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Diabetes Care

In This Issue of *Diabetes Care*

Edited by Helaine E. Resnick, PhD, MPH

Equal CAD Risk in Diabetic Men and Women Under the Age of 60 Years

A new report that examines longitudinal data from three large prospective studies concludes that although the rates of coronary artery disease (CAD) are higher in nondiabetic men under the age of 60 years than in similarly aged women, there is equal risk of CAD in both sexes when diabetes is present. The study's results raise fundamental questions about certain sex-specific clinical practice guidelines—such as aspirin therapy—that tend to be more aggressive for primary CAD prevention in men than in women. The new report in this issue of *Diabetes Care* (**p. 830**) focuses on the interaction of sex and diabetes on CAD risk in more than 11,500 men and women aged ≤60 years. Follow-up of these cohorts, which had different underlying CAD risk, averaged between 7 and 15 years, and 54% of all participants were female. Among nondiabetic people across the three cohorts, unadjusted CAD event rates were higher among men than women, but the rates were similar when diabetes was present. The absence of significant differences in CAD risk by diabetes status among men reflected their higher levels of CAD risk regardless of diabetes, even in the younger age-groups. In contrast, diabetic women in each cohort had CAD rates that were 4–5 times higher than in their nondiabetic counterparts—results that consistently showed the impact of diabetes on CAD risk among younger women. These results were remarkably consistent across the cohorts despite differences in underlying risk. Analyses that combined data from the three cohorts and adjusted results for demographic and cardiovascular disease risk factors indicated that in the absence of diabetes, men were 2.43 (95% CI 1.76–3.35) times more likely than women to have a CAD event, but the data showed no sex difference in CAD risk (0.89 [95% CI 0.43–1.83]) when diabetes was present. These findings suggest that when applied to people under the age of 60 years, sex-specific CAD prevention guidelines that favor more aggressive treatment in diabetic men may be ignoring meaningful prevention opportunities for younger women. — *Helaine E. Resnick, PhD, MPH*

Kalyani et al. Sex differences in diabetes and risk of incident coronary artery disease in healthy young and middle-aged adults. Diabetes Care 2014;37:830–838

Arterial Stiffening and Hyperfiltration in Type 1 Diabetic Adolescents With Elevated (but Normal) ACR

Although there are compelling data indicating that screening and interventions targeting albumin excretion in type 1 diabetes (T1D) may favorably impact long-term cardiovascular risk, the association between early rises in albumin excretion and concurrent changes in cardiovascular disease risk factors is poorly understood. New findings in this issue of *Diabetes Care* (**p. 805**) indicate that T1D adolescents with elevated albumin-to-creatinine ratios (ACRs) that are still in the normal range have unfavorable biochemical and vascular profiles. The new data are from a subset of participants who took part in the baseline examination of AdDIT, a multicenter clinical trial of statin/ACE inhibitor treatment in adolescents with T1D. Eligible children aged 10–16 years with T1D were first grouped into tertiles of ACR, and then 400 in the highest ACR tertile were enrolled in the trial cohort and another 329 who were in the middle and lower ACR tertiles were enrolled into the observational cohort. The median ACRs across the three tertiles were 0.52, 0.71, and 1.24, indicating that even in the highest tertile ACR was in the normal range. The investigators conducted an extensive cross-sectional examination of baseline data with a focus on carotid intima-media thickness, pulse wave velocity (PWV), tonometry, as well as renal function and metabolic measures. Key findings included data showing that a number of measures were significantly less favorable in the trial cohort children relative to their observational cohort counterparts. These included PWV, non-HDL cholesterol, ApoB/ApoA-1 ratio, creatinine, and estimated glomerular filtration rate—all suggesting that T1D adolescents in the highest ACR tertile have early evidence of arterial stiffening, hyperfiltration, and lipid abnormalities. Given these baseline data, future results of the AdDIT may provide useful guidance for clinicians in their efforts at early and effective treatment of adolescents with T1D. — *Helaine E. Resnick, PhD, MPH*

Marcovecchio et al. Adolescent Type 1 Diabetes Cardio-Renal Intervention Trial (AdDIT): urinary screening and baseline biochemical and cardiovascular assessments. Diabetes Care 2014;37:805–813

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Intensive Glucose Lowering Associated With Higher Cardiovascular Mortality in Younger Versus Older Adults

New data in this issue of *Diabetes Care* (**p. 634**) shed light on the complex issues surrounding both the safety and clinical benefits of intensive glucose lowering in older adults. A tertiary analysis from the glycemic portion of the ACCORD trial, a randomized trial focusing on the impact of intensive glucose lowering (A1C target of <6%) on cardiovascular end points, explored the response of older and younger participants to allocation to the intensive treatment arm. Of the 10,251 type 2 diabetic patients in ACCORD, 6,776 were aged <65 years and 3,475 were aged ≥65 years at the time of randomization. The new analyses showed that both older and younger ACCORD participants who were allocated to the intensive control group attained similar levels of glycemic control—about 6.4%—indicating that age was not related to participants' ability to achieve this target. Although severe hypoglycemia occurred with about three times greater frequency among both older and younger participants who were allocated to intensive relative to standard control, within both treatment arms, older adults experienced higher absolute rates of serious hypoglycemia. With the exception of cardiovascular mortality, an outcome for which younger participants who were allocated to the intensive control arm had significantly higher event rates, none of the other eight outcomes showed an interaction between age and intensive treatment. These findings add to a growing literature supporting the importance of including older adults in major trials and underscore the importance of individualizing glucose-lowering therapy in older adults. — *Helaine E. Resnick, PhD, MPH*

Miller et al. Effects of randomization to intensive glucose control on adverse events, cardiovascular disease, and mortality in older versus younger adults in the ACCORD trial. Diabetes Care 2014;37:634–643

Intranasal Insulin May Aid Diabetes-Associated Cognitive Decline

This issue of *Diabetes Care* features a report (**p. 751**) suggesting that administration of intranasal insulin may eventually be a safe and effective means for improving diabetes-associated cognitive decline in older adults. The new report explored the acute effects of intranasal insulin on perfusion, vasoreactivity, and cognition in a randomized, crossover study of 29 older adults with and without type 2 diabetes. This proof-of-concept study involved comparing a variety of imaging studies and neuropsychological tests among intervention participants who received 40 IU of intranasal insulin and control subjects who received an equal volume of saline. Baseline measurements indicated expected trends in the diabetic compared with nondiabetic groups: Diabetic individuals had less favorable measures of verbal learning, processing speed, and executive function, and they also had lower gray matter volume. Postintervention data showed good tolerance for the intranasal insulin, no adverse events, and no impact on systemic glucose levels. Beyond these early indications suggesting this therapy may be safe in both diabetic and nondiabetic individuals, the new report also offered preliminary data hinting at the potential future benefit of this intervention on cognition. In all participants, both visual memory and verbal fluency improved with intranasal insulin relative to placebo. Changes in regional perfusion and vasoreactivity were also observed, particularly in the area of the middle cerebral artery (MCA), which contains key areas for learning, memory, and language. Although these measures were less favorable among diabetic participants at baseline, intranasal insulin resulted in significantly improved perfusion in the right insular cortex among these participants, and the improvements were more pronounced among diabetic individuals compared with their nondiabetic counterparts. Importantly, in the cohort as a whole, performance on neurocognitive testing was associated with improved perfusion and vasodilation in the MCA area. Although the authors caution that insulin versus placebo differences within the diabetic and nondiabetic groups were not significant due to small sample sizes, these findings suggest that continuing this line of investigation may shed light on novel approaches to treatment of diabetes-associated cognitive decline. — *Helaine E. Resnick, PhD, MPH*

Novak et al. Enhancement of vasoreactivity and cognition by intranasal insulin in type 2 diabetes. Diabetes Care 2014;37:751–759

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