



ON ISSUES IN THE MANAGEMENT OF ATHEROSCLEROSIS • NOVEMBER 2008

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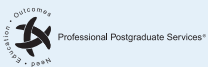
LEARNING OBJECTIVES: After reading articles in this issue of *OnsiteInsight*[®], participants should be able to:

- Describe current and emerging markers for cardiovascular risk prediction in addition to traditional Framingham Risk Scoring
- Relate findings from clinical trials on the management and treatment of atherosclerosis and its contributors, and apply to clinical practice as appropriate
- Explain the role of factors that contribute to the development of atherosclerosis

TARGET AUDIENCE: Primary care physicians, cardiologists, endocrinologists, and other healthcare professionals involved in the management of patients at risk for, or with cardiovascular disease.

RELEASE/VALID THROUGH DATES:
11/17/2008–11/17/2009

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FACULTY: JoAnne Foody, MD, Associate Professor, Harvard Medical School, Director, Cardiovascular Wellness Center, Brigham and Women's Hospital, Boston, Massachusetts, has indicated that she has served on the Speaker Bureau for Novartis Pharmaceuticals Corporation and as a retained consultant for Merck & Co., Inc., Pfizer Inc., and sanofi-aventis.

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The data reported in this issue of *OnsiteInsight*[®] were presented during the American Heart Association (AHA) Scientific Sessions 2008 from November 8–12, 2008, in New Orleans, Louisiana.

JUPITER: Statin Promotes Reduction in First CV Events Subjects Had High CRP, Low LDL-C

In patients without elevated LDL-C levels—but with increased CRP levels—treatment with Rosuvastatin was shown in JUPITER to produce a 44% risk reduction in the primary endpoint (major CV events). The results, released at the AHA Scientific Sessions, come 8 months after the study was halted more than 2 years ahead of schedule for “unequivocal benefit” of statin therapy vs placebo.

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APPROACH: Rosiglitazone Doesn't Meet Primary Endpoint

Richard Nesto, MD, presented results from the APPROACH trial, which sought to examine whether specific glucose-lowering agents affect the progression of atherosclerosis among patients with type 2 diabetes and CV history (n=672). Therapies used in the study were rosiglitazone (a thiazolidinedione; n=333) and glipizide (a sulfonyleurea; n=339).

Data were assessed using IVUS measurements at baseline and 18 months. The primary endpoint was change in percent atheroma volume (PAV); secondary endpoints were change in normalized atheroma volume and change in most diseased 10-mm subsegment.

Results:

- For the primary endpoint (change in PAV): rosiglitazone, -0.21%; P=0.19; glipizide, +0.43%; P=0.53. Treatment difference of -0.64% was nonsignificant (P=0.12).
- There was, however, a significant difference in normalized atheroma volume (rosiglitazone, -3.9 mm³; P<0.05; glipizide, +1.2 mm³; P=0.54; treatment difference: -5.12 mm³; P=0.04)
- Statistically significant difference in incidence of hypoglycemia with rosiglitazone at 8% compared with glipizide at 28% (P<0.0001).
- No statistically significant between-group differences in major CV events. ❖

APPROACH=Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History

Mean Change in Lipid Parameters

	Glipizide	Rosiglitazone	P
HDL-C	6.1	14.6	<0.001
CRP	-54.4	-68.1	<0.001
LDL-C	-8.4	-3.1	0.002
TG	-5.4	-8.7	0.16

Combination Therapy for Mixed Dyslipidemia, Hypertriglyceridemia

Numerous presentations explored the use of combination therapy for mixed dyslipidemia and hypertriglyceridemia. Bays and colleagues assessed the effects of prescription omega-3 acid ethyl esters (P-OM3; 4 g/d) coadministered with escalating doses of atorvastatin (10, 20, 40 mg) among patients with non-HDL-C <160 mg/dL* and TG 250–599 mg/dL* over 16 weeks. Primary endpoint: between-group difference in non-HDL-C at Week 8; other lipoproteins were also assessed. P-OM3 + atorvastatin 10 mg significantly reduced non-HDL-C and improved lipoprotein secondary endpoints. Benefits were also seen with 20- and 40-mg atorvastatin doses.

Bays et al also presented data from a 1-year safety/efficacy extension study of subjects enrolled in three 12-week RCTs who had mixed dyslipidemia and received the novel fenofibrate, ABT-335[†], plus low- or moderate-dose rosuvastatin, simvastatin, or atorvastatin, or ABT-335 or statin monotherapy.

Combination fibrate/statin therapy substantially improved multiple lipid parameters, including TG, HDL-C, LDL-C, non-HDL-C, and CRP after 4 weeks; improvements were sustained long term (over 64 wks), and mean final values were within optimal levels for high CHD risk/risk equivalent subjects defined by national guidelines. Fibrate plus moderate-dose statin therapy was generally well tolerated.

*Not FDA approved for this indication.

[†]Investigational agent; not yet FDA approved

MESA: Predicting CHD in Asymptomatic Subjects

Low LDL-C is associated with fewer adverse CV events. However, even those with low LDL-C experience CHD events and may benefit from more aggressive therapy. Blankstein et al presented data from MESA, which identified risk factors for CHD events among asymptomatic individuals with LDL-C ≤ 100 mg/dL. Traditional risk factors and biomarkers were assessed for their independent association with CHD events. CAC and CIMT were also assessed to determine whether subclinical atherosclerosis markers provided incremental information.

Age, male gender, hypertension, diabetes, low HDL-C, high TG, CAC >0 , and CIMT ≥ 1 mm predicted CHD events. The relationship of these risk factors remained strong after adjusted for CAC or CIMT. ❏

MESA=Multi-Ethnic Study of Atherosclerosis

Presentations Highlight Risk Assessment

A series of presentations featured novel approaches to risk assessment. Munir and colleagues presented data examining the impact of arterial age on risk of CHD events using a web-based arterial age calculator^a from the MESA study that incorporates CAC. FRS and arterial age were calculated for all participants aged 40–50 years ($n=2,000$) who were part of the Prospective Army Coronary Calcium Project. MESA arterial age calculation produced modest increase in CHD risk estimation, primarily among men.

Carrigan et al presented data from a study assessing whether coronary atherosclerotic plaque assessed by multislice computed tomography provides incremental prognostic value over FRS among subjects (aged 54 ± 12 years; 61% male) without known CAD ($n=227$). Proximal coronary atherosclerotic plaque predicted MACE, as did extent of atherosclerotic plaque. ❏

MESA=Multi-Ethnic Study of Atherosclerosis
TNT=Treating to New Targets

^aAvailable at: <http://mesa-nhlbi.org/Calcium/ArterialAge.aspx>

Is Epicardial Fat a CAD Risk Factor?

While increasing abdominal visceral fat is considered to be a coronary risk factor associated with MetSyn, there are few data regarding the role of epicardial fat as a potential CAD risk factor. Iwayama and colleagues used multidetector computed tomography (MDCT) to examine the relationship between epicardial fat volume (EFV) and clinical parameters in 13 obese and 11 nonobese subjects with CAD who underwent elective CABG, and in 3 obese and 11 nonobese subjects who were free from CAD.

EFV was significantly higher in subjects with, than in those without, CAD (40.6 ± 14.7 mL vs 20.0 ± 14.7 mL; $P < 0.05$), and was found to be correlated with BMI but not with other coronary risk factors such as HbA1c, FPG, lipid profile, and BP. Although there was no difference in EFV in obese subjects with and without CAD (48.3 ± 27.9 mL vs. 41.2 ± 11.0 mL; NS), it was significantly higher in nonobese subjects with, than in those without CAD (32.1 ± 9.2 mL vs 14.2 ± 9.2 mL; $P < 0.05$). ❏

EPIC-Norfolk: Inflammatory Markers and CHD Risk

Individuals with elevated apo B/apo A-I ratio or inflammatory marker levels are at increased CHD risk. To evaluate the contributions of these factors to CHD risk, Rana and colleagues measured apo B/apo A-I ratio and inflammatory marker (CRP, adiponectin, fibrinogen, myeloperoxidase, sPLA2, Lp-PLA2) activity in subjects aged 45–79 years from EPIC-Norfolk ($n=844$ cases and 1,762 matched controls; 1,651 men, 955 women).

Results:

- Subjects in the top tertile had the highest levels of CRP, fibrinogen, and Lp-PLA2 activity, and the lowest adiponectin levels.

- Versus men in the bottom apo B/apo A-I ratio tertile and ≤ 1 inflammatory marker in the top tertile (bottom for adiponectin), men in the top apo B/apo A-I ratio tertile had a future CHD odds ratio of 1.7 (95% CI, 1.1–2.5); men with 4, 5, or 6 inflammatory markers in the top tertile had a future CHD odds ratio of 2.1 [95% CI, 1.4–3.1).
- Considering similar tertiles for women, odds ratios for future CHD were: 1.7 (95% CI, 1.05–2.9) and 2.2 (95% CI, 1.2–3.9).
- Increased levels of inflammatory markers were also seen in subjects with an elevated apoB/apoA-I ratio. ❏

EPIC-Norfolk=European Prospective Investigation of Cancer-Norfolk

Burden of Risk Is High Even in “Low-Risk” Individuals

Several presentations focused on the impact of low risk factor burden on primary prevention of CVD.

- Citing data demonstrating the significance of low risk, Martha Daviglus, MD, PhD, encouraged renewed research efforts to better understand low-risk determinants, including BP and diabetes.
- Likewise, Earl Ford, MD, urged aggressive targeting of BP and diabetes, adding that the vast majority of literature supports increased BMI as a CV risk factor. He cited data from four NHANES cohorts that estimate a 7.6% prevalence of low risk.
- Speaking on implications of low risk on subclinical atherosclerosis, Axel Schermund, MD, noted that CAC scores have provided very good data and, if taken into consideration, have the potential to reclassify low-risk FRS patients into the high-risk category. He added that “true low risk” is seen in only 3–5% of patients.
- Early education is important for primordial CVD prevention, said Michael Miller, MD, who identified smoking, hypertension, hyperlipidemia, and sedentary lifestyle as targeted risk factors for education. ❏

NHANES=National Health and Nutrition Examination Survey

ONSITEINSIGHT® Glossary

apo B	apolipoprotein B
BMI	body mass index
BP	blood pressure
CAC	coronary artery calcium
CIMT	carotid intima-media thickness
CV	cardiovascular
FPG	fasting plasma glucose
FRS	Framingham Risk Score
hs-CRP/CRP	high-sensitivity C-reactive protein
IMT	intima-media thickness
IVUS	intravascular ultrasound
MI	myocardial infarction
NT-proBNP	N-terminal prohormone brain natriuretic peptide
RCTs	randomized controlled trials
Lp-PLA2	lipoprotein-associated phospholipase A2
MetSyn	metabolic syndrome
sPLA2	secretory phospholipase A2
TLC	therapeutic lifestyle changes

Multi-Marker Approach to Predicting Subclinical Atherosclerosis

The current standard of care for CV risk assessment is stratifying persons as high, intermediate, or low risk based on FRS. However, the large number of events occurring in low-risk persons has led to the investigation of biomarkers for risk assessment. To assess whether multiple biomarkers can improve prediction of subclinical atherosclerosis, Rohatgi and colleagues analyzed CAC, CRP, NT-proBNP, and four novel biomarkers among Dallas Heart Study subjects (n=2,240), and calculated a biomarker score. An increasing score was associated with an increase in CAC prevalence. Compared with FRS alone, the addition of the biomarker score improved reclassification into higher- and lower-risk categories. 🚩

JPAD: Aspirin for Primary Prevention of Atherosclerotic Events in Diabetes

The JPAD study assessed the efficacy of low-dose aspirin (ASA) for primary prevention of atherosclerotic CV events among patients with type 2 diabetes and without documented CVD. Subjects (n=2,539) aged 30–85 years were randomized to low-dose ASA (81 or 100 mg/d) or placebo.

The incidence of the primary endpoint, a composite of fatal and nonfatal atherosclerotic events, was not significantly different in the low-dose ASA group vs the placebo group in the overall study population (ASA, 68 events vs 86 placebo; HR, 0.80; 95% CI, 0.58–1.10; P=0.16), although a benefit was seen in patients aged ≥65 years (HR, 0.68; 95% CI, 0.46–0.99; P=0.047). 🚩

JPAD=Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes

JUPITER CONTINUED FROM COVER

The 17,802 subjects with CRP levels ≥2.0 mg/L and LDL-C levels <130 mg/dL were randomized to rosuvastatin 20 mg/d or placebo; median follow-up was 1.9 years. The study population was diverse: 38% were women, and 25% African-American or Hispanic.

Rates of the primary endpoint (combined MI, stroke, arterial revascularization, hospitalization for unstable angina, or death from CV causes) were 0.77 and 1.36 per 100 person-years of follow-up in the rosuvastatin and placebo groups, respectively (HR for rosuvastatin, 0.56; 95% CI, 0.46–0.69; P<0.00001). A 47% risk reduction in the combined endpoint of MI, stroke, or death from CV causes (HR, 0.53; 95% CI, 0.40–0.69; P<0.00001) and a 20% risk reduction in all-cause mortality (HR, 0.80; 95% CI, 0.67–0.97; P=0.02) were also seen.

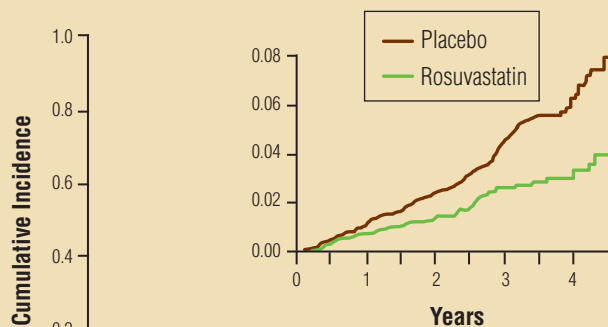
At 12 months, subjects in the rosuvastatin group had a 50% lower median LDL-C level (55 mg/dL), a 37% lower median CRP level (2.2 mg/L), and a 17% lower median TG level (99 mg/dL) vs those taking placebo (P<0.001 for all three). These effects persisted throughout the study.

Benefits seen with rosuvastatin were consistent across all subgroups regardless of age, sex, ethnicity, or other baseline characteristics (including high CRP and no other risk factor). No increase in serious adverse events was observed in the rosuvastatin group, though small increases in HbA1c and physician-reported diabetes were noted.

Commenting on the results, Paul M. Ridker, MD, suggested that application of the screening and treatment strategy tested in JUPITER over 5 years could prevent ~250,000 heart attacks, strokes, revascularization procedures, and CV deaths in the US alone. 🚩

JUPITER=Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin

JUPITER: Primary Endpoint



No. at Risk	Years									
Rosuvastatin	8901	8631	8412	6540	3893	1958	1353	983	538	157
Placebo	8901	8621	8353	6508	3872	1963	1333	955	531	174

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Focus on Inflammation, Atherosclerosis for CVD Risk Reduction

A satellite symposium chaired by Daniel J. Rader, MD, explored the management of LDL-C, inflammation, and atherosclerosis to reduce CVD event risk.

- Valentin Fuster, MD, PhD, discussed evidence for the future use of biomarkers, imaging, and genetics to assess CVD risk, noting the importance of integrating these factors for risk assessment. He referenced the High Risk Plaque Program, a trial using eight vascular imaging techniques to evaluate relative prognostic value of multiple screening technologies for assessing CVD risk earlier in high-risk patients.
- John R. Crouse III, MD, discussed controversies surrounding coronary remodeling and atherosclerosis progression in the context of recent trials (METEOR, SANDS, ENHANCE, ORION). He highlighted the pros/cons of B-mode ultrasound and MRI for evaluating arterial remodeling and atherosclerosis progression. He noted that CAC is a better discriminator of CAD than IMT, as shown in studies such as MESA.
- Christie M. Ballantyne, MD, discussed mechanisms of atherosclerotic risk reduction, stressing early identification and treatment of patients via traditional risk factors, CRP, or imaging with early initiation of TLC and statin therapy. He noted that non-HDL-C and apo B appear to be the best measures for assessing baseline risk and response to therapy. †

ENHANCE=Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression
MESA=Multi-Ethnic Study of Atherosclerosis
METEOR=Measuring Effects on Intima-Media Thickness: an Evaluation of Rosuvastatin
ORION= Outcome of Rosuvastatin treatment on carotid artery atheroma: a magnetic resonance Imaging Observation
SANDS=Stop Atherosclerosis in Native Diabetics Study



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Modifying HDL-C and CV Risk

Numerous studies examined modification of HDL-C and risk. Highlights: Briel and colleagues discussed data from a meta-analysis of RCTs using lipid-modifying interventions to assess the association between treatment-induced change in HDL-C and CHD death risk, CHD events (CHD death, nonfatal MI), and total death adjusted for changes in LDL-C. The majority of trials used statins. There was no support for treatment-induced changes in HDL-C reducing risk for CHD or deaths in interventions based on data analyzed. Results support LDL-C reduction as the primary goal of lipid-modifying therapy.

El Harchaoui et al presented data from EPIC-Norfolk in which independent relationships of HDL size and particle concentration were studied in 822 subjects with CHD and 1,401 matched controls. Particle size and concentration were lower in those with CHD than in controls. HDL size was strongly associated with MetSyn risk factors. HDL particle number was not affected by metabolic parameters. After adjustment for apo B and TG, the HDL size/CHD risk association was abolished; particle concentration was still associated with CHD risk. Both HDL size and particle concentration were independently associated with other CV risk factors.

Shear and colleagues presented data from a post-hoc analysis of ILLUMINATE, which assessed the clinical benefit of the experimental CETP inhibitor, torcetrapib[†], on a background of atorvastatin 10–80 mg. The trial was terminated early for increased all-cause mortality and major CV events in the torcetrapib/atorvastatin group. Results from the present study showed that evidence of harm was limited to torcetrapib/atorvastatin 10 mg for all-cause mortality and major CV events. Changes in on-treatment predictors of risk were also studied; post-randomization changes in HDL-C, LDL-C, BP, electrolytes, or aldosterone were of the same magnitude in the 10- and 80-mg atorvastatin subgroups. The authors note that results suggest that high-dose atorvastatin may have mitigated the risk of torcetrapib, which is unexplained by typical biomarkers. ‡

[†]Investigational agent; not yet FDA approved

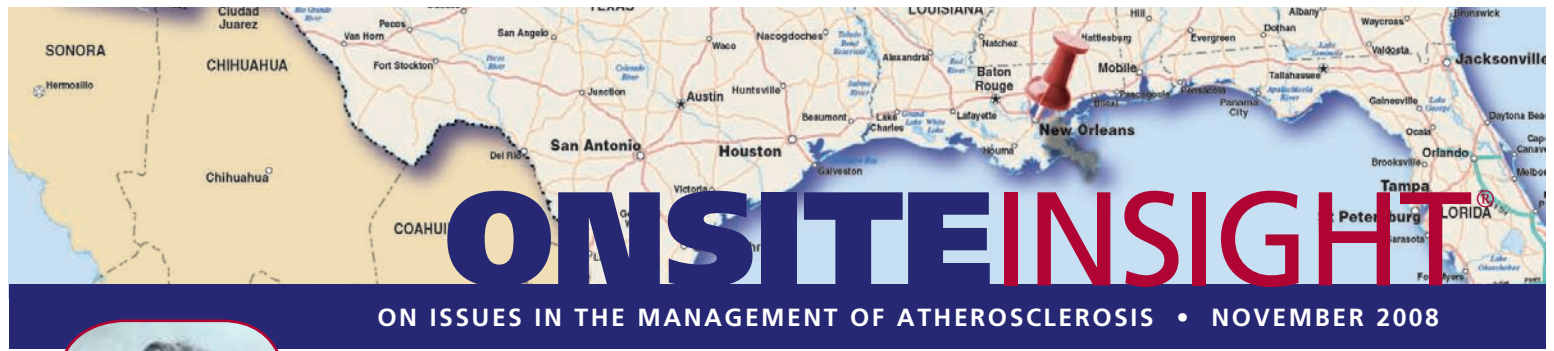
EPIC-Norfolk=European Prospective Investigation of Cancer-Norfolk

ILLUMINATE=Investigation of Lipid Level Management to Understand its Impact on Atherosclerotic Events

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The 2008 American Heart Association Scientific Sessions provided new insights into the management of atherosclerosis and its attendant risk.

Late-breaking clinical trials, including Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Type 2 Diabetes Patients with Cardiovascular History (APPROACH) and Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes (JPAD), addressed controversial topics in the management of subjects with diabetes and management of cardiovascular (CV) prevention.

Given the potential anti-atherosclerotic effects of the thiazolidinedione class of agents, APPROACH sought to determine whether the choice of therapeutic agent could affect the progression of atherosclerosis among individuals with diabetes. Intravascular ultrasound (IVUS) was used in this study to measure progression of atherosclerosis among subjects with both diabetes and established coronary artery disease. For the primary endpoint (change in percent atheroma volume), there was a nonsignificant -0.64% ($P=0.12$) treatment difference between groups (rosiglitazone, -0.21% ; $P=0.19$; glipizide, $+0.43\%$; $P=0.53$). Researchers found no statistically significant differences in the secondary endpoint of major CV events between groups, although the study was not powered to evaluate clinical outcomes. Results from APPROACH are in line with similar and statistically significant results from the Pioglitazone Effect on Regression of Intravascular Sonographic Coronary Obstruction Prospective Evaluation (PERISCOPE)¹ trial, an earlier, slightly smaller study that used two different diabetes drugs—pioglitazone and glimepiride—from the same two classes.

JPAD also explored treatment approaches among subjects with diabetes. In these individuals, low-dose aspirin as primary prevention was shown to offer a nonsignificant 20% relative reduction in the risk of atherosclerotic events. Despite the fact that the trial's primary endpoint (a composite of fatal and nonfatal atherosclerotic events) was neutral, secondary analyses showed benefit with low-dose aspirin among subjects aged ≥ 65 years and a reduced risk for fatal coronary and cerebrovascular events in the entire cohort. These benefits were achieved with no increased risk for hemorrhagic stroke.

A highlight of the meeting was presentation of data from the Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), a landmark study in the field of primary prevention whose results provide a new paradigm for risk assessment and clinical care. In this study of individuals with low LDL-C (<130 mg/dL) but elevated hsCRP (≥ 2.0 mg/dL), 20 mg of rosuvastatin significantly reduced the primary endpoint—a composite of nonfatal MI, nonfatal stroke, hospitalization for unstable angina, arterial revascularization, and confirmed death from CV causes—by nearly half (44%) in less than 2 years.

Among subjects in JUPITER, median LDL-C levels were reduced 50%, decreasing from 108 mg/dL at baseline to 55 mg/dL at 12 months. Median CRP levels also declined from 4.2 mg/L at baseline to 2.2 mg/L at 12 months (37% decrease). In addition, median TG levels were reduced 17% from baseline (to 99 mg/dL) in those treated with statin therapy.

The proportion of individuals with MI, stroke, revascularization, or hospitalization for unstable angina or death from CV causes was 1.6% in the rosuvastatin group vs 2.8% in the placebo group (absolute risk reduction [ARR] 1.2%). Similarly, the proportion of subjects with CV death, MI, and stroke was reduced from 1.8% in the placebo group to 0.9% in the rosuvastatin group (ARR 0.9%). While significantly more subjects in the rosuvastatin arm developed new diabetes and had significantly higher HbA1C levels, other reported serious adverse events were similar between the placebo and statin-therapy groups.

JUPITER explored the role of statins in the primary prevention of CV events among subjects who, until now, were infrequently included in clinical trials of statins: women, Hispanics, and African-Americans. Irrespective of gender, race or ethnicity, robust results were seen among all rosuvastatin-treated subjects.

Given these striking results, how can clinicians integrate these findings into clinical practice? JUPITER underscores the fact that arbitrary LDL cutpoints

poorly reflect CV risk. In the study population, with median age of 66 years, systolic BP 134 mm Hg, BMI 28.3 kg/m², and 41% prevalence of metabolic syndrome, event rates were 1.36% per year in the placebo group, placing subjects squarely in the intermediate-risk category despite “normal” LDL levels. JUPITER underscores the need for improved risk stratification and expansion of current guidelines to incorporate populations who are not included in current risk estimates. Multiple sessions at the AHA meeting addressed the substantial burden of CV risk in the population, underscoring the limitations of current risk estimates, and the need to explore novel approaches to risk assessment.

JUPITER supports the LDL hypothesis and demonstrates that lower LDL is better when it can be achieved safely and efficaciously with statins in individual subjects. In JUPITER, subjects had a significant 50% reduction in LDL-C levels, and LDL-C should remain an important endpoint that clinicians should treat. This study demonstrated that statins are effective even among individuals not considered candidates for pharmacologic therapy per current guidelines. Moreover, results suggest that targets for LDL-C should be lower than that recommended by current guidelines. While JUPITER continues to support the important role of LDL, questions remain regarding the role of non-LDL particles in atherosclerosis. Combination approaches to hypertriglyceridemia and low HDL-C appear efficacious in papers presented at the AHA meeting; whether these strategies will improve CV outcomes remains unknown.

JUPITER provides provocative results. However, the public health implications of the study are challenging. Only 20% of subjects screened were enrolled, and it is unclear what the generalizability of the study may be for clinical practice. While results are impressive, with NNTs ranging from as low as 31 for 4 years for a single primary endpoint event to over 80 for CV death, application of these findings in clinical practice will require consideration of baseline risk, clinical safety, and efficacy.

Finally, while CRP measurements had a central role in JUPITER, the widespread role of this inflammatory marker in clinical practice remains to be determined. For now, it appears that CRP measurement is an easy way to identify individuals who, by standard risk constructs, are not identified as intermediate risk and for whom aggressive statin therapy provides significant mortality benefit. Whether other risk stratification approaches may similarly identify those individuals who might benefit from LDL reductions remains unclear.

1. Nissen SE, Nicholls SJ, Wolski K; PERISCOPE Investigators. Comparison of pioglitazone vs glimepiride on progression of coronary atherosclerosis in patients with type 2 diabetes: the PERISCOPE randomized controlled trial. *JAMA*. 2008;299(13):1561-1573.