SUPPLEMENTAL MATERIAL

Canagliflozin and Stroke in Type 2 Diabetes: Results From the Randomized CANVAS Program Trials

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Definitions of stroke and stroke subtypes used by Endpoint Adjudication Committee

Stroke

A non-fatal stroke was an event that met the current classification definition below and does not result in death within 30 days from onset. The definition was based on the new "tissue" definition of stroke (Sacco et al. Stroke 2013;44:2064). Stroke will also be classified by the Endpoint Adjudication Committee (EAC) according to historical criteria. Any recurrence or exacerbation of the condition within 30 days is considered part of the original episode, whereas beyond that time period it is considered a separate event. Adjudications were based on the best available evidence from the clinical care of the patient with a stroke-like event, with anonymised copies of the medical record sent to stroke experts on the adjudication committee. Events were confirmed if two independent assessors agreed. The documents were sent to a third adjudicator in the event of a disagreement. Three way disagreements were resolved by a full meeting of the adjudication committee.

1. Historical classification

An acute disturbance of focal neurological function resulting in symptoms lasting more than 24 hours.

2. Current classification

Stroke is defined as an acute episode of neurological dysfunction caused by focal or global brain, spinal cord, or retinal vascular injury.

a. Ischemic stroke

Ischemic stroke is defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.

Hemorrhage may be a consequence of ischemic stroke. In this situation, the stroke is an ischemic stroke with hemorrhagic transformation and not a hemorrhagic stroke.

b. Hemorrhagic stroke

Hemorrhagic stroke is defined as an acute episode of focal or global cerebral or spinal dysfunction caused by a nontraumatic intraparenchymal, intraventricular, or subarachnoid hemorrhage.

c. Undetermined stroke

Undetermined stroke is defined as a stroke with insufficient information to allow categorization as ischemic or hemorrhagic.

Transient Ischemic Attack

Transient ischemic attack (TIA) is defined as a transient episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction.

The distinction between a TIA and an ischemic stroke is the presence of infarction, not the transience of the symptoms. In addition to laboratory documentation of infarction, persistence of symptoms is an acceptable indicator of infarction. Thus, symptoms lasting ≤24 hours versus >24 hours may be used by the EAC to distinguish between transient ischemia and infarction. The committee will endeavor to review any relevant documentation of the cerebrovascular event. However, in the absence of documentation regarding duration of the symptoms, the committee may on occasion use any other reliable source of information such as the diagnosis of the treating physician to determine if the event was a TIA or stroke.

General Considerations

Evidence of vascular central nervous system injury without recognized neurological dysfunction may be observed. Examples include microhemorrhage, silent infarction, and silent hemorrhage. When encountered, the clinical relevance of these findings may be unclear. If observed, they should be precisely defined and categorized by the EAC.

Table I. Baseline characteristics of participants with and without cerebrovascular disease (stroke or TIA) at baseline

	With cerebrovascular disease			Without cerebrovascular disease			*P* value[§§](with vs. without)
	Canagliflozin (N=1113)	Placebo (N=845)	Total (N=1958)	Canagliflozin (N=4682)	Placebo (N=3502)	Total* (N=8184)	
Age — y, mean±SD	63.9±8.5	64.5±8.3	64.1±8.4	63.0±8.2	63.2±8.2	63.1±8.2	<0.001†
Female — no. (%)	433 (38.9)	348 (41.2)	781 (39.9)	1603 (34.2)	1249 (35.7)	2852 (34.8)	<0.001‡
Race — no. (%)							<0.001‡
White	934 (83.9)	711 (84.1)	1645 (84.0)	3574 (76.3)	2725 (77.8)	6299 (77.0)	
Asia	99 (8.9)	75 (8.9)	174 (8.9)	678 (14.5)	432 (12.3)	1110 (13.6)	
Black	34 (3.1)	31 (3.7)	65 (3.3)	142 (3.0)	129 (3.7)	271 (3.3)	
Other[§]	46 (4.1)	28 (3.3)	74 (3.8)	288 (6.2)	216 (6.2)	504 (6.2)	
Region — no. (%)							<0.001‡
North America	220 (19.8)	158 (18.7)	378 (19.3)	1205 (25.7)	847 (24.2)	2052 (25.1)	
Central and South America	68 (6.1)	55 (6.5)	123 (6.3)	469 (10.0)	429 (12.3)	898 (11.0)	
Europe	352 (31.6)	292 (34.6)	644 (32.9)	1691 (36.1)	1274 (36.4)	2965 (36.2)	
Rest of the world	473 (42.5)	340 (40.2)	813 (41.5)	1317 (28.1)	952 (27.2)	2269 (27.7)	
Current smoker — no. (%)	179 (16.1)	137 (16.2)	316 (16.1)	841 (18.0)	649 (18.5)	1490 (18.2)	0.03‡
Hypertension — no. (%)	1035 (93.0)	791 (93.6)	1826 (93.3)	4153 (88.7)	3146 (89.8)	7299 (89.2)	<0.001‡
Heart failure — no. (%)	280 (25.2)	216 (25.6)	496 (25.3)	523 (11.2)	442 (12.6)	965 (11.8)	<0.001‡
Atrial fibrillation — no. (%)	95 (8.5)	74 (8.8)	169 (8.6)	256 (5.5)	188 (5.4)	444 (5.4)	<0.001‡
Duration of diabetes	13.1±8.1	13.5±8.0	13.3±8.1	13.6±7.6	13.7±7.8	13.6±7.7	0.07†
Microvascular disease — no. (%)							
Retinopathy	340 (30.5)	243 (28.8)	583 (29.8)	863 (18.4)	683 (19.5)	1546 (18.9)	<0.001‡
Nephropathy	238 (21.4)	199 (23.6)	437 (22.3)	756 (16.1)	581 (16.6)	1337 (16.3)	<0.001‡
Neuropathy	481 (43.2)	344 (40.7)	825 (42.1)	1306 (27.9)	979 (28.0)	2285 (27.9)	<0.001‡
Atherosclerotic vascular disease — no. (%)[‖]							
Coronary	595 (53.5)	445 (52.7)	1040 (53.1)	2639 (56.4)	2042 (58.3)	4681 (57.2)	0.001‡
Peripheral	341 (30.6)	237 (28.0)	578 (29.5)	835 (17.8)	700 (20.0)	1535 (18.8)	<0.001‡
Any	1113 (100.0)	845 (100.0)	1958(100.0)	3014 (64.4)	2352 (67.2)	5366 (65.6)	<0.001‡
Cardiovascular disease[#]	1010 (90.7)	744 (88.0)	1754 (89.6)	2746 (58.7)	2156 (61.6)	4902 (59.9)	<0.001‡
Amputation — no. (%)	21 (1.9)	14 (1.7)	35 (1.8)	115 (2.5)	88 (2.5)	203 (2.5)	0.07‡

Body mass index	32.1±5.8	31.8±5.6	32.0±5.7	31.9±5.9	32.0±6.0	32.0±6.0	0.83†
Blood pressure — mmHg							
Systolic	136.7±15.4	137.2±15.6	136.9±15.5	136.4±15.9	136.8±15.8	136.6±15.8	0.43†
Diastolic	78.1±9.6	78.2±9.7	78.1±9.6	77.5±9.6	77.7±9.7	77.6±9.7	0.04†
HbA1c — %	8.3±1.0	8.2±0.9	8.2±0.9	8.2±0.9	8.3±0.9	8.3±0.9	0.69†
Cholesterol — mmol/L							
Total	4.5±1.3	4.5±1.3	4.5±1.3	4.3±1.1	4.3±1.1	4.3±1.1	<0.001†
HDL	1.2±0.3	1.2±0.3	1.2±0.3	1.2±0.3	1.2±0.3	1.2±0.3	<0.001†
LDL	2.4±1.0	2.4±1.0	2.4±1.0	2.3±0.9	2.3±0.9	2.3±0.9	<0.001†
Ratio of LDL to HDL	2.1±1.0	2.1±1.0	2.1±1.0	2.0±0.9	2.0±0.9	2.0±0.9	0.01†
Triglycerides — mmol/L	2.0±1.5	2.0±1.6	2.0±1.6	2.0±1.3	2.0±1.5	2.0±1.4	0.90†
eGFR — mL/min/1.73 m²	75.0±20.1	74.0±20.9	74.6±20.4	77.1±20.3	76.7±20.8	76.9±20.5	<0.001†
UACR — mg/g, median (IQR)	14.2 (7.0-44.4)	12.8 (7.0-52.6)	13.5 (7.0-46.4)	12.0 (6.6-40.4)	11.9 (6.5-42.2)	12.0 (6.6-40.9)	0.001**
Normoalbuminuria — no. (%)	748 (67.9)	571 (68.2)	1319 (68.0)	3264 (70.4)	2424 (70.1)	5688 (70.3)	0.03††
Microalbuminuria — no. (%)	271 (24.6)	177 (21.1)	448 (23.1)	1051 (22.7)	767 (22.2)	1818 (22.5)	
Macroalbuminuria — no. (%)	83 (7.5)	89 (10.6)	172 (8.9)	323 (7.0)	265 (7.7)	588 (7.3)	
Drug therapy — no. (%)							
Insulin	553 (49.7)	440 (52.1)	993 (50.7)	2337 (49.9)	1765 (50.4)	4102 (50.1)	0.64‡
Sulfonylurea	496 (44.6)	348 (41.2)	844 (43.1)	2032 (43.4)	1485 (42.4)	3517 (43.0)	0.92‡
Metformin	818 (73.5)	593 (70.2)	1411 (72.1)	3629 (77.5)	2785 (79.5)	6414 (78.4)	<0.001‡
GLP-1 receptor agonist	29 (2.6)	33 (3.9)	62 (3.2)	193 (4.1)	152 (4.3)	345 (4.2)	0.03‡
Statin	831 (74.7)	607 (71.8)	1438 (73.4)	3499 (74.7)	2663 (76.0)	6162 (75.3)	0.09‡
Antithrombotic‡‡	934 (83.9)	698 (82.6)	1632 (83.4)	3302 (70.5)	2537 (72.4)	5839 (71.3)	<0.001‡
RAAS inhibitor	910 (81.8)	678 (80.2)	1588 (81.1)	3735 (79.8)	2793 (79.8)	6528 (79.8)	0.18‡
β-blocker	599 (53.8)	435 (51.5)	1034 (52.8)	2440 (52.1)	1947 (55.6)	4387 (53.6)	0.53‡
Diuretic	541 (48.6)	436 (51.6)	977 (49.9)	1995 (42.6)	1518 (43.3)	3513 (42.9)	<0.001‡
DPP-4 inhibitor	120 (10.8)	104 (12.3)	224 (11.4)	577 (12.3)	460 (13.1)	1037 (12.7)	0.14‡
Calcium channel blocker	436 (39.2)	364 (43.1)	800 (40.9)	1494 (31.9)	1149 (32.8)	2643 (32.3)	<0.001‡

CANVAS, CANagliflozin cardioVascular Assessment Study; CANVAS-R, CANagliflozin cardioVascular Assessment Study–Renal; DPP-4, dipeptidyl peptidase-4; eGFR, estimated glomerular filtration rate; GLP-1, glucagon-like peptide-1; HbA1c, glycated hemoglobin; HDL, high-density lipoprotein; IQR, interquartile range; LDL, low-density lipoprotein; RAAS, renin–angiotensin–aldosterone system; SD, standard deviation, UACR, urinary albumin-to-creatinine ratio.

*One participant was randomized at two different sites, and only the first randomization is included in the intention-to-treat analysis set.

†*P* value corresponds to the test for no difference between with and without stroke history cohorts from analysis of variance (ANCOVA) model.

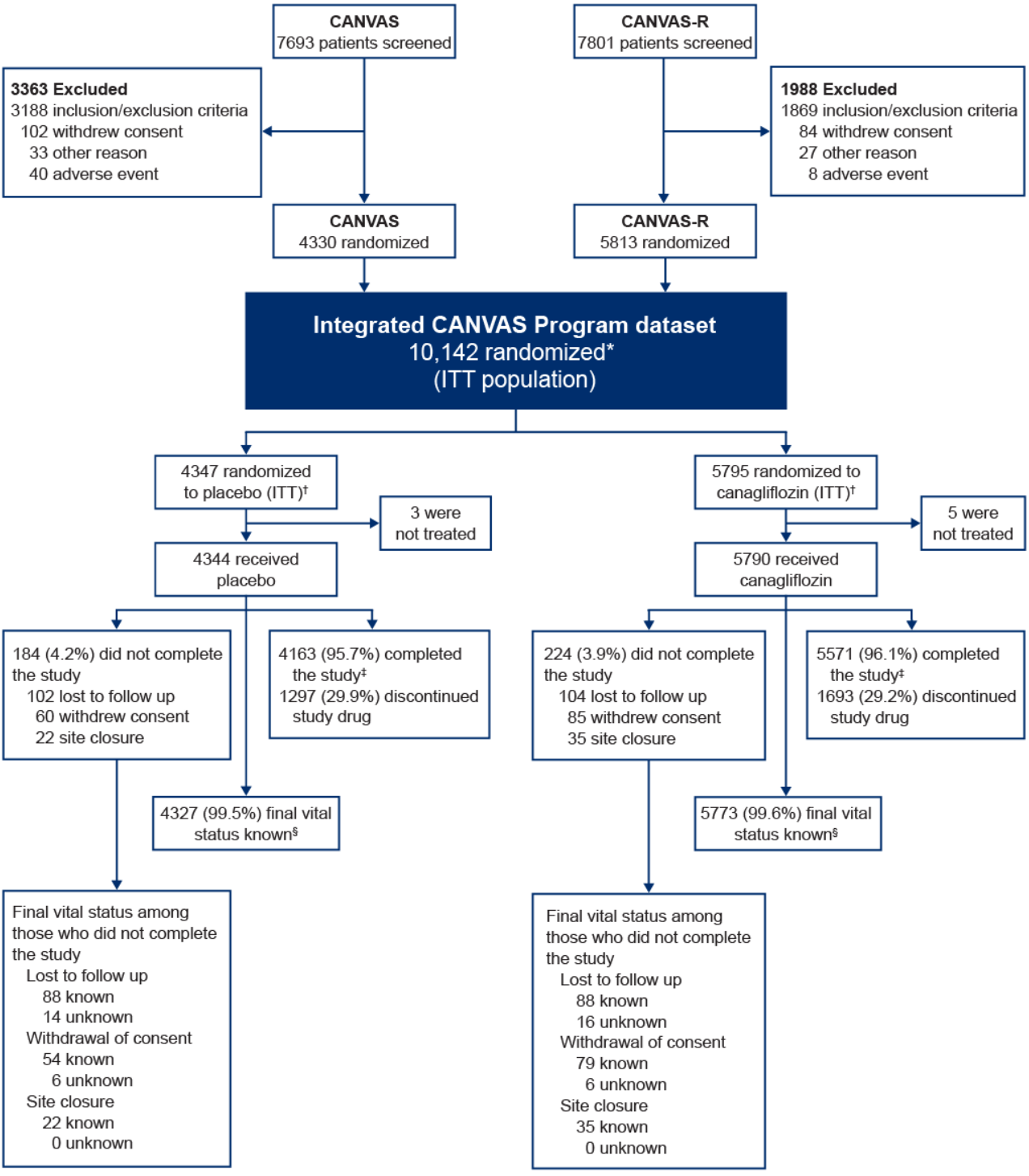
‡*P* value corresponds to generalized Cochran-Mantel-Haenszel test for no general association.

§Includes American Indian or Alaska Native, Native Hawaiian or other Pacific Islander, multiple, other, and unknown.

‖Some patients had more than one type of atherosclerotic vascular disease.

[#]A history of cardiovascular disease was defined as a history of symptomatic atherosclerotic vascular disease (coronary, cerebrovascular, or peripheral).
[**]*P* value corresponds to Wilcoxon rank sum test of equal medians.
[††]*P* value corresponds to Van Elteren test for no association.
[‡‡]Includes antiplatelets and anticoagulants.
[§§]*P* value for comparison between total participants with cerebrovascular disease at baseline and total participants without.

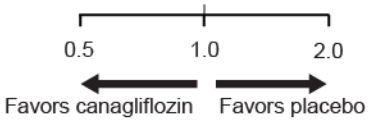
Figure I. CANVAS Program: trial flow chart.



ITT, intent-to-treat.
*One patient was randomized at 2 different sites and therefore the second randomized ID was excluded from the ITT analysis set.
†Percentages calculated based on the ITT analysis set.
‡A patient is considered as having completed the study, regardless of whether the patient is on or off study drug, if the patient is followed until a time point between the notification of the trial end date (November 1, 2016) and the trial end date (February 23, 2017), or until the time of death for those who died prior to the trial end date.
§Including results from the search of public records.

Figure II. Effects of canagliflozin on stroke risk according to the interval between stroke and last dose of randomized treatment*

Treatment status at time of stroke	Number of participants with an event	Participants with an event per 1000 patient-years		HR (95% CI)
		Canagliflozin	Placebo	
On randomized treatment	221	6.87	9.10	0.80 (0.61, 1.05)
On randomized treatment + within 7 days of treatment discontinuation	251	7.94	9.95	0.84 (0.65, 1.08)
On randomized treatment + within 30 days of treatment discontinuation	267	8.24	10.45	0.83 (0.65, 1.06)
On randomized treatment + within 90 days of treatment discontinuation	271	8.22	10.42	0.83 (0.65, 1.06)
On randomized treatment + to the end of the study	309	7.93	9.62	0.87 (0.69, 1.09)



HR, hazard ratio; CI, confidence interval.
*On-treatment is usually defined as within 30 days of treatment.