International variation in characteristics and clinical outcomes of patients with type 2 diabetes and heart failure: Insights from TECOS

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Background International differences in management/outcomes among patients with type 2 diabetes and heart failure (HF) are not well characterized. We sought to evaluate geographic variation in treatment and outcomes among these patients.

Methods and results Among 14,671 participants in the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS), those with HF at baseline and a documented ejection fraction (EF) (N = 1591; 10.8%) were categorized by enrollment region (North America, Latin America, Western Europe, Eastern Europe, and Asia Pacific). Cox models were used to examine the association between geographic region and the primary outcome of all-cause mortality (ACM) or hospitalization for HF (hHF) in addition to ACM alone. Analyses were stratified by those with EF <40% or EF ≥40%. The majority of participants with HF were enrolled in Eastern Europe (53%). Overall, 1,267 (79.6%) had EF ≥40%. β-Blocker (83%) and angiotensin-converting enzyme inhibitor/angiotensin receptor blocker (86%) use was high across all regions in patients with EF <40%. During a median follow-up of 2.9 years, Eastern European participants had lower rates of ACM/hHF compared with North Americans (adjusted hazard ratio: 0.45; 95% CI: 0.32-0.64). These differences were seen only in the EF ≥40% subgroup and not the EF <40% subgroup. ACM was similar among Eastern European and North American participants (adjusted hazard ratio: 0.79; 95% CI: 0.44-1.45).

Conclusions Significant variation exists in the clinical features and outcomes of HF patients across regions in TECOS. Patients from Eastern Europe had lower risk-adjusted ACM/hHF than those in North America, driven by those with EF ≥40%. These data may inform the design of future international trials. (Am Heart J 2019;218:57-65.)

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Practice patterns vary across geographic regions in the treatment of heart failure (HF).[1-3] Type 2 diabetes (T2D) is associated with increased risk of incident HF and HF mortality independent of its associations with ischemic heart disease and hypertension.[4-6] Geographic variation in patient characteristics and outcomes has been demonstrated in several HF clinical trials, but differences among patients with concomitant T2D and HF are not well characterized. Results from several recent international outcome trials of T2D therapies have shown improved cardiovascular outcomes in patients with T2D treated with novel antihyperglycemic therapies including glucagon-like peptide-1 receptor agonists and sodium-glucose cotransporter 2 inhibitors, but regional variations have not been well characterized.[7,8] Given recent sodium-glucose cotransporter 2 inhibitor data supporting a marked benefit on HF outcomes,[9,10] there is increasing interest in exploring these comorbid disease states and better understanding potential geographic variation. With broad international enrollment and a modest prevalence in this cohort of T2D patients with comorbid HF, we analyzed data from the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) to evaluate geographic variation in patient characteristics, treatment, and clinical outcomes.

Methods

Study overview

The design and results of TECOS have been previously published.[11,12] Briefly, TECOS randomized in a double-blind, placebo-controlled manner 14,671 patients in 38 countries to the dipeptidyl peptidase-4 inhibitor sitagliptin or placebo. Eligible patients were age 50 years or older, had T2D with a glycated hemoglobin (HbA1c) between 6.5% and 8.0%, and had *established atherosclerotic cardiovascular disease* defined as a history of major coronary artery disease, ischemic cerebrovascular disease, or atherosclerotic peripheral arterial disease. Patients with an estimated glomerular filtration rate of <30 mL/min/1.73 m^2 of body surface area were excluded. For the primary cardiovascular outcome—time to first event of a composite of cardiovascular mortality, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for unstable angina— sitagliptin was noninferior to placebo. Compared to placebo, sitagliptin therapy also did not significantly affect rates of hospitalization for heart failure (hHF). All outcome events were centrally adjudicated by a clinical-events classification committee blinded to randomized assignment. All patients provided written informed consent, and the study was approved by the ethics committee for each participating site.

Study population

Patients were enrolled from December 2008 to July 2012. For the present analyses, we included patients with a history of HF at baseline who had a documented ejection fraction (EF). EF was collected on patients based on 1 of 4 categorical variables: normal function (EF >55%), mild dysfunction (EF = 40%-55%), moderate dysfunction (EF = 25%-39%), or severe dysfunction (EF <25%). For the present analyses, we defined HF with preserved EF (HFpEF) to include those with normal function or mild dysfunction (ie, EF ≥40%), and HF with reduced EF (HFrEF) to include patients classified with moderate or severe dysfunction (ie, EF< 40%) in accord with the American College of Cardiology Foundation/American Heart Association HF guideline definition for HFrEF.[1] Notably, we were not able to use the contemporary HFpEF cutoff of ≥50% given the categorization of baseline HF data collected in TECOS.

Study definitions and outcomes

TECOS participants were grouped into 5 global regions according to the prespecified subgroup analysis for the overall trial as published in the original trial design: North America (Canada and the USA), Latin America (Argentina, Brazil, Chile, and Colombia), Western Europe (Belgium, Finland, France, Germany, Italy, Netherlands, Norway, Spain, Sweden, and United Kingdom), Eastern Europe (Bulgaria, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Slovakia, and Turkey), and Asia Pacific and Other (Australia, China, Hong Kong, India, Israel, South Korea, Malaysia, New Zealand, Singapore, South Africa, and Taiwan).

The primary clinical outcome for the present analyses was time to the first composite event of all-cause mortality (ACM) or *bHF*; the latter was defined as hospital admission for congestive HF and treatment with intravenous diuretics, inotropes, or vasodilator therapy. The secondary outcome was time to ACM. Median follow-up was 2.9 years (interquartile range: 2.3-3.6).

Statistical analysis

Baseline characteristics including medical management were summarized by region using frequencies and percentages for categorical variables and medians and 25th and 75th percentiles for continuous variables. The composite primary and secondary outcomes were assessed by region using adjusted Cox proportional hazard models, with North American participants used as the reference group for all analyses. Tests were also conducted for interaction between geographic region and degree of glycemic control (reference: HbA1c ≥7.5) and sex (reference: male) in association with the primary outcome.

Models were adjusted for covariates previously identified as being associated with our primary and secondary outcomes in the large Nateglinide and Valsartan in Impaired Glucose Tolerance Outcomes Research

Table I. Baseline characteristics of participants with T2D and HF by geographic region

Characteristic	Total (N = 1591)	US/Canada (n = 237)	Latin America (n = 154)	W Europe (n = 191)	E Europe (n = 847)	Asia Pacific (n = 162)
Demographics						
Age, y	66 (60-72)	67 (61-73)	66 (60-73)	70 (64-74)	65 (60-71)	65 (60-72)
Female	484 (30%)	49 (21%)	47 (31%)	29 (15%)	325 (38%)	34 (21%)
White	1316 (83%)	185 (78%)	43 (28%)	188 (98%)	845 (100%)	55 (34%)
Hispanic ethnicity	200 (13%)	20 (8%)	144 (94%)	30 (16%)	6 (1%)	0 (0%)
Smoking						
Current	182 (11%)	35 (15%)	10 (6%)	23 (12%)	99 (12%)	15 (9%)
Former	692 (43%)	142 (60%)	86 (56%)	112 (59%)	279 (33%)	73 (45%)
Never	717 (45%)	60 (25%)	58 (38%)	56 (29%)	469 (55%)	74 (46%)
Medical history						
CAD	1433 (90%)	223 (94%)	134 (87%)	182 (95%)	734 (87%)	160 (99%)
MI	1032 (65%)	151 (64%)	108 (70%)	120 (63%)	553 (65%)	100 (62%)
PAD	189 (12%)	29 (12%)	24 (16%)	42 (22%)	85 (10%)	9 (6%)
COPD	244 (15%)	58 (24%)	23 (15%)	38 (20%)	104 (12%)	21 (13%)
Prior CABG	515 (32%)	118 (50%)	49 (32%)	68 (36%)	220 (26%)	60 (37%)
Hypertension	1462 (92%)	221 (93%)	134 (87%)	164 (86%)	800 (94%)	143 (88%)
Hyperlipidemia	1329 (84%)	229 (97%)	116 (75%)	155 (81%)	699 (83%)	130 (80%)
Stroke	240 (15%)	31 (13%)	25 (16%)	26 (14%)	140 (17%)	18 (11%)
Atrial fibrillation/flutter	326 (20%)	63 (27%)	25 (16%)	51 (27%)	160 (19%)	27 (17%)
Depression	122 (8%)	64 (27%)	16 (10%)	13 (7%)	20 (2%)	9 (6%)
HF classification						
LVEF dysfunction						
Severe dysfunction (<25%)	55 (3%)	16 (7%)	3 (2%)	9 (5%)	15 (2%)	12 (7%)
Moderate dysfunction (25%-39%)	269 (17%)	65 (27%)	36 (23%)	44 (23%)	84 (10%)	40 (25%)
Mild dysfunction (40%-55%)	679 (43%)	84 (35%)	68 (44%)	68 (36%)	408 (48%)	51 (31%)
Normal function (>55%)	588 (37%)	72 (30%)	47 (31%)	70 (37%)	340 (40%)	59 (36%)
NYHA class						
1	336 (21%)	36 (15%)	36 (23%)	54 (28%)	152 (18%)	58 (36%)
2	771 (48%)	67 (28%)	76 (49%)	80 (42%)	497 (59%)	51 (31%)
3	250 (16%)	22 (9%)	33 (21%)	26 (14%)	155 (18%)	14 (9%)
4	10 (1%)	2 (1%)	1 (1%)	0 (0%)	6 (1%)	1 (1%)
Not available	224 (14%)	110 (46%)	8 (5%)	31 (16%)	37 (4%)	38 (23%)
Vitals						
SBP, mm Hg	132 (122-145)	124 (114-137)	140 (124-150)	130 (121-142)	135 (128-145)	130 (118-144)
DBP, mm Hg	80 (70-85)	70 (64-78)	78 (70-86)	75 (67-80)	80 (75-88)	75 (69-82)
BMI, kg/m^2	31 (28-35)	33 (29-37)	29 (26-32)	31 (27-34)	32 (29-35)	28 (25-31)
Diabetes health						
Diabetes duration, y	9 (5-16)	12 (8-18)	9 (6-16)	11 (6-17)	8 (5-13)	11 (6-16)
eGFR, mL/min/1.73m^2	68 (55-83)	65 (48-77)	60 (52-75)	61 (49-76)	73 (59-87)	61 (49-74)
HbA1c, %	7 (7-8)	7 (7-8)	7 (7-8)	7 (7-8)	7 (7-8)	7 (7-8)
HbA1c % category						
<7	444 (28%)	66 (28%)	41 (27%)	69 (36%)	226 (27%)	42 (26%)
7-7.4	580 (36%)	79 (33%)	55 (36%)	53 (28%)	333 (39%)	60 (37%)
≥7.5	567 (36%)	92 (39%)	58 (38%)	69 (36%)	288 (34%)	60 (37%)

Data shown are n (%) or median (25th, 75th percentiles). *CAD*, coronary artery disease; *MI*, myocardial infarction; *PAD*, peripheral arterial disease; *COPD*, chronic obstructive pulmonary disease; *CABG*, coronary artery bypass graft; *LVEF*, left ventricular ejection fraction; *NYHA*, New York Heart Association; *SBP*, systolic blood pressure; *DBP*, diastolic blood pressure; *BMI*, body mass index; *eGFR*, estimated glomerular filtration rate.

(NAVIGATOR) clinical trial, which assessed the impact of valsartan and nateglinide on cardiovascular outcomes in patients with impaired glucose tolerance. Enrollment in NAVIGATOR was global, with the greatest number of patients similarly enrolled from Europe. The adjustment covariates chosen from NAVIGATOR models for cardiovascular outcomes[13,14] are similar to previous studies from TECOS.[15] The ACM outcome was adjusted for HbA_{1c}, age, estimated glomerular filtration rate, diabetes duration, body mass index, hemoglobin, low-density lipoprotein cholesterol, treatment assignment, female sex, current smoker, history of cerebrovascular disease, coronary artery disease, peripheral arterial disease, chronic obstructive pulmonary disease, atrial fibrillation, and time to ACM. The primary outcome was adjusted for the above covariates as well as systolic blood pressure and time to hHF. Separate analyses for the primary and secondary outcomes were run for participants with

Table II. Odds of receiving evidence-based HF therapies at baseline in patients with HFrEF by geographic region

Therapy drug	Region	OR (95% CI)	P	OR (95% CI) adjusted*	P
A C E I / ARB	Latin America	1.25 (0.44-3.52)	.33	1.40 (0.41-4.86)	.47
	Western Europe	1.11 (0.45-2.76)		1.21 (0.45-3.25)	
	Eastern Europe	2.27 (0.94-5.51)		2.26 (0.81-6.29)	
	Asia Pacific and Other	2.14 (0.73-6.29)		2.28 (0.68-7.61)	
β-Blocker	Latin America	0.58 (0.24-1.42)	.27	0.62 (0.20-1.88)	.76
	Western Europe	1.11 (0.45-2.76)		0.96 (0.36-2.55)	
	Eastern Europe	1.65 (0.72-3.76)		1.09 (0.42-2.83)	
	Asia Pacific and Other	1.25 (0.49-3.20)		1.31 (0.45-3.80)	
MRA	Latin America	3.80 (1.70-8.47)	.007	5.35 (1.97-14.50)	.002
	Western Europe	1.44 (0.69-2.99)		1.66 (0.75-3.66)	
	Eastern Europe	2.33 (1.25-4.32)		3.17 (1.50-6.68)	
	Asia Pacific and Other	1.37 (0.65-2.86)		1.07 (0.46-2.52)	

The reference group for OR computations is North America. *ACEI/ARB*, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker.
* Adjusted for age, sex (female), atrial fibrillation, peripheral artery disease, coronary artery disease, estimated glomerular filtration rate, diabetes duration, smoking status, height, weight, systolic blood pressure, hemoglobin, and glycated hemoglobin. Estimated with imputed data.

HFrEF and HFpEF. Models for the HFrEF and HFpEF subgroups were not adjusted because there were too few events in some regions to reliably fit adjusted models. All statistical computations were generated using SAS, version 9.4 (SAS Institute Inc., Cary, NC).

The TECOS trial was funded by Merck Sharp & Dohme Corp, a subsidiary of Merck & Co., Inc, Kenilworth, NJ. The study was designed and run independently by the Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit in an academic collaboration with the sponsor. All analyses were performed by Duke Clinical Research Institute and the University of Oxford Diabetes Trials Unit, independent of the sponsor. The authors are solely responsible for the design and conduct of this study, all analyses, the drafting and editing of the paper, and its final contents. All authors agreed to submit the report for publication; the funder had no role in this decision.

Results

Analysis cohort

A total of 2,643 participants had a history of HF at baseline, and EF data were available for the 1,591 participants included in these analyses. More participants had HFpEF (n = 1267, 80%) than HFrEF (n = 324, 20%). Most of the enrolled HF participants were from Eastern Europe (n = 847), followed by North America (n = 237), Western Europe (n = 191), Asia Pacific (n = 162), and Latin America (n = 154). Study participants had a median (25th-75th percentiles) age of 66 (60-72) years, and 30% were female. Median HbA_{1c} at baseline was 7%.[7,8]

Baseline characteristics by geographic region

Participants enrolled in North America and Western Europe were generally older and had higher prevalence of coronary artery disease and atrial fibrillation as compared with participants enrolled in Eastern Europe and Latin America. Participants enrolled in North America, Asia Pacific, and Western Europe had a higher proportion of HFrEF (34%, 32%, and 28%, respectively) as compared with participants enrolled in Latin America and Eastern Europe (25% and 12%, respectively). North American and Western European participants had on average longer diabetes duration than Eastern European and Latin American participants, although median HbA1c did not differ (Table I). Similar characteristics were seen in the overall TECOS population with history of HF at baseline (n = 2643) (Table I in the Data Supplement).

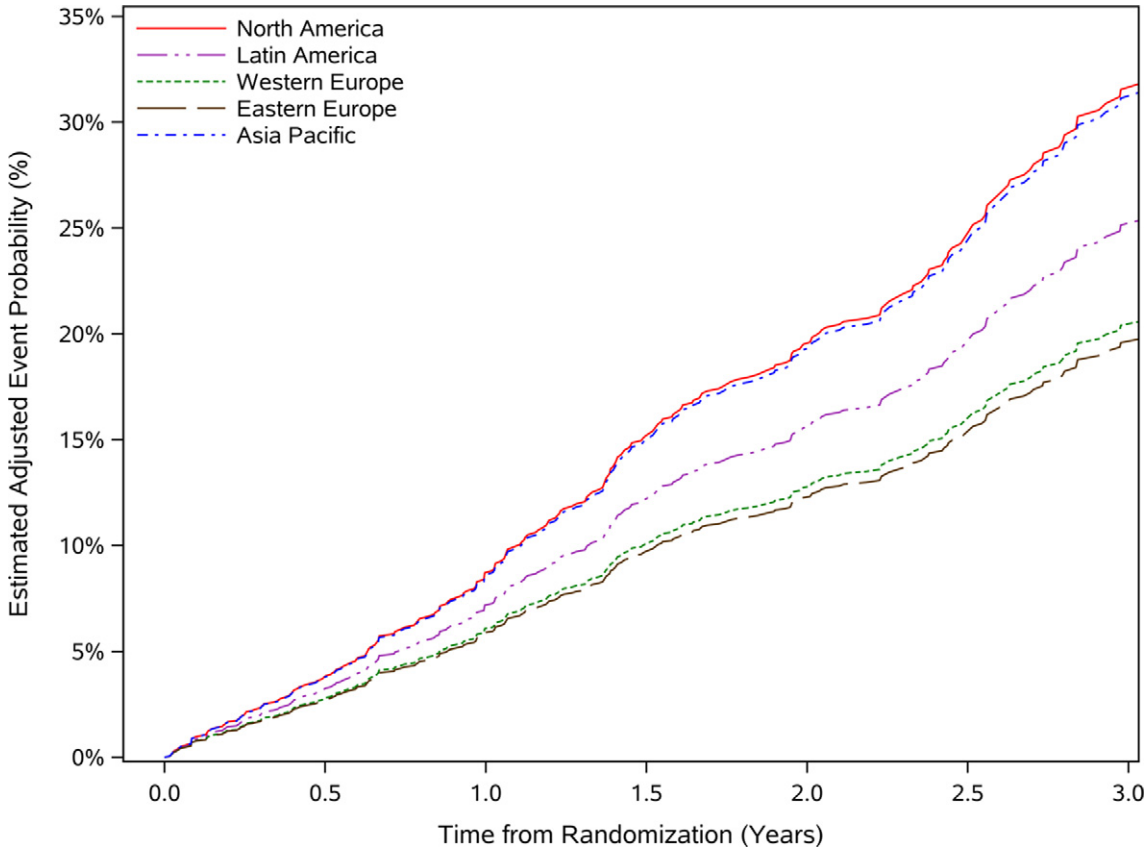
Medical management of HF by geographic region

In the overall HF population, diuretic use was highest in participants from North America (78%), followed by participants from Western Europe (73%), and was lowest in participants from Latin America (52%) (Table II in the Data Supplement). In the subgroup with HFpEF, diuretic (loop or thiazide) use was also highest in North America (76%) compared with other regions. In participants with HFrEF, angiotensin-converting enzyme inhibitor/angiotensin receptor blocker and β-blocker therapy was high and did not differ notably across the geographic regions (adjusted *P* values for both >.4). Regarding mineralocorticoid receptor antagonist (MRA) use, participants with HFrEF in Eastern Europe (adjusted odds ratio [PR]: 3.17; 95% CI: 1.50-6.68) and Latin America (OR 5.35; 95% CI: 1.97-14.50) were much more likely to be prescribed these medications than those from North America (*P* = .002) (Table II).

Association between geographic region and clinical outcomes

In the overall HF population, compared with participants from North America, participants from Eastern Europe had the lowest incidence of the primary outcome (unadjusted hazard ratio [HR]: 0.38, 95% CI: 0.28-0.52; adjusted HR: 0.45, 95% CI: 0.32-0.64) (Fig. 1, Table III). Western Europe also differed from North America with respect to the primary outcome after adjustment

Fig. 1



Adjusted Kaplan-Meier curves for ACM or hHF by geographic region in patients with T2D and HF with a documented baseline ejection fraction.

(adjusted HR 0.49; 95% CI: 0.32-0.77). These results were also seen across all TECOS enrolled patients with documented history of HF at baseline (n = 2,643) (Table III in the Data Supplement). Participants from Eastern Europe had the lower incidence for ACM (unadjusted HR: 0.60; 95% CI: 0.41-0.88), but these differences were not significant after multivariable adjustment (HR: 0.79; 95% CI: 0.44-1.45) (Table III). An exploratory analysis of cardiovascular death and hHF showed similar outcomes, with participants from Eastern Europe having lower event rates (adjusted HR: 0.57; 95% CI: 0.37-0.87). (See Tables I–V.)

In participants with HFpEF (n = 1,267), Eastern Europeans (unadjusted HR: 0.40; 95% CI: 0.27-0.59) and Western Europeans (unadjusted HR: 0.50; 95% CI: 0.28-0.88) had significantly lower incidence of the primary outcome as compared with participants with HFpEF enrolled in North America. ACM in HFpEF participants was also significantly lower in Eastern Europeans (unadjusted HR: 0.60; 95% CI: 0.37-0.97) as compared with North Americans (Table IV).

In participants with HFrEF (n = 324), the incidence of the primary outcome did not significantly differ in participants enrolled in Eastern Europe as compared with participants enrolled in North America (unadjusted HR: 0.65; 95% CI: 0.39-1.09). Overall, there were no significant differences in the primary outcome by region among participants with HFrEF. Similarly, the incidence of ACM did not differ by geographic region in participants with HFrEF (P = .65) (Table V).

The observed association between geographic region and the primary outcome in all enrolled participants was not modified by the degree of glycemic control achieved (P = .93 for interaction) or by sex (P = .58 for interaction).

Discussion

Overall, among TECOS participants with a history of HF and available EF, the majority of the HF cohort had HFpEF. Participants with HF from Eastern Europe were more likely to have HFpEF versus HFrEF than from any

Table III. Clinical outcomes by geographic region

Outcome	Geographic region	Total events	HR (95% CI)	*P*	Adjusted HR (95% CI)	Adjusted p
ACM/hHF*	North America (ref)	69		<.001		<.001
	Latin America	38	0.89 (0.60-1.32)		0.67 (0.43-1.05)	
	Western Europe	33	0.59 (0.39-0.90)		0.49 (0.32-0.77)	
	Eastern Europe	103	0.38 (0.28-0.52)		0.45 (0.32-0.64)	
	Asia Pacific and Other	51	1.07 (0.75-1.54)		0.97 (0.65-1.45)	
ACM†	North America (ref)	39		<.001		.20
	Latin America	30	1.35 (0.84-2.18)		1.19 (0.50-2.82)	
	Western Europe	22	0.77 (0.45-1.29)		0.43 (0.20-0.94)	
	Eastern Europe	87	0.60 (0.41-0.88)		0.79 (0.44-1.45)	
	Asia Pacific and Other	33	1.20 (0.75-1.90)		0.64 (0.29-1.43)	

* Adjusted for systolic blood pressure, glycated hemoglobin, age, diabetes duration, body mass index, hemoglobin, sitagliptin use, chronic obstructive pulmonary disease, atrial fibrillation, history of cerebrovascular disease or coronary artery disease or peripheral vascular disease, estimated glomerular filtration rate, low-density lipoprotein, female sex, current smoker, time to HF hospitalization, and time to ACM.
† Adjusted for glycated hemoglobin, age, estimated glomerular filtration rate, diabetes duration, mass index, hemoglobin, low-density lipoprotein, sitagliptin use, chronic obstructive pulmonary disease, atrial fibrillation, history of cerebrovascular disease or coronary artery disease or peripheral vascular disease, female gender, current smoker, and time to ACM.

other region. There were significant differences in baseline characteristics, comorbidity burden, and HF medical management by geographic region. Patients enrolled from Eastern Europe had lower incidence of ACM/hHF as compared with patients enrolled from North America. This relationship was also observed in the subset of patients with HFpEF. In patients with HFrEF, there was no significant difference in the incidence of ACM/hHF for patients from Eastern Europe compared with those from North America. The relationship between geographic region and outcomes was not modified by degree of glycemic control or by sex.

Results of the present analyses complement the evidence examining regional differences in international HF trials. In the ATLAS trial, there were significant variations in evidence-based medication use between Europe and North America. North American patients more frequently had diabetes and prior coronary revascularization, whereas Western European patients had less ischemic cardiomyopathy.[16] More recently, an analysis from the PARADIGM-HF trial found similarly low rates of MRA use in North American patients with chronic HFrEF. These data found higher rates of cardiovascular death in patients from Latin America and Asia Pacific as compared with patients from North America.[17] Data from PARADIGM-HF pooled with another large international HFrEF trial, ATMOSPHERE, found lower rates of HF hospitalizations in Eastern Europe as compared with North America.[18]

Although previous analyses have shown differences in medication use between patients with T2D and HFrEF,[19] our analysis adds to the available literature examining clinical outcomes in patients across these 2 highly comorbid conditions with mechanistic implications across all EF. We found significantly higher MRA use among patients with HFrEF enrolled from Eastern Europe and Latin America as compared with patients enrolled from North America. Reasons for this are multifactorial but may in part involve comorbidity burden and provider choices. In addition, given the significantly higher frequency of diuretic use among patients enrolled in North America, there may be more avoidance of MRAs in these patients due to concerns of inducing hypovolemia and/or worsening kidney function.

We found significantly lower incidence of the primary outcome among patients enrolled from Eastern Europe as compared with patients enrolled from North America. The persistent association even after multivariable adjustment is hypothesis generating in the context of this observational analysis. However, it is notable that these observations seem to be driven in large part by the HFpEF population, as the primary outcome did not differ significantly by region in patients defined as having HFrEF. In addition, differences in the primary outcome seem to be largely due to differences in hHF, as the secondary outcome of ACM did not differ by geographic region after multivariable adjustment. The observed findings may result from practice variation around clinical disease state definition; thresholds for hHF; unmeasured genetic variations; and dietary, lifestyle, and medication administration differences that exist between geographic regions, although it is notable that weight, body mass index, and blood pressure did not differ significantly among patients from North America and Eastern Europe. Our findings are similar to those of the ASCEND-HF trial, which found that patients enrolled in Central Europe had lower event rates for the primary outcome of ACM/hHF at 30 days as compared with those from North America.[20]

The observed differences in outcomes may also be due, in part, to differences in the inclusion of patients diagnosed as HFpEF by geographic region. The lack of universal identification criteria for HFpEF in addition to the lack of availability/feasibility of routine biomarker use (eg, N-terminal pro–B-type natriuretic peptide) and

Table IV. Clinical outcomes by geographic region in patients with HFpEF

Outcome	Geographic region	Total events (region)	Unadjusted HR (95% CI)	P
A C M / hHF	North America (ref)	37		<.001
	Latin America	25	0.97 (0.58-1.61)	
	Western Europe	17	0.50 (0.28-0.88)	
	Eastern Europe	77	0.40 (0.27-0.59)	
	Asia Pacific and other	27	0.98 (0.59-1.61)	
ACM	North America (ref)	22		.004
	Latin America	20	1.44 (0.78-2.65)	
	Western Europe	12	0.66 (0.32-1.33)	
	Eastern Europe	67	0.60 (0.37-0.97)	
	Asia Pacific and other	18	1.03 (0.55-1.94)	

invasive hemodynamic diagnosis (eg, right and left heart catheterizations) may result in important differences in patient characteristics across sites and/or regions. Given the relatively high proportion of patients with HFpEF in the present analyses, TECOS may have included patients with varying degrees of diastolic dysfunction. In addition, some of the patients classified as HFpEF may have had other diseases with overlapping symptomology such as unrevascularized severe coronary artery disease, advanced pulmonary disease, or pulmonary hypertension rather than HF. If the enrollment of these patients without true HFpEF was skewed by region, we would expect lower event rates, particularly for the outcome of hHF, as observed in our analysis.

Previous global HF trials enrolling HFpEF patients have shown similar results. In the PROTECT study, mortality/hospitalization at 60 days was significantly lower in patients from Russia as compared with patients from Western Europe. These results were similarly driven by lower incidence of rehospitalization.[21,22] Patients from Russia and Eastern Europe had a higher proportion of patients with left ventricular EF >40% as compared to those enrolled from North America.[21] In addition, in the TOPCAT trial, patients with HFpEF from Russia/Georgia had lower clinical event rates of cardiovascular mortality and hHF. Enrollment criteria included patients with signs and symptoms of HF in addition to either a history of hospitalization for HF as a major component of the care (per site discretion) within the previous 12 months, or natriuretic peptide levels (B-type natriuretic peptide or N-terminal pro–B-type natriuretic peptide ≥100 or 360 pg/mL, respectively).[23] Patients enrolled from the Americas were well balanced within these strata, whereas in Russia/Georgia, 89% of patients were enrolled by subjective hospitalization stratum. As has been well reported, spironolactone was associated with beneficial effects in the North American cohort in subanalyses.[24] Patient selection as well as site misconduct may have contributed to these findings, as subsequent testing found lower frequency of detecting spironolactone metabolites in samples from patients enrolled from Russia.[25] The present results further reflect international variability, either inherent or driven by different site practices, that raise significant challenges to conducting large, international randomized clinical trials.

These observations are particularly important with the approval of newer agents originally intended to improve glycemic control. For example, recently completed trials in T2D[26,27] and ongoing clinical trials will assess the efficacy of these agents across all EFs in patients with T2D. Such trials (eg, EMPEROR-Preserved [ClinicalTrials.gov Identifier NCT03057951]) will enroll a geographically diverse population, and considerations regarding the proper identification, enrollment, and treatment allocation of patients will be important in ensuring internal validity.

There are several limitations of our study that should be acknowledged. First, the analysis used a nonrandomized subset of patients enrolled in the TECOS trial, specifically those with a history of HF and documented EF at baseline. Our study included a subset of the overall TECOS study population, including only those with available data on left ventricular ejection fraction, which differed with respect to patient characteristics and medication use from the overall TECOS population. Furthermore, detailed inclusion/exclusion criteria may limit generalizability. As this analysis was post hoc, it is subject to the biases of exploratory analyses, and the limited sample size may have been underpowered with respect to the primary analysis in groups other than Eastern Europe. There were too few events in some of the regions, especially Western Europe, to reliably fit adjusted models for outcomes by HFrEF versus HFpEF. The regional differences in the HFpEF population may be due to confounding not adjusted for in our models. Conversely, given the relatively modest number of events in patients with HFrEF, our analyses may be of reduced statistical power. We defined *HFrEF* as EF <40% based on available information from the TECOS data collection. Therefore, we have limited information on important differences/regional variation in patients with borderline or midrange EF (40%-55%). Our findings may in part be subject to patient differences not fully accounted for by multivariable adjustment. The lack of collection of biomarker data such as circulating natriuretic peptide concentrations in conjunction with echocardiographic and/or invasive hemodynamic monitoring for the diagnosis of HFpEF could have led to the inclusion of patients without true HFpEF. Finally, differences in medical management by region may be related to

Table V. Clinical outcomes by geographic region in patients with HFrEF

Outcome	Geographic region	Total events	Unadjusted HR (95% CI)	*P*
ACM/hHF	North America (ref)	32		.16
	Latin America	13	0.83 (0.44-1.59)	
	Western Europe	16	0.86 (0.47-1.57)	
	Eastern Europe	26	0.65 (0.39-1.09)	
	Asia Pacific and other	24	1.31 (0.77-2.22)	
ACM	North America (ref)	17		.65
	Latin America	10	1.32 (0.60-2.88)	
	Western Europe	10	1.06 (0.48-2.32)	
	Eastern Europe	20	1.03 (0.54-1.97)	
	Asia Pacific and other	15	1.60 (0.80-3.21)	

extrinsic factors including insurance coverage, prescription prices, and medication availability that likely vary between and across geographic regions.

Conclusions

Overall, our analyses highlight large regional variation in baseline characteristics, medical management, and clinical outcomes in patients with T2D, atherosclerotic cardiovascular disease, and HF enrolled in a large multinational clinical trial. Our analysis also highlights the heterogeneity that may exist in the inclusion of patients with HFpEF in international trials. Standardization of HF definition and disease severity may be indicated in future trials enrolling similar populations. Future trials involving a large multinational cohort should be further analyzed to determine whether randomized treatment effects vary by enrollment region.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.ahj.2019.08.016.

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