with statins OR 1.35; 95% CI 1.21-1.51), and revascularizations (non-adherence with statins OR 1.11; 95% CI 1.01- 1.22) (Winland et al., 2000). Jackevicus et al. (2008) also reported that in postmyocardial infarction patients, those who did not take any of their discharge medications had an 80% increase in mortality at 12 months compared with fully compliant patients; those who were partially compliant with their medications had a 44% increase in mortality. The IDEAL investigators (Holme et al., 2009) recently reported that the benefit of high-dose atorvastatin versus simvastatin in postmyocardial infarction patients may have been underestimated owing to an excess of non-adherence in the atorvastatin group. Adjusting for adherence, the benefit in the atorvastatin group increased to 15% from11%, reaching statistical significance. Moreover, those adherents to either statin had significant reductions in cardiovascular and non-cardiovascular end points, suggesting that those who were adherent gained significant health benefit, and may have been more health conscious. In Kulikl et al. (2008), study of patients discharged from the hospital after the coronary artery bypass graft (CABG) surgery, demonstrated that statin therapy initiated with one month of CABG discharge is independently associated with a lower risk of all-cause mortality and major adverse cardiovascular events (MACE) even after adjustment for patient, hospital, and surgeon characteristics. These results support existing practice guidelines and confirm that in the absence of serious contraindications, essentially all patients should be prescribed long term statin therapy after CABG. Several studies have demonstrated that preoperative statin therapy improves clinical out comes after CABG, including a reduced risk of death, myocardial infarction, and arrhythmias in the first 60 days after surgery (Dotani et al., 2008; Pan et al., 2004). Statin therapy initiated with in the first few months after hospital discharge independently reduces all cause mortality and MACE after CABG. Statin therapy provides high levels of protection for all cause mortality and non-hemorrhagic strokes (Hey-Hadavi et al., 2007). The stroke prevention by Aggressive Reduction in cholesterol levels (SPARCL) trial demonstrated that high- dose atorvastatin reduced the risk of subsequent stroke in patients with transient ischemic attack (TIA) or stroke and the absence of coronary artery disease patients in the SPARCL study randomized to high dose atorvastatin had significantly lower rates of stroke (RR 0.85, 95% CI, 0.73 -0.99), stroke or TIA (RR 0.77, 95%CI 0.67-0.88), and coronary events (0.65, 95% CI,

0.49-1.87) than placebo treated patients (Amarenco et al., 2006). A spate of recent clinical trials using statins to lower low – density lipoprotein cholesterol (LDL-C) have demonstrated beyond reasonable doubt that coronary events both morbid and mortal, can be prevented (WHO, 2009). The mean reduction in total cholesterol, LDL-C, and triglyceride levels was -20, -28, and -13% respectively, and HDL-C was increased by an average of 5% among the 5 trails included in meta-analysis (Bates et al., 2009). A meta-analysis from 5 clinical trials demonstrated that a significant reduction in the odds of major coronary events and coronary deaths ($p< 0.001$) was observed among the participants allocated to active treatment. The reduction in coronary events was 31% (95% CI), 26-36% and the reduction in fatal coronary disease was 29% (95% CI, 20-36%) (Kulik et al., 2008) (Tables 6 and 7).

Economic costs of statin non-adherence

The direct medical costs and indirect costs due to lost productivity from coronary heart diseases (CHD) in the united states are estimated to exceed $142 billion in 2006 (Gibson et al., 2006). Recent evidence has demonstrated that patient financial incentives (i.e. co-payments, coinsurance) also affect statin adherence (Strandberg et al., 39). As statin cost sharing levels increase, adherence to statins falls. Patient cost- sharing also has been demonstrated to be financial barrier to the utilization of other classes of medication that are typically used to treat chronic disease (Gibson et al., 2006; Goldman et al., 2006).

Peterson and McGhan have suggested that for patients who were ‘almost 100% compliant with statins versus those with initial non-adherence the cost per life year saved (LYS) was US $4,500 to > $250,000 depending on patient age, presence or absence of risk factors and whether the statin is being used for primary or secondary prevention’. An intervention study suggested that the cost per patient to improve statin adherence for 1 year was approximately US $154-279 (Peterson and McGhan, 2001). A separate study showed that the lower drug costs of non-adherence with lipid lowering therapy were far outweighed by the excess costs of increased cardiovascular disease (Gibson et al., 2006). A separate study modeled the effect of increasing the cost of copayments for statins in those at low risk of cardiovascular disease and reducing or abolishing the copayments for statins for those at high risk of cardiovascular disease (Goldman et al., 2006). The analysis concluded that such a change would increase adherence, and in such groups of patients would lead to 79,837 fewer hospitalizations and 31,411 fewer presentations to emergency departments, with projected savings of US $1 billion annually. Finally, a recent study by Pletcher et al. (2009) concluded that full implementation of the ATP III guidelines would require 11 million Americans to initiate or intensify statin therapy; in doing so 20,000 myocardial infarctions and 10,000 deaths would be avoided at a cost of US $42,000/QALY. Though these costs were dependent on the cost of statin therapy, at lower medication prices the economic benefits became significantly more cost effective (Goldman et al., 2006).

Health psychology perspective

In addition to the effects of depression, several other psychological issues may bear on a patient’s adherence behavior. Patient adherence is now viewed as the consequence of a complex interaction that involves numerous patient variables, effectiveness of physician communication, and the quality of the doctor–patient relationship during the medical consultation. Patient-centered care is more than just interviews with empathy; it requires the use of skills and tools that maximize a health care partnership and shared management of a chronic condition (Hermans et al., 2010). The psychological contributors to patient adherence behaviors are highly interactive and can be considered from the perspective of the patient, the doctor’s perspective and the doctor–patient relationship. From the patient’s perspective, issues such as satisfaction, health beliefs, and preferences for health care, can all influence intentional non-adherence. A patient’s view on treatment, as measured by the Beliefs about Medicines Questionnaire (BMQ), can determine their adherence behaviour and provides valuable information for a doctor attempting to address patient concerns (Hermans et al., 2010). One study further proposes that social cognitive theory outlines a core set of determinants, one of which is perceived self-efficacy, that influence the adherence behaviour of an individual patient. Adherence self-efficacy is the belief in one’s ability to organize and perform behaviors that are necessary to achieve one’s health goals (Thiebaud et al., 2005). Several health psychology studies have found that adherence self-efficacy is associated with adherence to therapy and better use of health-related coping strategies (Molloy et al., 2008). Additionally, personality and cognitive function research into health behaviors has provided some evidence to support the possibility that conscientiousness and IQ can predict adherence behaviour to cholesterol-lowering treatment (Stilley et al., 2004). Furthermore, social support may also be a factor in patience adherence (Molloy et al., 2008). The recently developed Adherence Estimator measures three proximal patient beliefs associated with intentional non-adherence to new medications. Preliminary psychometric evidence

Table 6. Overall risk reductions of major coronary events and Deaths from coronary diseases, cardiovascular, and all causes trials.

Variable	No of events		Relative risk reduction,% (95% CI)	Absolute risk reduction 1000 (95%)	P value
	Placebo	Statin			
Major coronary events	2042	1490	31 (26-36)	36(29-43)	<0.001
4s, (Strandberg et al.,1994)	622	431	38(29-46)	86(61-111)	<0.001
WOSCops, 1997	248	174	31(16-44)	23(11-34)	<0.001
CARE (Klein et al., 2006)	274	212	25(10-38)	30(10-49)	0.002
AFCAPS/TexCAPS (Downs et al., 1998)	183	116	38(21-50)	20(10-30)	<0.001
LIPID, 1998	715	557	25(16-34)	35(21-50)	<0.001
Coronary events	748	543	29 (20-36)	13(9-18)	<0.001
4s	189	111	43 (38-55)	35(20-50)	<0.001
WOSCops	52	38	27 (-10-52)	4(1-10)	0.13
CARE	119	96	20 (-5-39)	11(-2-25)	0.11
AFCAPS/TexCAPS	15	11	27 (-58-66)	1(-2-4)	0.44
LIPID	373	287	25 (12-36)	19(8-30)	<0.001
Cardiovascular deaths	868	646	27(19-34)	14(10-19)	<0.001
4s ,	207	136	36(20-49)	32(16-48)	<0.001
WOSCops	73	50	32 (3-52)	7(0-14)	0.03
CARE	130	112	15 (-11-34)	9(-5-23)	0.23
AFCAPS/TexCAPS	25	17	32(-25 -63)	2(-1-6)	0.22
LIPID	433	331	25(14-36)	23(11-34)	<0.001
Non cardiovascular deaths	429	400	7(-7-19)	2(-2-6)	0.29
4s ,	49	46	6(-41-38)	1(-7-10)	0.760
WOSCops	62	56	10 (-29-38)	2(-5-8)	0.57
CARE	66	68	-3 (-45-27)	-1 (-12-10)	0.87
AFCAPS/TexCAPS	52	63	-21(-76-16)	-3(-10-3)	0.30
LIPID	200	167	17(-2-33)	7(-1-160	0.08
All cause deaths	1297	1046	21(14-28)	16(11-22)	<0.001
4S	256	182	31(16-44)	33(16-51)	<0.001
WOSCoPs	135	106	22(0-40)	9(0-18)	0.05
CARE	196	180	9(-12-26)	8(-10-25)	0.38
AFCAPS/texCAPS	77	80	-4(-43-24)	-1(-8-6)	0.81
LIPID	633	498	24(14-33)	30(17-44)	<0.001

indicates that the best predictors of adherence behaviour are the patient's perceived need for medications, their perceived concerns about medications and their perceived affordability of medications (Thiebaud et al., 2005). From the physician's perspective, communication is an important component of patient care (Bates et al., 2009). Evidence suggests that physicians poorly predict patient adherence. Indeed, unintentional non-adherence may reflect an inadequate understanding on the part of the patient, of the condition, treatment, or prevention regimen prescribed and may be averted with enhanced communication by the physician. Improving provider–patient communication can have beneficial effects on health outcomes (Thiebaud et al., 2005) and it is important that physicians attend to both the cognitive and emotional care of their patients if optimal treatment adherence is to be achieved (Fuertes et al., 2007). This emotional aspect is important and much of the literature on health management suggests that service providers with high emotional intelligence receive higher patient satisfaction scores (Weng, 2008). The value of emotional intelligence as a useful concept in patient-centered care is still being ascertained, but it may provide an explanation of why some practitioners are more successful in achieving higher rates of adherence to therapy in their patients.

The final contribution to the triad that influences patient adherence behaviour is the relationship between the patient and the physician. The quality of this interaction, referred to by Fuertes et al. (2007) as the physician–patient working alliance, has been recently studied using the Working Alliance Inventory (WAI). The results of this

Table 7. Overall risk reduction for major coronary events by sex and age: results from 5 randomized controlled.

Variable	No. of events		Relative risk reduction,% (95% CI)	Absolute risk reduction 1000 (95%)	P value
	Placebo	Statin			
Sex					**<0.001**
Women	247	180	29(13-42)	33(13-52)	0.01
4S (Strandberg et al., 1994)	91	60	37(10-56)	69(17-122)	0.04
CARE(Klein et al., 2006)	39	23	43(3-66)	54(4-104)	0.17
AFCAPS/TexCAPS (Downs et al., 1998)	13	7	46(-31-78)	12(-5-29)	0.30
LIPID, 1998	104	90	15(-15-37)	18(-16-51)	<0.001
Men	1795	1320	31(26-35)	37(29-44)	<0.001
4S	531	371	38(28-47)	90(62-118)	<0.001
CARE	235	189	22(5-36)	26(5-47)	0.02
AFCAPS/TexCAPS	170	109	37(20-50)	22(10-33)	<0.001
LIPID	611	467	27(17-36)	39(23-55)	<0.001
Age					**<0.001**
≥ 65y	740	539	32(23-39)	44(30-58)	<0.001
4S	168	122	38(19-53)	98(43-154)	<0.001
CARE	111	69	42(20-57)	65(27-103)	0.01
AFCAPS/TexCAPS	112	78	32(23-39)	44(30-58)	0.001
LIPID	349	270	25(11-37)	42(17-67)	<0.001
< 65 y	1302	951	31(24-36)	32(24-40)	<0.001
4S	454	309	38(27-47)	83(55-110)	<0.001
CARE	163	143	14(-9-32)	14(-8-37)	0.21
AFCAPS/TexCAPS	71	38	47(22-63)	19(8-31)	0.001
LIPID	366	287	25(12-37)	31(13-48)	<0.001

study provide preliminary evidence of a correlation between a patient's rating of this alliance and their adherence behaviour and suggest that these interpersonal dynamics seem to have 'real value' and are likely to make a difference in medical care (Fuertes et al., 2007).

Management of statin non-adherence

Improving statin adherence

Improving statin adherence is likely to lead to a reduction in cardiovascular end points and health care costs. Osterberg and Blacshke (2005) described four methods that may improve adherence. These include patient education and support, improved dosing schedules, increased availability of medical staff and improved communication between physicians and patients. Patient education is essential. It is well acknowledged that the level of awareness in the community as to what the desirable levels of cholesterol are is poor; in Northern Europe only approximately 1/2 of respondents could identify the normal level of plasma cholesterol. Patient awareness of cholesterol levels varies considerably; those with higher educational levels and coronary artery disease are more likely to have undergone cholesterol testing and to know their level (Erhardt and Hobbs, 2002). Moreover, many patients with hyper-cholesterolemia will be asymptomatic and as such may not perceive the need to take medications. In an intervention in Spain with tutorials and postal follow-up questionnaires, adherence was 32.7% (81 vs 61%) higher in the intervention group than those not receiving the intervention (Cannon et al., 2004). A recent study from the UK found that patients given a brief counselling session at statin initiation followed by mailed education were 10% more likely to fill a statin prescription at 4 months than patients who followed usual care (Sprafka et al., 1989). Despite these positive studies, a recent study of 8104 statin-treated patients who were randomized to either usual care or an adherence-enhancing program for 12 months reported no difference in the achievement of target LDL-C between the two groups. These divergent results highlight the complex nature of achieving optimal compliance. Multiple authors have also suggested using simple, nontechnical and jargon-free explanations to communicate the benefits of therapy (Marquez et al., 1998). Moreover, it is essential to understand a patient's anxieties about therapy and to support their efforts to

improve adherence. This can be achieved by improving the patient–physician working alliance and by focusing on the psychodynamics of the interaction between patient variables and physician's cognitive and emotional skills (Mahler et al., 1999).

In a clinic-based study from North Carolina, intervening with a multidisciplinary team in patients with abnormal lipid profiles led to significant improvements in medication adherence, plasma cholesterol levels and attainment of LDL-C goals compared with no intervention (Thomas et al., 2003). Similar improvements in health outcomes including medication adherence, risk factor modifications and dietary improvements were seen in a large intervention study in Europe in patients with established vascular disease (Fulmer et al., 1999).

Statins are prescribed once daily, but potency varies. Rosuvastatin and atorvastatin have the longest plasma half-lifes; this potentially allows the medication to be taken with other morning medications, rather than at night as simvastatin and pravastatin must be. Combination therapy of a statin plus another medication in a single tablet (e.g., Simcor, simvastatin/ niacin combination; or a statin and antihypertensive medication, e.g., Caduet, atorvastatin/amlodipine) has been introduced and may improve adherence. Finally, memory aids for patients such as dosette boxes and alarms may also prove useful (Friedman et al., 1996). Prescribing a statin in hospital has been shown significantly to improve adherence and reduce mortality. In a study of 600 patients with angiographically proven coronary artery disease, those given inpatient statin therapy had significantly higher adherence (77 vs 40%; $p < 0.0001$) and lower mortality (5.7 vs11.7%; $p = 0.05$) at follow-up than those prescribed statins in primary care (Fonarow et al., 1997). The GRACE investigators also reported that there was a significantly higher likelihood of patients taking their aspirin if prescribed by a cardiologist (Ho et al., 2006).A structured in-hospital prescribing program such as the Cardiovascular Hospitalization Atherosclerosis Management Program (CHAMP) has been shown to improve the implementation of evidence-based risk-reduction strategies as well as improving long-term medication adherence and reducing morbidity (Muhlestein et al., 2001). As indicated earlier, the presence or absence of cardiovascular disease is an important determinant of statin adherence. Some practitioners have advocated the use of imaging to improve medication adherence in those without symptomatic cardiovascular disease. In a study of 505 patients followed for a mean of 3.6 years, Kalia et al. (2006) used coronary computerized tomography angiography and calcium score to determine the presence or absence of coronary disease. In those with a low coronary calcium score (0- 99) adherence rates were 44- 63%, whilst in those with high scores (> 400) adherence rates reached 90%. This approach is invasive, costly and exposes the patient to ionizing radiation, and as such has limited use.

However, it does suggest that other imaging modalities costly and exposes the patient to ionizing radiation, and as such has limited use.(e.g., carotid ultrasound for intima-medial thickness, plaques or stenosis) may be able to achieve similar results. Medical staff attitudes and availability are also important in managing patients with poor adherence to statins. The institution of evidence-based practice at the time of a cardiovascular event in hospital also increases adherence. Patients who default on appointments are also likely to be non-adherent to medication and are a group who would benefit from targeted education and support. Medical practitioners also need to recognize medication compliance as a major clinical problem. Several studies have shown that 40-66% of practitioners may not routinely ask patients about medication compliance; appropriate education of practitioners may improve this gap (Wilson et al., 2007; Allen et al., 2002). Physicians should consider routine screening for non-adherence in their clinical practice, using for example the Adherence Estimator for patients placed on new treatments, to target patients at risk of non-adherence. For reliable estimates of non-adherence and to reduce the effect of social desirability bias, patients should self-complete this predictive tool rather than have it directly administered in an interview format by a health care provider (Osterberg and Blaschke, 2005). Improved interprofessional communication involving the physicians, nurses and other allied health staff, and patients is also essential. The use of a qualified nurse who is adequately resourced has been shown to be cost-efficacious, especially for smoking cessation. A prospective randomized intervention study in 2002 reported that the use of nurse practitioners following myocardial infarction resulted in a greater number of patients achieving the ATP III target LDL level than those randomized to usual care (Wilson et al., 2007). The use of advanced practice nurses for follow-up rather than physicians at the Cleveland Clinic has resulted in a reduction in LDL-C of approximately 0.9 mmol/L from baseline, as well as being positively received by patients (>83% of responses were positive) (Benner et al., 2004). The use of a dedicated pharmacy program may also achieve significant improvements in medication adherence and desirable reductions in LDL-C. Two hundred patients taking at least four chronic medications were enrolled in a 6-month interventional study, followed by half the patients being randomized to continued intervention or usual care. The intervention included medication education, regular pharmacist follows up and the dispensing of time-labeled medication packs. Following the initial intervention, adherence to lipid-lowering therapy rose from 61 to 97% with a fall in LDL-C of 9.5%. Following the randomization phase, those in the intervention group maintained high levels of adherence (96%), whilst in those receiving usual care adherence fell

Table 8. Significant pharmacological interactions with statins that may cause clinical myopathy and lead to non-adherence.

	Statin - cytochrome (Cyp) P450 metabolic enzyme				
	Simvastatin	**Atorvastatin**	**Fluvastatin**	**Rosuvastatin**	**Pravastatin**
Interacting medication	**Cyp 3A4**	**Cyp 3A4**	**Cyp 2C9**	**Cyp 2C9 (min)**	**Non-Cyp**
			Cyp 2C		**metabolism**
Cyclosporine A	+	+	-	+	+
Azole antifungals	+	+	-	-	-
HIV protease inhibitors	+	+	-	-	-
Macrolide antibiotics	+	+	-	-	-
Non-dihydropyridine calcium channel antagonists	-	-	-	-	-
Amiodarone	-	+	-	-	-
Antidepressants	+	+	-	-	-
Gemfibrozil	+	+	-	+	+

Source: Modified from Bates et al. (2009).

to 69% (Bellosta et al., 2004).

Therapeutic options for the statin-intolerant patients

Once a patient has discontinued statin therapy owing to an adverse effect, resuming therapy is important as there is substantial health benefit to be gained. In all patients with statin intolerance there must be a careful search for potential interactions (Table 8) (Bellosta et al., 2004), including interactions with other lipid-lowering therapies such as gemfibrozil, as well as with antibiotics (especially macrolides), immunosuppressive agents (especially cyclosporine A and tacrolimus) and protease inhibitors. Choosing an agent that is metabolized by a different cytochrome P450 isoenzyme than the statin in question can effectively guide therapy. Medical conditions that predispose to statin intolerance include excessive alcohol consumption, hypothyroidism, malnutrition and renal and hepatic dysfunction. Correction of these medical problems or dose reduction may improve statin tolerability. Asian patients can be prone to myopathy with conventional doses of statins and should always be initiated at the lowest prescriptible dose (Bellosta et al., 2004); this is especially important with rosuvastatin, which should be prescribed at an initial dose of 5 mg daily (Schachter, 2005). In those patients in whom intolerance is the reason for non-adherence, a comprehensive multi-disciplinary plan should be implemented to manage this intolerance. Initially an alternative statin should be tried. This may include substitution of one statin for another or nonconventional dosing regimens. Substituting one statin for another may be effective owing to differences in physiochemical and pharmacodynamic properties. Longer-acting statins such as simvastatin and atorvastatin are lipophilic and have active metabolites (Stein et al., 2008). Rosuvastatin has a long plasma half-life, but minimal active metabolites. These statins and their respective metabolites may accumulate in muscle and brain, leading to toxicity. Substitution of these statins with a statin undergoing extensive first pass metabolism, such as fluvastatin, or with a statin not dependent on cytochrome p450 metabolism, such as pravastatin, or a less lipid-soluble statin (such as pravastatin and rosuvastatin), may be effective in reducing toxicity (Bellosta et al., 2004). Should this be ineffective, then an alternative regimen can be used; several strategies have been reported and should be considered. A regimen of ezetimibe or fluvastatin XL or a combination of fluvastatin XL and ezetimibe therapy was trialled in 199 patients who had previously been statin intolerant due to muscle toxicity. After a period of 12 weeks, only 10 patients discontinued therapy due to muscle toxicity; each of the therapeutic options was equally well tolerated. In each of the groups there were significant improvements in plasma cholesterol and apolipoprotein B concentrations. Significantly, 80% of the combination therapy group reached their NCEP (National Cholesterol Eduction Program) cholesterol target levels. In a retrospective analysis, another group reported that alternate day therapy with rosuvastatin (mean dose 5.6 mg) was tolerated by 73% of patients previously intolerant to statins due to muscle toxicity (Ruisinger et al., 2009). A reduction in LDL-C of 35% was observed. Similar findings were recently reported from a retrospective analysis of 50 patients previously intolerant of statins due to muscle toxicity; these patients were able to tolerate a mean dose of 10 ± 4 mg a week of rosuvastatin. Finally, a cyclical regimen of dosing followed by a drug holiday may be effective in reducing symptoms. It has been suggested that Vitamin D deficiency increases the risk of statin mytoxicity, but this notion has not been tested in a clinical trial (Young et al., 2007). Some practitioners advocate the use of coenzyme Q10 (CoQ10) in patients with statin

myopathy. The evidence at present is contradictory. In a small study of patients with statin myopathy randomized to CoQ10 or vitamin E there was an improvement in muscle symptoms in those treated with CoQ10, but not vitamin E (Ahmed et al., 2009). A divergent result was reported by Young et al. (2007); in this study patients were either pretreated with CoQ10 or a placebo and then had an uptitration of simvastatin from 10 to 40 mg over 12 weeks. At the end of the study, despite a significant rise in serum CoQ10 concentrations, there was no difference in muscle symptoms or in the dose of simvastatin tolerated between the two groups. In patients who are intolerant of statin therapy the switch to another class of medication may be required; the options are ezetimibe, a fibrate, nicotinic acid, bile acid binding resins or fish oils. Ezetimibe as monotherapy can be expected to lead to a fall in LDL-C of approximately 15-20%, with a much lower risk of statin myopathy (Knopp et al., 2003). If muscle symptoms arise on ezetimibe therapy, then thrice-weekly dosing may be tolerated. In a small retrospective study of 94 statin-intolerant patients, a thrice-weekly regimen resulted in a fall in LDL-C of 17-20% and was tolerated by 85% of patients (Maccubin et al., 2009). Fibrates are effective in reducing cardiovascular disease and are an attractive option for those who are statin and ezetimibe intolerant. Fenofibrate has largely replaced gemfibrozil owing to a lower risk of drug interactions. Recent data indicate that fenofibrate is well tolerated and particularly effective in reducing microvascular complications in diabetic patients. Nicotinic acid (vitamin B3) is extremely effective in reducing LDL-C and triglycerides and raising high-density lipoprotein cholesterol. Unfortunately, nicotinic acid is associated with significant adverse effects, most notably skin flushing, and itch mediated through prostaglandin D2 release; these side effects are moderately to significantly intolerable in 20% of patients (Maccubin et al., 2009). Newer formulations such as niaspan (a slow release preparation) and niacin combined with laropiprant (a prostaglandin D2 inhibitor) are better tolerated and are effective in improving the lipid profile. Finally, bile acid sequestrants are also effective in improving reducing cholesterol levels; however, older preparations such as cholestyramine have significant gastrointestinal side effects and interfere with medication absorption. Newer preparations such as colesevelam have improved tolerability (http://www.bma.org.uk/ap.nsf/). Finally, recommending 'nutriceuticals', such as plant sterols, policosanol and Chinese red rice (containing naturally occurring lovastatin) may be useful in sparing the use, or in increasing the dose, of a statin. These supplements can reduce LDL-C by up to 10% (Becker et al., 2009). For patients with LDL-C > 4 mmol/L (160 mg/dl) who cannot tolerate or are refractory to cholesterol-lowering drugs and exhibit progressive coronary artery disease, consideration should be given to LDL-aphaeresis (http://www.bma.org.uk/ap.nsf/)(Table 8).

DISCUSSION

This systemic meta-analysis demonstrates that there is association between non-adherence to statin therapy and its impact on cardiac events. For patients with good adherence to statin therapy, the risk of cardiovascular events is significantly reduced than that of patients with poor adherence. Non-adherence to statin therapy is a frequently occurring problem in Cardiology. Non-adherence is widely observed in clinical settings, suggesting discrepancy in patient adherence with statin therapy between controlled clinical trials and routine practice. Adherence to satin therapy in clinical trials tends to be much higher than every day practice. Non-adherence to cardiovascular medications is ubiquitous. It is chiefly seen in primary prevention settings, but also paradoxically so amongst patients with diabetes and stroke (Bates et al., 2009). This may be due to, in primary prevention setting patients may be less willing to receive statin since they perceive their vascular risk to be low (Search, 2008).

The reason for non-adherence to statin therapy relate inter alia to patient, physician, and fiscal factors. Several factors are shown to be predictive of poor adherence, such as age, race, education level, house hold income, family support, cigarette smoking, patients' beliefs, comorbodities, number of concurrent medications and drug side effects. Previous studies revealed that patients aged ≥60 years were better adherants, whereas those under 45 or over 75 years old showed significantly lower adherence rates (Benner et al., 2002). Elderly patients are a group who may be at particular risk of statin non-adherence. There are several reasons for this. These include polypharmacy, susceptibility to drug side effects, cognitive dysfunction, physical disability (poor eyesight, arthritis) and depression. The younger are also at risk for non-adherence because they do not take responsibility for their own health (Wilson et al., 2007). The number of close family members was also significantly associated the amount of house hold care received by the elderly family members. Higher levels of adherence were reported among Caucasians compared with African-origin groups (Benner et al., 2002). The reasons that the black is less adherent than the white is may be: chronic stress due to direct and indirect effect of racism, culture of diet and accessibility to care because of economy (Shear et al., 1992). Higher education and house income, cohesive family, positive attitude towards healthy living and patient-health care provider relationship may be correlated with increased adherence levels (Benner et al., 2002). Heavy smoking, complex regimens and presence of intolerable side effects may deter patients from adhering to the treatment (Colivicchi et al., 2007).

Adverse effects of statins experienced by patients are also an important cause of non-adherence to medication. There is a core of patients who are non-adherent to statins because of clinical side effects, most frequently myopathic and neuromuscular symptoms (Golomb and Evans, 2008). Non-adherence to statin has a significant effect on cardiovascular outcomes. A study by Bouchard et al (2007) indicted that adherence to statins that exceeds 90% is associated with a significant reduction in nonfatal CAD events. The 4S study (Strandberg et al., 1994) demonstrated that important reductions in coronary event-related morbidity and mortality in patients with known CHD.

A recent evidence has demonstrated that patients' financial incentives (that is, copayments, coinsurance) also affect statin adherence. As statin cost-sharing levels increase, adherence to satin falls. Reduction in drug costs, increase in government subsidies and reduction in patient copayments are other adjunctive approaches that will assuage non-adherence. Well-designed research studies into the most cost-efficient and strategies for improving adherence should be given priority for funding. Evidence-based government initiatives can have direct and indirect effects that improve patient adherence to cardiovascular drugs, including statins; this may be particularly relevant to primary prevention where adherence is a major problem (McGovern et al., 2008).

Psychological issues may bear on a patients' adherence behavior. An individual's personality and adherence self-efficacy are also important predictors of non-adherence and physicians who improve their levels of communication and emotional intelligence are more likely to understand and collaborate with their patients and reduce the incidence of non-adherence. Use of evidence-based medicine, clear communication with patients and a concerted commitment to regular follow-up of patients are likely solutions. Attention to the physician– patient working alliance and patient health beliefs will also promote adherence behavior (Bates et al., 2009). CoQ10 supplementation, identification of recognized drug interactions and use of low-dose regimens of lipophilic statins can improve patient acceptability. That said, there will be a small proportion of patients that remain intolerant of all statins and, depending on the lipoprotein profile, will require alternative drug therapy, including ezetemibe, fenofibrate or fish oils (Bates et al., 2009). The present review has limitations: relevant studies may have been missed or in correctly categorized, because one person selected the studies and extracted data. Another limitation is that the absence of an ideal method to measure adherence, a wide variety of measurement and definitions for adherence.

CONCLUSION AND RECOMMENDATIONS

In this meta-analysis non-adherence to statin therapy proved to be a significant problem for preventive cardiology. It is associated with increased risk of cardiac morbidity and mortality. Non-adherance of statin medication is not solely a patient problem but is impacted by both care providers and health care system. Most studies investigating the relationship between adherence and clinical outcomes found that non-adherence had a negative effect on outcome; suggesting that the management of CVD may be improved by improving patient adherence to statins medication.

Further research into the problem of non-adherence with statin medication is necessary to increase the number of published studies in this area and to increase awareness of the problem. By increasing awareness, it may be possible to improve patient adherence. The availability of different targeted interventions, including behavioral training and regular follow up with health care system designed specifically to improve patient adherence, and hence to improve clinical outcomes. Beside this, getting patients to take their medications as prescribed is a worthy goal for patients to derive the maximal benefit of prescribed therapy.

CONFLICT OF INTERESTS

The authors have not declared any conflict of interests.

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ABBREVIATIONS

ACE, Angiotensin converting Enzyme; **AFCAPS/ texCAPS,** Air Force/Texas Coronary Atherosclerosis Prevention Study; **ASTEROID,** A Study to Evaluate the Effect of Rosuvastatin on Intravascular Ultrasound-Derived Coronary Atheroma Burden; **ATP III,** Adult Treatment Panel III; **LYS,** cost per life year saved; **CABGE,** Coronary Artery Graft Bypass surgery; **CARE,** Cholesterol and Recurrent Events; **CHAMP,** Cardiovascular Hospitalization Atherosclerosis Management Program; **CHD,** Coronary Heart Disease; **CURVES,** Comparative dose efficacy study of atorvastatin versus simvastatin; **EXCEL,** Expanded Clinical Evaluation of Lovastatin; **GRACE,** Gender, Race and Clinical Experience; **HMG-COA,** Hydroxy methyl glutaryl coenzyme A; **HMO,** Health Maintenance organizations; **HPS,** Heart Protection Study; **IDEAL,** Incremental Decrease in End Points through Aggressive Lipid Lower; **JUPITER,** Justification for the Use of Statins

in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin trial; **LDL-C,** Low density lipoprotein cholesterol; **LIPID,** Long-Term Intervention with Pravastatin in Ischaemic Disease; **MACE,** Major adverse cardiovascular events; **NCEPG,** National Cholesterol Education program guidelines; **SPARCL,** Stroke Prevention by Aggressive Reduction in Cholesterol Levels; **TIA,** Transient Ischemic Attack; **VLDL-C,** Very low-density lipoprotein cholesterol; BMQ, Beliefs about Medicines Questionnaire; **WOSCoPS,** West of Scotland Coronary Prevention Study; **4S study,** Scandinavian Simvastatin Survival Study; **WAI,** Working Alliance Inventory.

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