Supplemental information on cardiovascular consequences of discontinuing low-dose rivaroxaban in patients with chronic coronary or peripheral artery disease

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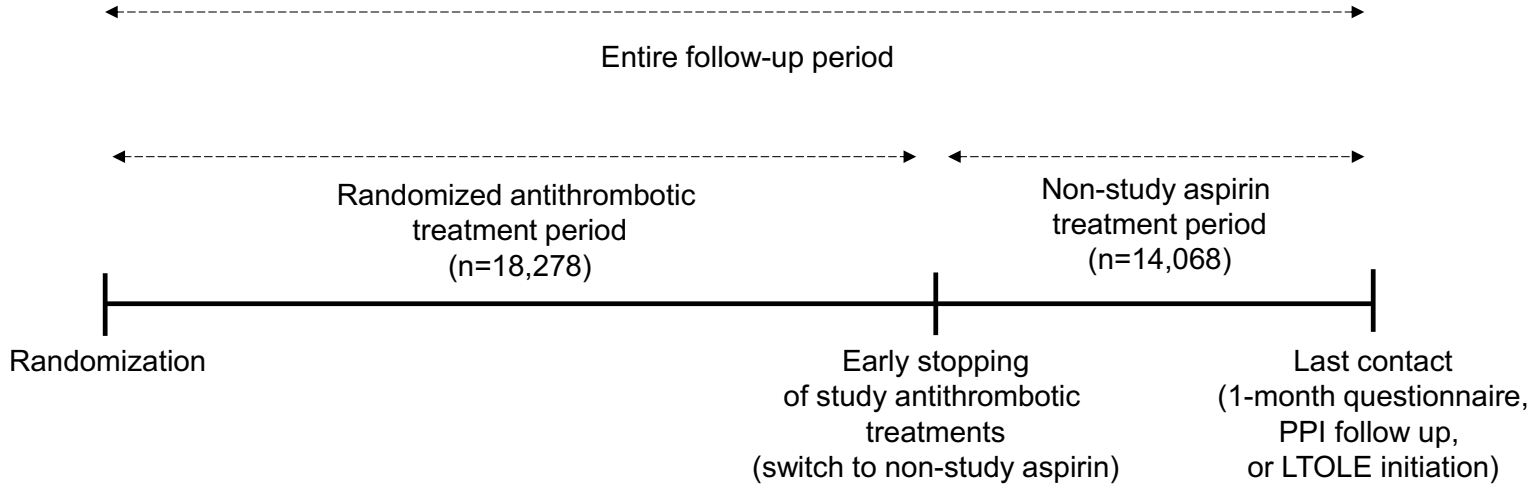
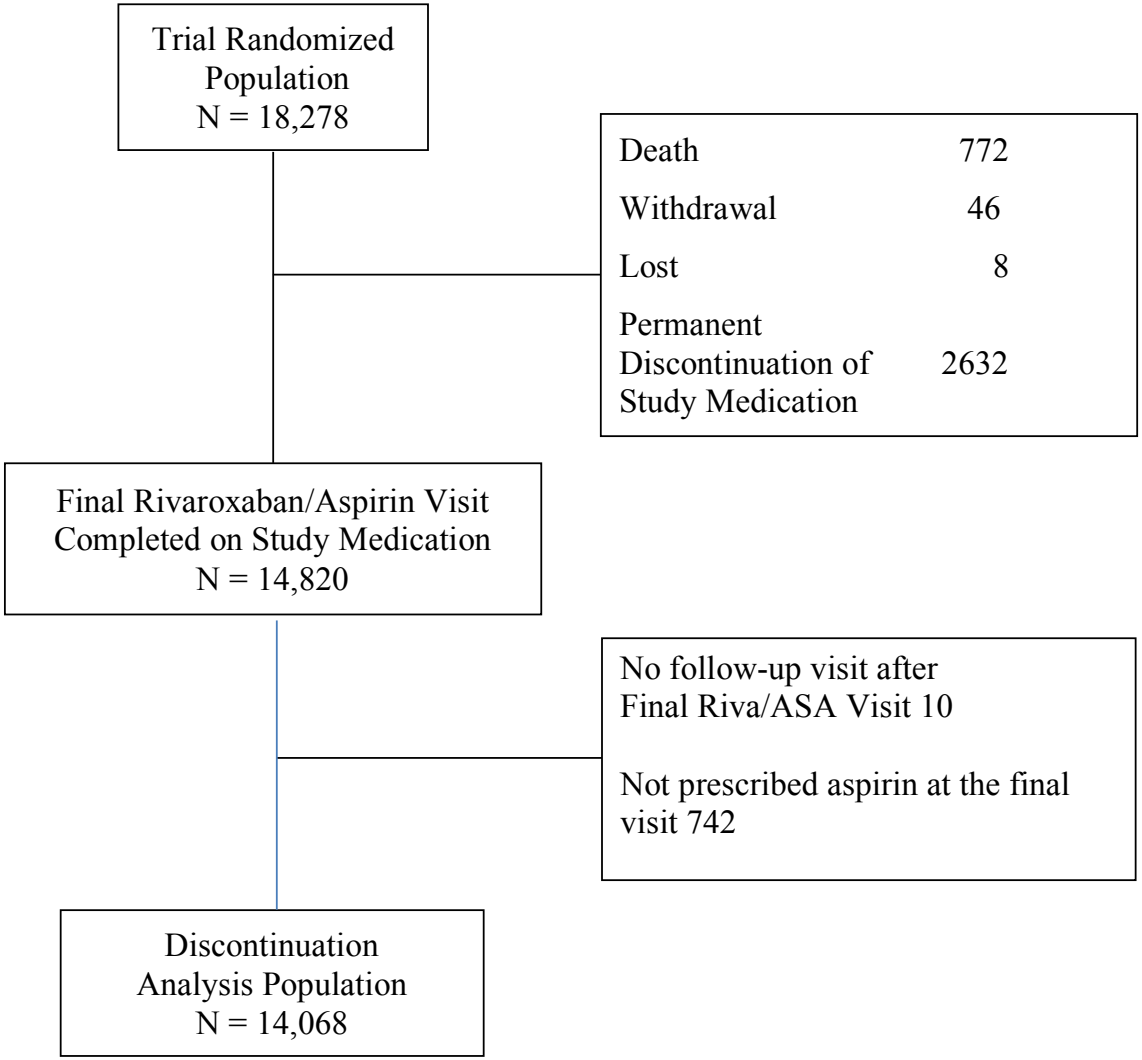
Dagenais GR, *et al. Heart* 2021;0:1–8. doi: 10.1136/heartjnl-2020-318758

Supplement Figure 1 Study follow-up period



Supplement Figure 2 Flow of randomized participants during the trial and the last rivaroxaban discontinuation evaluation



Supplement Table 1 Outcomes of participants during the follow-up period before and after study rivaroxaban/aspirin discontinuation

	Overall	**Rivaroxaban 2.5 mg bid plus aspirin 100 mg od**	**Aspirin 100 mg od**
Randomized	18,278	9152	9126
Death before early stopping visit	772 (4.2)	351 (3.8)	421 (4.6)
Withdrawal of consent before early stopping visit	46 (0.3)	21 (0.2)	25 (0.3)
Permanent discontinuation before early stopping visit	2632 (14.4)	1362 (14.9)	1270 (13.9)
Lost to follow up - no early stopping visit	8 (0.0)	5 (0.1%)	3 (0.0)
No Follow-up after early stopping visit	10 (0.1)	5 (0.1%)	5 (0.1)
On randomized antithrombotic therapy at early stopping visit and followed at least once thereafter	14,810 (81.0)	7408 (80.9)	7402 (81.1)
Not switched to non-study aspirin	742 (4.1)	381 (4.2)	361 (4.0)
Clopidogrel	405 (54.6)	212 (55.6)	193 (53.5)
Other antiplatelet	59 (8.0)	29 (7.6)	30 (8.3)
Anticoagulant	87 (11.7)	50 (13.1)	37 (10.3)
None	198 (26.7)	94 (24.7)	104 (28.8)

Analysis population	14,068 (95.0)	7027 (94.9)	7041 (95.1)
Analysis population and participating in LTOLE|	5164 (36.7)	2592 (36.9)	2572 (36.5)
Analysis population and randomized to pantoprazole/placebo	9118 (64.8)	4579 (65.2)	4539 (64.5)
Pantoprazole	4545 (32.3)	2285 (32.5)	2260 (32.1)
Placebo	4573 (32.5)	2294 (32.7)	2279 (32.4)

Data are expressed in percent (%). bid indicates twice a day; od, once a day; N, number; LTOLE, long-term open-label extension.

Supplement Table 2 Outcomes in post rivaroxaban/aspirin participants from final rivaroxaban/aspirin visit to 6 months post final rivaroxaban/aspirin visit

	Rivaroxaban 2.5 mg bid plus aspirin 100 mg od (N=7027)		**Aspirin 100 mg od (N=7041)**		**Rivaroxaban 2.5 mg bid plus aspirin 100 mg od vs aspirin 100 mg od**
	N (%)	**Per 100 py**	**N (%)**	**Per 100 py**	**HR| (95% CI)**
Myocardial infarction, stroke, or cardiovascular death	61 (0.9)	2.1	54 (0.8)	1.9	1.12 (0.78-1.62)
Death	41 (0.6)	1.4	43 (0.6)	1.5	0.95 (0.62-1.45)
Cardiovascular death	23 (0.3)	0.8	24 (0.3)	0.8	0.95 (0.54-1.68)
Non-cardiovascular death	18 (0.3)	0.6	19 (0.3)	0.7	0.94 (0.49-1.79)
Stroke	26 (0.4)	0.9	7 (<0.1)	0.2	3.69 (1.60-8.51)
Hemorrhagic stroke	1 (<0.1)	<0.1	0	0	-
Ischemic or uncertain stroke	25 (0.4)	0.9	7 (<0.1)	0.2	3.55 (1.54-8.21)
Myocardial infarction	19 (0.3)	0.7	27 (0.4)	1.0	0.70 (0.39-1.26)
Revascularization	79 (1.1)	2.8	103 (1.5)	3.7	0.76 (0.57-1.02)

	Rivaroxaban 2.5 mg bid plus aspirin 100 mg od (N=7027)		**Aspirin 100 mg od (N=7041)**		**Rivaroxaban 2.5 mg bid plus aspirin 100 mg od vs aspirin 100 mg od**
	N (%)	**Per 100 py**	**N (%)**	**Per 100 py**	**HR| (95% CI)**
Heart failure	15 (0.2)	0.5	15 (0.2)	0.5	1.00 (0.49-2.04)
Acute limb ischemia	4 (<0.1)	0.1	8 (0.1)	0.3	0.50 (0.15-1.64)
Total vascular amputations	3 (<0.1)	0.1	4 (<0.1)	0.1	0.74 (0.17-3.33)
Venous thromboembolism	5 (<0.1)	0.2	8 (0.1)	0.3	0.62 (0.20-1.90)
Hospitalization	405 (5.8)	14.7	406 (5.8)	14.9	0.99 (0.86-1.14)
CV hospitalization	188 (2.7)	6.7	201 (2.9)	7.2	0.93 (0.76-1.13)
Non-CV hospitalization	228 (3.2)	8.2	225 (3.2)	8.1	1.01 (0.84-1.21)

Data are in percent (%) or per 100 person-years (/100 py).

bid indicates twice a day; od, once a day; HR, hazard ratio; CI, confidence interval; py, person-years; CV, cardiovascular

Supplement Table 3 Outcomes in post rivaroxaban/aspirin participants from final rivaroxaban/aspirin visit to maximum of washout/LTOLE initiation visit considering Fine-Gray sub-distribution hazard competing risk models using non-CV death for the composite outcome and CV death and all-cause mortality for myocardial infarction and stroke

	Rivaroxaban 2.5 mg bid plus aspirin 100 mg od group vs aspirin 100 mg od group	
	Cox PH HR(95% CI)	**Fine-Grey models HR(95% CI)**
Composite of CV death, myocardial infarction or stroke	1.079 (0.838 - 1.390)	1.078 (0.837 - 1.389)
CV death	1.256 (0.849 - 1.856)	1.255 (0.849 - 1.855)
Myocardial infarction	0.721 (0.480 - 1.084)	0.720 (0.479 - 1.082)
Stroke	1.741 (1.054 - 2.874)	1.739 (1.053 - 2.870)

Abbreviations as in Supplemental 3

The competing risk of non-CV death for the composite outcome and CV death, and all-cause mortality for MI and stroke did not substantially change the effect size of the treatment of the trial (Cox PH)

Supplement Table 4 Baseline characteristics at entry in the trial in all participants randomized to rivaroxaban plus aspirin and aspirin and in participants who continued during the follow-up period after study rivaroxaban/aspirin discontinuation

	OVERALL	**All randomized**	**Stopped study antithrombotic treatments at early stopping visit and switched to non-study aspirin**	**P value**
	N (%)	**N (%)**	**N (%)**	
Randomized	32,346	18,278	14,068	
Age years (SD)	68.1 (7.9)	68.3 (8.0)	67.9 (7.9)	<0.0001
Women – N (%)	7169 (22.2)	4046 (22.1)	3123 (22.2)	0.89
Blood pressure – mmHg (SD)				
__Systolic	135.4 (17.4)	135.5 (17.5)	135.3 (17.3)	0.14
__Diastolic	77.6 (9.9)	77.6 (9.9)	77.7 (9.9)	0.36
Cholesterol - mmol/litre (IQR)	4.03 (3.48,4.76)	4.03 (3.46,4.76)	4.03 (3.48,4.76)	<0.0001
Tobacco Use – N (%)	6983 (21.6)	3916 (21.4)	3067 (21.8)	0.41
Known hypertension – N (%)	24,372 (75.4)	13,794 (75.5)	10,578 (75.2)	0.57

	OVERALL	**All randomized**	**Stopped study antithrombotic treatments at early stopping visit and switched to non-study aspirin**	**P value**
	N (%)	**N (%)**	**N (%)**	
Known diabetes – N (%)	12,125 (37.5)	6926 (37.9)	5199 (37.0)	0.09
Prior Stroke - N (%)	1189 (3.7)	687 (3.8)	502 (3.6)	0.37
Prior MI – N (%)	20,238 (62.6)	11,379 (62.3)	8859 (63.0)	0.19
Heart Failure – N (%)	7051 (21.8)	3948 (21.6)	3103 (22.1)	0.32
Coronary Artery Disease – N (%)	29,412 (90.9)	16,575 (90.7)	12,837 (91.3)	0.08
Peripheral Arterial Disease – N (%)	8647 (26.7)	5001 (27.4)	3646 (25.9)	0.0036
Estimated GFR – N (%)				
15-29 ml/min	269 (0.8)	163 (0.9)	106 (0.8)	0.17
30-59 ml/min	6904 (21.3)	4006 (21.9)	2898 (20.6)	0.0041
>=60 ml/min	25,167 (77.8)	14,105 (77.2)	10,062 (78.6)	0.0018
Race – N (%)				
White or Caucasian	20,056 (62.0)	11,355 (62.1)	8701 (61.9)	0.61

	OVERALL	**All randomized**	**Stopped study antithrombotic treatments at early stopping visit and switched to non-study aspirin**	**P value**
	N (%)	**N (%)**	**N (%)**	
Black or African American	301 (0.9)	168 (0.9)	133 (1.00)	0.81
Asian	5011 (15.5)	2848 (15.6)	2163 (15.4)	0.61
Other	6978 (21.6)	3907 (21.4)	3071 (21.8)	0.33
Region				
North America	4473 (13.8)	2613 (14.3)	1860 (13.2)	0.0055
South America	7371 (22.8)	4108 (22.5)	3263 (23.2)	0.13
Western Europe	10,031 (31.0)	5710 (31.2)	4321 (30.7)	0.31
Eastern Europe	5820 (18.0)	3211 (17.6)	2609 (18.6)	0.0232
Asia Pacific and other	4651 (14.4)	2636 (14.4)	2015 (14.32)	0.80
Medications – N (%)				
ACE inhibitor or ARB	22,963 (71.0)	12,941 (71.0)	10,022 (71.2)	0.39
Calcium-channel blocker	8570 (26.5)	4897 (26.8)	3673 (26.1)	0.17

	OVERALL	**All randomized**	**Stopped study antithrombotic treatments at early stopping visit and switched to non-study aspirin**	**P value**
	N (%)	**N (%)**	**N (%)**	
Diuretic	9552 (29.5)	5471 (29.9)	4081 (29.0)	0.07
Beta-blocker	22,694 (70.2)	12,790 (70.0)	9904 (70.4)	0.41
Lipid lowering agent	29,129 (90.1)	16,401 (89.7)	12,728 (90.5)	0.0267
NSAID	1747 (5.4)	1002 (5.5)	745 (5.3)	0.46
Non-Study PPI	11,480 (35.5)	6533 (35.7)	4947 (35.2)	0.28

SD indicates standard deviation; IQR, interquartile range; MI, myocardial infarction; GFR, glomerular filtration rate; PPI, proton pump inhibitor; ACE, angiotensin converting enzyme; ARB, angiotensin receptor blocker; NSAID, non- steroidal anti-inflammatory drugs

Population Health Research Institute (PHRI) Data Sharing Policy

Effective Date: July 27, 2018

Data will be disclosed only upon request and approval of the proposed use of the data by a review committee. Membership in the review committee will be determined by the executive leadership of the study. Generally only those requests made by a journal's statistician regarding the data related to the results of the publication will be considered unless the review committee sees high merit in other requests. The following principles will apply to requests:

1. The review committee will have established criteria to review the request to ensure that patient privacy and rights, and PHRI data and research integrity can be maintained with the sharing of the data. This includes (but is not limited to) demonstrated competence related to data security and data analysis by the investigator requesting access. The review committee will also ensure that provision of data to external parties does not contravene any prior agreement with any other parties.
2. PHRI will make individual participant data available, including data dictionaries, within the requirements and/or restrictions of REB/IRB and subject to the conditions set forth in the consent forms of the study. Data provided will be limited to data which underlies the results in the main publication after de-identification. Any analyses and

publications should be reviewed and approved by PHRI before publication to ensure that the analyses are accurate and that the publication is not misleading.

3. The study protocol and the statistical analysis plan for analysis of the primary results will be shared.
4. For those requests that originate from concerns expressed by the journal about the data or statistical analyses, the data will be available to the journal statisticians in a timely manner.
5. Data can be disclosed for all other requests from 2 years after the main paper is published plus 6 additional months for each year of study conduct. However, there will be a maximum of 7 years to the time limit restriction.
6. Data will be shared to achieve the objective in the approved proposal with no additional analysis permitted without approval. Only proposals for analyses that do not compete with ongoing analyses or analyses proposed by study investigators will be approved.
7. Data will be made available by one of the following mechanisms. 1) The Statistics Department at PHRI can perform the analysis in accordance with the SAP provided by the investigator and under his/her supervision or 2) Arrangement can be made to transfer the data to a secure location using a process that has been verified by the Director of Statistics at PHRI.
8. Every proposal must identify and provide funding sufficient to defray the cost of data preparation, storage, transfer and analysis for the organization incurring these costs (this may include studies not fully funded from external sources i.e. industry or peer review grants). On occasions where the new analyses proposed are of sufficient

scientific interest to PHRI, then a collaborative agreement for joint analyses and publication can be developed and charges may be reduced.

9. The data will be provided for a specified time limit that can allow completion of the analyses that is proposed. At the end of the proposed analyses, the requesting party undertakes to return or destroy the data base provided and provide written documentation of this.

References

1. Taichman DB, Sahni, P, Pinborg A et al. Data Sharing Statements for Clinical Trials - A Requirement of the International Committee of Medical Journal Editors. N Engl J Med 2017; 376: 23:2277-9.
2. International Consortium of Investigators for Fairness in Trial Data. Devereaux PJ, Guyatt G, Gerstein H, Connolly S, Yusuf S. Toward Fairness in Data Sharing. N Engl J Med 2016; 375:405-7. Supplemental Endorsers of Article listed in 2