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Should Statin Therapy Be Allocated on the Basis of Global Risk or on the Basis of Randomized Trial Evidence?

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Abstract

Current clinical guidelines recommend the use of a global risk assessment tool, such as those pioneered by the Framingham Heart Study, to determine eligibility for statin therapy in patients with absolute risk levels greater than a certain threshold. In support of this approach, several randomized trials have reported that patients with high absolute risk clearly benefit from statin therapy. Therefore, the guideline recommendations would seem intuitive and effective, albeit on the core assumption that the mortality and morbidity benefits associated with statin therapy would be greatest in those with high predicted absolute risk. However, if this assumption is incorrect, using predicted absolute risk to guide statin therapy could easily result in underuse in some groups and overuse in others. Herein, the authors question the utility of global risk assessment strategies based on the Framingham risk score for guiding statin therapy in light of current data that have become available from more recent and robust prospective randomized clinical trials since the publication of the National Cholesterol Education Program Adult Treatment Panel III guidelines. Moreover, the Adult Treatment Panel III guidelines do not support treatment of some patients who may benefit from statin therapy. In conclusion, the authors propose an alternative approach for incorporating more recent randomized trial data into future statin allocation algorithms and treatment guidelines.

Current clinical guidelines recommend the use of a global risk assessment tool, such as those pioneered by the Framingham Heart Study (FHS), to determine eligibility for statin therapy in patients with absolute risk levels greater than a certain threshold. For example, the National Cholesterol Education Program Adult Treatment Panel (ATP) III guidelines are based on the Framingham risk score (FRS) and indicate that very high risk patients may further benefit from a low-density lipoprotein (LDL) cholesterol level <70 mg/dl as opposed to <100 mg/dl. In support of this approach, several randomized trials have reported that patients with high absolute risk from multiple risk factors, previous coronary artery disease, or previous stroke clearly benefit from statin therapy.^{1–6} Therefore, the guideline recommendations would seem intuitive and effective, albeit on the core assumption that the mortality and morbidity benefits associated with statin therapy would be greatest in those with high predicted absolute risk. However, if this assumption is incorrect, using predicted

absolute risk to guide statin therapy could easily result in underuse in some groups and overuse in others.

The widely used FRS has some utility for the risk assessment of coronary artery disease events over a 10-year period. However, it is limited for predicting the absolute risk in some populations, such as women and individuals of low income or nonwhite race or ethnicity.⁷ For example, in a retrospective study of 56 women aged <65 years who presented with their first myocardial infarction (MI), none of these women had high predicted absolute risk scores, only 5% were in the “intermediate risk” category, and 95% were labeled as low risk.⁸ On the basis of the ATP III guidelines, only 83% of these women would have been eligible for statin therapy, perhaps resulting in missed opportunities for more aggressive preventive management in this population.^{9,10} Data from the Third National Health and Nutrition Examination Survey (NHANES) indicate that FRS-based risk estimates identify only 0.9% of asymptomatic adult women as high risk. However, data from the FHS indicate that 39% of women aged 50 years who are free of cardiovascular disease will ultimately have a cardiovascular event.¹¹ Regardless of gender, the FRS-based risk estimates may falsely reassure patients (and their health care providers) who are at low short-term but high lifetime risk for cardiac events, even if these patients have significant subclinical atherosclerosis.^{11–14} Moreover, the FRS does not incorporate family history of premature atherosclerosis, which has been identified as an important cardiac risk factor.^{15–17} The limitations of the FRS-based absolute risk assessment raise the possibility that current guidelines for lipid-lowering pharmacotherapy preclude the treatment of some patients who may benefit from statin therapy to stabilize their existing subclinical atherosclerosis and slow progression of their underlying disease.¹⁸

Recent results from 6 randomized placebo-controlled clinical trials of statin therapy also question the role of global risk assessment tools in defining eligibility for statin therapy, with data showing benefit of statins in some populations deemed to be low risk by the current guidelines and lack of benefit in other populations deemed to be at high absolute risk. Therefore, it is necessary to reexamine the hypothesis that absolute risk should dictate statin therapy in the context of current data (Table 1).

Two of these trials examined patients with congestive heart failure, a group with exceptionally high absolute risk. In the Controlled Rosuvastatin Multinational Trial in Heart Failure (CORONA), conducted from 2003 to 2005 at 371 sites in 19 European countries, Russia, and South Africa, the investigators randomly allocated 5,011 patients with a mean age of 73 years and New York Heart Association class II to IV ischemic systolic heart failure to rosuvastatin 10 mg or placebo.¹⁹ After a follow-up period of 33 months, nearly a third of the trial participants experienced the primary outcome of nonfatal MI, nonfatal stroke, or cardiovascular death, confirming the very high absolute risk in such patients. However, despite a 45% reduction in LDL cholesterol and good patient adherence to the study medication, there was no significant benefit associated with statin therapy on the primary outcome, as well as in subgroup analysis including cholesterol, high sensitivity C-reactive protein (hs-CRP), the left ventricular ejection fraction, N-terminal-pro- brain natriuretic peptide, gender, and age.

An almost identical finding was observed in the Effect of Rosuvastatin in Patients With Chronic Heart Failure (GISSI-HF) trial conducted at 357 medical centers in Italy. The investigators randomized 4,574 patients with a mean age of 68 years and New York Heart Association class II to IV chronic heart failure to rosuvastatin 10 mg/day or placebo.²⁰ During a follow-up period of >4 years, 57% were hospitalized or died for cardiovascular reasons and 29% died from any cause, again demonstrating the very high absolute risk in these patients. However, as in CORONA, there was no benefit associated with statin therapy on cardiac events, all-cause mortality, or subgroup analysis despite a 27% to 32% reduction of LDL cholesterol.

The disconnect between absolute risk and statin efficacy observed in CORONA and GISSI-HF is not unique to patients with heart failure, as demonstrated in 2 other recent trials of patients on hemodialysis. In the German Diabetes and Dialysis Study, 1,255 patients from 178 centers in Germany with a mean age of 66 years and type 2 diabetes mellitus receiving maintenance hemodialysis were allocated to atorvastatin 20 mg or to placebo.²¹ After a follow-up period of 4 years, the cumulative incidence of MI, stroke, or cardiovascular death approached 50%, indicating exceptionally high risk. Although atorvastatin reduced LDL cholesterol levels by 42% in this population, there was no significant effect on clinical outcomes.

Similarly, A Study to Evaluate the Use of Rosuvastatin in Subjects on Regular Hemodialysis: An Assessment of Survival and Cardiovascular Events (AURORA) recruited 2,776 patients who underwent maintenance hemodialysis from 284 dialysis centers in 25 countries. During a follow-up period of >3 years, the rosuvastatin group had a 43% LDL cholesterol reduction, but there was no benefit on either individual end points or the composite end point of time to MI, stroke, or cardiovascular death, despite a 5-year cumulative incidence of these events of >35%.²² It is possible, however, that the outcomes in this particular population may be driven by factors other than atherosclerosis. Although statins would certainly affect a population in which atherosclerotic events predominate, they would not be expected to affect deaths from congestive heart failure or valvular calcification. Moreover, this population of patients may have had late-stage atherosclerotic disease beyond a certain threshold after which statins do not have preventive benefit. For example, statins may affect coronary atherosclerotic plaque or aortic sclerosis at an early stage but not at late or end stage, such as diffuse calcified atherosclerotic coronary disease or severe aortic stenosis.^{23,24}

Although these 4 trials documented a lack of efficacy for statin therapy and suggested that LDL cholesterol is not a modifiable risk factor in at least some high-risk and very high risk patients, 2 other recent trials, Management of Elevated Cholesterol in the Primary Prevention Group of Adult Japanese (MEGA) and Justification for the Use of Statins in Primary Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), demonstrate efficacy for statin therapy in patient groups that are considered at low risk according to traditional global risk algorithms. Most of the subjects in these trials would not merit statin therapy on the basis of the current ATP III guidelines. In the JUPITER trial, 17,802 apparently healthy men and women from 1,315 sites in 26 countries with age as a common risk factor (mean age 66 years), baseline LDL cholesterol levels <130 mg/dl, and baseline

hs-CRP levels ≥ 2 mg/L were randomized to rosuvastatin 20 mg or placebo. After a follow-up period of about 2 years, statin therapy was associated with 50% and 37% reductions in LDL cholesterol and hs-CRP levels, respectively. Statin therapy was also associated with a 44% relative risk reduction in the hard end point of MI, stroke, or cardiovascular death as well as a similar reduction in arterial revascularization.²⁵ Subgroup analyses, including those based on gender, race, body mass index, and FRS, yielded consistent results for the primary outcome.

All participants in the JUPITER trial had LDL cholesterol levels below treatment targets for primary prevention, and nearly half had FRS $<10\%$ for hard events. Women benefited to a similar degree regardless of whether their FRS ranged from 5% to 10% or were $>10\%$.²⁶ Moreover, the absolute event rates as well as consequent number-needed-to-treat calculations (95 at 2 years, estimated 25 at 5 years) were better than those of previous primary prevention trials that selected patients on the basis of hyperlipidemia rather than elevated levels of hs-CRP. If one includes mortality and the incidence of venous thromboembolic events in the primary end point, the estimated number needed to treat was only 18, which is far less than previous primary prevention trials. Interestingly, the reduction in event rate was twofold greater than would be predicted from the observed reduction in LDL cholesterol. Although it is not clear whether this effect is related to the lowering of hs-CRP and LDL cholesterol or of hs-CRP alone, the data suggest that hs-CRP could be considered a risk stratification tool in low-risk older men and women who are otherwise apparently healthy but have $\geq 5\%$ risk for MI over the next decade.^{25,27,28} Because the Reynolds risk score incorporates hs-CRP as well as family history of premature coronary artery disease into the traditional FRS risk estimates, the Reynolds risk score may be a more effective tool for assessing absolute cardiovascular risk, especially in women.^{25,27,28}

Consistent with the findings of JUPITER are the results of the MEGA trial, which randomized 7,832 apparently healthy Japanese men and women to pravastatin 10 to 20 mg/day with diet modification or diet modification alone.²⁹ (Of note, cardiac morbidity and mortality rates are much lower in Japan than in Western countries, and global risk algorithms have been less reliable in this population.) After >5 years of follow-up, statin therapy was associated with a 33% reduction in coronary events and a 30% relative risk reduction in cardiovascular events but only an 11% reduction in LDL cholesterol levels. Therefore, MEGA and JUPITER demonstrated that even in a low-risk population, statin therapy is more effective at reducing cardiovascular events than would be predicted from the reduction in LDL cholesterol alone. Interestingly, JUPITER reported a clear benefit in women, although the FRS risk estimates for this subgroup were almost universally $<10\%$. Although women have lower FRS and a lower estimated lifetime cardiovascular risk than men, a recent meta-analysis of randomized placebo-controlled trials (consisting of 20,147 women) suggested that statins reduce primary cardiovascular event rates to a similar extent in men and women.²⁶

Given trial evidence that some patients at low predicted absolute risk for cardiovascular events benefit from statin therapy while some patients at high absolute risk do not, it may be prudent to reconsider our strategy for identifying populations that would benefit from statin therapy. The degree of hs-CRP reduction may eventually prove to be of equal or greater

importance compared to absolute and percentage reductions in LDL cholesterol. Apolipoprotein B-containing lipoproteins have been implicated as an important contributor to atherosclerosis, especially in patients with elevated cardiometabolic risk.³⁰ Because non-high-density lipoprotein (HDL) cholesterol levels quantify concentrations of all apolipoprotein B, non-HDL cholesterol may be a better predictor of cardiovascular events than LDL cholesterol, especially in the presence of elevated triglyceride levels.^{10,31} Inflammation and coronary artery calcification may be important for the refinement of risk stratification, and several noninvasive imaging techniques may be used to assess global cardiovascular risk.¹⁰

A simple alternative approach for identifying patients could entail prescription of statin therapy on the basis of actual results of the more recent randomized trials without making assumptions that go beyond the data that were available at the time of publication of the ATP III guidelines. Such an approach would not only be “evidence based” but would prove simple to implement in primary and secondary prevention. For example, on the basis of completed secondary prevention trials, all patients with previous MIs or previous strokes should receive statin therapy regardless of their LDL cholesterol levels, assuming no contraindications to therapy. Statin doses should be titrated to an LDL cholesterol goal of <100 mg/dl and a non-HDL cholesterol goal of <130 mg/dl. Many clinicians could aim for an LDL cholesterol level of <70 mg/dl on the basis of the 2004 update to the ATP III guidelines and the many secondary prevention studies that support these recommendations. Moreover, on the basis of completed primary prevention trials, it is reasonable to treat men aged >50 years and women aged >60 years if they did not already qualify for treatment and if they had any of the following characteristics: LDL cholesterol >160 mg/dl, total cholesterol/HDL cholesterol ratio >5, or hs-CRP >2 mg/L after a period of 6 to 12 months of aggressive lifestyle changes.²⁵ Contemporary studies suggest that patients with these demographic and laboratory features have a higher lifetime risk for cardiovascular events, and therefore would also benefit from routine reassessments of their cardiovascular risk factors every 5 years. For younger asymptomatic patients with low short-term but high lifetime cardiovascular risk (as determined by the presence of 2 traditional risk factors), it is reasonable to implement aggressive prevention efforts focusing on the need for dietary and exercise habits. Moreover, helping these younger patients understand their risk may be an effective motivating tool for improving on their lifestyle risk factors.³² Clinical judgment would be necessary for those with family histories of premature atherosclerosis because fewer data are available for these groups. In subgroup analyses from large studies such as the JUPITER trial, these patients appear to benefit from statin therapy in primary prevention after the ages of 50 and 60 years for men and women, respectively.

Although the FRS is the cornerstone for the current guidelines for statin therapy, no randomized controlled statin trial has been conducted using the FRS-based ATP III risk algorithm to select study participants, nor has the FRS itself ever been randomized or tested as a tool for targeting statin therapy. Although the FRS serves as a simple and inexpensive method of cardiovascular risk assessment that seems to effectively identify some patients who will benefit from statin therapy, the growing evidence base suggests a need to move beyond predicted risk assessment and at least amend, if not replace this tool as a means for identifying patients who will benefit from statins over the long term. The alternative

approach (outlined above) includes basic queries for cardiovascular event history, age, and laboratory values without the need to calculate and/or evaluate any numerical scores and is data driven and simple to implement. Although the FRS and the alternative approach are limited by a lack of prospective evaluation, the alternative approach is based on current data from more recent prospective randomized clinical trials. A potential 2-step strategy could entail applying the FRS approach as an initial risk screen, and if the predicted absolute risk is deemed low or intermediate on this basis, the alternative approach could be applied to identify additional patients who may benefit from statin therapy. Although such a strategy may still result in the treatment of some patients who will not derive benefit from statins, the added risk and cost of this approach would likely be outweighed by the overall risk reductions achieved by treatment of more vulnerable patients.

The practice of evidence-based medicine warrants the allocation of statins on the basis of the current data available from prospective randomized clinical trials rather than total reliance on simple extrapolation of observational data. It is necessary to incorporate the more recent data into future statin allocation algorithms and treatment guidelines, perhaps in combination with evidence-based global risk assessment, to optimize cardiovascular disease prevention efforts now and in the future.

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Table 1

Summary of data from recent randomized placebo-controlled clinical trials of statin therapy

Trial	n	Women (%)	Absolute Risk in Placebo Based on FRS (%)	Median Follow-Up (years)	LDL-C Reduced With Statins (%)	Primary End Point	NNT Calculated for the Study Duration	Event Rate of Placebo (Events/100 Patient-Years)	Event Rate of Statin (Events/100 Patient-Years)	ARD (Event Rate of Placebo - Event Rate of Statin)	HR (95% CI)	RRR (%) (95% CI)
CORONA ¹⁹	5,011	24	High (33)	2.7	45	CVD, NFMI, NFS	NA	12.3	11.4	0.90	0.92 (0.83–1.02)	0
GISSI-HF ²⁰	4,574	23	High (57)	3.9	32	Time to CVD, TTHA from CV event	NA	14.4	14.6	–0.27	1.01 (0.91–1.11)	0
German Diabetes and Dialysis Study ²¹	1,255	46	High (43)	4.0	42	CVD, FMI	NA	9.8	9.2	0.55	0.92 (0.77–1.10)	0
AURORA ^{22,23}	2,776	38	High (35)	3.8	43	CVD, NFMI, NFS	NA	9.5	9.2	0.30	0.96 (0.84–1.11)	0
JUPITER ²⁶	17,802	38	Low (2)	1.9	50	CVD, NFMI, NFS, UA, AR	95 (25)*	1.36	0.77	0.59	0.56 (0.46–0.69)	44 (31–54)
MEGA ³⁰	7,832	68	Low (2)	5.3 [†]	18	CVD, NFMI, UA, CVI	119	0.5	0.33	0.17	0.67 (0.49–0.91)	33 (9–51)

* For JUPITER, the calculated NNT was 95 at 1.9 years (median follow-up period). The estimated NNT (extrapolated over a 5-year risk projection) was 25.

[†] All trials reported median values for the follow-up period except for MEGA, which reported the mean value.

AR = arterial revascularization; ARD = absolute rate difference (this should be interpreted with caution for trials with negative results); CI = confidence interval; CV = cardiovascular; CVD = cardiovascular death; CVI = cardiac or vascular intervention; FMI = fatal MI; HR = hazard ratio; LDL-C = LDL cholesterol; NA = not available; NFMI = nonfatal MI; NFS = nonfatal stroke; NNT = number needed to treat (this value is not available for trials with null results); RRR = relative risk reduction (this is set to a value of zero if the p value is not <0.05); TTHA = time to hospital admission; UA = unstable angina.