

Statins for Secondary Prevention of Cardiovascular Disease: The Right Dose

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Key Words

Simvastatin · Dose-response studies · Cost effectiveness · Cholesterol · Coronary artery disease · Medication compliance

Abstract

Since the publication of the 4S trial in 1994, there has emerged a consensus that statins save lives and decrease myocardial infarctions and strokes in coronary artery disease (CAD) patients irrespective of baseline serum cholesterol. However, there is controversy over the correct dose and the utility of the treatment-to-goal (cholesterol, low-density lipoprotein) approach. To answer remaining questions about the optimal statin dose in CAD patients, we 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. The results show 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. These results suggest 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.

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Introduction and Background

In November 1994, the cholesterol controversy entered a new phase when the landmark 5-year randomized blinded 4S trial of simvastatin (S) versus placebo unequivocally established that treating coronary artery disease (CAD) patients with elevated serum cholesterol significantly decreased deaths (30% compared to placebo), myocardial infarctions (MIs; 30%) and strokes (approx. 35%) [1]. In the 4S trial, in the treatment arm, approximately two thirds of the patients took 20 mg and one third 40 mg S [1]. These results were subsequently confirmed in other statin secondary prevention trials. For example, the 6-year LIPID trial compared pravastatin (40 mg) with placebo in CAD patients with a lower cholesterol concentration than in the 4S trial and showed a 22% decrease in overall mortality and a 24% decrease in cardiac mortality (both $p < 0.001$) [2]. One characteristic of these statin trials was that the beneficial effect increased with time [1, 2]. Hence, to obtain a realistic account of the

benefit of statins in secondary prevention, trials need to last a minimum of 5 years.

Based on these statin trials, there was general agreement that all CAD patients (currently approx. 20 million in the United States) should be treated with statins irrespective of their serum cholesterol since CAD patients with lower serum cholesterol also benefit [2–4]. However, 2 treatment approaches emerged: one camp thought that the objective of treatment should be to lower serum cholesterol or low-density lipoprotein (LDL) to a certain goal based, in part, on Framingham risk data [5, 6]. (High serum cholesterol is an unequivocal risk factor in the Framingham score [5, 6].) The notion of treatment-to-goal (cholesterol) was based on the theory that serum cholesterol, especially LDL, was a major contributory cause of CAD (and ischemic stroke) [5, 6], but the proponents of this method of treatment could not deny that lowering total serum cholesterol and LDL, independent of initial total cholesterol and LDL levels, was crucial [2–4]. In other words, those with lower initial total serum cholesterol (and LDL) benefited as much as those with higher levels in being treated with statins [2–4].

On the other hand, a smaller group noted that the large long-term statin clinical trials were not based on titration to total cholesterol or LDL goals but were parallel fixed-dose design trials [7–9]. This group argued for giving a fixed statin dose to all CAD patients, but they were somewhat vague about what dose to use [7–10]. They also suggested that the effects of statins may be, in large part, independent of their effect on cholesterol and LDL lowering [9]. Along these lines, we note that statin ‘potency’ is traditionally thought of as dependent on the magnitude of lowering of serum cholesterol and LDL. However, this cholesterol-based definition of potency does not establish that *in vivo* potency (in preventing clinical events like death, MI or stroke) is related to serum cholesterol or LDL lowering. In the current analysis, we assume there is no difference in the *in vivo* potency between 80 mg of S and 80 mg of atorvastatin (A) in preventing events, an assumption justified below, notwithstanding the twofold greater ‘potency’ of A over S in lowering serum cholesterol.

In clinical pharmacology trials, before using a surrogate like serum cholesterol or LDL, if possible, it is important to first establish the effect of the drug on hard endpoints as a function of dose; in this case, death, MI and stroke in CAD patients [11]. If surrogates can be validated, for example bone mineral density in the treatment of osteoporosis (with bisphosphonates) as a surrogate for fractures, then they may become useful. In many cases, sur-

rogates are unnecessary, for example with proton pump inhibitors you just treat with a fixed dose since basically everyone responds with a reduction in stomach acid. You do not need to measure stomach acid. Finally, in some cases like premature ventricular contractions as a surrogate for cardiac death, suppressing the premature ventricular contractions with drugs was actually harmful [9].

To clarify how best to treat CAD patients with statins, in the following analyses we eschew employing serum cholesterol (total, LDL, high-density lipoprotein) and triglycerides as intermediates and look only at clinical events as a function of dose. (We remain neutral on the role of lipoproteins as a contributory cause of CAD and stroke morbidity and mortality [5, 6, 9].) This approach is now possible because data from 3 long-term parallel-group controlled randomized trials of S and A in CAD patients have become available in the last 5 years [12–15]. Unlike the older trials that pit S or A versus placebo [1], these newer trials (TNT [12], IDEAL [13] and SEARCH [14, 15]), analyzed by the intention-to-treat principle, pit 2 doses of these statins, a low dose versus a high dose (80 mg) one against another, in single randomized long-term controlled trials. With these newer data, we can make better judgments of how best to treat CAD patients with S or A. Our hypothesis is that it is now possible to select a single dose of cheap generic S (or A) for almost all patients with CAD using the principles of clinical pharmacology generally employed by the FDA [11] and cost considerations. Obviously, the results and conclusions apply only to S and A, the statins studied in the TNT, IDEAL and SEARCH trials. Extrapolation of these results to other statins would be speculative. Finally, as suggested by others [7–9], the utility of the treatment-to-goal (cholesterol) approach in secondary prevention [5, 6] is unproven and not required for good care of CAD patients as will be documented below.

Methods

In the following analysis, we investigate the key clinical endpoints in the 4S, TNT, IDEAL and SEARCH trials as a function of dose. A key point in our analysis is that the endpoints as a function of dose were decided in advance. Specifically, the 2 primary endpoints are total deaths and CAD deaths; the secondary endpoints are nonfatal MIs and fatal/nonfatal strokes. Also, the plan to pool low and high doses of S and A in the TNT, IDEAL and SEARCH studies was decided in advance (see below) and subsequently justified by the results of the analyses. Coronary revascularizations must be considered a tertiary endpoint since first, revascularizations depend on judgment (and are not spontaneous events like the primary and secondary endpoints), and second,

Table 1. Characteristics of secondary dose-response prevention trials

	4S [1]		TNT [12]		IDEAL [13]		SEARCH [14, 15]	
	placebo	S	A	A	S	A	S	S
Dose, mg	0	approx. 20 ^a	10	80	approx. 20 ^a	80	20	80
Cholesterol (baseline), mmol/l	total 5.5–8.0	total 5.5–8.0	LDL 3.3–6.4	LDL 3.3–6.4	–	–	total >4.5	total >4.5
Medication compliance, %	87	90	–	–	95	89	_b	_b
Follow-up for mortality, %	100	100	99	99	>99	>99	>99	>99

^a Approx. 20 = the large majority of patients took 20 mg; minority 40 mg.

^b Over 5 years, compliance fell from >90 to <80%.

Table 2. Individual trial data – number of patients

	TNT [12] (4.9 years) ^a			IDEAL [13] (4.8 years)			SEARCH [14, 15] (6.7 years)		
	10 mg A	80 mg A	Δ%	approx. 20 mg S	80 mg A	Δ%	20 mg S	80 mg S	Δ%
Total patients	5,006	4,995		4,449	4,439		6,033	6,031	
Deaths	282 (5.6)	284 (5.7)	–0.1	374 (8.4)	366 (8.3)	0.1	970 (16.1)	964 (16.0)	0.1
Cardiac deaths	127 (2.5)	101 (2.0)	0.5	178 (4.0)	175 (3.9)	0.1	439 (7.3)	447 (7.4)	–0.1
MIs	308 (6.2)	243 (4.9)	1.3	321 (7.2)	267 (6.0)	1.2	463 (7.7)	397 (6.6)	1.1
Strokes	155 (3.1)	117 (2.3)	0.8	174 (3.9)	151 (3.4)	0.5	279 (4.6)	255 (4.2)	0.4

Figures in parentheses are the percentages of total patients in that category. Δ% = The difference in percent between the low-dose and high-dose arms. ^a Median length of trial.

we now know there are many unnecessary revascularizations performed [16–18]. Finally, 2 types of statistical analyses were employed. First, we analyzed the differences between proportions using the z-statistic on pooled data from the 3 trials [19]. A correction was made for multiple comparisons by multiplying the p value by 4. Also, the 95% confidence intervals for the difference between 2 proportions were calculated [19]. Second, we performed a meta-analysis on the 3 trials (TNT, IDEAL and SEARCH) [12–15] focusing on the hazard ratio and absolute risk reduction; we also performed the Q test for heterogeneity for both measures [20]. We employed a standard method to estimate the hazard ratios for CAD deaths and nonfatal MI in the SEARCH trial based on the reported incidence rates [21].

The Data

The TNT, IDEAL and SEARCH trials [12–15] and the placebo-controlled 4S trial [1] provide the key data for analysis: some of their characteristics are shown in table 1. All of these trials were similar in that they enrolled patients with CAD and so are not contaminated with

lower-risk primary prevention patients. As can be seen (table 1), these secondary prevention trials are excellent trials in that minimal patients were lost to mortality follow-up, so the results on mortality are unarguable.

The outcome data for the primary and secondary endpoints in the TNT, IDEAL and SEARCH trials are shown in table 2. As can be seen, there is no clear difference in overall or coronary mortality of 80 mg A or S versus the lower doses in any of the 3 trials. In terms of the secondary endpoints, in all 3 trials there was a 1.1–1.3 and 0.4–0.8% advantage of the 80-mg dose compared to the lower dose on MI and stroke, respectively (table 2). Overall, there is no evidence that 80 mg A is more effective than 80 mg S or vice versa on the primary or secondary endpoints (table 2). In the IDEAL and SEARCH trials, 80 mg of A (IDEAL) or S (SEARCH) was compared with approximately 20 mg of S; the results showed no advantage of 80 mg of A over 80 mg of S or vice versa (table 2).

In table 3, to obtain greater statistical power and accuracy, the primary and secondary endpoint data (de-

Table 3. Comparison of the combination of the TNT, IDEAL and SEARCH with the 4S trial

	Combination [12–15]			4S trial [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	608 (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 4. Meta-analysis of the TNT, IDEAL and SEARCH trials [20, 21]

	Risk difference, %	Hazard ratio
Death	0.04 (–0.58 to 0.67)	0.99 (0.93 to 1.06)
Cardiac death	0.25 (–0.17 to 0.68)	0.98 (0.88 to 1.08)
MI	1.25 (0.72 to 1.77)	0.80 (0.73 to 0.87)
Stroke	0.58 (0.17 to 0.98)	0.85 (0.76 to 0.97)

The absolute risk difference in percent and the hazard ratios between low-dose and high-dose patients are shown. Beside each value are the 95% confidence intervals. There was no evidence for heterogeneity in any of the values with all p values greater than 0.25 (Q statistic).

fined above) from the TNT [12], IDEAL [13] and SEARCH [14, 15] trials (see table 2) from the low- and high-dose patients have been combined. The results are compared with the 4S trial. The rationale for combining the high- and low-dose patients in the TNT, IDEAL and SEARCH trials (planned before the data were combined) is that all 3 trials compare an apparently equi-effective high dose (80 mg of S or A) versus either approximately 20 mg of S or 10 mg of A, the ‘low-dose’ groups (table 2). The combination of the 3 two-dose trials greatly increases the confidence from which to make judgments.

To further analyze the data for relative risks, a meta-analysis of the data in tables 2 and 3 is shown in table 4. This analysis confirms and extends the simple analysis in table 3. There was no evidence of heterogeneity in the meta-analysis (table 4) [20].

As can be seen in table 3, there was a highly significant absolute 3.3 and 3.5% decrease in overall and cardiac mortality in the 4S trial. However, there was no advantage of the 80-mg dose on total or cardiac mortality over the lower dose in the combination data (tables 3 and 4). It is worth noting that the SEARCH and IDEAL studies used approximately the same S dose (in the low-dose arms) as the 4S trial. Based on the data from the 4S trial, one would need to treat 26 patients for 5 years to prevent 1 coronary death. No deaths are prevented in going from the low dose to the high dose (80 mg) of S or A (table 3).

However, in the combination comparisons of the secondary endpoints (high dose vs. low dose), there was a 1.2% ($p < 0.001$) and 0.5% ($p < 0.05$) difference for MI and stroke, respectively (table 3). This is a smaller decrease than the 6.7 or 4.5% decrease (depending how you define MI) and 1.1% decrease in stroke seen in the 4S trial (table 3). One possible reason for the smaller percentage of MIs in the low-dose arm in the combination studies versus the S arm in the 4S study is the greater than 10-year difference in the time of execution of the studies [1, 12–15]. In that time period, the care of CAD

patients improved with much greater use of proven MI preventatives like aspirin, ACE inhibitors, β -blockers and other drugs. Also the definition of MI in the 4S study was broader than in the later trials as noted in table 3. If only definite MIs are included, the 7.4% MI occurrence in the S arm of the 4S trial is not so different from the low-dose arm (7.1%) of the combined data in table 3. In other words, you would have to treat only 15 patients for approximately 5 years to prevent 1 'major coronary' or 21 patients to prevent 1 definite MI case (table 3) in the 4S trial versus 83 patients for approximately 5 years in the combined analysis going from the low dose to 80 mg of S or A. What is clear is that the relative decrease in MIs going from low dose to 80 mg A or S was much less than going from placebo to approximately 20 mg S (table 3) in the 4S trial, or 40 mg of pravastatin in the LIPID trial [2]. Such a result is typically seen in dose-response studies, i.e., higher doses approach the asymptote of efficacy [11]. In the case of stroke, the number of strokes in the 4S study is too small to make comparisons with the combination data (table 3). However, in the much larger placebo-controlled HPT trial [3] with 40 mg S versus placebo, stroke incidence was decreased by 1.3% ($p < 0.001$), an absolute risk reduction consistent with the 4S study result (table 3).

The clinical safety of S has been studied for over 2 decades and of A for more than 1. Forty milligrams of S and A are safe doses suitable for widespread use [1, 3, 22]. For example, in the Heart Protection Study [3], 10,000 primary and secondary prevention patients received 40 mg of S for approximately 5 years with side effects comparable to the 10,000 patients that received placebo. However, in the TNT [12], IDEAL [13], and SPARCL [23] (hypertension) trials, 80 mg of A was not as well tolerated as placebo or lower doses; on 80 mg of A, there were more dropouts and 2–3% of the patients had elevated liver function tests versus <1% on lower doses. Moreover, in the IDEAL study, 11% of patients were not compliant with 80 mg A versus 5% with approximately 20 mg of S (table 1). Any small advantage of A (80 mg) will be lost if there is less medication compliance; moreover, monitoring liver function tests at 80 mg increases the cost and burden of using 80 mg A. Similarly, 80 mg of S is not well enough tolerated to be used routinely as a preventative. For example, in the SEARCH trial [14, 15, 24], there were 53 cases of myopathy (approx. 1.0%) on 80 mg S and 3 on 20 mg S; there were 7 cases of rhabdomyolysis on 80 mg and none on 20 mg S [24]. Thus, it appears that 40 mg of S and A are generally safe but higher doses cause liver and muscle side effects [3, 12, 13, 22–24].

Discussion

In terms of the primary endpoint (total deaths and coronary deaths), the data in table 3 clearly show that approximately 20 mg of S (and other statins like pravastatin in the LIPID trial [2]) decrease total deaths and coronary deaths more than placebo in CAD patients. With approximately 20 million people with CAD, if they all took approximately 20 mg S (and not placebo), there would be over 700,000 lives saved over a 5-year period if the population of patients and their treatment was comparable to the CAD patients in the 4S trial (table 3). However, raising the dose to 80 mg of S or A does not improve total or coronary deaths (tables 2–4).

In terms of the secondary endpoints of MI and, to a lesser extent, stroke, there is a statistically significant difference between high-dose (80 mg S or A) and low-dose S or A (tables 3 and 4). However, you would have to treat approximately 83 and approximately 200 CAD patients to prevent 1 MI or stroke case, respectively, with 80 mg S or A versus the low dose (tables 2 and 3) assuming as good compliance with 80 mg as in the clinical trials – a dubious assumption (see below).

In view of the data in tables 2–4, the excellent safety record of 40 mg of S and A [3, 20] and the less well-tolerated dose of 80 mg of S or A, it would seem that almost all patients with CAD should be treated with 40 mg of cheap generic S or alternatively A when it becomes generic and inexpensive. Based on standard dose-response curves, the dose of 40 mg S (or A) should result in efficacy data between 20 and 80 mg, presumably much closer to 80 mg (than to 10–20 mg) since 80 mg is approaching the maximum response (asymptote) (table 3). In almost all good dose-finding studies, the ideal dose should be bracketed by a dose slightly too low and too high (tables 2 and 3). In short, we now have such outcome data with S and A as a function of dose (tables 1–4) which allows us to pick an optimal dose for CAD patients. In other words, the risk/benefit ratio (and cost considerations) settle on 40 mg S, the dose used in the 5-year HPT trial in which 10,000 patients received 40 mg S safely [3]. At this time, it would require a prohibitively large expensive trial to compare 40 versus 80 mg of S (or A) in CAD patients for 5 years to assess safety and relative efficacy. However, there may be a few patients, for example those with genetic hypercholesterolemic syndromes, who benefit from higher doses of statins [22], or alternatively a few patients who for tolerability reasons or potential drug interactions, for example with inhibitors of cytochrome P 450A3 or cyclosporin [22], require a lower dose. In some

patients, for example those with liver disease, the use and dose of statins are difficult and of uncertain benefit [22].

With 40 mg of S for most CAD patients, monitoring cholesterol levels (except to assess medication compliance) is unnecessary since every patient is begun on and generally maintained on the optimal dose. Thus, we have outlined a very simple program that should improve medication compliance and can be employed for almost all CAD patients [7–9].

In all discussions of clinical trial efficacy studies, it is crucial to recognize that real-world practice is generally quite different from the milieu of the clinical trial (table 1). We know, in general, that medication compliance in the community with effective chronic therapies like statins runs approximately 50% after 5 years, a sad commentary [25, 26]. This is much lower than the medication compliance in the clinical trials (table 1). Thus, it is crucially important to focus on measures likely to improve compliance; these include simple once daily (or less) regimens, lack of necessity for titration, physician feedback to patients on medication compliance, excellent tolerability, inexpensive cost-effective drugs and the ability of physicians to be enthusiastic about the drug and regimen [25–27]. With the program for statins in CAD outlined above, these criteria can be predominantly met – and this approach should improve medication compliance. Based on the data in table 3, the 20 years of safety data and the compliance considerations above, the 40-mg dose of S for the large majority of CAD patients should yield the maximum amount of benefit for the population of CAD patients. There are no scientific data that the selection of a different dose for an individual patient (except as qualified above) would be superior. The notion that greater lowering of LDL is associated with better outcomes is confounded by such factors as higher statin doses, better medication compliance and other factors [7–9]. Such unscientific considerations about LDL lowering are completely unlike the controlled randomized trials referred to above which have one dependent variable (dose) and clinical outcomes [1, 12–15].

Implications

The statin program outlined herein for CAD patients was presaged by several authors [7–9], but they did not have as complete a database. This practical program, of course, does not answer all the myriad questions about LDL as a contributory cause of CAD or stroke, or the speculative ‘need’ to treat-to-goal based on the Framingham or other risk scores [5, 6, 28]. Rather it bypasses these

questions and hypotheses and bases its recommendations on placebo-controlled and dose-response (outcomes) data (tables 1–4). (To prove that treatment-to-goal is better than just treating almost all CAD patients with 40 mg S would require a very large randomized long-term prospective controlled clinical outcome trial. This is now incumbent on the proponents of the more complicated treatment-to-goal approach if they disagree with the simple one-dose argument in secondary prevention.)

Since there has been steady progress in the prevention of CAD and stroke over time, the data in tables 3 and 4 must be placed into perspective. First, there are currently other effective medical treatments for CAD patients including aspirin, ACE inhibitors, β -blockers (for some) and others. The clinical trials in tables 1–4 were all done on top of the other drugs that the patients were taking [1, 12–15]. Thus, the statin effect is probably additive to the beneficial effects of these drugs, although synergy cannot be ruled out. Such questions require further study. In fact, based on currently available knowledge, a once-daily cost-effective cocktail of drugs for almost every CAD patient (including a statin and aspirin) should be prescribed. (It is worth noting that in the US generic S costs approx. 50 USD per year per patient in discount retail pharmacies whereas brand name statins cost approx. 1,000 USD per year. Since there are approx. 20 million CAD patients in the USA, the switch from brand name to generic S in all secondary prevention patients would save 19 billion USD per year – a vast sum.) Of course, weight control, diet and exercise should be emphasized. Methods to ensure medication compliance must also be employed. This approach will continue to decrease substantially the cost, morbidity and mortality of CAD.

In summary, with the new data in hand, it is now possible to choose an optimal dose of S (or, when it becomes available, generic A) that is inexpensive, well tolerated and suitable for the large majority of CAD patients. Treatment-to-goal and monitoring measurements of serum cholesterol, LDL, or high-density lipoprotein are not necessary except to measure medication compliance. Those involved in the proposing and execution of the trials in tables 1–4 have provided data which finally allow rationalization of statin dosing. A dividend of this approach is the decrease in strokes (tables 3 and 4). However, a great deal more needs to be done, for CAD still remains the leading cause of death in America.

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