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Commentary

Tackling Cardiovascular Risk in Type 2 Diabetes: Does Baseline Glucose Control Matter?

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A large body of evidence has consistently demonstrated a direct relationship between hyperglycemia and atherosclerotic cardiovascular disease. With an increasing prevalence of abdominal obesity, the clinical implications of a range of dysglycemic states, spanning from impaired fasting glucose to established diabetes will produce escalating rates of micro and macrovascular complications. Beyond the importance of lifestyle measures in the management of these patients, there has been considerable attention focused on the potential for glucose lowering therapies to reduce cardiovascular risk.

While studies have unequivocally demonstrated a favourable effect of glucose lowering on microvascular complications in the patient with diabetes, the impact on macrovascular events has been variable. For many years, there was no compelling evidence to suggest that glucose lowering, using a variety of therapeutic agents, would reduce the rate of ischaemic events. In fact, concerns with regard to potential cardiovascular safety signals with rosiglitazone ushered in a new generation of clinical trials that permitted evaluation of both cardiovascular efficacy and safety with new agents developed primarily to improve glycemic control. Importantly, a number of large clinical outcomes trials have now demonstrated cardiovascular efficacy associated with treatment with both sodium glucose cotransporter 2 (SGLT2) inhibitors [1, 2] and glucagon-like peptide-1 (GLP-1) agonists [3]. As a result, these agents have been increasingly used in high cardiovascular risk patients with diabetes and evidence of persistent hyperglycemia, despite treatment with at least metformin.

In parallel, there has been interest in the potential therapeutic effects of glucose lowering agents in patients with lesser levels of dysglycemia. Studies have demonstrated that early use of metformin may have favourable effects on the artery wall in patients with prediabetes [4]. While the SGLT2 inhibitor outcome trials were performed in patients with suboptimal glycemic control, there is increasing interest in the use of these agents in all patients with diabetes, regardless of glycated haemoglobin levels at baseline. The benefits of initiating additional agents in the patient with more optimal glycemic control remain unknown.

In this issue of EClinicalMedicine, Asakura and colleagues present the findings of the PPAR study, in which they investigated the impact of pioglitazone on cardiovascular outcomes in patients with type 2 diabetes, very good glycemic control (HbA1c < 6.5%) and prior myocardial infarction [5]. In this prospective, open labelled, blind endpoint study, treatment with pioglitazone did not reduce the composite incidence of cardiovascular events during a two-year treatment period and on longer observation out to seven years. The authors conclude that use of pioglitazone is unlikely to be of clinical benefit in patients with good glycemic control and that other effects of pioglitazone do not appear to confer benefit in this setting.

The findings are of interest, however they must be placed in the context of what is already known of pioglitazone. While the pioglitazone did not have a favourable effect on the primary endpoint in the landmark PROACTIVE trial, it did reduce cardiovascular events in patients with prior myocardial infarction, when their baseline HbA1c was suboptimally controlled [6]. The IRIS trial demonstrated a benefit with pioglitazone in patients with prior stroke and tighter glycemic control [7]. Underlying these findings, are observations that pioglitazone arrests progression of coronary atherosclerosis in patients with diabetes [8], a benefit that associated with lowering of the triglyceride/HDL cholesterol ratio [9]. These findings suggest that pioglitazone has anti-atherosclerotic properties and that the observations of the PPAR study would seem to be at odds with that.

The ultimate question posed by the PPAR investigators remains the clinical conundrum of initiating evidence based therapies for diabetes in high cardiovascular risk patients with more optimal levels of glycemic control. Given the likelihood that both well controlled diabetes and prediabetes states confer accelerated atherosclerotic risk, there may remain benefits of using established therapies at an earlier stage. The motivation for this will likely be greater in the setting where agents have established mortality benefits. This suggests that there is considerable work that needs to be performed to determine the optimal approaches to reducing cardiovascular risk across the spectrum of dysglycemia. Accordingly, while clinical trials have played an important role in establishing the effects of specific agents, it will be critical for

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future studies to determine how to most effectively implement these therapies in clinical practice.

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