Comments on HOPE 3

In case there are some admirers left of that *strange* trial, and taking into account that this is a rapid overview of the ***Hope 3 rosuvastatin*** article [N Engl J Med. 2016 Apr 2] only, we see:

1. No effect on **all-cause mortality.**

2. No effect on **cardiovascular mortality.**

3. As cardiovascular disease is a *serial killer*, we could conclude that rosuvastatin is shown useless in that trial (as in the previous trials). We could stop the analysis at this point.

4. Since the authors do suggest that rosuvastatin was protective, it means that these patients are as "deaths cured"' or "death prevented", which is probably not what they expected when taking the pills.

5. All this despite the LDL reduction that was close to 30%.

6. HOPE 3 investigators curiously examine the effects of rosuvastatin on **two** "combined primary endpoints" (called "*first and second coprimary outcome*" as shown on Table 2, below) suggesting that there were two primary hypotheses. This is not "in line" with basic Methods in clinical trial sciences [one trial, one primary hypothesis]. That strange and novel strategy should have been presented long before starting the trial. In any case, the probability of a difference between rosuvastatin and placebo for the first coprimary outcome [the only one to be considered] should have been adapted, a kind of Bonferroni correction; p should have been much lower than 0.05 to be significant; which is not "clinical significance".

7. HOPE 3 investigators present the comparison of rosuvastatin with placebo (Table 2, below) as if there were only two randomized groups. In fact, **there were 4 groups** as there was a second randomization to test an antihypertensive treatment; and also the combination of cholesterol-lowering and blood pressure lowering. In summary, these investigators tested many more than two primary hypotheses. They say that they can pool the data from all the patients taking rosuvastatin (plus antihypertensive) to make the comparison with all the patients taking a placebo, including those taking antihypertensive; thus comparing two groups of about 6300 patients rather than 4 groups of about 3100 patients each) because there was no interaction between treatments. This is not exactly true as we see a clear interaction between treatments for at least two components (myocardial infarction and stroke) of the two coprimary outcomes (see Table S20 in the supplementary materials, below). It would have been therefore imperative to present data and full statistics for the 4 groups together to examine the effects of rosuvastatin vs. placebo. It is a mistake not to do that.

6- HOPE 3 investigator also say that there were fewer heart attacks; but after almost 6 years and with about 13,000 patients randomized, there were only 114 heart attacks (45 vs 69 in a simplistic analysis of 2 groups only, Table 2 below).

7. In fact, things are not so clear when looking at Table 2: they report for the first coprimary outcome (CV deaths + myocardial infarction + stroke) 304 events in the placebo group and 235 in the rosuvastatin group, thus numbers different from the sum of 171+69+99 (total 339, placebo group)

and 154+45+70 (total 269, rosuvastatin) according to the numbers given in Table 2. This means that they do not use the same numbers in the Table and in the statistics. This is a way of misleading the readers.

Table 2. Primary, Secondary, and Other Outcomes.*

Outcome	Rosuvastatin Group (N=6361)	Placebo Group (N=6344)	Hazard Ratio (95% CI)	P Value
Coprimary outcomes — no. (%)				
First coprimary outcome	235 (3.7)	304 (4.8)	0.76 (0.64–0.91)	0.002
Second coprimary outcome	277 (4.4)	363 (5.7)	0.75 (0.64–0.88)	<0.001
Secondary outcome — no. (%)	306 (4.8)	393 (6.2)	0.77 (0.66–0.89)	<0.001
Components of the coprimary and secondary outcomes — no. (%)				
Death from cardiovascular causes	154 (2.4)	171 (2.7)	0.89 (0.72–1.11)	
Myocardial infarction	45 (0.7)	69 (1.1)	0.65 (0.44–0.94)	
Stroke	70 (1.1)	99 (1.6)	0.70 (0.52–0.95)	

Once we have understood that rosuvastatin does not reduce cardiovascular mortality (prevent fatal events), the question is: how many nonfatal AMI (or stroke) have been prevented with rosuvastatin? To precisely answer (given the above reasoning), we need to know the exact numbers of nonfatal AMI (and stroke) among patients receiving rosuvastatin only (n=3181) and those receiving placebo only (n=3168). These numbers are curiously not provided by the investigators; probably because these numbers are very small and the differences between the two groups still smaller. This way of presenting the rosuvastatin data are definitely not fair.

In addition, definitions and diagnostic conditions of AMI are quite suspect in HOPE 3, as seen below, (screen dumps from the supplementary appendix, a gold mine of information) and without the knowledge of which event was really included in the Tables and statistics… For example the questionable term "probable non-procedure related myocardial infarction" may or may not have been included in their "*First coprimary outcome*" (Table 2, above). This was not made clear in the NEJM article or in the article in the Can J of Cardiology (see below). It is probable that the majority of events (whatever they were) were included in order to increase the number of 'events' following the multiple changes to the protocol that were made up to the end of 2015. See below. Same regarding strokes.

MYOCARDIAL INFARCTION
Definite Non-procedural MI
EITHER
Cardiac Ischemic Symptoms lasting ≥ 20 minutes, determined by the site investigator to be secondary to ischemia
OR
ECG or changes consistent with acute infarction or ischemia MI:

- New diagnostic Q waves (Q wave in leads V2 and V3 ≥ 0.02 sec or QS complex in leads V2 and V3; Q wave ≥ 0.03 sec and ≥ 0.1 mV deep or QS complex in leads I,

We actually read: "*determined by the site investigator to be secondary to ischemia*"… Charming, no? The definition of a major endpoint (such as AMI) should be given before starting the trial and should be the same everywhere (all the participating centers) and verified by a "central outcome Committee" from raw clinical data (in a way independent from the sponsor).

We also read that in case of missing biomarkers, definitely a big issue when determining whether an event is really an AMI or not:

Probable Non-procedural MI
In cases of missing cardiac biomarkers:

- Ischemic symptoms lasting ≥20 minutes considered to be of cardiac origin and requiring hospitalization with ECG changes consistent with acute ischemia or with thrombolysis or coronary revascularization within 12 hours.

In cases of missing information on symptoms and ECG report or tracing:

- History of hospitalization for MI with cardiac enzymes showing a typical pattern of MI as for definite MI. However, the local PI should find out if the participant had chest pain or if the event occurred in a peri-operative period.

In cases of missing information on cardiac markers, ECG findings and duration of typical symptoms:

- History of hospitalization for MI with a documented finding compatible with recent MI on follow-up ECG or on imaging (cardiac echocardiography, nuclear scan, MRI)

We actually read: "*considered to be of cardiac origin…*"

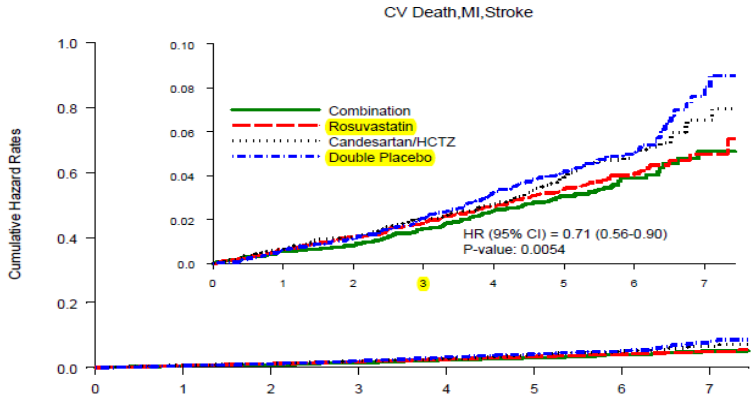
Question: are the "probable non-procedural (and procedural) AMI" included in the "coprimary outcome 1"? If yes, we have a big problem of credibility. In any case, statistics with and without these "probable" events should be presented.

Note also the "strange" definition (not in line with the classical definition given in academic textbooks) of chronic heart failure as if it is just a sort of dyspnea:

HEART FAILURE
A diagnosis is made based on signs and symptoms. Heart Failure symptoms include dyspnea (at rest or on exertion), orthopnea, paroxysmal nocturnal dyspnea; and signs: rales, edema, elevated jugular venous pressure includes:

Moreover, if one does not just analyze 2 but the 4 groups together (and it is imperative to 'control' the possible interactions between treatments as much as possible), as discussed above, one finds that exactly nothing happened during the first 3 years of treatment regarding the 'primary endpoint' ("coprimary outcome 1"; see the graph below).The red curve (rosuvastatin) and the blue curve (double placebo) run together.

Figure S9: Cumulative Incidence of Co-Primary Outcome 1 in the Candesartan/HCTZ+Rosuvastatin, Rosuvastatin Alone, Candesartan-HCTZ Alone and Double Placebo Groups



No. at Risk								
Combination	3180	3151	3125	3077	3014	2526	1068	276
Rosuvastatin	3181	3145	3116	3076	3025	2520	1054	255
Candesartan/HCTZ	3176	3131	3091	3050	2991	2482	1031	254
Double Placebo	3168	3133	3101	3050	2979	2488	1042	246

Cumulative hazard curves are shown for those receiving rosuvastatin + BP lowering, rosuvastatin alone, BP lowering alone, and double placebo. The hazard ratios (HR), 95% confidence intervals (CI), and P values are presented for the comparison between dual active therapy (rosuvastatin + BP lowering) and dual placebo.

Three years of treatment without any effect on the major fatal and nonfatal cardiovascular events.

The blue curve starts separating near year 4, but more so after year 6 at a time when the patient population only contains about 1000 and then only about 250 people (year 7). In other words, with so few nonfatal AMI (and stroke) in each of the 4 groups, one would think that not much (if anything) would be happening in that small remaining population beyond the first 3 years.

In any case, suddenly at about 4-5 years (while the curves should statistically not divert much but rather converge in accordance with the very classical rule called "*regression to the mean*"), they suddenly start deviating in a major fashion … mathematically not plausible.

Let's have a look at Table S20 below, reporting the curious endpoint "*reasons for hospitalizations*". About AMI and stroke, it is not clear if this is for fatal and/or nonfatal events.

Remember that regarding the "first coprimary outcome", much of the difference – other than CV mortality which is not different – would lie in those endpoints (37 vs. 26 for AMI and 53 vs. 37 for stroke; i.e. a total between-groups difference of 27 (11+16) which is so small as to make the 'primary endpoint' not likely to be statistically significant in post-hoc analysis specifically comparing rosuvastatin alone with double placebo. Then, if we compare the sum of AMI + stroke in the 4 groups (Table S20, below), we see a quite large difference between the candesartan/rosuvastatin group (n=51) and the double-placebo group (n= 90). Same for percutaneous coronary intervention (32 vs. 14); showing interaction between treatments (P values 0.02 and 0.01) which requires 4-group analyses as already discussed.

Table S20: Reasons for Hospitalization in the Candesartan/HCTZ+Rosuvastatin, Rosuvastatin Alone, Candesartan/HCTZ Alone and Double Placebo Groups

	Candesartan/HCTZ+ Rosuvastatin N=3,180 N (%)	Rosuvastatin Alone N=3,181 N (%)	Candesartan/HCTZ Alone N=3,176 N (%)	Double Placebo N=3,168 N (%)	P value
Total Hospitalizations	560 (17.6)	506 (15.9)	552 (17.4)	573 (18.1)	0.62
Cardiovascular Hospitalizations	141 (4.4)	140 (4.4)	178 (5.6)	191 (6.0)	0.005
Myocardial infarction	20 (0.6)	26 (0.8)	27 (0.9)	37 (1.2)	0.02
Stroke	31 (1.0)	37 (1.2)	47 (1.5)	53 (1.7)	0.02
Transient ischemic attack	5 (0.2)	9 (0.3)	8 (0.3)	4 (0.1)	1.0
Congestive heart failure	11 (0.3)	8 (0.3)	13 (0.4)	14 (0.4)	0.56
Unstable/new/worsening angina	20 (0.6)	18 (0.6)	21 (0.7)	26 (0.8)	0.38
Cardiac arrest	2 (0.1)	5 (0.2)	4 (0.1)	8 (0.3)	0.06
Supraventricular arrhythmia	20 (0.6)	12 (0.4)	17 (0.5)	25 (0.8)	0.46
Sustained ventricular tachycardia/arrhythmia	3 (0.1)	3 (0.1)	3 (0.1)	5 (0.2)	0.51
Pulmonary embolism	5 (0.2)	3 (0.1)	4 (0.1)	7 (0.2)	0.58
Coronary angiography	28 (0.9)	26 (0.8)	25 (0.8)	41 (1.3)	0.12
CABG	8 (0.3)	5 (0.2)	10 (0.3)	14 (0.4)	0.21
Percutaneous Coronary Intervention	14 (0.4)	20 (0.6)	26 (0.8)	32 (1.0)	0.01

Then again, when considering CV mortality (table S18, below: 91 vs 79, a difference of 12); in short, for the "coprimary outcome 1" (combining CV mortality + nonfatal AMI and stroke) a difference of 39 (12+27) between the rosuvastatin alone and the double placebo; although some events are counted twice, once in CV mortality (n=12) and once in the sum of AMI and stroke (n=27) since we do not have the exact numbers of nonfatal AMI and stroke; 27 representing both fatal and nonfatal AMI and stroke. In any case, this makes over a 7 year follow-up; an average of 5.6 per year.

Table S18: Causes of Death in the Candesartan/HCTZ+Rosuvastatin, Rosuvastatin Alone, Candesartan/HCTZ Alone and Double Placebo Broups*

	Candesartan/HCTZ+ Rosuvastatin N=3,180 N (%)	Rosuvastatin Alone N=3,181 N (%)	Candesartan/HCTZ Alone N=3,176 N (%)	Double Placebo N=3,168 N (%)
Total death	163 (5.1)	171 (5.4)	179 (5.6)	178 (5.6)
Cardiovascular death	75 (2.4)	79 (2.5)	80 (2.5)	91 (2.9)
Non cardiovascular death	88 (2.8)	92 (2.9)	99 (3.1)	87 (2.7)
Cancer	55 (1.7)	53 (1.7)	55 (1.7)	59 (1.9)
Pulmonary	10 (0.3)	10 (0.3)	10 (0.3)	7 (0.2)
Gastrointestinal	6 (0.2)	2 (0.1)	6 (0.2)	2 (0.1)

We now understand why the analysis of 4 groups regarding the "coprimary outcome 1" is not given or discussed in the NEJM article reporting the effects of rosuvastatin against placebo. Numbers are very small and we do not know whether the difference between rosuvastatin alone and double placebo is significant especially after correcting for the multiple amendments…

Whatever the true P values, **it is time to reason as medical doctors and not as statisticians**. If one accepts the accuracy of the data (to be verified...) as they are reported, it would mean that one has to treat 3181 patients with rosuvastatin for 5.6 years to avoid 39 fatal and nonfatal CV *complications*, or 7 "*events*" per year.

Put differently, treating 1000 patients for 1 year with rosuvastatin, one would avoid at best 1 or 2 nonfatal events (stroke or AMI) with no effect on life expectancy and no benefit to be expected during the first 3 years. Given the small numbers, it is likely that the fictitious (calculated) benefit is probably an illusion; and definitely not clinically consistent.

Still more important, it is obviously more efficacious (rather than treating 1000 patients with rosuvastatin) to identify the few patients at highest risk to develop AMI or stroke during the 6-year follow-up and anticipate. This is maybe medical fiction, but it is likely that it is among patients older than 80, smoker, diabetic, uncontrolled hypertensive, sedentary, nondrinker, and not following a Mediterranean diet that we would find the next victims. We must specifically help (protect) them; not the 980 others and not with rosuvastatin.

NB: Just in case you have not found the conflicts of interest among our friends, here is the list from the Can. J. Cardiology (although curiously not given the NEJM article):

Canadian Journal of Cardiology
Volume 32 2016

Disclosures

Eva Lonn has received institutional research funding from Astra Zeneca, Amgen, Bayer, GlaxoSmithKline (GSK), Eli Lilly, Sanofi, Servier and received honoraria for lectures or consulting from Amgen, Sanofi, and Servier. Antonio Dans has received research funding and or honoraria for lectures and travel support from Merck Sharp and Dohme, Boehringer Ingelheim, Bristol-Myers Squibb (BMS), Bayer, Sanofi, and Glaxo. Claes Held reports institutional research grants from GSK, BMS/Pfizer, Merck, and Roche and institutional grants and personal fees from AstraZeneca outside the submitted work. Petr Jansky received speaking honoraria from Bayer, Boehringer Ingelheim, Novartis, Pfizer, BMS, Sanofi, Eli Lilly, AstraZeneca, and Abbott. Kamlesh Khunti has received funds for research and acted as consultant to or received honoraria from AstraZeneca, Boehringer Ingelheim, Jansen, Eli Lilly, MSD, Novartis, Novo Nordisk, Roche, Sanofi-Aventis, Takeda, and Unilever. Lawrence A. Leiter has received research funding from, has provided CME on behalf of, and/or has acted as a consultant to: Amgen, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GSK, Janssen, Merck, Novo Nordisk, Pfizer, Sanofi, Servier, and Takeda. Basil Lewis has received research support and as consultant and advisory board honoraria from AstraZeneca, Pfizer, MSD, and Amgen and honoraria for speaking engagements from Pfizer and BMS. Patricio Lopez-Jaramillo has received honoraria for speaking engagements with Merck, MSD, Boehringer Ingelheim, Sanofi, AstraZeneca, Novartis, Roche, and Abbott. Alexandr Parkhomenko has received research funding from AstraZeneca, GSK, Servier, Amgen, BHFZ, and Bayer and honoraria for speaking engagements/advisory boards from Sanofi, Servier, Bayer, BHFZ, Boehringer Ingelheim, and AstraZeneca. Ron J.G. Peters has received consultancy fees from AstraZeneca unrelated to the HOPE-3 Study. Christopher M. Reid is supported by a National Health and Medical Research Council Fellowship and has received research funding from BMS, AstraZeneca, Servier, and Bayer. Karen Sliwa has received research funding from the Medical Research Council South Africa and the Sir Maurice Foundation, University of Cape Town. Jun Zhu has received a grant from Boehringer Ingelheim and BMS and honoraria received from Sanofi, Boehringer Ingelheim, Bayer, BMS, and AstraZeneca. Salim Yusuf has received institutional research funding from Astra Zeneca. The other authors have no conflicts of interest to disclose.

Here is more … for those interested:

LSEVIER

Canadian Journal of Cardiology 32 (2016) 311–318

Clinical Research

Novel Approaches in Primary Cardiovascular Disease Prevention: The HOPE-3 Trial Rationale, Design, and Participants' Baseline Characteristics

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Another interesting issue is in the article by Lonn et al in **Can J Cardiology 2016; 32:311**. This Methods article has been published at the same time as the 3 main articles reporting HOPE 3 results but after the death of David Sacket who, according to me, would have had another opinion.

There were a multitude of changes to the protocol (that they should have done while blinded, of course); noteworthy is the increase of the sample size and an extension of the study period … they should have modified the p-value in relation to these amendments. See for instance:

The trial was originally planned to start in the spring of 2007 to recruit 11,000 participants and to complete follow-up by March 2013. Original power calculations considered the factorial design of the trial; estimated yearly placebo event rates of 1% for the original primary outcome; anticipated recruitment completion by the end of 2009 as well as a mean follow-up of 5 years; a 25% RRR for each intervention alone (comparisons at the margins of the factorial design—these are independent comparisons, with no effect on the type I error rate [the effect of a modest 10% subadditivity was included in the sample size estimates]); cumulative nonadherence rates of 6% in 1 year, 11% by 2 years, 15% by 3 years, and 23% by 5 years; drop-in rates of 3% in the first year and 2% per year in subsequent years (11% over 5 years), and rates of loss to follow-up of < 1%. These original calculations also estimated that the trial had > 90% power to detect 40%-50% relative reductions in risk for the double active (ie, rosuvastatin 10 mg/d plus candesartan/HCTZ 16/12.5 mg/d) vs the double-placebo comparison.

Recruitment started in May 2007, lasted 3.66 years and was skewed, with higher enrollment rates during the last year of recruitment. Because of the delay in recruitment and the lower than expected in-trial observed event rates, an additional 1705 study participants were enrolled, for a total sample size of 12,705, and the steering committee amended the protocol twice. The first amendment, approved on February 29, 2012, allowed for 2 coprimary outcomes (see earlier discussion). The second amendment, approved on June 30, 2013, was for an extension of follow-up of 2.5 years to October 2015 to ensure accrual of at least 500 first coprimary events. This will result

The trouble with these changes is that some of them were done just before the unblinding at the end of 2015 (as per quote). Not pretty, not verifiable.

Conclusion: despite desperate effort to claim the opposite, HOPE 3 appears to be a negative trial (about the benefits of rosuvastatin) in terms of statistics and more importantly, the main reported data are not clinically consistent.

The authors and the co-authors, the editorialists of NEJM and all idiots who will claim again that statins are beneficial are, or will be, totally discredited.

And this, moreover, without talking about an almost **total absence of adverse effects of statins** (over 6 years) except for some eye disease and muscle symptoms, not in agreement with the most recent data from *pharmacovigilance.*

Not one more diabetic in 6 years? Great!