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Scientific Update™

Getting Behind Traditional Targets to Achieve Optimal Cardiovascular Risk Reduction

Originally presented by: Lawrence A. Leiter, MD; Jean-Louis Chiasson, MD; and Richard Lewanczuk, MD

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By GORDON MOE, MD

The concept of global risk in assessing multiple risk factors for cardiovascular (CV) events is well accepted. The impact of these risk factors occurs in a continuum, affecting even those below certain proposed thresholds for intervention for individual risk factors. This issue of *Cardiology Scientific Update* discusses the opportunities and evidence for early intervention in pre-disease states, as well as multi-drug strategies available for the comprehensive treatment of CV-metabolic diseases, including new treatments and new information on existing treatments .

Risk factor thresholds – An antiquated idea?

Recent clinical management guidelines have specified risk factor thresholds, beyond which intervention is required. Although set at successively lower levels over the years, these thresholds potentially deny patients intervention beyond specified values.[1] However, epidemiological and case-controlled studies have demonstrated a close to continuous relationship between coronary heart disease (CHD) mortality and blood pressure (BP), cholesterol, tobacco consumption, and HbA_{1C}.[2-6] One of the largest case-controlled studies – INTERHEART – demonstrated that conventional risk factors (eg, abnormal lipids, smoking, hypertension, diabetes, abdominal obesity, psychosocial factors, consumption of fruits, vegetables, and alcohol, and regular physical activity) account for most of the risk of myocardial infarction (MI) worldwide in both sexes, at all ages, and in all geographical regions.[4]

In the 3,564 men and 4,362 women in the Framingham Heart Study who were followed for 111,777 person-years, the lifetime risk of developing cardiovascular disease (CVD) increased with the intensity and number of individual risk factors.[7] Table 1 illustrates the extent of disease concentrated in the 10% of the population with the most extreme values of the physiological variables that constitute risk factors. However, this 10% experience only about 20% of the disease events.[1] Therefore, offering preventive treatment only to people with relatively high values of a variable implies that only a small proportion of those destined to have disease events will be targeted. The impact of 3 different strategies, namely: 1) population health strategy – lowering cholesterol uniformly in the entire population; 2) single raised risk factor strategy – treating people with a total cholesterol concentration of >6.2 mmol/L with statins; 3) high baseline risk strategy – treating people with an increased risk of CHD or CVD; on the number of deaths that could be avoided in Canada using the Canadian Heart Health Survey is shown in Table 2.[8] With the population health strategy, reducing total cholesterol concentrations in everyone by 2% would lead to 5,160 fewer deaths from CHD over 10 years (42 deaths per 100,000). On the other hand, treatment of a single risk factor in the population or treatment of people with a high baseline risk of CHD or CVD (assuming 100% adherence) would prevent 15,500 and 35,800 deaths (125 deaths/100,000 and 290 deaths/100,000), respectively, over 10 years.

These data, therefore, suggest that there are likely no thresholds for traditional CV disease risk factors and that management decisions should be based on the perceived global risk of patients, with attention to multiple risk factors.

Does the metabolic syndrome increase CV risk above and beyond that of traditional risk factors?

Metabolic syndrome (MetSyn) is associated with abdominal obesity, blood lipid disorders, inflammation, insulin resistance, or full-blown diabetes, and an increased risk of developing CVD.[9] The criteria and cut-off values proposed by the National

St. Michael's Hospital, 30 Bond St., Suite 7049, Queen Wing, Toronto, Ontario M5B 1W8 Fax: (416) 864-5941

Table 1: The burden of extreme risk levels

Physiological variable	Associated disorder	% of cases of disorder in the 10% of the population with the most extreme values
Systolic blood pressure	Stroke	28%
Systolic blood pressure	Ischemic heart disease	21%
Serum cholesterol	Ischemic heart disease	21%
Body mass index	Ischemic heart disease	22%
Body mass index	Diabetes	23%
Bone mineral density	Hip fracture	22%

Cholesterol Education Program – Adult Treatment Panel III (NCEP–ATP III)[10,11] and endorsed by the International Diabetes Federation (IDF)[12] to diagnose the likely presence of MetSyn have been discussed in previous issues of *Cardiology Scientific Update*. The criteria from the Canadian Dyslipidemia Guidelines are shown in Table 3.[13] A question clinicians frequently ask is whether the presence of MetSyn increases CV risk above and beyond that of traditional risk factors and whether lowering individual risk factors reduces CV risk in patients with the syndrome? In an analysis of the West of Scotland Coronary Prevention Study (WOSCOPS),[14] the presence of MetSyn predicted CHD events (hazard ratio [HR]=1.30, 95% confidence interval (CI),1.00-1.67, *P*=0.045) in a multivariate model incorporating conventional risk factors (Figure 1). In the Kuopio Ischemic Heart Disease Risk Factor Study, a population-based, prospective, cohort study in 1,209 Finnish men aged 42 to 60 years at baseline (1984-1989), who were initially without CHD, cancer, or diabetes, men with MetSyn, as defined by the NCEP, were 2.9 (95% CI, 1.2-7.2) to 4.2 (95% CI, 1.6-10.8) times more likely to die of CHD after adjustment for conventional CV risk factors. Men with MetSyn, as defined by the World Health Organization (WHO), were 2.9 (95% CI, 1.2-6.8) to 3.3 (95% CI, 1.4-7.7) times more likely to die of CHD after adjustment for conventional CV risk factors.[15] In a recent meta-analysis of 37 studies that included 43 cohorts (inception 1971 to 1997) and 172,573 individuals,[16] MetSyn conferred a relative risk (RR) of CV events and death of 1.78 (95% CI,1.58-2.00).

Table 2: Effect of 3 preventive strategies on deaths from CHD over 10 years in Canadians aged 20-74 years

Strategy	No. (%) of population treated	No. of deaths avoided	
		Over 10 yrs	Per 100,000
Population health	12,300,000 (100)	5,160	42
Single risk factor	1,370,000 (11.1)	15,500	125
High baseline risk	1,590,000 (12.9)	35,800	290

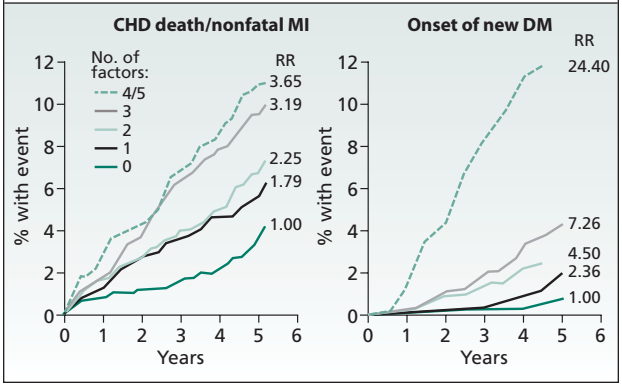
Table 3: Metabolic syndrome criteria from the 2006 Canadian Dyslipidemia Guidelines

Risk factor	Defining level
Abdominal obesity	Waist circumference
Men	>102 cm
Women	>88 cm
Triglyceride	≥1.7 mmol/L
HDL cholesterol	
Men	<1.0 mmol/L
Women	<1.3 mmol/L
Blood pressure	>130/85 mm Hg
Fasting glucose	5.7-7.0 mmol/L

There is emerging evidence that lowering even mildly increased risk factors may confer benefit, although the data are by no means uniform at this stage. In a recent post hoc analysis of the Treating to New Targets (TNT) study,[17] irrespective of treatment assignment, significantly more patients with MetSyn (11.3%) had a major CV event at a median of 5 years than those without MetSyn (8.0%; hazard ratio 1.44; 95% CI, 1.26-1.64; p<0.0001). This increased risk was significantly reduced by intensive therapy with atorvastatin 80 mg beyond that achieved with atorvastatin 10 mg in the entire cohort.

It is known from the Framingham Heart Study that high normal BP (ie, systolic BP [SBP] 130-139 mm Hg) is associated with increased CV risk.[18] In the Trial of Preventing Hypertension (TROPHY) study, subjects with an SBP of 130-139 mm Hg and diastolic BP (DBP) of ≤ 89 mm Hg, or an SBP of ≤139 mm Hg and a DBP of 85 to 89 mm Hg, were randomly assigned to receive 2 years of candesartan or placebo, followed by 2 years of placebo for all.[19] After the first 2 years, hypertension developed in 154 participants in the placebo group and in 53 of those in

Figure 1: Metabolic syndrome as a predictor of CHD death and diabetes in the West of Scotland Coronary Prevention Study[14]



the candesartan group (relative risk reduction [RRR] 66.3%; *P*<0.001). After 4 years, hypertension developed in 240 subjects in the placebo group and 208 of those in the candesartan group (RRR 15.6%, *P*<0.007).

Targeting glucose – evidence-based solutions for CV prevention

There is a growing prevalence of diabetes worldwide. Globally, the number of patients with diabetes is expected to increase from 171 million in 2000, to 221 million by 2010,[20] and 366 million by 2030 (WHO 2004, www.who.int/diabetes/facts/world_figures/en/).[21] The classification of glucose intolerance is summarized in Table 4. Accompanying this trend of an increasing prevalence of diabetes is a growing global prevalence of impaired glucose tolerance (IGT), with 314 million people as of 2003, projected to reach 472 million by 2025 (International Diabetes Federation Diabetes Atlas, www.eatlas.idf.org/). The risks of postprandial hyperglycemia (PPG) is shown in Figure 2. Patients with IGT carry a risk of progressing to type 2 diabetes and CV events.[22-25] PPG can potentially increase the risk of adverse CV outcomes through several mechanisms, including impairing endothelium, increasing oxidative stress, and increasing BP.[26-28] Several studies have demonstrated that early interventions in patients with IGT, through lifestyle modification[29-31] or drug treatment,[30-35] reduce the risk of development of diabetes (Figure 3).

Acarbose is an α-glucosidase inhibitor that reduces PPG by delaying carbohydrate absorption from the intestine.[36] Acarbose decreases postprandial plasma glucose and insulin, and improves insulin sensitivity in subjects with IGT.[37] Thus, if PPG played a role in the development of type-2 diabetes and CV risk, acarbose would be expected to prevent the development of diabetes and reduce CV events.

The effect of acarbose in preventing or delaying conversion of IGT to type-2 diabetes was evaluated in the Study to Prevent NIDDM (STOP-NIDDM) trial.[33] In this multicentre, placebo-controlled trial, 1,429 patients with IGT were randomized to 100 mg acarbose or placebo 3 times daily. Results for the primary endpoint – the development of diabetes – are shown in Figure 4. Reducing PPG with acarbose was associated with a reduced risk of diabetes and increased conversion to normal glucose tolerance. Treatment with acarbose was also associated with a 34% RRR in the incidence of new cases of hypertension HR, 0.66; 95% CI, 0.49-0.89; *P* =0.006).[38]

In a substudy of 132 IGT subjects whose carotid artery intima media thickness (IMT) was measured, the annual increase in IMT was reduced by about 50% in the acarbose group.[39] The effect on one of the secondary endpoints, CV events, is shown in Figure 5. Among these events, the major reduction was in the risk of MI (HR, 0.09; 95% CI, 0.01-0.72; *P* = 0.02). Data on this clinical outcome should be interpreted with some caution since it is not the primary outcome.

In the more recent Diabetes Reduction Assessment with Ramipril and Rosiglitazone Medication (DREAM) study,[32] 5,269 adults with IFG or IGT or both, and no previous CVD were randomized to receive rosiglitazone or placebo. The primary outcome was a composite of incident diabetes or death. At study end, 11.6% of the individuals given rosiglitazone and 26.0% of those given placebo developed the composite primary outcome (HR, 0.40; 95% CI, 0.35-0.46; P<0.0001). CV event rates were similar in both groups, although 0.5% of participants

Table 4: Classification of glucose tolerance

Category	FPG (mmol/L)	PG 1-hour following 75 g of glucose	PG 2-hour following 75 g of glucose
Impaired fasting glucose (IPG)	6.1-6.9	–	–
Impaired glucose tolerance (IGT)	<7.0	–	7.8-11.0
Diabetes	≥7.0	–	≥11.1
Gestational diabetes	≥5.3	≥10.6	≥8.9

Adapted from Meltzer S, et al. *CMAJ* 1998;159:S1-S29

Figure 2: The risk of postprandial hyperglycemia (PPG)

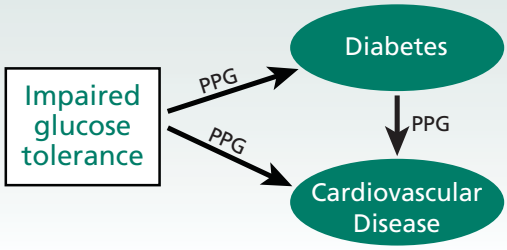
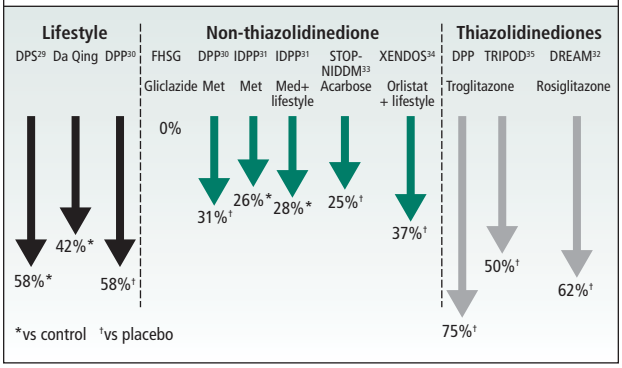
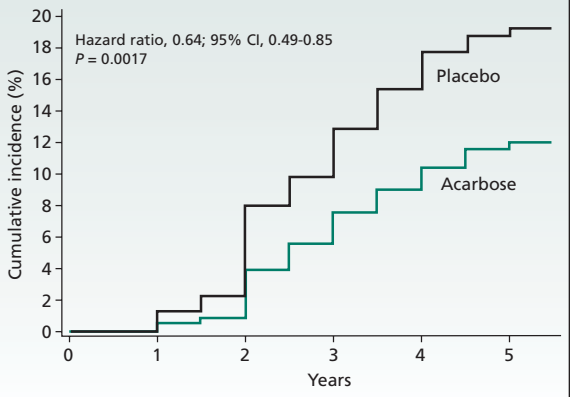


Figure 3: Early intervention and the risk of diabetes



DPS = Diabetes Prevention Study, Da Qing=The Da Qing IGT and Diabetes Study, DPP=Diabetes Prevention Program, FHSG= Fasting Hyperglycaemia Study, IDPP= Indian Diabetes Prevention Programme, STOP-NIDDM= Study to prevent non-insulin-dependent diabetes mellitus, XENDOS= XENical in the prevention of diabetes in obese subjects, TRIPOD=Troglitazone in Prevention of Diabetes, DREAM=Diabetes Reduction Assessment With Ramipril and Rosiglitazone Medication

Figure 4: The STOP-NIDDM trial: Effect of acarbose on the incidence of type 2 diabetes in IGT subjects



in the rosiglitazone group and 0.1% of the placebo group developed heart failure ($P = 0.01$). Since most subjects with IGT also have other conventional risk factors, these risk factors should, therefore, be aggressively managed.

Although data to date are promising with regard to the treatment of plasma glucose for the prevention of diabetes, further studies are needed before treatment of plasma glucose to prevent CV events can be recommended. Ongoing, large scale, clinical outcome trials that will assess the impact of early treatment of subjects with IGT include the Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) and the Acarbose Cardiovascular Evaluation (ACE) studies.

Treatment of hypertensive patients is more than BP control

As discussed in previous sections, the risks of CV events and renal failure are not confined to the subset of the population with particularly high levels of BP. Instead, risk occurs as a continuum, affecting even those with below-average levels of BP. Globally, about 62% of cerebrovascular disease and 49% of CHD are attributable to suboptimal BP control.[40] There is little disagreement about the fact that hypertension is a common and major cause of premature mortality and morbidity and a driver of healthcare costs.[41,42] However, the debate continues as to whether the type of drugs used by physicians to lower BP is important in improving clinical outcomes. The results of large meta-analyses of treatment trials continues to favour the hypothesis that BP differences largely account for CV outcome. As well, the hypothesis that "new" antihypertensive drugs (eg, calcium-channel blockers [CCBs], alpha-blockers [α-blockers], angiotensin-converting enzyme inhibitors [ACEIs], or angiotensin receptor blockers [ARBs]) might influence CV prognosis, in addition to their antihypertensive effects, remains unproven (Figure 6).[43,44] Many trials have been interpreted to support an effect beyond BP-lowering or the superiority of a particular drug or drug class over another on the basis of near-equal reductions in BP in compared regimens.[45-49] On the other

Figure 6: Correlation between reduction in systolic blood pressure and cardiovascular mortality or events

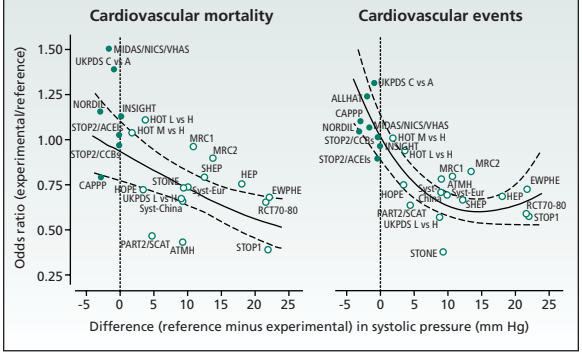
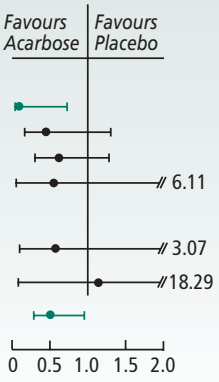


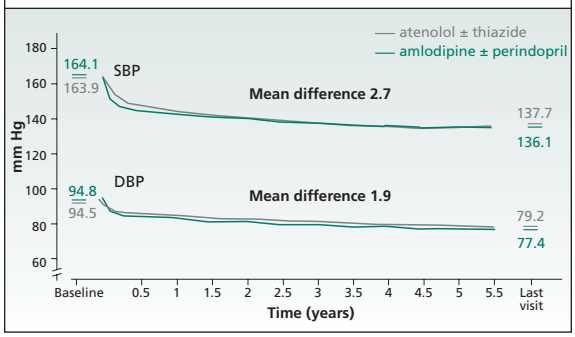
Figure 5: The STOP-NIDDM trial: Effects of acarbose on cardiovascular events in subjects with IGT

	Study population Acarbose (n=682)	Placebo (n=686)	Hazard ratio (95% CI)	p-value
Coronary heart disease				
Myocardial infarction	1*	12	0.09 (0.01-0.72)	0.0226
Angina	5	12	0.45 (0.16-1.28)	0.1344
Revascularization procedures	11	20	0.61 (0.29-1.26)	0.1806
Cardiovascular death	1	2	0.55 (0.05-6.11)	0.6298
Congestive heart failure	0	2	—	—
Cerebrovascular accident/stroke	2	4	0.56 (0.10-3.07)	0.5061
Peripheral vascular disease	1	1	1.14 (0.07-18.29)	0.9255
Any cardiovascular event	15**	32	0.51 (0.28-0.95)	0.0326



*Number of subjects with a specific cardiovascular event
**Number of subjects with any one cardiovascular related event

Figure 7: SBP and DBP pressure in the ASCOT-BPLA



hand, an almost equal number of trials have been interpreted to support a predominantly BP-lowering effect, and there are some trials that can be interpreted both ways.[46,47,50,52,53]

The majority of active-controlled trials did not completely achieve equal BP reductions between the tested regiments; for example:

- In the Anglo-Scandinavian Cardiac Outcomes Trial-Blood Pressure Lowering Arm (ASCOT-BPLA), the amlodipine and perindopril-based regimen prevented more major CV events and induced less diabetes than the atenolol and diuretics-based regimen.[46] However, there was a difference in achieved BP, which was 2.7 and 1.9 mm Hg (systolic and diastolic BP, respectively) better with the first regimen (Figure 7).
- In the A Coronary disease Trial Investigating Outcome with Nifedipine GITS (ACTION) study,[54] an analysis of the hypertensive subgroup revealed that nifedipine GITS lowered BP by an additional 6.6/3.5 mm Hg (systolic/diastolic) relative to placebo, which may explain the benefit of nifedipine on the primary endpoint of combined death, MI, refractory angina, new overt heart failure, debilitating stroke, and peripheral revascularization in the hypertensive subgroup, which was not demonstrated in the overall study population.
- The Felodipine Event Reduction (FEVER) trial was conducted on moderately complicated hypertensive patients from China. A difference in BP of 4.2/2.1 mm Hg (systolic/diastolic), induced by adding low-dose felodipine to low-dose hydrochlorothiazide, was associated with a reduction in CV events.[50]

The importance of "how" a physician lowers BP and whether this is important in improving clinical outcomes in hypertension remains a topic of debate. It is very likely that BP-lowering plays a key role and there may be beneficial effects beyond BP control.[55] However, it is also very likely that certain drug regimens/combinations are more effective in lowering BP than others,[46,47] or that providing additional BP control may be accompanied by incremental outcome benefit.[50,54]

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