Risk factor modification and cardiovascular events: the gap is not yet bridged

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The current state of risk prevention for cardiovascular events has emerged from more than 50 years of epidemiological studies. Biomarkers such as body weight, hyperglycemia, hypertension, and increased serum concentrations of low-density lipoprotein cholesterol have helped to assess cardiovascular risk and have been proposed as therapeutic targets. Drug development programs have used a growing array of markers to identify and evaluate novel drugs, establish dose ranges, prioritize research efforts, and establish new treatment guidelines. Nonetheless, our highly promising contemporary treatment regimens have not been consistently shown to improve clinical outcomes.

Type 2 diabetes mellitus is widely accepted to be a condition associated with a high risk for coronary events, and patients with type 2 diabetes mellitus have been identified as targets for aggressive treatment. However, data from recent studies, including the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [1] and the Veterans' Affairs Diabetes Trial (VADT) [2], led the investigators to conclude that aggressively and rapidly decreasing glycated hemoglobin (HbA$_{1c}$) to less than 7% in type 2 diabetes mellitus does not improve cardiovascular outcomes. On the contrary, a slight, but statistically significant increase in cardiovascular death was observed in the intensive glycemic control arm in the ACCORD study (*Table I*).

Following these observations, the role of comorbidities including obesity, hypertension, and dyslipidemia – termed the "cardiometabolic syndrome" – has been emphasized in patients with type 2 diabetes mellitus. Lifestyle interventions designed to modify behaviors such as overeating and inactivity have proven to be effective [3] in reducing the prevalence of these comorbidities and cardiovascular events.

Four large randomized trials recently completed have evaluated the impact of intensive risk factor treatment on cardiovascular mortality, major adverse cardiovascular events, and the extent of coronary artery disease in patients with type 2 diabetes mellitus.

The Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research (NAVIGATOR) study examined the effects of the approved diabetes medication, nateglinide – a relatively weak, rapidly acting, sulfonylurea-like drug – and the angiotensin receptor blocker, valsartan, on the development of diabetes and cardiovascular disease [4,5]. Neither drug, nor their combination, offered significant protection from the progression of impaired glucose tolerance to diabetes or from the progression of cardiovascular disease.

The Assessment on the Prevention of Progression by Rosiglitazone on Atherosclerosis in Diabetes Patients With Cardiovascular History (APPROACH) study [6], evaluated the potentially glucose-independent effects of rosiglitazone, a thiazolidinedione, on coronary atherosclerosis, as assessed by intravascular ultrasound. The authors concluded that rosiglitazone did not significantly decrease the primary endpoint of progression of coronary atherosclerosis in patients with type 2 diabetes mellitus and coronary atherosclerosis.

The ACCORD blood pressure (ACCORD BP) study [7] investigators evaluated the potential benefits of targeting a systolic blood pressure less than 120 mm Hg, compared with a value less than 140 mm Hg, in patients with type 2 diabetes.

In the ACCORD Lipid study [8], patients were randomly assigned to receive either simvastatin plus fenofibrate or simvastatin alone. The goal of treatment with fenofibrate was to reduce plasma triglyceride concentrations and increase plasma high-density lipoprotein cholesterol concentrations in patients who were already taking a statin to reduce plasma low-density lipoprotein cholesterol.

In summary, therefore, aggressive control of risk factors did not result in a significant improvement in clinical outcomes. So, despite a sound rationale for the global treatment of cardiovascular risk factors, the

Table I. Main findings of the ACCORD study. Outcomes of intensive glycemic control.

- Increased mortality (prespecified secondary outcome and safety measure: 22% higher rate in the intensively treated group; hazard ratio 1.22, 95% confidence interval [CI] 1.01 to 1.46; $P = 0.04$)
- Did not reduce primary outcome over 3.5 years of follow-up (composite of non fatal myocardial infarction, non fatal stroke, fatal cardiovascular disease: 10% lower rate in the intensively treated group; hazard ratio 0.90, 95% CI 0.78 to 1.04; $P = 0.16$)
- Mortality results consistent over several subgroup analyses
- Authors concluded that harm outweighed the potential benefits of intensive treatment

results of these trials fell far below expectations, being largely negative, and raising many disturbing questions.

It has been widely validated that the presence of prespecified clinical and biochemical features are good *indicators* of increased risk for cardiovascular disease. The possibility of easily identifying and monitoring such indicators has therefore been translated into intensified clinical efforts aimed at their suppression, thereby shifting the relationship between risk factors and cardiovascular disease from ''indicators'' to ''causal mechanisms''.

Changes in clinical features are used directly for determining the clinical benefit of a treatment strategy, and as such are named ''surrogate end-points''. However, the clinical endpoint is the characteristic or variable that truly reflects how a patient feels, functions, or survives. Principal factors that may explain the failure of clinical features to translate into clinical outcomes include:

1. *The surrogate does not cause the disease.* In fact, although many potential surrogates correlate with clinical outcome, very few are able to reflect the full therapeutic effect on the clinical outcome, suggesting the existence of a bridging gap between the two variables. In the APPROACH study, for example, treatment effect was rated as effective or not, depending on the change in plaque volume measured by intravascular ultrasound. However, convincing evidence that links this parameter to benefit with respect to cardiovascular risk is still lacking. Moreover, although atherosclerotic disease often results in flow-limiting lesions, most patients die of an acute coronary syndrome, usually associated with non flow-limiting lesions.
2. *The surrogate is involved in only one pathway of a multiple-pathway disease.* The study populations being considered in the aforementioned studies were diabetic patients, with accompanying comorbidities such as obesity, hypertension, and dyslipidemia. It is now well accepted that there is a common, as well as complex, network of underlying pathophysiological mechanisms leading to a

clinical state of increased risk for cardiovascular events. The results of these trials are a further master stroke for the paradigm of the pathophysiology of type 2 diabetes mellitus or other cardiovascular risk factors regarded as a simple ''cause-and-effect'' disease.

3. *The effect of the intervention may prove to be beneficial irrespective of the ''suppression'' of a surrogate.* This is the case with the clinical benefit from statin therapy, which is called a ''pleiotropic'' effect (to all intents and purposes, an ''unidentified surrogate endpoint'').

Conclusion

We are left with an apparent paradox: most of the reduction in cardiovascular mortality and morbidity reported in recent years has been attributed to preventive measures, but these same preventive measures, when individually tested in high-risk subgroups of patients, often fail to improve clinical outcomes.

The paradox could be explained either by a beneficial effect of the tested drug that is independent of specific risk factor reduction, or by a predominant effect of non pharmacological interventions commonly given in association with drug prescriptions, such as advice on lifestyle changes, rehabilitation programs, and changes in diet. ■

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