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Generic Statins in Cardiovascular Medicine

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Abstract

Cardiovascular disease is the leading cause of death and disability in Europe. Several large, population-based trials and their meta-analyses have shown the beneficial effects of statins in reducing mortality and cardiovascular morbidity both primary and secondary prevention. Use of generic drugs, which are bioequivalent to brand-name drugs, can help contain prescription drug spending. However, there is concern among patients and physicians that brandname drugs may be clinically superior to generic drugs. The aim of our study was to review the efficacy of generic statin therapy in both primary and secondary vascular prevention.

Treatment with generic statins seem to be safe and quite effective. Lipid parameters should be monitorized, there are class effects in the lipid lowering potency of different drugs. Based on comparism trials, worsening lipid profile was associated with unfavourable outcome. From an economic point of view, society could gain a lot from substituting statin therapy, especially from therapeutic substitution. Moreover, prescribing generic or preferred medications within a therapeutic class seemed to be associated with improvements in adherence to therapy.

Keywrds: Statin; Primary prevention; Secondary prevention; Generic substitution; Vascular disease; Atherosclerosis

Introduction

Cardiovascular disease is the leading cause of death and disability in Europe [1]. Several large, population-based trials and their meta-analyses have shown the beneficial effects of statins in reducing mortality and cardiovascular morbidity both primary and secondary prevention [1,2]. Statins have been associated with a variety of pleiotropic effects, including atherosclerotic plaque stabilization, decreased inflammation, improvement in endothelial function, and altered thrombogenicity [1,2].

International clinical guidelines recommend total cholesterol of <190 mg/dl and low-density lipoprotein (LDL) cholesterol of <115 mg/dl as objectives for the general population, and of <175 mg/dl and <100 mg/dl respectively in secondary prevention and diabetes [3,4].

The problem of rising prescription drug costs has emerged as a critical policy issue, straining the budgets of patients and public/private insurers and directly contributing to adverse health outcomes by reducing adherence to important medications [4-8]. The primary drivers of elevated drug costs are brand-name drugs, which are sold at high prices during a period of patent protection [8]. To control spending, many payers and providers have encouraged substitution of inexpensive bioequivalent generic versions of these drugs, which can legally be marketed by multiple manufacturers after the brand-name manufacturer's market exclusivity period ends [8]. Some physicians and patients have expressed concern that bioequivalent generic and brandname drugs may not be equivalent in their effects on various clinical parameters, including physiological measures such as heart rate or blood pressure, important laboratory measurements, and outcomes such as health system utilization or mortality [8].

The aim of our study was to review the efficacy of generic statin therapy in both primary and secondary vascular prevention.

Statins in primary prevention

Statins, especially generic statins are widely used in the primary prevention of vascular diseases. On the other hand, the benefitial effects of statins in this population are controversial. Several review and meta-analyses examined the efficacy of statins in primary prevention trials. Results were controversial, the first three published review and meta analysis showed that primary prevention with these drugs provided only small and clinically hardly relevant improvement of cardiovascular morbidity/mortality while secondary prevention provided considerable improvement of cardiovascular morbidity/mortality [9,11] (Table 1).

To clarify the disconcordant results of the above mentioned studies (using strict inclusion–exclusion criteria) including 19 trials (63899 patients) represented a comprehensive meta-analysis of statin therapy for primary prevention and this meta-analysis concluded that statins have a clear role in primary prevention of CVD mortality and major events [12] (Table 1).

Interestingly, a very recent Cochrane analysis showed that limited evidence showed that primary prevention with statins may be cost effective and improve patient quality of life. In the authors' conclusion caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk [13]. This was also in concordance with recently published articles [14,15].

On the other hand, results are still controversial. There are also numerous meta-analysis showing benefitial effects of statin therapy in primary prevention [16-19] (Table 1, Figure 1). In a very recent meta-analysis which was included in the ESC guidelines showed that

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Study	Population	Results	Conclusion
Vrecer et al. [9]	Data from 15 trials with 63,410 participants and mean duration of treatment of 3.6 years, were included in this overview.	Overall (**primary** and **secondary** studies) statin therapy significantly reduces relative risk of **coronary** events (RR, 0.73, 95% CI, 0.68, 0.77, *p < 0.0001), relative risk of cardiovascular **disease** mortality (RR, 0.78, 95% CI, 0.73, 0.84, *p < 0.0001), relative risk of non-fatal **stroke** (RR, 0.74, 95% CI, 0.67, 0.82, *p < 0.0001), relative risk of total (fatal and non-fatal) **stroke** (RR, 0.77, 95% CI, 0.70, 0.84, *p < 0.001) and relative risk of all-cause death (RR, 0.85, 95% CI, 0.81, 0.89, *p < 0.0001). There was a slight and insignificant reduction of relative risk in non-cardiovascular mortality (RR, 0.94, 95% CI, 0.86, 1.03, p = 0.1677) and fatal strokes (RR, 0.86, 95% CI, 0.70, 1.07, p = 0.1912).	While secondary prevention with statins provided considerable improvement of cardiovascular morbidity / mortality, primary prevention with statins provides only small and clinically hardly relevant improvement of cardiovascular morbidity/mortality.
Thavendiranathan et al. [10]	Seven trials with 42,848 patients were included. Ninety percent had no history of CV disease. Mean follow-up was 4.3 years.	Statin therapy reduced the RR of major coronary events, major cerebrovascular events, and revascularizations by 29.2% (95% CI, 16.7%-39.8%) (P<.001), 14.4% (95% CI, 2.8%-24.6%) (P = .02), and 33.8% (95% CI, 19.6%-45.5%) (P<.001), respectively. Statins produced a nonsignificant 22.6% RR reduction in coronary heart disease mortality (95% CI, 0.56-1.08) (P = .13). No significant reduction in overall mortality (RR, 0.92 [95% CI, 0.84-1.01]) (P = .09) or increases in cancer or levels of liver enzymes or creatine kinase were observed.	In patients without CV disease, statin therapy decreases the incidence of major coronary and cerebrovascular events and revascularizations but not coronary heart disease or overall mortality.
Ward et al. [11]	Thirty-one randomised studies were identified that compared a statin with placebo or with another statin, and reported clinical outcomes.	Meta-analysis of the available data from the placebo-controlled studies indicates that, in patients with, or at risk of, CVD, statin therapy is associated with a reduced relative risk of all cause mortality, cardiovascular mortality, CHD mortality and fatal myocardial infarction (MI), but not of fatal stroke. It is also associated with a reduced relative risk of morbidity [non-fatal stroke, non-fatal MI, transient ischaemic attack (TIA), unstable angina] and of coronary revascularisation.	The cost-effectiveness modelling presented here has shown that statin therapy in secondary prevention is likely to be considered cost-effective while in primary prevention, the cost-effectiveness ratios are dependent on the level of CHD risk and age,
Mills et al. [12]	They included 20 randomized clinical trials.	They pooled 19 trials (n = 63,899) for all-cause mortality and found a relative risk (RR) of 0.93 (95% confidence interval [CI]: 0.87 to 0.99, p = 0.03 [I(2) = 5%, 95% CI: 0% to 51%]). Eighteen trials (n = 59,469) assessed cardiovascular deaths (RR: 0.89, 95% CI: 0.81 to 0.98, p = 0.01 [I(2) = 0%, 95% CI: 0% to 41%]). Seventeen trials (n = 53,371) found an RR of 0.85 (95% CI: 0.77 to 0.95, p = 0.004 [I(2) = 61%, 95% CI: 38% to 77%]) for major cardiovascular events, and 17 trials (n = 52,976) assessed myocardial infarctions (RR: 0.77, 95% CI: 0.63 to 0.95, p = 0.01 [I(2) = 59%, 95% CI: 24% to 74%]). Incidence of cancer was not elevated in 10 trials (n = 45,469) (RR: 1.02, 95% CI: 0.94 to 1.11, p = 0.59 [I(2) = 0%, 95% CI: 0% to 46%]), nor was rhabdomyolysis (RR: 0.97, 95% CI: 0.25 to 3.83, p = 0.96 [I(2) = 0%, 95% CI: 0% to 40%]).	Statins have a clear role in primary prevention of CVD mortality and major events.
Taylor et al. [13]	Fourteen randomised control trials (16 trial arms; 34,272 participants) were included.	Eleven trials recruited patients with specific conditions (raised lipids, diabetes, hypertension, microalbuminuria). All-cause mortality was reduced by statins (RR 0.83, 95% CI 0.73 to 0.95) as was combined fatal and non-fatal CVD endpoints (RR 0.70, 95% CI 0.61 to 0.79). Benefits were also seen in the reduction of revascularisation rates (RR 0.66, 95% CI 0.53 to 0.83). Total cholesterol and LDL cholesterol were reduced in all trials but there was evidence of heterogeneity of effects. There was no clear evidence of any significant harm caused by statin prescription or of effects on patient quality of life.	Although reductions in all-cause mortality, composite endpoints and revascularisations were found with no excess of adverse events, there was evidence of selective reporting of outcomes, failure to report adverse events and inclusion of people with cardiovascular disease. Only limited evidence showed that primary prevention with statins may be cost effective and improve patient quality of life. Caution should be taken in prescribing statins for primary prevention among people at low cardiovascular risk.
Ray et al. [14]	Data were available on 65,229 participants followed for approximately 244,000 person-years, during which 2793 deaths occurred.	The use of statins in this high-risk primary prevention setting was not associated with a statistically significant reduction (risk ratio, 0.91; 95% confidence interval, 0.83-1.01) in the risk of all-cause mortality. There was no statistical evidence of heterogeneity among studies (I(2) = 23%; 95% confidence interval, 0%-61% [P = .23]).	This literature-based meta-analysis did not find evidence for the benefit of statin therapy on all-cause mortality in a high-risk primary prevention set-up.
Brugts et al. [18]	10 trials enrolled a total of 70 388 people, of whom 23 681 (34%) were women and 16 078 (23%) had diabetes mellitus. Mean follow-up was 4.1 years.	Treatment with statins significantly reduced the risk of all cause mortality (odds ratio 0.88, 95% confidence interval 0.81 to 0.96), major coronary events (0.70, 0.61 to 0.81), and major cerebrovascular events (0.81, 0.71 to 0.93). No evidence of an increased risk of cancer was observed. There was no significant heterogeneity of the treatment effect in clinical subgroups.	In patients without established cardiovascular disease but with cardiovascular risk factors, statin use was associated with significantly improved survival and large reductions in the risk of major cardiovascular events.

Table 1: Primary prevention meta-analysis with statins.

further reductions in LDL cholesterol safely produce definite further reductions in the incidence of heart attack, of revascularisation, and of ischaemic stroke, with each 1·0 mmol/L reduction reducing the annual rate of these major vascular events by just over a fifth. There was no evidence of any threshold within the cholesterol range studied, suggesting that reduction of LDL cholesterol by 2–3 mmol/L would reduce risk by about 40–50% [20]. The benefitial results can be seen in primary prevention populations (Figure 2).

Generic statins on primary prevention

Some physicians and patients have expressed concern that bioequivalent generic and brandname drugs may not be equivalent in their effects on various clinical parameters, including physiological measures such as heart rate or blood pressure, important laboratory measurements, and outcomes such as health system utilization or mortality [8]. In a systematic review and meta-analysis studies compared generic and brand-name cardiovascular drugs using clinical efficacy and safety end points were collected. The authors also separately identified editorials addressing generic substitution. They concluded that evidence did not support the notion that brand-name drugs used in cardiovascular disease were superior to generic drugs, a substantial number of editorials counselled against the interchangeability of generic drugs [8].

Only a few head-to-head comparism could be found. The above mentioned article included two generic sattin studies (based on simvastatin). Wiwanitkit et al. [21] conducted a randomized crossover study in Thailand comparing generic and brand simvastatin. Their study demonstrated no significant differences in the therapeutic effect and safety between the generic and original simvastatin products [21]. The study of Assawawitoontip et al. [22] led to the same result.

In their study, Kim et al. [23] examined the efficacy and tolerability of a generic and a branded formulation of atorvastatin 20 mg/d in hypercholesterolemic Korean adults at high risk for cardiovascular disease. A total of 211 patients completed the study (50.7% male; 100% Asian; mean [SD] age, 61.7 [9.2] years) (106 patients in the group that received the generic formulation and 105 patients in the group that received the branded formulation). LDL-C concentrations were reduced from the baseline by 44% and 46% after 8 weeks of treatment with the generic and branded formulations, respectively (P = NS).

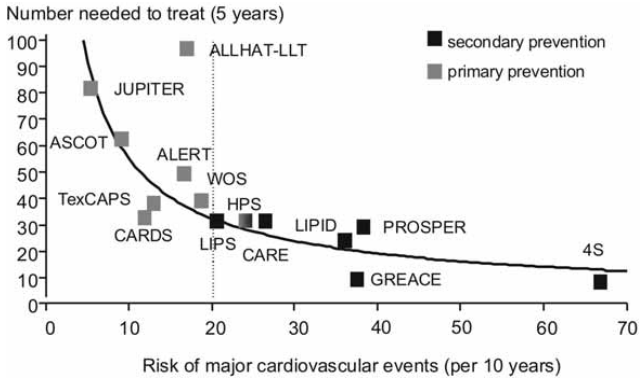

Figure 1: Relationship between the number of persons to prevent one major coronary event (number needed to treat NNT, based on 5 years) and "global" cardiovascular risk in statin trials (expressed as the rate of fatal and non-fatal events per 10 years), Taken from Ref [19].

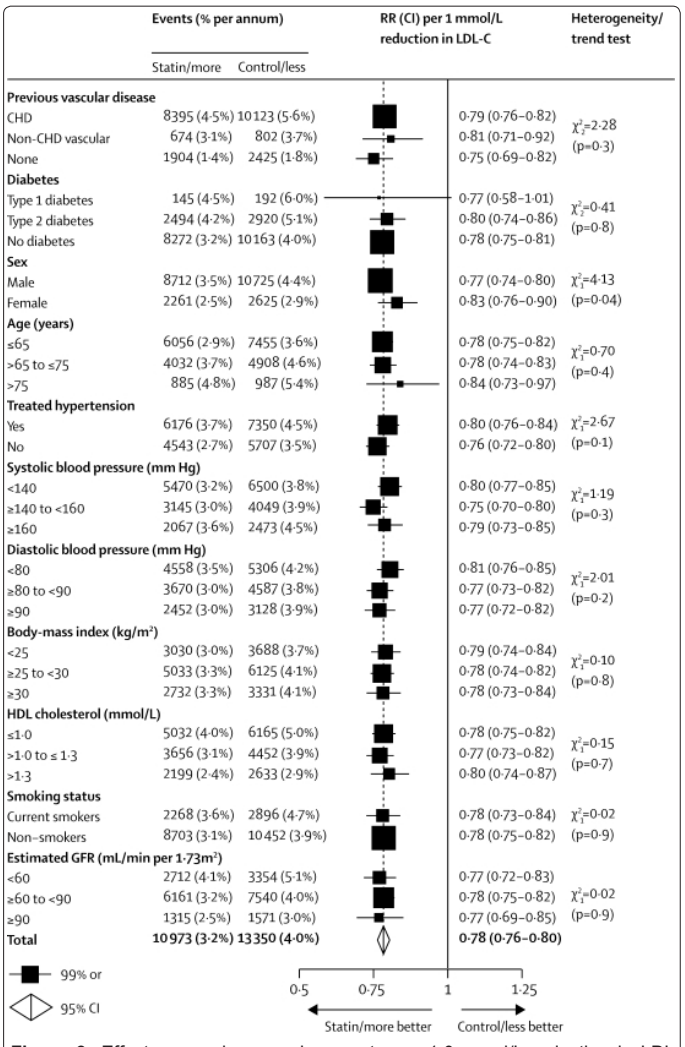

Figure 3: Effects on major vascular events per 1·0 mmol/L reduction in LDL cholesterol, by baseline prognostic factors, Taken from Ref [20].

The percentage changes from baseline to study end in HDL-C, TC, TG, apo A1, apo B, and hsCRP concentrations and sdLDL fraction the proportions of patients who achieved the LDL-C goal between the 2 groups did not reach statistical significance. The most commonly reported events were hepatobiliary laboratory abnormality (1.7%), general somatic discomfort (1.7%), and epigastric pain (0.8%) in the group that received the generic formulation, and myalgia (1.7%), epigastric pain (0.9%), and elevation of creatinine phosphokinase (0.9%) in the group that received the branded formulation. No serious adverse events were reported in either group [23].

In a Chinese study the efficacy and safety of two generic forms of 10 mg atorvastatin tablets were studied compared to the reference product [24]. This was a single-dose, randomized-sequence, open-label, 2-period crossover study with a 2-week washout period between doses. Healthy Chinese males (study population: 46) were randomly assigned to receive 20 mg of either the test or reference formulation, and 13 blood samples were obtained over a 48-hour interval. Plasma concentrations of parent atorvastatin and ortho-hydroxy-atorvastatin (primary active metabolite) were simultaneously determined using a validated liquid chromatography-isotopic dilution mass spectrometry

method. Pharmacokinetic parameters, including C(max), T(max), t((1/2)), AUC(0-t), and AUC(0-infinity)), were calculated. The mean values of C(max), AUC(0-t), and AUC(0-infinity)) for the test and reference formulations of atorvastatin (8.78 and 10.76 ng/mL, 38.22 and 40.02 ng/mL/h, 42.73 and 44.51 ng/mL/h, respectively) and ortho-hydroxy-atorvastatin (5.78 and 5.77 ng/mL, 47.32 and 48.47 ng/mL/h, 52.36 and 53.14 ng/mL/h) were not significantly different. The 90% CIs for natural log-transformed ratios of C(max), AUC(0-t), and AUC(0-infinity)) of both atorvastatin (0.73-0.91, 0.92-1.02, and 0.91-1.01, respectively) and ortho-hydroxy-atorvastatin (0.83-1.05, 0.92-1.02, and 0.93-1.02) were within the bioequivalence acceptance limits. Three subjects (6.5%) reported a total of 4 mild AEs (1 abdominal discomfort and 3 venipuncture syncope), which were not considered to be associated with administration of the study drug. This single-dose (20 mg) study found that the test and reference formulations of atorvastatin calcium 10-mg tablet met the regulatory definition for assuming bioequivalence in these healthy fasted male volunteers. Both formulations were generally well tolerated in the population studied.

These studies suggest the boiequivalance of generic statins. Despite of their larger use, several recent cost-effectiveness analysis showed the superiority of brand statins in reaching the target lipid levels in different risk categories.

In a Canadian study compared the costeffectiveness of atorvastatin and generic simvastatin in terms of annual drug cost per patient treated to Canadian LDL-C targets. It was conducted from the perspective of the Canadian provincial drug-reimbursement plans. In this hypothetical cohort of 1000 dyslipidemic patients, treatment with atorvastatin would allow achievement of LDL-C targets in more patients than treatment with simvastatin, at an annual incremental cost of $1088 per additional patient treated to target [25]. Recently, the costeffectiveness of rosuvastatin have been shown in several economical studies above generic substitutions [26-28].

In general, from an economic point of view, society could gain a lot from substituting statin therapy, especially from therapeutic substitution [29]. Moreover, prescribing generic or preferred medications within a therapeutic class was associated with improvements in adherence to therapy as recently has been shown by Shrank and his collegues [30]. Switching the brand statin to an equivalent dose of generic statin (maybe from another class) can be associated with no change in lipid control [31].

At last, randomized controlled trial data, an internally validated vascular disease model, and US costs of statin therapy and other medical care were used to project lifetime risks of vascular events and evaluate the cost-effectiveness of 40 mg simvastatin daily. This analysis suggested that treatment with generic simvastatin appears to be cost-effective for a much wider population in the United States than that recommended by current guidelines [32].

Statins in secondary prevention

The role of statins in the secondary prevention of vascular events is well established (Figure 1 and 2). In the case of periperal arterial disease a Cochrane meta-analysis were carried out in 2007 [33]. Eighteen trials were included, involving a total of 10,049 participants. Trials differed considerably in their inclusion criteria, outcomes measured, and type of lipid-lowering therapy used. Only one trial (PQRST) reported a detrimental effect of active treatment on blood lipid/lipoprotein levels. The pooled results from all eligible trials indicated that lipid-lowering therapy had no statistically significant effect on overall mortality (Odds Ratio (OR) 0.86; 95% Confidence Interval (CI) 0.49 to 1.50) or on total cardiovascular events (OR 0.8; 95% CI 0.59 to 1.09). However, subgroup analysis which excluded PQRST showed that lipid-lowering therapy significantly reduced the risk of total cardiovascular events (OR 0.74; CI 0.55 to 0.98). This was primarily due to a positive effect on total coronary events (OR 0.76; 95% CI 0.67 to 0.87). Greatest evidence of effectiveness came from the use of simvastatin in people with a blood cholesterol >/= 3.5 mmol/litre (HPS). Pooling of the results from several small trials on a range of different lipid-lowering agents indicated an improvement in total walking distance (Weighted Mean Difference (WMD) 152 m; 95% CI 32.11 to 271.88) and pain-free walking distance (WMD 89.76 m; 95% CI 30.05 to 149.47) but no significant impact on ankle brachial index (WMD 0.04; 95% CI -0.01 to 0.09). At the moment, statins seem to be the most effient drugs for improving walking distance in this population [34].

Meta-analysis of randomised trials of statins in combination with other preventive strategies, including 165 792 individuals, showed that each 1 mmol/L (39 mg/dL) decrease in LDL cholesterol equates to a reduction in relative risk for stroke of 21.1% (95% CI 6.3-33.5, p=0.009). In secondary prevention of non-cardioembolic stroke, intense reduction of LDL cholesterol by statins also significantly reduced the risk of recurrent stroke (relative risk 0.84, 0.71-0.99, p=0.03) and major cardiovascular events (0.80, 0.69-0.92, p=0.002). Future directions include assessment of a target LDL cholesterol concentration of less than 1.8 mmol/L (70 mg/dL), the effects of triglyceride-lowering therapy alone or in combination with statins, and the effects of treatments to raise HDL cholesterol concentrations [35].

In the case of coronary heart disease a meta analysis of 76 RCTs involving 170,255 participants was carried out. Statin therapy reduced all-cause mortality, Relative Risk (RR) 0.90 [95% confidence interval (CI) 0.86-0.94, P ≤ 0.0001, I(2)=17%]; cardiovascular disease (CVD) mortality (RR 0.80, 95% CI 0.74-0.87, P<0.0001, I(2)=27%); fatal myocardial infarction (MI) (RR 0.82, 95% CI 0.75-0.91, P<0.0001, I(2)=21%); non-fatal MI (RR 0.74, 95% CI 0.67-0.81, P ≤ 0.001, I(2)=45%); revascularization (RR 0.76, 95% CI 0.70-0.81, P ≤ 0.0001); and a composite of fatal and non-fatal strokes (0.86, 95% CI 0.78-0.95, P=0.004, I(2)=41%). Adverse events were generally mild, but 17 RCTs reported on increased risk of development of incident diabetes [Odds Ratio (OR) 1.09; 95% CI 1.02-1.17, P=0.001, I(2)=11%]. Studies did not yield important differences across populations. The authors could not find not find any differing treatment effects between statins [36].

Generic statins in secondary prevention

Generic switcing is a cost-saving method, but associated with worsening lipid profile. In a recent study Tunceli et al. identified 18,061 patients who, between September 1, 2004 and October 31, 2008, were either switched from or remained on their initial high-efficacy LDL-C lowering therapy: ezetimibe/simvastatin fixed-dose combination (E/S), rosuvastatin, or atorvastatin. The difference in percent change in LDL-C levels from baseline were 25.2 (95% confidence interval 21.2229.2), 13.0 (6.0220.0), and 3.1 (0.325.9) greater in switchers to simvastatin in the E/S, rosuvastatin, and atorvastatin comparisons, respectively, after adjusting for age, sex, and starting dose of the initial therapy. For switchers, the percent of patients at LDL-C ,100 mg/dL at follow-up decreased from 83.5% to 63.8% in the E/S, 67.7% to 52.7% in the rosuvastatin, and 65.1% to 60.2% in the atorvastatin cohorts. The percent of patients at LDL-C, 70 mg/dL at follow-up was lower for

all switcher groups compared with nonswitchers. Interestingly, hard endpoints were not analyzed in this study [37].

The IDEAL trial showed that treatment with 80 mg atorvastatin reduced major cardiovascular events by (RR 0.87; 95% CI 0.77–0.98) or any coronary event (RR 0.84; 95% CI 0.76–0.91). In the prevention of cardiovascular events among patients with a previous MI, high-dose atorvastatin appears to be a moderately cost-effective strategy compared with generic simvastatin 20–40 mg in Denmark, Norway, and Sweden. In Finland, it is best used in high-risk patients at current prices. The key driver of the cost-effectiveness was the price-difference between 80 mg atorvastatin and generic simvastatin [38].

This result was confirmed by a US study based on Among 13,584 matched pairs, treatment with atorvastatin vs simvastatin was associated with a reduced risk of cardiovascular-related hospitalization, higher adherence, and less use of other lipid-lowering drugs. The increase in statin costs associated with atorvastatin vs simvastatin therapy was almost completely offset by reductions in medical service and indirect costs [39]. During the 2-year outcome period, atorvastatin vs simvastatin patients experienced significantly lower rates of total inpatient cardiovascular events (7.5% vs 8.2%; P=.02). Treatment with atorvastatin vs simvastatin was also associated with fewer days of medically related absenteeism (12.2 vs 12.5; P=.02) and fewer total work loss days (23.0 vs 23.1; P=.04), higher rates of medication adherence (36.3% vs 33.1%; P<.001), and lower rates of nonadherence (11.4% vs 12.4%; P<.001), as well as lower concomitant use of other lipid-lowering medication (20.3% vs 24.9%; P<.001). As expected, pharmacy costs derived from index drug costs remained higher for atorvastatin because of the generic simvastatin ($946 vs $489; P<.001), but atorvastatin patients had slightly lower nonindex drug costs for all other drugs ($1293 vs $1315; *P*=.01) and for other cardiovascular-related drugs ($250 vs $275; *P*<.001). Treatment with atorvastatin vs simvastatin was also associated with lower cardiovascular-related medical service costs ($2889 vs $3115; *P*=.02), lower medically related absenteeism costs ($2692 vs $2798; *P*=.03), and model obtained via stepwise selection, treatment with atorvastatin vs simvastatin was associated with a statistically significant 11% reduction in the hazard of cardiovascular related hospitalization (hazard ratio, 0.89; 95% confidence interval, 0.85-0.95; P=.001).

Analyzing the data of the ALLIANCE study, it also led to the same result. Medical cost offsets associated with reduced events, resulted in accepted cost-effectiveness ranges comparing atorvastatin with a generic statin. Atorvastatin-based regimens produced cost savings from a managed-care perspective when the anticipated impact of the generic availability of atorvastatin was modeled [40].

On the other hand, there is a big difference between randomized multicentre and „real-life studies". In a two-centre London survey showed that among 1008 patients (755 who had PCI and 253 who had CABG) the use of aspirin, statins, angiotensin-converting enzyme (ACE) inhibitors or angiotensin receptor blockers (ARB), beta blockers and calcium channel blockers were, respectively, 97, 98, 81, 76 and 18%. The combination of any 4 classes of drug were used in 65% of patients [41]. Almost all patients who did not receive aspirin or a statin had clinical contraindications and were on alternative drugs (Figure 3). In about 12% of patients without an ACE inhibitor (or ARB) and 7% of

Category of drug	Number of patients not using recommended drug	Reasons given for not using specified drug (number of patients)	Alternative drug class used (number of patients)	Number and proportion of cases with no medical justification for withholding treatment and no valid alternative
Aspirin	32 (3%)	Gastrointestinal bleed (12) Dyspepsia (6) Taking warfarin (6) Other[a] (4) No clinical reason[b] (4)	Clopidogrel (23) Warfarin (8)	1 (0.1%)
Statin	23 (2%)	Myalgia (6) Diarrhoea (8) No clinical reason[b] (9)	Ezetimibe (18) Nicotinic acid (3)	2 (0.2%)
Beta blocker	235 (23.5%)	Asthma (79) Bradycardia (9) Hypotension (15) Other[c] (27) No clinical reason[b] (105)	Calcium channel blockers (82)	74 (7.4%)
ACE inhibitor or ARB	198 (19.8%)	Hypotension (20) Renal impairment (11) Other[d] (18) No clinical reason[b] (149)	Nitrates (22)	124 (12.4%)

[a]Bronchospasm (3), allergy (1).
[b]Use of recommended class of drug overlooked and no contraindication to its use.
[c]Patient on digoxin or amiodarone (8), intention to start treatment in primary care (8), sexual dysfunction (4), peripheral vascular disease (3), psoriasis (2), nightmares (1), aortic stenosis (1).
[d]Intention to start treatment in primary care (16), patient refused more medications (1), allergy (1).

Figure 3: Medical reasons for withholding recommended medications in 1008 patients with CHD, Taken from Ref [41].

	Combination [12-15]			4S trail [1]		
	Low dose (10-20 mg A or S)	High dose (80 mg A or S)	Δ% (95% CI)	placebo	S	Δ% (95% CI)
Patients	15,488	15,465		2,223	2,221	
Deaths	1,626 (10.5)	1,614 (10.4)	0.0 (-0.7 to 0.7)	256 (11.5)	182 (8.2)	3.3 (1.5 to 5.1)**
Cardiac deaths	744 (4.8)	723 (4.7)	0.1 (-0.4 to 0.6)	189 (8.5)	111 (5.0)	3.5 (2.0 to 5.0)**
MIs	1,092 (7.1)	907 (5.9)	1.2 (0.7 to 1.7)**	502 (22.6)[a]	353 (15.9)	6.7 (4.3 to 9.1)**
Strokes	6.8 (3.9)	525 (3.4)	0.5 (0.1 to 0.9)*	66 (3.0)	43 (1.9)	1.1 (0.2 to 2.0)*
In the combination, the high-dose arm (80 mg) is compared with the low-dose arm; in the 4S trial, the drug treatment arm is compared to placebo. In parentheses beside the number of patients is the percent of total patients in that category. Δ% is the percentage difference in the low-dose versus high-dose arms (combination) or S arm versus placebo (4S trial); the 95% confidence intervals for Δ% (95% CI) are shown in parentheses. * $p < 0.05$ by proportions test; ** $p < 0.001$ by proportions test with $Z > 3$.				[a] In the 4S trial, major coronary was defined as definite or probable or silent MI, resuscitated cardiac arrest or intervention-associated MI. This accounts, in part, for why there are more MIs in the 4S trial than in the TNT, IDEAL and SEARCH trials which used less inclusive definitions. In the 4S trial, if only definite MIs are counted, the numbers are 270 (12.1%) on placebo and 164 (7.4%) on S with a differential of 4.7% ($p < 0.001$).		

Table 2: Comparison of the combination of the TNT, IDEAL and SEARCH with the 4S trial (Taken from Ref [42]).

patients without a beta blocker, no reason to withhold such treatment was identified. Branded drugs were used in 52% of patients; the most commonly prescribed being atorvastatin in 33%. Clinical reasons for using branded rather than generic drugs were identified in 13% of cases.

So switching to a cheap, generic statin may be associated with worsening lipid profile thereby increasing the risk of unfavourable clinical outcome. To answer remaining questions about the optimal statin dose in CAD patients, Spector and Snapinn have performed simple and meta-analyses of 3 large long-term (approx. 5 years) dose-clinical response studies (TNT, IDEAL, and SEARCH) and compared the results with older data including long-term safety data [42]. The results showed that raising the dose of simvastatin or atorvastatin to 80 mg confers no mortality advantage, an increase in adverse reactions and only a slight decrease in myocardial infarctions and stroke versus a lower dose (Table 2). These results suggested a cost-effective approach of a single safe dose (40 mg of inexpensive generic simvastatin or atorvastatin) for almost all CAD patients and makes treatment-to-goal and cholesterol monitoring (except to check for medication compliance) unnecessary; moreover, it is likely to improve the weakness in statin use – medication compliance. So the above mentioned findings reinforce switching drugs even when showing that less potent statins were associated with worse outcomes.

Final Conclusion

The very recent ESC guidelines in the management of dyslipidaemias recommended that clinicians again should exercise judgement to avoid premature or unnecessary implementation of lipid-lowering therapy. Lifestyle interventions will have an important long-term impact on health, and the long-term effects of pharmacotherapy must be weighed against potential side effects (for example de novo diabetes) [43,44]. Regarding costeffectiveness and quality of life, caution is still needed in prescribing statins for primary prevention among people at low total CV risk. For subjects at moderate risk, an LDL-C target of < 3 mmol/L (less than ~ 115 mg/dL) should be considered.

Extrapolating from the available data, an absolute reduction to an LDL-C level < 1.8 mmol/L (less than ~70 mg/dL) or at least a 50% relative reduction in LDL-C provides the best benefit in terms of CVD reduction. In the majority of patients, this is achievable with statin monotherapy. Therefore, for patients with very high CV risk, the treatment target for LDL-C is ,1.8 mmol/L (less than ~70 mg/dL) or a ≥50% reduction from baseline LDL-C. Target levels for subjects at high risk are extrapolated from several clinical trials. An LDL-C level of < 2.5 mmol/L (less than ~ 100 mg/dL) should be considered for them [44].

Treatment with generic statins seem to be safe and quite effective. Lipid parameters should be monitorized, there are class effects in the lipid lowering potency of different drugs (1). As previously shown, worsening lipid profile has been associated with unfavourable outcome. On the other hand, a recent meta-analysis showed the efficacy of 40 mg simvastatin or 40 mg atorvastatin in secondary prevention trials. So the above mentioned findings reinforce switching drugs even when showing that less potent statins were associated with worse outcomes.

In general, from an economic point of view, society could gain a lot from substituting statin therapy, especially from therapeutic substitution [29]. Moreover, prescribing generic or preferred medications within a therapeutic class was associated with improvements in adherence to therapy [30]. Switching the brand statin to an equivalent dose of generic statin (maybe from another class) can be associated with no change in lipid control [31].

Patients' global risk and underlying diseases should also be considered. There are primary and secondary prevention problems worldwide [45-48].

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