Carotid **O**cclusion **A**nticoagulation **T**rial (COAT)*

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*Formerly known as: Treatment with AntiCoagulation for Occlusion of the Carotid Artery Trial

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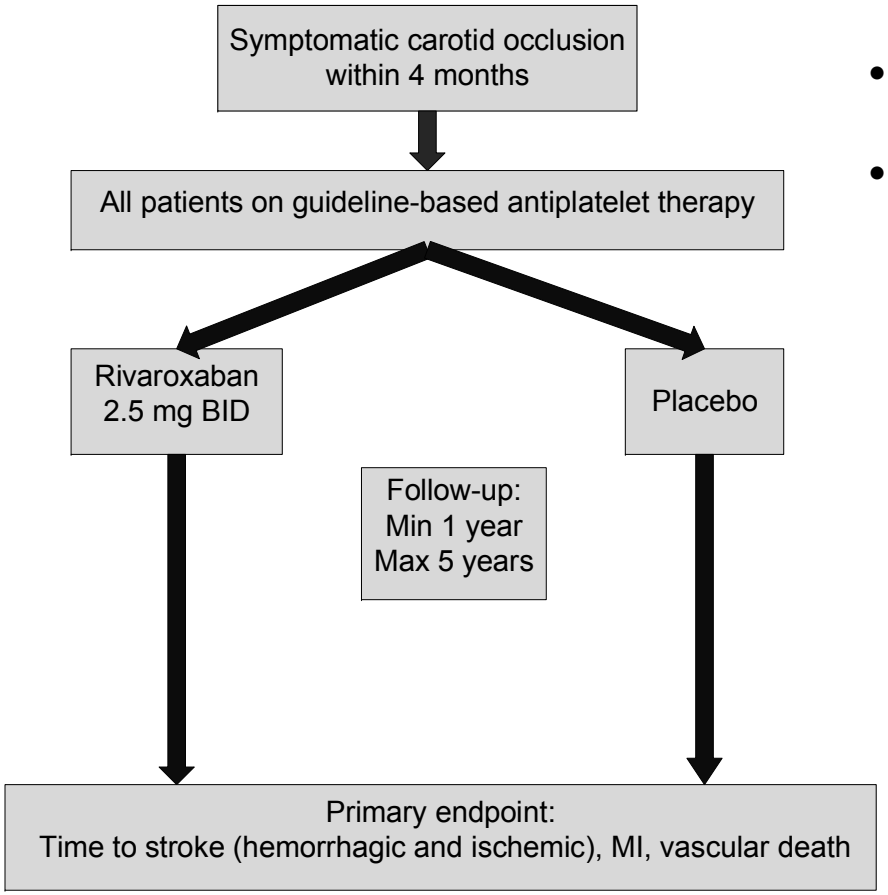
Proposed trial design: COMPASS-like trial

- Proposed sample size = 1140 (570 each arm)
- Double-blind, RCT



- Dx based on non-invasive imaging
- Near-occlusion allowed

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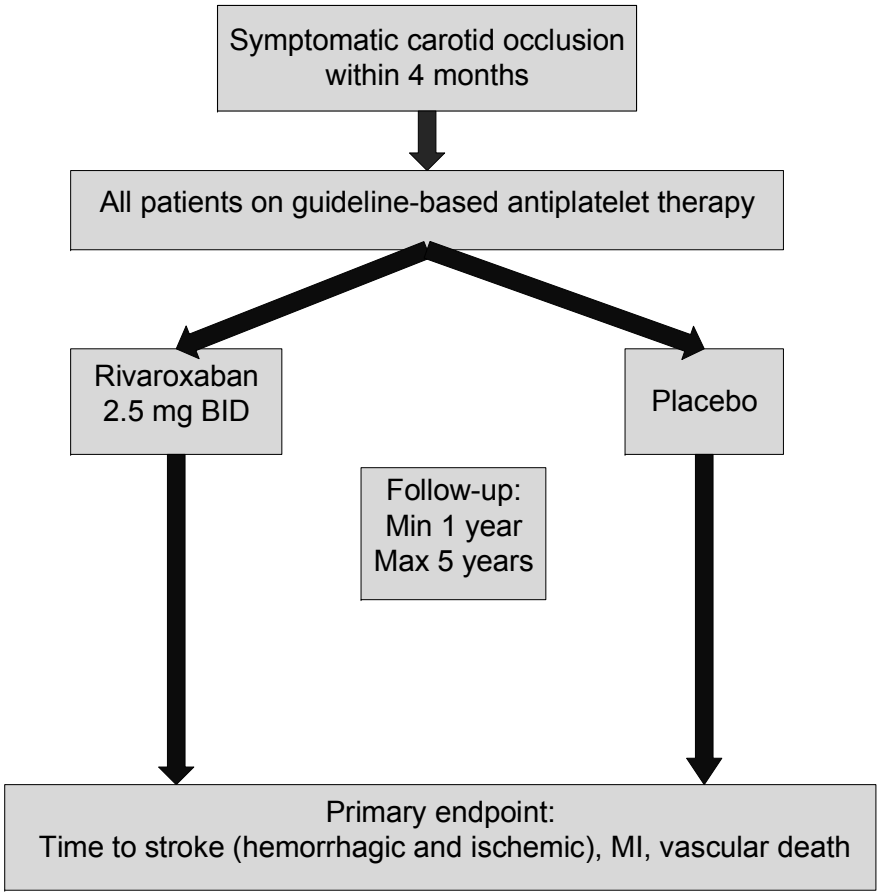

- Large simple trial
- Vast majority of sites should be able to enroll
- Simple to identify patients
- Simple to enroll
- Attempt to maximize patient inclusion

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ORIGINAL ARTICLE

Rivaroxaban with or without Aspirin in Stable Cardiovascular Disease

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ABSTRACT

BACKGROUND

We evaluated whether rivaroxaban alone or in combination with aspirin would be more effective than aspirin alone for secondary cardiovascular prevention.

METHODS

In this double-blind trial, we randomly assigned 27,395 participants with stable atherosclerotic vascular disease to receive rivaroxaban (2.5 mg twice daily) plus aspirin (100 mg once daily), rivaroxaban (5 mg twice daily), or aspirin (100 mg once daily). The primary outcome was a composite of cardiovascular death, stroke, or myocardial infarction. The study was stopped for superiority of the rivaroxaban-plus-aspirin group after a mean follow-up of 23 months.

RESULTS

The primary outcome occurred in fewer patients in the rivaroxaban-plus-aspirin group than in the aspirin-alone group (379 patients [4.1%] vs. 496 patients [5.4%]; hazard ratio, 0.76; 95% confidence interval [CI], 0.66 to 0.86; $P<0.001$; $z=-4.126$), but major bleeding events occurred in more patients in the rivaroxaban-plus-aspirin group (288 patients [3.1%] vs. 170 patients [1.9%]; hazard ratio, 1.70; 95% CI, 1.40 to 2.05; $P<0.001$). There was no significant difference in intracranial or fatal bleeding between these two groups. There were 313 deaths (3.4%) in the rivaroxaban-plus-aspirin group as compared with 378 (4.1%) in the aspirin-alone group (hazard ratio, 0.82; 95% CI, 0.71 to 0.96; $P=0.01$; threshold P value for significance, 0.0025). The primary outcome did not occur in significantly fewer patients in the rivaroxaban-alone group than in the aspirin-alone group, but major bleeding events occurred in more patients in the rivaroxaban-alone group.

CONCLUSIONS

Among patients with stable atherosclerotic vascular disease, those assigned to rivaroxaban (2.5 mg twice daily) plus aspirin had better cardiovascular outcomes and more major bleeding events than those assigned to aspirin alone. Rivaroxaban (5 mg twice daily) alone did not result in better cardiovascular outcomes than aspirin alone and resulted in more major bleeding events. (Funded by Bayer; COMPASS ClinicalTrials.gov number, NCT01776424.)

The authors' full names, academic degrees, and affiliations are listed in the Appendix. Address reprint requests to Dr. Eikelboom at the Population Health Research Institute, McMaster University and Hamilton Health Sciences, David Braley Research Bldg., Hamilton General Hospital, 237 Barton St. E., Hamilton, ON L8L 2X2, Canada, or at eikelbj@mcmaster.ca.

*A complete list of the Cardiovascular Outcomes for People Using Anticoagulation Strategies (COMPASS) Investigators is provided in the Supplementary Appendix, available at NEJM.org.

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COMPASS – ASA + low-dose rivaroxaban vs. ASA alone

Stroke/MI/vasc death
↓ from 5.4% to 4.1%
HR 0.76 (95%CI 0.66-0.86)

Stroke
↓ from 1.6% to 0.9%
HR 0.58 (95%CI 0.44-0.76)

Death
↓ from 4.1% to 3.4%
HR 0.82 (95%CI 0.71-0.96)

Mean follow-up 23 months

- Similar or enhanced effect in subgroup with prior stroke (n=1032) and subgroup with carotid stenosis (n=1919)
- Cardioembolic and lacunar stroke excluded from enrollment
- Recent stroke < 1 month excluded from enrollment

Major bleeding
↑ from 3.1% to 1.9%
HR 1.7 (95%CI 1.4-2.1)
No difference in fatal bleeding (0.2 v 0.1%) or ICH (0.2% v 0.2%)

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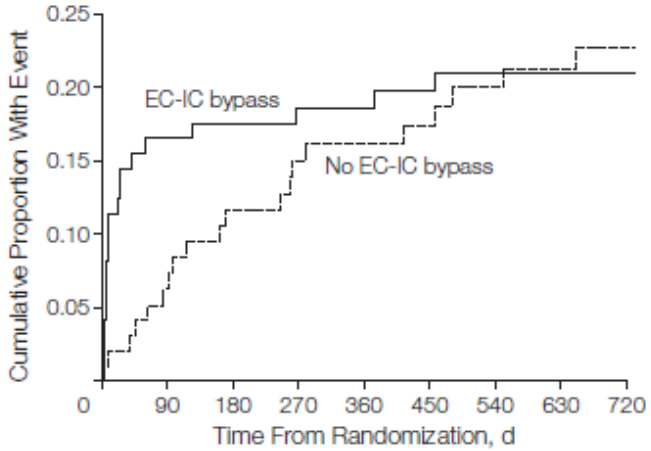
Symptomatic carotid occlusion is high-risk

- ~10%/year stroke risk, ~5%/year MI risk in population-based studies
- Risk higher with hemodynamic failure (~1/2 pts), hemispheric events, earlier after sx onset
- COSS - endpoint: all stroke 30 days, ipsilateral stroke at 2 years
COSS:



No. at risk									
EC-IC bypass (surgical group)	97	80	79	77	69	67	65	65	53
No EC-IC bypass (nonsurgical group)	98	87	81	74	69	65	62	57	51

All stroke in medical arm COSS:
27% @ 2 yrs

COSS pilot study:
~10% @ 2 yrs without hemodynamic failure

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Emboli + hypoperfusion interact but varies by infarct topography

Our data:
MES+ 37% carotid occlusion vs. 39% carotid stenosis

Table 4. Relevant Previous Literature

Lead Study Author	Carotid Occlusion With MES Detected, (%)	Carotid Stenosis With MES Detected (%)	Time From Symptom Onset to Transcranial Doppler	Study Limitations
Eicke et al[32]	5/13 (38)	7/42 (17)	Not reported	Symptomatic and asymptomatic cases in each group
Babikian et al[33]	4/23 (17)	22/76 (29)	<6 mo	Symptomatic and asymptomatic cases in each group
Droste et al[34]	4/10 (40)	17/41 (41)	0–3474 d	Included patients with competing high-risk cardioembolic sources
Orlandi et al[35]	0/8 (0)	14/33 (42)	<120 d	…

MES indicates microembolic signals.

Secondary aim: To assess whether treatment effect varies based on infarct topography (perfusional versus embolic infarct pattern)

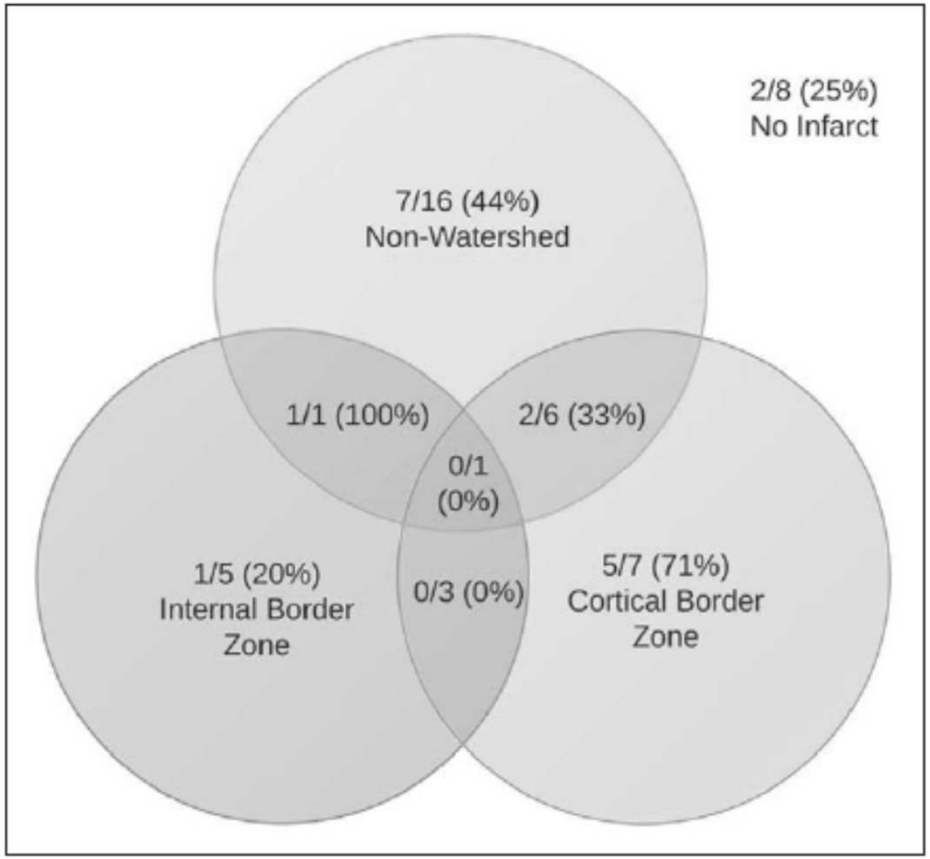

Figure 2. Presence of microembolic signals (MES+) by infarct topography.

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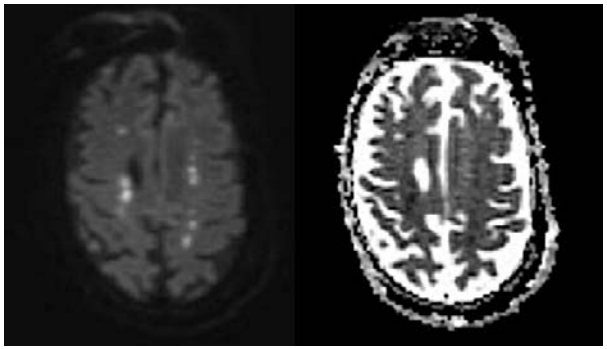
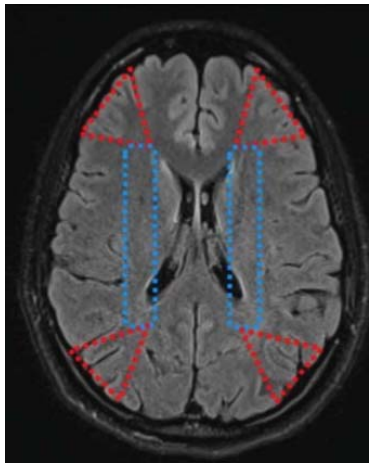
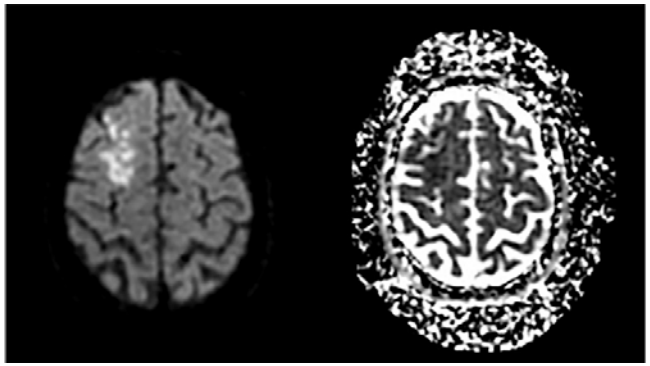
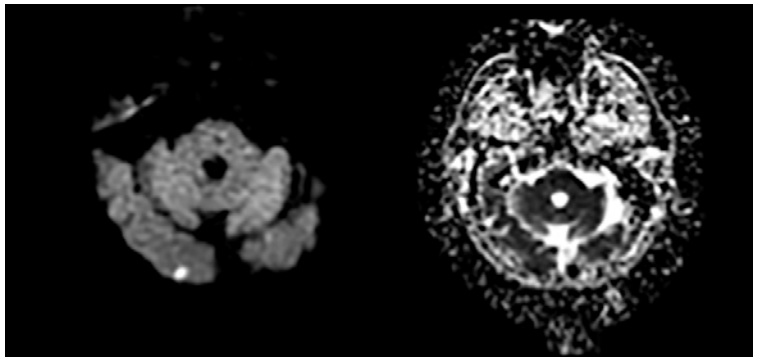
Treatment effect vs. infarct topography









Secondary aim: To assess whether treatment effect varies based on infarct topography (perfusional versus embolic infarct pattern)

Both local and central rating of infarct topography will be performed.

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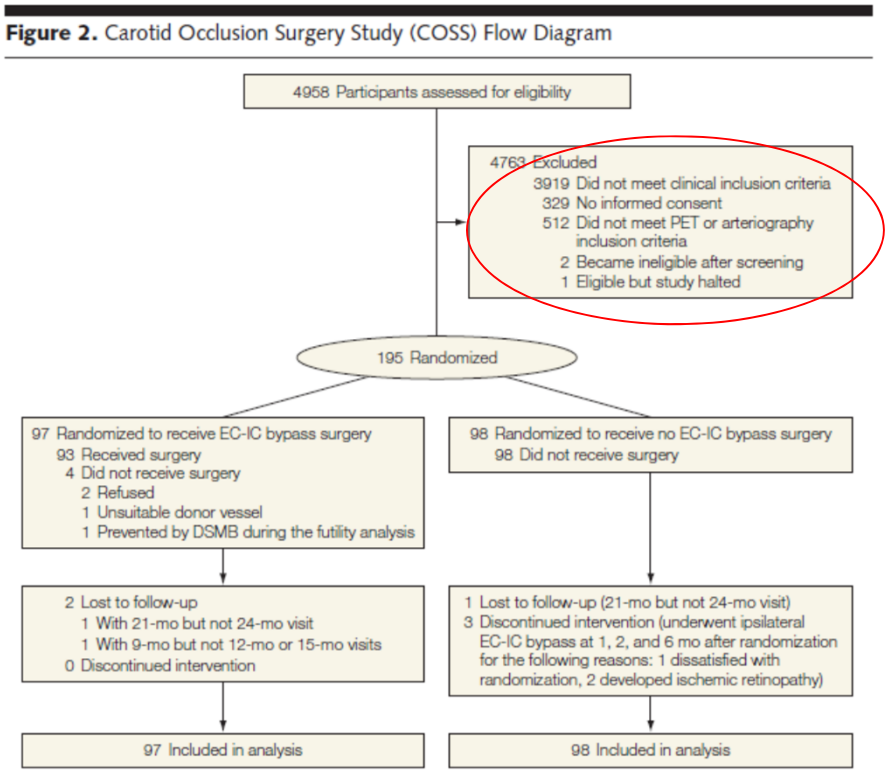
Sample size (Statistician: Sharon Yeatts)

- Proposed sample size 1140 patients (570 per arm)
- Assumptions:
  - 80% power, alpha 0.05
  - 15% attrition
  - 36 month recruitment duration, min 1 year F/U
  - Interim analysis for futility/efficacy
  - HR 0.69 for rivaroxaban vs placebo (estimated absolute composite event rate 9% vs. 13%/year)

Feasibility – COSS as an example

- June 2002-June 2010
- 195 pts
- 49 clinical centers, 18 PET centers
- Large number (512) of patients excluded for not meeting PET or catheter angiography criteria
- Subjects had to agree to surgery



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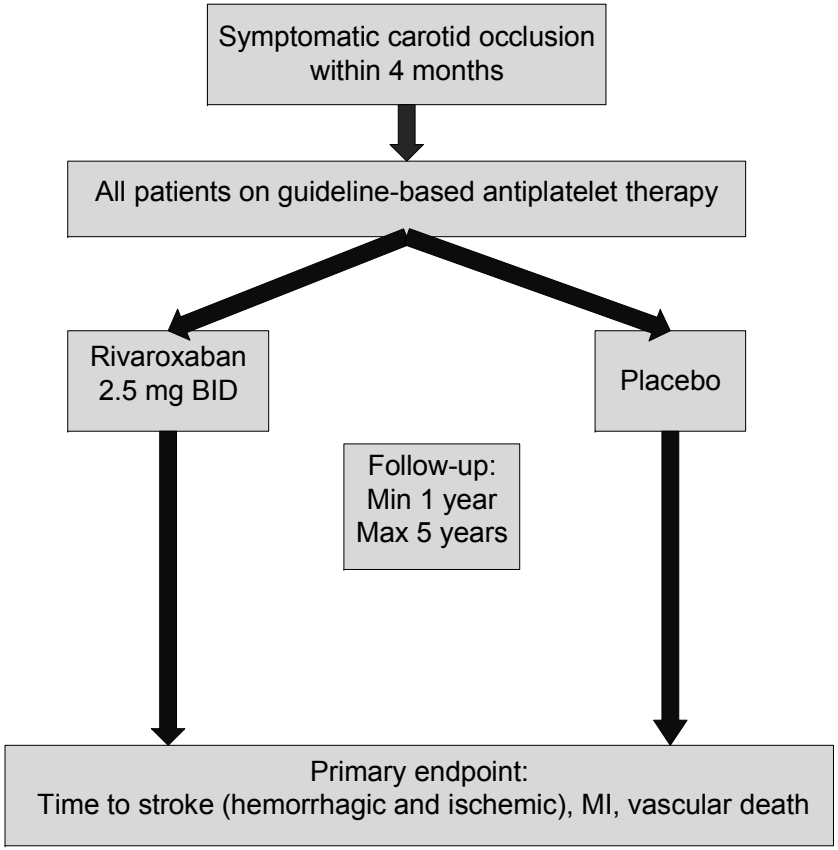
Feasibility – population based eligibility assessment from GCNK

- 0.84% of TIA pts
- 1.81% of stroke pts
- Rough comparison – about 2-3x greater number of patients than intracranial stenosis

Thanks for your attention

Carotid Occlusion Anticoagulation Trial (COAT)

- Proposed sample size = 1140 (570 each arm)
- Double-blind, RCT



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