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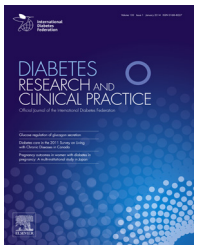

Strategies for glucose control in a study population with diabetes, renal disease and anemia (Treat study)

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ABSTRACT

Glucose lowering medication use among patients with type 2 diabetes and advanced renal disease (eGFR < 60) in a large multinational outcome trial (TREAT) is assessed. We demonstrate statistically significant differences regionally in use of metformin at lower eGFR and increasing reliance upon insulin with/without other medications at low eGFR.

Introduction: As renal disease advances, most of the oral anti-diabetic agents requiring renal clearance must be reduced or discontinued. The potential for prolonged hypoglycemia, fluid/volume overload and congestive heart failure may complicate medication choices. In order to evaluate patterns of glycemia management we describe glucose lowering medication use among patients with advanced renal disease and type 2 diabetes in a large multinational outcome trial designed to focus on patients with eGFR < 60 in order to commence a dialog on best practices. We felt that analysis of this data would be able to describe regional variations in treatment within a multinational trial in order to understand potential outcome differences attributed to complications.

Results: The patients entering this study had moderate glycemic control. Insulin therapy either alone (32%) or in combination with other agents (17%) reflected a shift towards insulin use in those subjects with decreased renal function when compared with standard populations with normal kidney function. The use of multiple oral agents, or oral agents plus insulin was quite common. While gender did not appear to play a role in medication choices, there were significant regional variations. For example, oral agents were used more in North America compared with other regions (Latin America, Australia/Western Europe, Russia/Eastern Europe). Patients enrolled at more advanced ages were less likely to be on a regimen of rapid-acting insulin alone consistent with recommendations that suggest a preference for longer-acting preparations in the geriatric population (1). Higher degrees of obesity were associated more complex treatment regimens. Despite this population being at high risk for cardiovascular events, the use of beta blockers (50%), statins (64%) and aspirin (48%) were

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relatively low, especially in the group that did not require medications to achieve adequate glycemic control.

Conclusions: Current attempts to compare strategies for diabetes therapy must control for baseline demographic group differences influencing treatment choice. Future recommendations for glycemic control in patients with Grade 3 or higher chronic kidney disease require additional studies, with matched populations. We suggest that evaluation of studies similar to TREAT will assist in determining the optimal therapeutic regimens for populations with moderate to severe renal dysfunction, a condition in which repeated hospitalizations for fluid overload/heart failure add to the high cost of diabetes care.

1. Introduction

Over the past 20 years there has been progress in slowing the decline in renal function in patients with diabetes primarily via renin angiotensin system blockers [1–4]. However, combinations of angiotensin converting enzyme inhibitors and angiotensin receptor blockers or direct renin inhibitors do not improve outcomes [5–7]. Similarly, cardiovascular complications have occurred with the use of certain effective glucoregulating agents such as thiazolidinediones. This particular drug class associated with fluid/volume overload/congestive heart failure [8,9]. There are ongoing attempts to develop a rational approach to manage hyperglycemia in individuals with type 2 diabetes with increasing armamentarium of non-insulin glucose lowering agents [10–13]. Only limited observational retrospective data are available, which describe the range of therapies currently used in older cohorts with glomerular filtration rates of <60 ml/min [14].

Since the population with type 2 diabetes and advanced renal disease has been increasing, the appropriate choice of glucose lowering agents in this group of subjects remains an unresolved issue. There are few studies to guide clinicians as to which medications should be used in practice in this aging population. The largest contemporary study reports that 35% of subjects with type 2 diabetes over 60 years of age have an eGFR < 60 ml/min [14]. As renal function diminishes with advancing age and nephropathy, non-insulin agents cleared by the kidneys (the alpha glucosidase inhibitors, repaglinide, glyburide, sitagliptin, saxagliptin, alopgliptin and the SGLT-2 inhibitors) must be reduced or discontinued.

In order to evaluate patterns of treatment in patients with renal disease and type 2 diabetes, we reviewed baseline data from the TREAT (Therapy to Reduce cardiovascular Endpoints with Aranesp Trial) study. This trial enrolled 4038 patients during the years 2005–2009 in order to determine whether programmed use of darbepoietin improved healthcare outcomes among patients with type 2 diabetes and moderately severe renal insufficiency [15–17]. In this trial the use of glucose lowering medications was neither an inclusion nor an exclusion criterion, and no guidance regarding regimens to be used was given. Our goal is to explore regional differences in use of glucose lowering medications in renal disease in order to understand potential outcome differences attributed to diabetic complications. We hypothesized a strong relationship between levels of renal function and baseline prescriptions for diabetes at 24 sites in multiple geographic areas.

2. Methods

The authors had full and complete access to enrollment data from the TREAT trial. In brief 4038 patients with type 2 diabetes, anemia (hemoglobin ≤ 11.0 g/dl) and renal dysfunction (eGFR ≥ 20 to 60 ml/min/1.73 m^2) were randomized in TREAT (Therapy to Reduce cardiovascular Endpoints with Aranesp Trial). The details of the enrollment process have been reported elsewhere [15–17]. For the purpose of this analysis, all data are recorded as of the baseline randomization visit. These data included the following pertinent information: age, gender, current eGFR, race, body mass index, known duration of diabetes, presence with/without laser therapy or absence of retinopathy, presence or absence of a cardiovascular history (by presence of any of the following: coronary artery disease, heart failure, myocardial infarction, stroke, peripheral vascular disease, non-traumatic amputation, pacemaker, AICD, atrial fibrillation), smoking history (current, former), and blood pressure measurement. Laboratory testing included: serum creatinine, urine protein-creatinine, high sensitivity CRP, serum albumin, hemoglobin A1c, hemoglobin, white blood cells, platelets, transferrin saturation, serum ferritin, fasting triglycerides, and total/HDL/LDL cholesterols. Specific medication lists for each individual patient with daily dosage at the time of randomization were available. The TREAT trial was not designed to evaluate strategies of glucose control, variations in cost, regional variation or outcomes related to glucose control. No record of hypoglycemic events was kept centrally. C-peptide levels were not recorded.

In order to best describe complex baseline treatment regimens, we analyzed choices by the following criteria:

(1) Individual glucose lowering medications by standard pharmaceutical grouping.
(2) A second classification of regimen primarily defined by insulin usage.
    (a) No glucose lowering medications.
    (b) Non insulin agents (any agent other than insulin).