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eLITERATURE REVIEW
eDiabetes Review

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CVD RISK FACTORS IN PATIENTS WITH T2D

In this Issue...

Cardiovascular disease is the primary cause of morbidity and mortality in people with diabetes, and preventive therapies to control hyperlipidemia and hypertension have long been considered critical aspects of proper patient care. New evidence has led to the recent release of new guidance, challenging widely held beliefs and common practices.

In this issue, we review recent publications describing:

- New cholesterol guidelines from the American Heart Association and the American College of Cardiology (released at the end of 2013) that recommend a significant departure from the previous guidance
- The long-awaited JNC 8 blood pressure guidelines (published in January 2014) that have created controversy about blood pressure goals in various patient groups
- The concern that statins, the evidence-based drug of choice for LDL-C reduction, may increase the risk of developing diabetes
- The role of other lipid-lowering drugs on the residual risk of CVD events after optimal LDL – C reduction

LEARNING OBJECTIVES

After participating in this activity, the participant will demonstrate the ability to:

- Explain the implications of recent guidelines for cholesterol management.
- Describe recent clinical trials related to CVD outcomes in patients with diabetes.
- Summarize the recent blood-pressure guidelines and controversy among experts.

The Johns Hopkins University School of Medicine takes responsibility for the content, quality, and scientific integrity of this CME activity.

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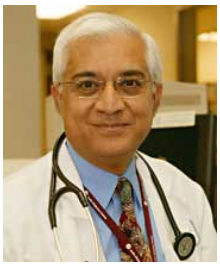

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Dr. Ganda has indicated that there will be no references to unlabeled/unapproved uses of drugs or products.

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COMMENTARY

Globally, cardiovascular events are the major cause of morbidity and mortality in patients with diabetes. The good news is that the major complications of diabetes have declined substantially during the past two decades, with a 68% decline in rates of myocardial infarction and ~50% decline in stroke and amputations.[1] This is likely the result of a combination of better access to care, health promotion efforts, and advances in treatment. However, obesity and diabetes continue at epidemic rates: some 24 million adults in the United States have diabetes;[2] the number of patients with diabetes worldwide soared to some 382 million in 2013; and cases are projected to reach 592 million by 2035.[3] Thus, the task of improving CVD outcomes in patients with diabetes will continue to remain a major challenge.

Elevated LDL-cholesterol (LDL-C) and hypertension are the key risk factors for atherosclerotic cardiovascular disease (ASCVD), including coronary disease and stroke. Efforts to improve their control have been a major focus during the past 20 years, thanks to the evolution and application of cholesterol and blood pressure guidelines in the US and elsewhere. Recently, the AHA (American Heart Association) and ACC (American College of Cardiology) published their revised guidelines on cholesterol management, and the JNC 8 panel published their revised blood pressure guidelines. Although both documents based their recommendations strictly on the basis of strong evidence from clinical trials, strong controversy has arisen.

The cholesterol guidelines are a significant departure from the past and provide an increased emphasis on the use of statins rather than any other cholesterol-lowering drug not proven to reduce CVD events. They recommend a more intensive therapy, even in primary prevention, for those at risk with or without diabetes and provide an updated risk calculator based on longitudinal data from several population cohorts. The lack of evidence for the CVD benefit of combining statins with other cholesterol-lowering drugs, including ezetimibe and bile acid sequestrants, was also reviewed recently by Gudzune et al.[4] Another major change is that these recommendations provide no defined goals for LDL-C or non-HDL-C, if sufficiently intensive statin therapy is used.

In the new blood pressure guidelines, the JNC 8 panel recommends a less intensive approach compared to those used in the past. Specifically, a more liberal systolic blood pressure goal has been recommended for those ≥ 60 years of age without diabetes or renal disease, which is different from that recommended by other major blood pressure guidelines from the American and International Societies of Hypertension, and others, including some of the authors of the JNC-8 itself.[5]

The impact and projections of the new cholesterol and blood pressure guidelines to the US population is discussed in the articles reviewed in this issue; in summary, these extrapolations find that some 13 million additional adults in the US are candidates for statin therapy, especially men > 60 years, and that some 13.5 million adults previously considered not at blood pressure goal by JNC 7 criteria would now be considered at goal.

One of the issues that has emerged recently is the impact of statin therapy on the development of diabetes. The risk is relatively small as reported in several studies and meta-analyses and mainly affects those already at increased risk for or have pre-diabetes; the risk/benefit ratio favors the use of statins even in those who develop diabetes. The largest meta-analysis of 17 trials is summarized in this issue (Navarese et al); it suggests that the risk of diabetes may be less pronounced with less potent statins, such as pravastatin, compared to than with more potent statins, such as rosuvastatin. The latter is, however, recommended by the new cholesterol guidelines as a preferred statin for those at the highest risk of CVD. Further, the interactions of specific statin molecules with the mechanisms of diabetes development remain incompletely understood.

The final topic discussed in this issue has to do with the residual CVD risk in patients treated with statins. It is well recognized that despite intensive statin therapy, many patients, particularly those with diabetes and metabolic syndrome, remain at considerable residual risk of subsequent CVD events. In the past, we have been using fibrate drugs and niacin to improve the dyslipidemia (characterized by high triglycerides and low HDL-C)

often encountered in patients with type 2 diabetes — with limited evidence of their benefits in such patients. In the ACCORD-lipid study, addition of fenofibrate in patients treated with statins resulted in possible, but inconclusive, benefit in the that patient subgroup.[6] The AIM-HIGH trial discussed here (Boden et al) randomized patients with diabetes and/or metabolic syndrome and with pre-existing CVD and low HDL-C to extended-release niacin or placebo. These patients were all optimally treated with intensive therapy to a LDL-C goal of < 70 mg/dl. In this setting, the addition of niacin resulted in no cardiovascular benefit despite the significant increase in HDL-C. Similar lack of benefits with niacin were recently reported in another larger trial (HPS2-THRIVE).[7] These findings have raised the possibility that HDL-C as a static measure may not be very helpful in determining the functionality of HDL, and point to a need to develop drugs that might directly improve HDL function. Thus, it appears that intensive statin therapy should remain the mainstay of lipid management in our armamentarium.

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THE 2013 ACC/AHA GUIDELINES FOR CHOLESTEROL MANAGEMENT

Stone NJ, Robinson J, Lichtenstein AH, et al. ACC/AHA guideline on the treatment of blood cholesterol to reduce atherosclerotic cardiovascular risk in adults: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013 November 12 (Epub ahead of print).

Link

This landmark article, authored by the Expert Panel Members of the American College of Cardiology (ACC) and the American Heart Association (AHA) Task Force on Practice Guidelines, provides a summary of the long-awaited guidelines for cholesterol management. The full report appeared simultaneously as a separate article.[1] There has been substantial progress in our understanding of the evidence-base for cholesterol management since the last set of guidelines were published by the Adult Treatment Panel III of the National Cholesterol Education Program in 2002[2] and updated in 2004.[3]

In addition to recommending that all individuals age > 21 years have LDL-C measured and other cardiovascular risk factor screened, with the exception of those with heart failure (NYHA Class II-IV) and end-stage renal disease (on hemodialysis), the guidance defines four distinct groups of people likely to benefit from LDL-cholesterol (LDL-C) reduction by treatment with HMG-CoA reductase inhibitors (statins), in addition to lifestyle recommendations:

1. For patients with established atherosclerotic cardiovascular disease (coronary, cerebrovascular, or peripheral vascular): treat with high-intensity statin therapy;
2. For patients with LDL-C ≥ 190 mg/dl: treat with high-intensity statin therapy;
3. For patients with diabetes (type 1 or 2), age 40-75 and LDL–C 70-189 mg/dl: treat with moderate-intensity statin if the 10-year risk of ASCVD is < 7.5%, or high-intensity statin if the 10-year risk of ASCVD is ≥ 7.5%; 4. For patients without diabetes, age 40-75 years and LDL-C 70-189 g/dl: treat with moderate– to high-intensity statin if the 10-year risk of ASCVD is ≥ 7.5%. In some cases where the 10-year risk 5 to ≤ 7.5%, moderate statin therapy may be considered.

The 10-year risk of atherosclerotic CVD may be calculated with the use of the new 10-year risk calculator available at my.americanheart.org/cvrisk calculator. This tool was developed from the longitudinal data from several community cohorts of white and African Americans. According to these recommendations, high-intensity statin treatments are aimed at LDL-C reduction of ≥ 50%, and moderate-intensity statin treatments aimed at achieving a 30 to < 50% reduction from the baseline. Specific examples include atorvastatin 40-80 mg or rosuvastatin 20-40 mg for high-intensity treatment, and atorvastatin 10-20 mg, rosuvastatin 5-10 mg, simvastatin 20-40 mg, pravastatin 40-80 mg, fluvastatin 40-80 mg, and pitavastatin 2-4 mg for moderate-intensity treatment.

For patients unable to tolerate high-intensity statin treatment because of statin intolerance, concomitant drug interactions, age > 75 years, unexplained elevations in ALT, or other reasons, an attempt should be made to prescribe at least a moderate-dose statin before considering any other cholesterol-lowering drugs. For risk assessment, CRP determination, ankle/brachial ratio, or coronary calcium score is not recommended. Finally, a major difference in the new guidelines is the lack of specific treatment targets for LDL-C or non- HDL-C.

Two concerns are that 1) many individuals under the age of 40 years who have considerable elevation of LDL-C with or without additional risk factors will not receive statin treatment until age 40; and 2) many individuals in the older age group might be "over-treated." [4]

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APPLYING 2013 CHOLESTEROL GUIDELINES TO THE U.S. POPULATION

Pencina MJ, Navar-Boggan AM, D'Agostino RB Sr., et al. Application of new cholesterol guidelines to a population-based sample. *N Engl J Med*. 370; 1422-1430.

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In this article, Pencina et al compare the eligibility for statin treatment as described in the 2013 ACC/AHA cholesterol guidelines[1] to the previous guidelines from the Adult Treatment Panel (ATP III)[2], using the data from the National Health Examination and Nutrition Survey (NHANES) sample of 2005-2010. Their findings were extrapolated to the 115.4 million US adult population age 40-75 years.

Compared to ATP III criteria, the 2013 ACC/AHA guidelines will increase the number of people eligible for statin therapy from 43.2 million to 56.0 million. Most of this increase will occur in people without prior cardiovascular disease, ie, in primary prevention, and in those in the age range of 60-75 years. Among this latter group, 87.4% of men and 53.6% of women would be eligible for statin treatment, compared to 30.4% and 21.2%, respectively, by the ATP III criteria. Moreover, most of this increase will result from clinical application of the new 10-year risk calculator. The newly eligible candidates will have generally higher blood pressure and lower cholesterol. Among the patients with diabetes, those eligible for statin treatment in the 40-75 year age group will increase from 13.3 to 16.4 million. The calculated 10-year risk increased from 10.7 to 15.5% in the 40-59 year age group, and from 9.9 to 18.0% in the 60-75 year age group, using the ATP III and ACC/AHA criteria, respectively.

Thus, the new cholesterol guidelines overall have a greater sensitivity and a lower specificity for projecting new cardiovascular events.

One of the limitations of such analyses is that the data were extrapolated from only 3773 subjects included in the NHANES population and the information on atherosclerotic events other than coronary disease was not available. In a 2013 report in Lancet, Ridker et al compared the predicted CVD events based on the ACC/AHA risk estimates with the observed event rates in 5 primary prevention cohorts.[3] They found an overall 40-50% over-estimation of eligibility using the recommended risk calculator, although a substantial number of people in these particular cohorts may have been relatively healthier.

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STATIN-INDUCED DIABETES—A META-ANALYSIS

Navarese, EP et al. Meta-Analysis of Impact of Different Types and Doses of Statins on New-Onset Diabetes Mellitus. *Am J Cardiol*. 2013; 111: 1128-1130.

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A significantly increased risk of new-onset diabetes in patients on statin therapy has been well-recognized since the 2008 Jupiter trial reported a 25% increase with rosuvastatin 20 mg compared to those on placebo.[1] Since then, several meta-analyses have confirmed a smaller but significant increase with various statins; in particular, the 2010 analysis by Sattar et al showed a 9% overall risk in 13 RCTs.[2] Of note, the risk-benefit ratio for CVD still clearly favors statin therapy in people at high-risk, and even those who develop diabetes during statin therapy have better CVD outcome compared to those on placebo.[2,3]

The precise mechanism for statin-induced diabetes remains unclear, although the majority of patients developing diabetes have prediabetes or features of metabolic syndrome, indicating a high risk for diabetes at baseline.[3] It has also been controversial whether intensive statin therapy or particular statin agents are more likely to precipitate diabetes. In the 2011 analysis of 5 RCTs by Preiss et al, dose-dependent intensive statin therapy led to a greater increase in diabetes with an odds ratio (OR) of 1.12 (CI 1.04-1.22).[4] However, this was not confirmed in a propensity score-matched cohort of patients with MI who were prescribed intensive or moderate dose statins and followed for five years (new diabetes in 13.6% vs 13%).[5]

This article by Navarese et al is the largest meta-analysis to date (17 RCTs including > 113,000 patients). The study compared new onset diabetes in patients receiving statin versus placebo, as well as high dose versus moderate dose statin. Pravastatin 40 mg, compared to placebo, was associated with the lowest risk (OR 1.07, CI 0.83-1.30), whereas rosuvastatin 20 mg showed the highest risk (OR 1.25; CI 0.82-1.90), and atorvastatin 80 mg was intermediate (OR 1.15, CI 0.9-1.50)—even though none of these differences achieved statistical significance. Simvastatin also appears to be associated with higher risk compared to pravastatin. The differences among various statins persisted after adjustments for cholesterol reduction. These findings suggest the possibility of molecule-specific effects on diabetogenesis, although the data thus far are inconclusive. The effects of the newest statin, pitavastatin, were not available in a large-enough cohort for inclusion in this report.

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EFFECT OF NIACIN ON CARDIOVASCULAR EVENTS IN PATIENTS WITH LOW HDL-CHOLESTEROL

Boden W et al. Niacin in patients with low HDL cholesterol levels receiving intensive statin therapy. *NEJM*. 2011; 365: 2255-2267.

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Armitage J. HPS2-THRIVE: randomized placebo-controlled trial of ER niacin and laropiprant in 25,673 patients with pre-existing cardiovascular disease. Presented at: American College of Cardiology Annual Scientific Sessions; March 9, 2013; San Francisco.

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Haynes R, Jang L, Hopewell JC, et al. HPS2-THRIVE randomized placebo-controlled trial in 25 673 high-risk patients of ER niacin/laropiprant: trial design, pre-specified muscle and liver outcomes, and reasons for stopping study treatment. Eur Heart J. 2013;34:1279–91.

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An inverse relationship between HDL-C and CHD, based on epidemiologic studies, has been well-recognized for several decades. Patients with type 2 diabetes are frequently characterized by low HDL-C and high triglycerides (TG), which often persist after statin treatment. This has been assumed to play a role in the residual CV risk after statin treatment. The most effective drug to raise HDL-C in those with low HDL-C is nicotinic acid (niacin). In angiographic studies, niacin was shown to be associated with atherosclerotic plaque regression, generally in the setting of suboptimal control of LDL-C at baseline,[1] and in the Coronary Drug Project (a secondary prevention RCT), niacin led to a reduction in coronary events compared to placebo.[2] However, whether niacin will reduce the residual risk of CVD events in patients with optimal LDL-C after statin treatment had never been studied until the AIM-HIGH (Atherothrombosis Intervention in Metabolic Syndrome with Low HDL/High Triglycerides: Impact on Global Health Outcomes) trial.

In this study, the AIM-HIGH investigators randomized 3414 very high-risk patients with established CVD and optimal LDL–C but low HDL-C already on simvastatin 20-40 mg (with ezetimibe if needed) to extended-release niacin or placebo. At baseline, 34% of the patients had type 2 diabetes and 81% had metabolic syndrome. During the trial, mean HDL-C in the niacin group increased significantly by 20% (35 to 42 mg/dl) (P < 0-001), triglyceride declined by 25% (164 to 122 mg/dl), and LDL-C declined by 10% (74 to 62 mg/dl). The study was stopped at a mean follow-up of three years because of lack of efficacy (HR 1.02 (CI 0.87-1.21). There was an unexpected (but nonsignificant) increase in the number of ischemic strokes (27 vs 15), which could be a chance finding.

Thus, despite a significant increase in HDL-C, the addition of niacin did not result in any further benefit in patients with established CVD and optimal LDL-C at baseline.

The futility of adding niacin to intensive statin therapy was recently confirmed in the HPS-2 THRIVE study. In this much larger trial in Europe and China (n = > 25,000 with established CVD; 32% with diabetes), in patients with a baseline mean HDL-C ~ 43 mg/dl, LDL-C ~ 64 mg/dl on simvastatin (and ezetimibe if needed), the addition of extended-release niacin–laropiprant vs placebo resulted in no benefit in CVD outcomes (HR 0.96, CI 0.09-1.02). Moreover, those randomized to niacin had a number of adverse events including gastrointestinal side-effects, skin rashes, infections, and increased number of new cases of diabetes during the trial. Thus, these studies have kindled a valid controversy about the utility of the HDL-raising drug, niacin, in the setting of an intensively lowered LDL-C.

It is interesting to note that in a small subgroup analysis of 100 patients from the AIM-HIGH trial, in both highest tertile of TG (> 198 mg/dl) and the lowest tertile of HDL-C (< 33 mg/dl), there was a trend toward CVD benefit (HR 0.74; P = 0.073).[3] This finding raises the possibility of some uncharacterized nonlipoprotein mediated adverse effects of niacin overall, with a possible benefit in a subgroup.

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JNC 8 HYPERTENSION GUIDELINES

James PA, Oparil S, Carter BL, et al. 2014 evidence-based guideline for the management of high blood pressure in adults: report from the panel members appointed to the Eighth Joint National Committee (JNC 8). *JAMA*. 2014;311(5):507-520.

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This article presents the long-awaited revised guidelines for treating hypertension in a report from the panel members appointed to the Eighth Joint National Commission 8 (JNC 8). These guidelines are relevant to adults in the general population as well as in various subgroups, including ethnic backgrounds, diabetes, and renal disease. Strong evidence led the panel to recommend raising the goal of blood pressure to < 150/90 mm Hg for all people 60 years of age or older (Grade A). For people younger than 60 years, the panel could not find strong evidence for a definite goal, and recommended a goal of < 140/90 mmHg based on expert opinion (grade E). Similarly, based on expert opinion (grade E), a goal of < 140/90 mmHg was recommended for people with kidney disease or those with diabetes age 18 and above.

The revision of BP goal in the diabetes population from < 130/80 in the past to < 140/90 was based on a lack of sufficient evidence from several trials, including the most recent blood-pressure sub-study of the ACCORD trial, which showed the control group with SBP goal of < 140 had similar outcomes to the group with lower goal.[1] Similarly, the panel could not find support for a diastolic goal of < 80 mmHg.

These recommendations for a higher goal in persons age 60 or greater has caused considerable controversy among the experts, and in fact, even among the JNC8 panel members. In a separate publication, five of the 17 JNC 8 authors have expressed a contrarian view:[2] in particular, they highlight the concerns of possible harm in people in the age group 60-80 years with increased CVD risk and comorbidities and recommend keeping the systolic goal of < 140 in people less than 80 years of age. This recommendation of < 140 systolic is also in line with those of several other guideline organizations from Europe, Canada, and United Kingdom and the AHA, as well as the American and International Hypertension Societies (ASH/ISH).[2]

Regarding the choice of antihypertensive drug therapy in patients with diabetes and the non-African American population, the panel recommended either a thiazide-type diuretic, a calcium channel blocker (CCB), or an ACEI or ARB alone or in combination (grade B). In the African American population, a thiazide-type diuretic or CCB is preferred, either alone or in combination, before adding other drugs. In patients with CKD, regardless of race or diabetes status, an ACEI or ARB are preferred as the initial therapy, followed by drugs from other classes. Beta-blockers are currently not recommended among the initial choice of drug unless other drug combinations are inadequate, as they are less likely to prevent stroke than the other major classes; however, they are the drugs of choice in patients with history of myocardial infarction or heart failure.[3]

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APPLYING JNC 8 HYPERTENSION GUIDELINES TO THE US POPULATION

Navar-Boggan AM, Pencina MJ,Williams K, Sniderman AD, Peterson ED. Proportion of US adults potentially affected by the 2014 hypertension guideline. JAMA. 2014; 311: 1424-1429.

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In this article, the authors compared the eligibility of US adults for hypertension treatment according to the 2014 JNC 8 guidelines[1] vs the JNC 7 guidelines available since 2003.[2] They extrapolated data from 16,372 adults in the NHANES survey between 2005-2010. In this analysis, the proportion of treatment-eligible adults decreased slightly (from 20.3% to 19.2 %) in the 18-59 year old age group, whereas a larger decrease (from 68.9% to 61.2%) occurred in older adults (≥ 60 years) due to the revised goal of < 150/90 mm Hg. Moreover, as expected, the new 2014 guidelines resulted in an increase in the proportion of adults meeting BP goals from 41.2 % to 47.5 % in the 18-59 year old age group, and more substantially from 40.0% to 65.% in adults ≥ 60 years of age.

Extrapolating these results to the adult US population, some 13.5 million people not previously considered at BP goal by the JNC-7 criteria would now be considered at goal (41.5 million under JNC 8 vs 28.0 million under the JNC 7 criteria). A majority of the adults meeting the revised 2014 goal are 60 years or older, and many have diabetes and/or CKD, recalling that the JNC goal for adults with these comorbidities was previously < 130/80 mm Hg, but is now < 140/90 mm Hg.[2] However, it is especially important to note that, despite some limitations in the NHANES survey, more than 50% of the eligible adults under both JNC 7 and JNC 8 guidelines in this analysis were untreated, indicating the considerable on-going burden of untreated hypertension in the US.

This revision of the systolic blood pressure goal in adults ≥ 60 years to 150 mm Hg in JNC 8 is being debated by some of the dissenting authors of the JNC 8 panel (in a separate publication),[3] as other professional society guidelines,[3-5] recommend the > 150/90 target only for those age 80 or greater.

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- Clinicians do not appropriately intensify therapy as necessary to maintain glycemic control.
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