

Supplementary Appendix

This appendix has been provided by the authors to give readers additional information about their work.

Supplement to: Kerr DJ, Dunn JA, Langman MJ, et al. Rofecoxib and cardiovascular adverse events in adjuvant treatment of colorectal cancer. *N Engl J Med* 2007;357:360-9.

Web Table 1: Cardiovascular event adjudication committee – Cardiology:

Bernard Chaitman, St Louis University School of Medicine, St Louis, MO, USA; Leonard S Dreifus, University of South Florida/Tampa, Lake Mary, FL, USA; George Vetrovec, Medical College of VA, Richmond, VA, USA; Neurology: Harold Adams, University of Iowa Hospitals and Clinics, Iowa City, IA, USA; Jay P Mohr, Columbia University, New York, NY, USA; Justin A Zivin, University of California, San Diego School of Medicine, LaJolla, CA, USA. Peripheral vascular: Jeffrey Ginsberg, McMaster University, Hamilton, Canada; Clive Kearon, McMaster University Clinic, Hamilton, Canada; Thom Rooke, Mayo Clinic, Rochester, MN, USA.

WEB TABLE 2: Listing of Investigator-Reported Potentially Thrombotic CV Events

CV Event	TCVSAE ⁵	APTC ⁶	Allocation	Treatment duration before event (days)
Events up to 14 days after discontinuation presented for adjudication				
⁸ Fatal acute myocardial infarction	Y	Y	Rofecoxib	531
Acute myocardial infarction	Y	Y	Rofecoxib	352
Acute myocardial infarction	Y	Y	Rofecoxib	331
⁸¹ Fatal acute myocardial infarction	Y	Y	Rofecoxib	420
¹ Oesophageal carcinoma	N	N	Rofecoxib	411
⁷ Acute myocardial infarction	Y	Y	Rofecoxib	465
Ischemic Cerebrovascular stroke	Y	Y	Rofecoxib	19
² Ischemic Cerebrovascular stroke	Y	Y	Rofecoxib	<11 ⁴
⁸² Fatal Acute myocardial infarction	Y	Y	Rofecoxib	<15 ⁴
⁷ Ischemic Cerebrovascular stroke	Y	Y	Rofecoxib	102
⁸ Sudden cardiac death	Y	Y	Rofecoxib	22
Transient ischemic attack	Y	N	Rofecoxib	369
Peripheral venous thrombosis	Y	N	Rofecoxib	123
⁷ Peripheral venous thrombosis	Y	N	Rofecoxib	386
Pulmonary embolism	Y	N	Rofecoxib	64
Unstable angina pectoris	Y	N	Rofecoxib	5
⁷ Transient ischemic attack	Y	N	Rofecoxib	84

Myocardial ischemia	N	N	Rofecoxib	142
⁷ Cardiac arrest (probable lung ca)	N	N	Rofecoxib	677
Myocardial ischemia	N	N	Rofecoxib	555
Alveolitis fibrosing	N	N	Rofecoxib	188
Transient ischemic attack	N	N	Rofecoxib	47
Transient ischemic attack	N	N	Rofecoxib	157
⁷ Acute myocardial infarction	Y	Y	Placebo	285
⁷⁸³ Sudden cardiac death	Y	Y	Placebo	592
⁷³ Cardiac thrombus	Y	N	Placebo	501
⁷³ Cerebral ischemia	N	N	Placebo	524
Ischemic Cerebrovascular stroke	Y	Y	Placebo	512
⁸ Sudden cardiac death	Y	Y	Placebo	173
Unstable angina pectoris	Y	N	Placebo	77
Pulmonary embolism	Y	N	Placebo	77
⁷⁸ Fatal hemorrhagic cerebrovascular stroke	N	Y	Placebo	190
Cerebral infarct	N	Y	Placebo	29
Loss of consciousness, disorientation, vomiting, syncope	N	N	Placebo	200
⁷ Angina pectoris	N	N	Placebo	106
Events after discontinuation + 14 days adjudicated by the VICTOR trial team (DK and RM)				
⁷ Cerebrovascular accident	Y	Y	Rofecoxib	196

Cerebrovascular accident	Y	Y	Rofecoxib	129
⁷⁸ Myocardial infarction	Y	Y	Rofecoxib	260
⁷ Myocardial infarction	Y	Y	Rofecoxib	198
⁷ Arterial thrombosis	Y	N	Rofecoxib	136
⁷ Transient ischaemic attack	Y	N	Rofecoxib	104
Cerebrovascular accident	Y	Y	Placebo	213
⁷⁸ Myocardial infarction	Y	Y	Placebo	172
⁷ Myocardial infarction	Y	Y	Placebo	38
⁷⁸ Myocardial infarction	Y	Y	Placebo	19
⁷⁸ Arterial thrombosis	Y	N	Placebo	253
⁷⁸ Pulmonary embolism	Y	N	Placebo	249
Unstable angina	Y	N	Placebo	15
⁷⁸ Arterial thrombosis	Y	N	Placebo	40

¹ Two events 30 days apart for the same patient

² Two events 4 days apart for the same patient

³ Three events for the same patient

⁴ Treatment discontinuation date is approximate

⁵ Thrombotic Cardiovascular Serious Adverse Event (TCVSAE)

⁶ Antiplatelet Trialists Collaboration (APTC)

⁷ Reported after study unblinding, 01/10/2004

⁸ Fatal event

WEB FIGURE 1: CARDIOVASCULAR RISK ASSESSMENT FORM

DOCUMENTED HISTORY OF VASCULAR DISEASE

Does the patient have a history of any of the following:	No	Yes
Myocardial infarction:	<input type="checkbox"/>	<input type="checkbox"/>
Angina (physician diagnosed):	<input type="checkbox"/>	<input type="checkbox"/>
Coronary intervention (e.g. prior bypass surgery, coronary angioplasty or stent):	<input type="checkbox"/>	<input type="checkbox"/>
Prior cardiac catheterisation showing coronary artery disease:	<input type="checkbox"/>	<input type="checkbox"/>
Carotid artery stenosis on ultrasound or angiography:	<input type="checkbox"/>	<input type="checkbox"/>
Cerebrovascular accident:	<input type="checkbox"/>	<input type="checkbox"/>
Transient ischaemic attack:	<input type="checkbox"/>	<input type="checkbox"/>
Peripheral vascular disease (e.g. history of claudication, prior peripheral vascular disease):	<input type="checkbox"/>	<input type="checkbox"/>

CARDIAC RISK FACTORS

Does the patient have a history of:	No	Yes	Unknown
Diabetes mellitus:	<input type="checkbox"/>	<input type="checkbox"/>	-
Hypertension:	<input type="checkbox"/>	<input type="checkbox"/>	-
Hyperlipidaemia (LDL >130 mg/dl and/or HDL <40 mg/dl):	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Does the patient have a family history of cardiac disease:	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

(i.e. father or brother with a diagnosis of heart attack or angina before the age of 55 or mother or sister with a diagnosis of heart attack or angina before the age of 65?)

Does the patient currently smoke: -

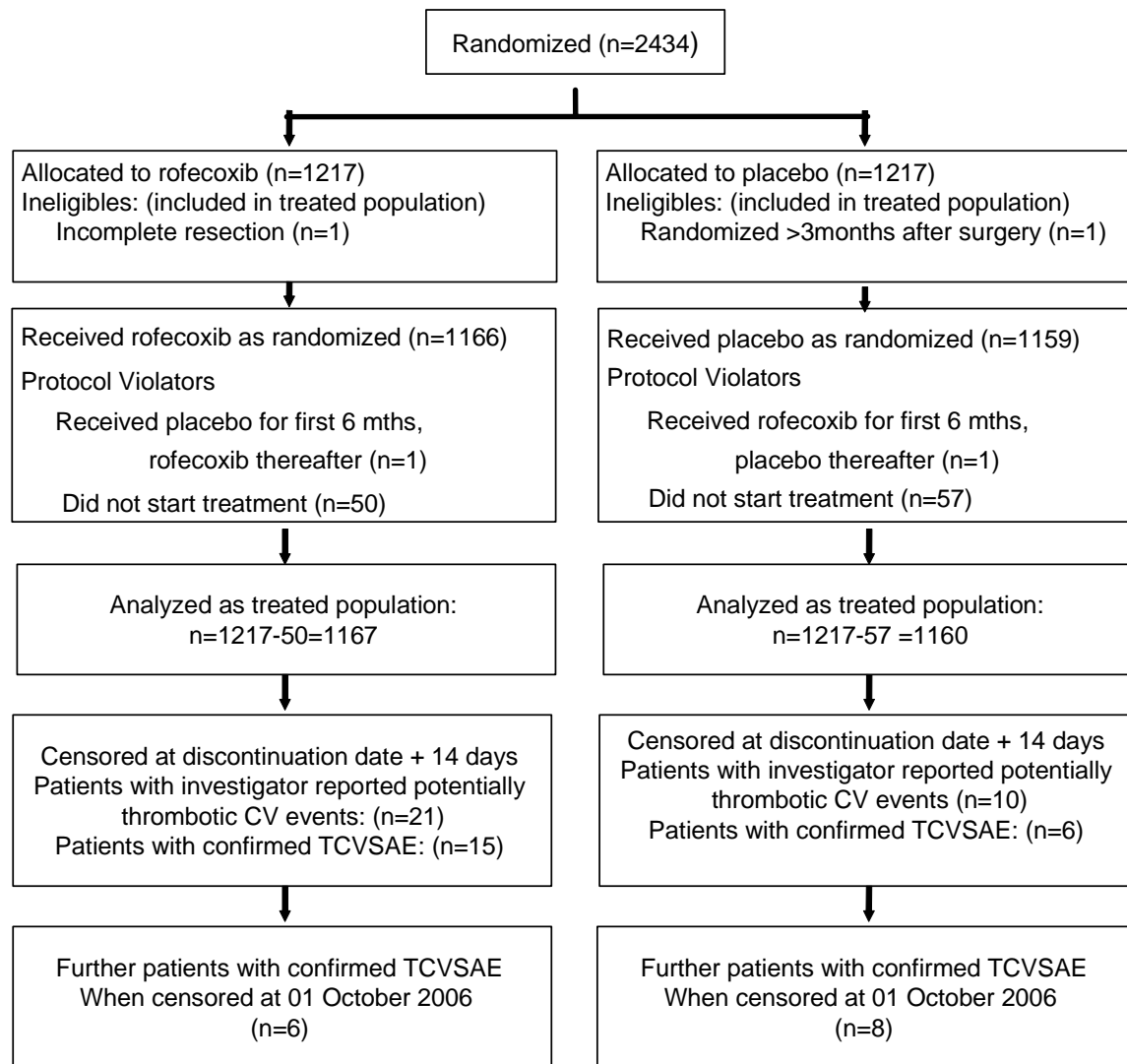
MEDICATIONS

Is the patient taking any of the following for prophylaxis against myocardial infarction or other thromboembolic disease:

	No	Yes	
Clopidogrel:	<input type="checkbox"/>	<input type="checkbox"/>	
Ticlopidine:	<input type="checkbox"/>	<input type="checkbox"/>	
Other anti-platelet agents:	<input type="checkbox"/>	<input type="checkbox"/>	*

* If yes, please specify agent(s): _____

WEB FIGURE 2: CONSORT DIAGRAM



CONSORT Checklist of items to include when reporting a randomized trial

PAPER SECTION And topic	Item	Description	Reported on Page #
<i>TITLE & ABSTRACT</i>	1	<u>How participants were allocated to interventions</u> (e.g., "random allocation", "randomized", or "randomly assigned").	1 & 2
<i>INTRODUCTION</i> Background	2	<u>Scientific background and explanation of rationale.</u>	5
<i>METHODS</i> Participants	3	<u>Eligibility criteria for participants</u> and the <u>settings and locations where the data were collected.</u>	6
Interventions	4	<u>Precise details of the interventions intended for each group and how and when they were actually administered.</u>	7
Objectives	5	<u>Specific objectives and hypotheses.</u>	6
Outcomes	6	<u>Clearly defined primary and secondary outcome measures</u> and, when applicable, any <u>methods used to enhance the quality of measurements</u> (e.g., multiple observations, training of assessors).	8 & 9
Sample size	7	<u>How sample size was determined</u> and, when applicable, <u>explanation of any interim analyses and stopping rules.</u>	9
Randomization --	8	<u>Method used to generate the random allocation</u>	7

Sequence generation		<u>sequence, including details of any restrictions</u> (e.g., blocking, stratification)	
Randomization -- Allocation concealment	9	<u>Method used to implement the random allocation sequence</u> (e.g., numbered containers or central telephone), clarifying whether the sequence was concealed until interventions were assigned.	7
Randomization -- Implementation	10	<u>Who generated the allocation sequence, who enrolled participants, and who assigned participants to their groups.</u>	7
Blinding (masking)	11	<u>Whether or not participants, those administering the interventions, and those assessing the outcomes were blinded to group assignment.</u> When relevant, <u>how the success of blinding was evaluated.</u>	7
Statistical methods	12	<u>Statistical methods used to compare groups for primary outcome(s); Methods for additional analyses,</u> such as subgroup analyses and adjusted analyses.	9
RESULTS Participant flow	13	<u>Flow of participants through each stage</u> (a diagram is strongly recommended). Specifically, for each group report the numbers of participants randomly assigned, receiving intended treatment, completing the study protocol, and analyzed for the primary outcome. <u>Describe protocol deviations from study as planned, together with reasons.</u>	10, Web Figure 2

Recruitment	14	<u>Dates defining the periods of recruitment and follow-up.</u>	10
Baseline data	15	<u>Baseline demographic and clinical characteristics of each group.</u>	10, Table 1
Numbers analyzed	16	<u>Number of participants (denominator) in each group included in each analysis and whether the analysis was by "intention-to-treat".</u> State the results in absolute numbers when feasible (e.g., 10/20, not 50%).	10
Outcomes and estimation	17	<u>For each primary and secondary outcome, a summary of results for each group, and the estimated effect size and its precision</u> (e.g., 95% confidence interval).	11, 12
Ancillary analyses	18	<u>Address multiplicity by reporting any other analyses performed,</u> including subgroup analyses and adjusted analyses, indicating those pre-specified and those exploratory.	12
Adverse events	19	<u>All important adverse events or side effects in each intervention group.</u>	11, 12
DISCUSSION Interpretation	20	<u>Interpretation of the results,</u> taking into account study hypotheses, sources of potential bias or imprecision and the dangers associated with multiplicity of analyses and outcomes.	13
Generalizability	21	<u>Generalizability (external validity) of the trial findings.</u>	13

Overall evidence	22	<u>General interpretation of the results in the context of current evidence.</u>	13
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