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**STRATEGIES FOR GLUCOSE CONTROL IN A STUDY POPULATION WITH
DIABETES, RENAL DISEASE AND ANEMIA (TREAT STUDY)**

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Abbreviated 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.

Abstract

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. Although 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 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.

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 (2-4). 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/minute (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 <60ml/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, alogliptin 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.

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/1.73m²) 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 cholesterol. 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)
 - c. Insulin only
 - d. Insulin plus any other agent

Statistical Analysis

All baseline information is summarized using means and standard deviations or, for skewed variables, medians and interquartile ranges for continuous variables and using counts and percentages for dichotomous variables. Tests for trend across eGFR categories are conducted using linear regression, Cuzick's nonparametric trend test, and Cochran-Armitage test for trend, respectively. Global tests of equality are conducted using ANOVA, the Kruskal-Wallis test and Pearson's chi-squared test, respectively. P-values less than 0.05 are considered to be significant. All analyses were conducted using STATA 13 (College Station, TX).

Results:

Demographic data for the entire group are listed in Table 1. As glucose control was not an inclusion criteria or an endpoint of the study, participating physicians managed glycemia according to their clinical preference. No information about complications or side effects relating to glucose regulation prior to randomization was available. The current report is thus a description of glucose lowering prescriptions at the time of trial randomization. Renal function was defined by eGFR (Modification of Diet in Renal Disease, MDRD method) and grouped as <25, 25-30, 30-35, 35-45 and >45 ml/min to approximate quintiles (18).

After a mean of 15 years duration of diabetes, >75% entering the study had a HbA_{1c} ≤8.0%. Depressed levels of renal function were associated with factors such as duration of diabetes, prevalence of retinopathy, greater prevalence of diagnosed heart failure with more severe disorders of both red cell and lipid production.

Table 2 lists the medications at baseline. As would be expected, groups with more severe renal dysfunction were more likely to have received erythropoietin prior to enrolling in the TREAT study. There was an incremental increase in antihypertensive use, and especially the use of loop diuretics with increasing renal impairment. Interestingly, the use of statins, beta-blockers, and antiplatelet agents did not appear to vary among groups defined by the level of renal dysfunction, or by region. Calcium channel blocker use was more common in the groups with lowest eGFR,

whereas use of angiotensin converting enzyme inhibitors was less common. While 10.6% of patients were receiving no medications for their diabetes, almost 50 % were taking insulin (with or without other medications), and among those on oral agents alone, the majority required more than one class of glucose lowering agent. The most common choices for oral agents included a sulfonylurea agent alone (32%), a TZD (thiazolidinedione) plus sulfonylurea (17%), a biguanide (metformin) plus sulfonylurea (15%), or a TZD alone (15%). For the combined delivery of insulin plus oral agents, the most common medications were insulin plus TZD (30%), insulin plus sulfonylurea (23%), insulin plus biguanide (15%) and insulin plus TZD plus sulfonylurea (10%).

The groups receiving insulin, either alone or in concert with other medications, were slightly younger and had higher HbA_{1c}, greater duration of diabetes with increased prevalence of retinopathy (including laser therapy) and peripheral vascular disease (including amputations). The combination of insulin plus other agents was associated with a higher body mass index than the other treatment choices. The group using insulin only demonstrated greater duration, more retinopathy and higher urine protein/creatinine ratio. The group of patients without diabetes medications was the oldest, with the shortest duration of diabetes, lowest prevalence of retinopathy, lowest HbA_{1c} and less use of agents that interrupt the RAS, calcium channel blockers, lipid lowering agents and aspirin. This older group also had the greatest prevalence of atrial fibrillation with anticoagulant usage. While there were no significant differences in former smokers across the quintiles of eGFR, the quintile with lowest eGFR had the highest occurrence (6.9%) of current smoking ($p < 0.05$).

There were regional variations in glucose control regimens in the TREAT study. Despite regional variations in baseline HbA_{1c}, acceptable average blood sugars were achieved in all regions. As shown in both Tables 1 and 3, centers in Latin America reported a lower prevalence of cardiovascular disease than other regions (North America, Western Europe plus Australia, Eastern Europe). The prevalence of patients treated with antidiabetic medications was similar in all regions, however there were considerable variations in the use of individual classes of medications. The use of insulin was notably less frequent, and the use of oral agents more frequent in North America when compared to other regions. This difference was driven by the use of thiazolidinediones (TZD), sulfonylurea medications and a larger number of other types of non-insulin glucose lowering agents. For a median eGFR of 34ml/min we recorded a 23% incidence of insulin-only usage in North America that was one half that seen in each of the other regions (42-51%, $p < 0.001$) while non-insulin use diminished as renal function decreased (Table 2, $p < 0.001$). As demonstrated in Table 3 there were also statistically significant regional differences in prescriptions for biguanides with more marked decrease in biguanide use at eGFR < 35 ml/min in North America than in other regions.

Discussion

The United States Centers for Disease Control statistics for people aged above 18 years demonstrate that 57% of patients with diabetes require non-insulin oral treatments alone, 14% insulin alone and 15% require both therapies (19). In this middle-aged population with diabetes where microvascular disease, chronic renal insufficiency, prevalent obesity and cardiovascular event history were often present, reasonable levels of HbA_{1c} were achieved. The study protocol did not dictate any restrictions of use of medications, which allows some generalization on usage according to geographical location. Among patients with type 2 diabetes and Class 3 or 4 CKD, the therapeutic choices for glucose homeostasis were: use of non-insulin agents alone (40%),

insulin alone (32%), both (17%), or control by diet alone (11%). Our findings reflect a shift towards more insulin use among patients with increasing renal impairment and associated higher cardiovascular risk. It appears that in this population with CKD in all regions examined reasonable glycemic control was achieved. There was regional variation in medication choice with agents other than insulin being used more frequently in North America than in other regions.

Several studies have suggested that some strategies for intensification of glucose management may be associated with greater or lesser long term risk (20-25), however these studies and meta-analyses have, for the most part, avoided consideration of the patient population at highest risk for cardiovascular or non-cardiovascular events and progression to fluid handling problems by virtue of diminished renal reserve. To date the largest trials focusing on therapy in patients with type 2 diabetes have focused on goal directed therapy (blood pressure and HbA_{1c} targets) in populations with less advanced renal disease (20, 24-30) without separating out the effects of the individual glucose lowering therapies. This TREAT analysis is the first such attempt in a large number of patients with eGFR < 60ml/min. The total number of study subjects with low GFR in the TREAT study appears to be greater than the combination of low GFR subjects in the ADVANCE (about 2000 of approximately 10,000) and ACCORD (about 1000 of approximately 10,000), studies. Furthermore, in those trials, the investigators have not described specifically the use of glucose lowering medications in the cohort with low GFR (29-32). Evaluation of studies with similar populations to those in TREAT would be helpful in identifying the best therapeutic strategies for populations with moderate to severe renal dysfunction, a condition in which repeated hospitalizations for fluid overload/heart failure are increasing.

Current therapeutic strategies for glycemia control for patients with diminished renal function are based upon the principles that hypoglycemia due to glyburide and glimepiride should be avoided (33-35), and that metformin should be withheld to avoid lactic acidosis secondary to a shift away from cytoplasmic pyruvate production at the level of lactic dehydrogenase favoring production of lactate (36,37). Considerable debate has occurred regarding lower limits of renal function that permit safe use of metformin. Most of the literature is based upon the historical relationship of metformin's more toxic precursor biguanide phenformin to lactic acidosis. Although subsequent observations with the use of metformin have suggested a lower incidence of such events than had been reported with phenformin, there has been no weakening of a proscription against its use by the USFDA for "Renal disease or renal dysfunction (e.g., as suggested by serum creatinine levels ≥ 1.5 mg/dL [males], ≥ 1.4 mg/dL [females] or abnormal creatinine clearance)" (38-40). Despite this "contraindication", metformin is still being used in patients with decreased renal function in North America as 28% of the biguanide use in our study occurred with eGFR <35ml/min compared to >40% in all other regions). It would be interesting to determine if there is any signal of risk in metformin use at lower eGFR in other large trial databases. If not, the data would support the recommendations of Lipska et al (41) for cautious monitoring (every three months) of eGFR once it is below 60 ml/min and halved doses when eGFR is below 45 ml/minute, with cessation of metformin for eGFR of 30ml/min or less. We would suggest that periodic monitoring should also include evaluation for dehydration, intercurrent disease and levels of hemoglobin and vitamin B12. .

Guidelines to favor one strategy for control of type 2 diabetes over another will require specific testing within the population with diminished renal reserve, rather than from observations from other trials which have in general neglected this population with low GFR. Since research support for comparative outcome trials is often unavailable, post hoc analyses are required to

evaluate data from large well-designed trials in order to determine the best outcomes in the increasing number of patients suffering from diabetes and renal impairment.

The population in TREAT received “real life” care and resembled patients with diabetes who are seen in renal clinics. The burgeoning impact upon the health care budget of this subgroup of patients with diabetes who have low GFR and are at higher risk of cardiovascular disorders including heart failure persuaded us to examine within this multicenter study insights into overall management of such individuals with a focus on glucose lowering agents. An incidental finding was that the use of statins and antiplatelet agents was lower than might be expected from the universal guidelines emphasizing the importance of reinforcing the role of multifactorial intervention in this population.

Limitations:

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. Furthermore, C peptide levels were not recorded. Choice of diabetes management was left to the treating physicians without attempt at matching. Likewise, no attempt was made to influence the use of antihypertensive drugs, statins, or antiplatelet agents in this high-risk population. No information is available regarding the role of patients in the choice of their medications nor was any data collected with respect to total or patient cost of medications. All of the patients in this study were anemic. Among diabetic cohorts with renal dysfunction prevalence of anemia rises with greater degrees of renal dysfunction such that at least half of a diabetic population is anemic below eGFR of 30ml/min. Interestingly anemia does not appear to be a risk factor for all cause or cardiovascular morbidity/mortality in diabetic cohorts unless chronic kidney disease is present (42). Since most diabetic patients are anemic by the time dialysis and transplant are being considered and there is no guideline suggesting choice of anti-diabetic agent on the basis of red cell count or volume it is unlikely that the choice of anemic patients for this analysis is not generalizable to diabetic patients with renal dysfunction who are not yet anemic.

Conclusions:

We report that within a clinical trial involving patients with type 2 diabetes and moderately severe renal disease and anemia enrolled from 24 sites in general adequate glycemic control was achieved in all regions. For a median eGFR of 34 ml/minute usage of insulin-only therapy was markedly less in North America when compared to all other regions. In addition glycemia control strategies were significantly different in cohorts the lower GFR groups with insulin used more frequently, and noninsulin therapy less frequently. We consider that comparisons between diabetes therapies must adjust for baseline and regional differences that influence treatment choice. Recommendations for glycemic control in patients with type 2 diabetes and Grade 3 or greater chronic kidney disease require additional studies, with matched populations in order to guide clinicians as to the best strategies.

**Table 1: Relationship
between levels of Renal
Function/Demographics**

eGFR Categories (MDRD, ml/min)	Category 1 ≤25 n=854	Category 2 >25-30 n=687	Category 3 30-35 n=645	Category 4 35-45 n=1060	Category 5 ≥45 n=789	P (trend)
Age (years)	66.11 ± 10.62	67.31 ± 10.89	67.96 ± 10.23	68.18 ± 10.43	67.11 ± 10.92	0.007
Male (%)	357 (41.8%)	275 (40.0%)	260 (40.3%)	452 (42.6%)	382 (48.4%)	0.006
Race						<0.001*
Black	172 (20.1%)	126 (18.3%)	110 (17.1%)	199 (18.8%)	208 (26.4%)	0.009**
Other	150 (17.6%)	136 (19.8%)	106 (16.4%)	153 (14.4%)	108 (13.7%)	0.002**
White	532 (62.3%)	425 (61.9%)	429 (66.5%)	708 (66.8%)	473 (59.9%)	0.81**
BMI	31.64 ± 7.24	31.51 ± 7.19	31.58 ± 7.40	31.38 ± 7.37	31.50 ± 7.83	0.58
Region						0.042*
North America	523 (61.2%)	420 (61.1%)	398 (61.7%)	661 (62.4%)	513 (65.0%)	0.12**
Latin America	116 (13.6%)	86 (12.5%)	61 (9.5%)	103 (9.7%)	72 (9.1%)	<0.001**
W. Europe / Australia	82 (9.6%)	64 (9.3%)	67 (10.4%)	97 (9.2%)	57 (7.2%)	0.14**
E. Europe / Russia	133 (15.6%)	117 (17.0%)	119 (18.4%)	199 (18.8%)	147 (18.6%)	0.05**
Duration of DM (years)	16.3 [10.1, 22.6]	16.0 [9.7, 22.1]	14.8 [7.9, 21.1]	15.2 [7.4, 21.7]	13.8 [7.3, 21.1]	<0.001
Retinopathy	449 (53.5%)	338 (50.8%)	293 (46.3%)	463 (44.7%)	318 (41.6%)	<0.001
CV history	572 (67.0%)	441 (64.2%)	427 (66.2%)	688 (64.9%)	512 (64.9%)	0.46
CAD	372 (43.6%)	301 (43.8%)	289 (44.8%)	484 (45.7%)	343 (43.5%)	0.7
HF	303 (35.5%)	241 (35.1%)	228 (35.3%)	342 (32.3%)	231 (29.3%)	0.004
MI	150 (17.6%)	128 (18.6%)	113 (17.5%)	201 (19.0%)	148 (18.8%)	0.49
Stroke	92 (10.8%)	79 (11.5%)	64 (9.9%)	124 (11.7%)	88 (11.2%)	0.72
PAD	168 (19.7%)	131 (19.1%)	121 (18.8%)	202 (19.1%)	156 (19.8%)	1
Atrial Fibrillation	89 (10.4%)	66 (9.6%)	73 (11.3%)	119 (11.2%)	76 (9.6%)	0.96
Current Smoker	59 (6.9%)	32 (4.7%)	25 (3.9%)	53 (5.0%)	35 (4.4%)	0.049
Former Smoker	339 (39.7%)	257 (37.4%)	254 (39.4%)	415 (39.2%)	302 (38.3%)	0.82
SBP	136.07 ± 19.74	137.07 ± 18.68	135.77 ± 18.88	135.44 ± 18.72	135.43 ± 17.39	0.17
DBP	72.47 ± 11.16	72.24 ± 11.76	71.86 ± 10.78	71.92 ± 10.90	72.73 ± 10.88	0.97
Creatinine (mg/dl)	2.9 ± 1.4	2.2 ± 0.4	1.9 ± 0.3	1.6 ± 0.3	1.3 ± 0.2	<0.001
Albumin (g/dl)	3.86 ± 0.47	3.93 ± 0.45	4.01 ± 0.41	4.00 ± 0.43	4.01 ± 0.44	<0.001
HbA1C	7.27 ± 1.51	7.26 ± 1.56	7.18 ± 1.38	7.31 ± 1.54	7.33 ± 1.52	0.3

Hemoglobin	10.14 ± 1.03	10.30 ± 0.99	10.38 ± 1.00	10.45 ± 0.92	10.53 ± 0.99	<0.001
White Blood Cells	7.20 ± 2.34	6.85 ± 2.03	7.01 ± 2.78	6.75 ± 2.08	6.65 ± 2.11	<0.001
Platelets	249.98 ± 78.33	242.43 ± 72.76	246.46 ± 75.60	246.62 ± 76.35	248.19 ± 80.25	0.95
Transferrin Saturation	0.25 ± 0.09	0.25 ± 0.10	0.25 ± 0.10	0.24 ± 0.08	0.24 ± 0.10	0.011
Ferritin	163.0 [87.0, 311.0]	140.0 [74.0, 253.0]	127.0 [66.0, 254.0]	124.0 [61.5, 238.5]	112.0 [55.0, 229.0]	<0.001
Cholesterol	182.44 ± 54.46	179.93 ± 58.63	177.22 ± 50.95	175.27 ± 50.38	172.84 ± 47.82	<0.001
LDL	95.46 ± 42.46	92.18 ± 42.77	91.02 ± 37.79	90.25 ± 39.68	88.17 ± 35.89	<0.001
HDL	47.21 ± 14.80	47.39 ± 13.81	47.71 ± 15.27	48.76 ± 14.67	49.73 ± 16.26	<0.001
Triglycerides	166.0 [118.0, 241.0]	163.0 [113.0, 240.5]	155.0 [111.0, 228.0]	153.0 [109.0, 225.0]	140.0 [101.0, 204.0]	<0.001
Urine Prot/Creat Ratio	1.3 [0.3, 3.6]	0.6 [0.2, 2.5]	0.4 [0.1, 1.6]	0.3 [0.1, 1.2]	0.2 [0.1, 1.1]	<0.001
CRP	3.4 [3.0, 7.4]	3.0 [3.0, 5.9]	3.0 [3.0, 6.8]	3.0 [3.0, 6.2]	3.0 [3.0, 6.9]	0.017

*global test (for categorical variable)

**trend test (for individual category)

**Table 2: Relationship
between levels of Renal
Function/Medications**

eGFR Categories (MDRD, ml/min)	Category 1 ≤25 n=854		Category 2 >25-30 n=687		Category 3 30-35 n=645		Category 4 35-45 n=1060		Category 5 ≥45 n=789		P (trend)
Oral DM agent	425	(49.8%)	362	(52.7%)	350	(54.3%)	645	(60.8%)	509	(64.5%)	<0.001
ACE-I or ARB	636	(74.5%)	548	(79.8%)	528	(81.9%)	853	(80.5%)	657	(83.3%)	<0.001
Beta Blocker	423	(49.5%)	344	(50.1%)	327	(50.7%)	523	(49.3%)	370	(46.9%)	0.31
ARB	50	(5.9%)	22	(3.2%)	31	(4.8%)	64	(6.0%)	42	(5.3%)	0.51
Statin	485	(56.8%)	402	(58.5%)	380	(58.9%)	640	(60.4%)	454	(57.5%)	0.45
Statin/other Lipid											
Lowering	543	(63.6%)	441	(64.2%)	417	(64.7%)	687	(64.8%)	504	(63.9%)	0.79
Aspirin	384	(45.0%)	280	(40.8%)	273	(42.3%)	455	(42.9%)	318	(40.3%)	0.18
Aspirin or other											
Antiplatelet	425	(49.8%)	320	(46.6%)	306	(47.4%)	519	(49.0%)	377	(47.8%)	0.75
Vitamin K antagonists	49	(5.7%)	46	(6.7%)	58	(9.0%)	72	(6.8%)	51	(6.5%)	0.56
Oral Iron Medication	364	(42.6%)	275	(40.0%)	276	(42.8%)	454	(42.8%)	338	(42.8%)	0.59
IV Iron Medication	11	(1.3%)	13	(1.9%)	13	(2.0%)	14	(1.3%)	11	(1.4%)	0.81
Prior Epo	123	(14.4%)	74	(10.8%)	68	(10.5%)	72	(6.8%)	48	(6.1%)	<0.001
CCB	441	(51.6%)	348	(50.7%)	267	(41.4%)	450	(42.5%)	294	(37.3%)	<0.001
K-sparing Diuretic	53	(6.2%)	22	(3.2%)	32	(5.0%)	74	(7.0%)	49	(6.2%)	0.15
Loop Diuretic	615	(72.0%)	431	(62.7%)	378	(58.6%)	547	(51.6%)	346	(43.9%)	<0.001
Other Diuretic	242	(28.3%)	214	(31.1%)	203	(31.5%)	370	(34.9%)	288	(36.5%)	<0.001
Other anti-hypertensive	234	(27.4%)	157	(22.9%)	136	(21.1%)	198	(18.7%)	126	(16.0%)	<0.001
DM Med Pattern											<0.001*
No Meds	91	(10.7%)	87	(12.7%)	69	(10.7%)	109	(10.3%)	73	(9.3%)	0.16**
Non-insulin Therapy	300	(35.1%)	258	(37.6%)	250	(38.8%)	445	(42.0%)	365	(46.3%)	<0.001**
Insulin Only	338	(39.6%)	235	(34.2%)	225	(34.9%)	299	(28.2%)	203	(25.7%)	<0.001**
Insulin + Other	125	(14.6%)	107	(15.6%)	101	(15.7%)	207	(19.5%)	148	(18.8%)	0.002**

*global test (for categorical variable)

**trend test (for individual category)

Table 3: Regional variations in biguanide medication use

		North Amer. n=2515	Latin Amer. n=438	W Europe / Australia n=370	E Europe / Russia n=715	P (global)
HbA1C - baseline		6.9 [6.2, 7.9]	7.5 [6.5, 8.6]	6.8 [6.2, 7.6]	7.0 [6.1, 8.0]	<0.001
eGFR - baseline		34.0 [26.3, 42.8]	31.1 [24.6, 40.8]	33.4 [25.8, 41.0]	34.5 [27.0, 43.3]	0.001
Age		68.1 ± 11.0	61.0 ± 9.4	69.1 ± 9.2	67.7 ± 9.4	<0.001
Male (%)		1129 (44.9%)	167 (38.1%)	165 (44.6%)	265 (37.1%)	<0.001
BMI		32.7 ± 8.0	27.8 ± 5.3	31.2 ± 6.2	29.6 ± 5.6	<0.001
Duration of DM (years)		14.8 [7.7, 21.5]	16.8 [10.9, 21.8]	16.2 [8.1, 23.1]	15.7 [8.8, 21.6]	<0.001
<u>Medical History.</u>						
	CAD	1171 (46.6%)	69 (15.8%)	132 (35.7%)	419 (58.6%)	<0.001
	HF	818 (32.5%)	61 (13.9%)	86 (23.2%)	382 (53.4%)	<0.001
	MI	508 (20.2%)	32 (7.3%)	53 (14.3%)	148 (20.7%)	<0.001
	Stroke	312 (12.4%)	29 (6.6%)	27 (7.3%)	79 (11.0%)	<0.001
	PAD	467 (18.6%)	68 (15.5%)	74 (20.0%)	170 (23.8%)	0.003
	AF	264 (10.5%)	9 (2.1%)	44 (11.9%)	108 (15.1%)	<0.001
<u>Antidiabetic medications</u>						<0.001
	No meds	266 (10.6%)	49 (11.2%)	50 (13.5%)	64 (9.0%)	
	Non Insulin only	1140 (45.3%)	144 (32.9%)	117 (31.6%)	219 (30.6%)	
	Insulin only	584 (23.2%)	201 (45.9%)	154 (41.6%)	362 (50.6%)	
	Insulin + Anything	525 (20.9%)	44 (10.0%)	49 (13.2%)	70 (9.8%)	
<u>Biguanide medication use</u>						<0.001
	No Medications	266 (10.6%)	49 (11.2%)	50 (13.5%)	64 (9.0%)	
	Biguanide only	59 (2.3%)	19 (4.3%)	23 (6.2%)	15 (2.1%)	
	Biguanide plus other meds (no insulin)	246 (9.8%)	53 (12.1%)	37 (10.0%)	53 (7.4%)	
	Biguanide plus other meds (incl insulin)	105 (4.2%)	26 (5.9%)	24 (6.5%)	33 (4.6%)	
	No biguanide, other meds (no insulin)	835 (33.2%)	72 (16.4%)	57 (15.4%)	151 (21.1%)	
	No biguanide, other meds (incl insulin)	1004 (39.9%)	219 (50.0%)	179 (48.4%)	399 (55.8%)	
	Biguanide use	410 (16.3%)	98 (22.4%)	84 (22.7%)	101 (14.1%)	<0.001
	Biguanide use by eGFR*					
	<25	36 (6.9%)	14 (12.1%)	14 (17.1%)	16 (12.0%)	0.009

25- 30	39 (9.3%)	9 (10.5%)	10 (15.6%)	15 (12.8%)	0.38
30-35	43 (10.8%)	17 (27.9%)	11 (16.4%)	12 (10.1%)	0.002
35-45	125 (18.9%)	32 (31.1%)	29 (29.9%)	29 (14.6%)	<0.001
>45	167 (32.6%)	26 (36.1%)	20 (35.1%)	29 (19.7%)	0.014

- percent of patients in eGFR category receiving biguanides

Table 4: Further data on the use of biguanides

By Renal Function

eGFR (ml/min)	≤25 n=854	>25-30 n=687	30-35 n=645	35-45 n=1060	≥45 n=789	p (trend)
Biguanide	80 (9.4%)	73 (10.6%)	83 (12.9%)	215 (20.3%)	242 (30.7%)	<0.001
Metformin	71 (8.3%)	65 (9.5%)	71 (11.0%)	179 (16.9%)	205 (26.0%)	<0.001
Metformin dose (mg)	1376 ± 607	1303 ± 631	1488 ± 708	1450 ± 722	1419 ± 628	0.40

By Region

region	North Amer. n=2515	Latin Amer. n=438	W Europe / Australia n=370	E Europe / Russia n=715	p (global)
Biguanide	410 (16.3%)	98 (22.4%)	84 (22.7%)	101 (14.1%)	<0.001
Metformin	335 (13.3%)	90 (20.5%)	74 (20.0%)	92 (12.9%)	<0.001
Metformin dose (mg)	1350 ± 626	1431 ± 676	1659 ± 840	1482 ± 605	0.004

- **Conflict of Interest Statement**

- TREAT was funded by Amgen. This analysis was conducted independently by the authors and used the data set held at the Brigham & Women's Hospital; the authors designed and conducted all analyses described herein and were solely responsible for the drafting and editing of this manuscript. Each author contributed important intellectual content during manuscript drafting or revision and accepts accountability for the overall work by ensuring that questions pertaining to the accuracy or integrity of any portion of the work are appropriately investigated and resolved.
- Dr. Weinrauch reports receiving travel expenses from Amgen and fees related to service on clinical events committees from Amgen, Sanofi, and Novartis and as site principal investigator for Roche, Wyeth, and Boehringer Ingelheim Pharmaceuticals trials.
- Dr. D'Elia reports no relevant conflict of interest
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