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Online Resource 1

Saphenous Vein Graft Occlusion and Bleeding after Three or Twelve Months of Dual Antiplatelet Therapy in TOP-CABG

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Supplementary methods, Tables S1-S8 and Supplementary Figure S1

Saphenous Vein Graft Occlusion and Bleeding after Three or Twelve Months of Dual Antiplatelet Therapy in TOP-CABG

Supplementary methods

S1. Data source and patient linkage

The public, de-identified TOP-CABG files were obtained from Dryad. The dataset contained the 2,290 participants in the parent trial's modified intention-to-treat population. Participant identifiers linked treatment assignment, SVG segment records, one-year imaging, and bleeding. Segment records were combined for each participant before outcomes were analysed.

S2. Definition of SVG occlusion

A participant had SVG occlusion if at least one evaluable SVG segment was occluded on one-year imaging. Those with evaluable imaging and no occluded segment were classified as having no observed occlusion. Participants without evaluable imaging were excluded from the complete-case analysis.

S3. Outcome categories

SVG occlusion was combined with Bleeding Academic Research Consortium type 2, 3, or 5 bleeding during follow-up to define four categories: neither outcome, SVG occlusion without bleeding, bleeding without SVG occlusion, and both. Both outcomes in one participant did not imply that they occurred at the same time.

S4. Number and fraction of occluded SVG segments

Participants were grouped by 0, 1, or at least 2 occluded SVG segments. These counts refer to segments, not necessarily separate conduits. The fraction of evaluable segments that were occluded was summarised as median and interquartile range. A two-sided Wilcoxon rank-sum test used a normal approximation without continuity correction because the fractions were discrete and mostly zero.

S5. Multinomial analysis

An unadjusted multinomial logistic regression compared 12-month with 3-month therapy, using neither outcome as the reference category. This model compares categories without ranking their clinical severity. The global likelihood-ratio test had three degrees of freedom; relative risk ratios for individual categories described the overall comparison.

S6. Weighting for missing imaging

A logistic model estimated imaging completion from randomised treatment and available baseline variables. Participants with evaluable imaging received unstabilised inverse-probability weights [12]. Weighted proportions and 12-month minus 3-month differences used robust weighted-mean variance conditional on the estimated weights. Weight distributions and effective sample sizes were checked.

S7. Common extreme assumptions for missing imaging

Both analyses included all 2,290 participants in the dataset. Every participant without evaluable imaging was assigned either no SVG occlusion or SVG occlusion, while observed bleeding was retained. Each assumption was applied equally to both treatment groups.

S8. Common-probability analysis

The same assumed probability q of SVG occlusion was applied to missing imaging in both groups, from q=0 to 1. Expected outcome proportions were then compared. This tests whether the direction of differences changes under shared assumptions; it does not address different missing-outcome probabilities between groups.

S9. Adjustment for trial site

Trial site was added to the multinomial model. The global treatment test and relative risk ratios were compared with the unadjusted results to assess sensitivity to site composition.

S10. Proportional-odds diagnostic

A proportional-odds model was compared with the multinomial model as a statistical diagnostic [13]. The likelihood-ratio test did not support that restriction. This test does not establish a clinical ranking of the four categories. No ordinal treatment effect was interpreted; the multinomial model was retained.

Table S1. Baseline characteristics

Characteristic	12-month	3-month	SMD
Participants in the modified intention-to-treat population	1,138	1,152	
Age, years	61.6 (8.5)	61.3 (8.3)	0.040
Male sex	902 (79.3%)	916 (79.5%)	-0.006
Diabetes	479 (42.1%)	509 (44.2%)	-0.042
Left ventricular ejection fraction, %	59.8 (8.1)	59.8 (8.0)	-0.003
Estimated glomerular filtration rate, mL/min/1.73 m²	94.6 (14.9)	94.3 (15.4)	0.017
SYNTAX score, available n	1,055	1,067	
SYNTAX score	29.8 (11.6)	31.2 (11.7)	-0.113
Number of SVG segments	2.46 (0.75)	2.51 (0.76)	-0.067

Values are mean (standard deviation) or n (%). SMD, standardised mean difference; SVG, saphenous vein graft.

Table S2. Outcome categories

Category	Overall n (%)	12-month n (%)	3-month n (%)	Difference (95% CI), pp
Neither outcome	1,487 (71.8)	721 (69.8)	766 (73.9)	-4.07 (-7.94 to -0.20)
SVG occlusion without bleeding	359 (17.3)	174 (16.8)	185 (17.8)	-1.00 (-4.26 to 2.27)
Bleeding without SVG occlusion	176 (8.5)	105 (10.2)	71 (6.8)	3.32 (0.92 to 5.72)
Both outcomes	48 (2.3)	33 (3.2)	15 (1.4)	1.75 (0.45 to 3.04)

n=2,070. Differences are 12-month minus 3-month therapy. Bleeding denotes BARC type 2, 3, or 5. BARC, Bleeding Academic Research Consortium; CI, confidence interval; pp, percentage points; SVG, saphenous vein graft.

Table S3. Multinomial model estimates

Contrast	RRR	95% CI	P
SVG occlusion without bleeding vs neither	1.00	0.79-1.26	0.991
Bleeding without SVG occlusion vs neither	1.57	1.14-2.16	0.005
Both outcomes vs neither	2.34	1.26-4.34	0.007
Global treatment term	chi-square=15.22	3 df	0.0016

The model compares 12-month with 3-month therapy. The relative risk ratio compares the ratio of each category to neither outcome between treatment groups. It is not the risk ratio for the outcome alone. CI, confidence interval; df, degrees of freedom; RRR, relative risk ratio.

Table S4. Number and fraction of occluded SVG segments

Measure	Overall	12-month	3-month	RRR (95% CI); P
0 occluded SVG segments	1,663 (80.3%)	826 (80.0%)	837 (80.7%)	Reference
1 occluded SVG segment	287 (13.9%)	145 (14.0%)	142 (13.7%)	1.03 (0.81-1.33); 0.789
≥2 occluded SVG segments	120 (5.8%)	62 (6.0%)	58 (5.6%)	1.08 (0.75-1.57); 0.673
Occlusion fraction, median (IQR)	0 (0-0)	0 (0-0)	0 (0-0)	Wilcoxon rank-sum P=0.613

n=2,070. Counts refer to SVG segments and do not necessarily represent separate conduits. The occlusion fraction is the number of occluded segments divided by the number of evaluable segments in each participant. The Wilcoxon rank-sum P value is two-sided, based on a normal approximation without continuity correction. CI, confidence interval; IQR, interquartile range; RRR, relative risk ratio; SVG, saphenous vein graft.

Table S5. Inverse-probability-weighting diagnostics

Diagnostic	Overall	12-month	3-month
Imaging completion	90.4%	90.8%	90.0%
Weight, mean (SD)	1.108 (0.157)	1.103 (0.134)	1.113 (0.177)
Weight, 1st-99th percentile	1.022-1.809	1.022-1.669	1.022-1.898
Weight, minimum-maximum	1.015-3.127	1.015-3.011	1.016-3.127
Effective sample size	2,029.5	1,018.1	1,011.6

Weights are unstabilised inverse probabilities of imaging completion. SD, standard deviation.

Table S6. Weighted outcome estimates

Category	12-month %	3-month %	Difference (95% CI), pp	P
Neither outcome	70.3	74.3	-4.04 (-7.90 to -0.18)	0.040
SVG occlusion without bleeding	16.7	17.6	-0.93 (-4.18 to 2.33)	0.577
Bleeding without SVG occlusion	10.0	6.7	3.33 (0.97 to 5.69)	0.006
Both outcomes	3.1	1.4	1.63 (0.37 to 2.90)	0.012

Differences are 12-month minus 3-month therapy. Variance is conditional on the estimated weights. CI, confidence interval; pp, percentage points; SVG, saphenous vein graft.

Table S7. Sensitivity to shared assumptions about missing imaging

Analysis	Neither outcome	SVG occlusion without bleeding	Bleeding without SVG occlusion	Both outcomes
Complete case	-4.07	-1.00	3.32	1.75
All missing assigned no SVG occlusion	-4.08	-0.77	3.25	1.60
All missing assigned SVG occlusion	-3.14	-1.71	3.06	1.78
Common probability q=0.5	-3.61	-1.24	3.16	1.69
Common probability q=0-1	No reversal	No reversal	No reversal	No reversal

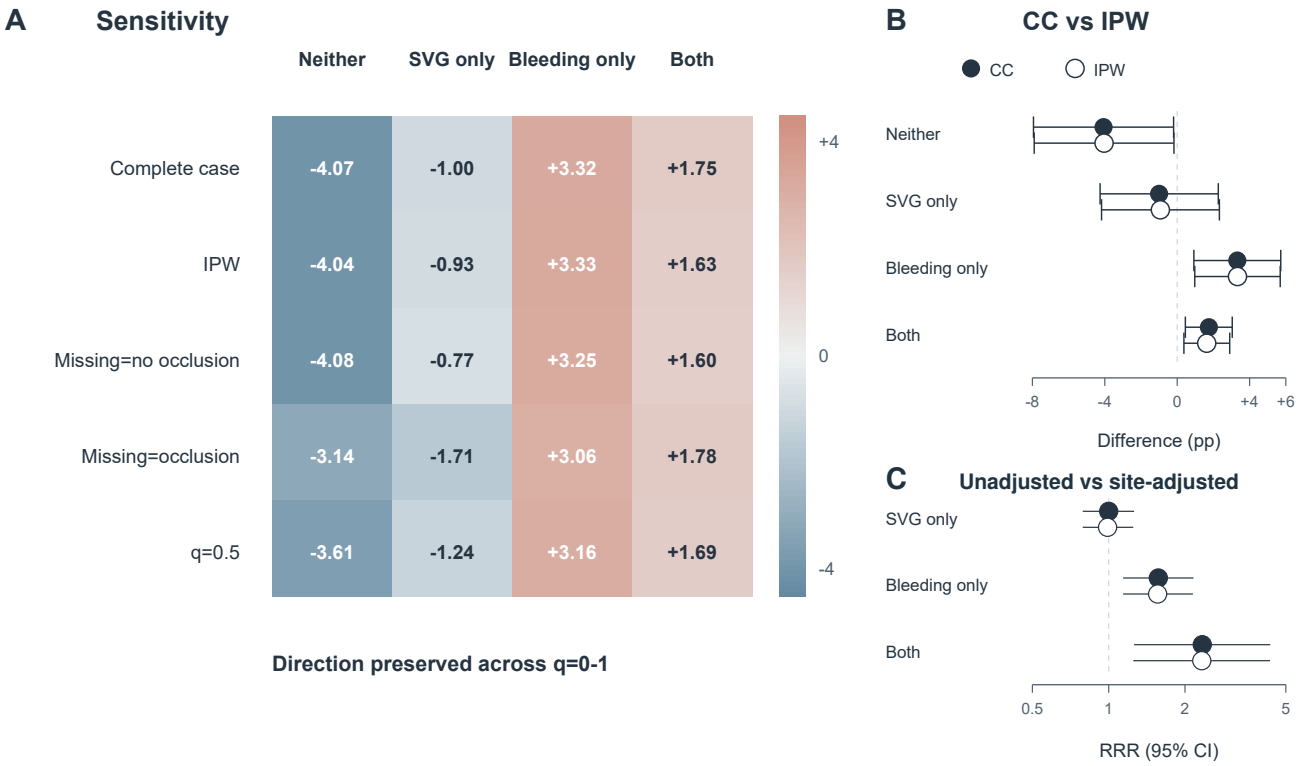
Values are percentage-point differences, calculated as 12-month minus 3-month therapy. J0, neither outcome; J1, SVG occlusion without bleeding; J2, bleeding without SVG occlusion; J3, both outcomes. The same occlusion probability q was assigned to missing imaging in both groups. Direction stability under this assumption does not exclude bias from different missing-outcome probabilities between groups.

Table S8. Site-adjusted estimates and proportional-odds diagnostic

Result	Estimate	95% CI	P
SVG occlusion without bleeding vs neither, RRR	0.99	0.79-1.25	0.941
Bleeding without SVG occlusion vs neither, RRR	1.56	1.14-2.15	0.006
Both outcomes vs neither, RRR	2.33	1.25-4.33	0.008
Global treatment term	chi-square=14.97	3 df	0.0020
Proportional-odds diagnostic	chi-square=8.66	2 df	0.013

The site-adjusted multinomial model includes treatment and trial site. The proportional-odds comparison is a statistical diagnostic; it does not determine the clinical ranking of the categories. The multinomial model was retained. CI, confidence interval; df, degrees of freedom; RRR, relative risk ratio.

Supplementary Figure S1. Analyses addressing missing imaging and trial site



(A) Absolute differences between treatment groups under the main analysis, inverse-probability weighting, two shared extreme assignments for missing imaging, and a common occlusion probability of q=0.5. Columns show neither outcome, SVG occlusion alone, bleeding alone, and both. Differences are 12-month minus 3-month therapy. The direction of each difference was unchanged across q=0 to 1. Here q is the assumed probability of occlusion among patients with missing imaging, applied equally to both groups. (B) Main and weighted estimates with 95% confidence intervals. (C) Unadjusted and site-adjusted relative risk ratios with 95% confidence intervals; the respective global P values were 0.00164 and 0.00201. CC, complete case; CI, confidence interval; IPW, inverse-probability weighting; RRR, relative risk ratio; SVG, saphenous vein graft.

Alt text: A heatmap shows the absolute differences under five analyses. Two additional plots compare the main estimates with weighted estimates and the unadjusted model with a model adjusted for trial site.