ESC European Society of Cardiology

European Heart Journal (2018) **39**, 2376–2386
doi:10.1093/eurheartj/ehy036

CLINICAL RESEARCH
Vascular medicine

Diabetes and long-term outcomes of ischaemic stroke: findings from Get With The Guidelines-Stroke

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Received 5 August 2017; revised 30 September 2017; editorial decision 18 January 2018; accepted 18 January 2018; online publish-ahead-of-print 9 February 2018

See page 2387 for the editorial comment on this article (doi: 10.1093/eurheartj/ehy033)

Aims There is a paucity of data on the influence of diabetes on long-term outcomes after ischaemic stroke (IS). We assessed whether outcomes after IS differ between patients with and without diabetes.

Methods and results Patients aged ≥65 years ($n = 409\,060$) in Get With The Guidelines-Stroke (nationwide registry of stroke patients from 1690 sites in the USA) were followed for 3 years post-discharge. The outcomes of interest were mortality, cardiovascular and non-cardiovascular hospitalizations, heart failure (HF), and recurrence of IS/transient ischaemic attack (TIA). Patients with diabetes (29.6%) were younger and had more comorbidities. At 3 years post-discharge after IS, diabetes was associated with higher risks of adverse outcomes: all-cause mortality [cumulative incidence 46.0% vs. 44.2%, absolute difference (AD) 1.8%; adjusted hazard ratio (aHR) 1.24, 95% confidence interval 1.23–1.25], all-cause readmission (71.3% vs. 63.7%, AD 7.6%; aHR 1.22, 1.21–1.23), composite of mortality and all-cause readmission (84.1% vs. 79.3%, AD 4.8%; aHR 1.21, 1.20–1.22), composite of mortality and cardiovascular readmission (69.5% vs. 64.3%, AD 5.2%; aHR 1.19, 1.18–1.20), IS/TIA readmission (15.9% vs. 13.3%, AD 2.6%; aHR 1.18, 1.16–1.20), HF readmission (10.3% vs. 6.4%, AD 3.9%; aHR 1.60, 1.56–1.64), non-cardiovascular readmission (58.3% vs. 50.3%, AD 8.0%; aHR 1.28, 1.26–1.29), and non-IS/TIA readmission (67.6% vs. 59.7%, AD 7.9%; aHR 1.23, 1.22–1.25). Accounting for the initial severity of stroke using the National Institute of Health Stroke Scale as well as using propensity score matching method as a sensitivity analysis, did not modify the results.

Conclusion Among older IS patients diabetes was associated with increased risks of death, cardiovascular and non-cardiovascular hospitalizations, HF, and IS/TIA recurrence.

Keywords Diabetes • Glycated haemoglobin • Stroke • Ischaemic stroke • Transient ischaemic attack

Introduction

Diabetes and stroke are each highly prevalent in the USA.[1,2] Patients with diabetes display an increased the risk of ischaemic stroke (IS) by at least twice that of those without the condition.[3] Diabetes and IS tend to coexist, with at least one in four patients with IS having diabetes.[4] Diabetes may promote adverse outcomes of IS through an acceleration of the atherosclerosis process.[5] However, it is unclear to what extent diabetes influences long-term IS outcomes other than mortality, especially cardiovascular events and hospitalizations. There

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have been a limited number of investigations on this topic. Such investigations may clarify our understanding of the natural history and clinical outcomes (including stroke recurrence) of patients with both IS and diabetes, including the magnitude of possible differences within clinically important subgroups defined by age, comorbidities, previous IS/transient ischaemic attack (TIA), initial severity of stroke, chronic kidney disease (CKD), or racial/ethnic background.[3]

Population-based studies have shown that two-thirds of all strokes occur in patients aged 65 years and older.[2] Older patients with IS have worse functional outcomes and higher recurrent event risk than younger patients.[6] Using Get With The Guidelines (GWTG)-Stroke registry data linked to Centres for Medicare & Medicaid Services claims, we assessed the association of diabetes and long-term outcomes of patients age 65 years of age and older with IS, including mortality, all-cause readmission, hospitalization for cardiovascular reasons, hospitalization for non-cardiovascular causes, heart failure (HF), and readmission for IS/TIA. We hypothesized that diabetes will be associated worse outcomes in older patients with IS, even after accounting for demographics and other comorbid conditions.

Methods

Data source

The study cohort was formed from the Get With The Guidelines (GWTG)-Stroke, a national prospective stroke registry and quality improvement program sponsored by the American Heart Association (AHA)/American Stroke Association (ASA). Details of the design and conduct of the GWTG-Stroke registry have been previously described.[7] In GWTG-Stroke, participating hospitals use an internet-based patient management tool (IQVIA, Inc, Durham NC) to add data to a central database on consecutive acute IS patients. The methods for data extraction have been previously described,[8] as well as the validity and reliability of data collection.[9] As the primary objective of data collection is quality improvement, each participating hospital received either human research approval to enrol cases without individual patient consent under the common rule or a waiver of authorization and exemption from subsequent review by their Institutional Review Board. The Duke Clinical Research Institute serves as the data analysis centre.

The patients enrolled in the GWTG-Stroke registry were those hospitalized with new IS or TIA, or patients who developed significant stroke/TIA symptoms such that stroke was the primary discharge diagnosis. The in-hospital data from the GWTG-Stroke registry were linked to the Centres for Medicare & Medicaid Services (CMS) claims data. The linked clinical and claims data set (GWTG-Stroke/CMS) was created by matching on a series of indirect identifiers, including admission date, discharge date, patient age or date of birth, and sex. This probabilistic linkage methodology has previously been successfully completed and validated using the 100% Medicare inpatient claims and GWTG-Stroke.[10] The Medicare claims for outpatient and skilled nursing facilities data were limited to fee-for-service Medicare patients aged ≥65 years at the time of first stroke diagnosis. Prior work has shown that patients in the linked GWTG-Stroke/CMS database are representative of the national Medicare IS population.[8] In case multiple stroke admission records were linked for a single patient, we used the earliest record for this analysis.

Study population (inclusion and exclusion criteria)

The study cohort was restricted to patients age 65 years and above with a final diagnosis of IS. Only patients aged ≥65 years were included in the study because this is the group of patients for whom data post-discharge follow-up data on outcomes can be obtained through linkage to the CMS data. Case ascertainment of admissions for IS was conducted using the *International Classification of Diseases 9th revision (ICD-9)* discharge codes for IS, with chart review for eligibility confirmation. Patients were further excluded if: (i) they were transferred in from another facility; (ii) transferred out to another acute care facility; (iii) left against medical advice or if the discharge status was unknown; and (iv) had an unknown diabetes status or (v) they died during hospitalization.

Diabetes ascertainment

Diabetes mellitus was defined by prior medical history of diabetes mellitus or new clinical diagnosis of diabetes mellitus during index hospitalization. We used an alternative definition of diabetes to perform a sensitivity analysis, which was based on a combination of criteria including a past history of diabetes, the use of diabetes medications prior to admission, the use of diabetes medications at discharge, and a new diagnosis of diabetes during index admission.

Outcomes

The primary outcome was all-cause mortality. The secondary outcomes included a composite of mortality and all-cause readmission, a composite of death and cardiovascular readmission, all-cause admission, admission for recurrent IS (IS/TIA) (stroke specific event), admission for recurrent IS only (stroke specific event), admission for acute myocardial infarction (AMI), admission for HF, cardiovascular readmission, non-cardiovascular admission, and non IS/TIA readmission. The outcomes were assessed at 1 year and at 3 years post-discharge. Mortality was ascertained on the basis of death dates from the CMS vital status files,[10,11] and admission on the basis of subsequent Medicare inpatient claims. The *ICD-9* discharge codes were used for defining outcomes and are shown in the Supplementary material online, *Table S1*.

Statistical analysis

We compared patient (demographic and clinical) and hospital characteristics between patients with and without diabetes. Categorical variables were presented as proportions, and differences tested using the Pearson's χ^2 test. Continuous variables were presented as median (interquartile range), and differences between groups were tested using the Wilcoxon rank sum test. Percent standardized differences were also provided for all variables between the diabetes and no-diabetes groups. The cumulative incidence of each outcome was estimated by diabetes status. The differences in mortality were tested using the log-rank test. For the hospitalization outcomes, we accounted for the competing risk of death, and assessed the differences between those with and without diabetes using the Gray's test. We used Cox proportional hazards models to test the association between diabetes and each clinical outcome. The models used a robust variance estimation to account for correlation within sites. The covariates included in the multivariable models were patients characteristics {age, sex, race [white, black, other], medical history [hypertension, dyslipidaemia, smoking, atrial fibrillation/flutter, previous stroke/TIA, coronary artery disease (CAD)/prior myocardial infarction, HF, carotid stenosis, peripheral vascular disease (PVD)], arrival via Emergency Medical Services (EMS), on vs. off hours admission, discharge year} and hospital characteristics (geographic region, teaching status, rural location, bed size, annual admissions for IS, primary stroke centre).

We performed a series of additional analyses, to assess the robustness of our findings and explore potential factors that may influence the relation of diabetes status and stroke outcomes. These analyses are as follows: (i) using an alternative diabetes definition, (ii) adjusting for NIHSS score in patients with recorded NIHSS, (iii) assessing the outcomes by

diabetes status among patients, who received thrombolysis with tissue plasminogen activator (tPA), and (iv) prespecified stratified analyses in clinically relevant subgroups by age (<80 and ≥80 years), sex (female and male), race (non-Hispanic black and other), baseline pre-existing cardiovascular disease and CKD [estimated glomerular filtration rate (eGFR) <60 and ≥60 ml/min/1.73m^2]. We also assessed the association between glycated haemoglobin (HbA_{1C} ≥7% vs. <7%) and outcomes in diabetes patients who had HbA_{1C} data recorded. To account for the association of diabetes treatment with outcomes, we assessed the outcomes among patients with diabetes discharged on insulin therapy compared to those not on insulin therapy at discharge. Missing covariates were handled by imputation based on the extent of missingness, as detailed in Supplementary material online, *Table S2*.

Analyses were performed using the SAS version 9.4 (SAS Institute Inc., Cary, NC, USA). All *P*-values are 2-sided tests and were considered statistically significant at <0.05.

Results

A total of 1 124 670 stroke patients were admitted between 1 April 2003 and 31 December 2011, to GWTG-Stroke fully-participating hospitals (1755 sites). Of these, we excluded a number of patients for following reasons: age <65 years ($n = 365\ 286$), transferred-out hospitalizations ($n = 12\ 220$), left against medical advice/discharge disposition not determined or missing ($n = 10\ 210$), unknown diabetes status ($n = 2202$), no link to CMS claims data ($n = 243\ 393$), non-index admission ($n = 30\ 692$), fee-for-service ineligible at index discharge ($n = 23\ 967$), or in-hospital death ($n = 27\ 640$). The final study sample contained 409 060 patients aged ≥65 years (from 1690 sites) followed for up to 3 years post-discharge (until 31 December 2014).

Baseline characteristics

The baseline patients (demographic and clinical) and hospitals characteristics between the diabetes and no-diabetes groups are shown in *Table 1*. Patients with diabetes (29.6%, $n = 120\ 989$) were more likely to be younger, from an ethnic minority (Hispanic or Black), to have a higher body mass index, as well as to have a history of comorbidities including hypertension, dyslipidaemia, CKD, prior IS/TIA, carotid stenosis, CAD, PVD, and HF. Accordingly, diabetic patients were also more likely to be on cholesterol-lowering medication, antihypertensives and antiplatelets.

Clinical outcomes

The cumulative incidence rates of mortality and other outcomes were significantly higher in those with diabetes compared with those without diabetes, over the 3-year follow-up period (*Tables 1 and 2*). At 1 year and 3 years post-discharge, the cumulative incidence rates of outcomes were different between the diabetes and non-diabetes groups (*Table 2* and *Figure 1*): all-cause mortality (absolute differences (ADs) at 1 year and 3 years 0.1% and 1.8%, respectively), all-cause readmission (ADs 7.7% and 7.6%), composite of mortality and readmission (ADs 5.4% and 4.8%), composite of death and cardiovascular readmission (ADs 3.7% and 5.2%), IS/TIA readmission (ADs 1.7% and 2.6%), IS readmission (ADs 1.4% and 2.3%), AMI readmission (ADs 0.8% and 1.7%), HF admission (ADs 2.1% and 3.9%), non-cardiovascular admission (ADs 6.8% and 8%), and non IS/TIA admission (ADs 7.5% and 7.9%). These differences were significant for all outcomes ($P < 0.0001$), except for all-cause mortality at 1 year ($P = 0.54$).

After multivariable adjustment for relevant patient characteristics (*Table 2* and *Figure 2*), compared with the no-diabetes group, diabetes was associated with higher risks of outcomes at 1 year, including all-cause mortality [adjusted hazard ratio (aHR) 1.20, 95% confidence interval (CI) 1.18–1.22], composite of mortality and all-cause readmission (aHR 1.19, 95% CI 1.18–1.20), composite of death and cardiovascular readmission (aHR 1.16, 1.15–1.18), all-cause readmission (aHR 1.21, 1.20–1.23), IS/TIA readmission (aHR 1.15, 1.12–1.17), IS readmission (aHR 1.17, 1.13–1.20), AMI readmission (aHR 1.52, 1.45–1.60), HF readmission (aHR 1.55, 1.50–1.61), non-cardiovascular readmission (aHR 1.27, 1.26–1.29), and non-IS/TIA readmission (aHR 1.22, 1.21–1.24). Similar differences in diabetes-related multivariable adjusted risk estimates were observed at 3-years for all outcomes: all-cause mortality (aHR 1.24, 1.23–1.25), all-cause readmission (aHR 1.22, 1.21–1.23), composite of mortality and all-cause readmission (aHR 1.21, 1.20–1.22), composite of death and cardiovascular readmission (aHR 1.19, 1.18–1.20), IS/TIA readmission (aHR 1.18, 1.16–1.20), IS readmission (aHR 1.20, 1.18–1.23), AMI readmission (aHR 1.55, 1.49–1.60), HF readmission (aHR 1.60, 1.56–1.64), non-cardiovascular readmission (aHR 1.28, 1.26–1.29), and non-IS/TIA readmission (aHR 1.23, 1.22–1.25).

In sensitivity analysis conducted on a one-on-one propensity score matched sample ($N = 216\ 562$), we found higher risks of adverse 1-year and 3-year IS outcomes among patients with diabetes compared with those without diabetes (see Supplementary material online, *Table S3*), which is consistent with the findings (both in terms of the magnitude and significance of associations) obtained in the primary analysis using traditional multivariable models.

Alternative definition of diabetes and outcomes

Using an alternative definition of diabetes, a higher proportion of participants ($N = 132\ 220$, 32.3%) were identified as having diabetes. In this newly defined group, similar results were observed both in terms of the magnitude and significance of the estimates of association of diabetes with outcomes. This included significantly higher cumulative incidence rates of all outcomes in those with diabetes (see Supplementary material online, *Table S4* and *Figure S1*), as well as significantly higher risk of all outcomes (all-cause mortality, all-cause admission, composite outcome of mortality and admission, composite of death and cardiovascular readmission, IS/TIA admission, IS admission, AMI admission, HF admission, non-cardiovascular readmission, and non-IS/TIA readmission) over the 1-year and 3-year follow-up periods (see Supplementary material online, *Table S4*).

Influences of stroke severity and use of tissue plasminogen activator on the association of diabetes and outcomes

Given that the National Institutes of Health Stroke Scale (NIHSS), a validated tool for assessing the initial stroke severity, has been shown to predict mortality in acute IS, we conducted an analysis restricted to participants with available data on the NIHSS ($N = 210\ 631$—51.5% of the initial sample of patients). The multivariable aHRs for all outcomes at 1 year and 3 years among those with data on NIHSS

Table I Baseline characteristics of ischaemic stroke patients by diabetes status in the GWTG-Stroke registry

Variables	Overall *n* = 409 060	Diabetes *n* = 120 989	No diabetes *n* = 288 071	*P*-value	Percent standardized differences
Demographics					
Age[a]	80 (73–86)	77 (71–83)	81 (74–87)	*<0.001*	*35.8*
Age ≥80	51.85	41.22	56.32	*<0.001*	*30.5*
Female	58.11	54.82	59.49	*<0.001*	*9.5*
Race/ethnicity				*<0.001*	
White	81.16	74.03	84.15		*25.1*
Black	9.98	14.82	7.94		*21.8*
Hispanic	3.66	5.50	2.89		*13.1*
Asian	1.67	2.10	1.48		*4.7*
Other	3.54	3.55	3.54		*0.1*
Medical history					
Atrial fibrillation/flutter	23.94	21.52	24.96	*<0.001*	*8.2*
CAD/prior MI	31.10	38.65	27.92	*<0.001*	*22.9*
Carotid stenosis	4.88	5.55	4.60	*<0.001*	*4.3*
Peripheral vascular disease	5.63	7.71	4.75	*<0.001*	*12.3*
Hypertension	78.54	85.62	75.56	*<0.001*	*25.7*
Smoker	9.81	8.68	10.28	*<0.001*	*5.5*
Dyslipidaemia	41.26	49.78	37.67	*<0.001*	*24.6*
Heart failure	7.29	9.63	6.30	*<0.001*	*12.3*
Previous stroke/TIA	29.97	33.51	28.48	*<0.001*	*10.9*
Prosthetic heart valve	1.57	1.55	1.58	*0.409*	*0.3*
Measurements					
BMI[a]	25.9 (22.8–29.8)	27.9 (24.4–32.1)	25.2 (22.2–28.7)	*<0.001*	*40.9*
SBP (50–250) (mmHg)[a]	155 (137–177)	155 (137–178)	155 (137–176)	*<0.001*	*2.6*
Blood glucose (20–800) (mg/dL)[a]	116 (100–145)	148 (115–197)	110 (97–128)	*<0.001*	*86.5*
Serum creatinine (0–150) (mg/dL)[a]	1.0 (0.8–1.3)	1.1 (0.9–1.5)	1.0 (0.8–1.3)	*<0.001*	*4.3*
eGFR[a]	59.7 (45.1–77.1)	57.5 (40.9–73)	60.2 (47.1–78.8)	*<0.001*	*14.2*
CKD (eGFR <60 mL/min/1.73 m^2)[b]	51.06	55.43	49.07	*<0.001*	*12.8*
Arrival information					
Arrival mode: EMS	60.07	58.82	60.60	*<0.001*	*3.6*
Ambulatory status at admission				*<0.001*	
Able to ambulate independently	33.93	33.08	34.32		*2.6*
With assistance from person	29.59	30.00	29.40		*1.3*
Unable to ambulate	36.48	36.92	36.28		*1.3*
On-time arrival (non-holiday, weekday, 7 a.m.–6 p.m.)	48.72	48.52	48.80	*0.100*	*0.6*
Initial NIHSS score (0–42)[a]	5 (2–11)	5 (2–11)	5 (2–11)	*<0.001*	*3.4*
Initial NIHSS score missing	48.51	49.19	48.22	*<0.001*	*1.9*
Discharge year				*<0.001*	
2011	20.19	21.31	19.72		*3.9*
2010	18.43	19.36	18.04		*3.4*
2009	16.52	16.96	16.33		*1.7*
2008	13.96	13.65	14.09		*1.3*
2007	11.95	11.18	12.27		*3.4*
2006	9.47	8.76	9.77		*3.5*
2005	5.79	5.41	5.95		*2.3*
2004	2.51	2.31	2.60		*1.8*
2003	1.17	1.06	1.22		*1.5*
Medications prior to admission					
Antiplatelets	50.72	56.20	48.25	*<0.001*	*16.0*
Anticoagulants	13.40	13.94	13.16	*<0.001*	*2.3*
Hypertension medications	76.35	84.18	73.05	*<0.001*	*27.4*
Cholesterol-lowering medications	41.69	53.90	36.55	*<0.001*	*35.4*

Continued

Table 1 *Continued*

Variables	Overall *n* = 409 060	Diabetes *n* = 120 989	No diabetes *n* = 288 071	*P*-value	Percent standardized differences
Hospital characteristics					
Rural location	4.53	4.69	4.46	*0.001*	*1.1*
Region				*<0.001*	
West	14.53	13.13	15.11		*5.7*
South	36.86	38.41	36.21		*4.5*
Midwest	22.31	22.69	22.15		*1.3*
Northeast	26.30	25.77	26.52		*1.7*
Primary stroke centre	46.74	46.48	46.85	*0.032*	*0.7*
Academic hospital	58.91	58.54	59.06	*0.002*	*1.1*
Number of beds[a]	356 (248–530)	358 (249–531)	355 (248–527)	*0.004*	*1.1*
Annual volume of IS admissions[a]	226 (154–345)	228 (153–343)	226 (154–345)	*0.221*	*0.4*

BMI, body mass index; CAD, coronary artery disease; CKD, chronic kidney disease; DM, diabetes mellitus; eGFR, estimated glomerular filtration rate; EMS, Emergency Medical Services; IS, ischaemic stroke; MI, myocardial infarction; NIHSS, NIH stroke scale; PVD, peripheral vascular disease; SBP, systolic blood pressure; TIA, transient ischaemic attack.
[a]Continuous variables are present as median (interquartile range), categorical variables are presented *n* (%).
[b]Chronic kidney disease defined using the modification of diet in renal disease equation as eGFR < 60 mL/min/1.73 m^2.

were significantly higher among those with diabetes compared with those without diabetes (see Supplementary material online, *Table S5*), to an extent that was similar to estimates observed in the main analyses. Among IS stroke patients who received tPA, the multivariable aHRs for IS outcomes at 1 year and 3 years were significantly worse among those with diabetes compared with those without diabetes, excepted for estimates of the associations of diabetes with IS readmission that were smaller in magnitude (see Supplementary material online, *Table S6*).

Glycated haemoglobin and insulin therapy associations with outcomes in patients with diabetes

Among patients with diabetes and available data on HbA_{1C} ($N = 58\,455$, corresponding to 48.3% of patients with diabetes), we examined the association of HbA_{1C} with IS outcomes, by subdividing patients into two groups: (i) HbA_{1C}<7% and (ii) $HbA_{1C} \geq 7\%$ (see Supplementary material online, *Table S7*). There were no significant differences in outcomes between the two groups, except for higher risks of all-cause readmission (aHR 1.03, 1.01–1.05), composite of death and cardiovascular readmission (aHR 1.03, 1.01–1.05), IS/TIA readmission (aHR 1.15, 1.11–1.20), HF admission (aHR 1.14, 1.08–1.20), IS readmission (aHR 1.20, 1.15–1.26), and AMI readmission (aHR 1.26, 1.16–1.37) among those with an $HbA_{1C} \geq 7\%$ at 3-year follow-up. In the data subset consisting of patients who received diabetes treatment at discharge ($N = 108\,969$), those treated with insulin at discharge had similar mortality outcomes but higher hazards of readmissions at 1-year, and worse 3-year IS outcomes, compared with diabetes patients discharged on non-insulin therapies (see Supplementary material online, *Table S8*).

Subgroups analyses

We conducted stratified analyses to assess the effect of age, sex, CKD (defined on the basis of eGFR), and race (non-Hispanic Black vs. non-Black) and history of previous cardiovascular disease. Across all subgroups, the hazard ratios for all outcomes at 1 year and 3 years were significantly higher among those with diabetes compared with those without diabetes (see Supplementary material online, *Table S9A and B*). The difference in subgroups pertained to age, with the risks of all outcomes being significantly higher among those aged <80 years vs. patients aged ≥80 years. Chronic kidney disease also appeared to have an influence on outcomes; CKD patients had worse outcomes than those without CKD for all outcomes except for the IS/TIA and HF readmissions. Of note, there were no differences in the risk of 1-year or 3-year IS outcomes between those with a history of cardiovascular disease and those without baseline cardiovascular disease.

Discussion

We examined long-term outcomes of IS by diabetes status in a large, real-world population of 409 060 older patients in the GWTG-Stroke Registry. Overall 29.6% of patients had diabetes. Those with diabetes had a higher burden of comorbidities (cardiovascular risk factors or prior cardiovascular events), as well as significantly higher long-term risks of death, all-cause hospitalization, recurrent IS, HF hospitalization, cardiovascular hospitalization, and non-cardiovascular hospitalizations over a 3-year period. The association of diabetes with worse outcomes persisted, with few exceptions, after accounting for demographics, comorbid conditions, and the IS severity. These findings highlight that there may be an important opportunity to apply a more systematic and structured approach to management of IS patients with pre-existing or newly defined diabetes.

While the association of diabetes and incident stroke has been reported in population-based studies,[3] a limited number of studies have evaluated the association between diabetes and long-term outcomes clinical outcomes among patients after acute IS. With a few exceptions,[12] prior studies of the impact of diabetes on long-term IS

Table 2 Unadjusted and adjusted hazard ratios for outcomes at 1 year and 3 years post-discharge among patients with ischaemic stroke

	Cumulative incidence		Unadjusted analysis		Adjusted analysis	
	N (%)	*P*-value[a]	HR (95% CI)	*P*-value[b]	HR (95% CI)	*P*-value[b]
At 1 year						
All-cause mortality						
Diabetes	32 670 (27.00)	*0.54*	1.00 (0.98–1.01)	*0.57*	1.20 (1.18–1.22)	*<0.0001*
No diabetes	77 402 (26.87)		Reference		Reference	
All-cause readmission						
Diabetes	62 749 (52.61)	*<0.0001*	1.23 (1.22–1.24)	*<0.0001*	1.21 (1.20–1.23)	*<0.0001*
No diabetes	127 971 (44.94)		Reference		Reference	
Composite of mortality and all-cause readmission						
Diabetes	75 995 (63.63)	*<0.0001*	1.14 (1.13–1.15)	*<0.0001*	1.19 (1.18–1.20)	*<0.0001*
No diabetes	165 843 (58.16)		Reference		Reference	
Composite of mortality and CV readmission						
Diabetes	56 137 (47.05)	*<0.0001*	1.10 (1.09–1.11)	*<0.0001*	1.16 (1.15–1.18)	*<0.0001*
No diabetes	123 675 (43.38)		Reference		Reference	
IS/TIA readmission						
Diabetes	11 759 (9.87)	*<0.0001*	1.20 (1.17–1.23)	*<0.0001*	1.15 (1.12–1.17)	*<0.0001*
No diabetes	23 364 (8.21)		Reference		Reference	
HF readmission						
Diabetes	6653 (5.60)	*<0.0001*	1.61 (1.56–1.67)	*<0.0001*	1.55 (1.50–1.61)	*<0.0001*
No diabetes	9868 (3.47)		Reference		Reference	
Non-CV readmission						
Diabetes	46 156 (38.77)	*<0.0001*	1.26 (1.24–1.27)	*<0.0001*	1.27 (1.26–1.29)	*<0.0001*
No diabetes	90 851 (31.95)		Reference		Reference	
Non-IS/TIA readmission						
Diabetes	57 783 (48.47)	*<0.0001*	1.24 (1.22–1.25)	*<0.0001*	1.22 (1.21–1.24)	*<0.0001*
No diabetes	116 608 (40.97)		Reference		Reference	
IS readmission						
Diabetes	9228 (7.74)	*<0.0001*	1.22 (1.19–1.25)	*<0.0001*	1.17 (1.13–1.20)	*<0.0001*
No diabetes	18 070 (6.34)		Reference		Reference	
AMI readmission						
Diabetes	2669 (2.24)	*<0.0001*	1.56 (1.49–1.64)	*<0.0001*	1.52 (1.45–1.60)	*<0.0001*
No diabetes	4060 (1.43)		Reference		Reference	
At 3 year						
All-cause mortality						
Diabetes	55 627 (45.98)	*<0.0001*	1.04 (1.03–1.05)	*<0.0001*	1.24 (1.23–1.25)	*<0.0001*
No diabetes	127 320 (44.20)		Reference		Reference	
All-cause readmission						
Diabetes	83 474 (71.30)	*<0.0001*	1.22 (1.21–1.24)	*<0.0001*	1.22 (1.21–1.23)	*<0.0001*
No diabetes	178 385 (63.74)		Reference		Reference	
Composite of mortality and all-cause readmission						
Diabetes	98 713 (84.12)	*<0.0001*	1.15 (1.14–1.16)	*<0.0001*	1.21 (1.20–1.22)	*<0.0001*
No diabetes	222 467 (79.28)		Reference		Reference	
Composite of mortality and CV readmission						
Diabetes	80 991 (69.45)	*<0.0001*	1.13 (1.12–1.14)	*<0.0001*	1.19 (1.18–1.20)	*<0.0001*
No diabetes	179 792 (64.30)		Reference		Reference	
IS/TIA readmission						
Diabetes	18 499 (15.94)	*<0.0001*	1.22 (1.20–1.24)	*<0.0001*	1.18 (1.16–1.20)	*<0.0001*
No diabetes	36 944 (13.27)		Reference		Reference	
HF readmission						
Diabetes	11 820 (10.27)	*<0.0001*	1.64 (1.60–1.68)	*<0.0001*	1.60 (1.56–1.64)	*<0.0001*
No diabetes	17 676 (6.39)		Reference		Reference	

Continued

Table 2 *Continued*

	Cumulative incidence		Unadjusted analysis		Adjusted analysis	
	N (%)	*P*-value[a]	HR (95% CI)	*P*-value[b]	HR (95% CI)	*P*-value[b]
Non-CV readmission						
Diabetes	67 775 (58.30)	<0.0001	1.25 (1.24–1.26)	<0.0001	1.28 (1.26–1.29)	<0.0001
No diabetes	140 119 (50.33)		Reference		Reference	
Non-IS/TIA readmission						
Diabetes	79 000 (67.62)	<0.0001	1.23 (1.22–1.24)	<0.0001	1.23 (1.22–1.25)	<0.0001
No diabetes	166 898 (59.72)		Reference		Reference	
IS readmission						
Diabetes	14 589 (12.57)	<0.0001	1.24 (1.21–1.26)	<0.0001	1.20 (1.18–1.23)	<0.0001
No diabetes	28 644 (10.29)		Reference		Reference	
AMI readmission						
Diabetes	5398 (4.72)	<0.0001	1.62 (1.56–1.67)	<0.0001	1.55 (1.49–1.60)	<0.0001
No diabetes	8136 (2.95)		Reference		Reference	

CI, confidence interval; CV, cardiovascular; HF, heart failure; HR, hazard ratio; IS, ischaemic stroke; TIA, transient ischaemic attack.
[a]Log-rank *P*-values were presented for mortality outcomes, Gray's *P*-values were presented for other outcomes.
[b]$P < 0.05$ indicates that the care differs significantly between those with and without diabetes.

outcomes have generally found that diabetes is related to worse outcomes in the aftermath of an IS, mostly overall mortality.[13–21] However, these studies have a number of limitations, which include the limited examination of outcomes other than mortality except in one study (that included vascular outcomes),[21] relatively small sample sizes[13] and a shorter follow-up period (<2 years).[12] Furthermore, these studies included limited adjustment for confounding factors, lacked the diversity of our population with respect to race/ethnicity as these have mostly been conducted in the European countries,[12,14–20] conflated ischaemic and haemorrhagic stroke types,[14,16–19] and did not account for the degree of blood glucose control. Our finding of an increased risk of IS recurrence among those with diabetes is consistent with prior data.[21–23] Indeed, the extant studies suggest an increased risk of recurrent IS among patients with previous stroke of up to 44%.[23] However, these studies have been small in size, and taken together these have included fewer patients than in the current investigation.[23] In addition to the study size, the observed differences in estimates of IS recurrence in relation to diabetes may be also related (at least in part) to variations in diabetes ascertainment or IS identification methods.

Our study provides significant complementary information on the associations of diabetes with outcomes of IS. In addition to mortality risk among IS patients, we examined long-term admission and cardiovascular hospitalization, as well as IS recurrence. Our findings highlight the importance of achieving more effective treatment of diabetes (in addition to using antihypertensives and statins where relevant) among IS patients, as this may potentially contribute to reducing cardiovascular events, HF, and mortality. However, whether blood glucose control would lead to reduction of first stroke, stroke recurrence rates, or other cardiovascular outcomes is still to be unequivocally demonstrated in clinical trials. The majority of trials of diabetes treatment, both old[24,25] and recent [using sodium-glucose cotransporter-2 (SGLT-2) inhibitors or glucagon-like peptide-1 (GLP1) receptor agonists],[26–28] have not demonstrated clear benefits in terms of reduction of the incidence of stroke, except one trial of the GLP1 agonist semaglutide that showed a significant 29% reduction in non-fatal stroke events.[29] It is however important to point out that none of these trials was powered for the stroke outcomes and if tested in appropriately powered trials, there may be benefit. It is also notable that the use of pioglitazone was shown to achieve a significant 24% reduction in the risk of stroke recurrence among insulin resistant patients.[30]

In terms of excess risk, HF hospitalizations had the highest aHRs at 1.6 highlighting the critical need to prevent HF in these patients. Treatment with a SGLT-2 inhibitor has been demonstrated to lower the risk of cardiovascular mortality and HF hospitalizations in patients with diabetes and may be an effective approach to mitigate many of the risks observed.[31] Thiazolidinediones may specifically affect IS/TIA recurrence[30] and coronary events[32]; GLP-1 agonists[27] may affect specific cardiovascular outcomes are also considerations. An additional reason to envisage a more integrated management of IS and diabetes is a potential improvement of functional outcomes and reduction of health costs, as diabetes among patients with IS may be associated with higher expenditures. Our study points to the potential importance of adopting a more structured approach to the detection and long-term management of diabetes among those admitted with IS. While the management of hyperglycaemia in the acute phase of stroke is well integrated by neurologists, they are less prepared or armed to implement an active detection of undiagnosed cases of diabetes and long-term diabetes management. Current IS management guidelines do not mandate active detection of diabetes[33,34]; including with the measurement of HbA_{1C}, which may help to detect pre-existing diabetes as post-stroke hyperglycaemia may be a transient phenomenon. This is particularly important as data indicate that up to 10% of patients admitted with IS and without previously known diabetes may in fact have the condition.[35,36] A collaboration between neurologists and endocrinologists, especially for the post-discharge management of diabetes, may be necessary to achieve better outcomes.

The mechanistic pathways underlying the difference in outcomes of IS between patients with diabetes mellitus and those without

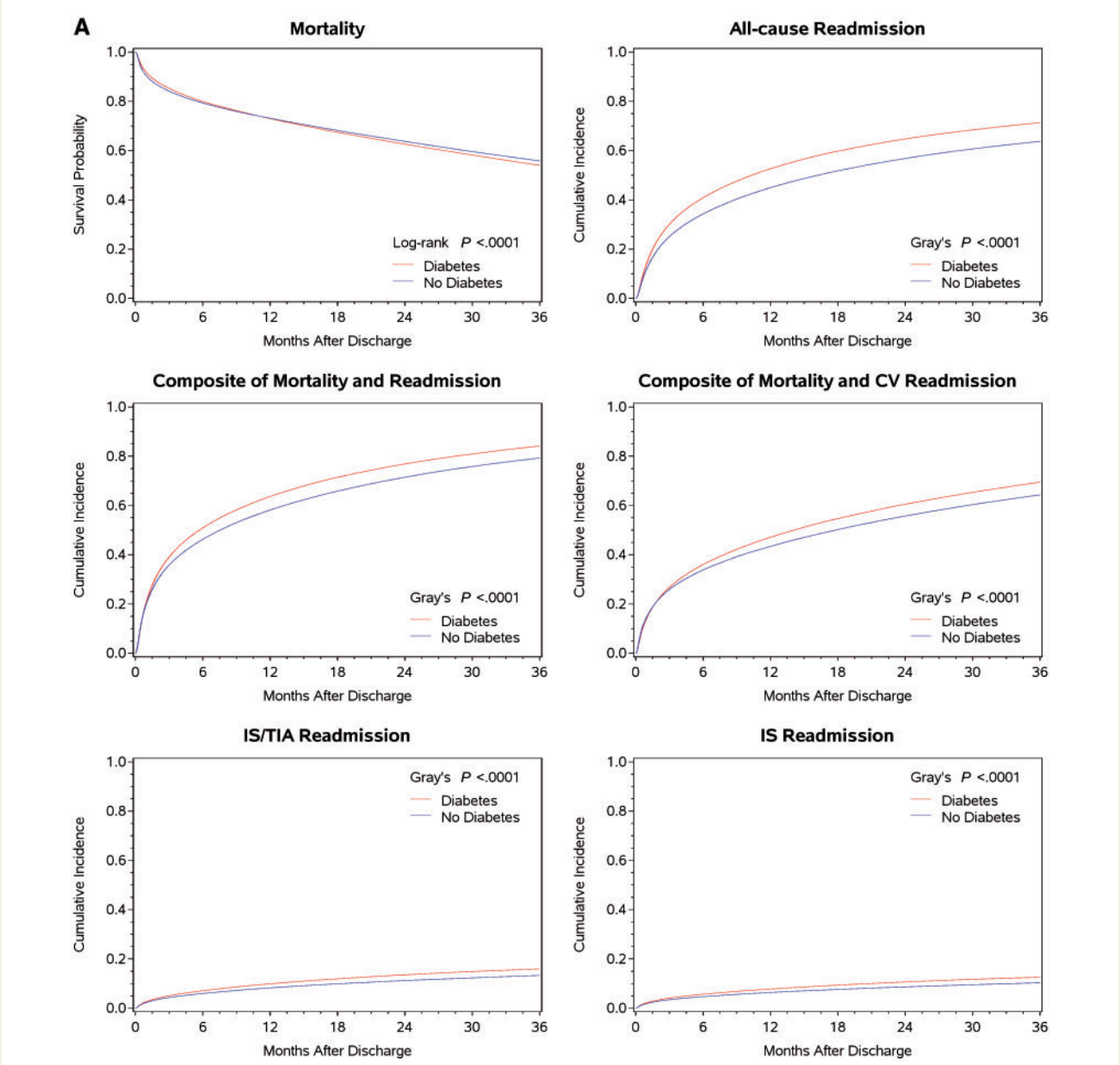

Figure 1 (*A* and *B*) The Kaplan–Meier curve for mortality outcome and cumulative incidence function plots for admission and composite outcomes at 3 years post-discharge.

diabetes mellitus remain to be explored. Our findings may reflect the possible diffuse atherosclerotic changes related to diabetes, including the cerebral vessels and other vascular beds, which may explain the higher rates of IS recurrence, composite of death and cardiovascular readmission. Indeed, diabetes is a well-known factor that contributes to the initiation and acceleration of the progression of atherosclerosis.[5] Insulin resistance may have a central role in the process, as suggested by mechanistic studies[37] and results from a recent clinical trial showing that improvement of insulin resistance led to better outcomes of IS.[30] It is possible that the duration of diabetes matters in the pathogenic process, as suggested by findings of prior studies on the duration of diabetes and IS.[38]

There are limitations to our study. First, we primarily included IS patients aged ≥65 years, thus we were unable to assess the relationship between diabetes and IS outcomes in other age groups. Second, participation to the GWTG-Stroke registry is voluntary, thus not all USA hospitals are included. While the generalizability of our findings to non-GWTG-Stroke registry hospitals remains to be established, our findings are likely to represent routine clinical practice as the GWTG-Stroke registry is the largest stroke registry in the world. Third, we probably missed patients without a prior diagnosis of diabetes and who were not screened during their index hospitalization, especially as undiagnosed diabetes in frequent in the USA population.[1] We also did not account for diabetes cases that arose during

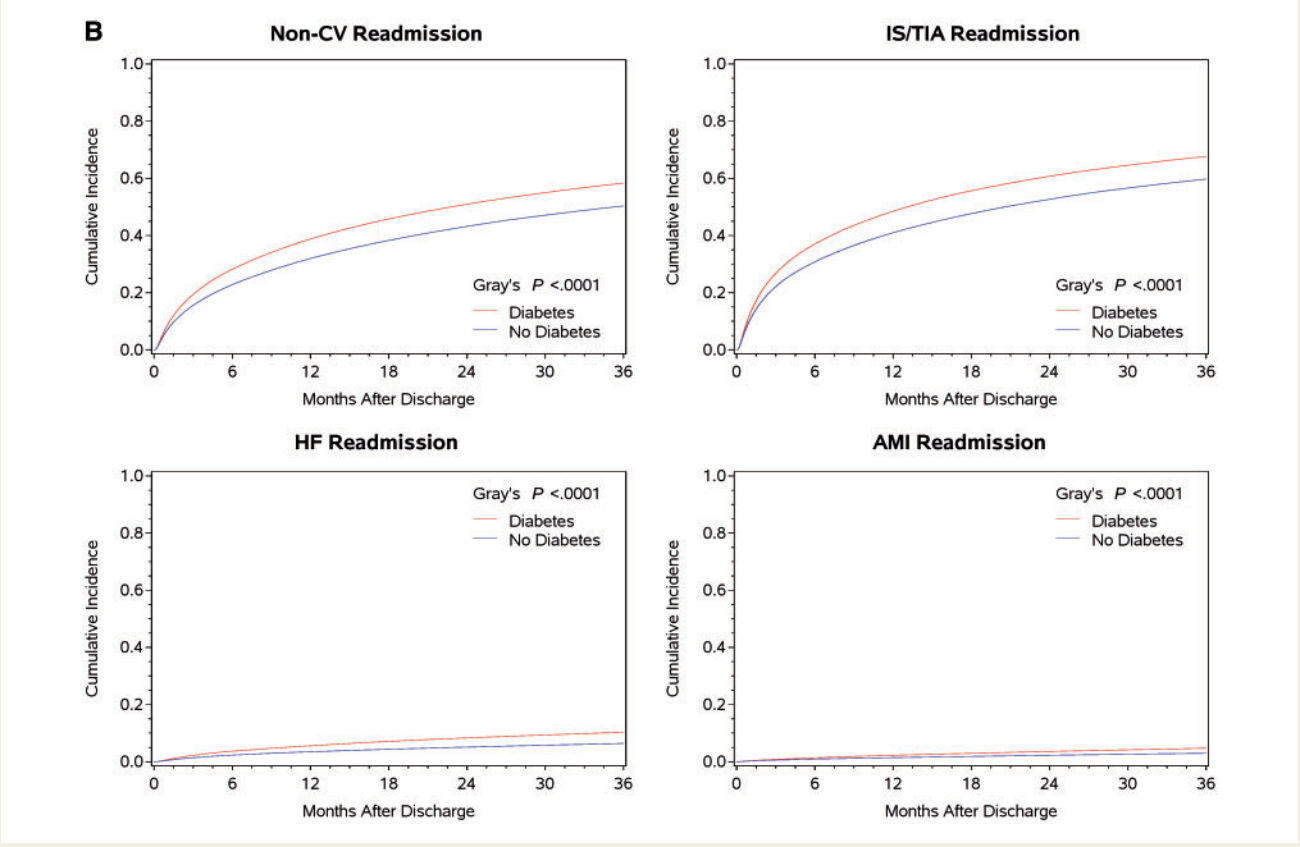

Figure 1 Continued

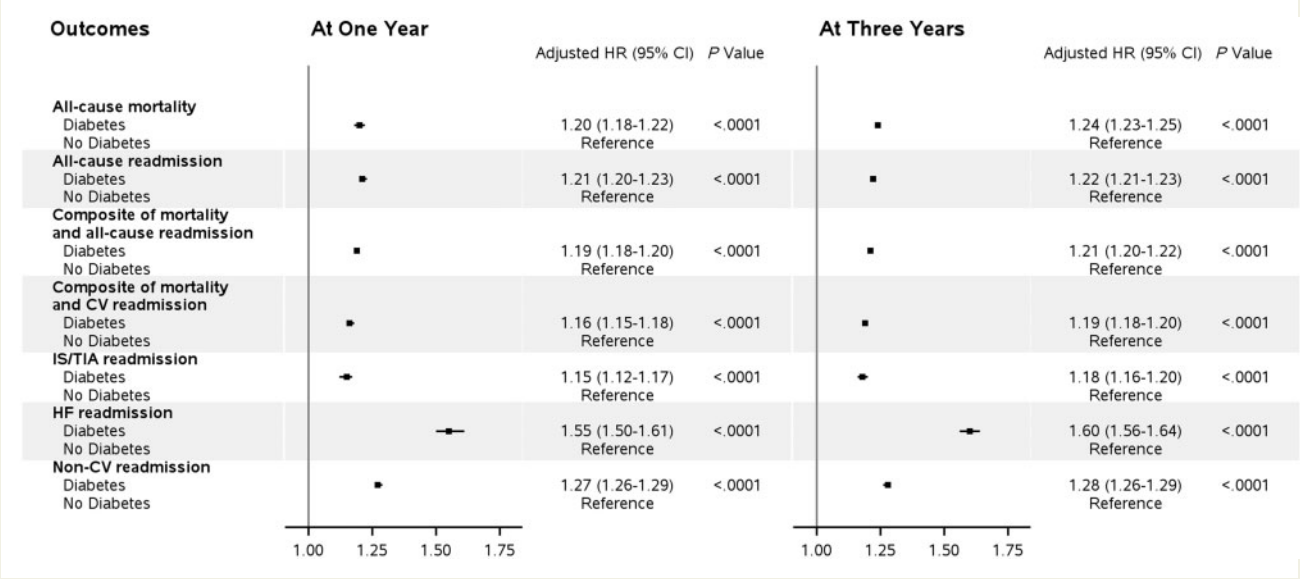

Figure 2 Comparative outcomes of ischaemic stroke between patients with and without diabetes.

the follow-up period. An underestimation of diabetes frequency would bias the estimates of the diabetes and IS outcomes towards the null, as illustrated by our sensitivity analysis using an alternative and more inclusive definition of diabetes. Third, we did not have information on the duration of diabetes, which may influence outcomes of IS among patients with diabetes. We had limited information on HbA_{1C} (only 48% of patients had data on HbA_{1C}) and did not account for the various glucose lowering medications other than insulin therapy. The latter may influence IS outcomes, especially as some medications classes may be associated with better or worse IS outcomes.[30,39] Fourth, we did not assess functional (e.g. long-term cognitive function) or quality of life outcomes. Finally, despite appropriate adjustment for confounders, residual confounding may have affected our estimates.

Conclusions

In a nationwide cohort of older patients with IS, among whom 30% had diabetes mellitus, a higher burden of mortality, recurrent events, and hospitalizations were observed in the diabetes group. This points to the potential importance of early detection and appropriate management of diabetes in IS patients, using specific therapies that have been demonstrated to improve outcomes. Further studies are warranted to clarify pathways through which diabetes affects outcomes of IS, as well as the best approaches (pharmacological and non-pharmacological) to mitigate more effectively diabetes in the setting of IS.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

Funding

This work was supported by the Get with the Guidelines-Stroke (GWTG-Stroke) program, which is provided by the American Heart Association (AHA)/American Stroke Association. The GWTG-Stroke program is supported, in part, by a charitable contribution from Janssen Pharmaceutical Companies of Johnson & Johnson. GWTG-Stroke has been funded in the past through support from Boeringher-Ingelheim, Merck, Bristol-Myers Squib/Sanofi Pharmaceutical Partnership, and the AHA Pharmaceutical Roundtable (PRT). J.B.E. was awarded an American Heart Association/American Stroke Association (AHA/ASA) - Young Investigator Database Research Seed Grant in 2015 to conduct this study. J.B.E. is supported by the National Heart, Lung, and Blood Institute (NHLBI) grant T32 HL125232.

Conflict of interest: D.L.B. discloses the following relationships—Advisory Board: Cardax, Elsevier Practice Update Cardiology, Medscape Cardiology, Regado Biosciences; Board of Directors: Boston VA Research Institute, Society of Cardiovascular Patient Care; Chair: American Heart Association Quality Oversight Committee; Data Monitoring Committees: Cleveland Clinic, Duke Clinical Research Institute, Harvard Clinical Research Institute, Mayo Clinic, Mount Sinai School of Medicine, Population Health Research Institute; Honoraria: American College of Cardiology (Senior Associate Editor, Clinical Trials and News, ACC.org), Belvoir Publications (Editor in Chief, Harvard Heart Letter), Duke Clinical Research Institute (clinical trial steering committees), Harvard Clinical Research Institute (clinical trial steering committee), HMP Communications (Editor in Chief, Journal of Invasive Cardiology), Journal of the American College of Cardiology (Guest Editor; Associate Editor), Population Health Research Institute (clinical trial steering committee), Slack Publications (Chief Medical Editor, Cardiology Today's Intervention), Society of Cardiovascular Patient Care (Secretary/Treasurer), WebMD (CME steering committees); Other: Clinical Cardiology (Deputy Editor), NCDR-ACTION Registry Steering Committee (Chair), VA CART Research and Publications Committee (Chair); Research Funding: Amarin, Amgen, AstraZeneca, Bristol-Myers Squibb, Chiesi, Eisai, Ethicon, Forest Laboratories, Ironwood, Ischemix, Lilly, Medtronic, Pfizer, Roche, Sanofi Aventis, The Medicines Company; Royalties: Elsevier (Editor, Cardiovascular Intervention: A Companion to Braunwald's Heart Disease); Site Co-Investigator: Biotronik, Boston Scientific, St. Jude Medical (now Abbott); Trustee: American College of Cardiology; Unfunded Research: FlowCo, Merck, PLx Pharma, Takeda. G.C. F. reports significant consulting for Novartis, and modest consulting for Amgen, Bayer, Gambro, Medtronic, and Janssen; G.C.F. is a member of the GWTG Steering Committee; G.C.F. holds the Eliot Corday Chair of Cardiovascular Medicine at UCLA and is also supported by the Ahmanson Foundation (Los Angeles, California). L.H.S. reports being the principal investigator of an investigator-initiated study of extended-window intravenous thrombolysis funded by the National Institutes of Neurological Disorders and Stroke (clinicaltrials.gov/show/NCT01282242) for which Genentech provides alteplase free of charge to Massachusetts General Hospital as well as supplemental per-patient payments to participating sites; serving as chair of the AHA/ASA GWTG stroke clinical work group and hospital accreditation Science Committee; serving as a stroke systems consultant to the Massachusetts Department of Public Health; serving as a scientific consultant to Medtronic (Victory AF and Stroke AF trials), and member of the data and safety monitoring board of the DeVOTE trial (novo Nordisk). All other authors (J.B.E.; H.X.; R.A.M.; Y.X.; E.E.S.; A.F.H.; and P.A.H) declared no conflict of interest. All authors had access to the data and a role in writing the manuscript.

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