Predictors of Stroke Associated With Coronary Artery Bypass Grafting in Patients With Diabetes Mellitus and Multivessel Coronary Artery Disease

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This study assesses demographic and clinical variables associated with perioperative and late stroke in diabetes mellitus patients after multivessel coronary artery bypass grafting (CABG). Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) is the largest randomized trial of diabetic patients undergoing multivessel CABG. FREEDOM patients had improved survival free of death, myocardial infarction, or stroke and increased overall survival after CABG compared to percutaneous intervention. However, the stroke rate was greater following CABG than percutaneous intervention. We studied predictors of stroke in CABG-treated patients analyzing separately overall, perioperative (≤30 days after surgery), and late (>30 days after surgery) stroke. For long-term outcomes (overall stroke and late stroke), Cox proportional hazards regression was used, accounting for time to event, and logistic regression was used for perioperative stroke. Independent perioperative stroke predictors were previous stroke (odds ratio [OR] 6.96, 95% confidence interval [CI] 1.43 to 33.96; p = 0.02), warfarin use (OR 10.26, 95% CI 1.10 to 96.03; p = 0.02), and surgery outside the United States or Canada (OR 9.81, 95% CI 1.28 to 75.40; p = 0.03). Independent late stroke predictors: renal insufficiency (hazard ratio [HR] 3.57, 95% CI 1.01 to 12.64; p = 0.048), baseline low-density lipoprotein ≥105 mg/dl (HR 3.28, 95% CI 1.19 to 9.02; p = 0.02), and baseline diastolic blood pressure (each 1 mm Hg increase reduces stroke hazard by 5%; HR 0.95, 95% CI 0.91 to 0.99; p = 0.03). There was no overlap between predictors of perioperative versus late stroke. In conclusion, late post-CABG strokes were associated with well-described risk factors. Nearly half of the strokes were perioperative. Independent risk factors for perioperative stroke: previous stroke, previous warfarin use, and CABG performed outside the United States or Canada. **(Am J Cardiol 2015;115:1382–1388)**

The Future Revascularization Evaluation in Patients with Diabetes Mellitus: Optimal Management of Multivessel Disease (FREEDOM) Trial investigated revascularization with coronary artery bypass grafting (CABG) versus percutaneous intervention (PCI) in patients with diabetes mellitus and multivessel coronary artery disease (CAD).[1,2] In these patients, CABG was superior to PCI with respect to survival free of the composite end point of death, myocardial infarction (MI), or stroke and in overall survival.[1,2] However, stroke was more common in the patients who underwent CABG, mitigating somewhat, although not eliminating, the benefit of CABG over PCI. If alterable risk factors for stroke could be found, the advantage of CABG could be enhanced. This report examines CABG-related strokes in patients with diabetes mellitus and multivessel CAD in the FREEDOM trial. This analysis is unique in 3 ways: (1) an exclusively diabetic population is studied; (2) the median follow-up is almost 4 years; and (3) patients were enrolled at over 100 high-volume centers.

Methods

This analysis is based on the data collected during the FREEDOM trial (FREEDOM *ClinicalTrials.Gov* number, NCT00086450) conducted from 2005 to 2010 at 140 international centers (funded by the National Heart, Lung, and Blood Institute). The design and results of the FREEDOM trial have been reported in detail.[1,2] The study enrolled 1,900 patients with diabetes mellitus and multivessel CAD confirmed by angiography who had diameter stenosis of >70% in ≥2 major epicardial arteries involving at least 2 separate coronary artery territories but without significant left main coronary artery stenosis. Minimum follow-up for

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See page 1388 for disclosure information.

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Table 1
Descriptive statistics, all subjects and with and without stroke

Variable	All subjects (n=898)	Stroke		
		No (n=862)	Yes (n=36)	P-value*
Death	82 (9%)	68 (8%)	14 (39%)	<0.001
All strokes	36 (4%)	NA	36 (100%)	
Death at any time after stroke (N=36)	14 (39%)	NA	14 (39%)	
Perioperative stroke (≤ 30 days post-procedure)	16 (2%)	NA	16 (44%)	
Death at any time after perioperative stroke (N=36)	9 (56%)	NA	9 (56%)	
Clinical Site				0.159
US or Canada	334 (37%)	325 (38%)	9 (25%)	
Other	564 (63%)	537 (62%)	27 (75%)	
Age at procedure, years				
Mean±SD	62.9±9.1	62.8±9.0	64.2±11.3	0.389
Median (IQR)	63.0 (56.2-70.0)	63.0 (56.2-69.7)	62.6 (55.7-74.9)	0.595
Women	271 (30%)	258 (30%)	13 (36%)	0.460
Race				0.660
White	692 (77%)	665 (77%)	27 (75%)	
Black	54 (6%)	52 (6%)	2 (6%)	
Asian	75 (8%)	73 (8%)	2 (6%)	
Other	77 (9%)	72 (8%)	5 (14%)	
Systolic blood pressure (mmHg) (N=897)		(N=861)	(N=36)	
Mean±SD	133±19	134±19	128±19	0.099
Median (IQR)	130 (120-142)	130 (120-142)	127 (115-140)	0.110
Systolic blood pressure categories (mmHg) (N=897)		(N=861)	(N=36)	0.049
<120	160 (18%)	148 (17%)	12 (33%)	
120-159	641 (71%)	621 (72%)	20 (56%)	
≥160	96 (11%)	92 (11%)	4 (11%)	
Diastolic blood pressure (mmHg) (N=897)		(N=861)	(N=36)	
Mean±SD	76.0±11.3	76±11	73±12	0.123
Median (IQR)	78.0 (70.0-80.0)	78 (70-80)	75 (68-80)	0.290
Diastolic blood pressure categories (mmHg) (N=897)		(N=861)	(N=36)	1.000
<80	473 (53%)	454 (53%)	19 (53%)	
80-99	394 (44%)	378 (44%)	16 (44%)	
≥100	30 (3%)	29 (3%)	1 (3%)	
Low Density Lipoprotein (mg/dL) (N=826)		(N=794)	(N=32)	
Mean±SD	92.9±36.3	92.5±36.1	103.7±41.5	0.086
Median (IQR)	88.4 (66.0-114.0)	88.0 (66.0-113.0)	102.0 (71.5-131.6)	0.115
Low Density Lipoprotein ≥105mg/dL (N=826)	274 (33%)	258 (32%)	16 (50%)	0.054
High Density Lipoprotein (mg/dL) (N=842)		(N=809)	(N=33)	
Mean±SD	39.5±11.6	39.6±11.6	38.6±11.3	0.871
Median (IQR)	38.0 (31.0-45.0)	38.0 (31.0-45.0)	38.0 (30.9-45.0)	0.918
Body Mass Index (kg/m^2) (N=897)		(N=861)	(N=36)	
Mean±SD	29.8±5.3	29.9±5.4	28.0±4.2	0.035
Median (IQR)	29.1 (26.3-32.3)	29.2 (26.3-32.3)	27.6 (25.9-30.8)	0.066
Left Ventricle EF (%) (N=630)		(N=606)	(N=24)	
Mean±SD	66.6±10.5	66.6±10.5	65.5±10.5	0.5907
1 Median (IQR)	67.5 (60.6-74.0)	67.5 (60.7-74.0)	65.7 (60.3-72.2)	0.441
Syntax score (N=891)		(N=855)	(N=36)	
Mean±SD	26.0±8.8	26.0±8.8	26.1±7.9	0.420
Median (IQR)	26.0 (19.0-31.5)	26.0 (19.0-31.5)	25.5 (20.0-31.8)	0.820
Prior stroke	26 (3%)	21 (2%)	5 (14%)	0.003
Current smoker	150 (17%)	142 (16%)	8 (22%)	0.362
Previous Myocardial Infarction	230 (26%)	222 (26%)	8 (22%)	0.702
Prior renal insufficiency	52 (6%)	46 (5%)	6 (17%)	0.014
Prior peripheral vascular disease	93 (10%)	89 (10%)	4 (11%)	0.782
Prior hypertension (history)	762 (85%)	731 (85%)	31 (86%)	1.000
Prior arrhythmia (history)	35 (4%)	32 (4%)	3 (8%)	0.161
Warfarin use	7 (1%)	5 (1%)	2 (6%)	0.029
On cross-clamp during CABG	685 (76%)	654 (76%)	31 (86%)	0.228

(*continued*)