

Diabetes and cardiovascular disease: time for individualized risk reduction

"Recent data call for a change in the treatment emphasis; while the guidelines generally recommended a 'one-size-fits-all' approach to diabetes care, emphasis should be placed on an individualized approach that keeps patients who are less likely to benefit from tight glycemic control ... symptom-free without increased risk of hypoglycemia."

Cardiovascular disease (CVD) is the major cause of morbidity and mortality in people with diabetes, and represents up to 80% of premature death in this patient population [1,2]. Traditional CVD risk factors in the diabetic population include hypertension, insulin resistance, diabetic dyslipidemia, central obesity, smoking and sedentary lifestyles, while nontraditional risk factors include low-grade inflammation, oxidative stress, endothelial dysfunction, stimulation of the renin-angiotensin-aldosterone system and the prothrombotic state (increased PAI-1, increased platelet aggregation and increased fibrinogen) [3]. Control of CVD risk factors in diabetic patients is quite challenging, costly and burdensome, and is only achieved in a small proportion of the population, particularly among those at the highest risk of CVD, such as ethnic minorities and those with established CVD and chronic kidney disease (CKD), as well as the elderly diabetic patients [4-11]. Work by our group and others, including nationally representative samples, indicate that control of individual CVD risk factors according to the applicable practice guidelines is achieved in less than a third of the diabetic population [6,7,10] with only 3–7% of the diabetic population simultaneously achieving glycemic, blood pressure and lipid goals [6,7,10]. While tight glycemic control with hemoglobin A1c (HbA1c) of 6.5-7% has been recommended in various clinical practice guidelines, and is used as a measure of quality of care and in some instances as a determinant of reimbursement such as with Medicare, 'Pay for Performance' initiatives, evidence for CVD protection with this approach is generally lacking, especially with long-standing diabetes, elderly populations and in those with CKD [12,13]. Furthermore, accumulating evidence from major recently published trials [14-16], specifically designed to compare CVD outcomes

of tight glucose control versus less tight glucose control, provided no evidence of CVD protection, and possible harm with such an approach. For example, increased mortality was observed in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial [15], where the glycemic arm of the trial was prematurely terminated due to excess mortality associated with tight glucose control, with a HbA1c level of 6.5% achieved, compared with a HbA1c of 7.5% in the less tight control group [15]. The other two studies, namely the Action in Diabetes and Vascular Disease (ADVANCE trial; intensive blood glucose control and vascular outcomes in patients with Type 2 diabetes) [16] and the Veterans Affairs Diabetes Trial (VADT; glucose control and vascular complications in veterans with Type 2 diabetes) [14], have provided no evidence for CVD benefits with tight glycemic control. Several intriguing points were raised by these recent data. For example, in the subanalysis of the ACCORD trial, those without established cardiovascular events had a lower risk for new cardiovascular events with tight glycemic control, compared with those who already suffered an event, suggesting that tight glucose control might be beneficial in a newly diagnosed diabetic population without established CVD [15,17]. Other confounding factors that could possibly explain the CVD outcomes in these trials is the medication use, where rosiglitazone is suspected to increase CVD and metformin has been shown to have beneficial CVD effects [17,18]. These recent data call for a change in the treatment emphasis; while the guidelines generally recommended a 'onesize-fits-all' approach to diabetes care, emphasis should be placed on an individualized approach that keeps patients who are less likely to benefit from tight glycemic control, such as the elderly and frail, those with long-standing diabetes and



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those with advanced CKD, at a physiologically acceptable blood glucose level that makes them symptom-free without increased risk of hypoglycemia. A healthy lifestyle and preventive efforts to control weight, blood pressure and dyslipidemia with statin therapy, together with, aspirin use, smoking cessation and physical activity, should be emphasized, thereby decreasing the undue burden on the patients and the healthcare system, and minimizing the harm of severe hypoglycemia associated with tight glycemic control [19].

In this special issue of *Therapy* on diabetes and cardiovascular outcomes, we present to our readers an assortment of articles that cover CVD risk reduction in a comprehensive, yet pragmatic, way. We invited world-renowned scholars in the field to contribute to this issue with their expertise, with articles emphasizing lifestyle intervention, antidiabetic medication safety and control of major CVD risk factors such as hypertension and dyslipidemia, especially in high-risk populations. Other articles provide insights into glycemic control and present a rational and evidence-based approach pertinent to specific populations such as those with acute myocardial infarction. Highlights include an article discussing a novel approach to the treatment of hyperglycemia as well as dyslipidemia with one medication, colesevelam, a bile acid sequestrant, presented as a viable option for the diabetic population by Drs Surampudi, Nagireddy and Fonseca [20]. A special report by Dr Farbstein and Dr Levy provides intriguing information exploring pharmacogenetic interactions in the treatment of diabetes and prevention of its complications, including CVD [21]. This helps explain the ineffectiveness, and perhaps the risk seen, with some antidiabetic therapies among certain patient populations. In addition, research highlights are presented by Brian Irons from the latest articles that are of high clinical relevance in diabetes and CVD outcomes [22].

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