Empagliflozin and Cerebrovascular Events in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk

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Background and Purpose—In the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients), empagliflozin added to standard of care in patients with type 2 diabetes mellitus and high cardiovascular risk reduced the risk of 3-point major adverse cardiovascular events, driven by a reduction in cardiovascular mortality, with no significant difference between empagliflozin and placebo in risk of myocardial infarction or stroke. In a modified intent-to-treat analysis, the hazard ratio for stroke was 1.18 (95% confidence interval, 0.89–1.56; P=0.26). We further investigated cerebrovascular events.

Methods—Patients were randomized to empagliflozin 10 mg, empagliflozin 25 mg, or placebo; 7020 patients were treated. Median observation time was 3.1 years.

Results—The numeric difference in stroke between empagliflozin and placebo in the modified intent-to-treat analysis was primarily because of 18 patients in the empagliflozin group with a first event >90 days after last intake of study drug (versus 3 on placebo). In a sensitivity analysis based on events during treatment or ≤90 days after last dose of drug, the hazard ratio for stroke with empagliflozin versus placebo was 1.08 (95% confidence interval, 0.81–1.45; P=0.60). There were no differences in risk of recurrent, fatal, or disabling strokes, or transient ischemic attack, with empagliflozin versus placebo. Patients with the largest increases in hematocrit or largest decreases in systolic blood pressure did not have an increased risk of stroke.

Conclusions—In patients with type 2 diabetes mellitus and high cardiovascular risk, there was no significant difference in the risk of cerebrovascular events with empagliflozin versus placebo.

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Patients with diabetes mellitus are at increased risk of cardiovascular events and cardiovascular mortality.1 The risk of stroke in patients with diabetes mellitus is increased 2-fold compared with individuals without diabetes mellitus1; the risk of recurrent stroke is also increased.2 Trials of intensive glucose-lowering3 or of specific glucose-lowering agents,4,7 with the exception of pioglitazone6 and semaglutide,9 have not been shown to significantly reduce the risk of stroke in patients with type 2 diabetes mellitus even after prolonged follow-up.

Empagliflozin is a potent and selective inhibitor of SGLT2 (sodium glucose cotransporter 2) used in the treatment of type 2 diabetes mellitus. In the EMPA-REG OUTCOME trial (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients) in patients with type 2 diabetes mellitus and high cardiovascular risk, empagliflozin added to standard of care significantly reduced the risk of the primary outcome 3-point major adverse cardiovascular events (the composite of cardiovascular death, nonfatal myocardial...
infarction, or nonfatal stroke; hazard ratio [HR], 0.86; 95.02% confidence interval [CI], 0.74–0.99; \( P = 0.04 \)). This was driven primarily by a reduction in the risk of cardiovascular death (HR, 0.62; 95% CI, 0.49–0.77; \( P < 0.001 \)). There were no significant differences between empagliflozin and placebo in the risk of myocardial infarction (HR, 0.87; 95% CI, 0.70–1.09; \( P = 0.23 \)) or stroke (HR, 1.18; 95% CI, 0.89–1.56; \( P = 0.26 \)).

Given the importance of stroke prevention in patients with type 2 diabetes mellitus and the numeric difference in the proportion of patients with stroke events between the empagliflozin and placebo groups in the EMPA-REG OUTCOME trial, we performed a comprehensive analysis of cerebrovascular events in EMPA-REG OUTCOME, including sensitivity and subgroup analyses.

Methods

Study Design

The design of EMPA-REG OUTCOME has been described. Briefly, the study population comprised patients with type 2 diabetes mellitus, established cardiovascular disease, and estimated glomerular filtration rate (MDRD [Modification of Diet in Renal Disease] equation) >30 mL min\(^{-1}\) 1.73 m\(^{-2}\). Patients were randomized 1:1:1 to receive empagliflozin 10 mg, empagliflozin 25 mg, or placebo in addition to standard of care. Throughout the trial (or after week 12 for glucose-lowering medication), investigators were encouraged to treat cardiovascular risk factors to achieve optimal standard of care according to local guidelines. Patients were asked to attend the clinic at prespecified times, including a follow-up visit 30 days after the end of treatment. The trial was to continue until \( n \geq 691 \) patients had experienced an adjudicated event included in the primary outcome. Patients who prematurely discontinued study medication continued to be followed for ascertain-ment of cardiovascular outcomes, adverse events, and vital status.

The trial was conducted in accordance with the principles of the Declaration of Helsinki and the International Conference on Harmonization Good Clinical Practice guidelines and was approved by local authorities. An independent ethics committee or institutional review board approved the clinical protocol at every participating center. All patients provided written informed consent before study entry.

Outcomes

Definitions of the major clinical outcomes in EMPA-REG OUTCOME have been described. The definitions of transient ischemic attack (TIA) and stroke are provided in the online-only Data Supplement. Cardiovascular outcome events and deaths were prospectively adjudicated by 2 Clinical Events Committees (for cardiac and neurological events). We assessed time to first stroke (fatal or nonfatal), time to fatal stroke, time to first nonfatal stroke, time to first nonfatal disabling stroke (defined as adjudicated nonfatal stroke with investigator-reported seriousness criterion of persistent or significant disability/incapacity; stroke disability scores were not used), recurrent stroke during the trial, time to first nonfatal disabling stroke or fatal stroke, time to first cardiovascular death or nonfatal stroke, time to first TIA, and time to first nonfatal or fatal stroke or TIA. Ischemic stroke was classified post hoc according to TOAST criteria (Trial of Org 10172 in Acute Stroke Treatment)\(^{12}\) by the neurological Clinical Events Committee. The Clinical Events Committee charter for classification of ischemic stroke is provided in the online-only Data Supplement.

Analyses

It was prespecified that analyses would compare the pooled empagliflozin dose groups versus placebo. Outcomes were analyzed using a modified intent-to-treat approach in the treated set (patients treated with \( \geq 1 \) dose of study drug), using the time to first stroke event irrespective of whether another outcome event had occurred. Data for patients who did not have an event were censored on the last day they were known to be free of the outcome. Sensitivity analyses of fatal or nonfatal stroke were performed based on events that occurred during treatment or \( \leq 90 \) days, \( \leq 30 \) days, or \( \leq 7 \) days after a patient’s last intake of study drug (treated set plus 90 days, treated set plus 30 days, and treated set plus 7 days) and based on events that occurred during treatment or \( \geq 30 \) days after a patient’s last intake of study drug in patients who received \( \geq 30 \) days of study medication (cumulative; on-treatment set). A sensitivity analysis of TIA was performed on the treated set plus 90 days. Analyses were based on a Cox proportional hazards model, with treatment, age, sex, baseline body mass index, baseline HbA1c, baseline estimated glomerular filtration rate, and region as factors. Subgroup analyses included a subgroup factor and a treatment-by-subgroup factor interaction as additional effects. All analyses were performed at a nominal level of \( \alpha = 0.05 \) 2-sided without adjustment for multiplicity. Cumulative incidence function estimates were corrected for death as a competing risk. Because of the declining numbers of patients at risk, cumulative incidence plots have been truncated at 48 months.

The percentages of patients with recurrent stroke were analyzed descriptively in the treated set. In addition, analyses were conducted of the percentages of patients with stroke in patients with maximum decreases from baseline in systolic blood pressure \( \geq 30 \) mm Hg, with maximum increases from baseline in hematocrit \( \geq 90 \)th and \( < 90 \)th percentiles, in patients who had an event consistent with volume depletion (based on 8 preferred terms in the Medical Dictionary for Regulatory Activities) and in patients who had an atrial fibrillation event (based on the Medical Dictionary for Regulatory Activities preferred term). Changes from baseline in systolic blood pressure and hematocrit at the last value on treatment and at follow-up were analyzed descriptively.

Prespecified analyses were the modified intent-to-treat analyses and analyses in the on-treatment set for time to first fatal or nonfatal stroke, nonfatal stroke and TIA, and the assessment of recurrent strokes. Other analyses were post hoc.

Results

Study Population

A total of 7020 patients at 590 sites in 42 countries received \( \geq 1 \) dose of study drug. Baseline characteristics of the study population have been described. Briefly, mean (SD) age was 63.1 (8.6) years, mean (SD) body mass index was 30.6 (5.3) kg/m\(^2\), 71.5% were male, 25.9% had systolic blood pressure \( \geq 140 \) mm Hg or diastolic blood pressure \( \geq 90 \) mm Hg, 23.3% had a history of stroke, 5.5% of patients had atrial fibrillation, 89.1% were taking anticoagulant or antplatelet therapies, and 82.7% were taking acetylsalicylic acid. In total, 97% of patients completed the study, and 25% prematurely discontinued study drug. The median duration of treatment was 2.6 years, and the median observation time was 3.1 years. Vital status was available for 99% of patients.

Stroke and TIA

During the trial, 3.0% (69/2333) of patients in the placebo group and 3.5% (164/4687) of patients in the empagliflozin group had \( \geq 1 \) adjudicated fatal or nonfatal stroke. Ischemic stroke was reported in 2.7% and 3.2% of patients in the placebo and empagliflozin groups and hemorrhagic stroke in 0.3% and 0.2% of patients in these groups, respectively. A further 0.1% of patients in each group had a stroke for which the type was not assessable. There was no marked imbalance between the placebo and empagliflozin groups in any specific
type of ischemic stroke. Cardioembolism was the most common type of ischemic stroke that could be determined (Table I in the online-only Data Supplement).

In the prespecified modified intent-to-treat analysis of time to first stroke, there was no significant difference between empagliflozin and placebo in the occurrence of stroke (HR, 1.18; 95% CI, 0.89–1.56; \( P = 0.26 \)).\(^{10}\) The cumulative incidence of time to first stroke is shown in Figure 1A. In sensitivity analyses based on events that occurred during treatment or ≤90, ≤30, or ≤7 days after the last dose of study drug, there was no significant difference in the occurrence of stroke between empagliflozin and placebo, and the HR moved toward unity compared with the modified intent-to-treat analysis (Figure I in the online-only Data Supplement). The numeric difference in the proportion of patients with stroke between the empagliflozin and placebo groups was largely driven by events that occurred >90 days after a patient’s last intake of trial medication (Figure 1B; Figure I in the online-only Data Supplement). Three patients treated with placebo and 18 patients treated with empagliflozin experienced their first stroke >90 days after the last intake of trial medication (of whom 1 patient in the placebo group and 11 patients in the empagliflozin group experienced their first stroke >1 year after the last intake of trial medication).

The proportion of patients with recurrent stroke during the trial was similar between the empagliflozin and placebo groups (13 [0.3%] and 8 [0.3%], respectively; Table II in the online-only Data Supplement). Nonfatal disabling stroke (based on investigator-reported seriousness criterion [not stroke disability scores]) was reported in 10 patients (0.2%).

![Figure 1](https://example.com/figure1.png)

**Figure 1.** Time to first fatal or nonfatal stroke. **A.** Modified intent-to-treat analyses in the treated set; events observed from randomization to the end of the study in treated set (patients treated with ≥1 dose of study drug). **B.** Sensitivity analysis in treated set plus 90 days; events observed during treatment or ≤90 days after a patient’s last intake of trial medication in treated set (patients treated with ≥1 dose of study drug). Cumulative incidence function. Hazard ratios (HR) are based on Cox regression analyses. CI indicates confidence interval.
on empagliflozin and 6 patients (0.3%) on placebo (HR, 0.82; 95% CI, 0.30–2.26; \( P = 0.70 \)). Fatal stroke was reported in similar proportions of patients in the empagliflozin and placebo groups (0.3% and 0.5%, respectively; HR, 0.72; 95% CI, 0.33–1.55; \( P = 0.40 \)) as was the composite of nonfatal disabling stroke or fatal stroke (0.6% and 0.7%, respectively; HR, 0.81; 95% CI, 0.43–1.50; \( P = 0.50 \); Figure 2).

As empagliflozin reduced the risk of cardiovascular death by 38%, the composite outcome of cardiovascular death or nonfatal stroke was analyzed to account for cardiovascular death as a competing risk. Empagliflozin significantly reduced the risk of this composite outcome (HR, 0.79; 95% CI, 0.66–0.94; \( P = 0.009 \); Figure 2).

There was no significant difference in the risk of TIA (HR, 0.85; 95% CI, 0.51–1.42; \( P = 0.54 \)) or the composite of stroke or TIA (HR, 1.05; 95% CI, 0.82–1.35; \( P = 0.87 \)) with empagliflozin versus placebo (Figure 2; Figure II in the online-only Data Supplement).

**Subgroup Analyses**

In exploratory analyses of time to first stroke in >30 prespecified subgroups by baseline characteristics, analyses by region and HbA1c showed nominal heterogeneity at \( P < 0.05 \) (with no adjustment for multiple tests; Figure 3; Table III in the online-only Data Supplement). Compared with the total population, the HR for stroke in patients in Europe was higher (2.04; 95% CI, 1.26–3.29; \( P \) value for interaction of treatment and region: 0.01; Table III in the online-only Data Supplement). Baseline characteristics, including background medications, were similar between treatment groups within a given region (Table IV in the online-only Data Supplement). However, there were small differences in baseline characteristics between patients in Europe and North America (Table IV in the online-only Data Supplement), including a greater proportion of patients in Europe with a history of stroke (Europe: 29.9% placebo, 25.7% empagliflozin; North America: 14.9% placebo, 18.1% empagliflozin). Despite this, patients treated with placebo had a markedly lower stroke rate in Europe than North America (7.8/1000 versus 15.2/1000 patient-years). This pattern was not observed in patients treated with empagliflozin (stroke event rates were 15.7/1000 and 12.3/1000 patient-years in Europe and North America, respectively). In contrast to the HRs for stroke, the HR for TIA in European patients was <1 (0.61; 95% CI, 0.27–1.35) and in North American patients was 1.22 (95% CI, 0.53–2.78; \( P \) value for interaction of treatment and region: 0.24).

Compared with the total population, the HR for stroke in patients with baseline HbA1c \( \geq 8.5\% \) was higher (\( P \) value for interaction: 0.01; Table III in the online-only Data Supplement). An analysis by baseline HbA1c deciles showed no significant treatment-by-subgroup interaction (Figure III in the online-only Data Supplement).

Subgroup analysis by risk factors for stroke such as previous stroke, atrial fibrillation, smoking, and hypertension at baseline showed no statistically significant interaction with treatment for risk of stroke (Figure 3; Table III in the online-only Data Supplement).

**Changes in Systolic Blood Pressure, Changes in Hematocrit, and Events Consistent With Volume Depletion or Atrial Fibrillation in Relation to Stroke**

Because treatment with empagliflozin is associated with reductions in systolic blood pressure and small increases in hematocrit, we assessed changes in systolic blood pressure and hematocrit in relation to stroke. We assessed the occurrence of stroke in patients who did and did not have events consistent with volume depletion or atrial fibrillation.

Systolic blood pressure decreased in patients treated with empagliflozin (mean change from baseline to last value on treatment: −3.3 [SE, 0.3] mmHg) but had returned to its

![Figure 2. Time to first stroke, transient ischemic attack, and composite outcomes in modified intent-to-treat analyses. Cox regression analyses. Events from randomization to the end of the study in treated set (patients treated with ≥1 dose of study drug). Analyses were prespecified for time to first fatal or nonfatal stroke, time to first nonfatal stroke, and time to first transient ischemic attack. CI indicates confidence interval; and HR, hazard ratio.](http://stroke.ahajournals.org/).
Figure 3. Time to first stroke in subgroups defined by baseline characteristics. Post hoc Cox regression analyses. Events of fatal or nonfatal stroke observed from randomization to end of study in treated set (patients treated with ≥1 dose of study drug). Race: Black and Other not included in Cox regression as <14 patients with an event in these subgroups. Region: Africa not included in Cox regression (Continued).
baseline level at follow-up (30 days after end of treatment; Table). Patients with the largest decreases from baseline in systolic blood pressure (≥30 mm Hg) did not have an increased risk of stroke compared with other patients (Table V in the online-only Data Supplement).

In the empagliflozin group, hematocrit increased during treatment (mean change from baseline to last value on treatment: 3.61% [SE, 0.06]), but decreased toward baseline at follow-up (30 days after end of treatment; Table). Patients with the largest increases from baseline in hematocrit (increases ≥90th percentile, which corresponded to a change in hematocrit of 9 percentage points) did not have an increased risk of stroke compared with patients not meeting this threshold (Table V in the online-only Data Supplement).

The proportion of patients with a stroke event was not higher in those who did versus did not have an event consistent with volume depletion in placebo or empagliflozin groups (Table VI in the online-only Data Supplement).

The risk of stroke was comparable between patients with and without atrial fibrillation at baseline or during the study in the placebo and empagliflozin groups (Figure 3; Tables III and VII in the online-only Data Supplement).

### Discussion

In the EMPA-REG OUTCOME trial in patients with type 2 diabetes mellitus and high cardiovascular risk, empagliflozin added to standard of care significantly reduced the risk of the primary outcome of 3-point major adverse cardiovascular events by reducing the risk of cardiovascular death. There was no significant difference in the occurrence of stroke between empagliflozin and placebo in the prespecified modified intent-to-treat analysis, but there was a numeric difference between treatment groups. In these new analyses, we show that this numeric difference was driven by nonfatal ischemic stroke, with no isolated increase in any subtype of ischemic stroke, and that there was no significant difference between empagliflozin and placebo in the risk of stroke in on-treatment sensitivity analyses or in the risk of recurrent, fatal, or nonfatal disabling strokes, or TIA, which has similar pathophysiological mechanisms as stroke. Further sensitivity analyses demonstrated that the numeric difference in the proportion of patients with stroke between empagliflozin and placebo in the modified intent-to-treat analysis was primarily because of events that occurred >90 days after the last intake of study drug. In this context, it is important to note that measures of the hemodynamic effects of empagliflozin, specifically systolic blood pressure and hematocrit, returned to near baseline levels within 30 days after the last intake, making a causal association with empagliflozin unlikely and making it unlikely that there is an increased risk of stroke after empagliflozin is stopped.

In subgroup analyses of time to first stroke, analyses by region and HbA1c showed nominal heterogeneity. The increased HR for stroke with empagliflozin compared with placebo in patients in Europe compared with the total population could not be explained by differences in baseline characteristics between regions. Given the large number of subgroup factors and tests conducted, the differences in HR between Europe and other regions, and between patients with HbA1c ≥8.5% and <8.5% at baseline, are within the realm of chance variation. Analyses of time to first stroke in subgroups by other baseline characteristics, including factors associated with risk for stroke such as atrial fibrillation, smoking, previous stroke, and hypertension, showed no statistically significant interaction with treatment for the risk of stroke.

The risk of experiencing a stroke was comparable between patients with and without atrial fibrillation at baseline or during the study. A slightly lower proportion of patients treated with empagliflozin than placebo had anticoagulants introduced postbaseline, and it cannot be excluded that this could have contributed to the numeric difference in stroke.

Treatment with empagliflozin is associated with hemocoagulation, as shown by increases in hematocrit, and with reductions in systolic blood pressure. Concerns have been raised that elevated hematocrit and hypotension may be

### Table. Systolic Blood Pressure and Hematocrit at Baseline, Last Value on Treatment, and at Follow-Up

| Parameter                              | Placebo | Empagliflozin |
|----------------------------------------|---------|---------------|
| **Systolic blood pressure, mm Hg**     |         |               |
| n                                      | 1574    | 3376          |
| Baseline                               | 135.7 (0.4) | 135.3 (0.3)  |
| Last value on treatment                | 136.2 (0.4) | 132.0 (0.3)  |
| Change from baseline at last value on treatment | 0.5 (0.4)     | −3.3 (0.3)    |
| Follow-up                              | 135.6 (0.4) | 135.1 (0.3)  |
| Change from baseline at follow-up      | −0.2 (0.4)     | −0.2 (0.3)    |
| **Hematocrit (%)**                     |         |               |
| n                                      | 1508    | 3328          |
| Baseline                               | 41.45 (0.11) | 41.46 (0.08) |
| Last value on treatment                | 42.08 (0.12) | 45.07 (0.09) |
| Change from baseline at last value on treatment | 0.63 (0.08)    | 3.61 (0.06)   |
| Follow-up                              | 41.97 (0.12) | 43.24 (0.08) |
| Change from baseline at follow-up      | 0.52 (0.08)     | 1.78 (0.06)   |

Descriptive statistics. Data are mean (SE) in patients treated with ≥1 dose of study drug who had a measurement of the respective parameter at baseline, last value on treatment, and follow-up.
associated with an increased risk of stroke caused by sludging and hypoperfusion, respectively. In a meta-analysis of observational studies of patients with and without diabetes mellitus, orthostatic hypotension was associated with an increased risk of cardiovascular events, including stroke.16 In EMPA-REG OUTCOME, mean baseline hematocrit in the empagliflozin group was 41.4%, mean baseline systolic blood pressure was 135 mm Hg, and patients with the largest increases in hematocrit and the largest decreases in systolic blood pressure did not have an increased risk of stroke. The proportion of patients with a stroke event was consistent between patients who did and did not have an event consistent with volume depletion in both treatment groups.

A reduction in the risk of stroke was observed with intensive blood pressure lowering versus standard therapy in the ACCORD study (Action to Control Cardiovascular Risk in Diabetes), but this occurred after a mean follow-up of 4.7 years despite a large difference in systolic blood pressure (14.2 mm Hg) after 1 year.17 Thus, the lack of a risk reduction for stroke with empagliflozin in EMPA-REG OUTCOME may have been expected given the modest reduction in systolic blood pressure provided by empagliflozin over a median treatment time of 2.6 years and from a baseline of 135 mm Hg with 95% of patients taking antihypertensive therapy at baseline. The risk of stroke in the EMPA-REG OUTCOME trial was similar between patients with controlled (systolic blood pressure <140 mm Hg and diastolic blood pressure <90 mm Hg) versus uncontrolled blood pressure at baseline. Limitations of these analyses include that the results cannot be extrapolated beyond the treatment duration or observation time of the trial or to patient populations with other clinical characteristics.

In conclusion, in patients with type 2 diabetes mellitus and high cardiovascular risk in the EMPA-REG OUTCOME trial, empagliflozin, when compared with placebo, was not associated with either a reduction or an increase in the risk of cerebrovascular events.

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References

1. Emerging Risk Factors Collaboration; Sarwar N, Gao P, Seshasai SR, Gobin R, Kapogiannis G, Dr Angelanontino E, et al. Diabetes mellitus, fasting blood glucose concentration, and risk of vascular disease: a collaborative meta-analysis of 102 prospective studies. Lancet. 2010;375:2215–2222. doi: 10.1016/S0140-6736(10)60484-9.
2. Callahan A, Amarencio P, Goltstein LB, Sikesen H, Messig M, Samsa GP, et al; SPARCL Investigators. Risk of stroke and cardiovascular events after ischemic stroke or transient ischemic attack in patients with type 2 diabetes or metabolic syndrome: secondary analysis of the Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) trial. Arch Neurol. 2011;68:1245–1251. doi: 10.1001/archneurol.2011.146.
3. Bossaure G, Bejan-Angoultant V, Saadati-Elahi M, Lafont S, Bergeonneau C, Kassab B, et al. Effect of intensive glucose lowering treatment on all cause mortality, cardiovascular death, and microvascular events in type 2 diabetes: meta-analysis of randomised controlled trials. BMJ. 2011;343:d4169. doi: 10.1136/bmj.d4169.
4. Green JB, Bethel MA, Armstrong PW, Buse JB, Engel SS, Garg J, et al; TECOS Study Group. Effect of sitagliptin on cardiovascular outcomes in type 2 diabetes. N Engl J Med. 2015;373:232–242. doi: 10.1056/NEJMoa1501352.
5. Scirica BM, Bhatt DL, Braunwald E, Steg PG, Davidson J, Hirshberg B, et al; SAVOR-TIMI 53 Steering Committee and Investigators. Saxagliptin and cardiovascular outcomes in patients with type 2 diabetes mellitus. N Engl J Med. 2013;369:1317–1326. doi: 10.1056/NEJMoa1307684.
6. White WB, Cannon CP, Hellermann SR, Nissen SE, Bengtsson RM, Bakris GL, et al; EXAMINE Investigators. Alogliptin after acute coronary syndrome in patients with type 2 diabetes. N Engl J Med. 2013;369:1327–1335. doi: 10.1056/NEJMoa1305889.
7. Holman RR, Paul SK, Bethel MA, Matthews DR, Neil HA. 10-year follow-up of intensive glucose control in type 2 diabetes. N Engl J Med. 2008;359:1577–1586. doi: 10.1056/NEJMoa0806470.
8. Wilcox R, Bousier MG, Betteridge DJ, Scherhauer G, Pirags V, Kuper S, et al; PROActive Investigators. Effects of pioglitazone in patients with
type 2 diabetes with or without previous stroke: results from PROactive (Prospective Pioglitazone Clinical Trial in MacroVascular Events 04). Stroke. 2007;38:865–873. doi: 10.1161/01.STR.0000257974.06317.49.

9. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, et al; SUSTAIN-6 Investigators. Semaglutide and cardiovascular outcomes in patients with type 2 diabetes. N Engl J Med. 2016;375:1834–1844. doi: 10.1056/NEJMoia1607141.

10. Zinman B, Wanner C, Lachin JM, Fitchett D, Bluemki E, Hantel S, et al; EMPA-REG OUTCOME Investigators. Empagliflozin, cardiovascular outcomes, and mortality in type 2 diabetes. N Engl J Med. 2015;373:2117–2128. doi: 10.1056/NEJMoia1504720.

11. Zinman B, Inzucchi SE, Lachin JM, Wanner C, Ferrari R, Fitchett D, et al. Rationale, design, and baseline characteristics of a randomized, placebo-controlled cardiovascular outcome trial of empagliflozin (EMPA-REG OUTCOMETM). Cardiovasc Diabetol. 2014;13:102. doi: 10.1186/1475-2840-13-102.

12. Adams HP Jr, Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke. 1993;24:35–41. doi: 10.1161/01.STR.24.1.35.

13. Fitchett D, Zinman B, Wanner C, Lachin JM, Hantel S, Salsali A, et al; EMPA-REG OUTCOME® Trial Investigators. Heart failure outcomes with empagliflozin in patients with type 2 diabetes at high cardiovascular risk: results of the EMPA-REG OUTCOME® trial. Eur Heart J. 2016;37:1526–1534. doi: 10.1093/eurheartj/ehw728.

14. Asplund K, Karvonen J, Giampaoli S, Jousilahti P, Niamell M, Broda G, et al; MORGAM Project. Relative risks for stroke by age, sex, and population based on follow-up of 18 European populations in the MORGAM Project. Stroke. 2009;40:2319–2326. doi: 10.1161/STROKEAHA.109.547869.

15. Meschia JF, Bushnell C, Boden-Albala B, Braun LT, Bravata DM, Chaturvedi S, et al; American Heart Association Stroke Council; Council on Cardiovascular and Stroke Nursing; Council on Clinical Cardiology; Council on Functional Genomics and Translational Biology; Council on Hypertension. Guidelines for the primary prevention of stroke: a statement for healthcare professionals from the American Heart Association/American Stroke Association. Stroke. 2014;45:3754–3832. doi: 10.1161/STR.0000000000000046.

16. Hardie K, Hankey GJ, Jamrozik K, Broadhurst RJ, Anderson C. Ten-year risk of first recurrent stroke and disability after first-ever stroke in the Perth Community Stroke Study. Stroke. 2004;35:731–735. doi: 10.1161/01.STR.0000161835.50167.D9.

17. O’Donnell M, Al-Shahi R, Liu L, Zhang H, Chin SL, Rao-Melacini P, et al; INTERSTROKE Investigators. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. Lancet. 2010;376:112–123. doi: 10.1016/S0140-6736(10)60834-3.

18. Ricci F, Fedorowski A, Radico F, Romanello M, Tatasciore A, Di Nicola M, et al. Cardiovascular morbidity and mortality related to orthostatic hypotension: a meta-analysis of prospective observational studies. Eur Heart J. 2015;36:1609–1617. doi: 10.1093/eurheartj/ehv093.

19. ACCORD Study Group; Cushman WC, Evans GW, Byington RP, Goff DC Jr, Grimm RH Jr, Cutler JA, et al. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575–1585. doi: 10.1056/NEJMoia1001286.
Empagliflozin and Cerebrovascular Events in Patients With Type 2 Diabetes Mellitus at High Cardiovascular Risk

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on behalf of the EMPA-REG OUTCOME Investigators (Empagliflozin Cardiovascular Outcome Event Trial in Type 2 Diabetes Mellitus Patients)

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Supplementary Appendix (on-line only)

Supplementary Table I. Type of ischemic stroke according to TOAST classification.\(^1\) Post-hoc analysis.

| N (%)                      | Placebo (n=2333) | Empagliflozin (n=4687) |
|----------------------------|------------------|------------------------|
| Ischemic stroke            | 62 (2.7)         | 149 (3.2)              |
| Cardioembolism             | 22 (0.9)         | 49 (1.0)               |
| Large-artery atherosclerosis | 4 (0.2)         | 14 (0.3)               |
| Small-vessel occlusion (lacune) | 5 (0.2)  | 11 (0.2)               |
| Other determined etiology  | 0                | 2 (<0.1)               |
| Undetermined etiology      | 32 (1.4)         | 74 (1.6)               |

Treated set (patients treated with ≥1 dose of study drug).
# Supplementary Table II. Number of stroke events during the trial. Pre-specified analysis.

| N (%)                          | Placebo (n=2333) | Empagliflozin (n=4687) |
|-------------------------------|-----------------|------------------------|
| Fatal or non-fatal stroke (≥1 event) | 69 (3.0)       | 164 (3.5)              |
| 1 event                       | 61 (2.6)        | 151 (3.2)              |
| Non-fatal                     | 52 (2.2)        | 137 (2.9)              |
| Fatal                         | 9 (0.4)         | 14 (0.3)               |
| 2 events                      | 6 (0.3)         | 11 (0.2)               |
| 1<sup>st</sup> non-fatal      | 5 (0.2)         | 9 (0.2)                |
| 2<sup>nd</sup> non-fatal      |                |                        |
| 1<sup>st</sup> non-fatal      | 1 (<0.1)        | 2 (<0.1)               |
| 2<sup>nd</sup> fatal          |                |                        |
| 3 events                      | 1 (<0.1)        | 2 (<0.1)               |
| 1<sup>st</sup> non-fatal      | 1 (<0.1)        | 2 (<0.1)               |
| 2<sup>nd</sup> non-fatal      |                |                        |
| 3<sup>rd</sup> non-fatal      |                |                        |
| 4 events                      | 1 (<0.1)        | 0                      |
| 1<sup>st</sup> non-fatal      | 1 (<0.1)        | 0                      |
| 2<sup>nd</sup> non-fatal      |                |                        |
| 3<sup>rd</sup> non-fatal      |                |                        |
| 4<sup>th</sup> fatal          |                |                        |

Treated set (patients treated with ≥1 dose of study drug).
Supplementary Table III. Time to first stroke in subgroups defined by baseline characteristics. Post-hoc Cox regression analyses.

|                         | Placebo | Empagliflozin | HR (95% CI)          | p-value for interaction |
|-------------------------|---------|---------------|----------------------|-------------------------|
|                         | n (%)   | Rate/1000 patient-years | Rate/1000 patient-years |                          |
| All patients            | 69 (3.0)| 10.5          | 164 (3.5)            | 12.3                    | 1.18 (0.89, 1.56)       | –                     |
| Age                     |         |               |                      |                         |                         |                       |
| <65 years               | 26 (2.0)| 7.0           | 84 (3.2)             | 11.2                    | 1.60 (1.03, 2.49)       | –                     |
| ≥65 years               | 43 (4.2)| 14.9          | 80 (3.8)             | 13.5                    | 0.91 (0.63, 1.32)       | –                     |
| Sex                     |         |               |                      |                         |                         | 0.73                  |
| Male                    | 52 (3.1)| 10.9          | 118 (3.5)            | 12.3                    | 1.14 (0.82, 1.58)       | –                     |
| Female                  | 17 (2.6)| 9.3           | 46 (3.4)             | 12.1                    | 1.28 (0.73, 2.23)       | –                     |
| Race                    |         |               |                      |                         |                         | 0.45                  |
| White                   | 46 (2.7)| 9.8           | 114 (3.3)            | 11.8                    | 1.22 (0.87, 1.72)       | –                     |
| Asian                   | 20 (3.9)| 13.2          | 38 (3.8)             | 12.6                    | 0.95 (0.55, 1.64)       | –                     |
| Black/African American* | 2 (1.7) | 6.0           | 10 (4.2)             | 15.7                    |                         | –                     |
| Other*                  | 1 (4.2) | 18.0          | 2 (5.0)              | 19.2                    |                         | –                     |
| Ethnicity               |         |               |                      |                         |                         | 0.11                  |
| Hispanic/Latino         | 10 (2.4)| 8.7           | 13 (1.5)             | 5.4                     | 0.62 (0.27, 1.42)       | –                     |
| Not Hispanic/Latino     | 59 (3.1)| 10.9          | 151 (3.9)            | 13.8                    | 1.27 (0.94, 1.72)       | –                     |
| Region                  |         |               |                      |                         |                         | 0.01                  |
| Europe                  | 21 (2.2)| 7.8           | 85 (4.4)             | 15.7                    | 2.04 (1.26, 3.29)       | –                     |
| North America (plus Australia and New Zealand) | 19 (4.1)| 15.2          | 32 (3.4)             | 12.3                    | 0.82 (0.46, 1.45)       | –                     |
| Asia                    | 16 (3.6)| 12.0          | 35 (3.9)             | 13.0                    | 1.08 (0.60, 1.95)       | –                     |
| Latin America           | 10 (2.8)| 9.9           | 9 (1.2)              | 4.4                     | 0.44 (0.18, 1.07)       | –                     |
| Africa*                 | 3 (2.9) | 10.5          | 3 (1.4)              | 5.0                     |                         | –                     |
| Time since diagnosis of type 2 diabetes |         |               |                      |                         |                         | 0.84                  |
| ≤5 years                | 11 (2.6)| 9.3           | 22 (2.6)             | 9.2                     | 0.97 (0.47, 1.99)       | –                     |
| >5–10 years             | 13 (2.3)| 8.0           | 33 (2.8)             | 9.7                     | 1.26 (0.66, 2.40)       | –                     |
| >10 years               | 45 (3.4)| 12.0          | 109 (4.1)            | 14.4                    | 1.20 (0.85, 1.70)       | –                     |
| HbA1c                   |         |               |                      |                         |                         | 0.01                  |
| <8.5%                   | 54 (3.4)| 12.0          | 100 (3.1)            | 10.9                    | 0.91 (0.66, 1.27)       | –                     |
| ≥8.5%                   | 15 (2.1)| 7.2           | 64 (4.3)             | 15.2                    | 2.13 (1.21, 3.74)       | –                     |
| Body mass index         |         |               |                      |                         |                         | 0.92                  |
| <30 kg/m²               | 39 (3.5)| 12.2          | 92 (4.0)             | 14.0                    | 1.16 (0.80, 1.69)       | –                     |
| Variable                                                                 | eGFR | 8.9 | 72 (3.0) | 10.5 | 1.20 (0.78, 1.83) |   |
|--------------------------------------------------------------------------|------|-----|----------|------|------------------|---|
| ≥30 kg/m²                                                                | 30 (2.5) | 10 (2.0) | 7.2 | 37 (3.5) | 12.5 | 1.73 (0.86, 3.47) |   |
| ≥90 mL/min/1.73m²                                                         | 60 to <90 mL/min/1.73m² | ≤60 mL/min/1.73m² | Urine albumin-to-creatinine ratio | <30 mg/g | 30 to 300 mg/g | >300 mg/g | Blood pressure control | SBP ≥140 mmHg and/or DBP ≥90 mmHg | SBP <140 mmHg and DBP <90 mmHg | Cardiovascular risk | Only cerebrovascular disease | Only coronary artery disease | Only peripheral artery disease | 2 or 3 high-risk categories | Previous stroke | Yes | No | Atrial fibrillation | Yes | No | Heart failure | Yes | No | Hypertension | Yes | No | Smoking status
|                                                                           |      |     |         |      |                 |   | 32 (2.3) | 8.0 | 82 (2.9) | 10.2 | 1.28 (0.85, 1.93) |   | 37 (4.0) | 14.2 | 83 (4.7) | 16.5 | 1.14 (0.77, 1.68) |   | 32 (2.3) | 8.0 | 81 (2.8) | 9.7 | 1.23 (0.82, 1.85) |   | 13 (4.0) | 14.5 | 46 (7.2) | 26.1 | 1.80 (0.97, 3.34) |   | 30 (2.2) | 7.8 | 69 (2.5) | 8.6 | 1.11 (0.73, 1.71) |   | 5 (2.6) | 9.6 | 6 (1.5) | 5.4 | – |   | 21 (4.7) | 17.2 | 43 (4.9) | 17.6 | 1.05 (0.62, 1.78) |   | 25 (4.5) | 16.6 | 68 (6.3) | 22.7 | 1.43 (0.90, 2.26) |   | 44 (2.5) | 8.7 | 96 (2.7) | 9.2 | 1.06 (0.74, 1.52) |   | 4 (2.8) | 10.8 | 19 (7.7) | 29.5 | 2.67 (0.91, 7.86) |   | 65 (3.0) | 10.5 | 145 (3.3) | 11.4 | 1.09 (0.82, 1.47) |   | 7 (2.9) | 11.5 | 21 (4.5) | 17.4 | 1.48 (0.63, 3.49) |   | 62 (3.0) | 10.4 | 143 (3.4) | 11.8 | 1.14 (0.85, 1.54) |   | 66 (3.1) | 10.9 | 160 (3.8) | 13.2 | – |   | 3 (1.7) | 5.5 | 4 (1.0) | 3.2 | – |   | 3 (1.7) | 5.5 | 4 (1.0) | 3.2 | – |   | 28 (2.9) | 10.3 | 75 (3.9) | 13.7 | 1.33 (0.86, 2.06) |   | 33 (3.1) | 10.8 | 66 (3.1) | 10.7 | 0.99 (0.65, 1.51) |   | 8 (2.6) | 9.8 | 23 (3.7) | 13.3 | 1.39 (0.62, 3.10) |   | – |   | – | – |   | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – | – |
| Medication                        | Odds Ratio  | 95% CI     |
|----------------------------------|-------------|------------|
| **Metformin**                    | 0.60        |            |
| Yes                              | 1.23        | (0.88, 1.73)|            |
| No                               | 1.05        | (0.63, 1.75)|            |
| **Sulfonylurea**                 | 0.54        |            |
| Yes                              | 1.31        | (0.83, 2.08)|            |
| No                               | 1.10        | (0.77, 1.57)|            |
| **Insulin**                      | 0.06        |            |
| Yes                              | 1.57        | (1.03, 2.41)|            |
| No                               | 0.91        | (0.62, 1.33)|            |
| **Thiazolidinedione**            | –           |            |
| Yes*                             | –           |            |
| No                               | –           |            |
| **DPP-4 inhibitor**              | 0.12        |            |
| Yes                              | 2.06        | (0.94, 4.48)|            |
| No                               | 1.07        | (0.79, 1.45)|            |
| **Statin or ezetimibe**          | 0.89        |            |
| Yes                              | 1.17        | (0.84, 1.62)|            |
| No                               | 1.22        | (0.70, 2.13)|            |
| **Antihypertensive therapy**     | –           |            |
| Yes                              | –           |            |
| No*                              | –           |            |
| **ACE inhibitor or ARB**          | 0.45        |            |
| Yes                              | 1.24        | (0.90, 1.71)|            |
| No                               | 0.95        | (0.52, 1.75)|            |
| **Calcium channel blocker**      | 0.71        |            |
| Yes                              | 1.10        | (0.69, 1.75)|            |
| No                               | 1.23        | (0.86, 1.74)|            |
| **Beta-blocker**                 | 0.71        |            |
| Yes                              | 1.13        | (0.79, 1.61)|            |
| No                               | 1.26        | (0.79, 2.01)|            |
| **Diuretic**                     | 0.25        |            |
| Yes                              | 1.41        | (0.92, 2.17)|            |
| No                               | 1.01        | (0.70, 1.47)|            |
| **Loop diuretic**                | 0.08        |            |
| Yes                              | 2.30        | (1.02, 5.22)|            |
| No                               | 1.05        | (0.78, 1.42)|            |
| **Acetylsalicylic acid**         | 0.54        |            |
| Yes                              | 1.13        | (0.83, 1.54)|            |
| No                               | 1.42        | (0.73, 2.74)|            |
| **Vitamin K antagonist**         | 0.74        |            |
| Yes                              | 1.36        | (0.56, 3.32)|            |
| No | 62 (2.8) | 10.1 | 148 (3.3) | 11.7 | 1.16 (0.87, 1.57) | – |

*HR and 95% CI were not calculated as <14 patients with an event in this subgroup.

Treated set (patients treated with ≥1 dose of study drug).

p-value is for test of homogeneity of the treatment group difference among subgroups (test for treatment group by covariate interaction) with no adjustment for multiple tests. p=0.0535 for age.

ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blocker; CI, confidence interval; DBP, diastolic blood pressure; HbA1c, glycaated haemoglobin; HR, hazard ratio; SBP, systolic blood pressure.
### Supplementary Table IV. Baseline characteristics in subgroups of patients by region and treatment.

|                           | Europe (plus Australia and New Zealand) | North America | Latin America | Africa | Asia |
|---------------------------|------------------------------------------|---------------|---------------|--------|------|
|                           | Placebo (n=959) | Placebo (n=462) | Placebo (n=360) | Placebo (n=102) | Placebo (n=450) | Placebo (n=1926) | Empagliflozin (n=932) | Empagliflozin (n=721) | Empagliflozin (n=932) | Empagliflozin (n=211) | Empagliflozin (n=897) |
| Male                      | 690 (71.9) | 359 (77.7) | 234 (65.0) | 70 (68.6) | 327 (72.7) | 1373 (71.3) | 678 (72.7) | 469 (65.0) | 158 (74.9) | 658 (73.4) |
| Age, years                | 64.0 (8.5) | 65.1 (8.4) | 62.6 (8.1) | 59.8 (9.3) | 60.8 (9.4) | 63.8 (8.2) | 64.5 (8.6) | 62.5 (8.4) | 61.3 (8.8) | 61.0 (9.0) |
| Race                      |              |              |              |              |              |              |              |              |              |              |
| White                     | 941 (98.1) | 392 (84.8) | 304 (84.4) | 41 (40.2) | 0 | 1897 (98.5) | 788 (84.5) | 611 (84.7) | 105 (49.8) | 2 (0.2) |
| Black/African-American    | 4 (0.4) | 44 (9.5) | 36 (10.0) | 36 (35.3) | 0 | 9 (0.5) | 85 (9.1) | 77 (10.7) | 66 (31.3) | 0 |
| Asian                     | 14 (1.5) | 17 (3.7) | 6 (1.7) | 24 (23.5) | 450 (100.0) | 19 (1.0) | 45 (4.8) | 8 (1.1) | 39 (18.5) | 895 (99.8) |
| Other                     | 0 | 9 (2.0) | 14 (3.9) | 1 (1.0) | 0 | 1 (0.1) | 14 (1.5) | 25 (3.5) | 1 (0.5) | 0 |
| BMI, kg/m²                | 31.7 (4.7) | 33.3 (5.4) | 29.8 (4.5) | 30.8 (5.1) | 26.3 (3.8) | 31.5 (4.7) | 33.1 (5.4) | 30.0 (5.0) | 30.9 (5.0) | 26.4 (3.9) |
| Time since diagnosis of T2DM |              |              |              |              |              |              |              |              |              |              |
| <5 years                  | 183 (19.1) | 46 (9.9) | 66 (18.3) | 30 (29.4) | 98 (21.8) | 330 (17.1) | 110 (11.8) | 128 (17.8) | 52 (24.6) | 220 (24.5) |
| >5 to 10 years            | 232 (24.2) | 109 (23.6) | 75 (20.8) | 19 (18.6) | 136 (30.2) | 518 (26.9) | 213 (22.9) | 178 (24.7) | 52 (24.6) | 214 (23.9) |
| >10 years                 | 544 (56.7) | 307 (66.5) | 219 (60.8) | 53 (52.0) | 216 (48.0) | 1078 (56.0) | 609 (65.3) | 415 (57.6) | 107 (50.7) | 463 (51.6) |
| eGFR, mL/min/1.73m²       | 76.0 (20.5) | 66.6 (18.7) | 76.4 (21.0) | 75.9 (24.6) | 74.0 (22.1) | 76.5 (21.1) | 67.1 (18.7) | 76.3 (23.4) | 76.0 (24.2) | 74.4 (21.8) |
| Any CV risk factor        | 949 (99.0) | 456 (98.7) | 353 (98.1) | 102 (100.0) | 447 (99.3) | 1920 (99.7) | 925 (99.2) | 712 (98.8) | 211 (100.0) | 889 (99.1) |
| Condition                                      | CAD     | Multi-vessel CAD | History of MI | Coronary artery bypass graft | History of stroke | Peripheral artery disease | Single vessel CAD | Atrial fibrillation* | Any anti-hypertensive drugs | ACE inhibitors/ARBs | Beta-blockers | Diuretics | Calcium channel blockers | Mineralocorticoid receptor antagonists | Renin inhibitors | Other | Any lipid-lowering drugs |
|-----------------------------------------------|---------|------------------|---------------|-------------------------------|-------------------|--------------------------|-------------------|----------------------|------------------------|---------------------|---------------|-----------|------------------------|-------------------------------------|------------------|--------|------------------------|
|                                               | 679 (70.8) | 1408 (73.1)    | 414 (89.6)    | 824 (88.4)                    | 241 (66.9)        | 452 (62.7)               | 89 (87.3)       | 178 (84.4)          | 340 (75.6)             | 683 (76.1)           |              |           |                        |                                     |                  |         |                        |
| Multi-vessel CAD                              | 371 (38.7)  | 801 (41.6)      | 300 (64.9)    | 583 (62.6)                    | 121 (33.6)        | 203 (28.2)               | 58 (56.9)       | 102 (48.3)          | 250 (55.6)             | 490 (54.6)           |              |           |                        |                                     |                  |         |                        |
| History of MI                                | 476 (49.6)  | 985 (51.1)      | 210 (45.5)    | 429 (46.0)                    | 160 (44.4)        | 307 (42.6)               | 56 (54.9)       | 110 (52.1)          | 181 (40.2)             | 359 (40.0)           |              |           |                        |                                     |                  |         |                        |
| Coronary artery bypass graft                 | 189 (19.7)  | 399 (20.7)      | 201 (43.5)    | 389 (41.7)                    | 72 (20.0)         | 154 (21.4)               | 43 (42.2)       | 95 (45.0)           | 58 (12.9)              | 138 (15.4)           |              |           |                        |                                     |                  |         |                        |
| History of stroke                           | 287 (29.9)  | 495 (25.7)      | 69 (14.9)     | 169 (18.1)                    | 70 (19.4)         | 155 (21.5)               | 17 (16.7)       | 31 (14.7)           | 110 (24.4)             | 234 (26.1)           |              |           |                        |                                     |                  |         |                        |
| Peripheral artery disease                    | 226 (23.6)  | 450 (23.4)      | 86 (18.6)     | 199 (21.4)                    | 101 (28.1)        | 212 (29.4)               | 12 (11.8)       | 38 (18.0)           | 54 (12.0)              | 83 (9.3)             |              |           |                        |                                     |                  |         |                        |
| Single vessel CAD                            | 111 (11.6)  | 230 (11.9)      | 60 (13.0)     | 122 (13.1)                    | 13 (3.6)          | 28 (3.9)                 | 5 (4.9)         | 17 (8.1)            | 49 (10.9)              | 101 (11.3)           |              |           |                        |                                     |                  |         |                        |
| Atrial fibrillation*                        | 78 (8.1)    | 129 (6.7)       | 40 (8.7)      | 66 (7.1)                      | 13 (3.6)          | 20 (2.8)                 | 2 (2.0)         | 10 (4.7)            | 9 (2.0)                | 22 (2.5)             |              |           |                        |                                     |                  |         |                        |
| Any anti-hypertensive drugs                  | 917 (95.6)  | 1846 (95.8)     | 449 (97.2)    | 902 (96.8)                    | 338 (93.9)        | 669 (92.8)               | 101 (99.0)      | 200 (94.8)          | 416 (92.4)             | 829 (92.4)           |              |           |                        |                                     |                  |         |                        |
| ACE inhibitors/ARBs                          | 795 (82.9)  | 1616 (83.9)     | 377 (81.6)    | 765 (82.1)                    | 300 (83.3)        | 594 (82.4)               | 84 (82.4)       | 179 (84.8)          | 312 (69.3)             | 644 (71.8)           |              |           |                        |                                     |                  |         |                        |
| Beta-blockers                                | 629 (65.6)  | 1326 (68.8)     | 335 (72.5)    | 670 (71.9)                    | 209 (58.1)        | 407 (56.4)               | 69 (67.6)       | 133 (63.0)          | 256 (56.9)             | 520 (58.0)           |              |           |                        |                                     |                  |         |                        |
| Diuretics                                    | 461 (48.1)  | 953 (49.5)      | 214 (46.3)    | 445 (47.7)                    | 142 (39.4)        | 298 (41.3)               | 56 (54.9)       | 125 (59.2)          | 115 (25.6)             | 226 (25.2)           |              |           |                        |                                     |                  |         |                        |
| Calcium channel blockers                     | 354 (36.9)  | 668 (34.7)      | 137 (29.7)    | 251 (26.9)                    | 97 (26.9)         | 182 (25.2)               | 31 (30.4)       | 80 (37.9)           | 169 (37.6)             | 348 (38.8)           |              |           |                        |                                     |                  |         |                        |
| Mineralocorticoid receptor antagonists       | 62 (6.5)    | 140 (7.3)       | 15 (3.2)      | 43 (4.6)                      | 36 (10.0)         | 60 (8.3)                 | 10 (9.8)        | 12 (5.7)            | 13 (2.9)               | 50 (5.6)             |              |           |                        |                                     |                  |         |                        |
| Renin inhibitors                             | 15 (1.6)    | 17 (0.9)        | 1 (0.2)       | 5 (0.5)                       | 2 (0.6)           | 4 (0.6)                  | 0               | 0                   | 1 (0.2)                | 1 (0.1)             |              |           |                        |                                     |                  |         |                        |
| Other                                        | 95 (9.9)    | 183 (9.5)       | 54 (11.7)     | 105 (11.3)                    | 19 (5.3)          | 28 (3.9)                 | 3 (2.9)         | 16 (7.6)            | 20 (4.4)               | 51 (5.7)             |              |           |                        |                                     |                  |         |                        |
| Any lipid-lowering drugs                     | 736 (76.7)  | 1515 (78.7)     | 402 (87.0)    | 833 (89.4)                    | 271 (75.3)        | 551 (76.4)               | 98 (96.1)       | 189 (89.6)          | 357 (79.3)             | 732 (81.6)           |              |           |                        |                                     |                  |         |                        |
| Drug Type                        | n (%)          | n (%)          | n (%)          | n (%)          | n (%)          | n (%)          | n (%)          | n (%)          | n (%)          |
|----------------------------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|----------------|
|                                  | 705 (73.5)     | 1448 (75.2)    | 368 (79.7)     | 763 (81.9)     | 255 (70.8)     | 527 (73.1)     | 98 (96.1)      | 188 (89.1)     | 347 (77.1)     |
| Fibrates                         | 64 (6.7)       | 163 (8.5)      | 64 (13.9)      | 126 (13.5)     | 36 (10.0)      | 74 (10.3)      | 3 (2.9)        | 9 (4.3)        | 32 (7.1)       |
| Ezetimibe                        | 34 (3.5)       | 72 (3.7)       | 20 (4.3)       | 69 (7.4)       | 13 (3.6)       | 24 (3.3)       | 2 (2.0)        | 2 (0.9)        | 12 (2.7)       |
| Niacin                           | 7 (0.7)        | 9 (0.5)        | 23 (5.0)       | 75 (8.0)       | 1 (0.3)        | 3 (0.4)        | 0              | 1 (0.5)        | 4 (0.9)        |
| Other                            | 33 (3.4)       | 82 (4.3)       | 123 (26.6)     | 251 (26.9)     | 3 (0.8)        | 5 (0.7)        | 3 (2.9)        | 3 (1.4)        | 13 (2.9)       |
| Any anti-coagulant/anti-platelet drugs | 845 (88.1)   | 1694 (88.0)    | 418 (90.5)     | 847 (90.9)     | 309 (85.8)     | 616 (85.4)     | 100 (98.0)     | 192 (91.0)     | 418 (92.9)     |
| Acetylsalicylic acid             | 755 (78.7)     | 1540 (80.0)    | 395 (85.5)     | 807 (86.6)     | 299 (83.1)     | 588 (81.6)     | 96 (94.1)      | 185 (87.7)     | 382 (84.9)     |
| Vitamin K antagonists            | 87 (9.1)       | 148 (7.7)      | 44 (9.5)       | 63 (6.8)       | 10 (2.8)       | 24 (3.3)       | 5 (4.9)        | 11 (5.2)       | 10 (2.2)       |
| Clopidogrel                      | 81 (8.4)       | 183 (9.5)      | 18 (3.9)       | 36 (3.9)       | 51 (14.2)      | 108 (15.0)     | 7 (6.9)        | 15 (7.1)       | 92 (20.4)      |
| Non-vitamin K antagonist oral anticoagulants† | 4 (0.4)      | 4 (0.2)        | 7 (1.5)        | 6 (0.6)        | 1 (0.3)        | 0              | 0              | 0              | 1 (0.2)        |

*Based on 1 MedDRA preferred term.
†Direct factor Xa inhibitors or direct thrombin inhibitors.

BMI, body mass index; eGFR, estimated glomerular filtration rate; T2DM, type 2 diabetes; CV, cardiovascular; CAD, coronary artery disease; ACE, angiotensin-converting enzyme; ARB, angiotensin receptor blockers; MedDRA, Medical Dictionary for Regulatory Activities.
Supplementary Table V. Time to first fatal or non-fatal stroke by maximum increase from baseline in hematocrit or maximum decrease from baseline in systolic blood pressure based on data prior to or on date of first fatal or non-fatal stroke. Post-hoc analyses.

|                                                                 | Placebo | Empagliflozin |
|-----------------------------------------------------------------|---------|---------------|
| Incidence of stroke by maximum increase from baseline in hematocrit before or on date of first stroke (in patients with stroke) or censoring (in patients without stroke) |         |               |
| Patients with increase from baseline in hematocrit ≥90<sup>th</sup> percentile | 1/75 (1.3) | 11/705 (1.6) |
| Patients with increase from baseline in hematocrit <90<sup>th</sup> percentile | 65/2211 (2.9) | 133/3862 (3.4) |
| Incidence of stroke by maximum decrease from baseline in systolic blood pressure before or on date of first stroke (in patients with stroke) or censoring (in patients without stroke) |         |               |
| Patients with decrease from baseline in systolic blood pressure of ≥30 mmHg | 55/1907 (2.9) | 122/3596 (3.4) |
| Patients with decrease from baseline in systolic blood pressure of <30 mmHg | 14/415 (3.4) | 39/1049 (3.7) |

Treated set (patients treated with ≥1 dose of study drug).

Hematocrit: 90<sup>th</sup> percentile corresponds to a change from baseline of 9.0%.
**Supplementary Table VI.** Stroke in patients with and without events consistent with volume depletion*. Post-hoc analyses.

| N (%)                  | Patients with an event consistent with volume depletion | Patients without an event consistent with volume depletion |
|------------------------|--------------------------------------------------------|---------------------------------------------------------|
|                        | Placebo (n=125) | Empagliflozin (n=269) | Placebo (n=2208) | Empagliflozin (n=4418) |
| First stroke event after first volume depletion event or during study† | 3 (2.4) | 8 (3.0) | 63 (2.9) | 149 (3.4) |

Treated set (patients treated with ≥1 dose of study drug).

*Based on 8 Medical Dictionary for Regulatory Activities (MedDRA) preferred terms.

†Only the first stroke per patient was considered. For patients with volume depletion, only a stroke event after the first volume depletion event was considered. For patients without volume depletion, the first stroke in the study was considered.
**Supplementary Table VII.** Stroke in patients with and without atrial fibrillation*. Post-hoc analyses.

| N (%) | Patients with an atrial fibrillation event | Patients without an atrial fibrillation event |
|-------|-------------------------------------------|---------------------------------------------|
|       | Placebo (n=67)                             | Empagliflozin (n=161)                       | Placebo (n=2266)                             | Empagliflozin (n=4526) |
| **First stroke event after first atrial fibrillation event or during study†** | 2 (3.0)                                      | 6 (3.7)                                      | 65 (2.9)                                      | 154 (3.4)                |

Treated set (patients treated with ≥1 dose of study drug).

*Based on the Medical Dictionary for Regulatory Activities (MedDRA) preferred term ‘atrial fibrillation’.

†Only the first stroke per patient was considered. For patients with an atrial fibrillation event, only a stroke event after the first atrial fibrillation event was considered. For patients without an atrial fibrillation event, the first stroke in the study was considered.
Supplementary Figure I. Time to first fatal or non-fatal stroke in modified intent-to-treat and sensitivity analyses. Cox regression analyses.

| Patients with event/analysed (%) | Empagliflozin | Placebo | HR (95% CI) | p-value |
|----------------------------------|---------------|---------|-------------|---------|
| **Fatal or non-fatal stroke**    |               |         |             |         |
| Modified intent-to-treat analysis* |               |         |             |         |
| Treated set                      | 164/4687 (3.5) | 69/2333 (3.0) | 1.18 (0.89, 1.56) | 0.26 |
| **Sensitivity analyses**         |               |         |             |         |
| Treated set + 90 days†           | 146/4687 (3.1) | 66/2333 (2.8) | 1.08 (0.81, 1.45) | 0.60 |
| Treated set + 30 days‡           | 143/4687 (3.1) | 66/2333 (2.8) | 1.08 (0.79, 1.41) | 0.71 |
| Treated set + 7 days†            | 139/4687 (3.0) | 62/2333 (2.7) | 1.09 (0.81, 1.48) | 0.55 |
| On-treatment set‡                | 141/4607 (3.1) | 66/2308 (2.9) | 1.04 (0.78, 1.40) | 0.78 |

*Events observed from randomization to the end of the study in treated set (patients treated with ≥1 dose of study drug) (pre-specified).
†Events observed during treatment or ≤90 days, ≤30 days or ≤7 days after a patient’s last intake of trial medication in treated set (patients treated with ≥1 dose of study drug) (post-hoc).
‡Events that occurred during treatment or ≤30 days after a patient’s last intake of trial medication in patients who received study drug for ≥30 days (cumulative) (pre-specified).

HR, hazard ratio. CI, confidence interval.
**Supplementary Figure II.** Time to transient ischemic attack. (A) Pre-specified modified intent-to-treat analyses in the treated set* and (B) Post-hoc sensitivity analysis in treated set + 90 days†. Cumulative incidence function. Hazard ratios are based on Cox regression.

**A** Modified intent-to-treat analyses in the treated set*

**B** Sensitivity analysis in treated set + 90 days†

*Events observed from randomization to the end of the study in treated set (patients treated with ≥1 dose of study drug). †Events observed during treatment or ≤90 days after a patient's last intake of trial medication in treated set.

HR, hazard ratio. CI, confidence interval.
Supplementary Figure III. Hazard ratios for time to first stroke with empagliflozin compared with placebo by baseline HbA1c in deciles. Post-hoc Cox regression analyses.

Treated set (patients treated with ≥1 dose of study drug). Two patients were excluded from this analysis as baseline HbA1c was not available.

\(p=0.192\) for treatment by baseline HbA1c percentile category interaction.

HR, hazard ratio. CI, confidence interval.
Definitions of Transient Ischemic Attack and Stroke

**Transient ischemic attack (TIA)**

TIA: a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

**Stroke**

Stroke: the rapid onset of a new persistent neurologic deficit attributed to an obstruction in cerebral blood flow and/or cerebral hemorrhage with no apparent non-vascular cause (e.g., trauma, tumor, or infection). Available neuroimaging studies are considered to support the clinical impression and to determine if there is a demonstrable lesion compatible with an acute stroke. Strokes are classified as ischemic, hemorrhagic, or unknown.

**Diagnosis of stroke.**

For the diagnosis of stroke, the following 4 criteria should be fulfilled:

- Rapid onset of a focal/global neurological deficit with at least one of the following:
  - Change in level of consciousness
  - Hemiplegia
  - Hemiparesis
  - Numbness or sensory loss affecting one side of the body
  - Dysphasia/aphasia
  - Hemianopia (loss of half of the field of vision of one or both eyes)
  - Other new neurological sign(s)/symptom(s) consistent with stroke

NOTE: If the mode of onset is uncertain, a diagnosis of stroke may be made provided that there is no plausible non-stroke cause for the clinical presentation

- Duration of a focal/global neurological deficit ≥24 hours OR < 24 hours if this is because of at least one of the following therapeutic interventions:
  - Pharmacologic (i.e., thrombolytic drug administration)
– Non-pharmacologic (i.e., neurointerventional procedure [e.g. intracranial angioplasty])

OR

– Available brain imaging clearly documents a new hemorrhage or infarct

OR

– The neurological deficit results in death

• No other readily identifiable non-stroke cause for the clinical presentation (e.g., brain tumor, trauma, infection, hypoglycemia, peripheral lesion)

• Confirmation of the diagnosis by at least one of the following:*
  – Neurology or neurosurgical specialist
  – Brain imaging procedure (at least one of the following):
    ▪ CT scan
    ▪ MRI scan
    ▪ Cerebral vessel angiography
  – Lumbar puncture (i.e. spinal fluid analysis diagnostic of intracranial hemorrhage)

If a stroke is reported but evidence of confirmation of the diagnosis by the methods outlined above is absent, the event will be discussed at a full CEC meeting. In such cases, the event may be adjudicated as a stroke on the basis of the clinical presentation alone, but full CEC consensus is mandatory.

If the acute focal signs represent a worsening of a previous deficit, these signs must have either

• Persisted for more than one week

OR

• Persisted for more than 24 hours and were accompanied by an appropriate new CT or MRI finding

*Classification of stroke
Strokes are sub-classified as follows:

- **Ischemic (non-hemorrhagic):** A stroke caused by an arterial obstruction due to a thrombotic (e.g., large vessel disease/atherosclerotic or small vessel disease/lacunar) or embolic etiology. This category includes ischemic strokes with hemorrhagic transformation (i.e. no evidence of hemorrhage on an initial imaging study but appearance on a subsequent scan)

- **Hemorrhagic:** A stroke due to a hemorrhage in the brain as documented by neuroimaging or autopsy. This category includes strokes due to primary intracerebral hemorrhage (intraparenchymal or intraventricular) and primary subarachnoid hemorrhage

- **Not assessable:** The stroke type could not be determined by imaging or other means (e.g., lumbar puncture, neurosurgery, or autopsy) or no imaging was performed

**Clinical Events Committee Charter for Assessment of Ischemic Stroke**

Classification of the subtype of ischemic stroke:

- **Large-artery atherosclerosis**
  
  - Studies/findings should show significant stenosis or occlusion of a major brain artery or branch cortical artery, [presumably due to atherosclerosis]
  
  - Studies should exclude potential sources of cardiogenic embolism

  - Brain imaging findings/diagnostic studies
    
    - Computerised tomography (CT) or magnetic resonance imaging (MRI)
      
      - Cortical or cerebellar lesions and brain stem or subcortical hemispheric infarcts greater than 1.5 cm in diameter

    - Duplex imaging or arteriography
      
      - Stenosis of greater than 50% of an intracranial or extracranial artery
      
      - If these studies are normal or show only minimal changes, this diagnosis cannot be made.
Clinical findings

- Cerebral cortical impairment (including, but not limited to aphasia, neglect, restricted motor involvement)

OR

- Brain stem or cerebellar dysfunction

- History of intermittent claudication, transient ischemic attacks, carotid bruit or diminished pulses

Cardioembolism

- Studies should exclude potential large artery atherosclerosis sources of thromboembolism or embolism

- History of conditions listed on the high risk and medium risk categories

- Brain imaging/clinical findings

  - Refer to large artery atherosclerosis clinical and brain image findings

  - Must identify at least 1 cardiac source for an embolism.

  - Must have evidence of a prior transient ischemic attack (TIA) or stroke in more than one vascular territory or system embolism supports a clinical diagnosis of stroke.

  - A medium-risk cardiac source with no other cause of stroke is a ‘possible cardioembolic stroke’

- Cardioembolism sub-categories

  - High-risk cardioembolism

  - Mechanical prosthetic valve

  - Mitral stenosis with atrial fibrillation

  - Atrial fibrillation (other than lone atrial fibrillation)

  - Left atrial/atrial appendage thrombus
- Sick sinus syndrome
- Recent myocardial infarction (<4 weeks)
- Left ventricular thrombus
- Dilated cardiomyopathy
- Akinetic left ventricular segment
- Atrial myxoma
- Infective endocarditis

  - Medium-risk cardioembolism
    - Mitral valve prolapse
    - Mitral annulus calcification
    - Mitral stenosis without atrial fibrillation
    - Left atrial turbulence (smoke)
    - Atrial septal aneurysm
    - Patent foramen ovale
    - Atrial flutter
    - Lone atrial fibrillation
    - Bioprosthetic cardiac valve
    - Nonbacterial thrombotic endocarditis
    - Congestive heart failure
    - Hypokinetic left ventricular segment
    - Myocardial infarction (>4 weeks, <6 months)

- Small-vessel occlusion (lacune)
- There should be no evidence of cerebral cortical dysfunction, no potential cardiac sources for embolism.
- Large extracranial arteries should not have a >50% stenosis of an ipsilateral artery.
- Brain imaging findings
  - CT or MRI
    - Should be normal
    - OR
    - Brain stem or subcortical hemispheric lesion with a less than 1.5 cm diameter.

- Clinical findings
  - 1 traditional clinical lacunar syndrome
  - history of diabetes mellitus or hypertension.

- Stroke of other determined etiology
  - Studies should exclude large artery atherosclerosis and cardiac sources of embolism
  - Brain Image findings and clinical findings
    - Demonstrate clinical symptoms of stroke
    - CT or MRI findings of an acute stroke (regardless of size/location)
    - Blood tests or arteriography should support a rare cause of stroke such as nonatherosclerotic vasculopathies, hypercoagulable statue or hematologic disorders.

- Stroke of undetermined etiology
– Two or more causes identified (therefore unable to make final determination)
– Negative evaluation (available information present and complete)
– Incomplete evaluation (missing information/incomplete information)

A response to probable or possible will be chosen for all categories except undetermined

- Probable: A "probable" diagnosis is made if the clinical findings, neuroimaging data, and results of diagnostic studies are consistent with one subtype and other etiologies have been excluded.
- Possible: A "possible" diagnosis is made when the clinical findings and neuroimaging data suggest a specific subtype but other studies are not done.
References in Supplementary Appendix

1. Adams HP, Jr., Bendixen BH, Kappelle LJ, Biller J, Love BB, Gordon DL, et al. Classification of subtype of acute ischemic stroke. Definitions for use in a multicenter clinical trial. TOAST. Trial of Org 10172 in Acute Stroke Treatment. Stroke 1993;24:35-41.