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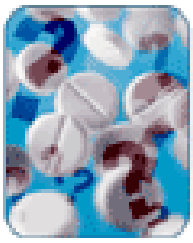
Less is More?—Not so Fast!



This *Heartbeat* will provide an overview of conclusions from a few studies presented at the American College of Cardiology Scientific Sessions in March 2010. Most of these studies showed no significant benefit of either add-on therapy or more aggressive therapy leading to the recurring theme of "less is more"—as suggested by the results of the following recent studies; RACE 2, ACCORD BP, ACCORD LIPID, NAVIGATOR and ACCORD Glycemia.

Further discussion directs us to other possibilities. Our current therapies may be stretched to capacity, the wrong additional therapy was added or we need to treat our patients individually rather than as groups—dependent on their individual risk. Each study can be interpreted differently but I definitely think "less is more" sends the wrong message to clinicians who are in my opinion, not aggressive enough in getting their diabetic patients to appropriate guideline goals.

RACE 2:

In the randomized **Rate Control Efficacy in Permanent Atrial Fibrillation** (RACE 2) trial, lenient rate control (resting heart rate [HR] < 110 bpm) is shown to be as effective as strict rate control (resting HR < 80 bpm and < 110 bpm with moderate exercise) and is easier to achieve.[1] The lenient strategy was "non-inferior" (p 0.001) to the strict approach for a composite primary endpoint that included cardiovascular death, heart failure (HF) hospitalization, stroke and other major events. Strict control has more side-effects because of higher dosing, more drugs [beta-blockers, nondihydropyridine calcium-channel blockers, and digoxin]) and greater cost. It's also more arduous for patients and providers. Current HR control practice isn't based on evidence from randomized clinical trials.

$CHAD_2$ score data hint that the strict approach may be more detrimental in the higher-risk population (score of 2 or greater). They are usually older with multiple co-morbidities and require more medications and thus have more side effects. Similarly the outcomes of those with $CHAD_2$ scores ≤ 1, whom are lower-risk, younger patients show they may do better with the strict approach—usually more active and benefiting from HR not increasing too much during physical exercise.

Limited size (614 patients) and follow-up time (3years) of the study would prohibit a change in guidelines based on this study. In the accompanying editorial Dorian advocates *individualized therapy* "emphasizing the adjustment of therapy on the basis of symptoms and general well-being".[2] This common sense approach can be safely recommended," whereas a "reflexive cookbook approach with specific heart-rate targets does not seem sensible."

Clinical Perspective: Treat the patient not the HR. All patients are not homogenous. *The degree of HR control in AF makes little difference in outcomes—contrary to widely advocated and practiced beliefs.* Start with a lenient rate-control strategy, and then if the patient remains

symptomatic or develops HF go to the strict approach. We would recommend more strict rate control in patients with hypertension and diastolic dysfunction where more rapid HRs have been shown to be detrimental and in younger patients who are more active.

ACCORD-BP:

Data from the **Action to Control Cardiovascular Risk in Diabetes** (**ACCORD)-BP** study show that there is no benefit to be gained in diabetics (34% of whom had cardiovascular disease [CVD]) from intensively lowering their systolic blood pressure to a goal of <120 mm Hg.[3] After a mean follow-up of 4.7 years, this trial of 4,733 patients showed no difference in the primary end point—a composite of fatal and nonfatal major CV events—between this group and those who received standard antihypertensive therapy to get their pressure down to <140 mm Hg. Serious adverse events that were attributed to blood-pressure medication (decreased renal function, bradycardia, hyperkalemia and hypotension) were more frequent in the intensive-therapy group. Secondary analysis revealed that stroke incidence was significantly lower in the intensive-care group—although overall incidence was low.

Clinical Perspective: The main conclusion to draw from ACCORD BP must be that *intensive blood-pressure control (below those currently recommended by the JNC 7 guidelines ≤ 130/80 mm Hg) in patients with diabetes is not justified by the evidence.* The average BP (133mm Hg) in the non-intensive group does support the Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation and Treatment of High Blood Pressure (JNC 7) [4] goal. After further analysis hopefully those at higher risk for stroke (most likely African-Americans) can be identified and we can treat those patients more aggressively. We support the JNC 7 goal (≤ 130/80 mm Hg) goal using generic ACE/ARB—amlodipine as first choice combination therapy.

ACCORD-Lipid:

Combination therapy with **fenofibrate** and **simvastatin** compared to simvastatin monotherapy failed to reduce the risk of fatal cardiovascular events, nonfatal MI, or nonfatal stroke, according to results from the **ACCORD-Lipid** trial.[5] There was a suggestion of benefit observed among patients with high triglyceride and low HDL-cholesterol levels in subgroup analysis. Further study is needed.

In this study, 5,518 subjects (mean follow-up 4.7 years) were treated with simvastatin (40 mg/day or less), with randomization to masked fenofibrate or placebo. All subjects had type 2 diabetes and were at high risk for CVD. Baseline lipid criteria included having a low-density lipoprotein cholesterol (LDL-C) between 60 and 180 mg/dl, high-density lipoprotein cholesterol (HDL-C) of 55 or less for women or blacks, 50 or less for all others, and triglycerides below 750 mg/dl not on lipid therapy (400 mg/dl if on lipid-lowering therapy). Secondary outcomes included the combination of the primary outcomes (first occurrence of nonfatal MI, nonfatal stroke, or CVD death) and revascularization or hospitalization for HF.

Clinical Perspective: Fenofibrate should not be used for high-risk diabetics. It did lower triglycerides but no clinical benefit was seen and more worsening of renal function was seen in the fenofibrate group. Patients with diabetes are already taking a lot of medications. *Adding a fenofibrate which is fairly expensive is inappropriate in light of undocumented benefit.* We've gotten used to seeing dramatic benefits of 5 year studies. Once statins are on-board it may not be possible or it just may take longer to show a benefit of ad-on therapy. High triglyceride/low HDL-C axis disorders identify higher risk patients. Measuring apoB or LDL-P in these patients and treating to appropriate goals is the present plan. Maximize statin treatment and consider niacin if sugars are controlled. There isn't evidence to refute the niacin recommendation at the present time and supportive evidence is mounting for use.

NAVIGATOR:

The **NAVIGATOR** study was a 2 x 2 factorial, double-blind, randomized trial of 9,518 patients with impaired glucose tolerance (fasting plasma glucose concentration between 95 mg/dl and 125 mg/dl) and either established CVD or risk factors for CVD. Patients were randomized to **nateglinide** (up to 60 mg three times per day) or placebo [6] and to **valsartan** (up to 160 mg/day) or placebo.[7] Subjects were followed for a median time of 5.0 years and received lifestyle modification. Primary outcomes were incident diabetes and CV events.

The study concluded that nateglinide for 5 years did not reduce the incidence of diabetes or CV event rates. Use of valsartan for 5 years did not lead to reduction in the rate of CV events; however, a minimal relative reduction (14%) was observed for incidence of diabetes.

Clinical Perspective: This *large study of nateglinide and valsartan for prevention of diabetes and/or CVD was largely negative, with no benefit observed in reduction of CV outcomes for either drug.* A small benefit was observed with valsartan in reduction of diabetes. Lifestyle modification (diet and exercise), which improves outcomes is recommended—as opposed to nateglinide and/or valsartan.

ACCORD-Glycemia:

ACCORD Glycemia was conducted in 10,000 high-risk patients with type 2 diabetes who were randomly assigned to either intensive glycemic control (HbA_{1c} < 6%) or standard glycemic control (HbA_{1c} 7%–7.9%).[8] The study was stopped early, in February 2008, because of higher mortality in the intensive-glycemic-control group. An observational post hoc analysis of the original **ACCORD (Glycemia)** trial, published last month concluded that it wasn't really intensive therapy (everyone assumed hypoglycemia) that was associated with the increased mortality, it was unsuccessful intensive therapy.[9] The problem was specific to the subgroup of people who tried the intensive strategy but could not get their HbA_{1c} levels down below 7.

Clinical Perspective: The findings of all of these studies should not detract from the most important point. Control of HR, glucose, blood pressure and lipids is important and reduces CV risk. Who to treat more aggressively is the question—many don't respond to more than guideline recommendations. Individualize therapy. One size doesn't fit everyone. We need to have different targets for different groups of people and perhaps different treatment strategies to reach those targets.

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