News & Views

Research Highlights

Highlights from the latest articles in diabetes & cardiovascular disease

Fenofibrate effects on cardiovascular outcomes in patients with diabetes and metabolic syndrome

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Evaluation of: Scott R, O'Brien R, Fulcher G *et al.*: Effects of fenofibrate treatment on cardiovascular disease risk in 9795 individuals with Type 2 diabetes and various components of the metabolic syndrome. *Diabetes Care* 32(3), 493–498 (2009).

The role of statin therapy in reducing cardiovascular disease (CVD) outcomes in patients with diabetes is well documented. The benefit of fibrate therapy in this population is less clear. While fibrate therapy helps to improve elevated triglyceride levels and depressed high-density lipoprotein cholesterol (HDL-C) concentrations, a common scenario in diabetes, their effects on reducing cardiovascular events in patients with diabetes has been mixed [1–3]. In 2005, results of the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study were published [4]. This randomized, placebo-controlled study evaluated whether fenofibrate reduces coronary events specifically in patients with Type 2 diabetes mellitus originally not receiving statin therapy. After 5 years of follow-up, the trial failed to demonstrate a significant reduction in its primary combined outcome of nonfatal myocardial infarction (MI) and death from coronary heart disease. It did, however, demonstrate a 24% relative reduction in nonfatal MI (p = 0.010), but a nonsignificant 19% increase in coronary heart disease mortality.

In a recent *post-hoc* analysis of the FIELD study, investigators evaluated whether there is a risk reduction in cardiovascular outcomes in study participants who also had metabolic syndrome [5]. Metabolic syndrome was determined to be present if the subject had at least two other features of the syndrome (hypertension, low HDL-C, elevated triglycerides or increased waist circumference) in addition to their diabetes. With the exception of waist circumference, each metabolic syndrome risk factor, in addition to diabetes, increased CVD event rates. Not surprisingly, more than 80% of study participants had metabolic syndrome. In this population, fenofibrate therapy failed to significantly reduce the 5-year CVD risk compared with placebo (adjusted hazard ratio [HR]: 0.89; 95% CI: 0.0–0.79, p = 0.052). In subjects with elevated triglyceride levels (≥2.3 mmol/l, 204 mg/dl) or with both elevated triglyceride levels and reduced HDL-C, the 5-year CVD risk was reduced by 23% (p = 0.010) and 27% (p = 0.005), respectively. It should be noted that the baseline low-density lipoprotein cholesterol (LDL-C) and triglyceride concentrations were not markedly elevated. The study demonstrated a 5.8% decrease in LDL-C and a 22% decrease in triglycerides. HDL-C increased by 1.2% at study completion.

This *post-hoc* analysis did not provide any additional evidence on the true role of fibrates in the treatment of dyslipidemia in patients with diabetes. While the FIELD study is the first to specifically assess the use of fenofibrate in patients with diabetes and, in the case of this *post-hoc* analysis, in those also with metabolic syndrome, reductions in clinical outcomes are modest at best, and found only in select patient groups. Given its large at-risk patient population and duration of follow-up, the results provide only a glimpse of the role of fenofibrate in reducing outcomes. The population studied did not

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have significantly elevated triglycerides or LDL-C, or markedly low HDL-C. In fact, their baseline lipid characteristics are not drastically different to other studies assessing the effects of statins in patients with diabetes [6,7]. The use of statins in this population has demonstrated significant reductions in cardiovascular events. Perhaps this *post-hoc* analysis best highlights the patient population that could potentially benefit from fenofibrate in patients who cannot tolerate statin therapy. Further research is required to better elucidate the role fibrate therapy may have in reducing cardiovascular outcomes in patients with diabetes.

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Is there an association between post-admission glucose concentrations and mortality in acute myocardial infarction?

Evaluation of: Kosiborod M, Inzucchi S, Krumholz H *et al.*: Glucose normalization and outcomes in patients with acute myocardial infarction. *Arch. Intern. Med.* 169(5), 438–446 (2009).

Admission hyperglycemia has been associated with an increased risk for hospital mortality rates in patients experiencing an acute myocardial infarction (AMI) [1]. It has also been demonstrated to be predictive of long-term mortality risk in patients with AMI with or without diabetes [2]. Despite these associations, the literature is conflicting regarding the benefits of acutely treating hyperglycemia in patients experiencing an AMI [3–5]. Some studies have demonstrated improved mortality with aggressive treatment of hyperglycemia, while others have not. This may be owing to different research designs, recruitment/power issues and difficulties obtaining proposed glycemic goals.

Kosiborod and colleagues attempted to discern if glycemic control after hospital admission for AMI is associated with mortality rates in subjects with admission hyperglycemia (defined as ≥110 mg/dl) [6]. This retrospective study utilized data from a large AMI database collected from 40 US hospitals. The authors further wished to define which post-admission glucose levels were associated with the lowest risk for mortality, and whether the use of insulin had an effect on the association. Nearly half of the 7820 patients studied had a diagnosis of diabetes mellitus, and 39% received insulin therapy during their hospital stay. After adjusting for various comorbidities, procedures, demographic factors and admission glucose concentration, the authors used multivariable logistic regression, and found the odds ratio for in-patient mortality increased with increasing post-admission glucose concentrations. When compared with those with glucose levels below 110 mg/dl, levels of 110 to less than 140, 140 to less than 170, 170 to less than 200, or 200 mg/dl and above, had mortality odds ratios of 2.1, 5.3, 6.9 and 13.0, respectively (all statistically significant). The results did not differ significantly according to whether or not the patient had a previous diagnosis of diabetes. The results also did not differ according to whether glucose reductions occurred spontaneously or by insulin therapy. Another interesting discovery was that admission glucose levels no longer predicted mortality after controlling for post-admission glucose. The authors also discerned what glucose range may be an optimal goal during AMI by assessing the mortality odds ratio for every 10 mg/dl of glucose above 70 mg/dl. They suggest that 80–130 mg/dl may be optimal.

This study adds to the current literature in helping to insert yet another piece to the puzzle regarding the benefit of treating hyperglycemia in AMI. Their data suggests it may be important to reduce glucose concentrations to near-normal levels during hospitalization for AMI to reduce short-term mortality. Whether this imparts a long-term effect on mortality is unknown. Given the retrospective design of the study, the data demonstrate an association that cannot provide information on a true cause and effect. However, it may provide useful

information for future prospective interventional studies for an appropriate glucose target during admission for AMI. Although some have suggested pleiotropic effects of insulin in AMI beyond effects on glucose concentrations alone, these data suggest it may be the glucose-lowering effect of insulin that predicts outcomes.

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Is there a need for coronary artery disease screening in asymptomatic patients with Type 2 diabetes?

Evaluation of: Young L, Wackers F, Chyun D *et al.*: Cardiac outcomes after screening for asymptomatic coronary artery disease in patients with Type 2 diabetes. The DIAD Study: a randomized controlled trial. *JAMA* 301, 1547–1555 (2009).

It is well known that Type 2 diabetes mellitus is considered a cardiovascular risk equivalent, and coronary artery disease (CAD) is the leading cause of death in this population. In addition, a significant proportion of the money spent on treating diabetes goes to treating cardiovascular complications [1]. As such, enhanced screening for CAD has been proposed as a means to identify asymptomatic patients at higher risk for a CAD event and limit the impact CAD has on the overall management of diabetes. Earlier identification of higher-risk patients has the potential to lead to preventative interventions to limit cardiovascular events. Indeed, noninvasive screening tools, such as coronary computed tomography or myocardial perfusion scintigraphy, have been shown to identify subclinical atherosclerosis, and may be predictive of potential cardiovascular events in asymptomatic patients with diabetes [2,3]. Routine screening of asymptomatic patients using such techniques, however, remains controversial, as it has not been proven that screening in this population actually reduces subsequent outcomes or enhances intervention.

Led by researchers from Yale University (CT, USA), the Detection of Ischemia in Asymptomatic Diabetics (DIAD) study sought to prospectively randomize 1123 patients with Type 2 diabetes to either no CAD screening or CAD screening using adenosine stress radionuclide myocardial perfusion imaging (MPI) [4]. Subjects enrolled had no prior history of CAD or symptoms of such, and were followed up for an average of 4.8 years. The study was designed to evaluate if routine MPI could identify individuals at higher CAD risk, but also if screening had any benefit in affecting the risk for MI or cardiac death. The authors found the HR for the combined outcome of MI or cardiac death was not affected by screening (0.88; 95% CI: 0.44–1.8; p = 0.73). None of the HRs for secondary events (e.g., stroke, unstable angina), revascularization procedures or mortality were found to be statistically significant. The use of angiotensin-converting enzyme inhibitors, aspirin or statin therapy increased over the study period, but did not differ between the two groups. In subjects with moderate or large perfusion defects (n = 33), compared with those with normal imaging results (n = 409), a significantly higher risk for MI or cardiac death was noted (HR: 6.3; 95% CI: 1.9–20.1; p = 0.001). This same trend held true for secondary outcomes, revascularizations and all-cause mortality. The positive-predictive value of moderate-to-large MPI defects was 12%, a relatively small number. It should be noted that the investigators expected a much higher rate of cardiovascular events than what was found at conclusion of the study (5–10 vs 2.9%, respectively).

This is the first study to prospectively evaluate noninvasive cardiac screening in asymptomatic patients with diabetes and assess its effects on subsequent cardiovascular risk. It suggests that this type of screening is unnecessary in the majority of this patient population. However, the study was underpowered to detect a significant difference between study groups, as the event rates were smaller than expected. As such, further prospective investigation is still needed, and the utility of screening in these patients remains questionable. The low event rate observed in this study could be taken as a positive sign that routine medical management of cardiovascular risk in asymptomatic patients with diabetes has improved and lowered the impact

of CAD in this population. Given the prevalence of diabetes, routine screening of similar patients as were enrolled in this study would raise significant healthcare cost issues. The American Diabetes Association, in a 2007 consensus statement, suggest noninvasive techniques be reserved in those not experiencing symptoms for selected individuals when there is strong clinical suspicion of very-high-risk CAD, and for those who can not meet medical treatment goals [5]. The results of this study do not negate the utility of noninvasive cardiac screening in those patients with diabetes actually experiencing some degree of cardiac symptoms.

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Association between admission hyperglycemia and poor outcomes in patients receiving thrombolytic therapy for stroke

Evaluation of: Poppe A, Majumbar S, Jeerakathil T *et al.*: Admission hyperglycemia predicts a worse outcome in stroke patients treated with intravenous thrombolysis. *Diabetes Care* 32, 617–622 (2009).

Hyperglycemia during ischemic stroke is a common occurrence. Current recommendations from the American Stroke Association and American Heart Association call for insulin therapy if hyperglycemia is detected in patients experiencing a stroke [1]. This recommendation stems from data documenting an association between admission hyperglycemia and worse outcomes in this population [2,3]. However, the outcome effects of treating hyperglycemia during stroke management has not been adequately studied [4,5]. Poppe and colleagues recently evaluated the issue of admission hyperglycemia and outcomes for stroke patients receiving thrombolytic therapy [6]. They cite numerous limitations of the current literature in this area for subjects receiving thrombolytic therapy, including but not limited to small sample sizes, little data on long-term (>30 day) outcomes, and some studies including subjects with either hemorrhagic or ischemic stroke.

Using data from a previous prospective Canadian study [7] and multivariable logistic regression, the authors analyzed the association of pre-thrombolytic therapy hyperglycemia (>8.0 mmol/l) and various outcomes during and after acute management of ischemic stroke. These outcomes included mortality, symptomatic intracerebral hemorrhage (SICH) and 90-day outcome. Of the 1098 subjects in the original trial with adequate glucose data to analyze, 16% had a history of diabetes and 27% experienced admission hyperglycemia. The adjusted relative risk (RR) for SICH was increased for those with admission hyperglycemia when compared with those without, but this did not reach statistical significance, with an RR of 1.69 (95% CI: 0.95–3.00). Hyperglycemia was associated with a poorer 90-day outcome (based on the 7-point modified Rankin Scale), with an RR of 0.7 (95% CI: 0.5–0.9), and a higher all-cause mortality risk, with an RR of 1.5 (95% CI: 1.2–1.9). The risk did not differ for those with or without a history of diabetes.

This study adds to the current literature regarding the risks of hyperglycemia during treatment of ischemic stroke with thrombolytics. This study was quite large compared with previous studies on the subject, and one of the few to document the association of hyperglycemia with longer-term outcomes, in this case up to 90 days. Whether hyperglycemia is the cause of poorer outcomes or an effect of a more severe stroke severity is yet to be determined. Studies specifically designed to lower hyperglycemia and that can control for the multitude of variables associated with worse outcomes in stroke are needed to answer the question of whether this part of stroke management improves outcomes.

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