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## **Disappointing Recent Cholesterol-Lowering Drug Trials: Is It Not Time for a Full Reappraisal of the Cholesterol Theory?**

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Recent cholesterol-lowering drug trials have been very disappointing for cholesterol experts and the cholesterol drug industry. Three events as important in terms of media coverage as of science and medicine are held each year around the issue of cholesterol: the annual meeting of the American College of Cardiology in March, the annual meeting of the European Society of Cardiology in August, and the American Heart Association meeting in November. Because thousands of cardiologists from all continents are at the same place at the same time, each of these meetings is an opportunity to roll out cholesterol drug marketing campaigns. Today, marketing is primarily based on the publication of results of randomized trials. Thus every year, the three cardiology ‘world meetings’ are the best time to re-launch the cholesterol-lowering drug machine. However, the year 2008 has been a sad year because trial results obviously do not support the theory according to which cholesterol lowering results have significant benefits in the prevention of coronary heart disease (CHD), including the so-called *‘the lower the better theory’*.

### **The ENHANCE Study**

The results of the ENHANCE study conducted in patients with familial hypercholesterolemia [1] were published in March 2008 – and were disappointing. Familial hypercholesterolemia is supposed to be a typical cholesterol-driven disease with dramatically high LDL cholesterol levels resulting in CHD complications. In ENHANCE, an association of ezetimibe, a drug acting by decreasing the absorption of cholesterol in the digestive tract, and simvastatin, which acts by decreasing the endogenous synthesis of cholesterol, was tested. For those who believe that cholesterol is the main



cause of CHD, ENHANCE was designed not to fail. Actually, the association of the two drugs in the same patient resulted in a drastic reduction of cholesterol levels, in particular LDL cholesterol (the so-called 'bad' cholesterol) levels. Since ezetimibe is not absorbed in the digestive tract and simvastatin given at a relatively low dose, the rate of side effects in ENHANCE was expected to be low. Thus, contamination of the potential effectiveness measurement of the treatment by side effects also was expected to be low. The test was not performed by measuring hard clinical endpoints such as cardiac death or myocardial infarction, but by repeated measurements of carotid intima-media thickness (IMT), a supposed marker of atherosclerosis progress.

Unexpectedly, the combination of the two drugs failed to provide incremental benefits over simvastatin alone, despite a drastic reduction in cholesterol [1]. In addition, both treatments did not result in significant effects on the primary endpoints: not only did the change in IMT not differ over time, from baseline to 24 months, between the two study groups, but there was a slight increase in IMT in both groups: at 2 years, the estimates were of  $+0.0095 \pm 0.0040$  mm in the simvastatin only group ( $p = 0.02$  vs. baseline) and  $+0.0121 \pm 0.0038$  mm in the combined therapy group ( $p < 0.01$  vs. baseline), which suggested that unexpectedly the lower the cholesterol, the greater was the increase in IMT [1]. These surprising and very disappointing data might explain why the results of ENHANCE were hidden from the medical community for nearly 2 years, while the drug was being used by millions of patients over the world, hoping that it was protecting their hearts [2–5].

It is noteworthy that until ENHANCE, IMT was used as a surrogate of CHD complications [6, 7]. This was supported by several studies showing that intensive cholesterol lowering inevitably resulted in IMT regression [8, 9]. If ENHANCE had been positive, IMT would have been celebrated again as an effective marker of the risk of CHD complication. Because ENHANCE was negative, cholesterol experts immediately claimed that IMT cannot be a marker of atherosclerosis progress or a surrogate of CHD [10, 11]. More surprisingly, after ENHANCE many cholesterol experts declared that familial hypercholesterolemia is not the adequate population to test the effects of cholesterol lowering [2–5]. Instead, a scientist would have concluded that if this potent association of drugs does not work in familial hypercholesterolemia, it can hardly be expected to work in any other case. Hence, ENHANCE was, by itself, a cause of confusion and debate among cholesterol experts. The data of ENHANCE led an American College of Cardiology panel to urge physicians to only prescribe cholesterol-lowering medications with proven clinical effectiveness, i.e. proven effects on hard clinical CHD endpoints such as cardiac death, myocardial infarction and stroke [4]. As a matter of fact, ezetimibe was approved and marketed in 2002 based solely upon a 20% reduction of cholesterol, but not on data related to its effectiveness on any clinical endpoint [12], as if cholesterol levels by themselves could be a surrogate of CHD. In addition, the effectiveness of the ezetimibe+simvastatin combination against hard clinical endpoints has never been demonstrated, as discussed below about the Simvastatin and Ezetimibe in Aortic Stenosis (SEAS) trial. As a consequence, many

physicians and scientists rightly questioned why the combination tablet already was on the market if there was no proven effect on clinical CHD complications [4, 5].

In March 2008, a press release announced the premature termination of JUPITER, a trial testing rosuvastatin, presumably the most effective statin in terms of cholesterol lowering, against a placebo in the primary prevention of CHD [13, 14]. With this announcement, investigators probably wanted to communicate that rosuvastatin, contrary to ezetimibe+simvastatin, resulted in an *'unequivocal evidence of reduction in cardiovascular morbidity and mortality'* as written in the press release [13, 14]. This was quite strategic for cholesterol experts at that particular time, because several trials testing cholesterol-lowering had been published during the previous years in various clinical circumstances, ASPEN, 4D, PREVENT IT, IDEAL, ILLUMINATE [15–19] and also ENHANCE [1], and all of them reported no convincing protective effect against CHD complications [1, 15–19]. The failure of ENHANCE, in particular, generated unprecedented media coverage, patient and physician concerns, and the involvement of the US Congress over the use of cholesterol-lowering drugs to reduce CHD risk [2–5, 10, 11]. The controversy even brought into question *'the role of blood cholesterol as a proven surrogate of atherosclerosis'* [11].

Following the publication of ENHANCE, two studies of cholesterol-lowering treatments following protocols approved by the FDA were either not published or abruptly terminated [20, 21]. CASHMERE tested atorvastatin in postmenopausal women. The trial results were unearthed by capital market analyst Robert Hazlett and showed no effect at all on IMT [20]. ACHIEVE tested a novel combination tablet associating niacin and laropiprant (a prostaglandin D<sub>2</sub> blocker used to prevent the flushing induced by niacin) in familial hypercholesterolemia [21]. The trial was prematurely stopped because, after the failure of ENHANCE in the same category of patients, sponsors and investigators thought that there was no hope to demonstrate a benefit [21]. This indicated that even in 2008, trials that were obviously negative or tended in the wrong direction were still not publicly discussed by investigators and sponsors and sometimes were halted before completion. This gives an idea of what was being done before the new clinical research regulation came into force in 2005–2006, after the Vioxx affair [22], with the obligation of declaring all the clinical trials and of publishing the results even when they are not favorable to the tested drug [23, 24]. All these attempts to mislead the medical and scientific community have highlighted the fact that the alleged effectiveness of cholesterol lowering to prevent CHD complications is very questionable for anyone wanting to open their eyes.

### **SEAS and GISSI-HF**

The results of two important trials were reported in 2008: SEAS and GISSI-HF [25, 26].

The SEAS trial was a randomized, placebo-controlled study evaluating ezetimibe+simvastatin, like ENHANCE [1]. This time, however, cholesterol lowering was tested against a placebo by evaluating its effects on hard clinical endpoints, including aortic valve replacement and CHD complications in patients with aortic stenosis [25]. The main assumption was that disease progression in aortic stenosis is strongly influenced by hypercholesterolemia [27, 28] and often associated with CHD complications [29, 30]. Thus, double benefits were expected in these patients: first, by preventing CHD complication and second, by preventing aortic valve complications. The primary endpoint of the trial was therefore a combination of CHD and aortic valve complications.

To summarize SEAS results, drastic cholesterol lowering had no significant effect on the primary endpoint [25]. While the authors tried to present the SEAS data in a positive light by claiming that cholesterol lowering had a significant effect on secondary endpoints such as coronary revascularization, SEAS actually confirmed the negative results of ENHANCE, but this time for hard clinical endpoints [25]. From a scientific point of view, SEAS is a critical study for several reasons.

First, SEAS confirmed previous recent trials [15–19], including ENHANCE [1], and the inability of cholesterol lowering to reduce the risk of CHD complications in certain populations. This raised the question of whether the failure of ezetimibe+simvastatin was due to some unknown side effects of the combined treatment or to the fact that cholesterol lowering actually is beneficial in certain populations of patients and not in others. In fact, some experts have claimed that previous positive trials were not the result of cholesterol lowering but of other properties of statins, the so-called pleiotropic effects of statins [31]. At this point in the controversy, cholesterol experts appeared to be divided into two groups: those who were claiming that cholesterol lowering is still important whatever the results of ENHANCE and SEAS, and those claiming that cholesterol lowering is not important as long as patients receive intensive statin treatment in order to induce pleiotropic protection [2–5, 32].

Second, the control group in SEAS received a placebo, whereas in ENHANCE the comparison group received simvastatin alone. This means that the difference in LDL cholesterol between the experimental and the control group was huge in SEAS, close to 50%, but still did not provide any protection. Thus, ENHANCE and SEAS taken together should have logically led to reject the *'the lower the better'* theory that states that the lower the cholesterol, the better the protection [33, 34].

Third, it is noteworthy that in SEAS, patients with low cholesterol levels in the experimental group had more cancers and died more frequently from cancers than those receiving the placebo [25]. Although it can be speculated that the increased cancer rate was a chance effect [35, 36], this raises another critical question: may intensive cholesterol lowering increase the risk of cancers in certain patients? No one can answer that question today. Given the millions of patients receiving intensive cholesterol-lowering treatment without any unambiguous cardiovascular benefits, the next critical question is whether we should not follow precautionary

principles on this public health issue and at least fully inform the public about these questions.

GISSI-HF was a double-blind randomized trial testing whether 10 mg rosuvastatin compared with a placebo could reduce mortality and cardiac complications in patients with chronic heart failure (CHF) from various causes [26]. Large observational studies, small prospective studies and post-hoc analyses (including meta-analyses) of large randomized trials have indeed suggested that cholesterol-lowering could be beneficial in CHF patients. Despite a 36% reduction of LDL cholesterol in the statin group compared with placebo, there was no difference between groups for total mortality (657 deaths versus 644 in the placebo group) and for other cardiovascular endpoints in GISSI-HF [26].

GISSI-HF thus confirmed the results of a previous trial published less than 1 year before, the CORONA trial [37]. In CORONA, 10 mg rosuvastatin also were tested against placebo in patients with CHF aged 60 years and more. Contrary to GISSI-HF, all patients in CORONA were CHD patients who had survived a previous myocardial infarction and presented left ventricular dysfunction. In other words, CORONA was a secondary prevention trial in high-risk patients because left ventricular dysfunction significantly increases the risk of CHD complications and cardiac death. Before CORONA, statin experts claimed that the higher the risk of cardiac death was, the higher the benefits of intensive cholesterol lowering would be [38, 39]. Official and international guidelines state that a statin should be given to all patients (whatever their cholesterol level) in high-risk secondary prevention, whereas in primary prevention, when the risk of cardiac death is lower, prescription should depend on the cholesterol level [34, 40, 41]. In CORONA, the primary composite outcome was cardiac death, nonfatal infarction and nonfatal stroke [37]. LDL cholesterol was reduced by 45% and CRP (an inflammatory marker) by 37% in the rosuvastatin group compared with placebo. CORONA was therefore designed not to fail. However, no significant difference was recorded for the primary composite outcome. Moreover, there were 488 and 487 cardiovascular deaths in the rosuvastatin and placebo groups, respectively. The numbers of deaths due to worsening heart failure were 191 and 193 in the placebo and statin groups, respectively. Thus, the unequivocal lessons of CORONA were that both drastic cholesterol lowering and the supposed pleiotropic (anti-inflammatory) effect of the statin had no effect at all in the secondary prevention of CHD in high-risk patients. CORONA and GISSI-HF therefore provided exactly the same information in two different populations, namely that cholesterol lowering does not improve the prognosis for high-risk CHD patients. The theory that the higher the risk (notably in secondary prevention of CHD), the higher the benefit [34, 38–41] should logically be rejected. Also, the theory according to which statin pleiotropy could have a significant clinical impact appears to be very elusive after GISSI-HF and CORONA.

Both GISSI-HF and CORONA raise many questions. The main one, however, is why the most recent statin trials conducted in secondary prevention and high-risk patients, including the patients with familial hypercholesterolemia recruited in

ENHANCE and those with aortic valve disease recruited in SEAS, have been negative. An alternative question is whether there were some technical problems and potential biases in these 4 trials that could have explained the failure. If not, the same question should be raised about the previous trials reporting high protection with statins, in particular those conducted during the 1990s, before the Vioxx affair and the new clinical research regulations [22]. How can we explain the discrepancy between these older positive trials on one hand, and CORONA, GISSI-HF, ENHANCE and SEAS, on the other?

Lastly, are the methods and results of previous trials reporting high benefits of cholesterol lowering verifiable today? Did the new regulations introduced after the Vioxx affair result in such a striking improvement of trial conduct that all trials are now negative?

### **The JUPITER Trial**

JUPITER tested the effects of 20 mg rosuvastatin in subjects without cardiovascular disease, normal cholesterol levels but relatively high CRP [42]. The authors reported a 50% decrease in LDL cholesterol, a 37% decrease in CRP and a decrease by about 50% in cardiovascular complications. However, there are methodological problems and major clinical inconsistencies in JUPITER. The main methodological problem in JUPITER regards the premature trial termination [42]. Investigators made the awkward decision to stop the trial after 393 cases of complications, before the number of at least 520 events calculated in their analysis plan was reached [42]. Taking only the hard complications of fatal and nonfatal myocardial infarction and stroke into account, they actually stopped the trial after only 240 events! The ethical argument according to which patients in the placebo group could no longer be left untreated is not relevant, and even the opposite, as many scientific articles constantly stress [43, 44]. Scientific rigueur is the primary ethical rule that has to be followed in clinical research. Ethics required that the trial should not have been discontinued prematurely, as evidenced by the inconsistency of clinical results (see below).

The results of JUPITER are reproduced in the table 1. They look dramatic. The primary endpoint is a mix of diverse complications listed in the bottom lines of the table, although some of them such as revascularization are irrelevant because they are not complications but medical decisions. This being said, we actually observe an impressive difference between the two groups in terms of hard clinical complications, myocardial infarction and stroke (157 against 83). However, there are no clear data on cardiovascular mortality in the table 1 as well as the text of the article. One may infer from the table (although this is not indicated in the text) that fatal myocardial infarction is the difference between 'any myocardial infarction' and 'nonfatal myocardial infarction', giving total numbers of 9 (31 less 22) in the rosuvastatin group and 6 (68 less 62) in the placebo group. We can make the same calculation for fatal stroke (the



**Table 1.** Reproduction of table 3 from the JUPITER paper [42]

Endpoint	Rosuvastatin (n = 8,901)	Placebo (n = 8,901)
Primary endpoint	142	251
Nonfatal myocardial infarction	22	62
Any myocardial infarction	31	68
Nonfatal stroke	30	58
Any stroke	33	64
Arterial revascularization	71	131
Hospitalization for unstable angina	16	27
Myocardial infarction, stroke, or confirmed deaths from cardiovascular causes	83	157
Death from any cause on known date	190	235

difference between ‘any stroke’ and ‘nonfatal stroke’), resulting in total numbers of 3 (33 less 30) in the rosuvastatin group and 6 (64 less 58) in the placebo group.

Cardiovascular mortality (fatal stroke + fatal myocardial infarction) is therefore identical in the two groups (12 against 12).

The lack of effect on cardiovascular mortality associated with a miraculous effect on nonfatal complications is puzzling and should have led to suspect a bias and to the continuation of the trial instead of a premature ending. In addition, the numbers of fatal myocardial infarction in both groups (9 and 6) are unexpectedly low compared with nonfatal infarction (62 and 22), suggesting that JUPITER patients, particularly in the placebo group, withstood the consequences of myocardial ischemia and infarction extremely well. This is apparent even within the first hour following the first symptoms of chest pain (the definition of sudden cardiac death), since curiously no sudden cardiac death is reported in the trial. Almost no non-sudden cardiac deaths are reported either during in the following hours, days and weeks.

We are clearly facing a major clinical inconsistency.

Mortality from myocardial infarction is known to be very high. In fact, the ‘case fatality rate’ in epidemiological reports has been reported in many populations with very different risks [45]. Out of 100 patients who have a myocardial infarction, an average of 50 die immediately or within the 3–4 weeks that follow, and almost never less than 40 out of 100 even in populations with low cardiovascular mortality [45]. In JUPITER, mortality during infarction (6 divided by 68 multiplied by 100) is 8.8% in the placebo group. This is extremely low, and here we have another major clinical inconsistency! But does the error lie? Which are the false figures? The case fatality rate in the rosuvastatin group (9 divided by 22 multiplied by 100) is 29%, a figure that fits better (although not perfectly) with the expected variations but raises another question: would rosuvastatin have tripled myocardial infarction-related mortality?



Is this clinically consistent? Another way to measure the trial's clinical consistency is to compare cardiovascular and total mortality. In most countries, cardiovascular mortality represents 45–60% of total mortality, rarely less than 35%. Yet in JUPITER, it represents only 6% of total mortality (12 divided by 190 × 100; table 1) in the statin group and 5% (12 divided by 235 × 100) in the placebo group. How incredibly low! This is another major epidemiological inconsistency.

Pending confirmation of JUPITER by a new trial that will – hopefully – follow traditional and validated clinical trial methods, the obvious conclusion is that JUPITER results are not clinically consistent and therefore not credible. We must bear in mind that two previous trials with rosuvastatin (CORONA and GISSI-HF) were negative for CHD prevention [26, 37]. Thus, no clinical trial so far has been published showing an unequivocal clinical benefit of rosuvastatin. And this right at the time where other anticholesterol drugs (tested in ENHANCE and SEAS) were shown to be totally ineffective whatever the type of hard or surrogate endpoints used to test the effects of cholesterol lowering [1, 25].

## Conclusion

For cholesterol experts and the cholesterol industry, recent cholesterol-lowering drug trials have definitely been very disappointing. The most recent trials were either negative (ENHANCE, SEAS, GISSI-HF, CORONA) or not clinically consistent and probably biased (JUPITER) because of premature termination. Taken together, in the light of other negative trials (ASPEN, 4D, PREVEND IT, IDEAL, ILLUMINATE) published after the Vioxx affair in 2005 and the following new clinical research regulations, these trials are puzzling. They suggest that the positive trials published before 2005 and the Vioxx affair should be urgently re-examined. At a minimum, experts independent of industry and free of conflict of interest should be asked to carefully check all the raw data recorded in the datasets and redo the statistical analyses.

The next question would then be: is it not time for a full reappraisal of the cholesterol theory?

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