

Hypertension and Diabetes: Should We Treat Early Surrogates?

What are the cons?

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Type 2 diabetes, a major public health problem of great concern, affects millions of patients in both developed and developing countries. These patients run a well-documented increased risk of cardiovascular disease (CVD), the risk of which is two- to threefold greater than that seen in nondiabetic subjects (1). Despite modern methods for treatment of diabetes and its risk factors and complications, the increased risk is still substantial. This is so even if data on risk factor control in national surveys, repeated on an annual basis, have shown improving trends for blood pressure and lipid control, e.g., in the National Diabetes Register in Sweden (2). Because hypertension and lipid disturbances are currently relatively easy to treat pharmacologically, this denotes that the majority of patients with diabetes are also to some extent receiving treatment for their CVD risk factors. Ideally, only studies that could prove the effect on clinical end points should be accepted as fundamental for evidence-based medicine in national or international guidelines. However, in addition, intermediate end points have been advocated for evaluation of intervention effects, as recently shown in studies evaluating drug effects on carotid or coronary atherosclerosis. This has provoked a clinical debate as that related in the following two sets of arguments, i.e., *pro* or *con* regarding the use of intermediate end points when hypertension in diabetes is treated.

On the *pro* side, arguments are concentrated in defense of using left ventricular hypertrophy, albuminuria, or arterial stiffness as useful surrogate markers, or intermediary end points, to guide the in-

tensity and mode of treatment. However, on the *con* side, other more critical arguments are given to state that only drugs that are also able to decrease the rate of clinical events should be used, e.g., those shown to reduce CVD, including myocardial infarction and stroke, and in addition also end-stage renal disease. These arguments were debated in Barcelona at the Controversies in Obesity, Diabetes, and Hypertension (CODHy) symposium on 1 November 2008 and are summarized here.

One study that showed a decrease in both intermediate end points and cardiovascular events is the successful long-term follow-up of the Danish Steno-2 trial (3). In that study, patients with type 2 diabetes and microalbuminuria, and many with concomitant hypertension, were vigorously treated for optimal risk factor control, with proven benefits after more than 13 years of follow-up. Therefore, both types of end points should ideally be ready to be evaluated within one and the same trial. However, not all trials could provide such excellent conditions as the Steno-2 trial (3) and, therefore, a clinical controversy exists. Should we, or should we not, rely on intermediate end point evaluation in clinical decision making? That is the question.

Patients with type 2 diabetes run an increased risk of CVD, sometimes described as equivalent to a state of post-myocardial infarction in nondiabetic subjects (4,5). The prominent CVD risk factors to detect, treat, and follow up are elevated blood pressure levels, hypercholesterolemia (with elevated LDL cholesterol), dyslipidemia (high triglycerides, low HDL cholesterol), as well as hypergly-

cemia and smoking. In addition, chronic inflammation and defects in fibrinolytic function as well as adverse psychosocial conditions could all contribute to this increased risk, besides the impact of background factors that are impossible to change, such as age, sex, and diabetes duration. Because type 2 diabetes and its associated risk factors could be seen as a model of early vascular aging (EVA) (6), this implies that surrogate markers of this process can also be measured. Some examples are intima-media thickness after ultrasound evaluation of arteries, coronary calcification via magnetic resonance imaging, increased pulse wave velocity (PWV), decreased ankle-brachial blood pressure index, impaired renal function, and (micro-) albuminuria (7). It has been argued that it is enough to measure these markers for clinical evaluation of effects. However, ultimately of greatest importance, according to the concept of Patient-Oriented End points that Matter (POEM) (8), is to decrease the risk of diabetes-related complications and mortality risk. This can only be achieved via long-term randomized controlled trials, sometimes combined for a meta-analysis, as was recently shown for the benefits of statin therapy in patients with diabetes (9). The proven risk factors that should be addressed by interventions are hypertension, hyperlipidemia, hyperglycemia, and smoking, as evidenced in the observational part of the U.K. Prospective Diabetes Study (UKPDS) (10).

GUIDELINES ARE BASED ON EVIDENCE FROM LARGE TRIALS

— For several years, data have accumulated on treatment benefits of control of these major risk factors based on reports from large-scale clinical trials involving patients with type 1 diabetes (i.e., the Diabetes Control and Complications Trial) or type 2 diabetes (i.e., UKPDS, Reduction of Endpoints in NIDDM with the Angiotensin II Antagonist Losartan [RENAAL], Irbesartan in Diabetic Nephropathy Trial [IDNT], Heart Protection Study [HPS], Collaborative Atorvastatin Diabetes Study [CARDS],

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Losartan Intervention For Endpoint reduction in hypertension [LIFE], Anglo-Scandinavian Cardiac Outcomes Trial [ASCOT], Ongoing Telmisartan Alone and in combination with Ramipril Global Endpoint Trial [ONTARGET], Avoiding Cardiovascular events through Combination therapy in Patients Living with Systolic Hypertension Trial [ACCOMPLISH]). Hence, to date, we have had strong support for some, but not all, of the goals for risk factor control stated in contemporary guidelines for treatment of patients with diabetes, jointly from both the American Diabetes Association and American Heart Association (11). This is also true for the corresponding joint guideline from the European Society of Cardiology and the European Association for the Study of Diabetes (12). For example, the recommended goal of blood pressure control in patients with diabetes and hypertension (<130/80 mmHg) (4,11,12) was not based on solid evidence from intervention studies, but from observational studies. This was most notably from the observational arm of UKPDS, where a linear association between systolic blood pressure and risk of coronary artery disease was noticed (13). Ideally, it takes a multiple risk factor control approach to show real health benefits, as was recently reported from the long-term follow-up (13.8 years) analysis of the Steno-2 study in Denmark (3). In this randomized controlled trial, patients with the combination of type 2 diabetes and microalbuminuria, many also being hypertensive, were randomized to either intensive risk factor control or to standard therapy. The basis for intensive intervention was a wide prescription of ACE inhibitors and statins, as well as other preventive drug medications. It transpired that such therapy lead to a decrease not only in diabetes-related cardiovascular end points, but also reduced total mortality by ~50%. These impressive results were gained after a long-term post-trial follow-up and further extended the results obtained during the 5 years of the main trial (3). Thus, the Steno-2 trial provides evidence for not only the randomized controlled trial design as the most effective model, but also for the objective to strive for hard end points (POEM) (8) and not to use surrogates, e.g., concentrating on the changes in microalbuminuria. These changes are themselves noteworthy and have indeed been used in other studies (14), but can never replace

the far more important major clinical CVD end points.

LESSONS FROM INTERVENTION TRIALS OF BLOOD PRESSURE CONTROL

— Important new evidence has been published based on data from two large-scale intervention studies (ADVANCE and ACCOMPLISH) aiming at controlling blood pressure in patients with type 2 diabetes (15,16). The multicenter international ADVANCE trial studied the effects of the routine administration of a fixed ACE inhibitor–diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels, or the use of other blood pressure-lowering drugs. The trial was performed by 215 collaborating centers in 20 countries. After a 6-week active run-in period, 11,140 patients with type 2 diabetes were randomized to treatment with a fixed combination of perindopril and indapamide or matching placebo, in addition to current therapy for CVD risk factor control. The primary end points were composites of major macrovascular and microvascular events, defined as death from CVD, nonfatal stroke or nonfatal myocardial infarction, and new or worsening renal or diabetic eye disease. All analyses were made by intention to treat. The macrovascular and microvascular composites were analyzed jointly and separately. After a mean 4.3 years of follow-up, 73% of those assigned active treatment and 74% of those assigned placebo remained on their randomized treatment. Compared with patients assigned placebo, those assigned active therapy had a mean reduction in blood pressure of 5.6/2.2 mmHg. The relative risk of a major macrovascular or microvascular event was reduced by 9% (861 [15.5%] active vs. 938 [16.8%] placebo; hazard ratio [HR] 0.91, 95% CI 0.83–1.00, $P = 0.04$). The separate reductions in macrovascular and microvascular events were similar, but were not independently significant. The relative risk of death from CVD was reduced by 18% (0.82% CI 0.68–0.98, $P = 0.03$) and all-cause mortality was reduced by 14% (0.86% CI 0.75–0.98, $P = 0.03$). No evidence was found that the effects of the study treatment differed by initial blood pressure level or concomitant use of other treatments at baseline (15).

Therefore, the authors concluded that the routine administration of a fixed combination of perindopril and indapamide

to patients with type 2 diabetes was well tolerated and reduced the risks of major vascular events, including death. Although the confidence limits were wide, the results suggest that over a 5-year period, one death due to any cause would be averted among every 79 patients assigned active therapy. However, in an accompanying editorial by Norman Kaplan (17), it was mentioned that probably other combinations of antihypertensive drugs would be able to achieve the same clinical benefits, since the blood pressure reduction per se seemed to be the most important. Another critical question is why no preventive effect on cerebrovascular events (stroke) was noticed. This might eventually be because a large proportion of the patients were already on statin therapy or received it during the study (45% at follow-up) as background medication, and it has been shown that statins contribute to stroke prevention. It could be hypothesized that, in the lower blood pressure interval, as found in the ADVANCE trial, the statin preventive effect could override the impact of blood pressure lowering by antihypertensive drugs.

FIXED DRUG COMBINATION BENEFITS

— More recently, the ACCOMPLISH trial provided overwhelming evidence that a combination of benazepril (ACE inhibitor) and amlodipine (calcium antagonist) was superior to a fixed combination of benazepril and hydrochlorothiazide in nondiabetic and diabetic patients, in spite of similar blood pressure reduction (16). The study was prematurely ended due to a pronounced difference in the composite end point of cardiovascular morbidity and mortality (risk ratio 0.80, 95% CI 0.72–0.90). The results resemble the benefit that was achieved with a similar ACE inhibitor/calcium antagonist therapy in the ASCOT trial (18).

FAILURES TO SHOW EFFECTS ON EARLY ATHEROSCLEROSIS

— Conversely, it is known that two promising drugs for metabolic control, the lipid-lowering ezetimib and the CBI-antagonist rimonabant, failed to decrease early signs of atherosclerosis, even if LDL cholesterol and C-reactive protein were reduced by ezetimib added to simvastatin versus simvastatin alone in the Ezetimibe and Simvastatin in Hypercholesterolemia Enhances Atherosclerosis Regression (ENHANCE) study (19) or that rimon-

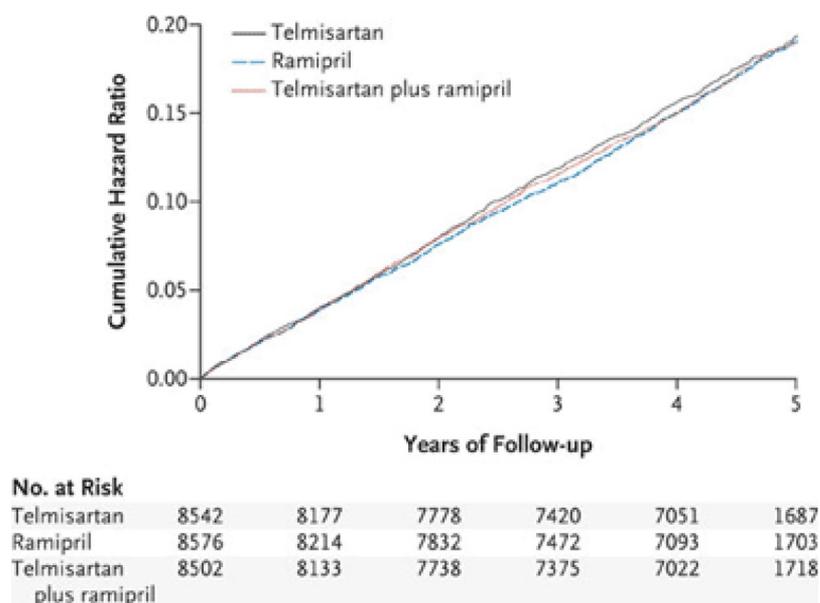


Figure 1—Kaplan-Meier curves for the primary outcome in the three study groups in the ONTARGET trial. The composite primary outcome was death from cardiovascular causes, myocardial infarction, stroke, or hospitalization for heart failure. Reprinted with permission from ONTARGET Investigators (22).

aband decreased weight, glucose, and lipids in the Strategy to Reduce Atherosclerosis Development Involving Administration of Rimonabant—The Intravascular Ultrasound Study (STRADIVARIUS) study (20). The only solution to effectively evaluate these two drugs, often prescribed to patients with type 2 diabetes, is to conduct a large-scale intervention trial for clinical end points. This also pertains to ezetimib, which is currently being tested, versus placebo in the large-scale IMPROVED Reduction of Outcomes: Vytarin Efficacy International Trial (IMPROVE-IT) study (21), while rimonabant was recently withdrawn because of mental side effects. The primary objective of IMPROVE-IT is to evaluate the clinical benefit of an ezetimib/simvastatin combination 10/40 mg single tablet, compared with simvastatin 40 mg. Clinical benefits are defined as the reduction in the risk of the occurrence of the composite end point of CV death, major coronary events, and stroke (21).

It is of interest that no extra benefit was recorded, contrary to expectations, when an angiotensin-2 receptor blocker (telmisartan) and an ACE inhibitor (ramipril) were combined, compared with ramipril alone in the ONTARGET trial (22) (Fig. 1). Even if previous studies have shown that such a combination is able to reduce proteinuria, an intermediary end point, this could not regretfully translate into extra clinical benefit in pre-

vention of CVD. On the contrary, a higher rate of early study termination was noted, due to renal adverse effects in the combination arm compared with monotherapy ramipril, a drug well proven in the placebo-controlled Heart Outcomes Prevention Evaluation (HOPE) trial (23). After this disturbing result, protagonists for the use of intermediary end points will have an even tougher task than before to substitute drugs other than real cardiovascular end points or end-stage renal disease.

TIGHT CONTROL OF HYPERGLYCEMIA AND MORTALITY RISK

Finally, it came as a surprise when, recently, the large intervention study Action to Control Cardiovascular Risk in Diabetes (ACCORD) was terminated because of an increased mortality rate in the intensive treatment arm for normalizing A1C levels to under 6% (Diabetes Control and Complications Trial standard) (24,25). The publication showed conflicting effects by treating an intermediate end point, the glycemic control (A1C), for increased total mortality but a reduction in nonfatal events (25). This was also reflected in the findings that treatment of hyperglycemia with rosiglitazone could in fact provoke some aspects of CVD, e.g., congestive heart failure, as shown in a meta-analysis (26). This viewpoint was later challenged and debated (27).

CONCLUSIONS— In summary, these examples all contribute to a critical attitude toward intermediary end points in cardiovascular prevention. In particular, the lack of effect on early signs of atherosclerosis by use of metabolically active drugs (ezetimib, rimonabant) and the failure to add extra clinical benefits of the angiotensin-2 receptor blocker–ACE-1 combination in ONTARGET are proof of concept that nothing can substitute a large randomized controlled end point trial. Such a trial should have a clear-cut and well-defined primary aim to evaluate effects on cardiovascular end points or its corresponding renal outcome.

Patients and physicians require definite end points to support and motivate compliance with long-term drug medication. This is POEM (8), and anything else is “ersatz” (German for substitute). Why drink surrogate coffee when you can have the authentic tasty one?

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