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Scientific Update™

Connecting Prevention Strategies for Improving Cardiovascular Outcomes

Originally presented by: Richard Lewanczuk, MD; Robert G. Josse, MD; Jacques de Champlain, MD; and Ross Feldman, MD

A Review of a Presentation at a Satellite Symposium at the Canadian Cardiovascular Congress 2006

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By: Gordon Moe, MD

Bob (a hypothetical patient) is a 48-year-old male who presents to his family practitioner with mildly elevated blood pressure (149/97 mm Hg). He smokes, is overweight (body weight 101 kg and waist circumference 104 cm), and has dyslipidemia (total cholesterol 6.5 mmol/L; low-density lipoprotein cholesterol [LDL-C] 4.3 mmol/L; high-density lipoprotein cholesterol [HDL-C] 0.9 mmol/L; and triglycerides 2.6 mmol/L). His hemoglobin A1C is 6.8% and the results of a 2-hour glucose tolerance test (GTT) indicate that his fasting blood sugar is 6.8 mmol/L and 2-hour test value is 10.7 mmol/L. This issue of *Cardiology Scientific Update* presents several issues that are relevant to the management of this patient and connects several strategies for improving his cardiovascular (CV) outcomes.

Targeting glucose
Evidence-based solutions for CV prevention

This hypothetical case highlights the importance of diabetes and glucose intolerance. Changes in human behaviour and lifestyle over the last century have resulted in a dramatic increase in the incidence of diabetes worldwide. It is anticipated that globally, the number of patients with diabetes will increase from 151 million in 2000, to 221 million by 2010,[1] and 370 million by the year 2030 (World Health Organization 2004, www.who.int/diabetes/facts/worldfigures/en/). Accompanying this trend is a growing global prevalence of impaired glucose tolerance (IGT), with 314 million people (8% of the population) being presently affected and projections to 427 million (9%) by 2025 (International Diabetes Federation Diabetes Atlas, www.eatlas.idf.org/). Patients with IGT carry a high risk of progressing to type 2 diabetes (T2DM).[2] Forty to 50% of people with IGT will develop T2DM within 10 years as their IGT deteriorates and pancreatic β-cell function declines. IGT also carries an increased risk of development of CV disease (CVD) and constitutes part of the metabolic syndrome. The cumulative incidence of DM will increase over the next 2 years as levels of 2-hour plasma glucose increase, at an average rate of 13.8% per year.[3]

Up to 66% of patients admitted with acute myocardial infarction (MI) have previously undiagnosed dysglycemia at time of discharge.[4] In patients with established coronary artery disease and normal glucose tolerance, a linear relationship exists between postload glucose, HbA_1C, and the number of stenosed vessels.[5]

In the Honolulu Heart Study,[6] 6394 nondiabetic men were followed for 12 years for the first development of coronary heart disease (CHD). The rate of fatal CHD increased linearly with amount of glucose. Men in the fourth quintile of postchallenge glucose (157-189 mg/dL) had twice the age-adjusted risk of fatal CHD as those in the lowest quintile. Relative risk increased 3-fold among those in the top quintile and remained statistically significant after adjustment for other risk factors, including body mass, total cholesterol, hypertension, left ventricular hypertrophy, and hematocrit.

Similar conclusions were drawn from the Second National Health and Nutrition Examination Survey (NHANES II) Mortality Study,[7] as well as the Funagata Diabetes Study, in which IGT, but not impaired fasting glucose (IFG), was a risk factor for CVD.[8] High postprandial glucose can contribute to the development of atherosclerosis by exerting effects on arterial walls, including immediate effects that occur rapidly in response to elevated plasma glucose levels, and long-term effects that result from non-enzymatic glycosylation of various proteins.[9]

The background information discussed above raises the possibility that targeting postprandial hyperglycemia may improve the metabolic derangements that drive glucose intolerance and the development of T2DM and CVD. A list of diabetes prevention studies is shown in Table 1 and the mechanisms of action of orally-administered antihyperglycemic agents are shown in Figure 1.

Acarbose is an α-glucosidase inhibitor that reduces postprandial hyperglycemia by delaying carbohydrate absorption from

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Table 1: Intervention studies for diabetes prevention

Study	Intervention	RR (%)
Da Qing IGT and Diabetes Study (N = 577)	Diet Physical exercise Diet and physical exercise	31 46 42
Finnish Diabetes Prevention Study (N = 522)	Diet and physical exercise	58
Diabetes Prevention Program Study (N = 3234)	Lifestyle intervention Metformin Troglitazone*	58 31 75
TRIPOD (N = 266)	Troglitazone*	55
STOP-NIDDM (N = 1418)	Acarbose	36
XENDOS (N = 3305)	Orlistat	37
Indian Diabetes Prevention Study (N = 531)	Lifestyle intervention Metformin Metformin and lifestyle	28 26 28
DREAM (N = 5269)	Rosiglitazone	60

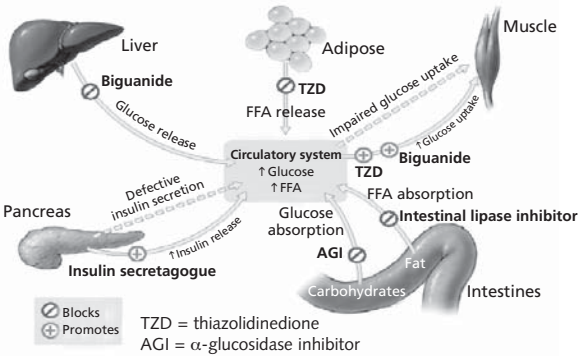
*Troglitazone is no longer available

the intestine.[10] Acarbose decreases postprandial plasma glucose and insulin and improves insulin sensitivity in subjects with IGT.[11] If insulin resistance and postprandial hyperglycemia play a role in the development of T2DM and CVD, there is a role for acarbose in the prevention of T2DM and CVD. The effect of acarbose in preventing or delaying the conversion of IGT to T2DM was evaluated in the Study to Prevent Non-Insulin-Dependent Diabetes Mellitus (STOP-NIDDM) trial.[12] In this multicentre, placebo-controlled trial, 1429 patients with IGT were randomized to 100 mg acarbose or placebo 3 times daily. The primary endpoint was the development of diabetes on the basis of a yearly oral glucose tolerance test (OGTT). Following a mean treatment duration of 3 years, 221 (32%) of the patients randomized to acarbose and 285 (42%) of those randomized to placebo developed diabetes (hazard ratio [HR], 0.75; 95% CI, 0.63-0.90]; p = 0.0015). The effects of reducing postprandial hyperglycemia with acarbose on one of the secondary endpoints – CV events – are shown in Figure 2. Among these events, the major reduction was in the risk of MI (HR, 0.09; 95% CI, 0.01-0.72; p = 0.02). Treatment with acarbose was also associated with a 34% relative risk reduction in the incidence of new cases of hypertension (HR, 0.66; 95% CI, 0.49-0.89; p = 0.006).[13] In a substudy of 132 IGT subjects, carotid artery intima media thickness (IMT) was increased by 0.02 mm in the acarbose group versus 0.05 mm in the placebo group (p = 0.027). The annual increase in IMT was reduced by about 50% in the acarbose group.[14]

To assess if treatment with an α-glucosidase inhibitior can reduce CV events in T2DM patients, a meta-analysis that included 7 randomized, double-blind, placebo-controlled studies of acarbose with a minimum treatment duration of 1 year was undertaken (Meta-analysis of Risk Improvement with Acarbose [MeRIA]).[15] The principal results are shown in Figure 3. Acarbose therapy led to favourable trends towards risk reduction for all selected CV event categories. Glycemic control, triglyceride levels, body weight, and systolic blood pressure (BP) also improved.

Therefore, the results of the STOP-NIDDM in patients with IGT, as well as the meta-analysis from MeRIA in patients with T2DM, support the concept that post-prandial hyperglycemia is a risk factor for CVD and should be considered a target of therapy to improve CV outcomes in these patients.

Figure 1: Major target organs and actions of antihyperglycemic agents in T2DM



Aspirin is the essential prevention partner

The benefit of acetylsalicylic acid (ASA, aspirin) in patients with known CVD is well-established.[16] Whether aspirin reduces the risk of CVD in subjects without known CVD is less certain. A recent meta-analysis examined the benefits and risks of ASA in the primary prevention of CVD in men and women.[17] Five randomized controlled trials, designed to assess the efficacy of ASA in the primary prevention of CVD, were included.[18-22] Odds ratios for coronary events in the 5 trials and the meta-analysis are shown in Figure 4. ASA reduced the risk for the combined endpoint of nonfatal MI and fatal CHD, but increased the risk for hemorrhagic strokes (odds ratio 1.4; 95% CI, 0.9-2.0) and major gastrointestinal (GI) bleeding (odds ratio 1.7; 95% CI, 1.4-2.1). All-cause mortality was not reduced. In terms of absolute benefit or harm, for 1000 patients with a 5% risk for CHD events over 5 years, ASA would prevent 6 to 20 MIs, but would cause zero to 2 hemorrhagic strokes and 2 to 4 major GI bleeding events. For patients with a risk of 1% over 5 years, ASA would prevent 1 to 4 MIs, but cause zero to 2 hemorrhagic strokes and 2 to 4 major GI bleeding events. The net benefit of aspirin increases with increasing risk. In the decision to use ASA for primary prevention, physicians should consider the patient's CV risk and the relative utility for the different clinical outcomes prevented or caused by ASA use.

Recent evidence suggests that ASA may exert vasculoprotective effects through mechanisms beyond its antiplatelet properties. Using ambulatory BP monitoring, it has been shown that ASA

Figure 2: Effect of acarbose on cardiovascular events in subjects with impaired glucose tolerance[13]

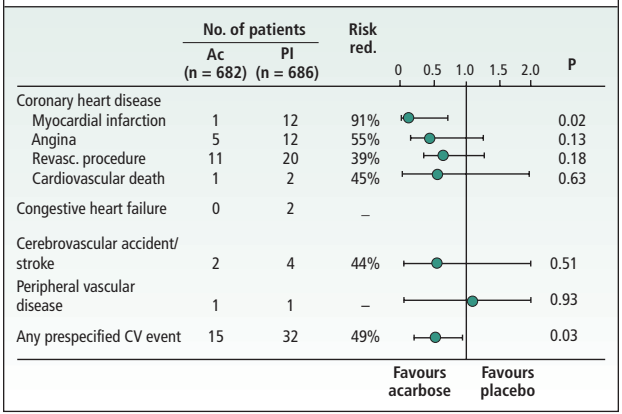


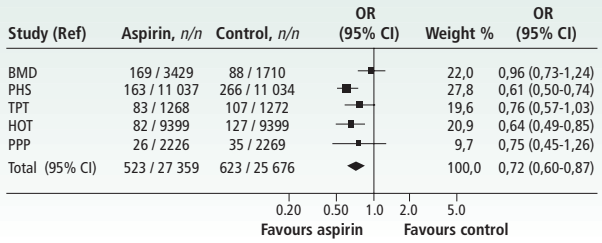
Figure 3: Effect of acarbose on cardiovascular events in subjects in T2DM[15]

	Hazard ratio (95% CI)	*p*-value	Favours Acarbose / Favours Placebo (0 0.5 1 1.5 2)
CV death	0.62 (0.19-2.05)	0.4368	
MI	0.36 (0.16-0.80)	0.0120	
Angina	0.79 (0.45-1.36)	0.3883	
Heart failure	0.55 (0.21-1.45)	0.2251	
Revascul proced.	0.78 (0.24-2.56)	0.6784	
Periph vasc disorder	0.75 (0.36-1.58)	0.4558	
Stroke/cerebro-vascular accident	0.75 (0.31-1.81)	0.5269	
Any CV event	0.65 (0.48-0.88)	0.0061	

– administered at bedtime – produces a sustained 24-hour average BP lowering of 7/5 mm Hg, while it slightly increases BP when administered in the morning. The reduction in mean nocturnal BP mean was double in non-dippers.[23] BP lowering from bedtime administration was comparable to other active antihypertensive drugs. One possible mechanism for the BP-lowering effect may be related to the potent antioxidant properties of ASA. For example, in the vascular tissues of normotensive and hypertensive rats, long-term oral treatment with ASA (100 mg/kg/day for 12 days) significantly reduced basal superoxide anion (O_2-) production, in association with reduced NAD(P)H oxidase activity.[24]

Treatment with ASA also inhibited the angiotensin II-induced hypertension and O_2- production. Moreover, ASA treatment significantly improved the impaired aortic relaxation response to acetylcholine and attenuated the age-dependent development of hypertension in spontaneously-hypertensive rats (SHRs). The antioxidant properties of ASA are, therefore, involved in the restoration of aortic vasorelaxation, in the attenuation of the development of hypertension in the SHR, as well as in the prevention of hypertension following long-term angiotensin II infusion. Chronic *in vivo* treatment with ASA also prevented the development of hypertension and reduced insulin resistance significantly in chronically glucose-fed rats.[25] ASA appeared to produce these effects through its antioxidant properties since it prevented the increase in aortic O_2- production observed in chronically glucose-fed rats. More recently, ASA was shown to prevent the induction of the COX-2 enzyme, which is highly pro-oxidant, in addition to its irreversible blockade of COX-1. Finally, the frequencies of onset of MI, sudden death, and stroke display marked circadian variations with parallel increases observed in the period from 06:00 to 12:00. A number of physiologic processes that could lead to plaque rupture, a hypercoagulable state, or coronary vasoconstriction are accentuated in the morning and ASA, which blocks some of these processes, has been shown to prevent disease onset.[26]

Figure 4: Meta-analysis of total coronary heart disease events in primary prevention



Optimizing BP control – the broader implications

Based on the Framingham model, Bob, the hypothetical patient, has total risk points of 13, which entails a moderate 12% 10-year risk for the development of coronary events.[27] In an attempt to reduce this risk, physicians need to address the factors that constitute the most significant and most remediable risks. For example, reducing this patient's dyslipidemia to an LDL-cholesterol level of <3.5 mmol/L with treatment would reduce his total risk points to 11 and his 10-year risk to 11%, whereas treating his BP to <140/90 mm Hg would decrease his total risk points by "1" at the most and his 10-year risk of coronary events to 10%. To achieve the latter goal would require the use of 2 to 3 antihypertensive drugs. This raises the question of how one would prioritize treatment – Should it be based on the risk factor that is farthest above target, or should it be based on the treatment that has the greatest impact on global risk?

To address this question, physicians should remember that the principal goal of treating hypertension is vascular protection and reducing the risk of atherosclerosis. Thus, based on the Canadian Hypertension Education Program (CHEP) recommendations for the management of hypertension,[28] a statin is used in patients with established atherosclerotic disease or the presence of 3 criteria associated with increased risk for atherosclerosis. For the similar common goal of vascular protection, low-dose aspirin is recommended, but it should be used with caution in a patient whose BP is not controlled. Lifestyle modification is the cornerstone of both antihypertensive and anti-atherosclerotic therapy (Figure 5). Indeed, lifestyle modifications (eg, a healthy diet, smoking avoidance, physical activity, and BP and cholesterol lowering) are common to control atherosclerotic risk factors, including hypertension, dyslipidemia, and diabetes.

Physicians may ask whether the co-existence of the metabolic syndrome would impact the BP treatment target and the choice of antihypertensive agents in Bob, our hypothetical case. In this regard, it is well-established that treatment of BP to target is associated with a reduction in the risk of all CV outcomes, including death, CHD, CV death, stroke, and heart failure.[29] Importantly, the absolute benefit, as measured by the number of patients needed to treat to prevent a CV event/death or death from all causes increases with the increasing number of concurrent risk factors, from "60" in patients needed to treat with stage 1 hypertension and no other risk factors, to "12" in those with CVD or target organ damage.[30]

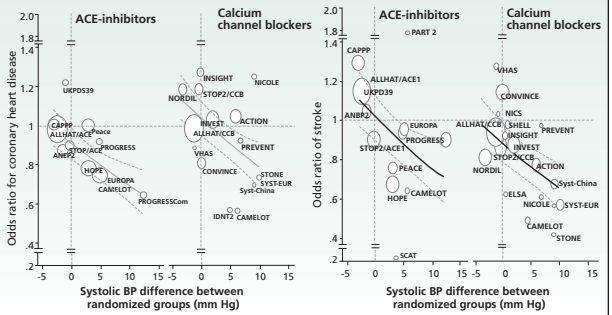
Based in results from the Hypertension Optimization Treatment (HOT) randomized trial,[21] the CHEP recommendations mandate a

Figure 5: Lifestyle modification in antihypertensive and antiatherosclerotic therapy

Intervention	Targeted change	SBP/DBP
Sodium reduction	-100 mmol/day	-5.8 / -2.5
Weight loss	-4.5 kg	-7.2 / -5.9
Alcohol reduction	-2.7 drinks/day	-4.6 / -2.3
Exercise	+ 3 times/week	-10.3 / -7.5
Dietary patterns	DASH diet	-11.4 / -5.5

Result of aggregate and metaanalyses of short term trials.

Figure 6: ACE inhibitors versus calcium channel blockers in high risk patients



lower BP treatment target in the *presence* of diabetes and a lower treatment target than in the *absence* of diabetes.[28] Whether lower BP treatment targets are also required in patients with established atherosclerosis is less clear at present since studies that assess the use of antihypertensive agents in patients with established atherosclerotic diseases, including CHD, have yielded conflicting results.[31-34]

The interpretation of these data is further confounded by a post hoc analysis of hypertensive patients with CHD in the International Verapamil-Trandolapril Study (INVEST), in which the risk for the primary outcome, all-cause death, and MI, but not stroke, were found to progressively increase with lower diastolic BP.[35]

With regard to the choice of antihypertensive agents, it is interesting to review a recent meta-analysis of 28 outcome trials that compared angiotensin-converting enzyme inhibitors (ACEIs) or calcium channel blockers (CCBs) with diuretics, beta-blockers, or placebo in 179,122 patients.[36] The odds ratios for CHD and stroke, plotted against the systolic BP differences between randomized groups are shown in Figure 6. In placebo-controlled trials, ACEIs decreased the risk of CHD ($p<0.001$), and CCBs reduced stroke incidence ($p<0.001$). There were no significant differences in CHD risk between regimens based on diuretics/β-blockers and regimens based on ACEIs or CCBs. The risk of stroke was reduced with CCBs ($p=0.041$), but not with ACEIs ($p=0.15$), compared with diuretics/β-blockers. On meta-regression analyses, prevention of CHD was explained by systolic BP reduction ($p<0.001$) and use of ACEIs ($p=0.028$), whereas prevention of stroke was explained by systolic BP reduction ($p=0.001$) and use of CCBs ($p=0.042$). These findings confirm that BP lowering is fundamental for the prevention of CHD and stroke. However, beyond BP reduction, ACEIs appear to be superior to CCBs for the prevention of CHD, while CCBs appear to be superior to ACEIs for the prevention of stroke. In practice, in the treatment of high-risk hypertensive patients, monotherapy is often not enough[37] and a multi-drug regimen, including a combination of ACEIs, CCBs, and other agents, is often required.

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