Annals of Medicine

ISSN: 0785-3890 (Print) 1365-2060 (Online) Journal homepage: informahealthcare.com/journals/iann20

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To cite this article: Dan Atar, Rafael Carmena, Peter Clemmensen, Annik K-Laflamme, Sven Wassmann, Peter Lansberg & Richard Hobbs (2009) Clinical review: Impact of statin substitution policies on patient outcomes, Annals of Medicine, 41:4, 242-256, DOI: 10.1080/07853890902729786

To link to this article: https://doi.org/10.1080/07853890902729786

Published online: 08 Jul 2009.

Annals of Medicine. 2009; 41: 242–256

informa
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REVIEW ARTICLE

Clinical review: Impact of statin substitution policies on patient outcomes

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Abstract

Background. The increasing awareness of cost issues in health care has led to the increasing use of policy-driven substitution of branded for generic medications, particularly relative to statin treatment for cardiovascular diseases. While there are potential short-term health care savings, the consequences for primary care are under-researched. Our objective was to review data on intensive statin therapy and generic substitution in patients at high cardiovascular risk.

Results. Current treatment guidelines for the prevention of cardiovascular disease are consistent in their recommendations regarding statin therapy and treatment targets. Clinical trials demonstrate that to reduce cardiovascular events, a statin is more effective than placebo, intensive statin therapy is more effective than moderate statin therapy in patients with established coronary disease, and in patients receiving intensive statin therapy the lowest risk is associated with the lowest low-density lipoprotein levels. However, in clinical practice, patients at high cardiovascular risk are prone to be undertreated. Observational studies suggest that mandatory statin substitution may increase the gap between achieved and recommended therapeutic targets.

Conclusions. Substitution of generic statins may be cost-saving, particularly at the primary prevention level. However, statin substitution policies have not been adequately studied on a population level. Data raise concern that mandated statin substitution may lead to unfavourable treatment choices at the level of the individual high-risk patient.

Key words: *Cardiovascular disease, statin, cholesterol, cost-effectiveness, low-density lipoprotein, policy, substitution, switching*

Introduction

There is an increasing policy-driven trend throughout Europe and globally toward substituting branded for generic medications. In the area of cardiovascular diseases this has led to controversy when applying the evidence base from trials conflicts with regulatory reimbursement processes.

Coronary heart disease (CHD) remains the single most common cause of death in the European Union, according to a 2008 report (1). Each year cardiovascular disease (CVD) causes over 4.3 million deaths in Europe. Modifiable and non-modifiable risk factors put some individuals at greater risk than others (2). The European guidelines consider individuals with known CVD, diabetes, or very high levels of individual risk factors to be at increased CVD risk and a priority for management of all risk factors (2). Generally speaking, an adult with a 10-year risk of CVD death of 5% or more is at high risk and thus a candidate for medical and life-style

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(Received 15 September 2008; revised 5 December 2008; accepted 7 December 2008)

ISSN 0785-3890 print/ISSN 1365-2060 online
DOI: 10.1080/07853890902729786

Key messages

- For the reduction of cardiovascular events in patients with coronary heart disease, a statin is more effective than placebo, intensive statin therapy is more effective than moderate statin therapy in patients with established coronary disease, and in patients receiving intensive statin therapy the lowest risk is seen in those with the lowest LDL levels.
- Substitution of generic statins may be cost-saving, particularly at the primary prevention level. However, statin substitution policies have not been adequately studied on a population level.
- Data raise concern that mandated statin substitution may lead to unfavourable treatment choices at the level of the individual high-risk patient.

Abbreviations

ACS	acute coronary syndrome
ALLIANCE	Aggressive Lipid Lowering Abates New Cardiac Events
ALT	alanine aminotransferase
AST	aspartate aminotransferase
A to Z	Aggrastat to Zocor
BP	blood pressure
CHD	coronary heart disease
CK	creatine kinase
CTT	Cholesterol Treatment Trialists
CVD	cardiovascular disease
ESC	European Societies of Cardiology
GRACE	Global Registry of Acute Coronary Events
GUSTO IIB	Global Use of Strategies to Open Occluded Coronary Arteries IIB
HbA1c	haemoglobin A1c
HPS	Heart Protection Study
ICER	incremental cost-effective ratios
IDEAL	Incremental Decrease in End Points Through Aggressive Lipid-Lowering
IPCI	Integrated Primary Care Information
LDL	low-density lipoprotein
MI	myocardial infarction
MIRACL	Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering
NHANES	National Health and Nutrition Examination Survey
NSTEMI	non-ST-segment elevation
OPUS-TIMI 16	Orbofiban in Patients with Unstable coronary Syndromes
OR	odds ratio
PACT	Pravastatin in Acute Coronary Treatment
PCT	primary care trust
PROVE-IT-TIMI-22	Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction-22
PURSUIT	Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy
QALY	quality adjusted life-years
RCT	randomized controlled trial
STEMI	ST-segment elevation acute MI
THIN	The Health Improvement Network
TNT	Treating to New Targets
ULN	upper limit of normal

interventions, although age must be taken into account when comparing absolute risks. Clinically and economically it is considered to be beneficial to identify and treat these people at greatest risk.

Patients continue to be underdiagnosed and undertreated for some of the most important modifiable risk factors, such as dyslipidaemia (3,4). Despite the fact that the use of statins significantly reduces cardiovascular events (5), patients at high risk are often not receiving treatment, or are receiving inadequate doses (3,4). Although substitution of lower-cost medications may have cost benefits, national health care policies that restrict the use of more effective statins may be counter-productive to achieving the lipid targets set by international medical societies; targets determined to optimize patient outcomes based on best-evidence clinical trial data (2). This is a particular concern in patients at high risk; although lower lipid targets are also associated with fewer events in primary prevention, political and economic realities support the need for cost-saving strategies in patients at lower cardiovascular (CV) risk.

The burden of high cardiovascular risk

Annually, CVD causes over 2.0 million deaths in the European Union (4.3 million deaths in Europe), which accounts for nearly half of all deaths (1). Across Europe, there is considerable variation in cardiovascular and all-cause mortality rates (Figure 1) (6). In the Health Survey for England (2003), 5.4% of the population had CHD, and 12.8% had a 10-year CHD risk of $>20\%$ (7). In the US National Health and Nutrition Examination Survey (NHANES) it was estimated that 10.6% of the adult

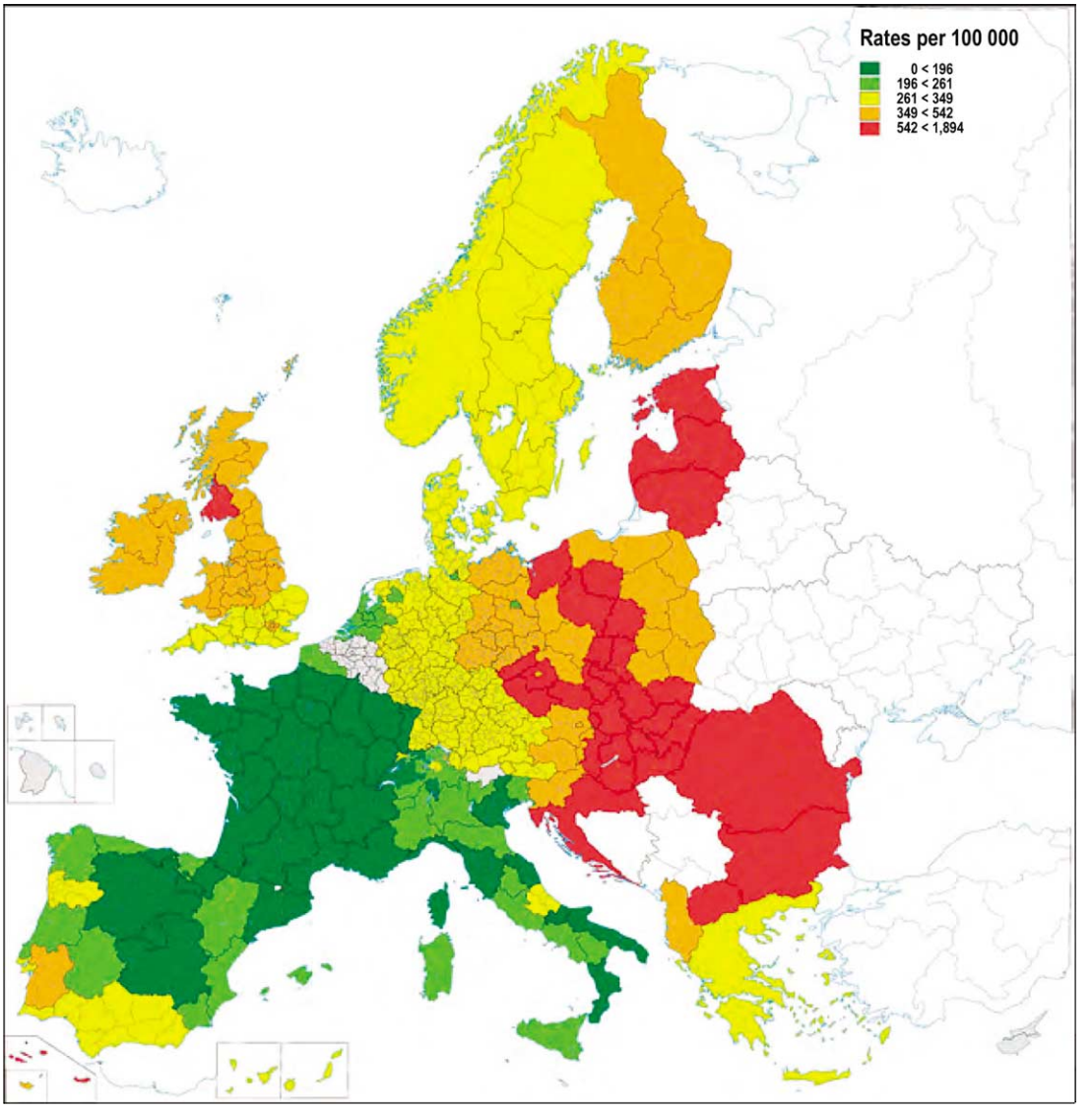

Figure 1. Cardiovascular mortality in men across European regions. Age-standardized mortality from cardiovascular disease (ischaemic heart disease and cerebrovascular disease combined), in European regions (men; age group 45–74 years), based on data from Eurostat and the National Statistical Offices of the respective countries (2000). Reprinted with permission from (6).

population were at high risk and 5.7% at very high risk (8).

The financial burden of CVD is enormous, accounting for an estimated expenditure of €192 billion a year in Europe (1). Direct health care costs, such as in-patient care, primary care, and out-patient care, account for 57%, while indirect costs, such as lost productivity, account for 21%. Of the CVD health care expenditure, 22% is due to CHD cost (€24 billion), of which over 52% is for in-patient care.

Of the major modifiable risk factors for cardiovascular events (smoking, dyslipidaemia, hyperglycaemia, and hypertension), dyslipidaemia may be the easiest to manage. In the most recent EUROASPIRE survey, 75% of patients achieved low-density lipoprotein (LDL) targets while only 39% achieved blood pressure targets (3). Similarly, in the STENO-2 study, targets were achieved by over 70% of individuals for total cholesterol, compared to 45% for systolic blood pressure, and only 15% for glycosylated haemoglobin (9). A subsequent observational analysis established that over 70% of the CV risk reduction was attributed to lipids, compared to about 10% to glycaemic control or systolic blood pressure (Figure 2) (10). A Finnish analysis found that reductions in serum cholesterol, smoking, and blood pressure accounted for 37%, 8.8%, and 7.5%, respectively, of the decline in CHD mortality from 1982 to 1997 (11).

Patients with acute coronary syndromes (ACS) are among those with the highest cardiovascular risk

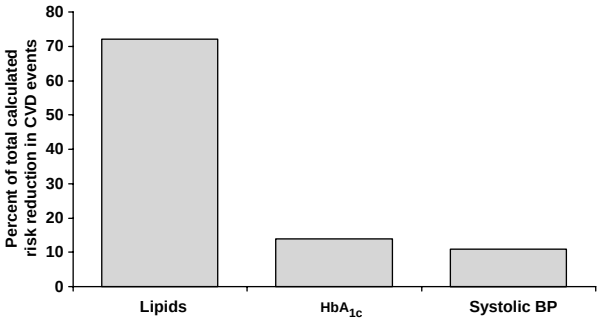

Figure 2. Lipid-lowering was the most important contributor to reduction in cardiovascular risk in the STENO-2 study. CV risk was estimated using the UKPDS risk engine. (BP = blood pressure; CVD = cardiovascular disease; HbA_{1c} = haemoglobin A_{1c}.) Reprinted with permission from (10).

(12,13). The Global Registry of Acute Coronary Events (GRACE) (1999–2001) enrolled 11,543 patients from 14 countries and reported in-hospital mortality rates of 7% among patients with ST-segment elevation acute myocardial infarction (STEMI) and 6% among those with non-ST-segment elevation (NSTEMI) (12). The 6-month postdischarge death rates were 4.8% in patients with STEMI, and 6.2% in patients with NSTEMI (13). Rehospitalization for heart disease and revascularization procedures were also important outcome measures occurring in 15%–20% of patients over the 6-month follow-up (13).

European reimbursement policies for statin therapy

Statin reimbursement policies vary widely across Europe, from countries in which all statins are reimbursed, to countries where only generic statins are reimbursed, and variations in between (Table I). Reimbursement policies are complex with many people and agencies involved: government and private health insurance policy-makers, pharmaceutical manufacturers, pharmaceutical regulatory boards, private health insurance companies, hospital formulary committees, hospital trusts, medical societies, etc. In some countries, physicians in

Table I. Examples of range of statin reimbursement policies in countries across Europe.

Country	Policy
Denmark	● Generic simvastatin, lovastatin, and pravastatin are reimbursed without restrictions
	● Branded statins can be prescribed if treatment goals are not achieved or generic statins not tolerated ('reimbursement' has to be if specifically stated on the prescription)
	● General Practitioner (GP) prescribing habits monitored electronically
United Kingdom	● National Health Service distributes funds to primary care trusts (PCT)
	● Generic simvastatin reimbursed
	● Prescribing target of 69%–75% set by Department of Health for GPs
	● Restricted use of high-dose statins for patients with acute coronary syndrome (ACS)
	● GPs reimbursed to achieve targets of: total cholesterol (TC) <5, and low-density lipoprotein (LDL) <3
Germany	● Fixed maximum reimbursement amount for statins, obligatory for compulsory health insurance
	● All generic statins fully reimbursed
	● Branded statins reimbursed up to fixed maximum amount; patient co-payment required
	● Ezetimibe fully reimbursed (different drug class, no fixed maximum reimbursement amount)
	● Pressure to prescribe inexpensive medication through definition of 'budgets'/patient/drug class/3 months
	● Branded statins more frequently prescribed for patients with private health insurance
Norway	● National reimbursement policy
	● Generic simvastatin reimbursed as 'preferred drug'
	● Branded statin reimbursed, but clinical justification required in patient chart, i.e. very high risk/secondary prevention/not reaching goal, etc.
	● Authorities monitor prescribing patterns: occasional external review of issued prescriptions/patients' records to ensure physician compliance with rules
Netherlands	● Generic statins are reimbursed without restrictions for high-risk patients
	● National guidelines advise to achieve an LDL target <2.5 mmol/L for patients with coronary heart disease (CHD) or type 2 diabetes mellitus. If goals cannot be achieved using generic statins other treatment strategies are allowed
	● Patients at risk (10-year >5%) but no CHD or diabetes: the LDL goal is <2.5 mmol/L or a 1 mmol/L LDL reduction. Branded statins are restricted
	● Compulsory health insurance (5–6 large companies)
	● Generally reimburse generic statin. Branded statins are reimbursed if doctors specify 'medical indication'
	● Pressure to prescribe generic statins: financial incentive for GPs if 80% of patients are prescribed simvastatin
Spain	● Pressure increasing to prescribe generic over branded statins
	● All statins reimbursed; patient pays 40%
	● Statins fully reimbursed in patients >65 years and patients with familial hypercholesterolaemia

Source: From individual authors and physicians' survey, February 2008.

hospitals continue to have prescription rights, but if general practitioners do not, prescription of non-generic statins issued in-hospital may not be continued by community physicians. Many countries that allow unrestricted access to generic statins only, will reimburse branded statins for high-risk patients if specific criteria are met and authorization is obtained. However, prescribing quotas and additional paperwork can provide barriers to patients receiving these medications.

Even in countries with the most open-market approaches to statin reimbursement, pressure is increasing to prescribe generic statins. Mechanisms used include setting quotas, monitoring prescribing patterns, providing selective clinical data, financial incentives such as extra funding for additional staff, and financial restrictions such as a maximum budget per patient, as well as patient initiatives such as tiered co-payment strategies (Table I).

One of the benefits of generic statin reimbursement policies has been to make statin therapy more accessible to the general population in some countries that previously had restricted access to these medications. Prescription strategy in favour of generic statins can decrease drug budgets, and may be especially beneficial in primary prevention. However, the hazard of restrictive reimbursement policies with substitution of lower-efficacy statins lies in the potential for undertreatment of patients at high cardiovascular risk.

In clinical practice there is a tendency not to titrate doses upward in order to reach recommended LDL goals (14–17). Frequent medical visits for dose titration may add cost and time, and lead to frustration for patients and physicians alike. In one study, only 45% of high-risk subjects who did not reach targets with the initial dose of a statin were uptitrated (14). In addition, physicians in family and general practice were less likely to titrate than cardiologists. This prescribing pattern means target levels are frequently not achieved in patients who require large reductions in LDL. With the vast number of patients and high-risk individuals now being on a statin, the major challenge seems to be achieving treatment goals.

Treatment guidelines

Despite the wide disparity in statin reimbursement policies, treatment goals are quite similar in countries across Europe. Some countries have set their own guidelines, and these vary for patients at lower risk but are consistent for patients at high risk. Current targets recommended in the most recent European guidelines (2,18–20) are based on evidence to date and should be attempted in order for patients to achieve the maximum benefit seen in clinical trials.

The joint guidelines from the European Societies of Cardiology (ESC) and other societies recommend aggressive lipid targets for patients at high risk (2,18–20). For the highest-risk subjects, especially those with established CHD or diabetes, the 2007 prevention guidelines recommend targets for LDL of <2.5 mmol/L ($\sim$100 mg/dL) with an option of <2.0 mmol/L (77 mg/dL) where feasible (2), and a target of <1.8–2.0 mmol/L (70–77 mg/dL) in patients with both CHD and diabetes (19). Statin therapy is recommended for all patients with stable CHD and stable angina based on their elevated level of risk and comprehensive evidence of benefit of cholesterol lowering (20).

ESC guidelines for patients with NSTE-ACS recommend statins for all patients irrespective of cholesterol levels, initiated early (within 1–4 days) after admission, with the aim of achieving LDL levels <2.6 mmol/L (<100 mg/dL). In addition, intensive lipid-lowering therapy to achieve a target LDL <1.8 mmol/L (<70 mg/dL) should be initiated within 10 days after admission (18).

While the management of blood lipids in high-risk individuals has substantially improved over the last decade, data from EUROASPIRE III (2007) show that high-risk patients in Europe continue to be undertreated (3). The use of statins increased from 18% in EUROASPIRE I (1995–96) to 87% in EUROASPIRE III (2007) (3). This was mirrored by an increase in the proportion of patients achieving LDL targets (<3.0 mmol/L or 115 mg/dL) from 11% to 75%. However, only 53% of patients achieved the LDL target of <2.5 mmol/L (96 mg/dL) set in 2003, and even fewer would be expected to achieve the optimal optional target of <2.0 mmol/L (77 mg/dL) set in 2007 (2,3,21). It becomes evident that a substantial proportion of patients are not achieving recommended lipid targets.

Intensive statin therapy in the prevention of CV events

There is a solid evidence base from randomized controlled trials (RCTs) of the benefits of lipid lowering with statins in reducing the risk of CV events. The Cholesterol Treatment Trialists' (CTT) Collaborators meta-analysis of data from 90,056 participants in 14 randomized trials of statins found that for each 1 mmol/L (39 mg/dL) reduction in LDL there was a 23% reduction in CV events overall (5), and a 22% reduction in patients with diabetes (22). The relationship between LDL lowering

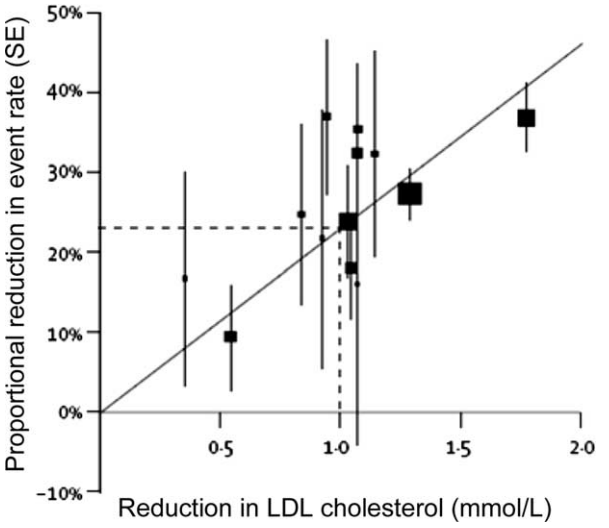

Figure 3. Linear relationship between low-density lipoprotein (LDL)-lowering and reduction in major coronary events in the Cholesterol Treatment Trialists' (CTT) Collaborators meta-analysis of data from 90,056 participants in 14 randomized trials of statins. Relation between proportional reduction in incidence of major coronary events and mean absolute low-density lipoprotein (LDL) reduction at 1 year. Reprinted with permission from (5).

and reduction in CV events retains its linearity throughout the widest range of LDL, with no apparent loss of benefit with reductions at either very high or very low LDL levels (Figure 3, right and left sides of graph).

This is exemplified by the Treating to New Targets (TNT) trial (23). The TNT study showed additional 22% reductions in relative risk of major CV events in patients with stable CHD when LDL levels were lowered beyond usually recommended targets (2.6 mmol/L, <100 mg/dL) (23). Further analysis showed highly significant reductions in major CV event rates with descending achieved LDL levels ($P<0.0001$ for trend across LDL), with the lowest rate occurring in the quintile of patients with LDL <1.7 mmol/L (64 mg/dL) (Figure 4) (24). There were no clinically important differences in adverse event rates across quintiles; including no increase in muscle complaints, suicide, haemorrhagic stroke, or cancer deaths at the lowest LDL levels.

Overall, four trials have assessed the effects of intensive versus moderate statin therapy in patients with established ischaemic heart disease: TNT (23) and the IDEAL (Incremental Decrease in End Points Through Aggressive Lipid-Lowering) (25) trials involving patients with stable CHD, and the PROVE-IT-TIMI-22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction-22) (26) and A to Z (Aggrastat to Zocor) (27) trials involving patients with ACS. Cannon et al. conducted a meta-analysis of these trials of 27,548 patients combined and found a significant 16% reduction in coronary death or MI, and a 16% reduction of coronary death or any CV event (Figure 5) (28). Another meta-analysis by Silva et al. of the same trials found significant reductions in CV death (14%), MI (16%), and stroke (18%) (29). None of these trials were powered to assess changes in all-cause mortality.

Although the focus of this article is on patients with coronary heart disease and those at high risk

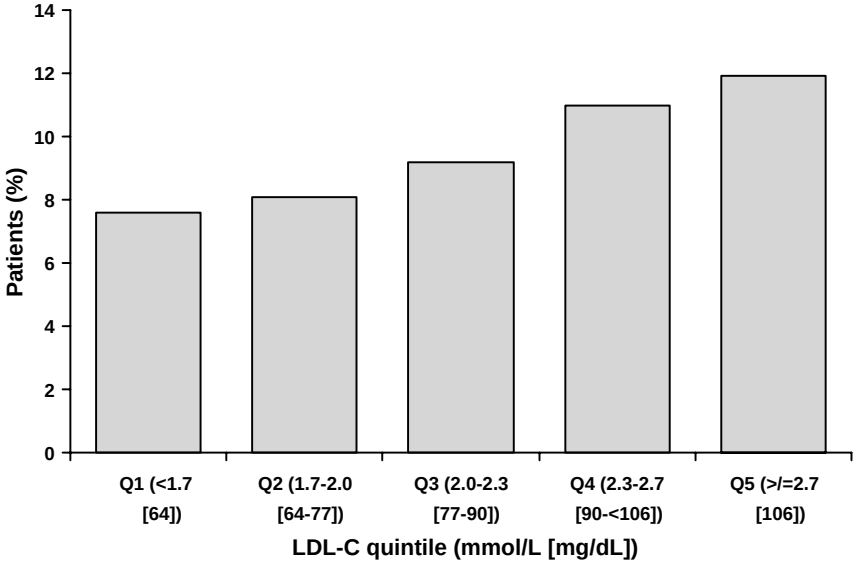

Figure 4. Rate of major cardiovascular events across quintiles in the Treating to New Targets (TNT) study. Patients with coronary heart disease and LDL <130 mg/dL (3.4 mmol/L) were randomized to therapy with atorvastatin 10 mg/day ($n=5,006$) or 80 mg/day ($n=4,995$). $P<0.0001$ for trend across LDL. Reprinted with permission from (24).

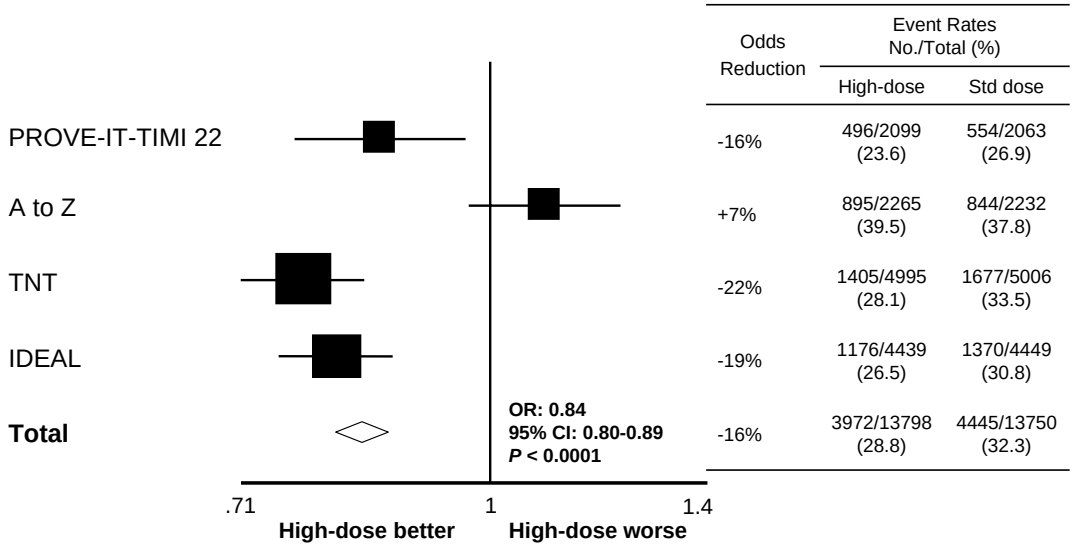

Figure 5. Intensive statin therapy was more effective than moderate statin therapy in reducing coronary death or any CV event in a meta-analysis of four trials including 27,548 patients with either stable coronary heart disease or acute coronary syndromes. Individual trials and pooled analysis showing reduction in the risk of coronary death or any CV event (myocardial infarction, stroke, hospitalization for unstable angina, or revascularization) ($P<0.0001$). (CV = cardiovascular; CI = confidence interval; OR = odds ratio.) Reprinted with permission from (28).

for cardiovascular events, there is accumulating evidence that LDL lowering is beneficial in primary prevention (30,31). JUPITER (Justification for the Use of statins in Primary prevention: an Intervention Trial Evaluating Rosuvastatin) demonstrated that rosuvastatin 20 mg/day significantly reduced the incidence of major cardiovascular events in patients with no cardiovascular disease, moderate to low LDL and elevated hs-CRP (high-sensitivity C-reactive protein), compared to placebo (31). While the role of intensive statin treatment in a wider patient population at lower cardiovascular risk merits discussion, it has to be recognized that the low incidence of major cardiovascular events in this population will provide a challenge to payers and policy-makers in regards to the cost-effectiveness of this strategy in primary prevention.

Observational studies add to the strength of RCT data on the substantial benefits of intensive lipid treatment with statins. These indicate how the controlled data translate into clinical practice in the 'real world'. The ALLIANCE (Aggressive Lipid Lowering Abates New Cardiac Events) study was designed as a real-life, clinical trial comparing a focused approach with atorvastatin to 'usual care' in a carefully defined CHD population (32). Other than treatment with atorvastatin in one arm of the study, all other interventions in terms of risk factor management and visits were usual care provided by a primary care provider. ALLIANCE included 2,442 subjects, two-thirds of whom were on a statin at base-line. As a result, atorvastatin therapy was associated with a greater reduction in LDL (34% versus 23% for usual care) and a higher percentage of patients achieving LDL targets (72% versus 40%). This was associated with a significant 17% reduction in CV events.

Observational data also provide compelling evidence for the benefits of statin therapy. While these data are retrospective and subject to preselection bias (such as putting patients at higher risk on more potent statins), they also provide evidence of how RCT results translate into general populations. An analysis of 3,499 new statin users in the Netherlands Integrated Primary Care Information (IPCI) database found a 30% lower risk of events in patients treated with atorvastatin 10 mg compared to other statins (simvastatin 20 mg, pravastatin 40 mg, and fluvastatin 40 mg) (33). During almost 2 years of follow-up, there was a 39% reduction in events in primary prevention patients ($n=2,702$) and an 18% reduction in secondary prevention ($n=797$). Similarly, an analysis of a large managed care claims database in the US assessed CV outcomes among patients newly initiated on atorvastatin ($n=168,973$) or simvastatin ($n=50,658$) over 1.5 years (34). When used for primary prevention, atorvastatin was associated with a 12% lower risk of CV events compared to simvastatin.

Role of early, intensive statin therapy in ACS

Patients with ACS experience the highest rate of death and recurrent ischaemic events during the early

period after the index event. Intensive lipid-lowering therapy with high-potency statin therapy has been shown to significantly improve outcomes in this patient group (26–29). The benefits of prompt initiation of statin therapy after ACS may be related to effects other than lipid lowering, such as plaque stabilization, anti-inflammatory effects, and restoration of endothelial function (35).

A meta-analysis of 13 trials and 17,963 patients with ACS showed that early initiation of statin therapy (within 14 days of hospitalization) also had a positive impact on outcome, with a significant 19% decrease in the rate of death and cardiovascular events over 2 years of follow-up (36). Survival benefit began after 4 months and achieved statistical significance by 12 months.

For patients with ACS, the choice of statin, degree of LDL reduction, dose, and time of initiation may be important factors in determining the magnitude of the benefits of early statin intervention. In the MIRACL (Myocardial Ischemia Reduction with Aggressive Cholesterol Lowering) trial in 3,086 adults, early treatment with atorvastatin 80 mg, initiated 24–96 hours after an ACS, significantly reduced the primary composite end-point of death and non-fatal ischaemic events by 16% compared to placebo (37). LDL levels were 1.9 mmol/L (72 mg/dL) in the atorvastatin group and 3.5 mmol/L (135 mg/dL) in the placebo group. However, in the PACT (Pravastatin in Acute Coronary Treatment) trial, which assessed more moderate lipid-lowering therapy (pravastatin 20–40 mg) or placebo within 24 hours after ACS in 3,408 patients, a non-significant reduction of only 6.4% in major CV events favouring pravastatin was found (38). The achieved LDL levels were not reported in this study.

The A to Z trial compared early initiation (mean 3.7 days) of an intensive step-wise statin regimen (simvastatin 40 mg $\times$ 1 mo, then 80 mg) with delayed initiation of a less intensive regimen (placebo $\times$ 4 mo, then simvastatin 20 mg) in 4,497 patients with ACS (27). Achieved LDL levels were 1.6 mmol/L (63 mg/dL) in the intensive statin group and 2.0 mmol/L (77 mg/dL) in the less intensive group at 8 months. While there was an 11% decrease in the risk of major CV events, this was not statistically significant, which may suggest the need to start with higher statin doses or that other mechanisms in addition to lipid lowering are important in early statin therapy for ACS.

PROVE-IT assessed the benefit of intensive (atorvastatin 80 mg) lipid-lowering therapy compared with moderate (pravastatin 40 mg) therapy within 10 days after ACS (26). Follow-up was continued over 18–36 months. At study end, LDL levels were reduced by 49% in the atorvastatin arm (median 1.6 mmol/L (62 mg/dL)) and 21% in the pravastatin arm (median 2.5 mmol/L (95 mg/dL); $P<0.001$). There was a 16% reduction in the primary end-point with intensive compared to non-intensive therapy ($P=0.005$).

A recent study also demonstrated the beneficial effects of intensive statin therapy with rosuvastatin in patients with ACS (39). Rosuvastatin prior to percutaneous coronary intervention (PCI) reduced periprocedural myocardial injury compared to no statin treatment (11.4% versus 5.8%) in 455 patients undergoing PCI.

Data from *post hoc* analyses of large RCTs provided some of the first evidence of the benefits of early statin therapy in patients with ACS. An analysis of data from 20,809 patients with ACS included in the PURSUIT (Platelet Glycoprotein IIb/IIIa in Unstable Angina: Receptor Suppression Using Integrilin Therapy) and GUSTO IIB (Global Use of Strategies to Open Occluded Coronary Arteries IIB) trials found that those who were receiving lipid-lowering therapy at discharge had significantly lower rates of all-cause mortality at 30 days (0.5% versus 1.0%, $P=0.001$) and 6 months (1.7% versus 3.5%, $P<0.0001$) compared with those who were not (40). *Post hoc* analysis of data from 10,288 patients in the OPUS-TIMI 16 (Orbofiban in Patients with Unstable coronary Syndromes) trial found significantly lower mortality in patients treated with statin therapy at 30 days (0.7% versus 2.4%, $P<0.0001$) and 10 months (3.1% versus 5.3%, $P<0.0001$) (41,42).

Among patients with ACS, large patient registries have demonstrated decreased mortality with the use of statin therapy (43–46). The nationwide Swedish RIKS-HIA (Register of Information and Knowledge about Swedish Heart Intensive care Admissions) registry of patients with acute MI (AMI) included 5,528 patients who were receiving statin treatment before or at the time of hospital discharge and 14,071 who were not. At 1 year, early statin use was associated with a significant 25% lower rate of death after adjustment for confounding factors and propensity for statin use (43).

Likewise, the Global Registry of Acute Coronary Events (GRACE) registry analysed 19,537 patients with ACS and found that the risks of in-hospital death or complications were significantly decreased in patients admitted on, and continuing, statins (34%), and in patients newly initiated on statins (62%) (44). In this analysis, adjustment for hospital of admission reduced the effect of taking statins to 16%. In addition, analysis of long-term outcomes in 8,492 patients in the GRACE registry found that statin prescription at the time of hospital discharge

was associated with a significant 34% reduction in 6-month all-cause death rates and 24% reduction in the composite end-point of MI, stroke, and death (45).

Data on 300,823 patients who had AMI from the National Registry of Myocardial Infarction-4 in the US also support early treatment in patients with ACS (46). New and continued treatment with a statin in the first 24 hours after admission were associated with 54% and 58% decreased risks of mortality, respectively, compared with no statin use (absolute risks: 4.0%, 5.3%, and 15.4%, respectively).

Taken together, a large body of data from RCTs and registries demonstrate that for the reduction of CV events in patients with established CHD, a statin is more effective than placebo, intensive statin therapy is more effective than moderate statin therapy, early initiation of statin therapy after ACS is more effective than delayed initiation, and in patients receiving intensive statin therapy the lowest risk is seen in those with the lowest LDL levels. These findings are supported by data from real-world observational studies supporting the use of more intensive statin therapy in community populations, and especially the use of early, intensive statin therapy in patients with ACS.

Safety of high-dose statin therapy

The safety of high-dose statin therapy has been a concern. The Silva meta-analysis of the four trials assessing intensive versus moderate statin therapy found that intensive statin therapy was associated with higher rates of any adverse events and discontinuations due to adverse events (29). Intensive therapy was associated with an increased risk for abnormalities on liver function testing (odds ratio (OR) = 4.48) and elevations in creatine kinase (CK) (OR = 9.97). Table II shows the rates of severe adverse events in the trials assessing intensive versus moderate statin therapy. The rates of abnormalities of liver function tests were higher with all intensive compared to moderate regimens, while the rates of muscle changes were increased in the A to Z trial with high-dose simvastatin, but not in the trials with high-dose atorvastatin.

In an analysis of pooled results from 49 trials involving 14,236 subjects on atorvastatin, there were no significant differences in the rate of adverse events or clinically significant laboratory abnormalities between 10 mg and 80 mg doses (47). Withdrawals due to treatment-related adverse events were observed in 2.4%, 1.8%, and 1.2% of patients in the atorvastatin 10 mg, atorvastatin 80 mg, and placebo groups, respectively.

Rosuvastatin and atorvastatin may have enhanced potency against HMG-CoA (3-hydroxy-3-methylglutaryl coenzyme A) reductase because of their enhanced binding strength for HMG-CoA reductase (48). Rosuvastatin also has additional sites of activity against HMG-CoA reductase compared to other statins. In large UK and Canadian databases including over 20,000 patients taking rosuvastatin and over 130,000 patients taking other statins, there was no evidence of increased risks of myopathy, rhabdomyolysis, acute liver or renal injury, or mortality with rosuvastatin compared to other statins (49,50).

The safety of very low LDL levels or large reductions in lipid lowering has also been a concern. A meta-analysis including 23 statin treatment arms with 309,506 person-years of follow-up found no significant relationship between achieved LDL levels and elevated liver enzymes or rhabdomyolysis (51). However, in this study the risk of cancer was significantly associated with lower achieved LDL levels but not the magnitude of reduction in LDL. In contrast, the CTT Collaborators meta-analysis

Table II. Low rates of laboratory abnormalities and rhabdomyolysis in trials comparing intensive versus moderate statin therapy in patients at high cardiovascular risk.

	AST and/or ALT $>3\times$ULN[a]		CK $>10\times$ULN[b]		Rhabdomyolysis[c]	
Trial (ref) / patient population: n – follow-up	Moderate	Intensive	Moderate	Intensive	Moderate	Intensive
PROVE-IT (26)/ACS: 4162–2 years	1.1%	3.3%	0.10%	0.15%	0%	0%
A to Z (27)/ACS: 4497–2 years	0.36%	0.84%	0.04%	0.4%	0%	0.13%
TNT (23)/CHD: 10001–4.9 years	0.18%	1.2%	0%	0%	0.06%	0.04%
IDEAL (25)/CHD: 8888–4.8 years	0.16%	1.37%	0%	0%	0.07%	0.05%

[a]PROVE-IT reported elevations in ALT; IDEAL reported number of abnormalities.
[b]A to Z reported 1 additional patient with an alcohol-related rise in CK without muscle symptoms.
[c]Case definition: TNT and IDEAL were based on the treating physician's diagnosis; A to Z defined as CK levels >10,000 U/L.
ACS = acute coronary syndromes; ALT = alanine aminotransferase; AST = aspartate aminotransferase; CHD = coronary heart disease; CK = creatine kinase; ULN = upper limit of normal.

found no evidence that statins increased the incidence of cancer overall or at any particular site in the overall patient group ($n = 90{,}056$) (5) or the subgroup with diabetes ($n = 18{,}686$) (22). This is supported by a recent cohort study comparing 24,439 patients taking statins with 7,284 control subjects (52). During a mean follow-up of 2.9 years there was no evidence of increased incidence rates of colorectal, lung, or breast cancers in either group; rates were very similar to rates in the general population.

Cost-effectiveness of intensive statin therapy

Since cost is the major driving factor behind statin reimbursement policies advocating wide-spread switching of patients to generic statins, the cost-effectiveness of statins should be considered. In patients at lower CV risk, less potent generic statins may be a cost-saving option, provided lipid targets can be achieved. However, in patients at high risk, drug acquisition costs should be balanced against the cost of revascularizations, hospital admissions with ACS, heart failure, or stroke, out-patient visits, and CV investigations over subsequent years.

Outcome data from the PROVE-IT (26) and A to Z (27) trials were used to analyse the cost-effectiveness of high-dose statin therapy in patients with ACS or stable CHD (53). High-dose statin therapy was cost-effective in patients with ACS; however, in patients with stable CHD, the cost-effectiveness was highly sensitive to model assumptions about statin efficacy and cost. In patients with ACS, the high-dose strategy resulted in a gain of 0.35 quality adjusted life-years (QALYs) and consistently yielded incremental cost-effective ratios (ICERs) below $30,000 per QALY compared to a conventional-dose strategy. A separate pharmacoeconomic analysis based on data from the PROVE-IT trial (26) also supported the cost-effectiveness of a high-dose strategy in patients with ACS (54). A pharmacoeconomic analysis of data from the TNT trial (26) has also been conducted, which further supported the cost-effectiveness of intensive statin therapy in patients with CHD (55).

An analysis using data from the IDEAL trial (25) evaluated the long-term cost-effectiveness of high-dose atorvastatin compared with generic simvastatin for secondary prevention (56). The Markov model included the risk of MIs and revascularization procedures as well as the long-term costs (direct and indirect), quality of life, and mortality associated with these events. High-dose statin was associated with 0.033 QALYs gained, with the cost per QALY gained being estimated at between 35,000 to 62,000 euros, depending mainly on the cost of generic simvastatin (20–40 mg) in various European countries. A higher risk of events was associated with lower ICERs.

A cost-consequence model was used to estimate the costs of medications and CV events in highest-risk patients over 2 years using real-world price and adherence data (57). Relative to simvastatin, atorvastatin would prevent 941 CV events after 1 year and 1426 events after 2 years per 100,000 patients. This would be expected to reduce the cost of cardiovascular events by $365 and $552 per patient (US$ 2006), respectively, offsetting 80% and 75% of the medication cost difference between atorvastatin and simvastatin after 1 and 2 years, respectively. For patients with ACS, atorvastatin was cost-saving compared with generic simvastatin ($-$$267) in this study. Another modelling study assessed the cost of achieving LDL targets in Greece, including costs of medications, lab tests, and out-patient visits, and found that the cost per patient was lower with atorvastatin than with simvastatin (58).

A US retrospective database analysis including over 10,000 patients newly prescribed statin therapy found that intensive therapy with rosuvastatin was cost-effective in reducing LDL and attaining LDL targets compared with atorvastatin, particularly in patients at moderate/high CV risk (59).

In contrast, an analysis using data from the Heart Protection Study (HPS) in patients with coronary disease, other occlusive arterial disease, or diabetes, assessed the cost-effectiveness of potential use of generic simvastatin 40 mg daily. They found that gains in life expectancy and cost savings decreased with increasing age and with decreasing risk of vascular disease. However, generic simvastatin therapy remained cost-effective in people as young as 35 years or as old as 85 with 5-year CVD risks as low as 5% at the start of treatment.

Studies on the consequences of policy-driven statin substitution

As with any therapeutic approach, substituting to generic statins should be evidence-based and consider the individual patient's CV risk. Expected reductions in LDL are 30%–47% with simvastatin (10–80 mg) and 22%–37% with pravastatin (10–80 mg) compared with 39%–60% with higher potency statins such as atorvastatin (10–80 mg) and 44%–63% with rosuvastatin (5–40 mg) (Food and Drug Administration (FDA)-approved US prescribing information). As a result low-dose generic statins are unlikely to get many patients, particularly those at high risk, to currently recommended LDL targets. In fact, among patients with diabetes, the likelihood of attaining

LDL targets was 87% with rosuvastatin, 77% with atorvastatin, 69% with simvastatin, 61% with fluvastatin, and 55% with pravastatin or lovastatin (60). In addition, a class effect in terms of the magnitude of reduction in CV events cannot be assumed based on the surrogate end-points of lipid lowering (61).

Policy-driven substitution of medications for less costly alternatives would seem logical and desirable if the same efficacy could be retained. However, observational data suggest that switching medications, even for medical reasons (such as inadequate efficacy or tolerability), is associated with problems, including decreased medication adherence, lower therapeutic doses, and increased LDL levels and CV events (62–65). These problems are being magnified on a population level when broad-sweeping policy-driven substitutions of statin therapy are instituted, with studies showing population-wide increases in LDL levels and CV events (66,67).

In addition, switching medications may impact medication adherence, compounding the increase in lipid levels. A retrospective observational analysis of 38,866 new statin users found that patients who switched statins were 19% less compliant, and 21%–48% less persistent over the long term (62). Greater statin potency (68) and greater early reductions in LDL levels (69) have been associated with greater long-term persistence suggesting a benefit to initiating and continuing therapy with more potent statins.

In one study, switching from atorvastatin to simvastatin was associated with lower therapeutic doses in 38% of patients overall, and 73%–100% of patients previously on atorvastatin 40 or 80 mg (63). An analysis of 122 patients who were switched to simvastatin from other statins found that 38% experienced an increase in LDL levels (64). In contrast, a report on the use of generic statins in the UK found that primary care trusts (PCTs) that used a high proportion of simvastatin and pravastatin were just as successful achieving cholesterol targets for high-risk patients as those that used more atorvastatin, rosuvastatin, or fluvastatin (70). However, total cholesterol targets (5 mmol/L) were higher than those currently recommended for patients at high risk (4.5 mmol/L with an optional 4.0 mmol/L) (2). Another study in primary care patients in the UK reported that a switch from atorvastatin to an equipotent dose of simvastatin was associated with no change in serum cholesterol levels, over the short or long term, and substantial cost savings (71,72). However, clinician judgement deemed that switching was not appropriate for 35% of identified patients on atorvastatin 10 or 20 mg. These data emphasize that while switching may be useful in some patients, it should not be a mandated policy for all. A LDL target-driven algorithm for switching patients from atorvastatin to other statins was a more successful approach compared to usual care switching (73). The percentage of patients achieving LDL goals increased after switching in the group using the target-driven algorithm (80% before and 97% after) and decreased after switching in the usual care group (90% before and 75% after).

The Health Improvement Network (THIN) retrospective database study conducted in the UK showed that a switch from atorvastatin to simvastatin was associated with a significant increase in the risk of death or major CV events (65). The analysis included 2,511 patients who had received atorvastatin for at least 6 months and were subsequently switched to simvastatin, and 9,009 matched 'control' patients who remained on atorvastatin. A significant 30% increase in the risk of death or first major CV event was associated with switching compared with patients who did not switch during a mean 1.2 years of follow-up. In addition, discontinuation (defined as $\geq$90 days of non-exposure to statin) rates were more than twice as high in patients who switched from atorvastatin to simvastatin compared to those who did not switch. Although this study was observational, it highlights the potential for poorer CV outcomes in patients switching statin therapy.

Observational studies assessing the impact of blanket generic drug substitution are particularly intriguing. In New Zealand, when reference pricing resulted in a switch from simvastatin to fluvastatin in the 1990s, 127 patients from the Otaga region were followed for 6 months (66). There was a 34% increase in LDL over this period. At the same time, there were 27 CV events in patients on fluvastatin compared to 9 with simvastatin. This trend reversed again when simvastatin was reinstituted after 6 months (66).

The ACS treatment policy change audit conducted in the UK found that a sweeping policy of switching of all patients with ACS from atorvastatin 80 mg to simvastatin 20–40 mg was associated with an increased mortality rate (67). This survey retrospectively examined patients before and after the switch; because of the cyclic variation in MIs the same 6-month time period was assessed over two consecutive years. Mortality rates were 5% in the atorvastatin group, and 17% in the simvastatin group. Cardiac and non-cardiac readmissions were also lower in the atorvastatin group. The study is

Table III. Observational studies on the consequences of policy-driven statin substitution.

Data sources (*n*-value)	Outcomes
US pharmacy claims database ($n=38,866$) (62)	Patients who switched statins for any reasons were: –19% less compliant –21%–48% less persistent over the long term
National US database ($n=453,409$) (63)	Switching from atorvastatin to simvastatin was associated with lower therapeutic doses in: –38% of patients overall –73%–100% of patients previously on atorvastatin 40 or 80 mg
US medical records database ($n=277$) (64)	Switching to simvastatin from other statins: –38% of patients experienced an increase in LDL levels
UK PCTs ($n=303$) (70)	PCTs with high versus lower proportions of generic statin use: –No difference in rate of successfully achieving total cholesterol targets for high-risk patients (<5 mmol/L)
UK PCT ($n=70$) (71,72)	Switch from atorvastatin to an equipotent dose of simvastatin: –No change in serum cholesterol levels, short or long term –Substantial cost savings –Switching not appropriate for 35% of patients on atorvastatin 10 or 20 mg
Colorado Indigent Care Program (n = 117) (73)	Switch from atorvastatin to other statins using a LDL target-driven algorithm versus usual care switching associated with more patients achieving LDL goals: –Target-driven algorithm (80% before and 97% after) –Usual care group (90% before and 75% after)
The Health Improvement Network (THIN) ($n=2,511$ switch patients versus $n=9,009$ controls) (65)	Switch from atorvastatin to simvastatin: –Significant 30% increase in risk of death or major CV events –Double rate of discontinuation
New Zealand Hospital records database ($n=127$) (66)	Switch from simvastatin to fluvastatin: –34% increase in LDL over 6 months –More CV events with fluvastatin ($n=27$) versus simvastatin ($n=9$)
UK ACS treatment policy change audit, hospital records database ($n=221$ patients with ACS) (67)	Hospital switch from atorvastatin 80 mg to simvastatin 20–40 mg: –Higher mortality rates: simvastatin (17%) versus atorvastatin (5%) –More cardiac and non-cardiac readmissions with simvastatin

ACS = acute coronary syndrome; CV = cardiovascular; LDL = low-density lipoprotein; PCT = primary care trust.

limited by the fact that it was a single centre study and included only 100 patients in each group.

Summary

There is increasing awareness of the need for cost containment measures in the health care arena. In CV disease prevention, current guidelines from diverse consensus groups give clear and consistent definitions of populations at risk and target LDL levels. However, the heterogeneity of reimbursement policies from country to country contrasts to the homogeneity of guidelines from around the world, all of which are presumed to have been developed based on assessments of current state-of-the-art clinical trial evidence. As health care policy restrictions increase there will continue to be consequential decreases in the physician's ability to make individualized patient decisions. Every physician has an economic responsibility to society in general, but how we balance this with clinical responsibility for individuals is a new, and hitherto unknown, challenge that has not been exposed sufficiently to scientific scrutiny.

The question raised in this article is whether a policy of one statin for all is appropriate. There is strong evidence that statin therapy is beneficial, and that patients at highest risk can benefit from more intensive therapy. There is some evidence that substitution of medications in patients who do not require a therapeutic change can have detrimental effects. The cardiovascular community prides itself on adhering to evidence-based medicine, therefore, policy-driven medication substitution on a population level designed to affect a vast number of patients also needs adequate, well designed, and comprehensive studies, in order to scientifically support, dismiss, or differentiate such actions.

Acknowledgements

Editorial support was provided by Pauline Lavigne MSc at CMED Interactive and was funded by Pfizer Inc.

Declaration of interest: All authors have read and approved submission of the manuscript, and the manuscript has not been published and is not being considered for publication elsewhere in whole or part in any language.

The authors alone are responsible for the content and writing of the paper.

Potential conflicts of interest are listed below.

In the following, the term "economic support" denotes speaker's honorarium, participation at congresses, consultancy fees or research grants.

DA has received economic support from: Astra Zeneca, Merck, MSD, Novartis, Pfizer, Pronova BioPharma, Schering-Plough.

RC has received economic support from: Astra Zeneca, BMS, GSK, Merck, MSD, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough.

PC has received economic support from: Astra Zeneca, Merck, MSD, Novartis, Pfizer, Sanofi-Aventis, Schering-Plough.

AKL is an employee of Pfizer.

PL has received economic support from: Merck, Merck Sharp & Dohme, Pfizer, Sanofi-Aventis, Schering-Plough.

SW has received economic support from Astra-Zeneca, Bayer, Boehringer Ingelheim, Daiichi Sankyo, GSK, Merck, MSD, Novartis, Pfizer, Sanofi-Aventis, UCB.

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