Section A: Clarification on effectiveness data

General

A1. Our clinicians indicate that maintaining patients on rivaroxaban beyond 12 months may be unlikely because, for example, the risk of an infarction is highest in the 12 months following an infarction. Please clarify how patients will be selected for treatment beyond 12 months?

Extension of treatment beyond 12 months should be done on an individual patient basis, because experience up to 24 months is limited. The treating physician should balance ischaemic risk against bleeding risk when considering how long to continue rivaroxaban treatment. In ATLAS ACS 2 TIMI 51, the efficacy benefits of rivaroxaban combined with standard antiplatelet therapy (ASA with or without clopidogrel) compared with standard antiplatelet therapy alone after an ACS event, including the significant CV mortality benefit associated with rivaroxaban 2.5 mg bid, increased over time for at least 2 years of treatment in both the overall population, [redacted]. Thus, although experience is limited, data support rivaroxaban treatment lasting up to 2 years after ACS, as recommended in the European product information.

A2. Please clarify when rivaroxaban should be started for maintenance therapy e.g. within 7 days after hospital admission for ACS

According to the SPC, treatment with Xarelto should be started as soon as possible after stabilisation of the ACS event (including revascularisation procedures); at the earliest 24 hours after admission to hospital and at the time when parenteral anticoagulation therapy would normally be discontinued.

In the ATLAS ACS 2 TIMI 51 trial, patients were randomised a median of 4.7 days after the index ACS event. All patients were required to have been stabilised and initial management strategies completed before enrolment, and all patients were enrolled within 7 days after hospital admission for ACS.

A3. The submission (p8) states that 'a PASS [post authorisation study] was considered conditional to the MA [marketing authorisation]'. Please could you provide further details of this study including any results that may be available.

At a meeting in February 2014, the Pharmacovigilance Risk Assessment Committee (PRAC) proposed not to start a separate Post Authorisation Safety Study (PASS) for ACS but to extend the existing epidemiological rivaroxaban PASS program. As we are still in discussion with EMA any results of this PASS are not yet available.

In total, the existing epidemiological rivaroxaban PASS program is comprised of 5 studies capturing drug utilisation, safety outcomes and effectiveness based on primary or secondary routine clinical practice including the ACS indication

- Synchronised database studies:
  - o The Health Improvement Network (THIN) - UK
  - o German Pharmacoepidemiological Research Database (GePaRD)
  - o PHARMO - Netherlands

- Ad hoc studies:
  - o A Modified Prescription Event Monitoring Study (M-PEM)
  - o Specialist Cohort Event Monitoring Study on ACS (SCEM)

A4. The submission (p131) states that 'The most recent 2012 ESC guidelines for patients with STEMI recommend low dose rivaroxaban…' Please provide further details including class of recommendation, definition and suggested wording of recommendation proposed by the guideline.

The guideline states in Table 22 "In selected patients who receive aspirin and clopidogrel, low-dose rivaroxaban (2.5 mg twice daily) may be considered if the patient is at low bleeding risk." The class of their recommendation is IIb, with level of evidence classified as B. Class IIb is defined as "Usefulness/efficacy is less well established by evidence/opinion". The suggested wording to use is "may be considered". Level of Evidence B is defined as "Data derived from a single randomized clinical trial or large non-randomized studies."

Literature searching

A5. Please clarify why line '#6' of the EMBASE and MEDLINE search strategies excludes 'Phase 1 Clinical Trial'/de. (p B361, Section 10.2 Appendix 2)

Phase I studies were excluded as stated in table 1 (p30) – eligibility criteria used in clinical review. Most phase 1 trials are undertaken in healthy subjects and so would not meet the population criteria specified in the scope. Relevant restrictions were added to the search strategies to remove publication types that have been indexed as being those not of interest.

A6. Please provide justification (including limitations) for restricting searches to English language studies only

It was expected that the majority of publications of interest to this review will be in English language and restricting to such publications was unlikely to exclude useful information.

Whilst it is appreciated that there is a theoretical risk of introducing language bias by not including non-English publications, it is understood that the studies relating to the economics, resource use and quality of life that would be considered to be the most relevant to the decision problem would be those undertaken in the UK, and therefore it is highly unlikely that these would be published in any language other than English.

Similarly, large international RCTs including populations from the USA and the UK are likely to be published in English.

Further, due to the wealth of clinical trial data in this area of medicine, it was decided pragmatically to restrict the searching to English Language studies only.

A7. Please clarify if any searching was undertaken for non-RCT evidence (p B366, Section 10.6, Appendix 6) as the submission states (p104) that 'there are no relevant non-RCTs included in this submission.'

Searching was not undertaken for non-RCTs as part of the clinical review. As outlined on p42, studies of this nature were not considered relevant to the decision problem.

As stated in the guide to the methods of technology appraisal 2013, *"the Institute has a preference for RCTs directly comparing the intervention with 1 or more relevant comparators and these should be presented in the reference-case analysis if available."* Also that "*RCTs directly comparing the technology under appraisal with relevant comparators provide the most valid evidence of relative efficacy. However, such evidence may not always be available and may not be sufficient to quantify the effect of treatment over the course of the disease. Therefore, data from non-randomised studies may be required to supplement RCT data. Any potential bias arising from the design of the studies used in the assessment should be explored and documented."*

In this case, evidence from a good quality RCT directly comparing the intervention with a relevant comparator was available; therefore it was considered that data from non-randomised studies were not necessary to supplement RCT data.

For the economic reviews, any studies (e.g. clinical trials or other prospective or cross-sectional studies) reporting resource utilisation and costs were included as well as economic evaluation studies, e.g. studies based on models, cost analyses performed alongside clinical trials, and budget-impact analyses.

For utilities, studies reporting utility estimates (general or disease specific), preference weights (including EQ-5D, SF-36, HUI, time trade-off, etc.), utility mapping studies and cost-effectiveness analyses, cost-utility analyses, cost-benefit analyses were reviewed.

Further to these "key reviews", a further review of the literature was conducted to identify (1) all clinical studies in ACS patients that report the risk of subsequent events after an initial ACS event and after secondary events (myocardial infarction, ischaemic stroke, or haemorrhagic stroke) and any combination of these, (2) increases in event rates due to age, and (3)life expectancy of patients with ACS events, for estimating transition probabilities for the extrapolation period of the model. This search included retrospective database studies, registry studies, prospective observational studies and long-term follow-up studies (e.g., open-label follow-up or randomised clinical trials).

Systematic review process

A8. Please confirm if study selection, data extraction and quality assesment was undertaken independently by a minimum of two reviewers. If not, why?

For the clinical review:
As stated in section 6.2.1 – validity assessment, (p33) *"two independent reviewers screened all citations and full-text papers and any discrepancies in their decisions were resolved by a third reviewer."*

As stated in section 10.2.7 (appendix 2 pB-362) *"Data were extracted as required for completion of sections 6.3 - 6.5 by one reviewer and independently checked for accuracy by a second reviewer. Disagreements were resolved by consensus and by consulting a third reviewer where necessary."*

Data from the phase III ATLAS-ACS 2 TIMI 51 clinical trial were extracted and quality assessed by one reviewer and checked by a second reviewer due to the large quantity of information to be included from this trial to populate the clinical section of the submission.

For the cost-effectiveness, utility and resource use systematic review:

As stated in section 7.1.1, p144, for the economic and utility reviews, *"A single reviewer screened all citations and full-text papers followed by a second check by an independent reviewer."*

As stated in appendix 10, 'The data abstraction strategy' (pB-372) *"Data were extracted by one reviewer and independently checked for accuracy by a second reviewer."* The same process was followed for quality assessment.

A pragmatic decision was made to use a single reviewer for the cost-effectiveness, utility and resource use systematic review in order to be able to review the large body of published evidence in this area (12477 records to be screened) whilst still retaining an appropriate balance between sensitivity and precision in the search strategies.

A9. Please provide a detailed breakdown of all excluded full text studies (i.e. full reason for exclusion and reference) for the rivaroxaban systematic review.

Detailed list of excluded studies with reference has been provided below:

Clinical review:

Citation ID	Study name	Title	Publication date	Volume	Issue	Start page	End page	Journal name
Excluded as publication type not of interest (reviews, commentaries and letters)								
9	Krantz, 2013	The ATLAS ACS 2-TIMI 51 trial and the burden of missing data: (Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome ACS 2-thrombolysis in myocardial Infarction 51)	2013	62	9	777	781	Journal of the American College of Cardiology
434	Mega 2012	Low-Dose rivaroxaban reduced mortality in patients with a recent acute coronary syndrome	2012	156	10	JC5	3	Annals of Internal Medicine
Excluded as copy duplicates (conference abstracts already retrieved through database searches)								
19	Cavender, 2013	Rivaroxaban reduces spontaneous and large myocardial infarctions: Findings from the ATLAS ACS 2 - TIMI 51 trial	2013	61	10	E3		Journal of the American College of Cardiology
36	Pride, 2012	Temporal relationship between major hemorrhagic events and mortality among patients with recent acute coronary syndrome: Insights from ATLAS ACS 2-TIMI 51	2012	126	21			Circulation
43	Mega, 2012	Evaluation of cardiac events in ATLAS ACS 2-TIMI 51	2012	126	21			Circulation
58	Arora, 2013	Bayesian net-clinical benefit analysis of rivaroxaban in patients with acute coronary syndromes	2013	61	10	E1534		Journal of the American College of Cardiology
76	Gibson, 2012	A net clinical outcome analysis comparing fatal or irreversible ischemic and bleeding events in ATLAS ACS 2 - TIMI 51	2012	126	21			Circulation
129	Mega, 2013	Rivaroxaban in the setting of continued dual antiplatelet therapy: Findings from the atlas ACS 2-TIMI 51 trial	2013	61	10	E4		Journal of the American College of Cardiology
596	O'Donoghue 2013	The efficacy and safety of low-dose rivaroxaban with or without a proton pump inhibitor: Insights from the atlas ACS 2-TIMI 51 trial	2013	128	22			Circulation

Economic review:

itation ID	Study name	Title	Publication date	Volume	Issue	Start page	End page	Journal name
Excluded as publication type not of interest (reviews, commentaries and letters)								
1746	Parekh 2013	Aspirin in the secondary prevention of cardiovascular disease	2013	368	3	204	205	New England Journal of Medicine
2342	Tsang 2013	Ticagrelor (Brilinta) for secondary prevention of thrombotic events following acute coronary syndrome	2013	88	12	821	822	American Family Physician
3299	Eriksson 2005	Cost-effectiveness of clopidogrel plus aspirin versus aspirin alone	2005	143	6	464	465	Annals of Internal Medicine
5905	Braithwaite 2011	Identifying favorable-value cardiovascular health services	2011	17	6	431	438	American Journal of Managed Care
21533	Hamilton 2013	Diagnosis and management of acute coronary syndrome	2013	3	3	124	133	African Journal of Emergency Medicine
Excluded as study design or outcome type not of interest								
56	Akbarzadeh 2013	Predictive value of the fragmented QRS complex in 6-month mortality and morbidity following acute coronary syndrome	2013	6		399	404	International Journal of General Medicine
90	Amin 2013	The disutility of nuisance bleeding: Insights from the translate ACS registry	2013	62	18	B45		Journal of the American College of Cardiology
113	Ariely 2013	A model framework evaluating factors affecting the value of treatment one year following an acute coronary syndrome event	2013	16	3	A288		Value in Health
170	Bakaeen 2012	Coronary artery bypass graft patency: Residents versus attending surgeons	2012	94	2	482	488	Annals of Thoracic Surgery
240	Bernacki 2013	Targeting patients with multiple readmissions in the year after non-ST-elevation myocardial infarction could lower hospital readmission rates	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
246	Berry 2013	Physical fitness and risk for heart failure and coronary artery disease	2013	6	4	627	634	Circulation: Heart Failure
286	Borden 2012	Finding high-value healthcare in acute myocardial infarction	2012	5	3			Circulation: Cardiovascular Quality and Outcomes
299	Bradley 2012	Contemporary evidence about hospital strategies for reducing 30-day readmissions: A national study	2012	60	7	607	614	Journal of the American College of Cardiology
329	Bueno 2011	Clinical and economic impact of antithrombotic management patterns in acute coronary syndromes: Rationale and design of the epicor study	2011	12	1	102		Atherosclerosis Supplements
333	Bueno 2013	EPICOR (long-tErm follow-up of antithrombotic management Patterns in acute CORonary syndrome patients) study: Rationale, design, and baseline characteristics	2013	165	1	8	14	American Heart Journal

352	Buyck 2013	Informal caregiving and the risk for coronary heart disease: the Whitehall II study	2013	68	10	1316	1323	The journals of gerontology Series A, Biological sciences and medical sciences
387	Cavalieri 2013	Reimbursement systems and quality of hospital care: An empirical analysis for Italy	2013	111	3	273	289	Health Policy
409	Charlap 2011	Does family history of coronary artery disease affect prognosis in hospital survivors of a first acute myocardial infarction?	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
418	Chen 2013	National trends in heart failure hospitalization after acute myocardial infarction for medicare beneficiaries 1998-2010	2013	128	24	2577	2584	Circulation
424	Chen 2013	Heart failure and outcomes after acute coronary syndrome in a representative medicare population	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
505	Cooke 2010	Race is associated with the timeliness but not destination of transfer to revascularization hospitals after acute myocardial infarction	2010	181	1			American Journal of Respiratory and Critical Care Medicine
555	Davidson 2013	Centralized, stepped, patient preference based, depression treatment for patients after acute coronary syndrome. CODIACS vanguard randomized controlled trial	2013	34		796		European Heart Journal
556	Davidson 2013	Centralized, stepped, patient preference-based treatment for patients with post-acute coronary syndrome depression: Codiacs vanguard randomized controlled trial	2013	125		313		Cardiology (Switzerland)
599	Dharmarajan 2012	The timing of 30-day readmissions after hospitalization for heart failure and acute myocardial infarction	2012	5	3			Circulation: Cardiovascular Quality and Outcomes
600	Dharmarajan 2013	Diagnoses and timing of 30-day readmissions after hospitalization for heart failure, acute myocardial infarction, or pneumonia	2013	309	4	355	363	JAMA - Journal of the American Medical Association
601	Dharmarajan 2013	Risks of death and hospital readmission by time following hospitalization for heart failure and acute myocardial infarction	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
641	Dunlay 2013	Participation in cardiac rehabilitation is associated with reduced rehospitalization following acute myocardial infarction	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
677	Erbel 2012	Energy 1`000 subject registry with a thin strut bare metal stent with passive coating presenting one year mace data on pre-specified subgroups	2012	60		B183		Journal of the American College of Cardiology
684	Esquinas 2013	Rationale and methodology of the impact of continuous positive airway pressure on patients with ACS and nonsleepy OSA: The ISAACC trial	2013	36	9	495	501	Clinical Cardiology

703	Fenk 2013	Quality of life after myocardial infarction: Four-year follow-up of the german myocardial infarction family study	2013	61	10	E1460		Journal of the American College of Cardiology
732	Fosbol 2012	Persistence of evidence based medications after non-st elevation myocardial infarction among patients with medicare part D prescription coverage	2012	126	21			Circulation
753	Fuller 2012	Ticagrelor (brilinta), an antiplatelet drug for acute coronary syndrome	2012	37	10	562	568	P and T
763	Gagne 2012	Active monitoring of the comparative effectiveness and safety of prasugrel vs. clopidogrel in routine care	2012	21		238	239	Pharmacoepidemiology and Drug Safety
797	Ghorbanibirgani 2012	Quality of life in patients with myocardial infraction	2012	125	19	e896		Circulation
841	Graham 2013	Frailty and outcome in elderly patients with acute coronary syndrome	2013	29	12	1610	1615	Canadian Journal of Cardiology
995	Hussein 2013	Effect of carotid revascularization endarterectomy versus stenting trial results on performance of carotid artery stent placement and carotid endarterectomy	2013	44	2			Stroke
1606	Muggah 2012	The impact of multiple chronic diseases on ambulatory care use; a population based study in Ontario, Canada	2012	12		452		BMC health services research
10667	Zimetbaum 2004	Prognostic utility of comparative methods for assessment of ST-segment resolution after primary angioplasty for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial.	2004	44	6	1215	23	Journal of the American College of Cardiology
919	Heidenreich 2013	Relationship between 30-day readmission and 30-day mortality for heart failure and acute myocardial infarction	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
935	Hess 2012	Relationship of early physician follow-up and 30-day readmission after non-st-segment elevation myocardial infarction among older patients	2012	126	21			Circulation
936	Hess 2012	Unplanned 30-day readmission risk among patients with acute myocardial infarction: A report from translate-ACS	2012	126	21			Circulation
938	Hess 2013	Embedding a randomized clinical trial into an ongoing registry infrastructure: Unique opportunities for efficiency in design of the Study of Access site for Enhancement of Percutaneous Coronary Intervention for Women (SAFE-PCI for Women)	2013	166	3	421	428	American Heart Journal
940	Hess 2011	Use of hospital claims data to estimate the clinical and economic burden of acute coronary syndrome rehospitalizations in real-world clinical practice	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
960	Hoffmann 2012	Coronary CT angiography versus standard evaluation in acute chest pain	2012	367	4	299	308	New England Journal of Medicine
1016	Jackson 2011	Analysis of downstream encounter data drives quality interventions for acute coronary syndrome	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
21444	Doughty 2002	Acute myocardial infarction in the young - The University of Michigan experience	2002	143	1	56	62	American Heart Journal
879	Hakkinen 2012	Patient classification and hospital costs of care for acute myocardial infarction in nine	2012	21	SUPP	19	29	Health Economics

		European countries			L. 2			(United Kingdom)
1020	Jalbert 2013	Outcomes after carotid artery stenting in medicare beneficiaries, 2005-2009	2013	22		520		Pharmacoepidemiology and Drug Safety
1051	Jollis 2012	Systems of care for ST-segment-elevation myocardial infarction: A report from the American heart association`s mission: Lifeline	2012	5	4	423	428	Circulation: Cardiovascular Quality and Outcomes
1052	Jone 2012	Socio-economic status and outcome after percutaenous coronary intervention	2012	98		A25		Heart
1053	Jones 2013	The association between timely percutaneous coronary intervention for st-elevation myocardial infarction and emergency department crowding	2013	20	5	S309		Academic Emergency Medicine
1055	Jones 2013	Quality measure performance varies among hospitals by proportion of low income patients	2013	20	5	S14		Academic Emergency Medicine
1067	Joynt 2012	Which hospitals fail to improve readmission rates?	2012	5	3			Circulation: Cardiovascular Quality and Outcomes
1068	Joynt 2013	The impact of hospital closures on outcomes for myocardial infarction and stroke	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
1074	Jungerwirth 2014	Association of hospitalist presence and hospital-level outcome measures among medicare patients	2014	9	1	1	6	Journal of Hospital Medicine
1125	Khambatta 2013	The association between patient race, treatment, and outcomes of patients undergoing contemporary percutaneous coronary intervention: Insights from the blue cross blue shield of michigan cardiovascular consortium (BMC2)	2013	165	6	893	901	American Heart Journal
1134	Khare 2013	Is there a correlation between emergency department crowding measures and acute myocardial infarction mortality?	2013	62	4	S85		Annals of Emergency Medicine
1135	Khare 2013	Are crowding measures associated with acute myocardial infarction mortality?	2013	20	5	S14		Academic Emergency Medicine
1168	Kline 2013	Randomized trial of a quantitative, computerized pretest probability of acute coronary syndrome and pulmonary embolism in emergency department patients: Safety, radiation exposure, and cost of care	2013	11		431		Journal of Thrombosis and Haemostasis
1225	Kucharska-Newton 2013	Outpatient care following myocardial infarction-the atherosclerosis risk in communities (ARIC) study	2013	127	12			Circulation
1230	Kulkarni 2013	Regional cardiologist density and 30-day and 1-year mortality in acute myocardial infarction and heart failure	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
1261	Lambert-Kerzner 2012	Patient-centered adherence intervention after acute coronary syndrome hospitalization	2012	5	4	571	576	Circulation: Cardiovascular Quality and Outcomes

1270	Landman 2012	Emergency medical services and hospital collaboration in the care of patients with acute myocardial infarction	2012	5	3			Circulation: Cardiovascular Quality and Outcomes
1285	Laut 2013	Determinants and patterns of utilization of primary percutaneous coronary intervention across 12 European countries: 2003-2008	2013	168	3	2745	2753	International Journal of Cardiology
1286	Laut 2013	Persistent geographical disparities in the use of primary percutaneous coronary intervention in 120 European regions: Exploring the variation	2013	9	4	469	476	EuroIntervention
1366	Lin 2012	Age, dementia, and evidence-based medication use after admission for acute coronary syndrome	2012	15	7	A607		Value in Health
1372	Lindau 2011	Sexual problems experienced by women after an MI	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
1388	Loehr 2012	Race and gender group specific trends in length of stay for acute myocardial infarction: The atherosclerosis risk in communities (ARIC) study, 1987-2008	2012	125	10			Circulation
1402	Lovasi 2013	Residential relocation by older adults in response to incident cardiovascular health events	2013	127	12			Circulation
1422	Maeda 2013	Factors influencing the variation in hospital inpatient prices between public and private payers	2013	16	3	A208		Value in Health
1582	Moreyra 2012	Income distribution and readmission rates for acute coronary syndrome after PCI with drug eluting stents	2012	126	21			Circulation
1692	Okunji 2011	Effects of health services and patient characteristics on length of stay for inpatients with type 2 diabetes and myocardial infarction	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
1699	Oldridge 2014	The HeartQoL: Part I. development of a new core health-related quality of life questionnaire for patients with ischemic heart disease	2014	21	1	90	97	European journal of preventive cardiology
1722	Page 2012	Costs and outcomes associated with clopidogrel discontinuation in Medicare beneficiaries with acute coronary syndrome in the coverage gap	2012	4	1	67	74	Drug, Healthcare and Patient Safety
1768	Patton 2013	Cross (-walk) at your own peril! Comparing and contrasting cea results when individual-level utilities are derived from external mapping algorithms rather than actually observed responses	2013	16	7	A599		Value in Health
1819	Pocock 2013	Predictors of 1-year mortality at hospital discharge after ACS stemi and NSTE-ACS: A new risk score from the epicor study	2013	62	18	B69		Journal of the American College of Cardiology
1933	Rodriguez 2012	Young age single largest predictor of variation in acute myocardial infarction hospitalizations nationwide	2012	126	21			Circulation
1947	Roncella 2012	Short TErm Psychotherapy IN Acute Myocardial Infarction (STEP IN AMI) Trial. Final results from a randomized trial	2012	33		954		European Heart Journal
1976	Rymer 2013	Persistent use of evidence-based medications after discharge among patients with non-ST elevation myocardial infarction treated at academic versus non-academic hospitals	2013	6	3			Circulation: Cardiovascular Quality and

								Outcomes
1982	Saddier 2012	Validity of myocardial infarction and stroke diagnosis codes in a managed care organization database	2012	21		397	398	Pharmacoepidemiology and Drug Safety
1991	Salhi 2013	Access to Care for Patients With Time-Sensitive Conditions in Pennsylvania	2013					Annals of Emergency Medicine
1993	Salisbury 2011	Selecting antiplatelet therapy after percutaneous intervention for an acute coronary syndrome: Weighing the risks and benefits of prasugrel versus clopidogrel	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
2007	Saracini 2012	Pharmacogenetics of clopidogrel: Comparison between a standard and a rapid genetic testing	2012	16	6	500	503	Genetic Testing and Molecular Biomarkers
2036	Schopfer 2012	Barriers and facilitators associated with utilization of cardiac rehabilitation programs at va facilities	2012	126	21			Circulation
2046	Schuyler 2013	Combined Use of Warfarin and Oral P2Y12 Inhibitors in Patients With Atrial Fibrillation and Acute Coronary Syndrome	2013					Clinical Cardiology
2057	Seidl 2012	Empirical analysis shows reduced cost data collection may be an efficient method in economic clinicl trials	2012	15	7	A463		Value in Health
2073	Shah 2012	Incorporation of stress echocardiography into an acute chest pain service provides excellent feasibility, early triaging and accurate risk stratification of patients with suspected acute coronary syndrome but non-diagnostic ECG and normal 12-h troponin	2012	98		A55		Heart
2074	Shah 2012	Cardiac Troponin-T is sensitive and specific enough to replace CK-MB in the care of acute myocardial infarction at all time points	2012	138		A145		American Journal of Clinical Pathology
2102	Shi 2013	National and regional trends in hospitalizations for ischemic stroke after acute myocardial infarction in the United States: 1999-2010	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
2103	Shi 2013	National and regional trends in hospitalizations for hemorrhagic stroke after acute myocardial infarction in the United States: 1999-2010	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
2137	Sinnaeve 2012	Contemporary pre-hospital management of ACS patients: Results from the EPICOR study	2012	33		314		European Heart Journal
2138	Sinnaeve 2012	Availability of cath lab facilities and contemporary inter-hospital transfer patterns for the management of ACS patients: Findings from the EPICOR study	2012	33		145		European Heart Journal
2146	Skobel 2012	Prevalence of sleep apnea in cardiac rehabilitation facilities in Germany, results of the Reha-Sleep registry	2012	33		1056		European Heart Journal
2156	Smolderen 2011	Health care insurance, financial concerns in accessing care, and nonelective readmissions following acute myocardial infarction	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
2157	Smolderen 2011	Depression recognition and disease-specific health status in AMI patients: Insights from the triumph registry	2011	4	6			Circulation: Cardiovascular

								Quality and Outcomes
2159	Smulders 2013	The role of cardiovascular magnetic resonance imaging and computed tomography angiography in suspected non-ST-elevation myocardial infarction patients: Design and rationale of the CARdiovascular Magnetic rEsoNance imaging and computed Tomography Angiography (CARMENTA) trial	2013	166	6	968	975	American Heart Journal
2177	Sousa 2012	Does left ventricular dysfunction affect the response to cardiac rehabilitation after an acute coronary syndrome?	2012	125	19	e788		Circulation
2189	Sridhar 2012	Ten-year-trends in ST-elevation and non-ST-elevation myocardial infarction hospitalizations and outcomes in the us: Analysis of data from the nationwide in-patient sample 2000-2009	2012	5	3			Circulation: Cardiovascular Quality and Outcomes
2212	Steinke 2012	Sexual concerns of cardiac patients: A psychometric analysis	2012	33		1065		European Heart Journal
2213	Steinke 2013	Sexual counselling for individuals with cardiovascular disease and their partners: A Consensus Document from the American Heart Association and the ESC Council on Cardiovascular Nursing and Allied Professions (CCNAP)	2013	34	41	3217	3235 d	European Heart Journal
2252	Susco 2013	Outcome of acute myocardial infarction in obstructive sleep apnea	2013	61	10	E166		Journal of the American College of Cardiology
2379	Van 2012	One-year follow up of cardiac anxiety after a myocardial infarction: A latent class analysis	2012	73	5	362	368	Journal of Psychosomatic Research
2419	Volpp 2012	Choosing wisely: Low-value services, utilization, and patient cost sharing	2012	308	16	1635	1636	JAMA - Journal of the American Medical Association
2473	Widimsky 2010	Reperfusion therapy for ST elevation acute myocardial infarction in Europe: Description of the current situation in 30 countries	2010	31	8	943	957	European Heart Journal
2487	Wilson 2013	Factors associated with quality and costs for elderly patients with acute myocardial infarction who present to emergency departments	2013	20	5	S15		Academic Emergency Medicine
2519	Yang 2013	Does the risk reduction provided by longer durations of clopidogrel use after stent placement in Taiwan`s national health insurance	2013	22		125		Pharmacoepidemiology and Drug Safety
3100	Cohen 2006	Clinical characteristics, process of care, and outcomes of Hispanic patients presenting with non-ST-segment elevation acute coronary syndromes: Results from Can Rapid risk stratification of Unstable angina patients Suppress ADverse outcomes with Early implementation of the ACC/AHA Guidelines (CRUSADE)	2006	152	1	110	117	American Heart Journal
3153	Cziraky 2010	Evaluation of clinical and direct economic outcomes following an acute coronary event among patients with suboptimal HDL-C or triglycerides administered either statin and niacin extended-release or statin monotherapy	2010	13	7	A341		Value in Health
3167	Dauber 2011	The relationship between reputation and costs in healthcare markets	2011	112	5			Anesthesia and Analgesia
3223	Dickerson 2001	Are all (beta)-blockers equally effective in reducing mortality after acute myocardial infarction (AMI)?	2001	50	8	652		Journal of Family Practice

3353	Fisher 2003	The implications of regional variations in Medicare spending. Part 1: The content, quality, and accessibility of care	2003	138	4	273	287	Annals of Internal Medicine
3354	Fisher 2003	The implications of regional variations in Medicare spending. Part 2: Health outcomes and satisfaction with care	2003	138	4	288	298	Annals of Internal Medicine
3375	Fowler 2010	Comparative performance of risk adjustment measures in a sample of commercially-insured patients under age 65-two simple measures outperform current standards	2010	13	3	A4		Value in Health
3493	Gregori 2008	Proper modeling strategies selection for the assessment of post-infarction costs	2008	129	1	53	58	International Journal of Cardiology
3517	Guzauskas 2010	A benefit-risk assessment of using CYP2C19 genotype information to guide antiplatelet therapy in patients with acute coronary syndrome	2010	13	3	A152	A153	Value in Health
3705	Kaakeh 2010	Assessment of the association between summary symptom measures and health status of patients with ischemic heart disease	2010	13	7	A362		Value in Health
3811	Kramer 2006	National evaluation of adherence to (beta)-blocker therapy for 1 year after acute myocardial infarction in patients with commercial health insurance	2006	152	3	454	460	American Heart Journal
4144	Monti 2012	Care pathway disparities in patients with cocaine induced myocardial infarction: A preliminary report from the CPAC study group	2012	7		S63	S64	Journal of Hospital Medicine
4159	Morrow 2006	Evaluation of a novel anti-ischemic agent in acute coronary syndromes: Design and rationale for the Metabolic Efficiency with Ranolazine for Less Ischemia in Non-ST-elevation acute coronary syndromes (MERLIN)-TIMI 36 trial (DOI:10.1016/j.ahj.2006.01.004)	2006	152	2	400	408	American Heart Journal
4259	Oldridge 2005	The Euro Cardio-QoL Project. An international study to develop a core heart disease health-related quality of life questionnaire, the HeartQoL	2005	12	2	87	94	European Journal of Cardiovascular Prevention and Rehabilitation
4585	Schneeweiss 2007	Adherence to (beta)-blocker therapy under drug cost-sharing in patients with and without acute myocardial infarction	2007	13	8	445	452	American Journal of Managed Care
4784	Sueta 2001	Hospital interventions improve care of North Carolina Medicare patients with acute myocardial infarction	2001	62	2	69	73	North Carolina medical journal
4793	Sumanen 2004	Occurrence of symptoms and depressive mood among working-aged coronary heart disease patients	2004	2				Health and Quality of Life Outcomes
4886	Tunceli 2011	Re-hospitalization rates of acute coronary syndrome patients in real world clinical practice: Observations from a national administrative claims data	2011	14	3	A52		Value in Health
4902	Valderrama 2011	Regional variation in emergency department visits for acute myocardial infarction-nationwide emergency department sample, 2008	2011	124	21			Circulation
5113	Zhao 2012	Readmission rates among patients with acute myocardial infarction and treated with aspirin with or without clopidogrel during hospitalization	2012	15	4	A133		Value in Health
5843	Boggon 2011	Resource use in patients with acute coronary syndrome - An observational study across secondary and primary care in a UK population	2011	14	7	A382		Value in Health
6218	Choudhry 2011	Full coverage for preventive medications after myocardial infarction	2011	365	22	2088	2097	New England Journal of Medicine
6311	Corfield 2011	Recent evidence on use of statins - Implications for when to offer a statin and which one to offer	2011	286	7645	343		Pharmaceutical Journal
6481	Delgado-	Health economic evaluation of ticagrelor in patients with acute coronary patients (ACS)	2011	14	7	A372		Value in Health

	Ortega 2011	based on the plato study from a Spanish health care perspective						
6675	Erickson 2009	Satisfaction with current health status in patients with a history of acute coronary syndrome	2009	25	3	683	689	Current Medical Research and Opinion
7176	Guzauskas 2012	A risk-benefit assessment of prasugrel, clopidogrel, and genotype-guided therapy in patients undergoing percutaneous coronary intervention	2012	91	5	829	837	Clinical Pharmacology and Therapeutics
7195	Hakkinen 2011	Analysing current trends in care of acute myocardial infarction using PERFECT data	2011	43	SUPP L. 1	S14	S21	Annals of Medicine
7221	Hampton 2011	The end of clinical freedom	2011	40	4	848	849	International Journal of Epidemiology
7688	Kaestner 2010	Evidence on the efficacy of inpatient spending on medicare patients	2010	88	4	560	594	Milbank Quarterly
8851	Noveanu 2009	What anesthesiologists should know about B-type natriuretic peptide	2009	75	12	698	702	Minerva Anestesiologica
9515	Sargent 2012	Smoking restrictions and hospitalization for acute coronary events in Germany	2012	101	3	227	235	Clinical Research in Cardiology
10225	Vandereyt 2012	Psychometric properties of the Flemish version of the MacNew heart disease health-related quality of life questionnaire	2012	67	1	31	39	Acta Cardiologica
10660	Spertus 2009	Patient health status and costs in heart failure: insights from the eplerenone post-acute myocardial infarction heart failure efficacy and survival study (EPHESUS).	2009	119	3	398	407	Circulation
10697	Nicholl 2004	A randomised controlled trial to measure the effect of chest pain unit care upon anxiety, depression, and health-related quality of life [ISRCTN85078221].	2004	2		39		Health and quality of life outcomes
10953	Herrmann-Lingen 2011	A stepwise psychotherapy intervention for reducing risk in coronary artery disease (SPIRR-CAD) - rationale and design of a multicenter, randomized trial in depressed patients with CAD.	2011	71	4	215	22	Journal of psychosomatic research
10991	Ovbiagele 2012	Utility of Framingham Coronary Heart Disease Risk Score for predicting cardiac risk after stroke.	2012	43	11	2942	7	Stroke; a journal of cerebral circulation
11463	Henry 2013	Long-term survival in patients with refractory angina.	2013 Sep	34	34	2683	8	Eur Heart J
21296	Bach 2004	The effect of routine, early invasive management on outcome for elderly patients with non-ST-segment elevation acute coronary syndromes	2004	141	3	186	56	Annals of Internal Medicine
21297	Bagai 2013	In-hospital ADP receptor inhibitor switching in myocardial infarction patients treated with percutaneous coronary intervention: Insights from the national cardiovascular data registry(registered trademark)	2013	128	22			Circulation
21316	Bergmeijer 2012	POPular Risk Score for individualized antiplatelet therapy following non-urgent PCI	2012	33		312	313	European Heart Journal
21358	Carstensen 2007	Field triage to primary angioplasty combined with emergency department bypass reduces treatment delays and is associated with improved outcome	2007	28	19	2313	2319	European Heart Journal
21359	Cecchini 2013	Assessing the health and economic impact of fiscal measures	2013	6		11		Obesity Facts
21377	Chew 2010	Six-month survival benefits associated with clinical guideline recommendations in acute coronary syndromes	2010	96	15	1201	1206	Heart

21385	Choudhry 2013	The impact of eliminating medication copayments on disparities in cardiovascular care	2013	28		S217	S218	Journal of General Internal Medicine
21403	Coopersmith 2012	A comparison of critical care research funding and the financial burden of critical illness in the United States	2012	40	4	1072	1079	Critical Care Medicine
21407	Crim 2013	Use of the TIMI risk score in the emergency department discriminates acute coronary syndrome among chest pain patients with known coronary artery disease	2013	128	22			Circulation
21416	Darling 2014	Point-of-care assessment of platelet reactivity in the emergency department may facilitate rapid rule-out of acute coronary syndromes: A prospective cohort pilot feasibility study	2014	4	1			BMJ Open
21420	De 2009	Increased mortality and morbidity due to acute myocardial infarction in a Public Hospital, in Feira de Santana, Bahia	2009	93	2	97	104	Arquivos Brasileiros de Cardiologia
21434	Dodson 2013	National trends in rehospitalization for bleeding after acute myocardial infarction in older patients, 1999-2010	2013	128	22			Circulation
21435	Doll 2013	Use and effectiveness of cardiac rehabilitation programs among patients referred after acute myocardial infarction	2013	128	22			Circulation
21436	Doll 2013	Change in angina symptom status after acute myocardial infarction and its association with readmission risk: An analysis of the triumph registry	2013	128	22			Circulation
21437	Doltra 2014	Long-term follow-up of coronary MR and CT angiography for prediction of cardiac events	2014	16				Journal of Cardiovascular Magnetic Resonance
21446	Droz 2013	The 3.5-year mortality impact of drugs in secondary prevention of myocardial infarction in real-life (interim analysis of the eole cohort)	2013	22		48	49	Pharmacoepidemiology and Drug Safety
21448	Duru 2012	The medicare part D low-income cost subsidy (LICS) and adherence to medications for secondary prevention of cardiovascular disease	2012	27		S324		Journal of General Internal Medicine
21464	Federspiel 2013	Stemi occurring in hospitalized patients is associated with less aggressive care and higher mortality than outpatient stemi	2013	128	22			Circulation
21478	Fosbol 2013	Early cessation of ADP receptor inhibitors among acute myocardial infarction patients treated with PCI: Insights from the Translate-ACS study	2013	61	10	E1592		Journal of the American College of Cardiology
21494	Garcia 2011	Hospital characteristics and mortality in elderly heart attack	2011	37		S223		Intensive Care Medicine
21500	Gerber 2008	Interaction between income and education in predicting long-term survival after acute myocardial infarction	2008	15	5	526	532	European Journal of Cardiovascular Prevention and Rehabilitation
21503	Gilby 2003	Meeting National Service Framework goals for patients presenting with acute myocardial infarction	2003	20	2	156	157	Emergency Medicine Journal
21517	Grodzinsky 2013	Frequency of angina after acute myocardial infarction among patients with nonobstructive coronary artery disease	2013	128	22			Circulation
21522	Gupta 2014	Characteristics, management, and outcomes of cocaine-positive patients with acute coronary syndrome (from the National Cardiovascular Data Registry)	2014	113	5	749	756	American Journal of Cardiology
21537	Hanmer 2012	Is insurance status associated with the transfer of hospitalized patients?	2012	27		S236		Journal of General Internal Medicine

21565	Huang 2007	Effect of socioeconomic status on acute myocardial infarction outcomes	2007	14	7	380+386		Journal of Clinical Outcomes Management
21598	Jones 2011	Limitations of self-reported readmission data after acute myocardial infarction: Insights from the triumph registry	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
21603	Karve 2013	Contemporary use of ticagrelor in interventional practice: Insights from bmc2	2013	128	22			Circulation
21621	Kleiman 2002	Prospective analysis of creatine kinase muscle-brain fraction and comparison with troponin T to predict cardiac risk and benefit of an invasive strategy in patients with non-ST-elevation acute coronary syndromes	2002	40	6	1044	1050	Journal of the American College of Cardiology
21689	Mafi 2012	Evidenced-based decision support to enhance stress test ordering: A QI project	2012	27		S524	S525	Journal of General Internal Medicine
21705	Matsumoto 2011	Prognostic utility of heart type fatty acid binding protein after acute myocardial infarction	2011	124	21			Circulation
21719	Mehta 2011	Association of mortality with years of education in patients with st-segment elevation myocardial infarction treated with fibrinolysis	2011	57	2	138	146	Journal of the American College of Cardiology
21720	Mehta 2005	Effect of glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction: The CREATE-ECLA randomized controlled trial	2005	293	4	437	446	Journal of the American Medical Association
21724	Merono 2013	Comparison of two different risk scores with the aim of early hospital discharge in patients with st-elevation myocardial infarction	2013	126		386		Cardiology (Switzerland)
21855	Rodriguez 2013	Young hispanic women experience higher in-hospital mortality following an acute myocardial infarction	2013	128	22			Circulation
21880	Schiele 2011	Constructing a composite quality score for the care of acute myocardial infarction patients at discharge	2011	32		674		European Heart Journal
21881	Schiele 2012	Unjustified age and gender differences in discharge treatment after acute ST elevation myocardial infarction. A French nationwide assessment of quality of care	2012	33		467		European Heart Journal
21896	Shaw 2008	Importance of socioeconomic status as a predictor of cardiovascular outcome and costs of care in women with suspected myocardial ischemia. Results from the national institutes of health, national heart, lung and blood institute-sponsored Women`s Ischemia Syndrome Evaluation (WISE)	2008	17	7	1081	1092	Journal of Women`s Health
21986	Vigen 2013	Patterns of outpatient follow-up after acute myocardial infarction: Follow-up frequency is associated with utilization of evidence-based therapies	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
22014	West 2013	Is there a need for specialist cardiac care for patients with non-st elevation myocardial infarction? An analysis of 85 780 patient episodes from the minap database 2008-2009	2013	99		A17	A18	Heart
22082	Meyers 2014	Determinants of health after hospital discharge: rationale and design of the Vanderbilt Inpatient Cohort Study (VICS).	2014	14		10		BMC Health Serv Res
22092	Marzolini 2013	Outcomes associated with cardiac rehabilitation participation in patients with musculoskeletal comorbidities.	2013 Dec	49	6	775	83	Eur J Phys Rehabil Med

22099	Jungerwirth 2014	Association of hospitalist presence and hospital-level outcome measures among medicare patients.	2014 Jan	9	1	1	6	J Hosp Med
22137	Coloma 2013	Drug-induced acute myocardial infarction: identifying `prime suspects` from electronic healthcare records-based surveillance system.	2013	8	8	e72148		PLoS One
22213	Cannon 2013	Reduction in first and recurrent cardiovascular events with ticagrelor compared with clopidogrel in the PLATO Study.	2013	127	6	673	80	Circulation
22225	Yan 2011	Prognostic significance of electrocardiographic-determined left ventricular hypertrophy and associated ST-segment depression in patients with non-ST-elevation acute coronary syndromes.	2011	161	5	878	85	American heart journal
22272	Bourassa 2002	Long-term survival differences among low-anxious, high-anxious and repressive copers enrolled in the Montreal heart attack readjustment trial.	2002	64	4	571	9	Psychosomatic medicine
22343	Henderson 2012	Rehabilitation after myocardial infarction trial (RAMIT): multi-centre randomised controlled trial of comprehensive cardiac rehabilitation in patients following acute myocardial infarction.	2012	98	8	637	44	Heart (British Cardiac Society)
22410	Tavazzi 1997	Attenuation of unfavorable remodeling by exercise training in postinfarction patients with left ventricular dysfunction: results of the Exercise in Left Ventricular Dysfunction (ELVD) trial.	1997	96	6	1790	7	Circulation
22488	Poirier 2012	Effectiveness of a Pedometer-Based Program Using a Socio-cognitive Intervention on Physical Activity and Quality of Life in a Setting of Cardiac Rehabilitation.	2012	28	1	27	32	Canadian Journal of Cardiology
22856	Halvorsen 2011	Health and cost consequences of early versus late invasive strategy after thrombolysis for acute myocardial infarction.	2011	18	5	717	23	European journal of cardiovascular prevention and rehabilitation
44	Agewall 2012	Low self-estimated quality of life after myocardial infarction and future cardiovascular risk	2012	33		1057	1058	European Heart Journal
67	Albert 2012	Matched-pairs analysis of results and quality of life after total arterial multi-vessel revascularization via antero-lateral mini-thoracotomy compared to sternotomy	2012	33		68		European Heart Journal
188	Barot 2013	Drug utilization in emergency medicine department at a tertiary care teaching hospital: A prospective study	2013	4	4	78	81	Journal of Basic and Clinical Pharmacy
939	Hess 2011	Effect of a decision aid on patient knowledge, patient satisfaction, safety, and resource use in emergency department patients presenting with chest pain: A randomized trial	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
220	Bekke-Hansen 2012	Faith and use of complementary and alternative medicine among heart attack patients in a secular society	2012	20	5	306	315	Complementary Therapies in Medicine
680	Eriksson 2013	Changes in hope and health-related quality of life in couples following acute myocardial infarction: A quantitative longitudinal study	2013	27	2	295	302	Scandinavian Journal of Caring Sciences
Studies with quality of life data only								
63	Al-Smadi 2013	Acute myocardial infarction patients treated by primary angioplasty lack personal control over their illness and display less risk factor modification compared to other treatment modalities	2013	34		1108		European Heart Journal

71	Alexander 2011	Frail older adults at risk for loss of independence following MI	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
85	Alter 2013	Socioeconomic Status, Functional Recovery, and Long-Term Mortality among Patients Surviving Acute Myocardial Infarction	2013	8	6			PLoS ONE
91	Amin 2011	Complete vs. `Culprit` only revascularization in stemi patients with multivessel coronary artery disease: Practice patterns, predictors of complete revascularization and impact on health status outcomes	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
92	Amin 2013	Nuisance bleeding with prolonged dual antiplatelet therapy after acute myocardial infarction and its impact on health status	2013	61	21	2130	2138	Journal of the American College of Cardiology
95	Anatchkova 2012	Psychosocial risk profiles in patients with acute coronary syndrome: First findings from trace-core	2012	5	3			Circulation: Cardiovascular Quality and Outcomes
116	Ariza-Sole 2013	Impact of frailty and functional status on outcomes in elderly patients with st-segment elevation myocardial infarction undergoing primary angioplasty: Rationale and design of the iffaniam study	2013	36	10	565	569	Clinical Cardiology
122	Arnold 2011	Perceived stress in acute myocardial infarction: Associations with long-term health status outcomes	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
123	Arnold 2012	Perceived stress in myocardial infarction: Long-term mortality and health status outcomes	2012	60	18	1756	1763	Journal of the American College of Cardiology
737	Fourcade 2012	Acute coronary syndrome related to sport: Profile and follow-up of a 25 cases prospective series with regard to quality of life	2012	33		293		European Heart Journal
908	Havranek 2011	Social network characteristics are associated with long term outcomes after myocardial infarction	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
1058	Jones 2013	The SAQ-7: A short version of the seattle Angina questionnaire	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
1187	Koltowski 2012	Lower periprocedural quality of life in stemi patients undergoing PCI with femoral access	2012	60		B119	B120	Journal of the American College of Cardiology
1206	Krawczyk 2012	The sicker refuse getting healthier: Cardiac rehabilitation acceptance paradox	2012	33		764		European Heart Journal
1333	Leung 2013	Health-related quality of life in patients with premature acute coronary syndrome: Does biological sex really matter?	2013	29	10	S277	S278	Canadian Journal of Cardiology

1625	Najafi 2013	Factor structure of the world health organization`s quality of life questionnaire-BREF in patients with coronary artery disease	2013	4	9	1052	1058	International Journal of Preventive Medicine
1698	Oldridge 2014	The HeartQoL: Part II. validation of a new core health-related quality of life questionnaire for patients with ischemic heart disease	2014	21	1	98	106	European journal of preventive cardiology
1994	Salisbury 2012	Incidence of non-cardiac chest pain in follow-up after acute myocardial infarction and association with clinical outcomes	2012	5	3			Circulation: Cardiovascular Quality and Outcomes
2070	Shaffer 2012	Elevated depressive symptoms predict worsening health-related quality of life following an acute coronary syndrome	2012	74	3	A66		Psychosomatic Medicine
2078	Shah 2012	Financial Stress and Outcomes after Acute Myocardial Infarction	2012	7	10			PLoS ONE
2086	Sharma 2013	Distressed personality (Type D): Pre chance to increase the risk of coronary events?	2013	65		S85		Indian Heart Journal
2120	Siebens 2012	Type D (distressed) personality predicts impaired health status in patients presenting with chest pain suggestive of an acute coronary syndrome	2012	33		179		European Heart Journal
2124	Silva 2013	Quality of life of patients after acute coronary syndrome	2013	45		46		Atencion Primaria
2179	Sousa 2013	Functional capacity benefits of cardiac rehabilitation after acute coronary syndrome are sustained in time and independent of left ventricle systolic function	2013	34		1084	1085	European Heart Journal
2338	Trzos 2012	Frequency of returning to work after ST segment elevation myocardial infarction	2012	33		766		European Heart Journal
2360	Tytova 2013	Depressive disorders in acute heart failure	2013	12		S127		European Journal of Heart Failure
2758	Arnold 2011	Translational research investigating underlying disparities in acute myocardial infarction patients` health status (TRIUMPH) design and rationale of a prospective multicenter registry	2011	4	4	467	476	Circulation: Cardiovascular Quality and Outcomes
3233	Dobias 2011	Long-term effects of spinal cord stimulation and video-assisted thoracoscopic sympathectomy in patients with refractory angina pectoris - 10 years experience	2011	32		574		European Heart Journal
3242	Dominiak 2011	Early rehabilitation in acute coronary syndrome patients improves self-assessing quality of life but not depression status	2011	32		388	389	European Heart Journal
3422	Garcia 2011	Prognosis and quality of life of elderly patients with heart attack	2011	37		S52		Intensive Care Medicine
3423	Garcia 2011	Myocardial infarction without ST elevation in octogenarians: Prognosis and quality of life	2011	37		S53		Intensive Care Medicine
3582	Hiatt 2004	Randomized trial of AT-1015 for treatment of intermittent claudication. A novel 5-hydroxytryptamine antagonist with no evidence of efficacy	2004	9	1	18	25	Vascular Medicine
3645	Ioannidis 2012	Prognostic value of Killip classification in terms of health-related quality of life	2012	16		S65	S66	Critical Care
3654	Izadnegahdar 2011	Sex differences in one month health status of young adults post acute myocardial infarction: Preliminary results from AMI55 study	2011	27	5	S152		Canadian Journal of Cardiology

3677	Jenkinson 2011	Development and validation of a short pro measure of health status for individuals with acute myocardial infarction: the myocardial infarction dimensional assessment scale (MIDAS)	2011	14	3	A52		Value in Health
3692	Johnston 2012	Quality of life in patients under investigation of angina pectoris	2012	46		14		Scandinavian Cardiovascular Journal
3775	Kjellstrom 2011	Health-related quality of life predicts survival in patients with type 2 diabetes and myocardial infarction: A report from the DIGAMI2 trial	2011	54		S9		Diabetologia
3893	Leifheit-Limson 2011	Major life events prior to hospitalization for acute myocardial infarction are associated with worse outcomes at 1 year	2011	124	21			Circulation
3974	Luo 2010	An evaluation of the statistical efficiency of the us population median-based EQ-5D index using data from the medical expenditure panel survey	2010	13	3	A22		Value in Health
4068	McGowan 2011	The relationship between psychological factors and impaired health-related quality of life post ST-elevation myocardial infarction	2011	97		A11		Heart
4210	Neil 2011	Health-related quality of life using the HeartQoL, a new questionnaire for patients with angina, myocardial infarction or ischemic heart failure	2011	18	1	S56		European Journal of Cardiovascular Prevention and Rehabilitation
4260	Oliveira;Rocha 2011	Psychological distress in cardiac rehabilitation: A dual relationship	2011	10		S240	S241	European Journal of Heart Failure, Supplement
4276	Ozer 2011	Sexual dysfunction and quality of life in female and male patients with myocardial infarction	2011	8		424		Journal of Sexual Medicine
4432	Rangel 2011	Predictors of poor compliance to a cardiac rehabilitation program	2011	32		386		European Heart Journal
4433	Rangel 2011	Predictors of compliance to a cardiac rehabilitation program	2011	10		S190	S191	European Journal of Heart Failure, Supplement
4546	Sales 2004	Assessing response bias from missing quality of life data: the Heckman method	2004	2				Health and Quality of Life Outcomes
4680	Simpson 2005	Quality of life after acute myocardial infarction: a comparison of diabetic versus non-diabetic acute myocardial infarction patients in Quebec acute care hospitals	2005	3				Health and Quality of Life Outcomes
4927	Venskutonyte 2011	Patient reported quality of life predicts long-term outcome in patients with type 2 diabetes and myocardial infarction. A report from the DIGAMI 2 trial	2011	32		541		European Heart Journal
5753	Bergman 2011	Does one`s sense of coherence change after an acute myocardial infarction? A two-year longitudinal study in Sweden	2011	13	2	156	163	Nursing & health sciences
6231	Chu 2010	Effect of Xuefu Zhuyu Capsule on the symptoms and signs and health-related quality of life in the unstable angina patients with blood-stasis syndrome after percutaneous coronary intervention: A randomized controlled trial	2010	16	5	399	405	Chinese Journal of Integrative Medicine
6447	de 2011	Patient-centred assessment of social support, health status and quality of life in patients with acute coronary syndrome	2011	21	2	21	29	Canadian journal of cardiovascular nursing = Journal canadien en soins infirmiers cardio-

								vasculaires
6592	Duenas 2011	Gender differences and determinants of health related quality of life in coronary patients: A follow-up study	2011	11				BMC Cardiovascular Disorders
21429	Dias 2012	Acute myocardial infarction with ST elevation and withoutST elevation: Impact on quality of life	2012	27	1	S174	S175	European Journal of Epidemiology
631	Dreyer 2013	Sex differences in pre-event health status of young patients with acute myocardial infarction: The virgo study	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
Excluded as population not of interest								
397	Chamberlain 2013	Atrial fibrillation in myocardial infarction patients: Impact on health care utilization	2013	166	4	753	759	American Heart Journal
506	Cooke 2011	Geographic variation in critical care bed supply and intensive care unit case mix: Does bed supply drive utilization?	2011	183	1			American Journal of Respiratory and Critical Care Medicine
22175	Kim 2013	Risk factors, incidence, and effect of cardiac failure and myocardial infarction in aneurysmal subarachnoid hemorrhage patients.	2013 Sep	73	3	450	7; quiz 457	Neurosurgery
76	Ali 2013	Feasibility of pre-hospital chest pain triage at home or in the ambulance by paramedics using the HEART score based upon a single high-sensitive troponin T analysis	2013	34		734		European Heart Journal
3462	Gohler 2009	Utility estimates for decision-analytic modeling in chronic heart failure - Health states based on New York Heart Association classes and number of rehospitalizations	2009	12	1	185	187	Value in Health
21330	Borah 2013	Impact of atrial fibrillation on healthcare costs after myocardial infarction-a community cohort study	2013	128	22			Circulation
78	Allen 2013	Quality of life impact of cardiovascular and affective conditions among older residents from urban and rural communities	2013	11	1			Health and Quality of Life Outcomes
138	Auer 2012	Horizon and perspective: Critical choices in estimating cost-effectiveness of cardiovascular prevention	2012	126	21			Circulation
154	Bachmann 2012	Association of midlife fitness with healthcare charges in later life: The cooper center longitudinal study	2012	5	3			Circulation: Cardiovascular Quality and Outcomes
410	Charlton 2013	Impact of deprivation on occurrence, outcomes and health care costs of people with multiple morbidity	2013	18	4	215	223	Journal of Health Services Research and Policy
457	Choudhry 2012	The impact of reducing cardiovascular medication copayments on health spending and resource utilization	2012	60	18	1817	1824	Journal of the American College of Cardiology
557	Davidson 2013	Centralized, stepped, patient preference-based treatment for patients with post-acute coronary syndrome depression: CODIACS vanguard randomized controlled trial	2013	173	11	997	1004	JAMA Internal Medicine
568	De 2012	Cost-effectiveness of optimizing prevention in patients with coronary heart disease: The EUROASPIRE III health economics project	2012	33	22	2865	2872	European Heart Journal

588	Den 2013	Long-term health benefits and costs of measurement of carotid intima-media thickness in prevention of coronary heart disease	2013	31	4	782	790	Journal of Hypertension
839	Graffigna 2013	Off pump coronary artery bypass surgery in octogenarians: Long term results and quality of life	2013	34		172		European Heart Journal
926	Henzler 2013	Coronary computed tomography and triple rule out CT in patients with acute chest pain and an intermediate cardiac risk for acute coronary syndrome: Part 2: Economic aspects	2013	82	1	106	111	European Journal of Radiology
991	Huffman 2013	Design and baseline data from the Management of Sadness and Anxiety in Cardiology (MOSAIC) randomized controlled trial	2013	36	2	488	501	Contemporary Clinical Trials
992	Hulten 2013	Cost and resource utilization associated with use of computed tomography to evaluate chest pain in the emergency department the rule Out Myocardial Infarction Using Computer Assisted Tomography (ROMICAT) study	2013	6	5	514	524	Circulation: Cardiovascular Quality and Outcomes
1120	Kern 2013	Health care utilization and cost among type 2 diabetes mellitus (T2DM) patients with cardiovascular disease (CVD) or cardiovascular disease risk factors	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
1140	Kilcup 2013	Postdischarge pharmacist medication reconciliation: Impact on readmission rates and financial savings	2013	53	1	78	84	Journal of the American Pharmacists Association
1141	Kilic 2014	Understanding variability in hospital-specific costs of coronary artery bypass grafting represents an opportunity for standardizing care and improving resource use	2014	147	1	109	115	Journal of Thoracic and Cardiovascular Surgery
2037	Schopfer 2013	Utilization of cardiac rehabilitation programs among veterans	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
1161	Kirkfeldt 2013	Myocardial infarction in Danish ICD patients: Risk, predictors and healthcare costs	2013	34		259		European Heart Journal
1179	Kohn 2013	Short-Term Consequences of Angiographically-Confirmed Coronary Stent Thrombosis	2013	8	10			PLoS ONE
1305	Lee 2012	Comorbid illness profiles predict greater costs: An analysis of 417,477 heart failure admissions	2012	18	8	S76		Journal of Cardiac Failure
1409	Luengo-Fernandez 2012	A population-based study of hospital care costs during 5 years after transient ischemic attack and stroke	2012	43	12	3343	3351	Stroke
1495	Mccomb 2013	Complete heart block: Audit of potential safety and cost effectiveness of direct transfer of patients needing pacing to a pacing center	2013	15		ii150		Europace
1511	McNulty 2012	Canadian cardiovascular society angina classification and change in quality of life following percutaneous coronary intervention for stable coronary disease	2012	126	21			Circulation
1602	Muedra 2013	Postoperative costs associated with outcomes after cardiac surgery with extracorporeal circulation: Role of antithrombin levels	2013	27	2	230	237	Journal of Cardiothoracic and Vascular Anesthesia

1650	Ng 2013	Regional variation in the receipt of coronary revascularization following diagnostic catheterization in British Columbia	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
1811	Pirk 2012	Increasing costs for german social health insurance (SHI) funds by abandonment of pentaerithrityltetranitrat (PETN) for patients with coronary heart disease (CHD)?-A cost analysis based on sick fund data	2012	15	7	A368		Value in Health
1834	Porten 2013	Influence of recognized risk factors and coronary artery calcium score on cardiovascular events and healthcare resource utilization	2013	61	10	E1547		Journal of the American College of Cardiology
1958	Rosselli 2013	Costs and consequences of oral anticoagulation in atrial fibrillation in Colombia	2013	16	7	A702		Value in Health
1973	Rutledge 2013	Anxiety associations with cardiac symptoms, angiographic disease severity, and healthcare utilization: The NHLBI-sponsored Women`s Ischemia Syndrome Evaluation	2013	168	3	2335	2340	International Journal of Cardiology
2053	Sedlis 2013	Health status and quality of life in patients with stable coronary artery disease and chronic kidney disease treated with optimal medical therapy or percutaneous coronary intervention (post Hoc findings from the COURAGE trial)	2013	112	11	1703	1708	American Journal of Cardiology
2075	Shah 2012	Chest pain unit using thrombolysis in myocardial infarction score risk stratification: An impact on the length of stay and cost Savings	2012	11	4	206	210	Critical Pathways in Cardiology
2140	Sipotz 2013	Health related quality of life and mental distress after PCI: Restoring a state of equilibrium	2013	11	1			Health and Quality of Life Outcomes
2198	Stauber 2012	The contribution of positive affect to quality of life in patients with coronary heart disease	2012	74	3	A29		Psychosomatic Medicine
2217	Stephenson 2013	The effects of compounded bioidentical transdermal hormone therapy on hemostatic, inflammatory, immune factors; cardiovascular biomarkers; quality-of-life measures; and health outcomes in perimenopausal and postmenopausal women	2013	17	1	74	85	International journal of pharmaceutical compounding
2248	Sunderland 2013	Compa rison of dab igat ran etexilate versus warfarin, asprin & no treatment for stroke prevention in atrial fibrillat ion in England, United Kingdom, ove r 5 years	2013	16	7	A519		Value in Health
873	Gupta 2012	A study on quality of life in patients following myocardial infarction	2012	56	1	28	35	Indian Journal of Physiology and Pharmacology
2322	Todorova 2012	Direct medical costs of diabetes-related complications in India	2012	15	7	A662		Value in Health
2323	Todorova 2012	Evaluating the clinical and cost outcomes associated with improving glycemic control in type 2 diabetes patients in India	2012	15	7	A501		Value in Health
2324	Todorova 2012	Estimating the costs of diabetes mellitus: An analysis in Malaysia	2012	15	7	A662		Value in Health
2357	Twerenbold 2012	Economic benefit of copeptin for rapid rule out of acute myocardial infarction	2012	33		622		European Heart Journal
2368	Vaccaro 2012	Addition of either pioglitazone or a sulfonylurea in type 2 diabetic patients inadequately controlled with metformin alone: Impact on cardiovascular events: A randomized controlled trial	2012	22	11	997	1006	Nutrition, Metabolism and Cardiovascular Diseases
2464	Werdan 2013	Long-term therapy with ivabradine in combination with beta-blockers in patients with stable angina pectoris and effect of beta-blocker background dose: Results from the	2013	34		175	176	European Heart Journal

		ADDITIONS 1-year follow-up						
2514	Yan 2012	Cost-effectiveness of transcatheter left atrial appendage occlusion compared with 5 alternative anticoagulation strategies for stroke prevention in atrial fibrillation: A Markov decision analysis	2012	60		B26		Journal of the American College of Cardiology
2560	Zhang 2011	Risk factor analysis of clinically significant improvements in quality of life measures for stable coronary patients	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
3036	Chamberlain 2012	Impact of atrial fibrillation on health care utilization among patients with myocardial infarction	2012	15	4	A130		Value in Health
3044	Chase 2011	Epidemiology and resource utilization among ED patients with dizziness	2011	18	5	S227		Academic Emergency Medicine
3090	Clarke 2003	The impact of diabetes-related complications on healthcare costs: Results from the United Kingdom Prospective Diabetes Study (UKPDS Study No. 65)	2003	20	6	442	450	Diabetic Medicine
3271	Earnshaw 2010	Cost-effectiveness of proton pump inhibitors for prevention of gastrointestinal adverse events when using aspirin for primary cardiovascular prevention	2010	13	3	A166		Value in Health
3284	Elgart 2012	Saxagliptin or sulfonylurea after metformin secondary failure: A cost-effectiveness analysis in colombia	2012	15	4	A180		Value in Health
3430	Gaspoz 2002	Cost effectiveness of aspirin, clopidogrel, or both for secondary prevention of coronary heart disease	2002	346	23	1800	1806	New England Journal of Medicine
3484	Gradman 2012	Are vasodilators of value in the care of patients hospitalized for acute heart failure?	2012	15	4	A114		Value in Health
3855	LaMori 2011	Burden of comorbidities among patients with atrial fibrillation	2011	14	3	A34		Value in Health
4065	McEwan 2010	Assessing the influence of incorporating secondary cardiovascular events into a type 2 diabetes mellitus (T2DM) cost-effectiveness model	2010	13	7	A293		Value in Health
4183	Murphy 2011	High rates of anxiety and depression in young cardiac patients	2011	20		S243		Heart Lung and Circulation
4297	Pant 2012	Rising health care cost in united states: Is defensive medicine the cause? Analysis in a chest pain rule out cohort	2012	59	13	E1845		Journal of the American College of Cardiology
4451	Raymond 2012	Patient-reported health related quality of life (EQ-5D) predicts readmission risk	2012	59	13	E1890		Journal of the American College of Cardiology
4516	Rubinshtein 2006	Initial experience with a cardiologist-based chest pain unit in an emergency department in Isreal	2006	8	5	329	332	Israel Medical Association Journal
4559	Saric 2011	Cost of diabetes in Croatia impact of complications on the costs of type II diabetes	2011	14	7	A477		Value in Health
4643	Shaw 2009	Induced Cardiovascular Procedural Costs and Resource Consumption Patterns After Coronary Artery Calcium Screening. Results From the EISNER (Early Identification of Subclinical Atherosclerosis by Noninvasive Imaging Research) Study	2009	54	14	1258	1267	Journal of the American College of Cardiology
4717	Solinas 2003	Prevalence, clinical characteristics, resource utilization and outcome of patients with acute chest pain in the emergency department. A multicenter, prospective, observational study in North-Eastern Italy	2003	4	5	318	324	Italian Heart Journal

4955	Voronkov 2011	Quality of life predictors in stable chronic heart failure	2011	10		S258		European Journal of Heart Failure, Supplement
4976	Wang 2010	Difference in outcomes measures of patients with valvular and non-valvular atrial fibrillation	2010	13	3	A159	A160	Value in Health
4977	Wang 2011	Analysis of myocardial infarction related clinical outcomes, health care utilization and costs of patients with non-valvular atrial fibrillation	2011	14	3	A33		Value in Health
9199	Radner 2011	Comorbidity affects all domains of physical function and quality of life in patients with rheumatoid arthritis	2011	50	2	381	388	Rheumatology
9467	Saini 2011	Cost-effectiveness analysis: Cardiovascular benefits of proton pump inhibitor co-therapy in patients using aspirin for secondary prevention	2011	34	2	243	251	Alimentary Pharmacology and Therapeutics
21424	Deitelzweig 2012	Evaluation of total medical costs with the use of apixaban and rivaroxaban vs. Warfarin among atrial fibrillation patients	2012	5	3			Circulation: Cardiovascular Quality and Outcomes
21425	Deitelzweig 2012	Comparison of total medical cost avoidance with the usage of new oral anticoagulants instead of warfarin among atrial fibrillation patients, based on the aristotle, RE-LY and ROCKET-AF trials	2012	59	13	E599		Journal of the American College of Cardiology
2195	Stargardt 2013	Measuring the relationship between costs and outcomes: The example of acute myocardial infarction in german hospitals	2013					Health Economics (United Kingdom)
21490	Galper 2012	Comparative effectiveness of U.S. population screening strategies for coronary heart disease (CHD): Evaluation of framingham risk score (FRS), society for heart attack prevention and education (SHAPE), texas heart attack prevention Bill, Jupiter, and treatall approaches	2012	59	13	E1711		Journal of the American College of Cardiology
21506	Goehler 2013	Comparison of long term health and economic outcomes of ED triage strategies for patients with acute chest pain	2013	128	22			Circulation
21815	Pitt 2009	ACS-NSQIP has the potential to create an HPB-NSQIP option	2009	11	5	405	413	HPB
22009	Weiss 2013	Care of patients with aortic abdominal aneurysmas within an interdisciplinary vascular center improves patients` outcome and is economically effective	2013	42		21	22	Vasa - Journal of Vascular Diseases
22125	Larsson 2014	Health-related quality of life improves during the first six months after cardiac arrest and hypothermia treatment.	2014 Feb	85	2	215	20	Resuscitation
22211	De 2013	Validity and reliability of three commonly used quality of life measures in a large European population of coronary heart disease patients.	2013 Sep 1	167	5	2294	9	Int J Cardiol
Excluded as primary prevention								
157	Bae 2012	Hospitalization costs of acute coronary syndrome patients undergoing percutaneous coronary intervention: Comparison between clopidogrel and prasugrel patients in a us hospital database	2012	60		B213		Journal of the American College of Cardiology
158	Bae 2012	Hospital length of stay after percutaneous coronary intervention among acute coronary syndrome patients treated with clopidogrel or prasugrel in a United States Hospital database	2012	5	3			Circulation: Cardiovascular Quality and Outcomes

159	Bae 2012	Hospitalization costs of acute coronary syndrome patients undergoing percutaneous coronary intervention: Comparison between clopidogrel and prasugrel patients in a united states hospital database	2012	15	7	A366		Value in Health
423	Chen 2013	Clinical and economic outcomes among hospitalized patients with acute coronary syndrome: An analysis of a national representative Medicare population	2013	5	1	181	188	ClinicoEconomics and Outcomes Research
425	Chen 2013	Clinical and economic burden of atrial fibrillation in medicare beneficiaries with acute coronary syndrome	2013	16	3	A185		Value in Health
1938	Roggeri 2012	Direct sanitary costs of patients with acute coronary syndrome treated with dual antiplatelet treatment with clopidogrel and aspirin in a subpopulation of the arno project-italy	2012	13	5	86S		Giornale Italiano di Cardiologia
3693	Johnston 2011	Patterns of acute clopidogrel use and inpatient costs in acute coronary syndrome patients undergoing coronary artery bypass grafting	2011	14	3	A87		Value in Health
22024	Xu 2013	Acute coronary syndrome patients with type 2 diabetes had higher healthcare costs versus patients without diabetes in the us population from 2006 to 2011	2013	99		A123		Heart
4086	Meadows 2010	Characterization of commercially insured patients with acute coronary syndrome (ACS) receiving percutaneous coronary intervention (PCI)	2010	13	3	A172		Value in Health
4493	Roggeri 2012	Direct sanitary costs of patients with acute coronary syndrome treated with dual antiplatelet treatment with clopidogrel and aspirin in a sub population of the arno project - Italy	2012	15	4	A131		Value in Health
21788	Page 2013	Atrial fibrillation and heart failure increase length of hospital stay, total healthcare utilization, and costs in acute coronary syndromes	2013	128	22			Circulation
22053	Chen 2014	Outcomes associated with comorbid atrial fibrillation and heart failure in medicare beneficiaries with acute coronary syndrome.	2014 Feb 20	14	1	80		BMC Health Serv Res
22077	Kolte 2014	Trends in incidence, management, and outcomes of cardiogenic shock complicating ST-elevation myocardial infarction in the United States.	2014 Feb	3	1	e000590		J Am Heart Assoc
22220	Kaul 2013	Health-related quality of life of ticagrelor versus clopidogrel in patients with acute coronary syndromes-results from the PLATO trial.	2013	16	4	574	80	Value in health : the journal of the International Society for Pharmacoeconomics and Outcomes Research
Excluded as intervention not of interest								
57	Akerborg 2012	Cost-Effectiveness of Dronedarone in Atrial Fibrillation: Results for Canada, Italy, Sweden, and Switzerland	2012	34	8	1788	1802	Clinical Therapeutics
68	Albert 2012	Total arterial multi-vessel revascularization. Matched-pairs analysis of results and quality of life after antero-lateral mini-thoracotomy compared to sternotomy	2012	60				Thoracic and Cardiovascular Surgeon
75	Alfonso-Cristancho 2013	Economic impact of dabigatran for prevention of stroke in patients with atrial fibrillation in colombia	2013	44	2			Stroke
124	Arnold 2013	Derivation and validation of a risk standardization model for benchmarking hospital	2013					Circulation

		performance for health-related quality of life outcomes after acute myocardial infarction						
162	Bagai 2013	Clinical outcomes and cost implications of routine early PCI after fibrinolysis: One-year follow-up of the trial of routine angioplasty and stenting after fibrinolysis to enhance reperfusion in acute myocardial infarction (TRANSFER-AMI) study	2013	165	4	630	637	American Heart Journal
244	Berry 2013	Fractional flow reserve versus angiography in guiding management to optimize outcomes in non-ST-elevation myocardial infarction (FAMOUS-NSTEMI): Rationale and design of a randomized controlled clinical trial	2013	166	4	662	668	American Heart Journal
313	Brixner 2013	Evaluation of cardiovascular risk factors, events, and costs across four BMI categories	2013	21	6	1284	1292	Obesity
130	Asher 2013	Clinical outcomes and cost effectiveness of treating patients with chest pain in a chest pain unit compared with routine care	2013	61	10	E1311		Journal of the American College of Cardiology
488	Collinson 2012	Economic analysis of the randomised assessment of treatment using panel assay of cardiac markers-contemporary biomarker evaluation study (RATPAC CBE)	2012	33		897		European Heart Journal
490	Collinson 2013	Randomised Assessment of Treatment using Panel Assay of Cardiac markers--Contemporary Biomarker Evaluation (RATPAC CBE)	2013	17	15	v	122	Health technology assessment (Winchester, England)
525	Crowder 2013	The effect of implementing high-sensitivity troponin testing on operational efficiency in three large urban emergency departments	2013	15		S44		Canadian Journal of Emergency Medicine
547	Danchin 2012	The importance of global economic level on AMI outcomes. Data from the Euro Heart Survey 2009 AMI snapshot	2012	33		950		European Heart Journal
825	Goldstein 2013	Relationship between routine multi-detector cardiac computed tomographic angiography prior to reoperative cardiac surgery, length of stay, and hospital charges	2013	29	3	709	717	International Journal of Cardiovascular Imaging
871	Gupta 2013	A study comparing quality of life in post mi patients with and without lifestyle intervention therapy	2013	126		138		Cardiology (Switzerland)
1001	Iglesias-Vazquez 2012	Costs and efficiency of an automated external defibrillation program in a scattered population area in the northwest of Spain	2012	19	6	719	720	Academic Emergency Medicine
1014	Ito 2012	Comparative cost-effectiveness of interventions to improve medication adherence aftermyocardial infarction	2012	21		17		Pharmacoepidemiology and Drug Safety
1078	Kaila 2012	Clinical outcomes in south asians with acute coronary syndromes undergoing percutaneous coronary intervention: Results from Alberta provincial project for outcomes assessment in coronary heart disease registry	2012	28	5	S260	S261	Canadian Journal of Cardiology
1094	Karina 2013	Centralized, stepped, patient preference-based treatment for patients with post-acute coronary syndrome depression: Codiacs vanguard randomized control trial	2013	61	10	E158		Journal of the American College of Cardiology
1159	Kip 2013	Cost effectiveness of implementing a multimarker assay for early exclusion of NSTEMI	2013	38	2	63		Nederlands Tijdschrift voor Klinische Chemie en Laboratoriumgeneeskunde
1175	Kockaya 2012	Potential impact of regional cerebral oxygen saturation monitoring during coronary artery bypass surgery on the patient reimbursement budget in Turkey	2012	15	7	A347		Value in Health

1185	Kolte 2013	Early invasive versus initial conservative treatment strategies in octogenarians with UA/NSTEMI	2013	126	12	1076	1083	American Journal of Medicine
1317	Lee 2012	Cost effectiveness of tirofiban in acute coronary syndrome	2012	15	7	A473		Value in Health
1515	Mehta 2013	Length of stay in high risk percutaneous coronary intervention in us: A 5 year contemporary experience	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
1546	Miller 2012	Left ventricular ejection fraction assessment among patients with acute myocardial infarction and its association with hospital quality of care and evidence-based therapy use	2012	5	5	662	671	Circulation: Cardiovascular Quality and Outcomes
1580	Moretz 2012	Cost analysis in acute coronary syndrome patients using a high-sensitivity Troponin i method	2012	11	3	167		Critical Pathways in Cardiology
1600	Mudrick 2013	Cardiac rehabilitation participation reduces 90-day hospital readmissions after acute myocardial infarction or percutaneous coronary intervention	2013	61	10	E1418		Journal of the American College of Cardiology
1765	Patel 2013	Cost of hospitalization for high risk percutaneous coronary intervention in the US: A 5-year contemporary perspective	2013	6	3			Circulation: Cardiovascular Quality and Outcomes
1916	Rihal 2013	The economic and clinical impact of routine weekend catheterization services	2013	61	10	E1506		Journal of the American College of Cardiology
1986	Safley 2013	Quality of life benefits of percutaneous coronary intervention for chronic occlusions	2013					Catheterization and Cardiovascular Interventions
2017	Satiani 2011	Potential cost savings with CMR-guided selective invasive strategy in non-st elevation acute coronary syndrome	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
2231	Strauss 2012	Does the zwolle percutaneous coronary intervention risk index identify low risk st-elevation myocardial infarction patients for early discharge?	2012	60		B151	B152	Journal of the American College of Cardiology
2313	Thyregod 2013	The Nordic Aortic Valve Intervention (NOTION) trial comparing transcatheter versus surgical valve implantation: Study protocol for a randomised controlled trial	2013	14	1			Trials
2353	Turkstra 2012	Cost-effectiveness of a secondary prevention program in patients with myocardial infarction: Results from a randomised controlled trial (proactive heart)	2012	15	7	A526		Value in Health
2354	Turkstra 2013	Cost-effectiveness of a coronary heart disease secondary prevention program in patients with myocardial infarction: Results from a randomised controlled trial (ProActive Heart)	2013	13				BMC Cardiovascular Disorders
2359	Tyson 2013	Carolina chest pain tracking protocol safely reduces cardiovascular inpatient testing and management costs	2013	61	10	E1556		Journal of the American College of Cardiology

2398	Vassileva 2012	Cost analysis of isolated mitral valve surgery in the United States	2012	94	5	1429	1436	Annals of Thoracic Surgery
2400	Vegter 2013	Cost-effectiveness of increasing statin adherence for primary and secondary prevention in community pharmacies	2013	16	7	A528		Value in Health
2424	Walker 2013	Cost-effectiveness of cardiovascular magnetic resonance in the diagnosis of coronary heart disease: An economic evaluation using data from the CE-MARC study	2013	99	12	873	881	Heart
2444	Wasserman 2013	Total costs and outcomes of drug-eluting stent placement with intravascular ultrasound (IVUS) compared with angiography alone: A cost-effectiveness analysis from the perspective of the italian health system	2013	16	7	A525		Value in Health
2445	Wasserman 2013	Total costs and outcomes of bare metal stent placement with intravascular ultrasound compared with angiography alone: A cost-effectiveness analysis from the perspective of the Italian health system	2013	34		30		European Heart Journal
2488	Winget 2011	Comparison of index hospital resource utilization and costs between patients undergoing elective percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) PCI	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
3068	Chinnaiyan 2012	Incremental value of coronary CT angiography over stress testing in predicting outcomes and resource utilization	2012	59	13	E1324		Journal of the American College of Cardiology
3076	Choudhry 2012	Monday 14 November 2011 Full coverage for preventive medications after myocardial infarction: The post-myocardial infarction free Rx event and economic evaluation (MIFREEE)trial	2012	33	1	140	141	European Heart Journal
3130	Couturier 2012	Cost-utility of post-discharge educational interventions in patients with acute coronary syndrome or chronic heart failure	2012	15	4	A122	A123	Value in Health
3163	Darling 2011	Reducing door-to-balloon times for STEMI: Effect on cost and outcomes	2011	18	5	S166		Academic Emergency Medicine
3225	Diercks 2009	Utilization and Impact of Pre-Hospital Electrocardiograms for Patients With Acute ST-Segment Elevation Myocardial Infarction. Data From the NCDR (National Cardiovascular Data Registry) ACTION (Acute Coronary Treatment and Intervention Outcomes Network) Registry	2009	53	2	161	166	Journal of the American College of Cardiology
3235	Dodhia 2012	Modelling the impact on avoidable cardiovascular disease burden and costs of interventions to lower SBP in the England population	2012	30	1	217	226	Journal of Hypertension
3280	Eisenstein 2009	Long-Term Clinical and Economic Analysis of the Endeavor Drug-Eluting Stent Versus the Driver Bare-Metal Stent. 4-Year Results From the ENDEAVOR II Trial (Randomized Controlled Trial to Evaluate the Safety and Efficacy of the Medtronic AVE ABT-578 Eluting Driver Coronary Stent in De Novo Native Coronary Artery Lesions)	2009	2	12	1178	1187	JACC: Cardiovascular Interventions
3377	Fragoulakis 2011	Economic evaluation of rosuvastatin versus atorvastatin, simvastatin and pravastatin in high risk patients treated for primary and secondary prevention of cardiovascular disease in Greece	2011	14	7	A378		Value in Health
3475	Goodacre 2001	Is a chest pain observation unit likely to be cost saving in a British hospital?	2001	18	1	11	14	Emergency Medicine Journal
3496	Grimaldi 2012	Are the statins effective to prevent first myocardial infarction in real life?	2012	15	4	A113		Value in Health
3526	Hachamovitch	The study of myocardial perfusion and coronary anatomy imaging roles in CAD	2009	16	6	935	948	Journal of Nuclear

	2009	(SPARC): Design, rationale, and baseline patient characteristics of a prospective, multicenter observational registry comparing PET, SPECT, and CTA for resource utilization and clinical outcomes						Cardiology
3580	Hess 2011	Effect of a decision aid on patient knowledge, patient satisfaction, safety, and resource use in low-risk emergency department patients with chest pain: A randomized trial	2011	18	5	S17		Academic Emergency Medicine
3750	Kessler 2010	Effect of bivalirudin on economic outcomes of stemi patients in an observational dataset	2010	13	3	A11		Value in Health
3751	Kessler 2010	Effect of bivalirudin on clinical outcomes of stemi patients in an observational dataset	2010	13	3	A149		Value in Health
3804	Kotowycz 2010	Safety and feasibility of early hospital discharge in ST-segment elevation myocardial infarction-A prospective and randomized trial in low-risk primary percutaneous coronary intervention patients (the Safe-Depart Trial)	2010	159	1	117	117	American Heart Journal
3887	Leesar 2003	Use of fractional flow reserve versus stress perfusion scintigraphy after unstable angina: Effect on duration of hospitalization, cost, procedural characteristics, and clinical outcome	2003	41	7	1115	1121	Journal of the American College of Cardiology
3903	Leon 2009	Late Safety, Efficacy, and Cost-Effectiveness of a Zotarolimus-Eluting Stent Compared With a Paclitaxel-Eluting Stent in Patients With De Novo Coronary Lesions. 2-Year Follow-Up From the ENDEAVOR IV Trial	2009	2	12	1208	1218	JACC: Cardiovascular Interventions
3927	Liew 2011	Dronedarone is cost-effective for the prevention of downstream cardiovascular morbidity and mortality in Australian patients with atrial fibrillation	2011	14	7	A381		Value in Health
3983	Machecourt 2005	Primary angioplasty is cost-minimizing compared with pre-hospital thrombolysis for patients within 60 min of a percutaneous coronary intervention center: The Comparison of Angioplasty and Pre-hospital Thrombolysis in Acute Myocardial Infarction (CAPTIM) cost-efficacy sub-study	2005	45	4	515	524	Journal of the American College of Cardiology
4329	Pei 2010	Discrete event simulation of cardiac hospitals performing percutaneous coronary interventions	2010	13	3	A167		Value in Health
4425	Rajamanickam 2012	Eliminating creatinine kinase-mb (CKMB) in ruling out acute myocardial infarction (MI) when troponin (Tn) is available can lead to saving hundreds of millions of healthcare dollars	2012	59	13	E1821		Journal of the American College of Cardiology
4480	Rinfret 2001	Ovality of life after balloon angioplasty or stenting for acute myocardial infarction: One-year results from the Stent-PAMI trial	2001	38	6	1614	1621	Journal of the American College of Cardiology
4537	Safley 2012	Economic impact of transradial percutaneous coronary intervention	2012	59	13	E310		Journal of the American College of Cardiology
4545	Saleh 2009	The effect of preoperative and hospital characteristics on costs for coronary artery bypass graft	2009	249	2	335	341	Annals of Surgery
4584	Schmitz 2012	Percutaneous coronary intervention of a noninfarct artery in selected patients with ST-elevation myocardial infarction maintains excellent clinical outcomes and achieves substantial cost savings compared to staged second-vessel intervention	2012	59	13	E45		Journal of the American College of Cardiology
5104	Zeymer 2010	Practice patterns and quality of life in acute coronary syndrome patients in 2008-2009: Baseline results for Germany from the antiplatelet treatment observational registry II (APTOR II)	2010	13	7	A366		Value in Health
5123	Zomer 2011	Predicting the impact of polypill use in a metabolic syndrome population: An	2011	32		972		European Heart

		effectiveness and cost-effectiveness analysis						Journal
5128	Zwart-Van 2001	Costs and effects of combining stenting and abciximab (ReoPro(registered trademark)) in daily practice	2001	77	41673	299	303	International Journal of Cardiology
5683	Baumler 2011	The effect of supplementary fees on the diffusion of medical devices in the German system of diagnosis related groups (G-DRG): The case of drug-eluting stents in patients with acute myocardial infarction	2011	14	7	A255	A256	Value in Health
7132	Groeneveld 2011	The impact of new cardiovascular device technology on health care costs	2011	171	14	1289	1291	Archives of Internal Medicine
10683	Cobelli 2002	Cost/utility ratio in chronic heart failure: comparison between heart failure management program delivered by day-hospital and usual care.	2002	40	7	1259	66	Journal of the American College of Cardiology
21294	Aziz 2011	Comparison of the utilization of evidence-based therapies and clinical outcomes between teaching and non-teaching medical services after the implementation of novel clinical pathways for the management of cardiac patients	2011	4	6			Circulation: Cardiovascular Quality and Outcomes
21339	Brunetti 2014	Prehospital telemedicine electrocardiogram triage for a regional public emergency medical service: Is it worth it? A preliminary cost analysis	2014					Clinical Cardiology
21502	Gheorghiade 2009	The effects of eplerenone on length of stay and total days of heart failure hospitalization after myocardial infarction in patients with left ventricular systolic dysfunction	2009	158	3	437	443	American Heart Journal
21515	Groarke 2011	Real world costs of non-cardiac chest pain admissions	2011	180		S405	S406	Irish Journal of Medical Science
21627	Kolte 2013	Comparison of early invasive versus initial conservative treatment strategies in octogenarians with unstable angina/non-st-elevation myocardial infarction	2013	128	22			Circulation
21628	Kolte 2013	Regional differences in management and outcomes of unstable angina/non-st-elevation myocardial infarction in the United States	2013	128	22			Circulation
21819	Porten 2013	Clinical outcomes and resource utilization in acute coronary syndrome patients receiving P2Y12 inhibitors and undergoing early coronary artery bypass graft surgery	2013	128	22			Circulation
21996	Wang 2010	Comparison of mortality, health care utility and cost of patients with warfarin treatment for non-valvular atrial fibrillation versus patients with other treatment	2010	13	7	A340		Value in Health
22068	Brunetti 2014	Prehospital Telemedicine Electrocardiogram Triage for a Regional Public Emergency Medical Service: Is It Worth It? A Preliminary Cost Analysis.	2014 Jan 22					Clin Cardiol
22151	Schuetz 2013	A standardized vascular disease health check in europe: a cost-effectiveness analysis.	2013	8	7	e6645 4		PLoS One
22278	Dixon 2011	Cost-effectiveness of point-of-care biomarker assessment for suspected myocardial infarction: the randomized assessment of treatment using panel Assay of cardiac markers (RATPAC) trial.	2011	18	5	488	95	Academic emergency medicine
22761	Onukwugha 2012	Cost-effectiveness of cytochrome P450 2C19 genotype screening for selection of antiplatelet therapy with clopidogrel or prasugrel (Provisional abstract)	2012	32	4	323	332	Pharmacotherapy
2333	Tralhao 2013	Can we improve duration of hospital stay in angioplasty treated ST-segment elevation acute myocardial infarction? The Zwolle risk score	2013	34		83		European Heart Journal
22376	Hall 2011	The RATPAC (randomised assessment of treatment using panel assay of cardiac markers) trial: A randomized controlled trial of point-of-care cardiac markers in the	2011	15	23	1	108	Health Technology Assessment

		emergency department.						
Excluded as country not of interest								
1035	Jian 2013	Long-Term efficacy of PCI vs. CABG for patients with multiple coronary chronic total occlusions	2013	99		A43		Heart
9101	Piha 2011	Estimated cost of acute coronary syndrome for 2011: Case of Brazil	2011	14	7	A544		Value in Health
21516	Groarke 2011	Impact of targeted subspecialist care versus generalist care on lengths of hospital stay and costs across common diagnostic groups	2011	180		S404	S405	Irish Journal of Medical Science
29	Abaci 2012	Long term cost-effectiveness analysis of ticagrelor in patients with acute coronary syndromes from a turkish health care perspective based on data from the plato trial	2012	15	7	A370		Value in Health
40	Ademi 2013	Outcomes and excess costs among patients with cardiovascular disease	2013	22	9	724	730	Heart Lung and Circulation
52	Ahmad 2013	Towards Renewed Health Economic Simulation of Type 2 Diabetes: Risk Equations for First and Second Cardiovascular Events from Swedish Register Data	2013	8	5			PLoS ONE
129	Asha 2013	Impact from point-of-care devices on emergency department patient processing times compared with central laboratory testing of blood samples: A randomised controlled trial and cost-effectiveness analysis	2013					Emergency Medicine Journal
174	Bakhai 2013	Treatment, outcomes, costs, and quality of life of women and men with acute coronary syndromes who have undergone Percutaneous coronary intervention: Results from the Antiplatelet Therapy Observational Registry	2013	125	2	100	107	Postgraduate Medicine
283	Bondesson 2013	Hospital utilization and costs for spinal cord stimulation compared with enhanced external counterpulsation for refractory angina pectoris	2013	19	1	139	147	Journal of Evaluation in Clinical Practice
356	Cakir 2012	The economic cost of acute coronary syndrome in Turkey	2012	15	7	A368		Value in Health
393	Chag 2013	The impact of the new resolute integrity stent platform on deliverability, acute outcomes and resource utilisation in a regional population from India and Bangladesh: Results from the DELIVER study	2013	9		3		EuroIntervention
402	Chang 2012	The socioeconomic burden of coronary heart disease in Korea	2012	45	5	291	300	Journal of Preventive Medicine and Public Health
433	Chevalier 2012	Cost-effectiveness of ticagrelor in the management of acute coronary syndromes in belgium	2012	15	7	A373		Value in Health
543	Daivadanam 2012	Catastrophic health expenditure & coping strategies associated with acute coronary syndrome in Kerala, India	2012	136	4	585	592	Indian Journal of Medical Research
566	De 2013	Gastroprotection in low-dose aspirin users for primary and secondary prevention of ACS: Results of a cost-effectiveness analysis including compliance	2013	27	4	341	357	Cardiovascular Drugs and Therapy
746	Friedrich 2012	Health-related quality of life, anxiety and depression after PCI: Restoring a state of equilibrium	2012	19	41765	149	150	Journal fur Kardiologie
787	Gasche 2013	Cost-effectiveness of ticagrelor and generic clopidogrel in patients with acute coronary syndrome in Switzerland	2013	143				Swiss Medical Weekly
858	Groarke 2013	Cost burden of non-specific chest pain admissions	2013	182	1	57	61	Irish Journal of Medical Science

884	Hamada 2012	Effects of the per diem prospective payment system with DRG-like grouping system (DPC/PDPS) on resource usage and healthcare quality in Japan	2012	107	41673	194	201	Health Policy
910	Hawkes 2013	Predictors of physical and mental health-related quality of life outcomes among myocardial infarction patients	2013	13				BMC Cardiovascular Disorders
1023	James 2013	Health economic evaluation of ticagrelor compared to generic clopidogrel in patients with acute coronary syndromes intended for non-invasive management based on the PLATO trial	2013	34		896		European Heart Journal
1142	Kim 2012	Hospital based cost survey of acute coronary syndrome in South Korea	2012	15	7	A632		Value in Health
1150	Kim 2013	Health-related quality-of-life after percutaneous coronary intervention in patients with UA/NSTEMI and STEMI: The Korean multicenter registry	2013	28	6	848	854	Journal of Korean Medical Science
1189	Kontsevaya 2013	Simulating the potential impact of improved blood pressure control on clinical and economic outcomes in Russia	2013	16	7	A539		Value in Health
1315	Lee 2012	Cost-effectiveness analysis of treating acute coronary syndrome patients with ticagrelor versus clopidogrel in Hong Kong: A markov analytic model	2012	15	7	A371		Value in Health
1321	Leibovitz 2013	Sitagliptin pretreatment in diabetes patients presenting with acute coronary syndrome: Results from the Acute Coronary Syndrome Israeli Survey (ACSIS)	2013	12	1			Cardiovascular Diabetology
1354	Liew 2013	Cost-effectiveness of 12-month treatment with ticagrelor compared with clopidogrel in the management of acute coronary syndromes	2013	35	8	1110	1117	Clinical Therapeutics
1553	Mishchenko 2013	Pharmacoeconomic evaluation acc eptability of clopidogrel versus acetylsalicylic acid in patients with cardiovascular disease for stroke prevention in Ukraine	2013	16	7	A525		Value in Health
1691	Okumura 2013	Out-of-pocket expenditure burdens in patients with cardiovascular conditions and psychological distress: A nationwide cross-sectional study	2013	35	3	233	238	General Hospital Psychiatry
1700	Oldroyd 2013	Evaluating the impact of depression, anxiety & autonomic function on health related quality of life, vocational functioning and health care utilisation in acute coronary syndrome patients: The ADVENT study protocol	2013	13				BMC Cardiovascular Disorders
1753	Park 2013	Quality of care and in-hospital resource use in acute myocardial infarction: Evidence from Japan	2013	111	3	264	272	Health Policy
1754	Park 2013	Decentralization and centralization of healthcare resources: Investigating the associations of hospital competition and number of cardiologists per hospital with mortality and resource utilization in Japan	2013	113	41641	100	109	Health Policy
1785	Permsuwan 2012	Long-term cost-effectiveness of ticagrelor in patients with acute coronary syndrome in Thailand	2012	15	7	A633		Value in Health
1822	Polanco 2013	Cost effectiveness analysis of ticagrelor in the treatment of patients with acute coronary syndrome in mexico: Outcomes for specific groups	2013	16	3	A287		Value in Health
1855	Pyadushkina 2012	Cost analysis of ticagrelor versus clopidogrel in patients with acute coronary syndrome in Russia	2012	15	7	A366		Value in Health
1876	Rancic 2013	Health-related quality of life in patients after the acute myocardial infarction	2013	8	2	266	272	Central European Journal of Medicine
1963	Ruan 2013	Multicentre clinical research on effect of traditional chinese medicine for post revascularization treatment of coronary artery disease	2013	163	3	S56		International Journal of Cardiology
2143	Six 2012	Consumption of diagnostic procedures and other cardiology care in chest pain patients after presentation at the emergency department	2012	20	12	499	504	Netherlands Heart Journal

2192	Stafford 2013	Tobacco smoking predicts depression and poorer quality of life in heart disease	2013	13				BMC Cardiovascular Disorders
2283	Tasic 2013	Impact of depression on sexual dysfunction and HRQoL in CAD patients	2013			1	10	Central European Journal of Medicine
2284	Tasic 2013	Health-related quality of life in patients with coronary artery disease after coronary revascularization	2013	8	5	618	626	Central European Journal of Medicine
2285	Tavella 2012	Cardiac rehabilitation may not provided a quality of life benefit in coronary artery disease patients	2012	12		406		BMC health services research
2387	Van 2012	Acute coronary syndrome: What is the cost-effectiveness of prevention, point-of-care technology and telemonitoring?	2012	1	3	173	177	Health Policy and Technology
2409	Vieira 2012	Cost-effectiveness analysis for surgical, angioplasty, or medical therapeutics for coronary artery disease: 5-year follow-up of medicine, angioplasty, or surgery study (MASS) II trial	2012	126	11 SUPP L.1	S145	S150	Circulation
2456	Wei 2013	Cardiovascular disease risk reduction in rural China: A clustered randomized controlled trial in Zhejiang	2013	14	1			Trials
2478	Wieser 2012	Cost of acute coronary syndrome in Switzerland in 2008	2012	142				Swiss Medical Weekly
2493	Wojcieszczyk 2012	Impact of different cardiac rehabilitation (CR) programs on quality of life and depression in women with ischemic heart disease (IHD)	2012	27				European Psychiatry
2506	Wu 2013	Economic evaluation of ticagrelor in treating patients with acute coronary syndrome in hong kong: A cost-utility analysis	2013	16	3	A289		Value in Health
2516	Yang 2012	Gender differences and the trend in the acute myocardial infarction: A 10-year nationwide population-based analysis	2012	2012				The Scientific World Journal
3073	Choi 2010	Anti-thrombolytic agent use and patterns of health-care utilization in patients with acute myocardial infarction (AMI) using Korea national health insurance claims database	2010	13	7	A524		Value in Health
3079	Chu 2012	Influences of the early invasive strategy on patients with chronic kidney diseases in non-st segment elevation acute coronary syndrome, a population-based study from nhird of Taiwan	2012	109	7	62S		American Journal of Cardiology
3154	Da 2001	How much do we pay for a benefit? A descriptive cost analysis of the use of statins. The need for a national costeffectiveness analysis	2001	76	5	409	418	Arquivos Brasileiros de Cardiologia
3236	Doerler 2011	Clopidogrel pre-treatment is associated with reduced in-hospital mortality in primary percutaneous coronary intervention for acute ST-elevation myocardial infarction	2011	32		415		European Heart Journal
3376	Fragoulakis 2011	Economic evaluation of Dabigatran etexilate 150dib for the stroke prevention in atrial fibrillation in Greece: A cost -effectiveness analysis under the Greek NHS setting	2011	14	7	A378		Value in Health
3419	Garcia-Castillo 2011	Long-term cost-effectiveness analysis of ticagrelor in patients with acute coronary syndrome (ACS) from a mexican public and private health care perspective based on data from the PLATO trial	2011	14	7	A379	A380	Value in Health
3541	Harald 2011	A nurse coordinated prevention program improves quality of life in coronary patients: Results from the RESPONSE trial	2011	18	1	S2		European Journal of Cardiovascular Prevention and Rehabilitation
3568	Heerey 2001	Cost of treating acute myocardial infarction in an Irish teahing hospital	2001	94	5	144	146	Irish Medical Journal

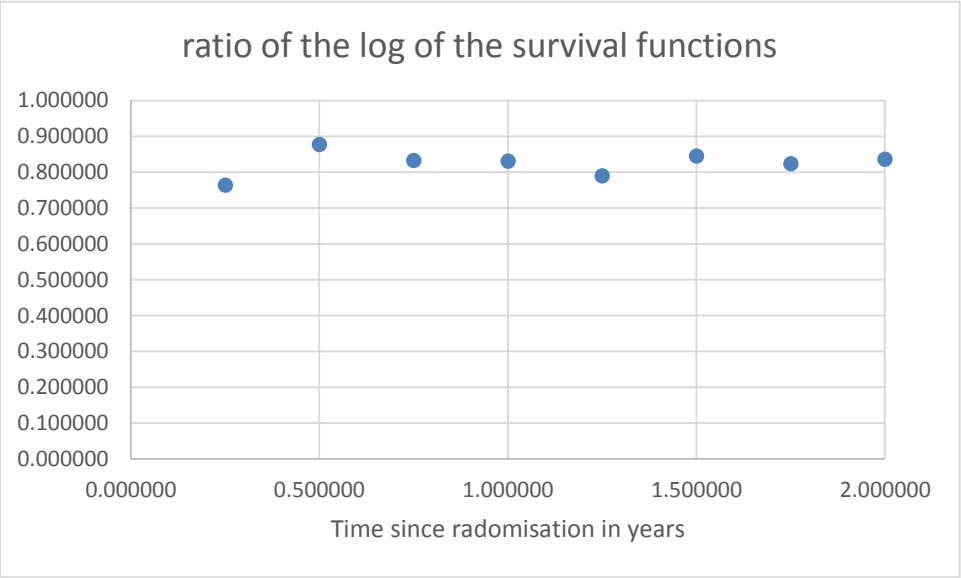
3575	Henriksson 2011	Long-term costs and health outcomes of treating acute coronary syndrome patients with ticagrelor based on the eu label-cost-effectiveness analysis based on the plato study	2011	14	3	A40		Value in Health
3763	Kim 2010	Health-related quality of life after percutaneous coronary intervention in patients with acute coronary syndromes	2010	13	7	A521		Value in Health
3764	Kim 2010	A national survey of societal cost of acute coronary syndrome in South Korea	2010	13	7	A349		Value in Health
3879	Lee 2010	The cost-effectiveness of amlodipine besylate versus placebo for the prevention of cardiovascular disease in Korea	2010	13	7	A356		Value in Health
3883	Lee 2012	Budget impact analysis of introducing ticagrelor for the treatment of acute coronary syndrome into the public health care sector of Hong Kong	2012	15	4	A117		Value in Health
3944	Liu 2011	In-hospital case-fatality rates and associated factors among patients with acute myocardial infarction in Beijing during 2007-2009	2011	124	21			Circulation
3971	Lunde 2007	Exercise capacity and quality of life after intracoronary injection of autologous mononuclear bone marrow cells in acute myocardial infarction: Results from the Autologous Stem cell Transplantation in Acute Myocardial Infarction (ASTAMI) randomized controlled trial	2007	154	4	710	710	American Heart Journal
3990	Mahoney 2010	Hospitalization costs in South Korea for patients without identified risk factors for bleeding who have acute coronary syndromes with planned percutaneous coronary intervention treated with prasugrel vs. clopidogrel in the TRITON-TIMI 38 trial	2010	13	7	A348		Value in Health
4196	Myers 2012	Post-myocardial infarction depression: Increased hospital admissions and reduced adoption of secondary prevention measures - A longitudinal study	2012	72	1	5	10	Journal of Psychosomatic Research
4261	Ondrackova 2010	Cost comparison study in acute coronary syndromes and acute heart failure patients	2010	13	7	A348		Value in Health
4292	Panattoni 2010	Cost effectiveness of prasagrel or chopidogrel for treatment of ACS patients based on genetic testing for CYP2C19 variants	2010	13	3	A166		Value in Health
4379	Polder 2006	Health care costs in the last year of life-The Dutch experience	2006	63	7	1720	1731	Social Science and Medicine
4402	Psenkova 2012	A cost-effectiveness analysis comparing dabigatran and standard treatment for stroke prevention in atrial fibrillation in Slovakia	2012	15	4	A121		Value in Health
4421	Raih 2011	Psychological distress and its impact on life quality of patients with multiple cardiovascular pathology	2011	32		58		European Heart Journal
4670	Sigvant 2011	Asymptomatic peripheral arterial disease: Is pharmacological prevention of cardiovascular risk cost-effective?	2011	18	2	254	261	European Journal of Cardiovascular Prevention and Rehabilitation
4921	Vega-Hernandez 2012	Direct medical costs of treating diabetes related complications in Mexico	2012	15	4	A178	A179	Value in Health
4922	Vega-Hernandez 2012	Direct medical management costs of diabetes-related complications in Brazil	2012	15	4	A179		Value in Health
4979	Wang 2011	Cost effectiveness of improved acute myocardial infarction treatment in China:	2011	124	21			Circulation

		Projections from the coronary heart disease policy model-China						
5070	Yan 2011	Health related quality of life of elderly patients undergoing percutaneous coronary intervention	2011	20		S34		Heart Lung and Circulation
5072	Yan 2012	Variation in health related quality of life improvement after percutaneous coronary intervention	2012	15	4	A70		Value in Health
10634	Lenne 2003	Cost-effectiveness analysis of clopidogrel versus aspirin in patients with atherothrombosis based on the CAPRIE trial (Structured abstract)	2003	6	1	55	68	Journal of Medical Economics
10981	Greiner 2013	Cost-effectiveness of ticagrelor and generic clopidogrel in patients with acute coronary syndrome in Switzerland (Provisional abstract)	2013	143	1	w13851		Swiss Medical Weekly
10982	Aylward 2013	Cost-effectiveness of 12-month treatment with ticagrelor compared with clopidogrel in the management of acute coronary syndromes (Provisional abstract)	2013	35	8	1110	1117	Clinical Therapeutics
11133	Araujo 2013	The Economic Burden of HIV/AIDS and Myocardial Infarction Treatment in Brazil.	2013	2013		864962		ScientificWorldJournal
11331	Poldervaart 2013	The impact of the HEART risk score in the early assessment of patients with acute chest pain: design of a stepped wedge, cluster randomised trial.	2013	13		77		BMC Cardiovasc Disord
11389	Pavlides 2013	Current management and quality of life of patients with acute coronary syndrome undergoing percutaneous coronary intervention in Greece: 12-Month results from antiplatelet therapy observational study II (APTOR II).	2013 Jul-Aug	54	4	255	63	Hellenic J Cardiol
21589	Jennings 2013	Trends in hospitalisation for acute mi in Ireland 1997-2008	2013	182		S391		Irish Journal of Medical Science
22020	Wolff 2004	Using checklists and reminders in clinical pathways to improve hospital inpatient care	2004	181	8	428	431	Medical Journal of Australia
22060	Jarvinen 2014	The long-term effect of perioperative myocardial infarction on health-related quality-of-life after coronary artery bypass grafting.	2014 Feb 4					Interact Cardiovasc Thorac Surg
22070	Uymaz 2014	Clinical outcome, pain perception and activities of daily life after minimally invasive coronary artery bypass grafting.	2014 Jan 14					Anadolu Kardiyol Derg
22214	Henriksson 2013	Cost-effectiveness of treating acute coronary syndrome patients with ticagrelor for 12 months: results from the PLATO study.	2013	34	3	220	8	European heart journal
22490	Vardas 2012	Inadequate heart rate control is associated with worse quality of life in patients with coronary artery disease and chronic obstructive pulmonary disease. The RYTHMOS study.	2012	53	2	118	26	Hellenic journal of cardiology : HJC = Hell?nik? kardiologik? epithe?r?s?
Language/non-English								
218	Behrendt 2013	Costs of Health Care of Patients with Acute Coronary Syndrome in Germany: Results of Data Analysis of a Statutory Health Insurance	2013					Gesundheits+?konomie & Qualit+?tsmanagement
Excluded as copy duplicates (conference abstracts already retrieved through database searches)								
484	Coleman 2013	Universal versus platelet reactivity assay-driven use of P2Y12 inhibitors in acute coronary syndrome patients: Cost-effectiveness analyses from five European perspectives	2013	62	18	B52		Journal of the American College of Cardiology

A10. Please present evidence to support the view that the treatment effect is constant over the lifetime of the patients and thus that proportional hazards is an appropriate assumption.

The base line model assumes two years of treatment with rivaroxaban and one year of treatment with clopidogrel and as such, no assumption is made that the treatment effect is constant over the life time. The model does utilise the proportional hazards model, but this is only to smooth the transition probabilities over the two year observation period and only has an effect on the timing of the difference in events during those two years of treatment.

We would like to emphasise that although, almost by definition, this choice does not impact model results, it is possible to check the assumption. One check is to see whether the ratio of the log of the cumulative hazard with and without treatment is constant over time. The figure below presents the result, and as can be seen the ratio of the log of the cumulative hazard remains relatively constant. Therefore we consider the model to be appropriate.



Quality assessment, data synthesis, analysis

A11. Please clarify to what extent the mITT analysis could influence the results compared with an ITT analysis. It is noted that an FDA briefing document for the Cardiovascular and Renal Drugs Advisory Committee for rivaroxaban suggests that three deaths in the intervention group were uncounted for in the ATLAS ACS 2 TIMI 51 trial because they occurred after withdrawal of consent.

ATLAS ACS2 TIMI 51 pre-specified three efficacy analysis sets in the ITT population, which included all randomised subjects [i.e. Modified Intent-to-Treat (mITT), Intent-to-Treat (ITT), and Intent-to-Treat Total (ITT-Total)], that differ from each other only in the censoring rules for determining evaluable events.

[redacted]

[redacted].

The mITT analysis set was the primary efficacy analysis set pre-specified in both the protocol and the SAP, and consisted of all randomised subjects and the endpoint events occurring at or after randomisation and up to the earliest of the Global Treatment End Date - GTED (3 Jun 2011), or 30 days after study drug was prematurely discontinued, or 30 days after randomisation for those subjects who were randomised but not treated. The ITT analysis set included all randomised subjects and endpoint events occurring at or after randomisation until the global treatment end date. ITT total included all events from randomisation up to last contact for each subject. All efficacy analyses excluded efficacy events from three sites in India (091001, 091019 and 091026) due to potential trial misconduct.

The primary efficacy endpoint was analysed in the ITT analysis sets using the same methods as those used for the primary efficacy analysis in the mITT analysis set. [redacted]

In conclusion, ATLAS ACS2 TIMI 51 included three efficacy analysis sets using the ITT population [i.e. Modified Intent-to-Treat (mITT), Intent-to-Treat (ITT), and Intent-to-Treat Total (ITT-Total), that differ from one another only in the censoring rules for determining evaluable events. The mITT analysis set was the primary efficacy analysis set and results for this analysis demonstrated significant reductions of the primary efficacy endpoint for both doses of rivaroxaban. [redacted]

[redacted]

Table 30-2 DEFF02: Effect of Rivaroxaban Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (Analysis Set: Excluding Sites 091001, 091019 and 091026)

[redacted]

Table 30-2 *continued* (DEFF02): Effect of Rivaroxaban Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (Analysis Set: Excluding Sites 091001, 091019 and 091026)

[redacted]

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Figure 6: (FEFF19A) Effect of Combined Rivaroxaban Compared with Placebo on the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) in All Strata (Study RIVAROXACS3001; Excluding Sites 091001, 091019 and 091026 Analysis Set)

[redacted]

A12. Please clarify the criteria for choosing the selected sites at which data for quality of life and medical resource utilsation were collected (p60). In addition, please clarify the EQ-5D measure used in the trial, for example was it EQ-5D-VAS or EQ-5D-VAS and EQ-5D-3L?

- EQ-5D was collected at sites in 8 countries (Australia, Canada, Spain, Netherlands, Korea, the United Kingdom, Sweden, and Japan). The selection criteria were primarily based on the HTA requirements of these countries.
- The EQ-5D was the EQ-5D-3L, as well as the EQ-5D-VAS.
- MRU was collected at every site.

A13. Please provide evidence to support the assumption that withdrawal rate is independent of treatment (i.e. no informative censoring)

The company has carefully conducted a series of analyses to look for evidence of informative censoring leading to consent withdrawal of subjects in the ATLAS ACS 2 TIMI 51 study by analysing important clinical events that occurred in the period prior to and after discontinuation from the study in subjects who withdrew consent.

Among the subjects who withdrew consent, the proportions of those who experienced bleeding events, MIs, strokes, and adverse events in the 30 days prior to their last contact date were similar for the placebo and rivaroxaban 2.5 mg b.i.d. groups.

Table 19: (DSUBCR1008) Incidence of Efficacy and Safety Events in the 30 Days Prior to the Last Contact Date (Study RIVAROXACS3001: All Randomized Subjects who Withdrew Consent)

Bleeding events	Rivaroxaban 2.5 mg BID n/N (%)	Rivaroxaban 5 mg BID n/N (%)	Placebo n/N (%)
Non-CABG TIMI Major Bleeding	1/448 (0.2)	3/441 (0.7)	0/405
CABG Related TIMI Major Bleeding	0/448	0/441	1/405 (0.2)
TIMI Minor Bleeding	1/448 (0.2)	2/441 (0.5)	1/405 (0.2)
TIMI Bleeding Requiring Medical Attention	7/448 (1.6)	8/441 (1.8)	6/405 (1.5)
MI, Stroke	4/441 (0.91)	4/434 (0.92)	4/396 (1.01)
Non-Bleeding AEs	20/241 (8.3)	18/222 (8.1)	20/220 (9.1)

All events are CEC adjudicated except for non-bleeding adverse events.
tsubcr1008.rtf generated by rdsubcr1008.sas, 24AUG2012 02:53

[redacted]

[redacted]

Table 20: Key Baseline Characteristics and Clinical Events in Subjects (Study RIVAROXACS3001)

[redacted]

07AUG2012 16:12
System Used: Arrow6.1(U)/rdsubcr1001

Study RIVAROXACS3001

Output DSUBCR1001B: Summary of Follow-up until MITT Scope Date* on All Cause Death among Subjects with Post-baseline Non-CABG TIMI Major Bleeds

[redacted]

24AUG2012 16:11
System Used: Arrow6.1(U)/rdsubcr1001e

Study RIVAROXACS3001

Output DSUBCR1001E: Summary of Follow-up until MITT Scope Date* on All Cause Death Incorporating New Vital Status Data among Subjects with Post-baseline Non-CABG TIMI Major Bleeds

[redacted]

24AUG2012 16:27
System Used: Arrow6.1(U)/rblcr1011

Study RIVAROXACS3001

Output DBLCR1011: Effect of Rivaroxaban Compared with Placebo on Bleeding Using TIMI Scale as Adjudicated by the CEC among the Newly Identified Death as of the Global Treatment End Date

[redacted]

A14. Please provide references for the following statement (p B-363, Section 10.3, Appendix 3) 'Although discontinuation rates were slightly higher than some similarly designed studies…'

This statement refers to the PLATO and TRITON TIMI 38 studies.

Wiviott SD, Braunwald E, McCabe CH, Montalescot G, Ruzyllo W, Gottlieb S, et al. Prasugrel versus clopidogrel in patients with acute coronary syndromes. New Engl J Med 2007;357(20):2001-15.

Wallentin B, Becker RC, Budaj A, Cannon CP, Emanuelsson H, Held C, et al. Ticagrelor versus clopidogrel in patients with acute coronary syndromes. New Engl J Med 2009;361(11):1045-57.

A15: Please provide supporting evidence to confirm that appropriate methods were used to account for missing data. In addition, comment on the impact of the missing data on the overall interpretability of the ATLAS ACS 2 TIMI 51 trial.

[redacted]

[redacted]

A16. Please provide further details on the rates of PCI and CABG (separately) by dose and study group for the total and licensed population

Data are available for the trial population but this information is academic in confidence. The data for the licensed population has not been generated to-date and we are currently working in collaboration with Janssen to provide the full dataset.

Table 13: (TSUB06A) Description of ACS Index Events (Study RIVAROXACS3001: All Randomized Subjects)

[redacted]

[redacted]

[redacted]

A17. The submission states that '…rates presented in the study publication are Kaplan Meier estimates whereas the data presented in the submission are crudes rates' (p78, Section 6.5.3). Please provide rationale and limitation of this approach. For completeness, please provide event rates as Kaplan Meier estimates for ALL primary and secondary endpoints for the total and licensed populations by dose, each strata and analysis type (e.g. mITT and ITT)

The presentation of crude rates is the objective method to show the proportion of patients that have experienced the respective endpoint in the study. It is clear, easy to understand and no assumptions have to be made. The limitation of this method is that the timing of an event as well as the length of the observation time is ignored. Especially in long term studies this is a marked weakness. The KM estimates give the expected cumulative risk of an endpoint and allow for comparison to other studies or observations. For the publication it was decided to present 2-year KM estimates. This is limited to the observation time of two years. To not limit the data presentation to the regulatory authorities both, crude rates as well as KM estimates, were presented in the submission documents. The KM estimates were presented in tables over time in steps of 30 days and as KM plots.

The Kaplan-Meier tables are presented below and are academic in confidence. Unfortunately the secondary endpoint data for the licensed population has not been generated to-date and we are currently working in collaboration with Janssen to provide the full dataset.

Trial population

Study RIVAROXACS3001

Output DEFF07A: Cumulative Risk of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC

[redacted]

Study RIVAROXACS3001

Output DEFF07A: Cumulative Risk of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output D8FF07A: Cumulative Risk of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF07A: Cumulative Risk of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF07B: Cumulative Risk of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC

[redacted]

Study RIVAROXACS3001

Output DEFF07B: Cumulative Risk of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (continued)

[redacted]

Output DEFF07B: Cumulative Risk of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF07B: Cumulative Risk of the Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF08A: Cumulative Risk of First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC

[redacted]

Study RIVAROXACS3001

Output DEFF08A: Cumulative Risk of First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF08A: Cumulative Risk of First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF08A: Cumulative Risk of First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF08B: Cumulative Risk of First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC

[redacted]

Study RIVAROXACS3001

Output DEFF08B: Cumulative Risk of First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC (continued)

[redacted]

Output DEFF08B: Cumulative Risk of First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF08B: Cumulative Risk of First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF09: Cumulative Risk of First Occurrence of Net Clinical Outcome as Adjudicated by the CEC

[redacted]

[redacted]

Output DEFF09: Cumulative Risk of First Occurrence of Net Clinical Outcome as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF09: Cumulative Risk of First Occurrence of Net Clinical Outcome as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF10A: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Revascularization as Adjudicated by the CEC

[redacted]

Study RIVAROXACS3001

Output DEFF10A: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Revascularization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF10A: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Revascularization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF10A: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Revascularization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF10B: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Revascularization as Adjudicated by the CEC

[redacted]

Study RIVAROXACS3001

Output DEFF10B: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Revascularization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF10B: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Revascularization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF10B: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Revascularization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF11A: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Hospitalization as Adjudicated by the CEC

[redacted]

Study RIVAROXACS3001

Output DEFF11A: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Hospitalization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF11A: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Hospitalization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF11A: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Hospitalization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF11B: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Hospitalization as Adjudicated by the CEC

[redacted]

Study RIVAROXACS3001

Output DEFF11B: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Hospitalization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF11B: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Hospitalization as Adjudicated by the CEC (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF11B: Cumulative Risk of First Occurrence of Cardiovascular Death, MI, Stroke and Severe Recurrent Ischemia Requiring Hospitalization as Adjudicated by the CEC (continued)

[redacted]

Licensed population

Table 1 / 7: Cumulative rate (Kaplan-Meier and crude rate) of event: Primary Efficacy Endpoint as Adjudicated by CEC in subjects with elevated biomarkers excl. prior stroke/TIA, Population 'Modified Intent-to-Treat (Excluding Sites 091001, 091019, and 091026)' Stratum: All Strata

[redacted]

Table 1 / 7: Cumulative rate (Kaplan-Meier and crude rate) of event: Primary Efficacy Endpoint as Adjudicated by CEC in subjects with elevated biomarkers excl. prior stroke/TIA, Population 'Modified Intent-to-Treat (Excluding Sites 091001, 091019, and 091026)' Stratum: All Strata (cont.)

[redacted]

Table 1 / 8: Cumulative rate (Kaplan-Meier and crude rate) of event: Primary Efficacy Endpoint as Adjudicated by CEC in subjects with elevated biomarkers excl. prior stroke/TIA, Population 'Modified Intent-to-Treat (Excluding Sites 091001, 091019, and 091026)' Stratum: ASA

[redacted]

Table 1 / 8: Cumulative rate (Kaplan-Meier and crude rate) of event: Primary Efficacy Endpoint as Adjudicated by CEC in subjects with elevated biomarkers excl. prior stroke/TIA, Population 'Modified Intent-to-Treat (Excluding Sites 091001, 091019, and 091026)' Stratum: ASA (cont.)

[redacted]

Table 1 / 9: Cumulative rate (Kaplan-Meier and crude rate) of event: Primary Efficacy Endpoint as Adjudicated by CEC in subjects with elevated biomarkers excl. prior stroke/TIA, Population 'Modified Intent-to-Treat (Excluding Sites 091001, 091019, and 091026)' Stratum: ASA + Thieno

[redacted]

[redacted]

A18: Rivaroxaban 2.5mg BID significantly reduces the rate of CV death and death from any cause, whereas this was not seen with rivaroxaban 5mg BID. Please clarify why, as this does not appear intuitive. In addition, a reduction in MI is observed with rivaroxaban 5mg BID but not rivaroxaban 2.5mg BID. Please clarify why.

The effect of rivaroxaban 2.5 mg b.i.d. on the primary efficacy endpoint was driven by a 34% reduction in CV deaths (HR: 0.66, 95% CI: 0.51, 0.86), including a directionally consistent numerical reduction in MIs; whereas the effect in the 5 mg b.i.d. group was largely driven by the reduction in MIs (HR: 0.79, 95% CI: 0.65, 0.97) with a directionally consistent numerical reduction in CV deaths.

It has been demonstrated that the efficacy of each dose of rivaroxaban is comparable in reducing the occurrence of the composite primary efficacy endpoint. Both rivaroxaban doses reduce the risk of important clinical events. The doses are more similar than they are different.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 4: (TEFFCR1010A) Effect of Rivaroxaban Compared with Placebo on the CEC-adjudicated Primary Efficacy Endpoint (First Occurrence of CV Death, MI, Stroke) and its Components up to 30 Days and Censored at the Earlier of the Day before the Start of PPI (Omeprazole/Esomeprazole) or of the Last Thienopyridine Use
(Study RIVAROXACS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)

[redacted]

Table 1-7 Similar Reduction in Fatal and non-Fatal MI with Both Rivaroxaban Doses (mITT, All Strata, each dose)

[redacted]

Table 1-6 Effect of Rivaroxaban on the Primary Efficacy Endpoint and Cardiovascular Death in Subjects Who Did Not Experience a Non-CABG TIMI Major Bleeding (treatment-emergent safety; excluding sites 091001, 091019, 091026, Stratum 2)

[redacted]

A19. Please provide tabulated results (including explanations, where appropriate) on whether the efficacy of rivaroxaban in the total and licensed population (by dose and each strata) varied by age, sex and geographical region.

The licenced population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis would therefore be subgroup data of a subgroup and Bayer believes the post-hoc selection may jeopardise the randomisation and the statistical confidence in the results of those analyses. As such, we have provided data for the trial population only. The following tables are academic in confidence. The results demonstrate that there is no siginifcant interaction of treatment group and each baseline subgroup based on the Cox proportional hazards model including treatment group, baseline subgroup and their interaction.

Study RIVAROXACS3001

Output DEFF21B: Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup

[redacted]

Study RIVAROXACS3001

Output DEFF21B: Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF21B: Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF21C: Effect of Rivaroxaban 5 mg BID Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup

[redacted]

Study RIVAROXACS3001

Output DEFF21C: Effect of Rivaroxaban 5 mg BID Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF21C: Effect of Rivaroxaban 5 mg BID Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup (continued)

[redacted]

A20: The NICE decision problem states that 'if evidence allows the following subgroups will be considered: people with NSTEMI; people with STEMI; people with diabetes mellitus; people who received prior primary PCI; and people who did not receive prior primary PCI in the acute phase of management. As evidence is available, please could you provide ALL primary and secondary endpoint data, (incuding safety data) for the total and licensed populations by dose and each strata.

The licenced population is a subgroup of the pivotal Phase III trial. Any further subgroup analysis ("level 2") would therefore be subgroup data of a subgroup and Bayer believes the post-hoc selection may jeopardise the randomisation and the statistical confidence in the results of those analyses. Such analyses are not statistically sound as the trial was not powered to draw conclusion about (non-pre-specified) subgroups of subgroups. In line with Yusuf and colleagues (1991)"*We believe that the overall "average" result of a randomised clinical trial is usually a more reliable estimate of treatment effect in the various subgroups examined than are the observed effects in individual subgroups. Interesting and compelling subgroup effects should be regarded seriously if they arise from appropriate analytic methods. We urge extreme caution, however, in interpreting striking results that are data derived even for the generation of hypotheses*." As such, and as discussed at the decision problem meeting with NICE in May 2014, such data has not been provided by Bayer.

Bayer however agrees that subgroup data can provide interesting information and therefore we are pleased to provide the "level 1" subgroup analysis performed on the pivotal Phase III trial. Please see the figures below.

In general, rivaroxaban treatment was consistently associated with improved outcomes on the primary efficacy endpoint across all major subgroups. A favourable HR for rivaroxaban compared with placebo was observed across the majority of subgroups, both for the combined rivaroxaban groups, as well as for the 2.5 mg b.i.d. and 5 mg b.i.d. doses individually compared with placebo. For the majority of analyses, interaction p values were >0.05.

The following tables are academic in confidence.

Study RIVAROXACS3001

Output DRFF21A: Effect of Combined Rivaroxaban Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup

[redacted]

Study RIVAROXACS3001

Output DEFF21A: Effect of Combined Rivaroxaban Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF21B: Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup

[redacted]

Study RIVAROXACS3001

Output DEFF21B: Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DBFP21C: Effect of Rivaroxaban 5 mg BID Compared with Placebo on Primary Efficacy Endpoint (First Occurrence of Cardiovascular Death, MI, Stroke) as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF22A: Effect of Combined Rivaroxaban Compared with Placebo on First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC by Subgroup

[redacted]

Study RIVAROXACS3001

Output DEFF22A: Effect of Combined Rivaroxaban Compared with Placebo on First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DEFF22B: Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC by Subgroup

[redacted]

Study RIVAROXACS3001

Output DRPF22B: Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DRFF22C: Effect of Rivaroxaban 5 mg BID Compared with Placebo on First Occurrence of All Cause Death, MI, Stroke as Adjudicated by the CRC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DRFF23A: Effect of Combined Rivaroxaban Compared with Placebo on First Occurrence of Net Clinical Outcome as Adjudicated by the CEC by Subgroup

[redacted]

Study RIVAROXACS3001

Output DRFF23A: Effect of Combined Rivaroxaban Compared with Placebo on First Occurrence of Net Clinical Outcome as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DBFF23B: Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on First Occurrence of Net Clinical Outcome as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DRFF23C: Effect of Rivaroxaban 5 mg BID Compared with Placebo on First Occurrence of Net Clinical Outcome as Adjudicated by the CEC by Subgroup

[redacted]

Study RIVAROXACS3001

Output DRFP23C: Effect of Rivaroxaban 5 mg BID Compared with Placebo on First Occurrence of Net Clinical Outcome as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Testing stopped at this point according to the hierarchical testing strategy.

Study RIVAROXACS3001

Output DBL10A: Effect of Combined Rivaroxaban Compared with Placebo on First Occurrence of Treatment-Emergent Non-CABG related TIMI Major Bleeding Events as Adjudicated by the CEC by Subgroup

[redacted]

Study RIVAROXACS3001

Output DBL10A: Effect of Combined Rivaroxaban Compared with Placebo on First Occurrence of Treatment-Emergent Non-CABG related TIMI Major Bleeding Events as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DBL10B: Effect of Rivaroxaban 2.5 mg BID Compared with Placebo on First Occurrence of Treatment-Emergent Non-CABG related TIMI Major Bleeding Events as Adjudicated by the CEC by Subgroup (continued)

[redacted]

Study RIVAROXACS3001

Output DBL10C: Effect of Rivaroxaban 5 mg BID Compared with Placebo on First Occurrence of Treatment-Emergent Non-CABG related TIMI Major Bleeding Events as Adjudicated by the CEC by Subgroup

[redacted]

Study RIVAROXACS3001

Output DBL10C: Effect of Rivaroxaban 5 mg BID Compared with Placebo on First Occurrence of Treatment-Emergent Non-CABG related TIMI Major Bleeding Events as Adjudicated by the CEC by Subgroup (continued)

[redacted]

A21. Please provide a full tabulated breakdown of the following by study group, dose, and strata for the total and licensed population (including p value):

- Protocol deviations
- Discontinuation of treatment, with reason
- Discontinuation from study, with reason
- Unknown vital status.

Please find attached the data for the full trial population. Unfortunately, the data for the licensed population have not been generated. We are happy to generate this data if the ERG can confirm they need this data, however we believe those data should not differ among the licensed population.

The following tables are academic in confidence.

Table 19: (TSUB14) Major Protocol Deviations (Study RIVAROXACS3001: All Randomized Subjects)

[redacted]

Table 7: (TSUB07B-derived) Primary Reasons for Premature Discontinuation From Double-Blind Treatment Period
(Study RIVAROXACS3001: Safety Analysis Set)

[redacted]

Table 8: (TSUB08A) Primary Reasons for Premature Discontinuation from Study (Study RIVAROXACS3001; All Randomized Subjects)

[redacted]

Table 8 Continued (TSUB08A): Primary Reasons for Premature Discontinuation from Study
(Study RIVAROXACS3001; All Randomized Subjects Analysis Set)

[redacted]

As discussed in the manufacturer's submission (page 102-103), there was an attempt to ascertain additional information on vital status after the end of study.

[redacted]

[redacted]

[redacted]

[redacted]

Table 10: (DSUBCR1003B) Summary of Vital Status Based on Newly Collected Data Among Missing Follow-up Subjects till the Global Treatment End Date
(Study RIVAROXACS3001: All Randomized Subjects)

A22. For completeness, please provide tabulated safety data for treatment related adverse events using the GUSTO bleeding event classification scale and the International Society on Thrombosis and Haemostasis (ISTH) event classification scale for the total and licensed populations by dose and each strata.

The tabulated overview of the treatment effect using the different bleeding scales is presented below and is academic in confidence.

Trial population

Study RIVAROXACS3001

Output DBL04: Effect of Rivaroxaban Compared with Placebo on Treatment-Emergent Bleeding using the TIMI, GUSTO and ISTH Scales as Adjudicated by the CEC

[redacted]

Study RIVAROXACS3001

Output DBL04: Effect of Rivaroxaban Compared with Placebo on Treatment-Emergent Bleeding using the TIMI, GUSTO and ISTH Scales as Adjudicated by the CEC (continued)

[redacted]

Licensed population

Table 1: Output DBL04: Effect of Rivaroxaban Compared with Placebo on Treatment-Emergent Bleeding using the TIMI,GUSTO and ISTH Scales as Adjudicated by the CEC in subjects with elevated biomarkers (excluding subjects with prior stroke/TIA) Analysis Set: Treatment-Emergent Safety

Subject Stratification: All Strata

[redacted]

Table 1: Output DBL04: Effect of Rivaroxaban Compared with Placebo on Treatment-Emergent Bleeding using the TIMI,GUSTO and ISTH Scales as Adjudicated by the CEC in subjects with elevated biomarkers (excluding subjects with prior stroke/TIA) Analysis Set: Treatment-Emergent Safety

[redacted]

A23. Please provide full tabulated details on compliance/adherence with study treatment (by dose) for each drug in the intervention arm (rivavaroxaban, thienopyrimidine and aspirin separately and combined) and in the control group (thienopyrimidine and aspirin separately and combined).

Across all treatment groups and strata, compliance was very high; [redacted] of 15,350 subjects valid for safety had compliance rates ≥85% over the course of the study. Approximately [redacted] of subjects in each stratum had compliance rates between 60 and <85%, and only [redacted] were less than 60% compliant with study drug. The following table is academic in confidence.

Table 20: (TSUB20) Compliance (Study RIVAROXACS3001; Safety Analysis)

[redacted]

Compliance data is only available for the investigated treatment (Rivaroxaban or placebo). Data on exposure to ASA and thienopyridine can be found in the tables below.

Table 17: (TSUB24B) Extent of Exposure to Concomitant Aspirin Between the First Dose of Study Drug and the Last Dose of Study Drug (Study RIVAROXACS3001: Safety Analysis Set)

[redacted]

Table 17 Continued (TSUB24B): Extent of Exposure to Concomitant Aspirin between the First Dose of Study Drug and the Last Dose of Study Drug
(Study RIVAROXACS3001: Safety Analysis Set)

[redacted]

Table 18: (TSUB25B) Extent of Exposure to Concomitant Thienopyridine Between the First Dose of Study Drug and the Last Dose of Study Drug (Study RIVAROXACS3001: Safety Analysis Set)

[redacted]

Table 18 Continued (TSUB25B): Extent of Exposure to Concomitant Thienopyridine between the First Dose of Study Drug and the Last Dose of Study Drug
(Study RIVAROXACS3001: Safety Analysis Set)

[redacted]

A24. For completeness, please confirm that an indirect comparison, to supplement the direct evidence, could not be generated due to there only being one trial using rivaroxaban plus clopidogrel and aspirin in patients with ACS.

The only evidence available on the efficacy and safety of rivaroxaban plus aspirin (with or without clopidogrel) in patients without prior history of stroke / TIA who are biomarker positive and eligible for secondary prevention of ACS outcomes is the ATLAS ACS 2 TIMI 51 trial. Therefore, it was not necessary to build an indirect comparison to supplement the direct evidence presented in the submission.

Section B: Clarification on cost-effectiveness data

Probabilistic data issues

B1. **Priority Question:** For the majority of parameters within the PSA, it has been assumed that the range is +/- 25% of the deterministic value. Please clarify why this method was used rather than using published standard errors, (for example those presented in Bagust el al (Table 16, p56) or calculating standard errors from trial data, or from NHS reference cost data).

Plus and minus 25% of the deterministic value offers in almost all cases a much wider interval than would be seen if the interval was based on published standard errors. The wider interval is preferred because it is felt that published standard errors often offer an unrealistic sense of confidence. This is for example true for those standard errors presented in Bagust et al where an utility estimate is presented for ACS patients without events of 0.842 with a standard error of 0.002. This may be a nice estimate of the mean within their trial sample, but it does not necessarily represent the average

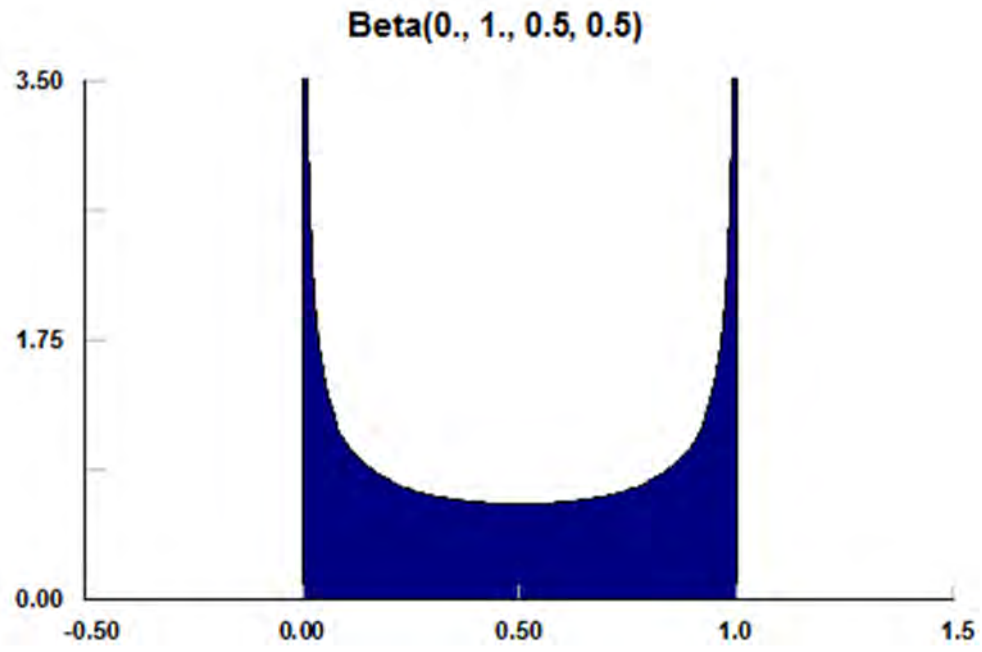
quality of life of a patient from any other ACS population especially given its dependency on age, the size of the infarction, etc.

The same is true for the standerd errors around NHS reference cost data which offer a similar sense of precison, which was felt to offer an unrealistic sense of confidence around the point estimate.

B2. **Priority Question:** Further to B1 the method of sampling from the +/- 25% range appears to be non-standard and apparently uses a Beta distribution with an alpha of 0.5 and beta of 0.5.

The probability density function of a Beta distribution with alpha=0.5 and beta=0.5 is presented in the diagram below which shows that this favours values towards the ends of the distribution.

Please clarify why this distribution was used for most of the parameters in the PSA.



We acknowledge that this was an error in the model, and that a beta distribution with an alpha of 1 and a beta of 1 would be more appropriate. Running the probabilistic analysis with this updated beta distribution results in a probability of cost-effectiveness of >99.9% at a willingness to pay threshold of £20,000 per QALY.

Applying an even more conservative distribution of beta (2,2) results in a probability of cost-effectiveness of >99.9% at a willingness to pay threshold of £20,000 per QALY.

For comparison, the probability of rivaroxaban being cost-effective when using a beta distribition with an alpha of 0.5 and a beta of 0.5 (as presented in the original manufacturer's submission), assuming a willingness to pay threshold of £20,000 per QALY, was >99.9%.

Therefore, the application of the beta (0.5, 0.5) distribution, whilst an error, does not impact on the conclusions regarding estimated cost-effectiveness of rivaroxaban.

B3. **Priority Question:** please clarify why there is no correlation assumed between the shape and scale parameters in the PSA of each of the Weibull distributions used in the observation period of the model.

Earlier versions of the model held all of the trial data, and estimates were obtained directly per group and per time period. We called this the non-parametric approach (the approach has been made available to NICE in the revised model provided alongside these responses).

The Weibull model was introduced in the model to enable subgroup analyses, as some of the smaller subgroups showed quite irregular behaviour – which is not unexpected where low patient numbers exist. For example, we saw much higher event rates in the later than the earlier stages of the trial for some subgroups. The application of the Weibull model was referred to as the paramteric approach. The results were almost identical when analysing the whole study using either approach and that there were only differences for the smaller sub-groups.

Naturally, using the Weibull model assumes that the paramteric model applies, and the confidence intervals are smaller than in the non-paramteric approach. Taking account of the covariance matrix of the parameters would – in this case – decrease the width of the confidence intervals even further. We chose to neglect this and as such obtain estimates that one might consider "conservative" in the sense that slightly wider confidence intervals were applied in the sensitivity analyses.

Time issues

B4. **Priority Question:** please clarify why 48 weeks is often considered to represent one year in both the model and in the submission? This causes a problem when transition probabilities are using different assumed cycle lengths than costs and utilities.

Efficacy and safety data for use in the model were extracted from the phase 3 ATLAS ACS 2 TIMI 51 clinical trial. Follow-up in this trial occurred every 12 weeks and as such data were available at 12-weekly intervals. The model was designed with 12-weekly cycle lengths up to year two to best reflect the clinical data available. Given that the 48 week interval is closer to 1 year than the 60 week interval, 48 weeks was considered to represent one year in the model. Wide confidence intervals of +/- 25% were applied in the model in order to address the uncertainty surrounding the cost and utility inputs applied. Analyses demonstrated that conclusions did not change even with the application of these intervals.

In addition, an analysis has been run whereby costs of events are adjusted to reflect (for example), 12 weeks rather than 3 months (original cost / 91.25 * 84, etc). The results from this analysis are presented below. It can be seen that results do not really change from what is presented in the model base case. Note that there was no need to adjust utilities as all utility inputs were normalised to annual values before application in the model and were applied on a cycle by cycle basis – therefore utilities already reflect the cycle length accurately.

	Delta Cost	*Delta QALY*	*ICER*
Base case	*£763.58*	*0.12*	*£6,202.84*
Cost Adjustment	*£862.45*	*0.12*	*£7,005.97*

B5. It is stated that the probability of transitioning from the 'no event' health state to the 'two MI' health state is calculated by multiplying the transition probabilities in the first four weeks in the first model cycle (manufacturer's submission, page 202). The first model cycle is stated as being 12 weeks; please clarify why this approach was appropriate.

Bayer apologise for this typographical error in the submission. For clarity:

- For example, the probability for a patient treated with rivaroxaban to move from the no event state to the MI health state between weeks 0 and 12 is calculated as follows (using the Weibull parameters presented in section 7.3.1):
    - TP(MI: 0-4 weeks) =exp(-((0/exp(12.543180))^exp(-1.017409)))-exp(-((4/exp(12.543180))^exp((-1.017409))) =1.76%.
- The parametric approach is based on first events only and to estimate the probability of a patient on rivaroxaban to move from no event state to the MI + MI health between weeks 0 and 12 is calculated by TP(MI:0-4 weeks) ×TP(MI: 0-4 weeks) = 1.76 % × 1.76 % = 0.03%.

Should read:

- For example, the probability for a patient treated with rivaroxaban to move from the no event state to the MI health state between weeks 0 and 4 is calculated as follows (using the Weibull parameters presented in section 7.3.1):
    - TP(MI: 0-4 weeks) =exp(-((0/exp(12.543180))^exp(-1.017409)))-exp(-((4/exp(12.543180))^exp((-1.017409))) =1.76%.
- The parametric approach is based on first events only and to estimate the probability of a patient on rivaroxaban to move from no event state to the MI + MI health between weeks 0 and 4 is calculated by TP(MI:0-4 weeks) ×TP(MI: 0-4 weeks) = 1.76 % × 1.76 % = 0.03%.

B6. Please clarify that the cycle lengths of the initial two cycles are 4 weeks and 8 weeks rather than 12 weeks as reported in the MS.

Bayer apologises for this lack of clarity. The lengths of the initial two cycles are 4 weeks and 8 weeks, not 12 weeks as reported in the manufacturer's submission.

Model data issues

B7. **Priority Question:** please clarify why the base case was considered to be appropriate when Table 70 (manufacturer's submission, page 325) shows that the model consistently over predicts event rates when compared to the observed trial data.

Adjustments were made to the model based on clinical feedback such that the model would reflect clinical expectations as closely as possible. There are three key reasons why the model seemingly over-predicts event rates compared to the observed trial data.

Firstly, in the model base case, clopidogrel may only be administered for a maximum of 1 year. This is in line with NICE recommendations for clopidogrel treatment in ACS patients. However, in the clinical trial some patients received clopidogrel for longer than one year. Therefore, the benefit of clopidogrel treatment in terms of reducing events was higher in the trial than in the economic model base case.

Secondly, as already described in the manufacturer's submission, the transition probabilities for the model base case were derived using a parametric approach due to difficulties in estimating the transition probabilities directly from the ATLAS 2 trial data, particularly for the later cycles within the observation period, where for some groups / events an increasing hazard rate was seen. The ATLAS 2 trial data is interpolated using a Weibull parametric approach to help "smooth" the data by removing fluctuations caused by fewer observations and to ensure a decreasing hazard rate, as would be expected clinically, is modelled. As such, some differences in terms of event risk will be present.

Thirdly, it was felt that discontinuation rates of rivaroxaban in the clinical trial differed to what would be seen in clinical reality. As such, the model applies an additional adjustment to discontinuation. In light of the posology description in rivaroxaban's label, it was expected that discontinuation in the second year of treatment would be higher than was seen in the ATLAS 2 study. Therefore, efficacy was adjusted such that it was assumed that 19% of patients would continue treatment in year 2, declining over the course of the year to 0% by the end of the second year. In the trial, 76.06% of patients continued treatment at the start of year 2, declining to 71.27% by the end of the year. The adjustment was made on the basis of discussions with key opinion leaders. The result (in terms of patients continuing treatment, is provided in the table below). With less patients continuing treatment in the model than the trial, event rates were consequently higher in the model.

Time (Wks)	*Treatment continuation Trial*	*Treatment continuation Model*
0-4	*93.10%*	*93.10%*
4-12	*89.54%*	*89.54%*
12-24	*86.94%*	*86.94%*
24-36	*82.23%*	*82.23%*
36-48	*78.45%*	*78.45%*
48-60	*76.06%*	*19.02%*
60-72	*73.49%*	*13.23%*
72-84	*72.06%*	*8.65%*
84-96	*71.27%*	*4.28%*

B8. **Priority Question:** please clarify why the relative risk reduction (RRR) of the combined endpoint of the ATLAS 2 trial is used as the RRR of rivaroxaban for MI death, MIs, ISs and HS/ICHs, not the relative risk reduction from each of the individual endpoints.

Data for each treatment arm were entered directly into the model for the observation period (baseline to two years). Data were implemented for each event / combination of events separately, based on analyses of the ATLAS ACS 2 TIMI 51 trial. A relative risk reduction for rivaroxaban was only applied during the extrapolation period, and would only be utilised if analyses of rivaroxaban treatment beyond 2 years are run. Given the labelling authorisation of rivaroxaban, these analyses are of no interest and the model has been updated to remove these inputs and limit the treatment duration of rivaroxaban to a maximum of 2 years.

B9. **Priority Question:** please clarify which calibration methods have been used in the model and the parameters which are calibrated by each calibration method.

The calibration methods that have been used can informally be decribed as a grid search per parameter over a list of parameters slowly iterating towards an "optimal" fit (using the solver add-in in Excel). The list of parameters concerns:

- The age specific increase in the probability to have an MI
- The age specific increase in the probability to have an ischemic stroke
- The age specific increase in the probability to have an haemorrhagic stroke
- The age specific increase in the probability to die of other vascular death
- The age specific increase in the probability to die of non-cardiovascular death
- The age specific increase in the probability to die of an MI, given an MI
- The age specific increase in the probability to die of a stroke, given a stroke.

The parameters defining "optimal" are those mentioned in table 46 of the manufacturer's submission, together with a life expectancy of 13.55 years. All of these parameters were taken from the literature.

B10. Please clarify how the numbers in Table 44 (manufacturer's submission, page 207) are calculated and the assumptions made in calculating these values.

The numbers in Table 44 (relative risk of subsequent events) are calculated based on a combination of information sourced from the ATLAS 2 trial data and Smolina et al (2012).

The following data on the occurrence of events over time is taken from the ATLAS 2 trial data:

Events	1st 6 months	2nd 6 months	Later
MI	100.00%	41.72%	30.45%
Stroke	100.00%	55.87%	47.36%
OCD	100.00%	33.00%	33.00%

Source: Tables for crude rates at 12 weekly intervals of the absolute (n) number of events by dose and stratum (intent to treat) – Data on file.

This data (above table) is calculated by looking at the occurrence of each event type during the first 6 months, second 6 months and later periods of the ATLAS 2 trial. Assuming that the number of events occurring in the first 6 months is the baseline from which to work from, it can be seen that the risk of events decreases over time. For example, if 100 MI events occurred in the first six months, 41.72 are expected to occur in the second six months (100% * 41.72%), and 30.45 in the second year (100% * 30.45%).

Further, a general assumption is made that patients have a 1.5 times increased risk of suffering a subsequent ACS event in the post 12 month period after an earlier event. This estimation is based on Smolina (2012), where the following is stated:

"The risk of death from any cause in survivors of first and recurrent MIs was respectively 2 and 3 times higher than the general UK population for similar age groups".

In the absence of any precise data, this estimate for recurrent-first MI of 3/2 = 1.5 is used as a proxy for the relative risk of both fatal and non-fatal events in the later periods (post 1 year) of the model, regardless of which prior events (MI / IS / HS, ICH) were experienced.

The relative risk inputs for the first 6 months and second 6 months after an event are subsequently estimated backwards from this value of 1.5 by considering the decline in events over time in reverse (from the table above). Further details are presented below:

- First 6 months
  - Relative risk in the post 12 months following an event is given by R(later)
  - The decreasing number of events in the first 6 months is given by D(first)
  - The decreasing number of events in the second 6 months is given by D(second)
  - The decreasing number of events in the post 12 months (later) D(later)
  - The relative risk of suffering a subsequent MI - for example in patients who have already experienced a secondary MI to the index event in the first 6 months - is given by:
    - R(first) = R(later)×D(first)/D(later)
    - R(first) = 1.5×100%/30.45%
    - R(first) = 4.9

- Second 6 months
  - The relative risk of suffering a subsequent MI in patients who have already experienced a secondary MI to the index event in the second 6 months is given by:
    - R(second)=R(later)×D(second)/D(later)
    - R(second)=1.5×41.72%/30.45%
    - R(second)=2.1

B11. Further to question B10, please clarify why, in Table 44, some events have a higher relative risk after 12 months of rivaroxaban treatment than during the 12 months of rivaroxaban treatment. For example, after MI or IS, the risk for HS/ICH over the 1st and 2nd 6 months is 1.0, but increases to 1.5 during the 'post 12 months' period.

Further to the explanation provided to question B10, the relative risks for non HS/ICH events after an HS/ICH, and for HS/ICH events after an MI or IS are assumed to be equal to 1 due to small number of HS/ICH events in the trial, making it impossible to estimate a relative change in the occurrence of events over time. The calculation used in the estimation of all other relative risks is explained above.

Please refer to table 80 of the manufacturer's submission (page 339), where the results of a scenario omitting the increased risk of events following a previous cardiovascular event (i.e. all relative risks were set to 1). The results of this analysis demonstrate the limited impact these input values have on the results. The reason for this is that so few patients actually have multiple events that the overall impact of increasing or decreasing the risk of subsequent events is negligible.

B12. Please clarify why the calibration method(s) used to calculate the values in Table 47 (manufacturer's submission, page 210) was not amended to limit the possibility of producing results that may not have face validity. For example for patients who experience a myocardial infarction (MI) in the model, the proportion of MIs that result in a fatality declines as age increases. There is a similar concern with how ischaemic and haemorrhagic stroke fatality rates are modelled over time.

The negative input values for the increase in risk due to age for fatal MI, fatal IS and fatal HS/ICH as a proportion of total (fatal + non-fatal) MI, total IS and total HS/ICH respectively are the result of an increasing competing risk of other cardiovascular death and non-cardiovascular death over time. This decreases the risk of death due to MI, IS and HS/ICH. Overall (i.e. considering all causes), the risk of death increases with age in the model.

B13. In the deterministic sensitivity analysis presented in Table 77 the lower and upper values of the ICER from changing each parameter is presented. Please clarify the upper and lower value each parameter was set at to produce the upper and lower bound of those ICERs. It is noted that some ICERs appear to be the same number for both upper and lower values.

Uncertainty margins of +/- 25 % either side of the base value are applied using a uniform distribution when conducting the univariate sensitivity analyses for cost per event, cost of rivaroxaban, and utility per event (this is line with the approach reported by Heeg et al 2007). Utility values are capped to 1 in the sensitivity analysis to avoid values greater than 1 that would not have face validity.

The duration of the transient health states for bleeding and revascularisation events are varied between 14 days and 84 days using a uniform distribution – the range of values was triggered from the clinical validations conducted during model development.

To assess the impact of the safety events a 95% CI on the beta distribution is applied to these events in the rivaroxaban arm only (which is estimated by taking (x +/- (1.96 ×SE)).

Discount rates are varied between 0% and two thirds higher than in the base case.

For all other remaining non-efficacy input parameters (relative risk of subsequent events, age specific increased risk, and initial case fatalities) large uncertainty margins are assumed in the absence of literature based information. A 50% margin either side (or factor of 0.5 and 1.5) of the input value is considered by applying a uniform distribution. This is considered a conservative approach that will overestimate the uncertainty surrounding these parameters.

The table below presents the actual extreme values applied in the sensitivity analysis for non-efficacy parameters, given the assumptions described above.

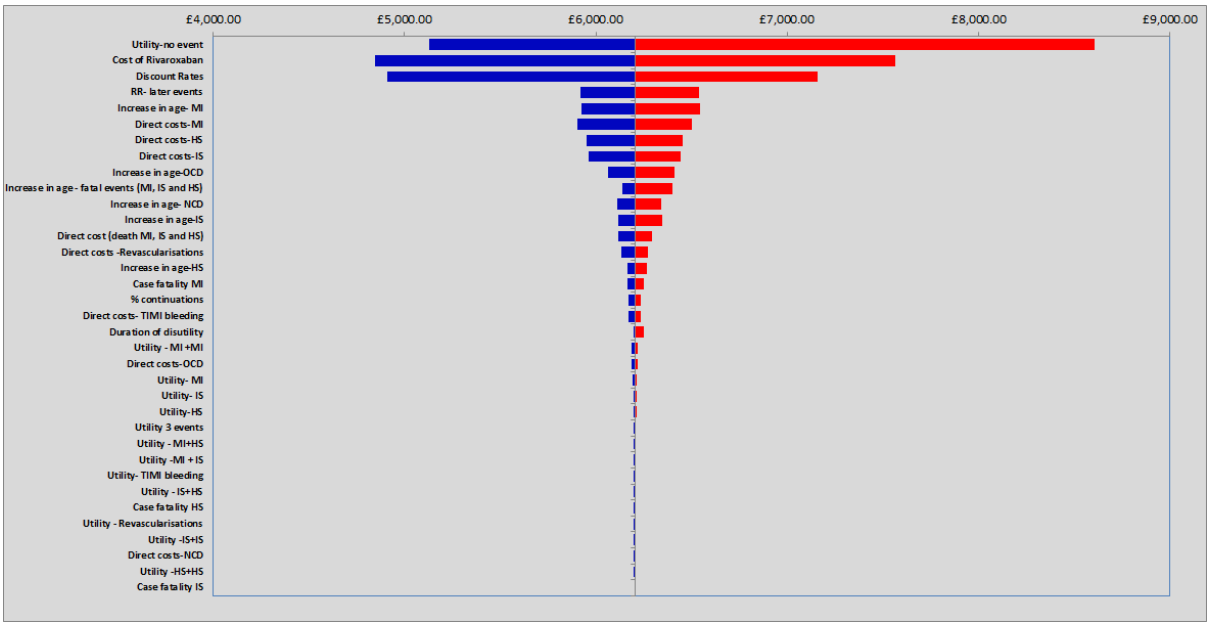
		Minimum Value	Maximum Value
Discount rates	3.50%	0.00%	5.83%
Daily cost rivaroxaban	£2.10	£1.58	£2.63
UTILITIES			
no event	0.84	0.63	1.00
MI 1st 6 months	0.78	0.58	0.97
MI 2nd 6 months	0.82	0.62	1.00
MI later (post 12 months)	0.82	0.62	1.00
IS 1st 6 months	0.70	0.53	0.88
IS 2nd 6 months	0.75	0.56	0.93
IS later (post 12 months)	0.79	0.59	0.99
HS 1st 6 months	0.70	0.53	0.88
HS 2nd 6 months	0.75	0.56	0.93
HS later (post 12 months)	0.79	0.59	0.99
MI + MI 1st 6 months	0.61	0.46	0.76
MI + MI 2nd 6 months	0.67	0.51	0.84
MI + MI later (post 12 months)	0.67	0.51	0.84
IS+ IS 1st 6 months	0.49	0.37	0.62
IS +IS 2nd 6 months	0.56	0.42	0.70
IS + IS later (post 12 months)	0.63	0.47	0.78
HS + HS 1st 6 months	0.49	0.37	0.62
HS + HS 2nd 6 months	0.56	0.42	0.70
HS +HS later (post 12 months)	0.63	0.47	0.78
MI + IS 1st 6 months	0.55	0.41	0.68
MI + IS 2nd 6 months	0.61	0.46	0.77
MI + IS later (post 12 months)	0.65	0.49	0.81
MI + HS 1st 6 months	0.55	0.41	0.68
MI +HS 2nd 6 months	0.61	0.46	0.77
MI + HS later (post 12 months)	0.65	0.49	0.81
IS + HS 1st 6 months	0.49	0.37	0.62
IS + HS 2nd 6 months	0.56	0.42	0.70
IS +HS later (post 12 months)	0.63	0.47	0.78
3 events 1st 6 months	0.38	0.29	0.48
3 events 2nd 6 months	0.46	0.34	0.57
3 events later (postr 12 months)	0.52	0.39	0.64
PCI/PTCA	0.79	0.59	0.99
CABG	0.74	0.56	0.93
TIMI Major bleeding	0.75	0.56	0.94
TIMI Minor bleeding	0.80	0.60	1.00
TIMI requiring medical attention	0.80	0.60	1.00
DIRECT COSTS			
MI - first three months (acute phase)	£3,585.55	£2,689.16	£4,481.94
MI- second three months	£1,980.14	£1,485.11	£2,475.18
MI second 6 months	£1,440.10	£1,080.08	£1,800.13
MI post 12 months	£1,080.08	£810.06	£1,350.10
IS- first three months (acute phase)	£7,756.05	£5,817.04	£9,695.06

IS -second three months	£3,060.21	£2,295.16	£3,825.26
IS second 6 months	£4,200.29	£3,150.22	£5,250.36
IS post 12 months	£3,120.22	£2,340.17	£3,900.28
HS first three months (acute phase)	£12,778.22	£9,583.67	£15,972.78
HS second three months	£3,060.21	£2,295.16	£3,825.26
HS second 6 months	£4,200.29	£3,150.22	£5,250.36
HS post 12 months	£3,120.22	£2,340.17	£3,900.28
PCI/PTCA	£2,081.77	£1,561.33	£2,602.21
CABG	£9,618.84	£7,214.13	£12,023.55
TIMI Major bleeding	£669.83	£502.37	£837.29
TIMI Minor bleeding	£67.79	£50.84	£84.74
TIMI requiring medical attention	£130.26	£97.70	£162.83
other cardiovascular death	£3,000.21	£2,250.16	£3,750.26
non cardiovascular death	£300.02	£225.02	£375.03
death MI	£1,500.10	£1,125.08	£1,875.13
death IS	£4,500.31	£3,375.23	£5,625.39
deathHS	£4,500.31	£3,375.23	£5,625.39
% INCREASE DUE TO AGE			
MI	8.70%	4.35%	13.05%
IS	10.65%	5.32%	15.97%
HS	10.73%	5.36%	16.09%
other vascular death	10.03%	5.01%	15.04%
non cardiovascular death	10.28%	5.14%	15.42%
case fatality MI	-13.90%	-6.95%	-20.84%
case fatality IS	-9.00%	-4.50%	-13.50%
case fatality HS	-9.00%	-4.50%	-13.50%
RELATIVE RISK OF SUBSEQUENT EVENTS			
AFTER MI			
1st 6 months			
MI	4.93	2.46	7.39
IS	3.17	1.58	4.75
HS	1.00	0.50	1.50
death MI	4.93	2.46	7.39
death IS	3.17	1.58	4.75
death HS	1.00	0.50	1.50
other vascular death	3.03	1.52	4.55
2nd 6 months			
MI	2.06	1.03	3.08
IS	1.77	0.88	2.65
HS	1.00	0.50	1.50
death MI	2.06	1.03	3.08
death IS	1.77	0.88	2.65
death HS	1.00	0.50	1.50
other vascular death	1.61	0.80	2.41
Later			
MI	1.50	0.75	2.25
IS	1.50	0.75	2.25
HS	1.50	0.75	2.25

death MI	*1.50*	*0.75*	*2.25*
death IS	*1.50*	*0.75*	*2.25*
death HS	*1.50*	*0.75*	*2.25*
other vascular death	*1.50*	*0.75*	*2.25*
AFTER IS			
1st 6 months			
MI	*4.93*	*2.46*	*7.39*
IS	*3.17*	*1.58*	*4.75*
HS	*1.00*	*0.50*	*1.50*
death MI	*4.93*	*2.46*	*7.39*
death IS	*3.17*	*1.58*	*4.75*
death HS	*1.00*	*0.50*	*1.50*
other vascular death	*3.03*	*1.52*	*4.55*
2nd 6 months			
MI	*2.06*	*1.03*	*3.08*
IS	*1.77*	*0.88*	*2.65*
HS	*1.00*	*0.50*	*1.50*
death MI	*2.06*	*1.03*	*3.08*
death IS	*1.77*	*0.88*	*2.65*
death HS	*1.00*	*0.50*	*1.50*
other vascular death	*1.61*	*0.80*	*2.41*
Later			
MI	*1.50*	*0.75*	*2.25*
IS	*1.50*	*0.75*	*2.25*
HS	*1.50*	*0.75*	*2.25*
death MI	*1.50*	*0.75*	*2.25*
death IS	*1.50*	*0.75*	*2.25*
death HS	*1.50*	*0.75*	*2.25*
other vascular death	*1.50*	*0.75*	*2.25*
AFTER HS			
1st 6 months			
MI	*1.00*	*0.50*	*1.50*
IS	*1.00*	*0.50*	*1.50*
HS	*4.93*	*2.46*	*7.39*
death MI	*1.00*	*0.50*	*1.50*
death IS	*1.00*	*0.50*	*1.50*
death HS	*4.93*	*2.46*	*7.39*
other vascular death	*1.00*	*0.50*	*1.50*
2nd 6 months			
MI	*1.00*	*0.50*	*1.50*
IS	*1.00*	*0.50*	*1.50*
HS	*2.06*	*1.03*	*3.08*
death MI	*1.00*	*0.50*	*1.50*
death IS	*1.00*	*0.50*	*1.50*
death HS	*2.06*	*1.03*	*3.08*
other vascular death	*1.00*	*0.50*	*1.50*
Later			
MI	*1.50*	*0.75*	*2.25*
IS	*1.50*	*0.75*	*2.25*
HS	*1.50*	*0.75*	*2.25*
death MI	*1.50*	*0.75*	*2.25*

death IS	*1.50*	*0.75*	*2.25*
death HS	*1.50*	*0.75*	*2.25*
other vascular death	*1.50*	*0.75*	*2.25*
> 2 Events			
Any Event	*1.50*	*0.75*	*2.25*
STARTING CASE FATALITY			
MI	*13.37%*	*6.69%*	*20.06%*
IS	*11.65%*	*5.83%*	*17.48%*
HS	*11.65%*	*5.83%*	*17.48%*
% CONTINUING TREATMENT			
After MI			
Rivaroxaban	*92.58%*	*74.06%*	*111.09%*
Clopidogrel	*60.00%*	*48.00%*	*72.00%*
After IS			
Rivaroxaban	*94.69%*	*75.75%*	*113.63%*
Clopidogrel	*54.29%*	*43.43%*	*65.14%*
DISUTILITY DURATIONS (years)			
Duration of Bleed	*0.08*	*0.04*	*0.23*
Duration of PTCA/PCI	*0.08*	*0.04*	*0.23*
Duration of CABG	*0.23*	*0.04*	*0.23*

In answering these questions, we have noted an error with the linking of some inputs for the univariate analysis. This has been fixed and the updated tornado diagram is provided below. Whilst all parameters do have an impact on the ICER, this is minimal in some cases – (less than a few pounds).



B14. It is unclear how the deterministic sensitivity analysis on the efficacy parameters has been conducted as the description is inadequate. Please clarify how the deterministic

sensitivity analyses on the efficacy parameters were conducted by providing full step by step details of the method used to calculate these values. Please also provide the regression output with a description of each variable used in the regression.

Uncertainty margins cannot be directly applied to efficacy data as it is currently presented in the cost-effectiveness model. The model presents individual transition probabilities that are time dependent with many zero values present in each transition probability matrix. It is always difficult to consider suitable (if any) uncertainty that surrounds the probability of 0. Hence, the regression approach was considered in the model.

The "regressions" tab in the model spreadsheet holds the results from a multivariate sensitivity analysis in which the efficacy parameters are varied. A normal distribution is applied to each Weibull (shape and scale) parameter for MI, IS, HS/ICH, and OCD for both the rivaroxaban and comparator arms. The normal distribution becomes active during the sensitivity analyses.

The differences in the incidence of MI's, strokes and other cardiovascular death are given relative to the mean differences on the "regressions" tab (such that the beta's from the regression indicate the relative importance of the different components).

Subsequently a regression analysis is carried out with the net present value as the variable to be explained. The regression outputs can be found in cells T1 to Z24 of the regressions sheet in the model, and the reported coefficients from the PSA correspond with columns A to D of the same sheet. The coefficients are subsequently used to inform the upper and lower limits of the predicted net present value which are used to formulate the tornado graph of efficacy parameters from the univariate sensitivity analysis.

B15. Please clarify why a deterministic sensitivity analysis on the relative risk reduction of rivaroxaban was not conducted.

If the deterministic sensitivity analysis on the efficacy parameters was designed to replace this sensitivity analysis, please clarify why using the regression methods was superior to conducting a deterministic sensitivity analysis on the relative risk reduction of rivaroxaban.

The first reason why the regression analysis, which is indeed designed to replace the deterministic sensitivity analysis, is thought to be superior to conducting a deterministic sensitivity analysis on the relative risk reduction of rivaroxaban is that we feel that there is not a single risk reduction of rivaroxaban. Rivaroxaban impacts on the risk of different events (MI, IS, HS, death) to different degrees and with different levels of significance.

The second reason – related to the first – is that within these different effects depending on the type of event, there will be a degree of dependency. The regression approach aims to capture that dependency.

B16. Figure 28 (manufacturer's submission, page 217) presents a relative difference in risk across age groups for men and women. Please clarify what the baseline risk is in this figure.

The values in this figure represent the change in risk for one age group versus the previous (younger) age group. Therefore, the estimates of the relative difference in risk between the 45 to 49 and 50 to 54 age groups are based on the values for each of these age groups respectively from figure 27 of the manufacturer's submission, i.e. for males: 5.063161 / 4.58223 = 1.105.

The youngest age group considered in this estimation is the 45 to 49 year old group, with an estimated baseline risk of non-fatal MI of 0.10% for males and 0.02% for females, based on the data presented by the ONS and Smolina (2012), as described in the manufacturer's submission.

B17. Please clarify why the incidence of first AMIs for men and women is negative for some age groups in Figure 26 (manufacturer's submission, page 216).

Please also clarify how the method used is deemed appropriate for the age groups considered in the model despite the lack of face validity at younger ages

The method applied in the model to estimate the increased risk of events due to age uses the logarithm of the reported event rate multiplied by 100,000, as the values in Smolina (2012) are presented as incidence rates per 100,000 people. This is then divided by the total population for the age group (taken from ONS data).

The risk of MI events is exceptionally low in the population aged 29 years and younger (from Smolina (2012) – 105 events per 100,000 men and 38 events per 100,000 women). When this is combined with ONS data as described above, the risk of MI in the 0-29 age group is estimated to be less than 1%. Taking the logarithm of such a small number results in a negative estimate. This is not an issue for the economic model itself, as we only use data from those patients who fall with the 45 to 49 years or older age groups.

B18. Please clarify why the Weibull distributions used when interpolating the data were not extrapolated to provide the probability that an event will occur in the future time periods.

The Weibull model was used to smooth the data over two years from the ATLAS 2 trial. Within such an environment it is expected that the hazard function will decrease over time, with the highest risk being in the first months. However, such an assumption is less realistic in the longer term, where risk is expected to start increasing again due to age. Further extrapolation with a Weibull model would contradict this reality, whilst the current approach captures this increased risk over the longer term.

B19. Please clarify what checks were conducted to see if the last cycle values from the interpolated data were not outliers.

Every patient group modelled was checked visually and the outliers that were found drove the decision to apply a parametric approach in the model. Such an approach forces the hazard function to decrease over time and minimises the effect of outliers.

B20. Please clarify why men and women have not been modelled separately in the cost effectiveness model.

It is not common practice, nor in our opinion advisable, to consider males and females separately in cardiovascular disease models. Doing so could potentially result in treatments being considered cost-effective in males but not in females (for example).

Furthermore, the differences in event rates, and benefit of rivaroxaban seen in the clinical trial data did not significantly differ between males and females. Therefore, there was no reason to believe that outcomes would differ between the genders. Please see response to question A19.

B21. Please clarify why it is not possible to transition from the clean health state to the multiple event health states in the extrapolation period (beyond the second year) of the model.

This is a choice made during model development based on the low probability of patients moving from clean to multiple event states during the observation (clinical trial) period, and the assumption that this probability would be even lower further away from the index event.

To change this (assuming suitable data are available), one would need to recalibrate the model such that the numbers of events and the mortality estimates would be just as they are now. It is quite likely that the same results would be seen as in the current base case given that the model is calibrated towards the numbers of events.

Utility issues

B22. **Priority Question:** please clarify why utility decrements due to ageing have not been applied in the model.

Including utility decrements due to ageing was excluded from the final model as it had minimal impact on results, did not change the conclusions of the analysis, and overcomplicated the model structure. Such functionality has been re-included and summary results from the analyses are tabulated below.

	Delta Cost	*Delta QALY*	*ICER*
Base case	*£763.58*	*0.12*	*£6,202.84*
Kind et al 1998	*£763.58*	*0.11*	*£6,747.92*
Ara [1]	*£763.58*	*0.12*	*£6,536.26*
Ara [2]	*£763.58*	*0.12*	*£6,358.40*

Below, some background information on how each of the age-adjusted utility methods were applied is provided.

Model 1: Ara et al (2008) presents age adjusted utility based on a study conducted by Kind et al (1998). Kind et al (1998) conducted a study to value utility by age in the general UK population (n= 3395) with the use of EQ-5D questionnaires. Kind et al (1998) found significant difference in the health related quality of life across the different age groups as presented in the table below.

Age (years)	*Utility*
45	*0.869*
50	*0.848*
55	*0.826*
60	*0.805*
65	*0.784*
70	*0.763*
75	*0.741*

** Utility = 1.060 -0.004 × age*

Model 2: Ara et al (2010) investigated the relationship between health state utility values, age, sex and history of cardiovascular disease (CVD) using an ordinary least square regression analysis. The regression analysis performed on a dataset including patients both and with without a history of CVD (n= 26,679), can be used to estimate the mean health state utility value in the general UK population. The formula to estimate the mean utility regardless of individuals' history of CVD is given by:

$$\textit{Utility} = 0.9508566 + 0.0212126 \begin{pmatrix} 1 = male \\ 2 = female \end{pmatrix} - 0.0002587 \times age - 0.0000332 \times age^2.$$

Model 3: the Ara regression analysis described above was performed on the participants with no history of CVD only (n= 25,080). The formula to estimate the mean utility for individuals without a history of CVD in the general UK population is given by:

$$\textit{Utility} = 0.9454933 + 0.0256466 \begin{pmatrix} 1 = male \\ 2 = female \end{pmatrix} - 0.0002213 \times age - 0.0000294 \times age^2.$$

To implement the different models for age adjusted utility to the event free health state the following steps were taken:

Model 1: the age adjusted utility values reported by Kind et al (1998) are mapped to the age range considered in the model (62-100) such that the correct utility value is applied to each year of the model. An example of mapping the utility values reported by Kind et al (1998) to the age considered in the model is presented in the table below.

Age in the model	*Utility from Kind et al (1998)*
62	*0.805*
63	*0.805*

64	*0.805*
65	*0.784*

Model 2: the formula reported in Ara (2010) for all individuals regardless of their CVD history is applied to each year of the model by taking an average estimated utility value for males and females. An example of applying the formula to a selected number of years is presented in the following table.

Age in the model	*Utility from Ara (2010)*
62	*((0.9508566+0.0212126×1-0.0002587×62-0.0000332×622) +(0.9508566+0.0212126×2-0.0002587×62-0.0000332×622))/2 = 0.839*
63	*0.835*
64	*0.830*
65	*0.826*

Model 3: the formula reported in Ara (2010) for individuals with no history of CVD is applied to each year of the model by taking the average estimated utility for males and females.

Age in the model	*Utility from Ara (2010)*
62	*((0.9454933+0.0256466×1-0.0002213×62-0.0000294×622) +(0.9454933+0.0256466×2-0.0002213×62-0.0000294×622))/2 = 0.857*
63	*0.853*
64	*0.849*
65	*0.845*

The age adjusted utilities discussed thus far refer to the event free health state. To further implement these age adjusted utilities to all the non-fatal health states considered in the model a relative factor between the clean "event free" health state, the non-fatal health states and between the tunnel states in the base case scenario are estimated and applied accordingly. An example of how the age adjusted utilities are applied to all non-fatal health states is presented below for MI:

- The relative factor between clean "event free" health state and MI first 6 months in the base case scenario is given by 0.842/0.7790 = 1.0809
- The relative factor for the tunnel states between the MI first 6 months and MI second 6 months is given by 0.8210/0.7790 = 1.0539
- The relative factor between MI second 6 months and MI later (post 12 months) is given by 0.821/0.821 = 1.
- If the baseline age adjusted utility of 0.805 for a 62 year old patient is considered (as reported by Kind et al 1998), the age adjusted utility for a patient in the MI first 6 month health state is given by (baseline utility / factor between clean and first 6 months) = 0.805 /1.0809 = 0.7448.
    - Dividing the baseline utility by the relative value ensures the utilities estimated for non-fatal events (in the first 6 months) are lower than the baseline utility value.
    - This is then applied to each year considered in the model – the baseline utility changes - however the factor remains constant

- The age adjusted utility for a patient in the MI second 6 months state is given by (age adjusted utility for MI first 6 months × factor (for the tunnel states) between MI first 6 months and MI second 6 months) = 0.7448 × 1.0539 = 0.7849.
    - This is then applied to each year considered in the model – the utility will change in accordance to the baseline utility - however the factor will remain constant. This ensures that the utility in the second six months following an event is never lower than in the first six months.
- The age adjusted utility for a patient in the MI later (post 12 months) state is given by (age adjusted utility for MI second 6 months × factor (for the tunnel states) between MI second 6 months and MI later) = 0.7849 × 1.
    - This is then applied to each year considered in the model – the utility will change in accordance to the baseline utility - however the factor will remain constant. This ensures that the utility in post 12 months following an event is never lower than in the first or second six months.
- The method for MI is also applied to IS and HS/ICH. For multiple events a multiplicative approach is applied as is used in the base case.

The option to run age-adjusted utility analyses is available in the model settings sheet of the cost-effectiveness model.

B23. For the utility scores from the trial presented in Table 53 (manufacturers submission page 243), please clarify the numbers of patients used in the calculation of each utility value and standard errors associated with each utility value.

Please see the table below which is academic in confidence.

[redacted]

B24. Please clarify why it was appropriate to model the utility of the post-stroke health states as improving by 33% over one year (manufacturer's submission, table 56, page 267). The advice from your clinician expert stated that an improvement of approximately 10% was appropriate in Table 58 (manufacturer's submission, page 275).

The only publication identified which presented differing utility values over time following a stroke was Ara et al (2010) and we were keen to include this functionality in the model in an attempt to best reflect clinical reality given feedback from our clinical expert that to assume no change in utility over time following a stroke would not be accurate.

The Ara publication suggests a 33% improvement in utility for patients over one year since a stroke event. The utility for stroke <12 months (history of stroke + other CV condition) is 0.479 and for "no event" <12 months (history of stroke + other CV condition) is 0.641. Taking the increase in utility over time between patients who experience no event and those who suffer from a stroke - (0.641-0.479)/0.479 = 0.33 (33%). Increasing our baseline stroke utility by 33% would give a one year post-stroke utility estimate of 0.941 ((1+0.33) * 0.703). This is not realistic as it is higher than the no event health state applied in the model (utility of 0.842). Therefore, an additional adjustment was made whereby the 0.941 estimate was multiplied by the baseline utility value to give a one year post-stroke utility of 0.792 (0.941 * 0.842).

Therefore, over one year stroke patients are expected to experience an improvement in utility from 0.703 to 0.792, which represents a 12.7% increase in utility. This is very much in line with advice from our clinical feedback which suggested a 10% increase in utility could be expected following a stroke.

Cost issues

B25. **Priority Question:** From reading the submission (page 316) and looking at the model, it is believed that the cost of treating a multiple event state is the sum of the two when two events occur. For example, if a patient suffers from a MI and an IS their cost of treatment will be the sum of the treatment costs of both events.

It is also believed that the follow up costs of both events are applied when two unlike events occur. This can lead to double counting of costs for patients suffering from multiple events if they enter these health states from the single event health states, as the cost of treating the first event has already been counted in the model.

Please clarify if this perceived error exists.

The description of how costs are applied in the model is correct. It is possible that an element of double-counting will exist in patients who experience two different events, but only if these events occur in different cycles of the model.

This functionality was implemented based on feedback we received from our clinical expert who stated that costs of multiple events in the extrapolation period should be summed (page 299, table 62 of manufacturer's submission). Our original assumption had been that costs of multiple events in the extrapolation period would equal the cost of the highest costing event both for the acute care cost and the follow-up care cost. The clinical expert disagreed with this and stated that these costs should be summed.

Applying one approach over the other is not expected to change the results of the model because the number of patients experiencing multiple events is very small. To confirm this, an analysis was run whereby the follow-up costs only of the most expensive event were applied. The results from this analysis are presented below:

	Delta Cost	Delta QALY	ICER
Base case	£763.58	0.12	£6,202.84
One follow-up cost for multiple events	£818.82	0.12	£6,651.58

Other issues

B26. **Priority Question:** Please clarify exactly how the non-parametric transition probabilities sensitivity analysis was conducted (Table 79, p 338). The response should provide sufficient detail so that the ERG can replicate the analysis.

This option was removed from the final structure in an effort to simplify the model and reduce the size of the file. At NICE's request, the option has been re-included and the analysis can be run by selecting the appropriate transition probabilities option on the 'model setting' tab.

B27. **Priority Question:** on page 450 of the manufacturer's submission, the formula for the change in the proportion of MI deaths over time is stated to be:

$$P_{MI}^{D}(t) = \exp\left(\ln(1 - \frac{\lambda_{MI}^{S}}{\lambda_{MI}^{S} + \lambda_{MI}^{D}}) . \frac{1}{(1 + r_{MI}^{change})^{t}} \right) P_{MI}(t)$$

Please clarify why the pmid1 function used to calculate the clean to MI death transition uses the following formula, assuming the cells have been correctly specified.

$$P_{MI}^{D}(t) = Exp\left(Ln\left(1 - \frac{\lambda_{MI}^{S}}{\lambda_{MI}^{S} + \lambda_{MI}^{D}} \right) * \left(1 + r_{MI}^{change}\right)^{t} \right) * P_{MI}(t)$$

Bayer apologises that this typographical error in the equation appeared in the manufacturer's submission. The second formula presented above is correct, demonstrating a decreasing hazard over time.

B28. Please clarify why a scenario analysis limiting the treatment duration of rivaroxaban to one year only in the model, was not presented.

This analysis is presented in the table below.

	Delta Cost	Delta QALY	ICER
Base case	£763.58	0.12	£6,202.84
1 Year treatment	£624.76	0.12	£5,322.56

B29. Please clarify why it is stated that the Kaplan Meier curves presented in Figures 20 to 23 (manufacturer's submission, page 192) do not make clinical sense.

The curves of the actuarial data show fluctuations in the data during the latter cycles of the observation period (e.g. an increased risk of events towards the end of the trial period in some cases – whilst we know that a patient's risk of events actually decreases over time since an initial ACS event).

Applying these data in the model may not truly reflect the natural survival progression following an event, and therefore an approach was taken to interpolate the data such that such fluctuations would be removed.

B30. Please clarify the rationale for applying country specific exclusion criteria to the clinical-effectiveness, utility and resource use systematic reviews prior to extracting the data?

There was no exclusion on the basis of country for the clinical review. The cost-effectiveness, utility and resource use systematic review was specified as part of a project of global interest to inform model development for those specified countries. UK studies were included therefore this review was considered to be relevant to the decision problem.

B31. Please clarify why 46 studies were identified by the cost-effectiveness systematic review but only 38 quality assessments presented in Appendix 11.

As stated in section 10.11 – Appendix 11, identified conference abstracts were not quality assessed. This was because abstracts report limited study details. Eight conference abstracts were included: Charland 2011, Hillegas 2014, Kim 2013, Lala 2011, Lin 2012, Mitmann 2011, Ojo 2012 and Zao 2011 accounting for the difference in numbers.

B32. Please clarify the source of Table 47 (manufacturer's submission, page 210). The column title for the percentages is '% Increase with age from literature' but the source is stated to be calibration.

Bayer apologises that this typographical error appeared in the table.Tthe column heading should read '% increase with age from calibration'.

B33. Are there data to support an assumption that efficacy and adverse events, particularly bleeding risk would be the same for elderly patients (over 70 years) and those with multiple complex morbidities compared with a younger population (under 65 years)? If there are no data, please clarify the approach taken when modelling the risk of bleeding.

[redacted]

[redacted]

[redacted]

[redacted]

[redacted]

Table 2-5 **DEFF1032B: Effect of Rivaroxaban 2.5 mg Compared with Placebo on First Occurrence of Primary Efficacy Events as Adjudicated by the CEC by Subgroup** (Study RIVAROXAXS3001: Modified Intent-to-Treat (Excluding Sites 091001, 091019 and 091026) Analysis Set)

[redacted]

Table 2-6 DBLPH05B: Effect of Rivaroxaban 2.5 mg Compared with Placebo on Non−CABG TIMI Major Bleeding Events in Fragile Population
(Study RIVAROXAXS3001: Treatment-Emergent Safety Analysis Set)

[redacted]

Further clarification question 23rd July 2014

In the report it is stated on seven occasions that the price of rivaroxaban is £2.10 per day. However in Table 63 it is stated that a 28 tablet pack would cost £58.80 and that two tablets would be needed per day (a schedule which is corroborated numerous times in the MS). These values imply a price of £4.20 per day. Please clarify which daily acquisition cost is correct with reference to any typographical error.

Bayer apologises that this error occurred in Table 63. We can confirm that rivaroxaban will be available for this indication as 2.5 mg film-coated tablets, provided as a pack of 56. The recommended dose is 2.5 mg twice daily which equates to a price of £2.10 per day. This equates to a pack price (56 tablets) of £58.80.