Getting to the "Heart" of the Matter on Diabetic Cardiovascular Disease: "Thanks for the Memory"

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Despite improved understanding of the pathogenesis of diabetes and the release of impressive new medications to control the condition, there remains a significant global diabetes burden. The latest International Diabetes Federation estimates indicate that 415 million (1 in 11 persons) have diabetes, and this will increase to 642 million or almost 10% of the general population by 2040 (1). Indeed, there are great individual, societal, and economic costs associated with diabetes. These costs clearly relate to the microvascular complications, which include retinopathy, nephropathy, and neuropathy, that have been attenuated by better glycemic control and macrovascular complications that are relatively abated by better lipid and blood pressure control. However, for individuals with diabetes, cardiovascular disease (CVD) remains the main problem. Diabetes and CVD are closely linked, and CVD remains the most prevalent cause of morbidity and mortality in both men and women with diabetes (2). Specifically, the relative risk for CVD morbidity and mortality in adults with diabetes ranges from 1 to 3 in men and from 2 to 5 in women compared with those without diabetes (3). Given the issues facing individuals with both diabetes and CVD, we urgently need effective evidence-based interventional strategies to reduce cardiovascular risk and improve outcomes.

With the aim of advancing toward this challenging goal, our editorial team is featuring in the present issue of *Diabetes Care* a collection of articles that may help to clarify the mechanisms linking diabetes to CVD. These articles comment on the control of risk factors and biomarkers for CVD and provide new updates on outcomes of landmark studies. In addition, we have included commentaries on cardiovascular safety of newer diabetes drugs and provide insights on mechanisms of action for cardioprotection observed with some new agents (4–13).

The need to control risk factors for CVD (lipids, blood pressure, and glucose) to reduce harmful events is no longer in question. There are adequate guidelines for suggested targets for each risk factor. Whereas the effects of controlling individual risk factors may be well known, more information is needed on the value of multifactorial risk factor control. On this topic, Wong et al. (4) pooled data from three large cohort studies. They evaluated 2,018 adults with diabetes but without prior CVD from the Atherosclerosis Risk in Communities (ARIC) study, the Multi-Ethnic Study of Atherosclerosis (MESA), and the Jackson Heart Study (JHS) (4). They examined the risk of coronary heart disease (CHD) and CVD events over 11 years for those at target for blood pressure, LDL cholesterol (LDL-C), and HbA_{1c} and in relation to the number of these factors that were adequately controlled. They found that individuals who had one, two, or all three risk factors at target (versus none at target) had incrementally lower risks of CVD and CHD events. An important observation is that levels of blood pressure, LDL-C, and HbA_{1c} were not often controlled at the same time. However, the best outcomes occurred when all risk factors were controlled. Clearly this report supports a comprehensive approach to CVD prevention.

Traditional risk factors may not tell the whole story, and given the heterogeneity of CVD risk in diabetes, we need additional markers that may allow stratification of risk. In this regard, Gori et al. (5) evaluated data from the ARIC study. They asked whether circulating cardiac biomarkers, such as N-terminal prohormone brain natriuretic peptide (NTproBNP) and high-sensitivity troponin T, enhance CVD risk stratification beyond what is possible with commonly used markers. Over a median follow-up of 13.1 years,

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the investigators showed that both troponin T >14 ng/L and NTproBNP >125 pg/mL were independent predictors of incident CVD events and provided additional ability to predict risk. These biomarkers need to be tested in future randomized cardiovascular outcome trials.

The value of intensified glycemic control early in the course of diabetes appears to be demonstrable only after long-term observation. Such a durable effect on complications from prior improvements of metabolic control has been termed "metabolic memory" or "legacy effect" (14). The concept appears to be applicable to all of the microvascular complications, and the metabolic benefit has been reported to persist for at least 10 years. Specifically, major beneficial effects of improved glycemic control in the Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) were demonstrated for retinopathy, nephropathy (reduced glomerular filtration rate), and autonomic manifestations of neuropathy (14). In addition, it also appears that this concept is applicable to macrovascular complications as assessed using measures showing less atherosclerosis when assessed as carotid intima-media thickness and computed tomography–measured coronary artery calcification (14). Further, it was reported that fatal and nonfatal myocardial infarctions and stroke were also reduced by the intensive glycemic management in DCCT, with a 58% reduction in CVD events after a mean of 18 years of follow-up from the beginning of the DCCT (14).

In this issue of *Diabetes Care*, we present additional reports of long-term observation following three landmark studies (DCCT/EDIC, Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation [ADVANCE], and Action to Control Cardiovascular Risk in Diabetes [ACCORD]) that further illuminate the concept of "metabolic memory." In the first of these studies, Gubitosi-Klug et al., reporting on behalf of the DCCT/EDIC investigators, assessed whether intensive therapy as compared with conventional therapy for 6.5 years in the DCCT affected the incidence of CVD after 30 years of observation (6). The group on intensive therapy initially had a 30% lower incidence of any CVD and a 32% lower incidence of major adverse cardiac events (MACE) (nonfatal myocardial infarction, stroke, or cardiovascular death). The investigators reported that the lower HbA_{1c} levels during the DCCT/EDIC statistically accounted for essentially all of the observed treatment effect. Thus, intensive glucose-lowering insulin therapy during the DCCT had long-term beneficial effects on CVD risk for more than 20 years after cessation of the more intensive intervention.

Wong et al. (7) comment on the long-term effects of intensive glucose control on the risk of end-stage kidney disease (ESKD) and other outcomes in the ADVANCE-ON follow-up to the ADVANCE trial, which studied high-risk patients quite early in the course of type 2 diabetes. They reported that intensive glucose control based on the sulfonylurea gliclazide for extended years during ADVANCE was associated with a long-term reduction in ESKD without evidence of any increased or decreased risk of cardiovascular events or death. These benefits were greater in those with preserved kidney function and well-controlled blood pressure. However, no intrinsic effects could be directly attributed to the specific sulfonylurea.

Gerstein et al. (8) report on the long-term follow-up of the ACCORD trial, which enrolled a population with both high cardiovascular risk and long duration of type 2 diabetes. In ACCORD, a mean of 3.7 years of intensive glycemic control had a neutral effect on the main composite cardiovascular end point, but an increase of all-cause and cardiovascular mortality led to early discontinuation of the randomized glycemic comparison. However, retinopathy and other microvascular end points showed improvement at that cut-off time. Notably, after a mean of 9 years of observation, all-cause mortality was no longer significantly increased. The excess of cardiovascular mortality was also attenuated during follow-up but remained statistically significant. The investigators suggest that for people with well-established type 2 diabetes and additional cardiovascular risk factors the main benefits of intensive glycemic control are noncardiovascular, but this conclusion may not be generalizable because of the extremely intensive glucose-lowering intervention in ACCORD.

Finally, the investigators from the Outcome Reduction With Initial Glargine Intervention (ORIGIN) trial report on its long-term observation study (ORIGIN and Legacy Effects [ORIGINALE]) (9). As previously reported, ORIGIN found neutral effects of 6.2 years of treatment with insulin glargine, as compared with standard oral step-therapy, on cardiovascular outcomes and cancers in a population with dysglycemia (12%) or early type 2 diabetes (88%), together with high cardiovascular risk. Both groups were successful in achieving near-normoglycemia with slightly better control in the insulin glargine group. There was also a reduction of incident diabetes in the previously dysglycemic participants who were randomized to glargine treatment, but that was not the key message of the study. ORIGIN fundamentally demonstrated cardiovascular neutrality of insulin glargine. The ORIGINALE study contribution was to show no further posttrial effects of these interventions that remained consistent during an additional 2.7 years.

Taken together, data from the long-term observational studies in this issue of *Diabetes Care* further support the concept of a "legacy effect" of early glucose-lowering treatment. That is, they suggest that intensive glycemic control early in the natural history of diabetes, at a time when CVD is not established, can reduce later CVD. However, this effect may be evident only after 10 or more years of follow-up, and studies of less than 10 years of duration may not be sufficient to determine whether an intervention has such a protective effect. The reports are also consistent with the view that once advanced CVD is present, intensive glucose lowering may not reduce cardiovascular risk. However, the BI 10773 (Empagliflozin) Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients (EMPA-REG OUTCOME) may seem to contradict such a notion.

Indeed, DeFronzo and colleagues comment in this issue of *Diabetes Care* (10) on the implications of the findings from the EMPA-REG OUTCOME trial, which showed dramatic and surprising cardiovascular benefit from treatment with empagliflozin. As well known, empagliflozin inhibits sodium–glucose cotransporter 2 (SGLT2), and in EMPA-REG OUTCOME its cardiovascular safety was tested in a population of patients with type 2 diabetes at high cardiovascular risk no different from that of the population in the

Trial Evaluating Cardiovascular Outcomes With Sitagliptin (TECOS), which showed no cardiovascular benefit (15). The study clearly demonstrated that empagliflozin reduced the primary MACE end point (cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke) by 14%. There was a 38% reduction in cardiovascular mortality with no significant decrease in nonfatal myocardial infarction or stroke and a 35% reduction in hospitalization for heart failure without affecting hospitalization for unstable angina (13,15). The authors felt that it was unlikely that the reduction in cardiovascular mortality could be explained by empagliflozin's glycemic or weight effects but rather by its fluid balance and hemodynamic effects, specifically decreased extracellular volume and reduced blood pressure (10). Again, this still may not be enough to explain the impressive cardiovascular benefits of empagliflozin.

Our final articles in this cardiovascular collection for this issue of *Diabetes Care* center on the cardiovascular safety of currently available agents and the U.S. Food and Drug Administration (FDA) requirements for drug makers to demonstrate cardiovascular safety for all new antihyperglycemic medications. Specifically, Fu et al. (11) in a retrospective observational study compared the risk of hospitalization for heart failure between patients with type 2 diabetes treated with dipeptidyl peptidase 4 (DPP-4) inhibitors versus sulfonylureas and between those treated with saxagliptin versus sitagliptin. The report included 218,556 patients in comparisons of DPP-4 inhibitors and sulfonylureas and 112,888 in comparisons of saxagliptin and sitagliptin. The authors concluded that in patients with type 2 diabetes, there was no evidence of increased risk of heart failure or other selected cardiovascular end points for DPP-4 inhibitors relative to sulfonylureas or for saxagliptin relative to sitagliptin. In a very thoughtful commentary to the observation study, Filion and Suissa (12) state that the study by Fu et al. "provides some welcome reassurance regarding the [heart failure] risk of DPP-4 inhibitors." However, they also add that "to impart actual real-world data, such observational studies should ideally strive to evaluate the full spectrum of users of these drugs, not only the treatment-naïve ones." Finally, in a perspective on the FDA requirements to assess cardiovascular safety of new antihyperglycemic medications, Smith et al. (13) report that to date, 17 large, prospective, randomized, controlled post-approval clinical trials (involving approximately 140,000 subjects) have been completed or are ongoing in accordance with a recent FDA Guidance. At this time, five of the completed trials (involving three different drug classes) have been successful in excluding an unacceptable level of ischemic cardiovascular risk. However, one trial suggested an increased risk of hospitalization for heart failure, whereas another showed improved cardiovascular mortality and decreased hospitalization for heart failure. Smith et al. provide a thoughtful analysis supporting the view, based on the evidence to date, that we need "to consider a more targeted approach to what is, in effect, a global cardiovascular safety trial requirement for all new type 2 diabetes medications in development."

As can be appreciated, the present issue of *Diabetes Care* provides a wide-ranging group of articles addressing CVD in diabetes. It is clear that our understanding of the field and data supporting clinical recommendations has grown tremendously in the recent past and is likely to continue to do so. Once again, the *Diabetes Care* editorial team is extremely honored to disseminate to our readers these excellent articles specifically focused on a highly relevant translational theme, in this case efforts to reduce heart disease. We believe that these articles, along with other recent reports, are helping to solve some of the mysteries about CVD in those with diabetes. If indeed the time of hyperglycemic exposure and the legacy effects of either poor or good glycemic control are major contributors, we may be able to improve treatment guidelines. By emphasizing early diagnosis and timely glycemic control, we may harness a protective metabolic memory to limit the development of CVD. At the same time, insights derived from the EMPA-REG OUTCOME observations may allow interventions later in the course of diabetes that are based on glycemic and nonglycemic effects to protect against end-stage events such as congestive heart failure and arrhythmias.

As always, our goal is to stimulate thinking that will assist both clinical care and research efforts. We hope that this will be accomplished by featuring the concept of "metabolic memory." To summarize in a few words what this special issue of *Diabetes Care* seeks to convey, we draw from a song that won the Oscar for Best Original Song in 1938 and became Bob Hope's theme for the rest of his career: "Thanks for the memory!"

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References

1. International Diabetes Federation. IDF Diabetes Atlas -7th Edition [Internet], 2015. Brussels, Belgium, International Diabetes Federation. Available from http://www.diabetesatlas.org/. Accessed 20 February 2016
2. Matheus AS, Tannus LR, Cobas RA, Palma CC, Negrato CA, Gomes MB. Impact of diabetes on cardiovascular disease: an update. Int J Hypertens 2013;2013:653789
3. Rivellese AA, Riccardi G, Vaccaro O. Cardiovascular risk in women with diabetes. Nutr Metab Cardiovasc Dis 2010;20:474–480
4. Wong ND, Zhao Y, Patel R, et al. Cardiovascular risk factor targets and cardiovascular

disease event risk in diabetes: a pooling project of the Atherosclerosis Risk in Communities Study, Multi-Ethnic Study of Atherosclerosis, and Jackson Heart Study. Diabetes Care 2016; 39:668–676
5. Gori M, Gupta DK, Claggett B, et al. Natriuretic peptide and high-sensitivity troponin for cardiovascular risk prediction in diabetes: the Atherosclerosis Risk in Communities (ARIC) study. Diabetes Care 2016;39:677–685
6. Diabetes Control and Complications Trial (DCCT)/Epidemiology of Diabetes Interventions and Complications (EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular outcomes in type 1 diabetes: the DCCT/EDIC study 30-year follow-up. Diabetes Care 2016;39:686–693
7. Wong MG, Perkovic V, Chalmers J, et al.; ADVANCE-ON Collaborative Group. Long-term benefits of intensive glucose control for preventing end-stage kidney disease: ADVANCE-ON. Diabetes Care 2016;39:694–700
8. ACCORD Study Group. Nine-year effects of 3.7 years of intensive glycemic control on cardiovascular outcomes. Diabetes Care 2016;39: 701–708
9. ORIGIN Trial Investigators. Cardiovascular and other outcomes postintervention with insulin glargine and omega-3 fatty acids (ORIGINALE). Diabetes Care 2016;39:709–716
10. Abdul-Ghani M, Del Prato S, Chilton R, DeFronzo RA. SGLT2 inhibitors and cardiovascular risk: lessons learned from the EMPA-REG OUTCOME study. Diabetes Care 2016;39:717–725
11. Fu AZ, Johnston SS, Ghannam A, et al. Association between hospitalization for heart failure and dipeptidyl peptidase 4 inhibitors in patients with type 2 diabetes: an observational study. Diabetes Care 2016;39:726–734
12. Filion KB, Suissa S. DPP-4 inhibitors and heart failure: some reassurance, some uncertainty. Diabetes Care 2016;39:735–737
13. Smith RJ, Goldfine AB, Hiatt WR. Evaluating the cardiovascular safety of new medications for type 2 diabetes: time to reassess? Diabetes Care 2016;39:738–742
14. Nathan DM; DCCT/EDIC Research Group. The Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications Study at 30 years: overview. Diabetes Care 2014;37:9–16
15. Zinman B, Wanner C, Lachin JM, et al.; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med 2015;373: 2117–2128