CONCLUDING REMARKS

Current Knowledge and Future Directions on Cardiovascular Disease in Diabetes

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IN THE EDITORIAL INTRODUCING this supplement Dr. Satish Garg, Editor-in-Chief of *Diabetes Technology & Therapeutics*, and his co-authors highlight recent data on the global increases in diabetes and the two to four times increased burden of cardiovascular disease (CVD) on people with diabetes.¹ Although advances have been made in many aspects of diabetes care, CVD incidence continues to increase in diabetes, with a particularly worrisome increase in Asia.² Data on CVD risk reduction from landmark studies such as the Diabetes Control and Complications Trial and the United Kingdom Prospective Diabetes Study are reviewed as well as more recent studies on which best practice guidelines to reduce CVD are based.

Lemkes et al.³ have reviewed a relatively new area of investigation in CVD, the glycocalyx and, specifically, its role in CVD in diabetes. The glycocalyx is the layer of glycosylated proteins that forms a barrier between the endothelium and the blood flow. Its biochemistry, methods of assessment, and role in CVD pathophysiology in diabetes promise to be topics of important discoveries in vascular biology and specifically its role in CVD in diabetes.

Clinical events such as acute myocardial infarction (AMI) continue to be increased in diabetes, and Hirsch and O'Brien⁴ have reviewed current best practices for both glycemic and non-glycemic factors at the time of AMI. The authors have done an excellent examination of the literature highlighting the controversies in this area. The appropriate goal for glucose management in hospitalized patients has been an intense focus of research in the past decade. For people with diabetes a goal glucose range of 140–180 mg/dL using intravenous insulin is suggested to be a reasonable target, although a topic of ongoing debate. Non-glycemic-based therapy at the time of AMI in people with diabetes includes reperfusion therapy, antithrombotic therapy, and initiation of β -blockers. Future research advances may include continuous glucose monitoring and/or use of insulin pumps and closed loop systems as tools to target glucose control.

At the other end of the age spectrum, pediatric-specific issues with CVD in youth with diabetes are reviewed by Truong et al.⁵ While often underappreciated, the atherosclerotic process begins before adulthood, and the data suggest

that this is accelerated in youth with diabetes compared with youth without diabetes. Numerous practice guidelines for CVD care in youth with diabetes have been published in the past decade on the best available data and expert opinion, and uncertainty exists on therapy in this population.⁶ Differences exist in the clinical approach to CVD in pediatrics and are the focus of ongoing investigation. Truong et al.⁵ have reviewed recent advances in imaging modalities that promise to provide insight into the earliest stages of CVD pathophysiology.

Home⁷ reviewed CVD and oral agent glucose-lowering therapies in the management of type 2 diabetes and discussed the fact that although supporting evidence for a protective role of these agents in CVD outcomes is not robust, there is enough evidence to support a likely benefit. In this review, the evidence for protection against CVD outcomes for the various classes of oral glucose-lowering therapies, and for particular agents within each class, is discussed. Another new therapy in diabetes is reviewed by Lebovitz and Banerji⁸: non-insulin injectable treatments (glucagon-like peptide [GLP-1] and its analogs) and CVD. GLP-1 is a gut hormone with receptors present in many tissues, including myocardium and endothelium. Beneficial effects of GLP-1 on cardiac function and reduction of myocardial infarction extent have been reported, at least partially mediated through activation of the GLP-1 receptor. GLP-1 analogs are able to elicit similar beneficial CVD effects, and in this review Lebovitz and Banerji⁸ have discussed results from animal studies and clinical trials regarding the effect of the GLP-1 analogs exenatide and liraglutide on CVD risk factors.

Snell-Bergeon and Wadwa⁹ have discussed the importance of hypoglycemia, diabetes, and CVD. Although much of the research on CVD in diabetes has focused on hyperglycemia and its deleterious effects on the vasculature, hypoglycemia has become a greater concern as intensive glycemic control and lower glycosylated hemoglobin targets have been adopted. Clinical trials of glucose lowering have demonstrated no CVD benefit, but increased hypoglycemia. In this review, the physiologic effects, risk factors, and prevalence of hypoglycemia are discussed, evidence regarding association of hypoglycemia with CVD complications is reviewed, and

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potential mechanisms through which hypoglycemia may increase CVD risk are outlined.

A particularly important topic for global public health is that of the current burden to the emerging economies of the world due to diabetes and CVD. Pradeepa et al.¹⁰ have emphasized both the current and anticipated burden imposed by diabetes and CVD to developing economies, especially in Asia.² For example, it is estimated that 80% (291 of the 366 million) of the people with diabetes worldwide live in low- or middle-income countries with even more dramatic projections for the future. The diabetes and CVD epidemic presents an ongoing challenge for health infrastructures of developing countries and the opportunity to improve future global health.

Aschner and Ruiz¹¹ have reported on metabolic memory for vascular disease in diabetes and explained that while the concept of the “metabolic memory” refers to improvements in micro- and macrovascular complications for an extended period of time following improved glycemic control, it also refers to the harmful effects of hyperglycemia, some of which are permanent. Mechanisms through which hyperglycemia may exert long-term and irreversible damage are discussed, and clinical trial data demonstrating “metabolic memory” are described.

Both type 1 and type 2 diabetes are increasing in the United States and worldwide, with much of the global increase in Asia. CVD continues to be the leading cause of mortality in diabetes and research, and clinical efforts need to focus on improving outcomes, especially cost-effective interventions in developing economies. This supplement of *Diabetes Technology & Therapeutics* serves as a summary of recent updates in the field of CVD in diabetes with the goal of stimulating advances in the field.

References

1. Garg SK, DiDomenico D, Switzer S: Ways to reduce cardiovascular disease in diabetes. *Diabetes Technol Ther* 2012;14(Suppl 1):S-1–S-2.
2. Garg SK: Rising epidemic of diabetes and hypertension in Asia. *Diabetes Technol Ther* 2012;14:1–2.
3. Lemkes BA, Nieuwdorp M, Hoekstra JBL, Holleman F: The glycocalyx and cardiovascular disease in diabetes: should we judge the endothelium by its cover? *Diabetes Technol Ther* 2012;14(Suppl 1):S-3–S-10.
4. Hirsch IB, O'Brien KD: How to best manage glycemia and non-glycemia during the time of acute myocardial infarction. *Diabetes Technol Ther* 2012;14(Suppl 1):S-22–S-32.
5. Truong UT, Maahs DM, Daniels SR: Cardiovascular disease in children and adolescents with diabetes: where are we, and where are we going? *Diabetes Technol Ther* 2012;14(Suppl 1):S-11–S-21.
6. Maahs DM: Cardiovascular disease (CVD) limbo: how soon and low should we go to prevent CVD in diabetes? *Diabetes Technol Ther* 2012;14:449–452.
7. Home P: Cardiovascular disease and oral agent glucose-lowering therapies in the management of type 2 diabetes. *Diabetes Technol Ther* 2012;14(Suppl 1):S-33–S-42.
8. Lebovitz HE, Banerji MA: Non-insulin injectable treatments (glucagon-like peptide-1 and its analogs) and cardiovascular disease. *Diabetes Technol Ther* 2012;14(Suppl 1):S-43–S-50.
9. Snell-Bergeon JK, Wadwa RP: Hypoglycemia, diabetes, and cardiovascular disease. *Diabetes Technol Ther* 2012;14(Suppl 1):S-51–S-58.
10. Pradeepa R, Prabhakaran D, Mohan V: Emerging economies and diabetes and cardiovascular disease. *Diabetes Technol Ther* 2012;14(Suppl 1):S-59–S-67.
11. Aschner PJ, Ruiz AJ: Metabolic memory for vascular disease in diabetes. *Diabetes Technol Ther* 2012;14(Suppl 1):S-68–S-74.

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