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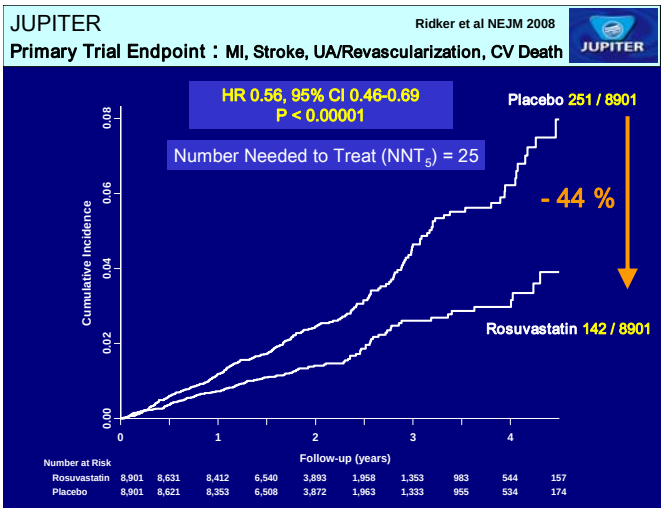
The JUPITER Trial: Should it change our Practice?

In the landmark JUPITER trial, a statin was shown to improve outcomes for patients with lipid levels that were considered optimal but who had elevated levels of high-sensitivity or cardio C-reactive protein (*hs*-CRP). A lot of new questions will logically follow, concerning the role of screening and the appropriate approach to therapy. Expert panels will develop recommendations on these issues derived from the data from JUPITER and other trials not yet performed. This *Heartbeat* will discuss the trial and provide a possible interim plan to make decisions on the basis of the JUPITER results analysis and discussions with colleagues.

The **J**ustification for the **U**se of Statins in **P**rimary Prevention: An **I**ntervention **T**rial **E**valuating **R**osuvastatin (**JUPITER**) is shaking up the field of primary prevention with new data showing that the treatment of apparently healthy patients with a statin cuts their risk of cardiovascular disease (CVD) morbidity and mortality by almost half.[1] In individuals with low low-density lipoprotein cholesterol (LDL-C) but elevated *hs*-CRP levels, investigators showed that **rosuvastatin** (Crestor, Astra Zeneca) 20 mg significantly reduced the primary end point—a composite of nonfatal myocardial infarction (MI), nonfatal stroke, hospitalization for unstable angina, revascularization, and confirmed death from CV causes—by 44% compared with individuals treated with placebo (Figure 1). *JUPITER provides further evidence for the LDL hypothesis that lower is better.*

Figure 1. JUPITER: Primary Trial Endpoint.



The trial, designed as a 4 year study and stopped prematurely (1.9 years) because of unequivocal benefit, showed that the benefits extended to all subgroups, including "robust reductions in CV events with statin therapy in women and black and Hispanic populations, for which data on primary prevention are limited".

This clinical trial, a double-blinded, placebo-controlled, randomized study that included 17,802 healthy men and women (out of 89,890 screened for enrollment) assigned to rosuvastatin 20 mg or placebo, was designed to assess whether statin therapy should be given to apparently healthy individuals with normal LDL-C but elevated *hs*-CRP (>2.0 mg/L). In patients treated with rosuvastatin, LDL-cholesterol levels were cut in half, decreasing from a median 108 mg/dL at baseline to 55 mg/dL at 12 months. CRP levels were also significantly reduced, declining from 4.2 mg/L at baseline to 2.2 mg/L at 12 months (Fig 2). Triglyceride levels were reduced 17% from baseline among those treated with statin therapy.

These effects persisted over the course of the study.

Figure 2. Baseline and change in LDL cholesterol and *hs*-CRP levels during study period.

Measure	Baseline	12 mo	24 mo	36 mo	48 mo
LDL-C (mg/dL)					
Rosuvastatin 20 mg	108	55	54	53	55
Placebo	108	110	108	106	109
***hs* -CRP (mg/L)**					
Rosuvastatin 20 mg	4.2	2.2	2.2	2.0	1.8
Placebo	4.3	3.5	3.5	3.5	3.3

p<0.001 for all between-group comparisons

After 1.9 years of follow-up, treatment with rosuvastatin significantly reduced the primary composite end point 44% compared with placebo. This reduction was observed among nearly all of the individual end points, including a 55% reduction in nonfatal MI, a 48% reduction in the risk of nonfatal stroke, and a 47% reduction in the risk of hard cardiac events (a composite of MI, stroke, and death from CV causes).

In terms of absolute benefits, the proportion of patients who had an MI, stroke, revascularization, or hospitalization for unstable angina or died from CV causes was 1.6% in the rosuvastatin arm and 2.8% in the placebo arm, an absolute risk reduction of 1.2%. Similarly, the proportion of patients with hard cardiac events—CV death, MI, and stroke—was reduced from 1.8% in the placebo arm to 0.9% in the rosuvastatin arm, an absolute reduction of 0.9%.

In an editorial accompanying the published study, **Dr Mark Hlatky** (Stanford University School of Medicine, CA) agreed that guidelines are likely to be revisited, although he is cautious on just how big an impact the findings will have on clinical practice.[2] "JUPITER provides yet more evidence about the effectiveness of statin therapy in reducing CV risk, even among persons who would not currently be considered for pharmacotherapy," writes Hlatky. "Guidelines for primary prevention will surely be reassessed on the basis of the JUPITER results, but the appropriate size of the orbit of statin therapy depends on the balance between the benefits of treatment and its long-term safety and cost."

Is *hs*-CRP overkill? Could it precipitate overuse of statins?

How much will *hs*- CRP add to current screening? It is highly correlated with being overweight and increased CV risk factors, so how many extra people do you identify with screening above just looking at those parameters? Participants in JUPITER were older (median age-66 years), overweight (median BMI 28.3 kg/m^2), with higher-than-normal blood pressure, and > 40% of patients had metabolic syndrome. Another 15% smoked and 10% had a positive family history. *These people are an obvious "set-up" for a biomarker test to see whether they were at higher-than-apparent risk, thus arguing against the additional benefit of using hs-CRP for screening.*

Furthermore, the test—a non-specific marker for low-grade inflammation—is highly variable and is elevated with infections (including gingivitis which is quite common), injuries (including DJD which is very common in this age group) and cancer. In fact, in the JUPITER trial, there were 612 new cancers and just 196 heart attacks and strokes combined. It's very likely that the participants who were diagnosed with cancer during the study already had malignant cells hiding somewhere in their bodies when they joined the trial. People who had had cancer recently were excluded from the study, but the study period was so short—less than two years for most—that a growing but yet-to-be-detected cancer would be as likely to have caused the elevated *hs*-CRP as vascular disease.

In addition, some people are genetically inclined to have higher than normal *hs* CRP. In a little-noted study of 50,000 patients, published recently in the *New England Journal of Medicine*, investigators in Denmark showed that even a lifetime of genetically elevated CRP was not predictive of heart disease.[3] This is in contrast to

LDL-C, where hereditary elevations invariably put arteries in jeopardy. *Abnormally high hs-CRP levels do not always reflect arterial injury or CVD risk and can lead to over use of statins.*

Conclusions:

N.B. *The results have to be evaluated in the light of two potential conflicts of interest.* The lead investigator stands to benefit from a patent involving the use of *hs*-CRP to evaluate the risk of CVD, and Astra Zeneca, who financed the study, is now trumpeting the results as "dramatic" and has also bought part interest in the *hs*-CRP patent.

Among apparently healthy men and women with elevated *hs*-CRP but low LDL-C, rosuvastatin reduced incident MI, stroke, and CV death by 44 percent. *Despite being classified as healthy, many JUPITER patients had a number of CV risk factors placing them in the high-moderate-risk category.*

Despite evaluating a population with lipid levels widely considered to be "optimal" in almost all current prevention algorithms, the relative benefit observed in JUPITER was greater than in almost all prior statin trials. However, the trial exposes the **current LDL-C thresholds** for lipid-lowering therapy not only as arbitrary, but more important, as **a poor indicator of CV risk.** This should reinforce using apoB or LDL particle number/concentration (LDL-P), via an NMR LipoProfile, to assess CV risk as recommended in the recent American College of Cardiology/ American Diabetic Association Consensus Guidelines.[4] *LDL-P has emerged as a superb predictor of risk and also as a goal of therapy.*

In JUPITER, rosuvastatin significantly reduced all-cause mortality by 20 % in individuals who do not currently qualify for statin therapy. *CHD risk stratification per NCEP/ATP-III Guidelines, apoB and LDL-P levels were not addressed.* The calculated mean **non-HDL**-C, TC minus HDL-C, (also not addressed) from the baseline blood levels (median, interquartile range) is 137mg/dL. Therapy is warranted if it is > 130mg/dL (or > 100mg/dL in very-high-risk patients).[5] Newer data reveal that this calculation is always equal or better than LDL-C at predicting CVD risk.

Benefits of rosuvastatin were consistent in all sub-groups evaluated regardless of age, sex, ethnicity, or other baseline clinical characteristics, including those with elevated *hs*- CRP and no other major risk factor.

Rates of hospitalization and revascularization were reduced by 47 percent within a two-year period, suggesting that the screening and treatment strategy tested in JUPITER is likely to be cost-effective, benefiting both patients and payers. Using Kaplan-Meier estimates, 95 patients would need to be treated with rosuvastatin for 2 years to prevent one occurrence of the primary endpoint. Over an average of 5 years of treatment, the number needed to treat to prevent one occurrence of the primary endpoint would be 25.

The results of **JUPITER** are inconclusive as to the value of *hs*-CRP testing in clinical care. At this time, no change is warranted to current guidelines recommending selective measurement of *hs*-CRP in asymptomatic patients at an intermediate level of risk based on standard clinical markers.

Writers of future medical guidelines will need to define which evaluations of lipid risk are best and just what those values should be so we can determine who should be treated. They will also need to clarify some issues like long-term safety, efficacy, and cost-effectiveness of using statins in asymptomatic, apparently healthy patients, and whether these findings can be considered a class effect of statins, or as specific to rosuvastatin, which exhibits several pharmacokinetic differences from other statins.

Plan of Attack: Until the new guidelines

JUPITER should change how we evaluate and treat for primary prevention.

The proven value of following a heart-healthy eating plan, being physically active, maintaining healthy weight, and not smoking cannot be overestimated and must be implemented.

1) Don't use *hs*-CRP screening routinely unless you need a "tie-breaker" in moderate-risk patients or strong family history—no apparent benefit.

2) Use non-HDL-C, apoB and LDL-P as more precise ways of determining CV risk. LDL-C is no longer the best way to estimate risk (half of all heart attacks and strokes occur in those with "OK" LDL-C values).

3) Treat with statins (more aggressively) to get to appropriate **Framingham goals of lipid therapy** (Table 1). It seems likely that there is a group of people who could benefit by taking statins for primary prevention, and it seems cost-effective.

Table 1. Framingham Offspring Study Percentiles.

Percentile	LDL-C (mg/dL)	Non-HDL-C (mg/dL)	LDL-P (nmol/L)	ApoB (mg/dL)
2	**70**	**83**	**720**	**54**
5	78	94	850	62
10	88	104	940	69
20	**100**	**119**	**1100**	**78**
30	111	132	1220	85
40	120	143	1330	91
50	**130**	**153**	**1440**	**97**
60	139	163	1540	103
70	149	175	1670	110
80	**160**	**187**	**1820**	**118**
90	176	205	2020	130
95	191	224	2210	140

n=3,367 (1,635 men; 1,732 women) Specimens were collected in 1988-1991 (exam cycle 4). Analysis was restricted to subjects with TG <400 mg/dL. Ethnic make-up was 99% Caucasian.

High Risk Goal is the 20th percentile (JUPITER patients)

Very High Risk Goal is the 2nd to the 5th percentile.

Looking at the big picture: absolute benefit vs. cost

Skyrocketing prices for drugs and medical devices have led a growing number of countries—including the US—to start asking the hardest of questions: How much is saving a life worth?

Because of the low absolute benefit shown in JUPITER, (common in primary prevention trials), the **cost** of treatment is a major issue. **Dr James Stein** (University of Wisconsin Medical School, Madison) and **Dr Jon Keevil** (University of Wisconsin, Madison) performed an analysis based on **National Health and Nutrition Examination Survey** data from 1999–2002. These data include 171 million adult Americans between 20 and 79 years of age, and the two used these data and JUPITER results to evaluate its potential financial impact.

There are 7.4 million adult Americans (4.3% of the population) who would have qualified for JUPITER. Prescribing rosuvastatin 20 mg daily vs not treating these patients would prevent 43,526 CVD events per year, or 29,509 MIs, strokes, or deaths and 18,443 deaths.

According to their math, if statin therapy costs $1200 per year, treating this entire subpopulation with rosuvastatin (Crestor) would cost $8.9 billion per year and prevent a CVD event at a cost of $203,000 per event per year. It would cost $480,000 to save a life. *If a generic statin is used and statin therapy costs $60 per year, the cost is $443 million per year. The cost of preventing a CVD event is $10,200 per event per year and $24,000 to save one life—much more acceptable numbers.*

*Generic pravastatin (two 40mg tabs) would cost about $80 per year (locally). It has a good side effect profile and in **WOSCOPS** it was associated with a decreased incidence of diabetes in contrast to the increased incidence in JUPITER.*

Our plan of attack obviously doesn't provide all the answers, and unfortunately generics will not get everyone to goal. For JUPITER patients, the > 40% reduction of LDL-C with pravastatin 80mg would theoretically get LDL-Cs down to at least 65mg/dL with maybe only a 40% reduction in events. That's probably satisfactory for the 45 million uninsured—rapidly rising in the present economy—and those with insufficient coverage or with an $80 brand-name deductible.

Current economic conditions have created an increased risk of non-compliance, with patients deciding not to fill prescriptions, to discontinue them, or to divide their dosages. Generics and low-cost prescription programs, e.g. Wal-Mart, Target and Rite-Aid ($10/three months) increase adherence to prescribed regimens.

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[1] Ridker PM, Danielson E, Fonseca FA et al. Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein (JUPITOR). *New Engl J Med* November 20 2008; 359: 2195-2207.

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