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In This Issue of *Diabetes Care*

By Max Bingham, PhD

Diabetes Is Directly Linked to Risk of Death and Hospitalization in Patients With Chronic Heart Failure

The presence of diabetes per se may substantially increase the risk of adverse clinical outcomes in patients with coexisting heart failure. The conclusion, reported by Dauriz et al. (**p. 671**), follows a prospective assessment of a large cohort of outpatients (*n* = 9,500) with chronic heart failure and suggests that diabetes status independently affects 1-year risk of all cause and cardiovascular disease mortality as well as first hospitalization rates for heart failure. While suspected for over a decade, conclusive evidence for a direct relationship between diabetes and survival outcomes in patients with chronic heart failure has been beset with conflicting or inconclusive data. The authors report that compared to patients without diabetes, the patients with diabetes had ~30% increased risk of death when coupled with chronic heart failure, which was independent of many known risk factors for heart disease. They note that the findings could impact routine clinical practice since the identification of patients that have had heart failure and concurrent diabetes might facilitate better care practices, and particularly that a cross team–based approach toward their care might be beneficial. The authors suggest that in the context of global estimates of increased life expectancy—but also in an era of reducing health care budgets—the apparent prognostic value of a diabetes diagnosis might well result in better care for these patients. Commenting more widely on the study, author Aldo P. Maggioni told *Diabetes Care*: "The management of comorbidities, such as diabetes mellitus, in patients with heart failure is essential if we want to contain the total, clinical, and also the economic burden related to this clinical syndrome. The worse outcomes of patients with coexisting diabetes and heart failure have been confirmed by this analysis, conducted by the European Society of Cardiology, including patients followed by cardiologists in a large number of European countries. A multidisciplinary approach and novel therapeutic strategies are needed to improve the outcomes of these very high–risk patients."

Dauriz et al. Association between diabetes and 1-year adverse clinical outcomes in a multinational cohort of ambulatory patients with chronic heart failure: results from the ESC-HFA Heart Failure Long-Term Registry. Diabetes Care 2017;40:671–678

Cardiac Arrhythmia Due to Hypoglycemia Varies According to Time of Day

Significant differences in heart rate variation due to hypoglycemia associated with type 1 diabetes may exist depending on whether episodes occur at night or during the day, according to Novodvorsky et al. (**p. 655**). The authors suggest that their findings may help to explain the rare but devastating condition known as the "dead-in-bed syndrome" but more importantly point toward hypoglycemia being proarrhythmogenic (i.e., that it promotes potentially dangerous changes in heart rate). The study involved 37 relatively young individuals with type 1 diabetes who underwent 96 h of continuous electrocardiogram (ECG) monitoring and also blinded continuous glucose monitoring (CGM). Frequencies of arrhythmias, heart rate variability, and cardiac repolarization were then assessed to compare characteristics during the day and night. Novodvorsky et al. report that out of ~2,400 h of continuous ECG and CGM recordings, 159 h were considered to be hypoglycemic episodes of which half were symptomatic during the day and only 25% were symptomatic during the night. At night, episodes were longer and characterized by more bradycardia (very low heart rates) than during periods of euglycemia. Bradycardia was also less frequent during the day. Hypoglycemia also resulted in various changes in ECG wave characteristics, which the authors suggest when taken together point toward hypoglycemia being proarrhythmogenic. According to the authors, various factors might affect the responses including a possible influence of body position. They say that in some cases there may be clinical implications because prolonged exposure to hypoglycemia and associated arrhythmias may be highly individual in terms of responses and therefore risk. According to author Simon R. Heller: "Thankfully the dead-in-bed syndrome is pretty rare—but shattering when it occurs. Our data support the belief that these deaths are due to cardiac arrhythmias. Importantly, we found that only a few individuals developed bradycardia raising the possibility that we might be able develop a screening test and identify those at risk."

Novodvorsky et al. Diurnal differences in risk of cardiac arrhythmias during spontaneous hypoglycemia in young people with type 1 diabetes. Diabetes Care 2017;40:655–662

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Maternal Hyperglycemia During Pregnancy Is Linked to Later Cardiometabolic Risks in Offspring

Children born to mothers who experienced gestational diabetes mellitus (GDM) during pregnancy are likely at risk for a range of cardiometabolic abnormalities by 7 years of age. This is at least according to a reevaluation of the HAPO (Hyperglycemia and Adverse Pregnancy Outcome) Chinese cohort by Tam et al. (**p. 679**). They now suggest there needs to be an emphasis put on the follow-up of both mothers who had GDM during pregnancy and their offspring, especially because young-onset diabetes and premature complications are now rampant in Asia. The study followed up on 970 mother-child pairs at 7 years after the birth of the child to assess a series of cardiometabolic risk factors in the children. The assessments also included oral glucose tolerance tests. In comparison to children born to mothers with normal glucose tolerance, the children that were born to mothers that suffered from GDM had higher rates of abnormal glucose tolerance, were overweight or had obesity, and had higher blood pressure (among a range of many other factors). There was also a trend toward reduced β-cell function, hinting that prediabetes might already be present. The glucose associations uncovered in the analysis were independent of maternal BMI prior to pregnancy, being born large for gestational age, or the presence of childhood obesity. Maternal hyperglycemia also increased the risk of being overweight or having obesity at 7 years of age, independent of maternal BMI prior to pregnancy. Accordingly, the authors are concerned that residual risk apparent in these children might remain into adolescence and adulthood thereby potentially fueling the wider increases in diabetes in the Asian region. A multicenter follow-up is reportedly underway in most of the original HAPO centers to assess the fuller impact and risk from GDM on the younger generation. Author Wing-Hung Tam reported that: "Given the long-term consequences of gestational diabetes mellitus, it is justifiable for universal screening in pregnancy to identify these high-risk women."

Tam et al. In utero exposure to maternal hyperglycemia increases childhood cardiometabolic risk in offspring. Diabetes Care 2017;40:679–686

A Direct Link Between Genetically Elevated Blood Glucose and Risk of Coronary Disease

A genetic predisposition to hyperglycemia may raise the odds of coronary artery disease risk, independent of other risk factors, including type 2 diabetes. According to Merino et al. (**p. 687**), this suggests that lowering glucose levels might prove beneficial for cardiovascular health—even in individuals without diabetes. Taking in genomic data from hundreds of thousands of individuals, the authors identified (via a Mendelian randomization approach) a range of genetic variants that were associated with increased fasting blood glucose. After excluding variants that were known to be associated with type 2 diabetes, they were left with a set of 12 variants that raised fasting glucose without increasing type 2 diabetes risk. Indeed, for every 1 mmol/L increase in blood glucose there was reportedly an increase in coronary artery disease risk odds of 43%. Even after accounting for variants with pleiotropic/heterogeneous effects on other risk factors for coronary artery disease (blood lipids, blood pressure, and obesity), the relationship stood firm conferring ~33% increased risk for the disease. While the study could not explore any mechanisms of action due to the design, the authors suggest that their observations fit well with data on a potential link between levels of blood glucose and structural changes in arterial walls (i.e., atherosclerosis). Consequently, they say that a lifetime exposure to elevated blood glucose may well be enough to have detrimental effects in terms of cardiovascular disease, irrespective of the presence of type 2 diabetes. Author Jose C. Florez said: "Our study uses genetic means to resolve an ongoing controversy of whether addressing glycemia has cardiovascular benefit. Randomized controlled trials of intensive glucose control in type 2 diabetes have not been conclusive. Here, we provide evidence in support of glucose as an independent cardiovascular risk factor; the corollary is that glucose lowering would be beneficial in preventing coronary artery disease outcomes."

Merino et al. Genetically driven hyperglycemia increases risk of coronary artery disease separately from type 2 diabetes. Diabetes Care 2017;40:687–693

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