Rivaroxaban, Aspirin, or Both to Prevent Early Coronary Bypass Graft Occlusion: The COMPASS-CABG Study

STUDY

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BACKGROUND

- Coronary artery bypass grafting (CABG) reduces mortality in patients with extensive coronary artery disease (CAD)
- One limitation of CABG surgery is early graft failure, mainly caused by thrombotic occlusion, which is associated with a risk of myocardial infarction (MI) and death
- Although routine use of aspirin (ASA) prevents early failure, as many as 30% of patients have at least one occluded graft one year after surgery
- In the COMPASS trial, rivaroxaban 2.5 mg twice daily plus ASA 100 mg daily compared to ASA 100 mg daily reduced the primary major adverse cardiovascular events (MACE) outcome of cardiovascular (CV) death, stroke, or MI; rivaroxaban 5 mg twice daily alone did not significantly reduce MACE

OBJECTIVE

- To determine whether rivaroxaban with or without aspirin would be more effective than aspirin for preventing bypass graft failure at one year in patients with CAD who had recent CABG surgery

METHODS

- **Design:** 3x2 partial factorial, multi-center, double-blind, randomized controlled trial
- **Duration:** 23 months
- **Inclusion Criteria:** stable CAD or PAD, CABG surgery within 4-14 days, at least 2 grafts implanted, estimated glomerular filtration rate of at least 30 ml/min
- **Exclusion Criteria:** a concomitant procedure requiring anticoagulation (e.g. mechanical valve placement), patients with atrial fibrillation requiring anticoagulation
- **Number Enrolled:** 1,448 patients
- **Regimen:** randomized in a 1:1:1 ratio to receive either rivaroxaban 2.5 mg twice daily plus aspirin 100 mg daily, rivaroxaban 5 mg twice daily, or aspirin 100 mg daily
- **Primary Outcome:** proportion of coronary bypass grafts that failed with complete occlusion of the graft (analyzed using mixed logistic regression)
- **Secondary Outcome:** proportion of patients with at least one failed graft (analyzed using logistic regression models)
- **Clinical Efficacy Outcomes:** primary composite of CV death, MI, or stroke (analyzed using Cox regression)
- **Power:** not reported
- **Data Handling Method:** intention-to-treat principle

RESULTS

Study Completion

- 1,448 patients randomized

Rivaroxaban 2.5 mg BID + ASA	Rivaroxaban 5 mg BID Only	ASA Only
502 patients →	483 patients →	463 patients →
396 had CTA at Year 1 (106 dropouts) →	381 had CTA at Year 1 (102 dropouts) →	362 had CTA at Year 1 (101 dropouts) →
1,242 grafts analyzed	1,166 grafts analyzed	1,154 grafts analyzed

Primary Outcome

- Of the 3,562 grafts evaluated, 296 (8.3%) were occluded

Rivaroxaban 2.5 mg BID + ASA	Rivaroxaban 5 mg BID Only	ASA Only
- Rate of graft occlusion: 9.1%	- Rate of graft occlusion: 7.8%	- Rate of graft occlusion: 8.0%

- Rivaroxaban + ASA versus ASA Only: OR = 1.13 (95% CI: 0.82 to 1.57; p = 0.45
- Rivaroxaban Only versus ASA Only: OR = 0.95 (95% CI: 0.67 to 1.33; p = 0.75

Secondary Outcome

Rivaroxaban 2.5 mg BID + ASA	Rivaroxaban 5 mg BID Only	ASA Only
- 86 patients (21.7%)	- 68 patients (17.8%)	- 75 patients (20.7%)

- Rivaroxaban + ASA versus ASA Only: OR = 1.06 (95% CI: 0.75 to 1.50; p = 0.74)
- Rivaroxaban Only versus ASA Only: OR = 0.83 (95% CI: 0.58 to 1.20; p = 0.32)

Clinical Efficacy Outcomes

Rivaroxaban 2.5 mg BID + ASA	Rivaroxaban 5 mg BID Only	ASA Only
- 12 patients (2.4%)	- 16 patients (3.3%)	- 16 patients (3.5%)

- Rivaroxaban + ASA versus ASA Only: HR = 0.69 (95% CI: 0.33 to 1.47; p = 0.34)
- Rivaroxaban Only versus ASA Only: HR = 0.99 (95% CI: 0.50 to 1.99; p = 0.98)

Bleeding Outcomes

Rivaroxaban 2.5 mg BID + ASA	Rivaroxaban 5 mg BID Only	ASA Only
- 2 patients (0.4%)	- 1 patient (0.2%)	- 5 patients (1.1%)

- Rivaroxaban + ASA versus ASA Only: HR = 0.37 (95% CI: 0.07 to 1.88; p = 0.37
- Rivaroxaban Only versus ASA Only: HR = 0.19 (95% CI: 0.02 to 1.61; p = 0.09

Authors' Conclusions

<table>
<tr><td></td><td colspan="2">Combination of rivaroxaban 2.5 mg twice daily plus ASA 100 mg daily or rivaroxaban 5 mg twice daily alone compared with ASA 100 mg daily alone did not reduce graft failure in patients with recent CABG surgery
In the first 30 days after CABG surgery, there was no fatal bleeding or tamponade despite starting anticoagulation as early as four days after surgery and without a run-in period
The combination of rivaroxaban plus ASA was associated with similar reductions in MACE as observed in the larger COMPASS trial
It is reasonable and safe to use the combination of rivaroxaban 2.5 mg twice daily plus ASA in patients who undergo CABG surgery</td></tr>
<tr><td rowspan="2">STRENGTHS/ LIMITATIONS</td><td>Strengths</td><td>Limitations</td></tr>
<tr><td>Randomized controlled trial
Assessed adverse effects (major bleeding events)
Appropriate statistical tests used
Clear secondary and primary outcome measures
Results were reported for each outcome stated in study</td><td>No power reported; risk of Type II error
Intention-to-treat principle only data handling method used
Adherence/compliance not addressed
Early termination of the trial (any further occlusions or bleeding unknown)
Results for second partial factorial randomization not reported but discussed in methods section
Unclear if there was standardization between all 602 centers
No wash-out period between CABG procedure and first treatment dose
Weak inclusion and exclusion criteria (on-pump versus off-pump CABG, venous versus arterial graft, age cut-off, etc.)
Did not report any other adverse events
Omitted reports of fatal bleeding and cardiac tamponade after 30 days post-surgery
Only 78.3% of patients underwent computed tomography angiography (CTA) at 12 months</td></tr>
<tr><td>CONCLUSION</td><td colspan="2">Overall, it would be very difficult to extrapolate the results of this study to actual clinical practice. The study was not powered to detect a benefit in rivaroxaban-based therapy, which was the study's main objective. The most important statistically, and potentially clinically, significant finding was the fact that there was a 2-fold increase in risk of bleeding within the first 30 days with rivaroxaban alone versus aspirin alone. This would be something to consider in patients undergoing CABG therapy who are at high risk of bleeding post-surgery. However, further research is needed. This research should include studies with adequate power to detect a difference in rivaroxaban-based therapy, in patients of varying age groups (40-60, for example), and with more succinct inclusion and exclusion criteria (off-pump only patients, for example).</td></tr>
<tr><td>REFERENCE</td><td colspan="2">Lamy A, Eikelboom J, Sheth T, et al. Rivaroxaban, Aspirin, or Both to Prevent Early Coronary Bypass Graft Occlusion: The COMPASS-CABG Study. Journal of the American College of Cardiology. 2019;73(2):121-130.</td></tr>
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