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[Prognosis Review]

The comparative and added prognostic value of biomarkers to the Revised Cardiac Risk Index for preoperative prediction of major adverse cardiac events and all-cause mortality in patients who undergo noncardiac surgery

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ABSTRACT

Background

The Revised Cardiac Risk Index (RCRI) is a widely acknowledged prognostic model to estimate preoperatively the probability of developing in-hospital major adverse cardiac events (MACE) in patients undergoing noncardiac surgery. However, the RCRI does not always make accurate predictions, so various studies have investigated whether biomarkers added to or compared with the RCRI could improve this.

Objectives

Primary: To investigate the added predictive value of biomarkers to the RCRI to preoperatively predict in-hospital MACE and other adverse outcomes in patients undergoing noncardiac surgery.

Secondary: To investigate the prognostic value of biomarkers compared to the RCRI to preoperatively predict in-hospital MACE and other adverse outcomes in patients undergoing noncardiac surgery.

Tertiary: To investigate the prognostic value of other prediction models compared to the RCRI to preoperatively predict in-hospital MACE and other adverse outcomes in patients undergoing noncardiac surgery.

Search methods

We searched MEDLINE and Embase from 1 January 1999 (the year that the RCRI was published) until 25 June 2020. We also searched ISI Web of Science and SCOPUS for articles referring to the original RCRI development study in that period.

Selection criteria

We included studies among adults who underwent noncardiac surgery, reporting on (external) validation of the RCRI and:

- the addition of biomarker(s) to the RCRI; or

- the comparison of the predictive accuracy of biomarker(s) to the RCRI; or

- the comparison of the predictive accuracy of the RCRI to other models.

Besides MACE, all other adverse outcomes were considered for inclusion.

Data collection and analysis

We developed a data extraction form based on the CHARMS checklist. Independent pairs of authors screened references, extracted data and assessed risk of bias and concerns regarding applicability according to PROBAST. For biomarkers and prediction models that were added or compared to the RCRI in ≥ 3 different articles, we described study characteristics and findings in further detail. We did not apply GRADE as no guidance is available for prognostic model reviews.

Main results

We screened 3960 records and included 107 articles.

Over all objectives we rated risk of bias as high in ≥ 1 domain in 90% of included studies, particularly in the analysis domain. Statistical pooling or meta-analysis of reported results was impossible due to heterogeneity in various aspects: outcomes used, scale by which the biomarker was added/compared to the RCRI, prediction horizons and studied populations.

Added predictive value of biomarkers to the RCRI

Fifty-one studies reported on the added value of biomarkers to the RCRI. Sixty-nine different predictors were identified derived from blood (29%), imaging (33%) or other sources (38%). Addition of NT-proBNP, troponin or their combination improved the RCRI for predicting MACE (median delta c-statistics: 0.08, 0.14 and 0.12 for NT-proBNP, troponin and their combination, respectively). The median total net reclassification index (NRI) was 0.16 and 0.74 after addition of troponin and NT-proBNP to the RCRI, respectively. Calibration was not reported. To predict myocardial infarction, the median delta c-statistic when NT-proBNP was added to the RCRI was 0.09, and 0.06 for prediction of all-cause mortality and MACE combined. For BNP and copeptin, data were not sufficient to provide results on their added predictive performance, for any of the outcomes.

Comparison of the predictive value of biomarkers to the RCRI

Fifty-one studies assessed the predictive performance of biomarkers alone compared to the RCRI. We identified 60 unique predictors derived from blood (38%), imaging (30%) or other sources, such as the American Society of Anesthesiologists (ASA) classification (32%). Predictions were similar between the ASA classification and the RCRI for all studied outcomes. In studies different from those identified in objective 1, the median delta c-statistic was 0.15 and 0.12 in favour of BNP and NT-proBNP alone, respectively, when compared to the RCRI, for the prediction of MACE. For C-reactive protein, the predictive performance was similar to the RCRI. For other biomarkers and outcomes, data were insufficient to provide summary results. One study reported on calibration and none on reclassification.

Comparison of the predictive value of other prognostic models to the RCRI

Fifty-two articles compared the predictive ability of the RCRI to other prognostic models. Of these, 42% developed a new prediction model, 22% updated the RCRI, or another prediction model, and 37% validated an existing prediction model. None of the other prediction models showed better performance in predicting MACE than the RCRI. To predict myocardial infarction and cardiac arrest, ACS-NSQIP-MICA had a higher median delta c-statistic of 0.11 compared to the RCRI. To predict all-cause mortality, the median delta c-statistic was 0.15 higher in favour of ACS-NSQIP-SRS compared to the RCRI. Predictive performance was not better for $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, Goldman index, Detsky index or VSG-CRI compared to the RCRI for any of the outcomes. Calibration and reclassification were reported in only one and three studies, respectively.

Authors' conclusions

Studies included in this review suggest that the predictive performance of the RCRI in predicting MACE is improved when NT-proBNP, troponin or their combination are added. Other studies indicate that BNP and NT-proBNP, when used in isolation, may even have a higher discriminative performance than the RCRI. There was insufficient evidence of a difference between the predictive accuracy of the RCRI and other prediction models in predicting MACE. However, ACS-NSQIP-MICA and ACS-NSQIP-SRS outperformed the RCRI in predicting myocardial infarction and cardiac arrest combined, and all-cause mortality, respectively. Nevertheless, the results cannot be interpreted as conclusive due to high risks of bias in a majority of papers, and pooling was impossible due to heterogeneity in outcomes, prediction horizons, biomarkers and studied populations.

Future research on the added prognostic value of biomarkers to existing prediction models should focus on biomarkers with good predictive accuracy in other settings (e.g. diagnosis of myocardial infarction) and identification of biomarkers from omics data. They should be compared to novel biomarkers with so far insufficient evidence compared to established ones, including NT-proBNP or troponins.

Adherence to recent guidance for prediction model studies (e.g. TRIPOD; PROBAST) and use of standardised outcome definitions in primary studies is highly recommended to facilitate systematic review and meta-analyses in the future.

PLAIN LANGUAGE SUMMARY

Can biomarkers improve predictions of the RCRI tool to predict heart-related complications in patients undergoing surgery other than heart surgery?

Background and review question

Although patients undergo surgery to maintain or increase life expectancy or to improve quality of life, surgery is not without risks. Some patients will develop a heart-related complication after surgery other than heart surgery, such as a heart infarction. Several tools try to predict someone's chance of developing a heart complication after surgery using information collected in the period before surgery. The Revised Cardiac Risk Index (RCRI) is such a tool that tries to estimate the chance of developing a heart complication during hospital admission in patients undergoing surgery other than heart surgery. It uses information on whether the patient has in the past experienced a heart infarction, heart failure and/or a stroke during his/her life, their use of insulin for the treatment of diabetes mellitus, their current renal (kidney) function and whether he/she will undergo high or non-high risk surgery. The RCRI is commonly used by physicians, but the predictions are not always very accurate. Therefore, several researchers have attempted to improve these predictions by adding extra information to this tool. This information can be derived from so-called biomarkers, which are, for example, measurements from blood, imaging techniques or other characteristics, such as age, smoking status or physical condition of the patient.

The aim of this systematic review was to investigate whether the addition of such biomarkers to the RCRI improves predictions of heart-related complications during hospitalisation in patients undergoing surgery other than heart surgery. In addition, we investigated whether biomarkers and other prediction tools resulted in better predictions of heart-related complications during hospitalisation compared to the predictions of the RCRI in patients undergoing surgery other than heart surgery.

Key results

We identified 69 different predictors that were added to the RCRI tool to improve predictions of these heart-related complications. The evidence is current to 25 June 2020. Predictions seem to improve with the addition of some biomarkers derived from blood. These are troponin (which measures muscular damage of the heart), brain natriuretic peptide (BNP) and (NT-pro)brain natriuretic peptide (NT-proBNP) (which both measure severity of heart failure).

In addition, there were 60 biomarkers that were studied to compare their predictions to the RCRI. Other studies included in this review suggest that BNP and NT-proBNP alone may predict heart-related complications even better than the RCRI. Sixty-five prediction tools other than the RCRI tried to improve its predictions. The American College of Surgeons National Surgical Quality Improvement (ACS-NSQIP) and ACS-NSQIP-MICA (myocardial infarction or cardiac arrest) surgical risk score tools could make better predictions than the RCRI, but this was only true for certain outcomes, and not for heart-related complications. However, for all of these research questions, we are not confident in the results due to large variation in the research methods applied and signs of less accurate research approaches having been used.

Authors' conclusions

Troponin, BNP and NT-proBNP may improve the ability of the RCRI to predict heart-related complications. The ACS-NSQOP-MICA and ACS-NSQIP surgical risk score tools seem to be better at predicting postoperative complications than the RCRI tool, but not heart-related complications. However, due to deficiencies in how the studies were conducted, we are uncertain whether the results we found apply to all patients undergoing surgery other than heart surgery. We need more and better research on biomarkers with promising predictive performance in other settings.

Summary of findings 1. Summary of findings - objective 1: added value of biomarkers to the RCRI

Population: patients undergoing noncardiac surgery

Index model: Revised Cardiac Risk Index (RCRI)

Comparator: RCRI extended with biomarker(s)

Outcome: postoperative occurrence of (in-hospital) major adverse cardiac events (MACE), all-cause mortality and other adverse outcomes

Timing: time point of prognostication: before surgery; prediction horizon: in-hospital, but all time spans are included

Setting: to inform physicians of the patient's risk of developing in-hospital events after noncardiac surgery

Outcomes	Biomarker	№ of participants (studies)	Measure	Pooled result		Comments
				Summary measure	Median (range)	
MACE	Troponin	3 studies 810 patients 77 MACE	Discrimination	Delta c-statistic	0.14 (0.06 to 0.33)	Surgical specialty was vascular and noncardiac surgery. Prediction horizon was 30-day MACE.
		0 studies	Calibration	—	—	—
		2 studies 577 patients 70 MACE	Reclassification	NRI	0.16 (0.09 to 0.22)	Surgical specialty was vascular surgery. Prediction horizon was 30-day MACE and long-term MACE (> 30 days).
		1 study 122 patients 29 MACE	—	IDI	0.05	Surgical specialty was vascular surgery. Prediction horizon was long-term MACE (> 30 days).
	NT-proBNP	7 studies 13,687 patients 1710 MACE	Discrimination	Delta c-statistic	0.08 (0.04 to 0.22)	Surgical specialty was vascular and noncardiac surgery. Prediction horizon was 30-day MACE.
		1 study 10,402 patients 1269 MACE	Calibration	Calibration plot	Good calibration	Surgical specialty was noncardiac surgery. Prediction horizon was 30-day MACE.

		2 studies 10,524 patients 1560 MACE	Reclassification	NRI	0.74 (0.26 to 1.22)	Surgical specialty was noncardiac and vascular surgery. Prediction horizon was 30-day MACE and long-term MACE (> 30 days).
		1 study 122 patients 29 MACE	—	IDI	0.23	Surgical specialty was vascular surgery. Prediction horizon was long-term MACE (> 30 days).
	Troponin + NT-proBNP	3 studies 575 patients 120 MACE	Discrimination	Delta c-statistic	0.12 (0.1 to 0.34)	Surgical specialty was vascular and noncardiac surgery. Prediction horizon was 30-day MACE.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
	BNP	0 studies	Discrimination	—	—	—
		0 studies	Calibration	—	—	—
		2 studies 874 patients unknown MACE	Reclassification	NRI	0.72 (0.47 to 0.96)	Results are based on two studies as one study did not report the total NRI. Surgical specialty was orthopaedic and vascular surgery. Prediction horizon was 30-day MACE. For one study, the number of outcomes was not reported.
All-cause mortality and MACE	NT-proBNP	3 study 12,214 patients 548 events	Discrimination	Delta c-statistic	0.06 (0.06 to 0.07)	Surgical specialty was vascular and noncardiac surgery. Prediction horizon was 30-day events.
		1 study 411 patients 74 events	Calibration	Hosmer Lemeshow	P = 0.03	Surgical specialty was vascular surgery. Prediction horizon was 30-day events.
		2 study 1812 patients 102 events	Reclassification	NRI	0.19 (0.13 to 0.25)	Surgical specialty was vascular and noncardiac surgery. Prediction horizon was 30-day events.
		1 study 411 patients 74 events	—	IDI	0.06	Surgical specialty was vascular surgery. Prediction horizon was 30-day events.

Myocardial infarction	NT-proBNP	2 studies 2626 patients 132 MI	Discrimination	Delta c-statistic	0.09 (0.06 to 0.11)	Surgical specialty was noncardiac surgery. Prediction horizon was within 3 days after surgery and in-hospital events.
		0 studies	Calibration	—	—	—
		1 study 572 patients 30 MI	Reclassification	NRI	0.46	Surgical specialty was noncardiac surgery. Prediction horizon was within 3 days after surgery.

IDI: integrated discrimination index; MACE: major adverse cardiac event(s); MI: myocardial infarction; NRI: net reclassification index
Troponin is a cardiac biomarker that reflects myocardial ischaemia.
Both BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal (NT)-pro hormone BNP) are released by cardiomyocytes due to myocardial stretch and used in clinical practice as a marker for heart failure.

Summary of findings 2. Summary of findings - objective 2: comparison of predictive performance of biomarkers to the RCRI

Population: patients undergoing noncardiac surgery

Index model: Revised Cardiac Risk Index (RCRI)

Comparator: predictive performance of biomarker(s) alone

Outcome: postoperative occurrence of (in-hospital) major adverse cardiac events (MACE), all-cause mortality and other adverse outcomes

Timing: time point of prognostication: before surgery; prediction horizon: in-hospital, but all time spans are included

Setting: to inform physicians of the patient's risk of developing in-hospital events after noncardiac surgery

Outcomes	Biomarker	№ of participants (studies)	Measure	Pooled result		Comments
				Summary measure	Median (range)	
MACE	ASA	6 studies 84,145 patients 5415 MACE	Discrimination	Delta c-statistic	-0.02 (-0.18 to 0.03)	Surgical specialty was orthopaedic, vascular and noncardiac surgery. One study reported on intraoperative MACE (hypotension, hypertension, bradycardia and tachycardia), which contributed most outcomes. Prediction horizon was intraoperative or in-hospital or 30-day MACE.
		1 study 29,437 patients 5249 MACE	Calibration	Calibration plot	Poor calibration	Poor calibration for both RCRI and ASA. This study reported on intraoperative MACE. Surgical specialty was noncardiac surgery.

		1 study 29,437 patients 5249 MACE	—	Hosmer Lemeshow	P < 0.0001	This study reported on intraoperative MACE. Surgical specialty was noncardiac surgery.
		0 studies	Reclassification	—	—	—
	BNP	6 studies 1451 patients NA MACE	Discrimination	Delta c-statistic	0.15 (0.0 to 0.24)	For one study, the number of outcomes was not reported. Surgical specialties were orthopaedic, general, vascular and noncardiac surgery. Prediction horizon was in-hospital or 30-day MACE.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
	NT-proBNP	6 studies 3256 patients 457 MACE	Discrimination	Delta c-statistic	0.15 (0.02 to 0.22)	Surgical specialty was vascular and noncardiac surgery. Prediction horizon was in-hospital, 30-day and 6-month MACE.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
	CRP	2 studies 145 patients 15 MACE	Discrimination	Delta c-statistic	-0.01 (-0.12 to 0.10)	Surgical specialty was vascular and noncardiac surgery. Prediction horizon was in-hospital and 30-day MACE.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
All-cause mortality and MACE	BNP	2 studies 248 patients 27 events	Discrimination	Delta c-statistic	0.21 (0.18 to 0.23)	Surgical specialty was noncardiac surgery. Prediction horizon was in-hospital or 30 day events.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
	Troponin	2 studies 1154 patients 52 events	Discrimination	Delta c-statistic	0.09 (0.09 to 0.10)	Surgical specialty was noncardiac surgery. Prediction horizon was in-hospital and 30-ay events.
		0 studies	Calibration	—	—	—

		0 studies	Reclassification	—	—	—
Myocardial infarction	ASA	2 studies 52,638 patients 106 MI	Discrimination	Delta c-statistic	0.02 (-0.07 to 0.12)	Surgical specialty was neurosurgery and noncardiac surgery. Prediction horizon was within 7 days or 30 days after surgery.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
All-cause mortality	ASA	5 studies 124,400 patients 1040 deaths	Discrimination	Delta c-statistic	0.05 (-0.05 to 0.24)	Surgical specialty was general, neurosurgery, vascular and noncardiac surgery. Prediction horizon was in-hospital or 30-day all-cause mortality.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
	BNP	2 studies 825 patients unknown deaths	Discrimination	Delta c-statistic	0.14 (0.08 to 0.21)	Surgical specialty was orthopaedic and vascular surgery. For one study, the number of deaths was not reported. Prediction horizon for one study was 30 days and the other was 1-year all-cause mortality.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
	NT-proBNP	2 studies 1314 patients 74 deaths	Discrimination	Delta c-statistic	0.10 (0.09 to 0.11)	Surgical specialty was orthopaedic and vascular surgery. Prediction horizon for one study was in-hospital and within 6 weeks after surgery.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
Other	ASA	6 studies 126,963 patients	Discrimination	Delta c-statistic	- [a]	Surgical specialty was neurosurgery and noncardiac surgery. Prediction horizon was within 7 days or 30 days after surgery.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—

[a]Bronheim 2018.

IDI: integrated discrimination index; MACE: major adverse cardiac event(s); MI: myocardial infarction; NRI: net reclassification index

ASA: American Society of Anesthesiologists physical status, which is a tool commonly used to classify a patient's physical fitness before surgery.

Troponin is a cardiac biomarker that reflects myocardial ischaemia.

Both BNP (B-type natriuretic peptide) and NT-proBNP (N-terminal (NT)-pro hormone BNP) are released by cardiomyocytes due to myocardial stretch and used in clinical practice as a marker for heart failure.

C-reactive protein (CRP) is a sensitive systemic marker of inflammation and tissue damage.

Summary of findings 3. Summary of findings - objective 3: comparison of predictive performance of other prediction models to the RCRI

Population: patients undergoing noncardiac surgery

Index model: Revised Cardiac Risk Index (RCRI)

Comparator: other prediction models

Outcome: postoperative occurrence of (in-hospital) major adverse cardiac events (MACE), all-cause mortality and other adverse outcomes

Timing: time point of prognostication: before surgery; prediction horizon: in-hospital, but all time spans are included

Setting: to inform physicians of the patient's risk of developing in-hospital events after noncardiac surgery

Outcomes	Prediction model	№ of participants (studies)	Measure	Pooled result		Comments
				Summary measure	Median (range)	
MACE	ACS-NSQIP-MICA	3 studies 1567 patients 95 MACE	Discrimination	Delta c-statistic	0.00 (-0.09 to 0.04)	Surgical specialty was neurosurgery, vascular and noncardiac surgery. Prediction horizon was in-hospital or 30-day MACE. The prediction horizon was not reported in one study.
		1 study 870 patients 76 MACE	Calibration	Calibration plot	Poor calibration	Poor calibration for both RCRI and NSQIP MACE. Calibration improved after recalibration of NSQIP MACE. Surgical specialty was noncardiac surgery.
				Calibration intercept	0.95 for RCRI and 2.37 for NSQIP-MICA	—
				Calibration slope	0.29 for RCRI and 0.70 for NSQIP-MICA	—
		0 studies	Reclassification	—	—	—

	ACS-NSQIP-SRS	2 studies 1087 patients 26 MACE	Discrimination	Delta c-statistic	0.06 (0.00 to 0.11)	Surgical specialty was noncardiac surgery. Prediction horizon was in-hospital or 30-day MACE.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
	Detsky	3 studies 3361 patients 191 MACE	Discrimination	Delta c-statistic	0.05 (-0.07 to 0.11)	Surgical specialty was orthopaedic, vascular and noncardiac surgery. Prediction horizon was in-hospital or 30-day MACE.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
	Goldman	3 studies 3361 patients 191 MACE	Discrimination	Delta c-statistic	-0.03 (-0.07 to 0.08)	Surgical specialty was orthopaedic, vascular and noncardiac surgery. Prediction horizon was in-hospital or 30-day MACE.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
	VSG-CRI	3 studies 2023 patients 208 MACE	Discrimination	Delta c-statistic	0.03 (0.00 to 0.05)	Surgical specialty was vascular surgery. Prediction horizon was in-hospital MACE. In one study, the prediction horizon was not reported.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
Myocardial infarction or cardiac arrest	ACS-NSQIP-MICA	6 studies 243,896 patients unknown MICA	Discrimination	Delta c-statistic	0.11 (-0.05 to 0.39)	Surgical specialty was general, vascular, orthopaedic and noncardiac surgery. Prediction horizon was 30-day MICA. The prediction horizon was not reported in one study.
		2 studies 181,920 patients 1889 MICA	Calibration	Calibration plot	Poor calibration	Calibration was poor for both scores, however calibration was better for the RCRI compared to the NSQIP-MICA. Calibration improved after recalibration of NSQIP-MICA. Surgical specialty was noncardiac surgery. Prediction horizon was 30-day MICA, but was not reported in one study.

		2 studies 43,047 patients 463 MICA	—	Hosmer Lemeshow	RCRI: P = 0.018 to P < 0.001 ACS-NSQIP-MICA P < 0.001	Surgical specialty was general and noncardiac surgery. Prediction horizon was 30-day MICA, but was not reported in one study.
		0 studies	Reclassification	—	—	—
	ACS-NSQIP-SRS	2 studies 9678 patients 94 MICA	Discrimination	Delta c-statistic	0.18 (0.13 to 0.22)	Surgical specialty was noncardiac surgery or not specified. Prediction horizon was 30-day MICA. The prediction horizon was not reported in one study.
		1 study 9015 patients 91 MICA	Calibration	Calibration plot	RCRI: poor calibration, ACS-NSQIP-SRS: acceptable calibration	Surgical specialty was noncardiac surgery. Prediction horizon was not reported.
		1 study 9015 patients 91 MICA		Hosmer Lemeshow	RCRI: P < 0.001 ACS-NSQIP-SRS P = 0.07	Surgical specialty was noncardiac surgery. Prediction horizon was not reported.
		0 studies	Reclassification	—	—	—
All-cause mortality	ACS-NSQIP-SRS	3 studies 2461 patients 155 deaths	Discrimination	Delta c-statistic	0.15 (0.12 to 0.47)	Surgical specialty was neurosurgery or noncardiac surgery. The prediction horizon was in-hospital or 30-day events. In one study the prediction horizon was not reported.
		0 studies	Calibration	—	—	—
		0 studies	Reclassification	—	—	—
	$CHADS_2$	3 studies 35129 patients 1177 deaths	Discrimination	Delta c-statistic	0.00 (-0.02 to 0.01)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events.
		0 studies	Calibration	—	—	—
		3 studies 35129 patients 1177 deaths	Reclassification	NRI	0.07 (0.01 to 0.12)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events.

	$CHADS_2VASc$	2 studies 2969 patients 121 deaths	Discrimination	Delta c-statistic	0.00 (-0.02 to 0.02)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events.
		0 studies	Calibration	—	—	—
		2 studies 2969 patients 121 deaths	Reclassification	NRI	0.09 (0.01 to 0.17)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events.
	R_2CHADS_2	3 studies 35129 patients 1177 deaths	Discrimination	Delta c-statistic	-0.03 (-0.03 to 0.03)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events.
		0 studies	Calibration	—	—	—
		3 studies 35129 patients 1177 deaths	Reclassification	NRI	0.03 (-0.09 to 0.13)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events.
Stroke	$CHADS_2$	4 studies unknown patients unknown events	Discrimination	Delta c-statistic	0.02 (-0.01 to 0.11)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events. For one study the number of included patients and number of events were not reported.
		0 studies	Calibration	—	—	—
		2 studies 33121 patients 391 events	Reclassification	NRI	0.05 (-0.06 to 0.17)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events.
	$CHADS_2VASc$	3 studies unknown patients unknown events	Discrimination	Delta c-statistic	0.04 (0.00 to 0.12)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events. For one study the number of included patients and number of events were not reported.
		0 studies	Calibration	—	—	—
		1 studies 961 patients 11 events	Reclassification	NRI	0.07	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events.
	R_2CHADS_2	3 studies unknown patients unknown events	Discrimination	Delta c-statistic	0.05 (0.01 to 0.12)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events. For one study the

						number of included patients and number of events were not reported.
		0 studies	Calibration	—	—	—
		2 studies 33,121 patients 391 events	Reclassification	NRI	-0.06 (-0.14 to 0.01)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events.
All-cause mortality or stroke	$CHADS_2$	3 studies 33,748 patients unknown events	Discrimination	Delta c-statistic	0.03 (0.02 to 0.07)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events. For one study, the number of outcomes was not reported.
		0 studies	Calibration	—	—	—
		3 studies 33,748 patients unknown events	Reclassification	NRI	0.31 (0.14 to 0.35)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events. For one study, the number of outcomes was not reported.
	$CHADS_2VASc$	2 studies 1588 patients unknown events	Discrimination	Delta c-statistic	0.04 (0.01 to 0.07)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events. For one study, the number of outcomes was not reported.
		0 studies	Calibration	—	—	—
		2 studies 1588 patients unknown events	Reclassification	NRI	0.30 (0.24 to 0.36)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events. For one study, the number of outcomes was not reported.
	R_2CHADS_2	3 studies 33,748 patients unknown events	Discrimination	Delta c-statistic	0.03 (0.01 to 0.06)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events. For one study, the number of outcomes was not reported.
		0 studies	Calibration	—	—	—
		3 studies 33,748 patients unknown events	Reclassification	NRI	0.17 (0.11 to 0.44)	Surgical specialty was noncardiac surgery. The prediction horizon was 30-day events. For one study, the number of outcomes was not reported.

MACE: major adverse cardiac event(s); MICA: composite outcome of myocardial infarction and cardiac arrest; NRI: net reclassification index; RCRI: Revised Cardiac Risk Index.
ACS-NSQIP-MICA provides a risk estimate of 30-day myocardial infarction or cardiac arrest (MICA) in patients undergoing noncardiac surgery (Gupta 2011).
The ACS-NSQIP surgical risk score (ACS-NSQIP-SRS) is a decision-support tool based, which can be used to estimate the risks of multiple outcomes (including myocardial infarction) for most operations (Bilimoria 2013).
The $CHADS_2$, CHA_2DS_2-VASc and $R_2CHA_2DS_2$ are risk scores that predict stroke in patients diagnosed with atrial fibrillation (Gage 2001; Lip 2010; Piccini 2013).

The Goldman index represents a multivariable approach to estimate cardiac risk in patients undergoing noncardiac procedures (Goldman 1977).
The Detsky index is a modified version of an index that was previously generated by Goldman in 1977 (Detsky 1986).
Vascular Study Group of New England Cardiac Risk Index (VSG-CRI) is a prediction model to predict a composite cardiac outcome of in-hospital myocardial infarction, clinically significant new arrhythmia or congestive heart failure (CHF) in patients undergoing vascular surgery (Bertges 2010).

BACKGROUND

Description of the condition

Worldwide, over 300 million patients undergo intermediate- to high-risk noncardiac surgery every year (Rose 2015), and this number has been increasing continuously (Weiser 2015). Despite the beneficial aspects of surgery, approximately 19% of these patients will suffer an in-hospital major adverse event (ISOSG 2016). The most common complications are infectious (33%) or have a cardiovascular origin (19%), with the highest mortality rates in the latter (7%). However, such complications are difficult to diagnose, as typical symptoms are often not present in most postoperative patients (e.g. chest pain may be masked by pain medication). Therefore, preoperative risk stratification of these patients using available clinical information is an important component of any strategy to prevent these complications and has been recommended by clinical guidelines (Fleisher 2014; Kristensen 2014). Informing patients and physicians about perioperative risks by, for example, performing additional diagnostic tests or interventions aimed at preventing postoperative complications might enhance patient management and optimisation before surgery.

Description of the prognostic model

The Revised Cardiac Risk Index (RCRI) is a predictive tool to be applied before surgery (Lee 1999). It estimates the postoperative probability of a major adverse cardiac events (MACE) in patients undergoing noncardiac surgery. The RCRI is specially developed for patients undergoing noncardiac surgery and contains six equally weighted predictors, including high-risk surgery, history of ischaemic heart disease, history of cerebrovascular disease, chronic heart failure, renal insufficiency and insulin-dependent diabetes (Table 1). Although the RCRI was published over two decades ago, it is still commonly recommended and used in daily clinical practice (Duceppe 2017; Fleisher 2014; Kristensen 2014), as the predictors are easy to collect and calculation of the score and probability are convenient. A systematic review that examined the performance of the RCRI in external validation studies concluded that the RCRI discriminated moderately well between patients at low versus high risk in predicting cardiac events after noncardiac surgery (Ford 2010). However, the predictive ability of the RCRI for patients undergoing vascular surgery was less accurate (Ford 2010).

To improve the predictive performance of the RCRI, the added value of different biomarkers to the RCRI has been extensively studied in recent years. These biomarkers could originate from blood, such as troponin (Gillmann 2014; Kopec 2017), (NT-pro)brain natriuretic peptide (BNP) (Choi 2010; Scrutinio 2014) and C-reactive protein (CRP) (Choi 2010; Scrutinio 2014). Besides biomarkers derived from blood, many imaging markers, such as electrocardiography (Noordzij 2006; van Klei 2007), and coronary computed tomographic angiography (Sheth 2015), have also been used to assess their added predictive value to the RCRI. Altogether, addition of new biomarkers to the RCRI seems to improve the predictive performance of the RCRI (Choi 2010; Gillmann 2014; Kopec 2017; Scrutinio 2014).

Besides the *addition* of new biomarkers to the RCRI, various studies have *compared* the predictive ability of biomarkers to the RCRI. Again, the biomarkers compared were most commonly derived from blood, such as (NT-pro) BNP (Katsanos 2015; Mercantini 2012) and troponin (Weber 2013), and from imaging, such as thoracic echocardiography (Park 2011).

Finally, the predictive ability of the RCRI has also been compared to other prediction models to predict various outcomes, including the ACS-NSQIP Surgical Risk Score (Bilimoria 2013; Cohn 2018; Gupta 2011; Markovic 2018) and the NSQIP-MICA model (Asuzu 2018; Gupta 2011).

Health outcomes

The RCRI was originally developed to predict postoperative in-hospital occurrence of MACE. Annually, over 10 million patients undergoing noncardiac surgery develop a MACE (Devereaux 2017; ISOSG 2016; van Waes 2016; Weiser 2015). MACE are a leading cause of morbidity and mortality in this patient population (Devereaux 2012; Devereaux 2017; Ekeloef 2016). Additionally, MACE have been associated with prolonged hospitalisation and increased medical costs (Mackey 2006). In cardiovascular research, MACE are most commonly used as a composite outcome and include, among others, cardiac death, (non)fatal myocardial infarction, cardiac arrest, arrhythmias, congestive heart failure or emergent coronary bypass graft surgery. However, varying composites of cardiac outcomes to define MACE are still used within different research groups and publications, which hampers comparison of results over different studies (Kip 2008). As a response to this phenomenon, the systematic review and consensus definitions for the Standardized Endpoints in Perioperative Medicine (StEP) initiative recently published a consensus statement on standardised definitions of cardiovascular outcomes in anaesthesia research (Beattie 2020). In this consensus statement, a MACE was defined as the composite of myocardial infarction, nonfatal cardiac arrest, cardiac death and coronary revascularisation within 30 days of surgery (Beattie 2020).

Besides the use of the RCRI to predict in-hospital MACE occurrence, several other outcomes have been studied, notably all-cause mortality (Katsanos 2015; Weber 2013), and noncardiac complications such as sepsis, respiratory failure, renal failure, readmission, discharge to a nursing facility etc. (Bronheim 2018; Ehlert 2016; Makary 2010; Press 2006).

Why it is important to do this review of these prognostic models

Elderly and multi-morbid patients undergoing noncardiac surgery are more likely to develop perioperative complications (Jammer 2015; Wolff 2002). This suggests that preoperative risk stratification in such patients is essential to direct healthcare towards those that most need it. Preoperative risk stratification of noncardiac surgical patients could easily be performed during the pre-anaesthesia outpatient clinic visit using routine measurements of biomarkers and/or the use of prognostic models including, for example, the RCRI and ACS-NSQIP-MICA model (Lee 1999; Mayhew 2019). More intensified monitoring of noncardiac surgery patients at increased postoperative risk of MACE or other major complications might result in better prevention of such complications and their consequences in the long term.

To date, many authors have aimed to improve predictions of cardiovascular outcomes in the perioperative period by reporting on the added predictive value of biomarkers to the RCRI (Choi 2010; Gillmann 2014; Kopec 2017; Scrutinio 2014). In addition,

others have compared the predictive performance of biomarkers themselves or other prediction models to the RCRI (Bronheim 2018; Park 2011; Weber 2013). As no systematic review has currently been conducted on this topic, we aimed to provide a comprehensive overview of all the evidence.

OBJECTIVES

Primary objective

The primary objective of this systematic review is to quantify the added predictive value of biomarkers to the RCRI to preoperatively predict the in-hospital occurrence of MACE and other adverse outcomes in patients undergoing noncardiac surgery (see Table 2 for the PICOTS).

Other objectives

The secondary objective is to investigate the prognostic value of biomarkers as compared to the RCRI to preoperatively predict the in-hospital occurrence of MACE and other adverse outcomes in patients undergoing noncardiac surgery.

The third objective is to examine the prognostic value of other prediction models as compared to the RCRI to preoperatively predict the in-hospital occurrence of MACE and other adverse outcomes in patients undergoing noncardiac surgery.

Investigation of sources of heterogeneity between studies

The RCRI was originally developed for the preoperative prediction of in-hospital MACE in the noncardiac, nonvascular surgical population (Lee 1999). We expected various sources of heterogeneity that we planned to investigate where possible:

- Differences in studied noncardiac surgical subpopulations, such as vascular (Gillmann 2014; Scrutinio 2014) and orthopaedic surgical patients (Katsanos 2015; Vetrugno 2014).
- Variation in the composites used to define MACE.
- Prediction of other outcomes besides MACE, including all-cause mortality and noncardiac complications.
- Prediction horizons varying from intraoperative events to long-term events (i.e. one year).
- Use of other definitions for the RCRI predictors or unclear predictor definitions, especially for the predictors ischaemic heart disease, congestive heart failure and high-risk surgery (Feringa 2007; Gualandro 2018; Katsanos 2015).
- Where biomarkers have been added or compared to the RCRI, variations in the assay used to measure a particular biomarker, the threshold used to define elevation and the way the biomarkers have been entered into the prediction model (i.e. continuous, categorical or dichotomous).

METHODS

Criteria for considering studies for this review

Types of studies

We considered all original research reports that studied the predictive accuracy of the RCRI for inclusion regardless of study design, or language. We excluded studies that were only published as conference abstracts because of the lack of sufficient information.

Types of participants (target population)

We included studies on adult (≥ 18 years) patients undergoing any type of noncardiac surgery.

Types of prognostic models

To address the three separate objectives of this review, we included all studies reporting on either:

- the addition to the RCRI of one or more preoperatively measured biomarker, including blood, imaging or other type of predictor(s);
- the comparison of the predictive accuracy of the RCRI model to one or more of these preoperatively measured biomarker(s);
- the comparison of the predictive accuracy of the RCRI model to other prognostic models.

We defined a biomarker as a characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes or pharmacologic responses to a therapeutic intervention (Biomarkers Definitions Working Group 2001). In essence, this broad definition includes all predictors that have been added or compared to the RCRI, including, for example, predictors from demographics, history taking, physical examination, blood or urine measurements, imaging and omics. We excluded studies reporting solely on the external validation of the original RCRI without any addition or comparison of a biomarker or another model, respectively, from this review.

Types of outcomes

The primary outcome of interest was in-hospital MACE, as used for the original RCRI model development paper (Lee 1999). For this definition, we made no distinction between fatal and nonfatal MACE. As secondary outcomes, we included all other outcomes that were studied for the external validation of the RCRI, such as all-cause mortality, myocardial infarction and noncardiac complications.

In addition, there is a wide variation in the prediction horizons, ranging from studies reporting on prediction of intraoperative events (Rohrig 2004) to long-term post-discharge events (Subramaniam 2011). Altogether, we made no a priori restrictions based on the type of outcome and prediction horizon used for inclusion in this review.

Search methods for identification of studies

Electronic searches

The original development study for the RCRI was published in 1999 (Lee 1999). Therefore, all our searches started from 1999 onwards. We searched the following databases on 25 June 2020: MEDLINE and Embase (Ovid, 1 January 1999 to 25 June 2020). We used a prediction model search filter developed by Geersing et al (Geersing 2012), and extended the filter to also identify studies reporting on the validation or updating of prediction models, as well as the added value of variables to existing prediction models. The Geersing search filter was originally designed for searches in Ovid MEDLINE (Geersing 2012); however, for this review we also adapted the search strategy for use in Ovid Embase. Further, we

used synonyms of the RCRI, including 'revised Goldman index' and 'Lee index'. The search strategies are reported in Appendix 1 and Appendix 2.

In addition, we searched in both ISI Web of Science and SCOPUS (1 January 1999 to 25 June 2020) for articles referring to the original RCRI development study (Lee 1999). As the RCRI is a revised model of the Cardiac Risk Index by Goldman (Goldman 1977) and Detsky (Detsky 1986), we also searched all references referring to these publications from 1999 onwards. We searched the clinical trial registers ClinicalTrials.gov (www.clinicaltrials.gov; searched 27 July 2020) and World Health Organization International Clinical Trials Registry Platform (WHO ICTRP) (apps.who.int/trialsearch; searched 27 July 2020; Appendix 3) for ongoing trials. We checked Retraction Watch Database for retractions of included articles (retractiondatabase.org/RetractionSearch) (searched 27 July 2020). There was no language restriction so as to reduce language bias.

We checked all identified ongoing studies for completion and published results on 25 November 2021.

Searching other resources

We carried out a cross-reference check of all retrieved articles in PubMed and relevant review articles to identify other eligible articles, including the review by Ford published in 2010 (Ford 2010).

Data collection and analysis

Selection of studies

Two review authors (JAD, LMV) independently screened the results of the searches for eligibility based on title and abstract. In case of disagreement, abstracts were included for full text screening.

In contrast with the protocol (Vernooij 2018), selection of studies based on full text was performed in two stages. In the first step, one review author (LMV) assessed whether the RCRI was mentioned in the 'Results' and/or 'Methods' section of the article. This was done by searching for the terms 'RCRI' or often used synonyms, i.e. 'revised Goldman index' and 'Lee index', or by searching where in the report the original paper was referenced. If this was not the case, these articles were excluded.

We screened the remaining studies for inclusion in the review. This screening was performed independently by two review authors from a team of four (JAD, TT, JAvW, LMV) according to the above criteria using a predefined electronic spreadsheet. Any disagreements were resolved through discussion or by involving a third review author (JAD or JAvW) when necessary.

Data extraction and management

We developed a predefined electronic data extraction form containing items based on the CHARMS checklist (Debray 2017; Moons 2014; Riley 2019). These items address potential critical appraisal issues and issues that may affect the applicability of the results in relation to the intended use of the prediction model. The data extraction form was first piloted on five included articles by three review authors (JAD, JAvW and LMV) and subsequently updated to optimise it to the final format. Two review authors from a team of four (JAD, TT, JAvW, LMV) independently extracted the data from the selected articles. In case of any disagreement, this was resolved by discussion or a third review author was involved to reach consensus.

We extracted data for the following items (see Appendix 4 for a detailed data extraction list): study design, participant eligibility criteria, study dates, case mix (such as age, sex), outcome definition and measurement, prediction horizon, RCRI predictor definitions and measurement, predictors that were added or compared, number of participants and events, details on (handling of) missing data, and model performance in terms of calibration, discrimination, reclassification and other measures for the original and extended model, and the biomarker and prediction model to which the model was compared.

Assessment of risk of bias of included studies

We used the Prediction model Risk of Bias Assessment Tool (PROBAST) for risk of bias and applicability assessment (Moons 2019; Wolff 2019). In short, we assessed risk of bias according to four domains, i.e. participants, predictors, outcomes and analysis. For each domain, we rated risk of bias as either 'Low risk of bias', 'High risk of bias' or 'Unclear risk of bias' based on signalling questions provided by the PROBAST tool (Moons 2019; Wolff 2019). Based on the domain level assessments, we established overall risk of bias and judgements per study as follows:

- 'low risk of bias': for studies in which all four domains were scored as low risk of bias;
- 'high risk of bias': for studies in which at least one domain was assessed as high risk of bias;
- 'unclear risk of bias': for studies in which at least one domain was rated as 'unclear' and the other domains were scored as 'low risk of bias'.

Besides assessment of risk of bias, PROBAST also provides judgement of the applicability of the included studies to the review question with the following response options: 'low concern', 'high concern' or 'unclear concern' regarding applicability. A similar approach as used for the risk of bias assessment holds for the overall judgement for applicability.

Risk of bias and applicability were independently assessed by two review authors in a team of four (JAD, TT, JAvW and LMV) for each included article. Consensus was reached by discussion or, in case of any disagreements, a third review author was involved for the final judgement (JAD, JAvW).

Measures of predictive performance to be extracted

For all three objectives, we extracted the reported predictive performance measures from each of the selected articles including calibration, discrimination and reclassification measures and the uncertainty around these measures (standard errors or confidence intervals). Calibration indicates the extent to which the expected number of outcomes (i.e. the probability of the outcome as predicted by the prediction model) and the observed frequency of the outcome agree (Harrell 2015; Riley 2019; Steyerberg 2009). Extracted calibration performance measures – if reported - were calibration plots, calibration slopes and observed to expected ratios (O:E ratio). Discrimination refers to the ability of the prediction model to discriminate between those with and without the outcome event (Harrell 2015; Riley 2019; Steyerberg 2009). The most commonly used discrimination measure is the concordance-

statistic, i.e. c-statistic, which we also extracted for this review. We also extracted the delta c-statistic, i.e. the difference between the c-statistic of the RCRI model alone versus the RCRI model added with the biomarker(s) (for objective 1) and for the comparison between biomarkers or prediction models to the RCRI (objective 2 and 3). Furthermore, we extracted reclassification measures including the integrated discrimination improvement (IDI) and the net reclassification index (NRI), when reported.

Dealing with missing data

In case of any missing data about the predictive performance measures of the RCRI, extended RCRI and other prediction models, we planned to contact the original investigators to provide this missing information. However, in contrast to the protocol (Vernooij 2018), we concluded that contacting authors for missing information would not lead to different review findings as we encountered large heterogeneity in the study population, outcome definitions, prediction horizons and studied biomarkers or prediction models. Missing data for the confidence intervals around the C-statistic were estimated using the guidance and formulas described by Debray et al (Debray 2017).

Assessment of heterogeneity

We investigated clinical and statistical heterogeneity based on the items mentioned in the section 'Investigation of sources of heterogeneity between studies'. In particular, we discussed differences in surgical populations studied, in the composition of MACE and other predicted outcomes, and in prediction horizons within the author team. To assess between-study heterogeneity across the included studies, we inspected the forest plots of the extracted predicted performance measures. To further explore causes of heterogeneity, we predefined subgroup analyses (specified in further detail below under 'Subgroup analysis and investigation of heterogeneity').

Assessment of reporting deficiencies

Current guidelines (Transparent Reporting of a multivariable prediction model for Individual Prognosis Or Diagnosis; TRIPOD) recommend the reporting of calibration and discrimination measures for all prediction models (Collins 2015; Moons 2015). However, several systematic reviews focusing on the methodological conduct and reporting of prognostic models found that these performance measures are frequently not reported (Bouwmeester 2012; Collins 2013; Collins 2014; Heus 2018; Laupacis 1997; Mallett 2010). Therefore, we also evaluated which predictive performance measures were reported and which were not reported in the selected studies. Most studies reporting on prognostic models are not prospectively registered and no protocol has been published (Peat 2014), which makes a formal assessment of potential reporting bias difficult. We used sensitive search strategies to increase retrieval (Geersing 2012).

Data synthesis

Data synthesis and meta-analysis approaches

An overview of all included articles was created, sorted by the biomarker added to the RCRI and on the predicted outcomes. This overview included parameters such as publication year, type of surgery, number of patients included, biomarker(s) added and outcome definition. We created a similar overview for the articles reporting on the comparison of the predictive accuracy of one or more biomarkers to the RCRI (objective 2), and for the articles comparing the predictive performance of other prediction models to the RCRI (objective 3). As one article could have reported more than one validation of the RCRI, e.g. by using multiple outcomes or study populations, the number of validations may not correspond to the number of included articles. Therefore, results on study characteristics and (composite) outcomes are presented per uniquely reported outcome for each objective separately. Risk of bias and concern regarding applicability, and reporting rates of predictive performance measures, are reported per included article.

We planned to perform a meta-analysis of the predictive performance (O:E ratio, c-statistic and net reclassification index) of the RCRI model across the various validation studies as compared to the RCRI with the biomarker(s) added (objective 1). However, this turned out to be impossible due to the low number of studies reporting on the added value of the *same* biomarker and due to the differences in included study populations and in the outcome definitions between studies.

Instead, we presented the performance measures (c-statistic) for RCRI models extended with biomarkers that were studied in at least three studies in forest plots, without presenting a pooled estimate. Meta-analysis of the c-statistic was also planned for the studies that compared the RCRI to biomarkers alone (objective 2), if there were at least three studies reporting on the same biomarker and with a similar outcome definition, prediction horizon and scale on how the predictor was studied (i.e. continuous, categorical or dichotomous). As there was no set of studies fulfilling these criteria, meta-analysis of the c-statistic for objective 2 also turned out not to be possible. We therefore visualised the results in forest plots without presenting a pooled estimate.

Similar to objective 1 and 2, meta-analysis of the c-statistics was not possible for the studies that compared the predictive performance of other prediction models to the RCRI. For prediction models for which the predictive performance was compared to the RCRI at least three times, we made forest plots to visualise the results without presenting a pooled estimate.

Meta-analysis of the O:E ratio had also been planned, but turned out not to be possible due to the low number of studies reporting any calibration measures. We performed all analyses in Rstudio using the packages metafor (Viechtbauer 2010) and metamisc (Debray 2018).

Subgroup analysis and investigation of heterogeneity

The following subgroup analyses were planned:

- vascular surgery patients versus other noncardiac surgery patients;
- patients undergoing elective versus emergency surgery;
- different prediction horizons, e.g. in-hospital, 30-day and long-term events;
- patients in different age categories.

For the same reasons as mentioned above, meta-analysis in these subgroups was not possible. Again, we stratified the forest plots according to the subgroups based on outcome, and reported the prediction horizon in the plot. Details on the surgical population and age categories are reported in the 'Description of included

studies' table. We explored potential sources of heterogeneity by assessing case mix variation and differences in study characteristics (e.g. study design and prospective versus retrospective data collection). We had planned meta-regression to explore the cause and extent of the between-study heterogeneity but this turned out not to be possible (Debray 2017; Riley 2011).

Sensitivity analysis

We had planned sensitivity analyses excluding studies with high risk of bias (at least four domains rated 'high') and excluding unpublished studies and studies with missing data but we did not perform these due to the large heterogeneity between studies.

Rating the certainty of evidence and summary of findings

We had planned a summary of findings table using GRADE to present the body of evidence of the included prognostic studies. However, GRADE guidance for grading the certainty of results from prognostic studies is currently not available (Kreuzberger 2020). Therefore, the summary of findings table presents descriptive results (i.e. without pooled estimates) for studies reporting on biomarkers/prediction models that were added or compared to the RCRI in at least three different studies and were validated using a similar outcome in at least two different studies. This means that outcomes that were only validated once in any of the included studies were not included in the summary of findings table.

RESULTS

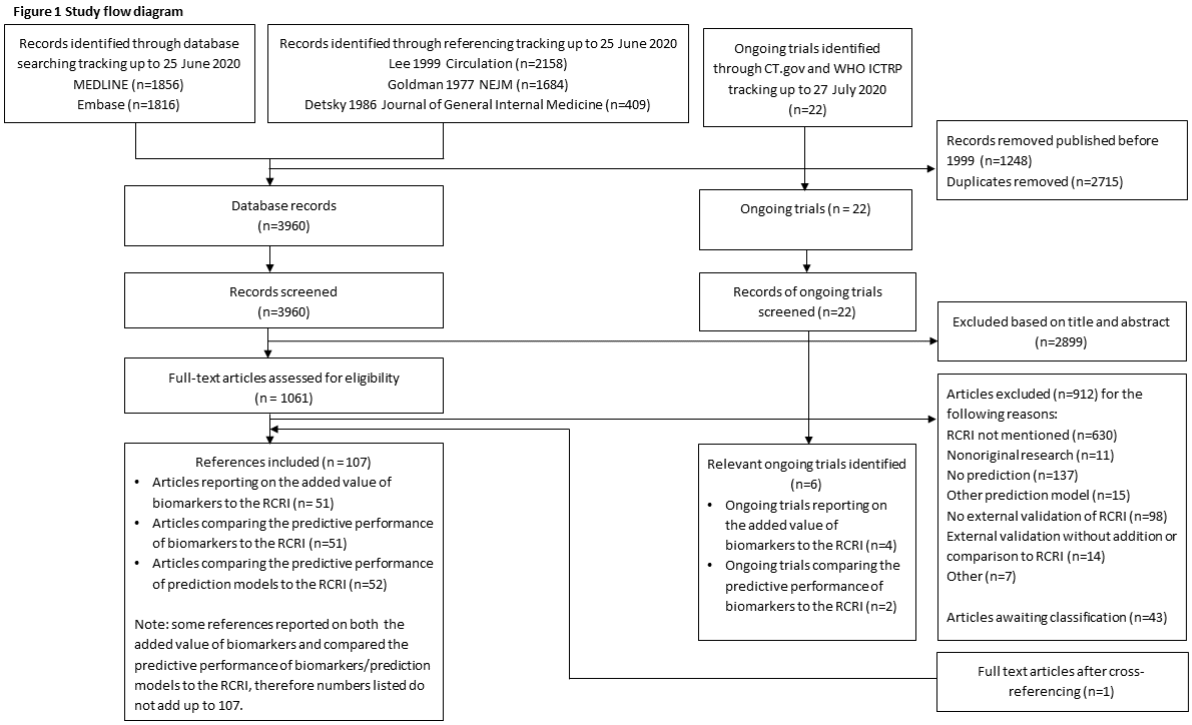
Description of studies

Results of the search

We identified a total of 3672 records through database searching and an additional 4251 records from citations to the development study of the RCRI (Lee 1999) and the studies of Goldman and Detsky (Detsky 1986; Goldman 1977). After removal of 2715 duplicates and 1248 articles that were published before the development study for the RCRI in 1999, we screened 3960 articles based on title and abstract, of which 1061 articles were selected for full-text screening. As mentioned before, we performed full-text screening in two stages. In the first stage, we characterised 43 articles as 'Awaiting classification' as the full text could not be retrieved. We discarded another 630 articles because they did not mention the RCRI in either the 'Methods' or 'Results' section of the article. In the second stage, we assessed the remaining 388 full-text articles for eligibility resulting in the inclusion of 106 articles. Cross-referencing of these 106 articles yielded the identification of one additional article leading to the inclusion of a total of 107 articles.

Of these 107 articles, 51 reported on the added value of predictors to the RCRI, 51 compared the predictive performance of the RCRI to biomarkers and 52 compared the RCRI to other prediction models. We found 30 (28%) articles reporting on both the added value of a certain predictor to the RCRI and comparison of the predictive performance of this biomarker. In 11 (10%) articles, the added value of a particular biomarker to the RCRI and the comparison of another prediction model was reported. Finally, the comparison of both a biomarker and a prediction model to the RCRI was presented in 13 (12%) articles. For further details of our search results, see Figure 1.

Figure 1. Study flow diagram



The search of databases of ongoing trials (clinicaltrials.gov and WHO ICTRP; searched 27 July 2020) revealed 22 records (Figure 1). No duplicates were identified. Four ongoing trials aim to investigate the added value of biomarkers to the RCRI (NCT03436238: hsTnT, NTproBNP, copeptin, MR-proADM and CT-proET1; NCT02860754: six-minute walking test and self-reported METS, NCT03016936: METs estimated by questionnaire and NT-proBNP; NCT02146560: BNP, HbA1c and others) and two other ongoing trials will compare the predictive ability of the RCRI alone to biomarkers (NCT01280253: NT-proNP, lactate, pro-calcitonin, adrenomedullin, copeptin, cystatin c; CTRI/2019/02/017668: hand grip strength, Modified Frailty Index). More detailed information is provided in Characteristics of ongoing studies.

Risk of bias and concern regarding applicability

We observed no differences in terms of assessment of risk of bias and concern regarding applicability among articles studying the added value of predictors or comparing the predictive performance of predictors or prediction models to the RCRI. Therefore, we evaluated the risk of bias and concern regarding applicability per domain (i.e. selection of participants, predictors, outcome and analysis) as described by the PROBAST tool (Moons 2019; Wolff 2019) for all included articles at once.

Overall, we rated risk of bias as high in at least one domain in 96 (90%) of all included articles. There was an overall 'high' concern regarding applicability in 84 (78%) articles. More detailed information is presented in Figure 2 and Figure 3.

Figure 2. Green refers to 'low' risk of bias; orange is 'unclear' risk of bias and red represents 'high' risk of bias.

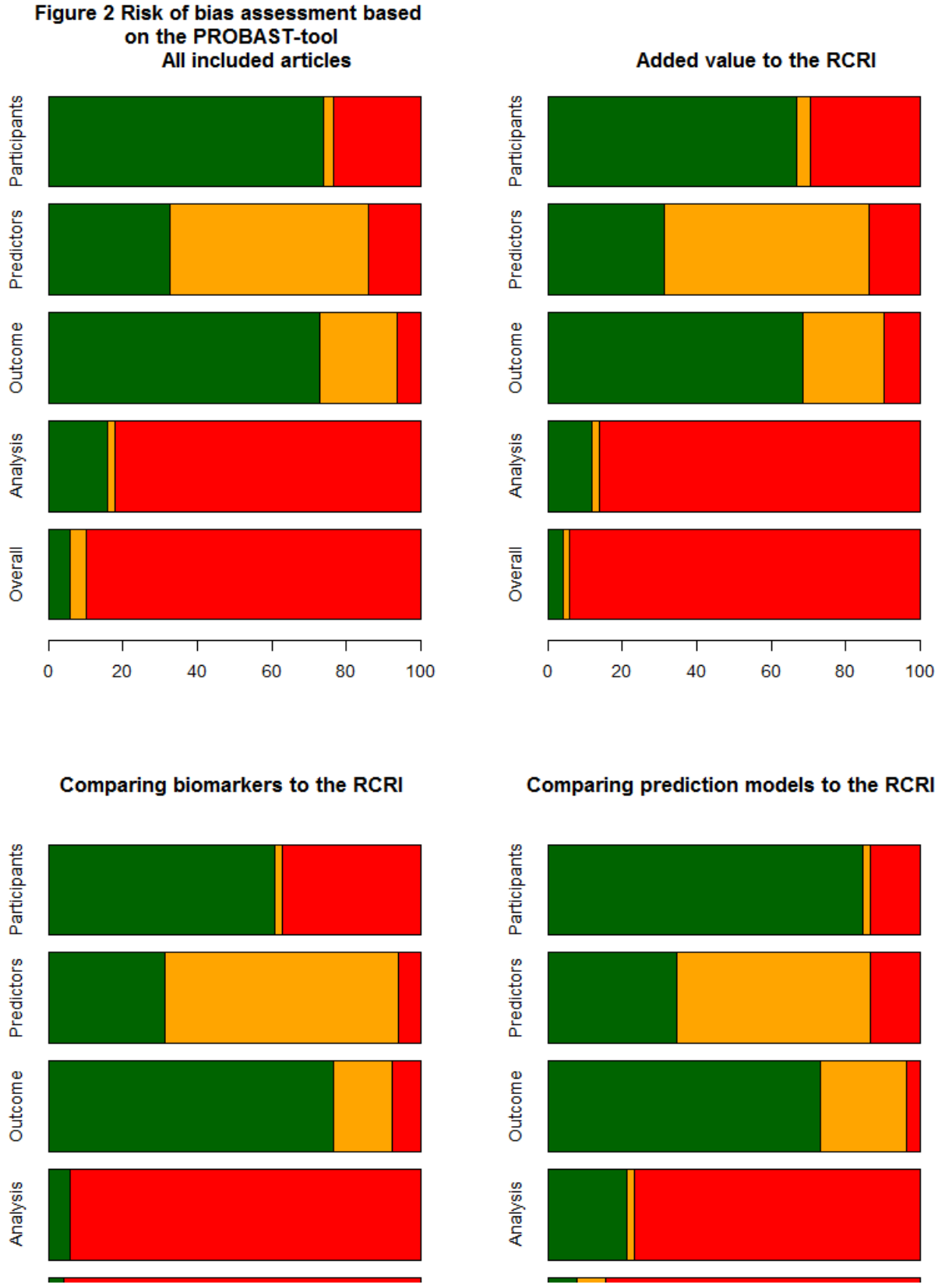


Figure 2. (Continued)

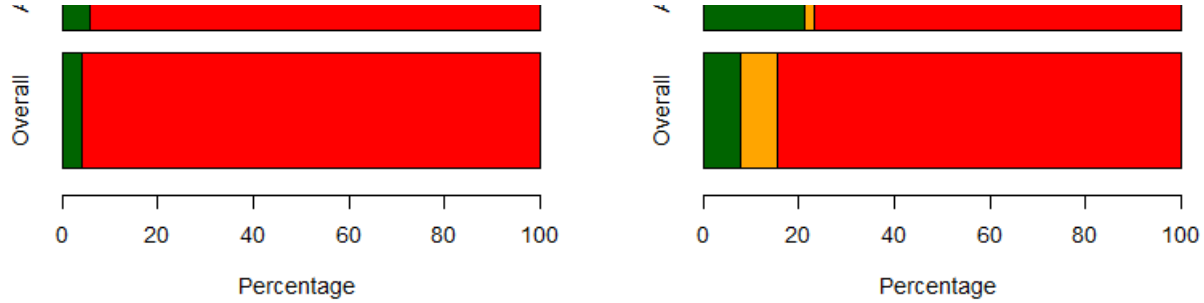


Figure 3. Green refers to 'low' risk of bias; orange is 'unclear' risk of bias and red represents 'high' risk of bias.

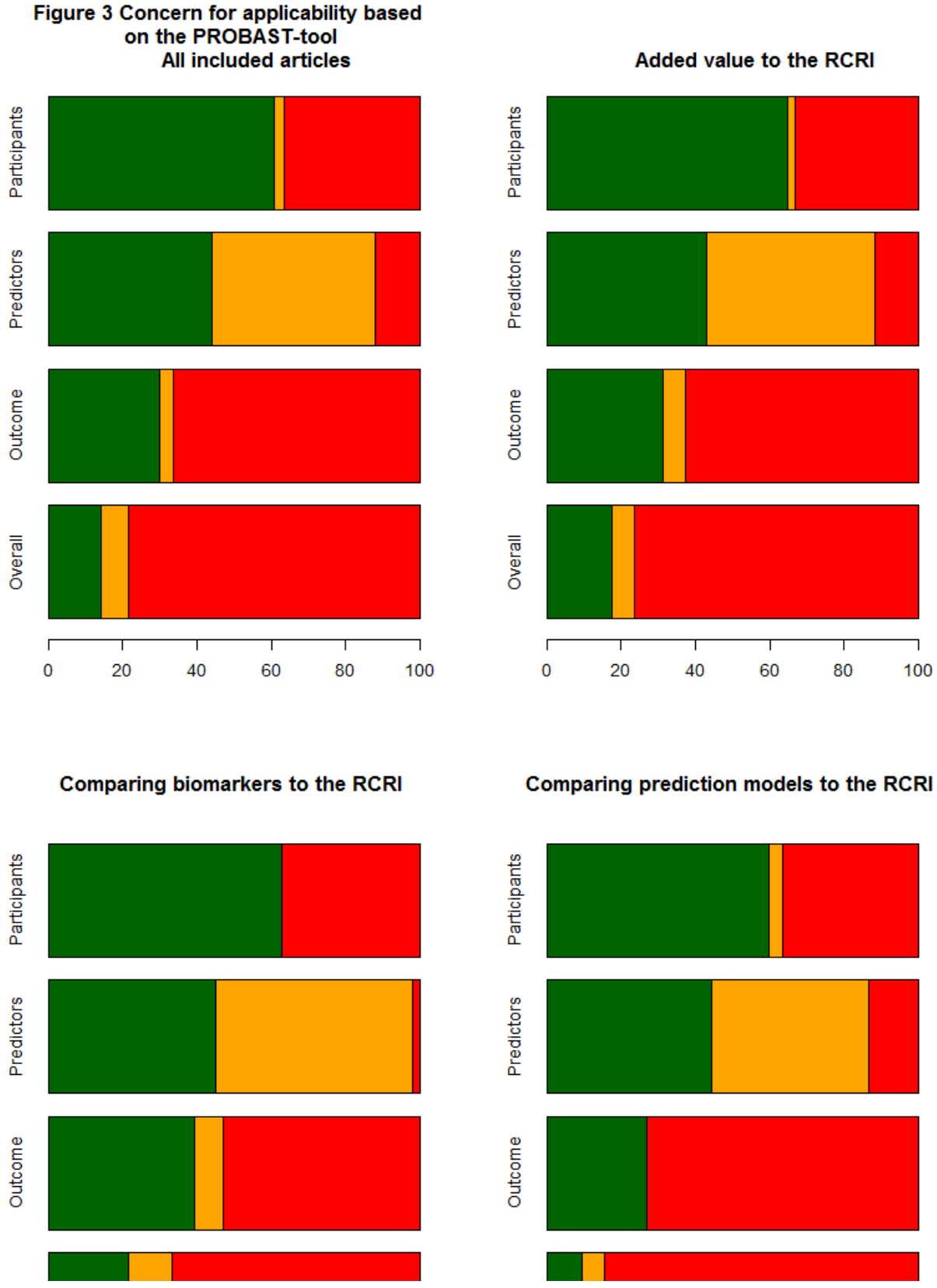
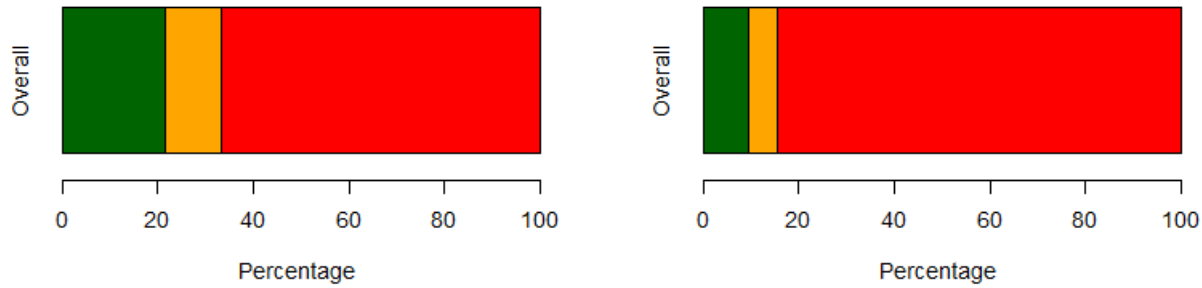


Figure 3. (Continued)



PROBAST domain 1: Participants

In 79 (74%) included articles, we judged the risk of participant selection bias as low. We rated risk of bias as high for 25 articles (23%) due to inappropriate exclusion of participants (e.g. exclusion of patients with preoperative severe cardiac comorbidities, who underwent coronary revascularisation or patients who were unsuitable for exercise testing) or inappropriate inclusion of participants (e.g. only inclusion of patients who were referred to a cardiologist, had a transthoracic echocardiography or without any known cardiovascular disease). We rated the remaining three articles (3%) as having unclear risk of bias as no eligibility criteria for inclusion in the study were described.

We judged concern regarding applicability for the domain 'Selection of participants' as low in 65 (61%) of all included articles. We rated 39 (36%) articles as having high concern regarding applicability because of the inclusion of patients undergoing a single procedure or with one particular comorbidity (e.g. atrium fibrillation), inclusion of very high-risk patients (i.e. high incidence of comorbidities) and inclusion of patients with a either broad or small age range. The three (3%) articles that we rated as having unclear risk of bias were also judged as having unclear concern regarding applicability for the same reasons.

PROBAST domain 2: Predictors

For the domain 'Predictors', we rated the majority of articles (57, 53%) as having unclear risk of bias as no information was provided on how the individual RCRI predictors were defined or measured. This was most often the case for 'history of congestive heart failure' (76%), 'history of ischaemic heart disease' (73%) and 'history of cerebrovascular disease' (64%). We judged a high risk of bias for this domain in 15 (14%) articles because of different predictor definitions compared to the definitions of the development study. Differences were most often observed for the definition of 'history of ischaemic heart disease' (19%) and 'history of congestive heart failure' (15%).

We rated concern regarding applicability as low in 47 (44%), unclear in 47 (44%) and high in 13 (12%) articles. Judgement was based on similar reasons as mentioned above for risk of bias.

PROBAST domain 3: Outcome

We rated seven (6%) of the included articles as having high risk of bias for the domain 'Outcome', mostly due to inappropriate assessment of the outcome. We judged 22 (21%) articles to have unclear risk of bias as in many studies there was no clear outcome definition, or no information on how the outcome was assessed or whether outcome assessors were blinded to predictor information. We rated the remaining 78 (72%) articles as low risk of bias for this domain.

The RCRI has been developed to predict postoperative in-hospital MACE. However, many articles used the RCRI for predicting other outcomes, including all-cause mortality and noncardiac complications, and therefore we judged these articles (71, 66%) as having high concern regarding applicability for this domain. We rated concern regarding applicability as unclear in four (4%) articles due to unclear outcome definitions.

PROBAST domain 4: Analysis

We rated risk of bias for the domain 'Analysis' as high in the majority of the included articles (88, 82%), mainly due to low numbers of outcome events. The PROBAST-tool recommends at least 100 outcome events as otherwise biased estimates of model performance become more likely (Moons 2019; Wolff 2019). Other reasons for scoring risk of bias as high were dichotomisation of predictors, and not reporting appropriate performance measures (i.e. discrimination and/or calibration) at all or without uncertainty measures (i.e. confidence intervals or standard errors). In addition, none of the included articles used multiple imputation for handling of missing data. Only 30 (28%) articles reported that they did complete case analysis and the remaining articles did not mention handling of missing data. We rated the remaining articles (17, 16%) as low risk of bias.

Included studies

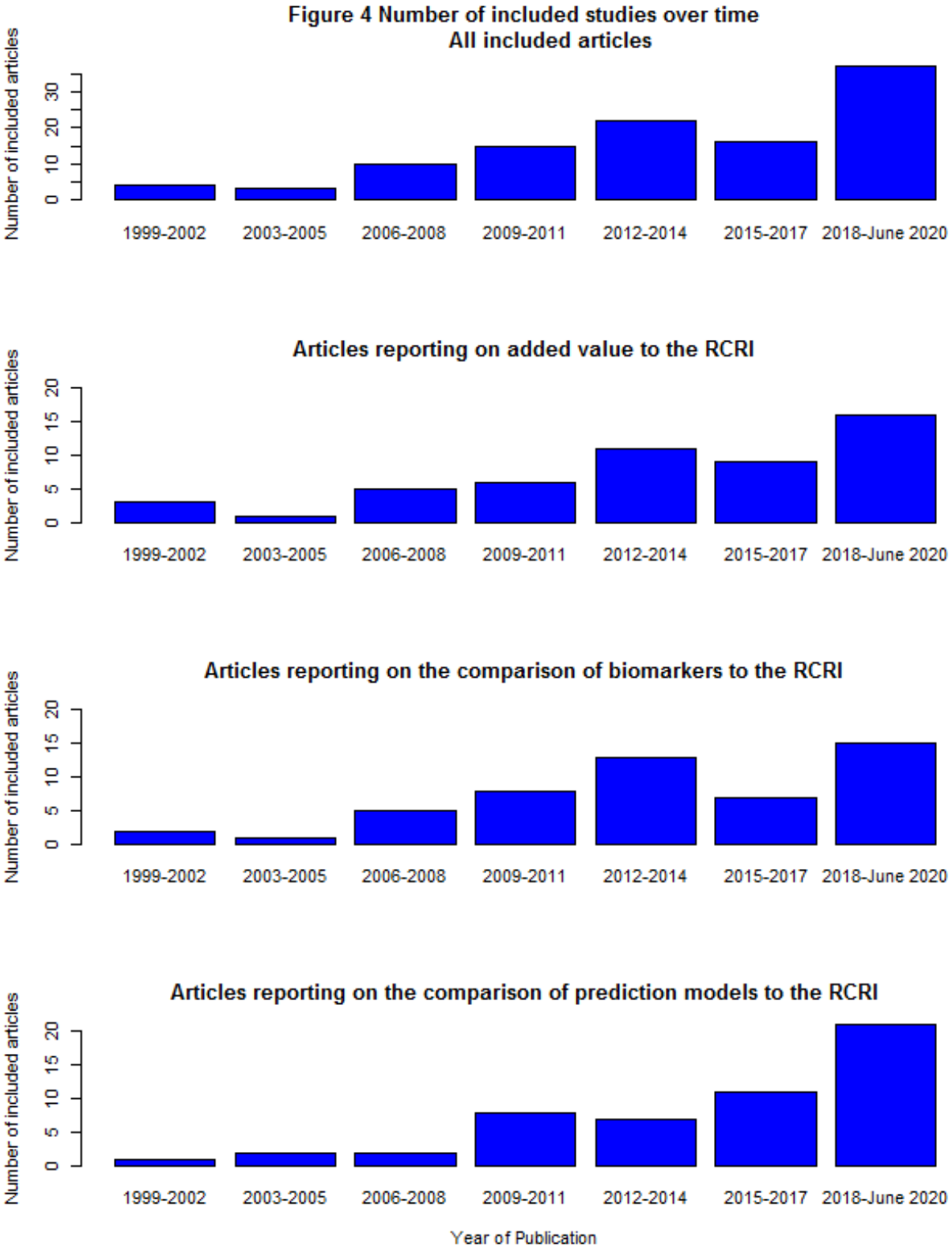
Some articles reported on the validation of the RCRI for different outcomes (i.e. multiple validations are described in one article). Accordingly, the number of validations is higher than the number of included articles. Therefore, study characteristics and (composite) outcomes are presented uniquely per reported outcome for each objective separately. Risk of bias and concern regarding applicability, and reporting rates of predictive performance measures, are reported per article. In addition, lists of biomarkers and prediction models that have been added and/or compared to the RCRI are provided. Biomarkers or prediction models, i.e. predictors that were reported in at least three separate included studies, are described in more detail. The summary of findings tables presents descriptive results (i.e. without pooled estimates) for studies reporting on biomarkers/prediction models that were added or compared to the RCRI in at least three different studies and were validated using a similar outcome in at least two different studies (Summary of findings 1; Summary of findings 2; Summary of findings 3).

Objective 1: the added predictive value of biomarkers to the RCRI

Study design and study population

In the 51 included articles reporting on the added value of biomarkers to the RCRI, 62 validations of the RCRI were observed. Most validations were done in cohort study data (n = 57, 92%) and 44 (71%) had their data collected prospectively. Study participants most often underwent noncardiac surgery (n = 36, 58%) followed by vascular surgery (n = 19, 30%) (Table 3). In one study, the surgical specialty was not specified (Makary 2010). Participants originated most frequently from Europe (n = 22, 36%) and Asia or North America (n = 14, 23% and n = 12, 19%, respectively). The number of included participants per validation ranged from 77 to 108,593 (median (interquartile range, IQR); 442 (223 to 1389)) and the number of events ranged from 11 to 1269 (38 (21 to 84)). In one study, the number of events was not reported. The most frequently used prediction horizons were either during hospital admission (n = 12, 19%), 30 days (n = 29, 47%) or within the first seven days after surgery (n = 6, 10%). However, there was a broad width in prediction horizons, ranging from one day to four years after surgery. In terms of predicted outcomes, MACE was most frequently the outcome of interest (n = 31, 50%) followed by all-cause mortality (n = 6, 10%) or a combination of both (n = 8, 13%). Although the RCRI was developed to predict MACE, 14 (23%) validations used all-cause mortality as an outcome and four validations used other complications (e.g. discharge to a nursing facility; 7%). The number of published articles on the added value of predictors to the RCRI increased over time with a peak in the most recent period, i.e. 2018 to June 2020 (Figure 4).

Figure 4. As the search was performed on June 25th, results are shown for the period between January 2018 and June 2020



Outcomes and composition of MACE

The majority of all included articles used MACE including MICA (composite outcome including myocardial infarction and cardiac arrest; n = 78, 45%) as an outcome or combined MACE with all-cause mortality (n = 15, 9%). However, MACE composition varied noticeably with 80 different definitions. Table 4 shows an overview of the outcome composites of MACE (i.e. MACE and combination of MACE and all-cause mortality). For the studies reporting on the added value of biomarkers to the RCRI, all but eight (81%) included myocardial infarction as one of the composites of MACE. Most definitions for MACE (22/33; 67%) did not specify if it concerned either fatal or nonfatal myocardial infarction. Besides myocardial infarction, there was no other outcome used as a composite in more than half of the definitions used. Other frequently used included outcomes as part of MACE were heart failure (29%), cardiac death (35%), cardiovascular death (22%), cardiac arrest (15%), myocardial injury (24%) and pulmonary oedema (20%) (Table 4).

Risk of bias and concern regarding applicability

We rated overall risk of bias as high in at least one domain in 48 (94%) articles reporting on the added value of predictors to the RCRI. More detailed information is described under the subheading 'Risk of bias and concern regarding applicability' and presented in Figure 2 and Figure 3. We rated most articles as having unclear risk of bias for predictors (n = 28, 55%) due to no information on the definitions of the individual RCRI items or no description on how the 'new' biomarkers were measured or added to the RCRI. For the domains 'outcome' and 'analyses', we rated n = 5 (10%) and n = 44 (86%) articles as having high risk of bias, respectively. We rated concern regarding applicability as high in at least one of the domains in 39 (76%) of the included articles. This was mainly because of high concern regarding applicability in the domain 'outcome' (n = 32, 63%) due to inappropriate outcomes used to be predicted (Figure 2; Figure 3).

We observed no differences in the reasons for judgement of high or unclear risk of bias and concern regarding applicability among the different objectives. More detailed information on this topic is described below under the subheading 'Risk of bias and concern regarding applicability'.

Predictive performance measures reported

All included articles but one (n = 106, 99%) reported at least one performance measure (Table 5). For studies on the added value of biomarkers to the RCRI, discrimination was reported in 48 (94%) articles, for which the majority of articles presented a c-statistic (n = 40, 78%). Compared to all included studies, c-statistics were reported less often for studies on the added value of biomarkers to the RCRI (92% and 79%, respectively). Calibration was presented in 39 (36%) articles by means of an observed/expected ratio (n = 22, 21%), calibration plot (n = 14, 13%) or a Hosmer Lemeshow test (n = 7, 7%). Again, calibration measures were less frequently reported in articles evaluating the added value of predictors to the RCRI compared to all included articles (20% versus 36%, respectively). In total, 36 articles (34%) reported both discrimination and calibration measures, of which nine (18%) investigated the added value of predictors to the RCRI. Reclassification measures, presented as integrated discrimination improvement (IDI) or net reclassification index (NRI), were more often reported in articles investigating the added value of biomarkers to the RCRI compared to all included articles, as expected (35% versus 22%, respectively).

Added biomarkers

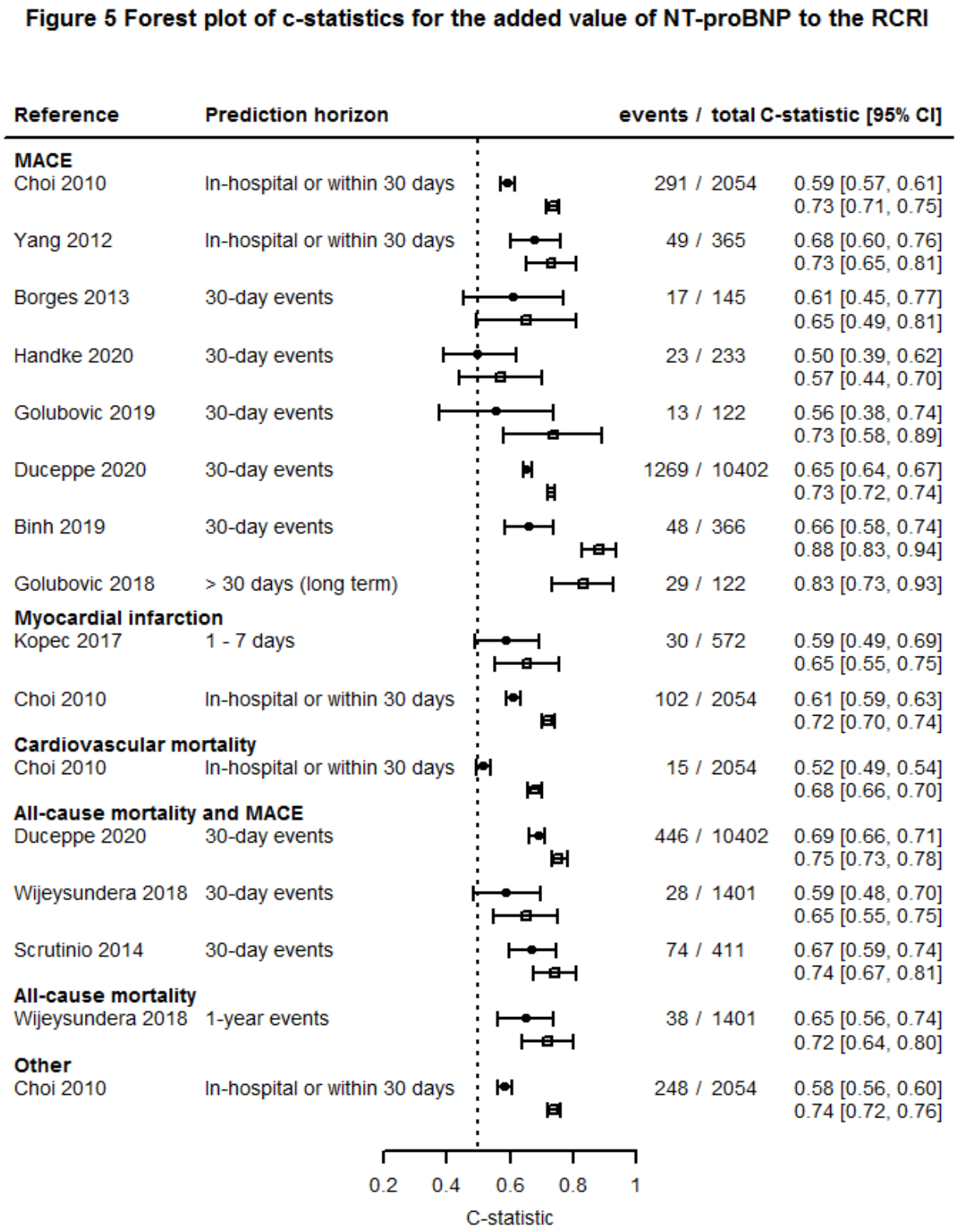
In Table 6, an overview of the biomarkers added to the RCRI is provided sorted by the number of studies reporting on a particular biomarker. We identified 69 different added predictors of which 20 (29%) were derived from blood, 23 (33%) from imaging and 26 (38%) from other sources including patient characteristics, such as smoking or age. In most instances, one predictor was added (n = 47, 68%) to the RCRI to improve risk prediction followed by two (n = 16, 23%) and three predictors (n = 6, 9 %) in the same model.

For the biomarkers that have been added to the RCRI in at least three different studies, study characteristics and findings are described in further detail below. These biomarkers are brain natriuretic peptide (BNP), copeptin, N-terminal pro-B type natriuretic peptide (NT-proBNP), troponin and the combination of NT-proBNP and troponin.

N-terminal pro-B type natriuretic peptide (NT-proBNP)

N-terminal pro-B type natriuretic peptide (NT-proBNP) is generated by cardiomyocytes in the context of numerous triggers, most notably myocardial stretch. NT-proBNP has been increasingly used as a marker to establish the presence and severity of heart failure in both chronic ambulatory or acute decompensated heart failure settings (Yancy 2013). We included 12 articles reporting on the added predictive value of NT-proBNP to the RCRI in 17 different analyses. Three articles showed added value for multiple outcomes (Choi 2010; Duceppe 2020; Wijeysundera 2018). Patients underwent either mixed noncardiac (n = 7) or vascular surgery (n = 5). NT-proBNP was added to the RCRI on a continuous scale in six articles, on a dichotomous scale using a predefined threshold in four articles and on a categorical scale in two articles. Figure 5 represents the added predictive value of NT-proBNP to the RCRI by means of the c-statistics to predict MACE, myocardial infarction, all-cause mortality, cardiovascular mortality or pulmonary oedema. The majority of predictions were performed for the in-hospital and/or 30-day events (n = 14). The number of reported events was relatively low in the majority of the studies, i.e. median 43, range 13 to 1269. Addition of NT-proBNP to the RCRI to predict MACE was reported in seven studies including 13,687 patients of whom 1710 suffered MACE (Biccard 2012; Binh 2019; Borges 2013; Choi 2010; Duceppe 2020; Golubovic 2018; Handke 2020; Yang 2012). The delta c-statistic was median 0.08 (range 0.04 to 0.22). Calibration was presented in one study and showed good calibration (Duceppe 2020). Reclassification was better for the model including NT-proBNP (n = 2 studies, 10,524 included patients with 1560 MACE, median NRI (range) 0.74 (0.26 to 1.22)) (Duceppe 2020; Golubovic 2018). For the composite outcome all-cause mortality and MACE, the delta c-statistic was 0.06 (range 0.06 to 0.07) and reported in three studies that included 12,214 patients of whom 548 suffered either all-cause mortality or MACE (Duceppe 2020; Scrutinio 2014; Wijeysundera 2018). The Hosmer Lemeshow test was reported in one study showing some overall miscalibration (P = 0.03) (Scrutinio 2014). The median NRI was 0.19 (0.13 to 25) (Scrutinio 2014; Wijeysundera 2018). For the prediction of myocardial infarction (MI), two studies (n = 2626, 131 MIs) showed improved discrimination (delta c-statistic; 0.09, range 0.06 to 0.11) (Choi 2010; Kopec 2017). No calibration was reported in these studies. In the study Kopec 2017, the total NRI was 0.46.

Figure 5. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents RCRI + NT-proBNP.



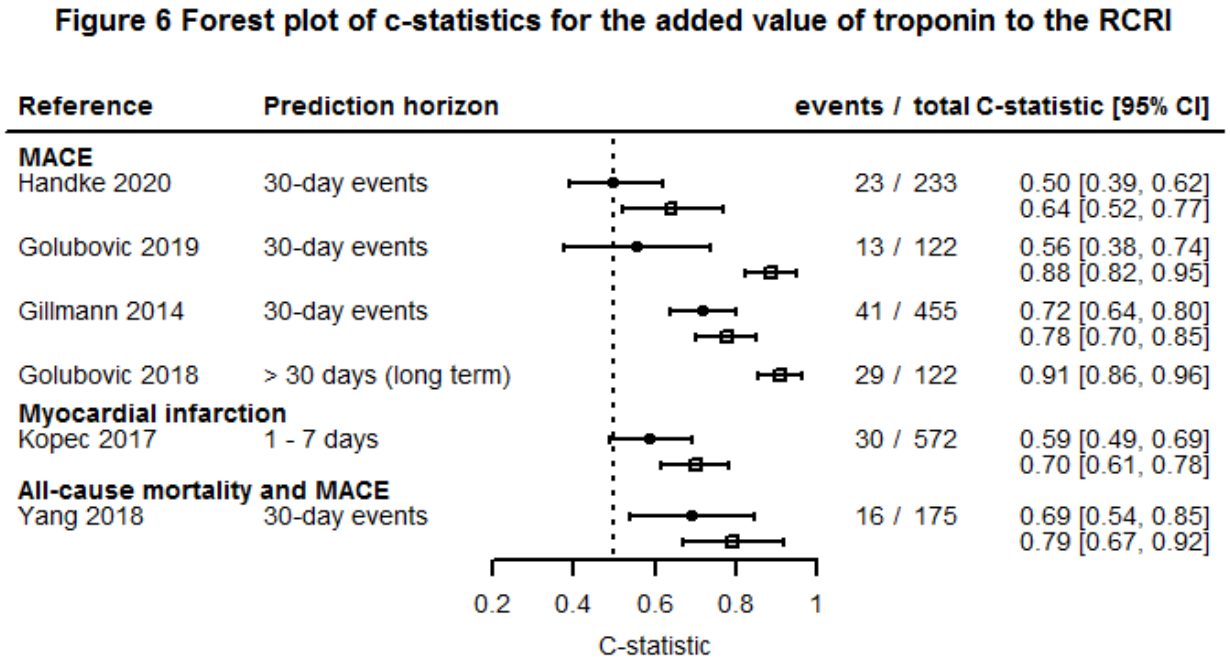
Brain natriuretic peptide (BNP)

Similar to NT-proBNP, BNP is released by cardiomyocytes in case of myocardial stretch. BNP is used in clinical practice as a marker to establish the presence and severity of both chronic ambulatory or acute decompensated heart failure (Yancy 2013). BNP was added to the RCRI in six analyses over five articles (Biccard 2011; Biccard 2012; Cuthbertson 2007; Katsanos 2015; Rodseth 2011), with one article describing two analyses using different outcomes and prediction horizons (i.e. in-hospital MACE and one-year all-cause mortality) (Katsanos 2015). Included articles reported most frequently on patients undergoing vascular surgery (n = 3). The outcome of interest in these articles was MACE (n = 3), all-cause mortality (n = 1), a combination of both (n = 1) or troponin elevation (n = 1). Prediction horizons ranged from in-hospital to one-year events. As none of the articles reported the c-statistics of the extended model (i.e. BNP added to the RCRI), no forest plot was provided. Two studies reported reclassification in terms of the NRI after addition of BNP to the RCRI to predict MACE (n = 1724 patients, unknown number of MACE) (Katsanos 2015; Rodseth 2011). The median NRI was 0.72 with a range of 0.47 to 0.96. None of the included studies reported on calibration.

Troponin

Troponin is a protein that is involved in the contraction of cardiac muscle and is released by injured cardiomyocytes. Release of troponin may be due to myocardial cell death caused by ischaemia but also by, for example, normal turnover of myocardial cells, apoptosis or increased permeability of the cell wall (Mair 2018; Thygesen 2018). We included five articles reporting on the added predictive value of troponin to the RCRI in six analyses, of which one article analysed two populations separately (Gualandro 2018). However, no c-statistics were reported for this study. Included populations concerned patients undergoing vascular (n = 4) or mixed noncardiac surgery (n = 3). Troponin was added on a continuous scale, dichotomous scale or not reported in two and four and one studies, respectively. Included studies aimed to predict 30-day MACE (n = 4), long-term MACE (n = 1), 30-day MACE or all-cause mortality (n = 1) or myocardial infarction within three days of surgery (n = 1). The extracted confidence intervals were wide, the studied patient populations (i.e. vascular and noncardiac) heterogeneous, and the numbers of included participants and events for the studies investigating the added value of troponin were low, i.e. median 238 (range 122 to 797) and median 30 (range 13 to 58), respectively. Three studies (n = 810, 77 MACE) investigated the incremental discriminative value of troponin to the RCRI model to predict MACE (delta c-statistic 0.14 (range 0.06 to 0.33); Figure 6) (Gillmann 2014; Golubovic 2018; Handke 2020). Reclassification was reported in two studies (n = 577, 70 MACE) resulting in a delta NRI of 0.16 (range 0.09 to 0.22) (Gillmann 2014; Golubovic 2018). None of the studies investigating the incremental value of troponin to the RCRI reported on calibration.

Figure 6. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents RCRI + troponin. As Golubovic 2018 solely reported on the c-statistics for the additive model, no c-statistic for RCRI alone is provided for this study.



Copeptin

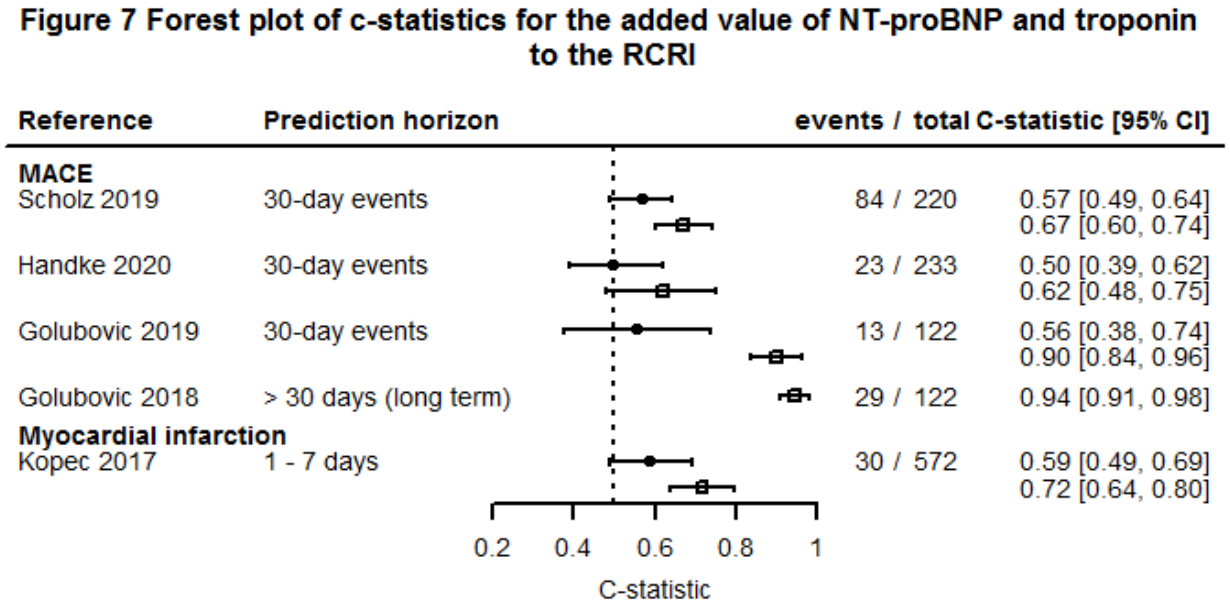
Copeptin is a novel marker of vasopressin activity, an antidiuretic hypothalamo-pituitary hormone, mainly regulated by changes in plasma osmolality, blood volume and blood pressure (Mauermann 2016). Copeptin was added to the RCRI in three articles of which two studies reported on either the prediction of 30-day or long-

term MACE in the vascular surgical population (Jarai 2011; Schrimpf 2015). The other study investigated the added value of copeptin to the RCRI to predict troponin elevation within two days after surgery in noncardiac surgical patients (Mauermann 2016). The NRI in this study was 0.78. The c-statistic for the RCRI alone and the extended model to predict MACE was reported in one article, i.e. 0.714 and 0.752, respectively (n = 477, 41 MACE) (Schrimpf 2015). The NRI was reported in one study (n = 198, 40 MACE) to evaluate reclassification of the incremental value of copeptin to the RCRI to predict MACE at 24 months after surgery (NRI; 0.33) (Jarai 2011). None of the selected studies reported on calibration. There was not sufficient information to summarise these studies in a forest plot.

NT-proBNP + troponin

We included four studies reporting on the added predictive value of the combination of NT-proBNP and troponin to the RCRI (Golubovic 2018; Handke 2020; Kopec 2017; Scholz 2019). Patients underwent vascular (n = 2) or mixed noncardiac surgery (n = 3). The scale used to add troponin and NT-proBNP to the RCRI was either continuous (n = 3) or dichotomous (n = 2). Reported outcomes were 30-day MACE (n = 3), long-term MACE (n = 1) or myocardial infarction within three days of surgery (n = 1). The number of included patients and events was low (i.e. median 227; range 122 to 572 and median 30; range 13 to 84, respectively) resulting in wide confidence intervals. In addition, the composition of MACE varied among the included studies and the patient populations (i.e. vascular and noncardiac) were heterogeneous. The addition of troponin and NT-proBNP to the RCRI to predict 30-day MACE resulted in a delta c-statistic of median 0.12 with a range of 0.10 to 0.34 (3 studies, n = 572, 120 MACE; Figure 7) (Golubovic 2018; Handke 2020; Scholz 2019). The added value of troponin and NT-proBNP to the RCRI to predict myocardial infarction was investigated by Kopec 2017). They reported a delta c-statistic of 0.13 and an NRI of 0.66 (n = 572, 30 MIs). None of the selected studies reported on calibration.

Figure 7. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents NT-proBNP+troponin+RCRI. As Golubovic 2018 solely reported on the c-statistics for the additive model, no c-statistic for RCRI alone is provided for this study.



Objective 2: comparison of the predictive value of single biomarkers to the RCRI

Study design and study population

In total, 51 studies compared the predictive performance of biomarkers to the RCRI and reported 89 validations (Table 3). Most articles reported on the validation of one outcome (n = 37), two outcomes (n = 8) or three or more (n = 4). One article reported on 24 validations of primarily noncardiac complications (Bronheim 2018). Similar to studies reporting on the added value of biomarkers to the RCRI, most studies were cohort studies (n = 57, 64%) and data were collected prospectively in 66 (74%) validations. In 24 (27%) and 42 (48%) validations, patients originated from Europe and North America, respectively. Most included patients who underwent noncardiac surgery (n = 30, 34%) followed by vascular surgery (n = 23, 26%). Bronheim et al validated 24 different outcomes in a neurosurgical population (Bronheim 2018). The surgical specialty was not specified in one study (Makary 2010). The median number of included participants was 594 (227, 52,066). The number of events was not reported in one study, which reported four validations (Rodseth 2011). The most frequently used prediction horizons were during hospital admission (n = 13, 15%), within the first seven days (n = 7, 8%) or 30 days (n = 59, 66%) after surgery. In 39% (n = 35) of the studies, MACE was the outcome to be predicted followed by all-cause mortality (n = 10, 11%) or a combination of both (n = 7, 8%). Five articles (10%) reporting on 29 validations predicted other outcomes than MACE or all-cause mortality, of which Bronheim et al reported predictions for 21 different (noncardiac) outcomes (Bronheim 2018). The number of published articles on the comparison of the predictive accuracy of

biomarkers to the RCRI increased over time with a peak in 2018 to June 2020 (Figure 4).

Composition of MACE

For the 38 articles that used MACE as the outcome to be predicted, we found 42 validations that compared the prognostic ability of biomarkers to the RCRI alone (Table 4). Within these 42 validations, 21 different MACE definitions were reported using composites ranging from intraoperative haemodynamic adversity to cardiac death. Myocardial infarction was the most frequently used composite of MACE (n = 35, 83%).

Risk of bias and concern regarding applicability

We rated an overall high risk of bias in 49 (96%) articles that compared the predictive performance of biomarkers to the RCRI. Compared to articles included in the other objectives, we rated risk of bias for participants as high more often (n = 19, 37%). Most articles scored unclear risk of bias for predictors (n = 32, 63%) due to no information on the definitions of the individual RCRI items. For the domain 'outcome' and for the domain 'analyses', n = 4(8%) and n = 48(94%) articles scored high for risk of bias, respectively. Concern regarding applicability scored high in at least one of the domains in 34 (67%) of the included articles. This was mainly because of high concern regarding applicability in the domain 'outcome' (n = 27, 53%) due to inappropriate outcomes used to be predicted (Figure 2; Figure 3).

As we did not observe differences in the reasons for judgements of high or unclear risk of bias and concern regarding applicability among the different objectives, more detailed information on this topic is described below under the subheading 'Risk of bias and concern regarding applicability' as part of the first objective.

Predictive performance measures reported

For studies comparing the prognostic ability of biomarkers to the RCRI alone, predictive performance measures on discrimination, calibration and reclassification were reported in 96%, 29% and 4%, respectively (Table 5). The c-statistic was presented in 88% of the included articles. Half of the articles that compared the predictive ability of biomarkers to the RCRI reported sensitivity and specificity. The negative and positive predictive value were reported in 24% and 22% of the included studies, respectively. Calibration was presented as an observed/expected ratio (24%), calibration plot (2%) or a Hosmer Lemeshow test (6%).

Comparison of biomarkers

An overview of biomarkers for which the predictive performance was compared to the RCRI is presented in Table 7. We identified 60 unique predictors derived from blood (n = 23, 38%), imaging (n = 18, 30%) or other type of characteristics (n = 19, 32%; e.g. age or metabolic equivalent (METS)). For biomarkers for which the predictive performance was compared to the RCRI in at least three different studies, the study characteristics are described in further detail below. These predictors were the American Society of Anesthesiologists classification (ASA), BNP, NT-proBNP, troponin and C-reactive protein (CRP).

American Society of Anesthesiologists (ASA) physical status

The ASA physical status is a tool commonly used to classify a patient's physical fitness before surgery. It describes five classes of physical status ranging from ASA1 (i.e. healthy, non-smoking patient) to ASA5 (patient is expected to die within 24 hours). ASA6 is sometimes used to describe a brain-death organ donor. The ASA classification is not a prediction model, but a subjective and rapid assessment tool mostly based on the experience of the anaesthesiologist (Mayhew 2019). The predictive ability of ASA was compared to the RCRI in 53 analyses over 14 included articles. Patients underwent a variety of surgical procedures, i.e. neurosurgery (number of studies = 3), vascular (n = 3), general (n = 1), orthopaedic (n = 1), mixed noncardiac surgery (n = 5) or unspecified (n = 1). The prediction horizon was most commonly within 30 days (n = 9) followed by in-hospital events (n = 4). MACE was the outcome to be predicted in six articles over seven analyses (Bronheim 2018; James 2014; Parmar 2010; Press 2006; Rohrig 2004; Vetrugno 2014). The delta c-statistic was 0.02 with a range of -0.03 to 0.18 in favour of the RCRI (n = 84,145, 5415 MACE). Rohrig 2004 reported on intraoperative MACE (hypotension, hypertension, bradycardia and tachycardia), which contributed most of the MACE outcomes. The prediction horizon was intraoperative or in-hospital or 30-day MACE (Rohrig 2004). Calibration was poor as presented in a calibration plot and Hosmer Lemeshow test ($P < 0.001$) reported in one study (Rohrig 2004). Other predicted outcomes were myocardial infarction (n = 2) and all-cause mortality (n = 6 articles, 10 validations). The delta c-statistic was 0.02 (range -0.07 to 0.12) and 0.05 (-0.05 to 0.24) in favour of ASA, respectively. Other noncardiac events were predicted in six articles over 34 validations (Table 8). Bronheim 2018 compared the ASA to the RCRI to predict 21 different outcomes, and Press 2006 predicted four different noncardiac outcomes. Figure 8 and Table 8 show the reported c-statistics for the ASA and RCRI. Besides the study by Rohrig 2004, none of the studies reported on calibration or reclassification.

Figure 8. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents ASA.

Figure 8 Forest plot of c-statistics for the comparison of the predictive performance of ASA classification to the RCRI

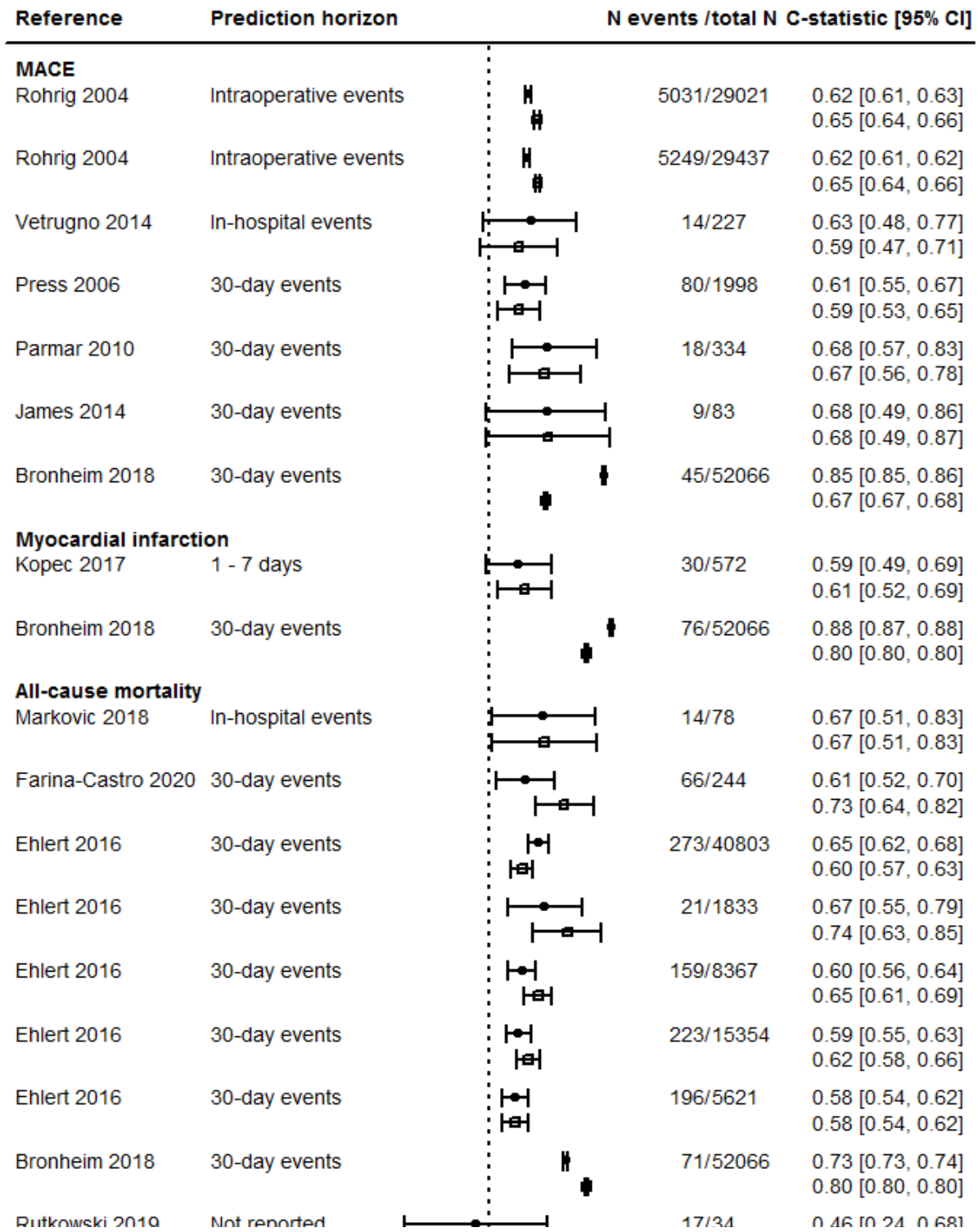
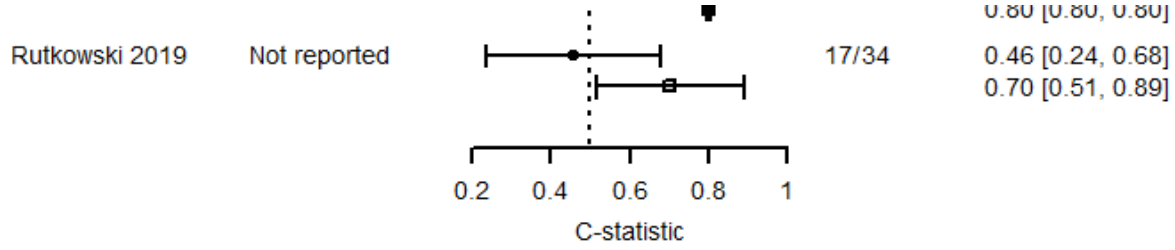


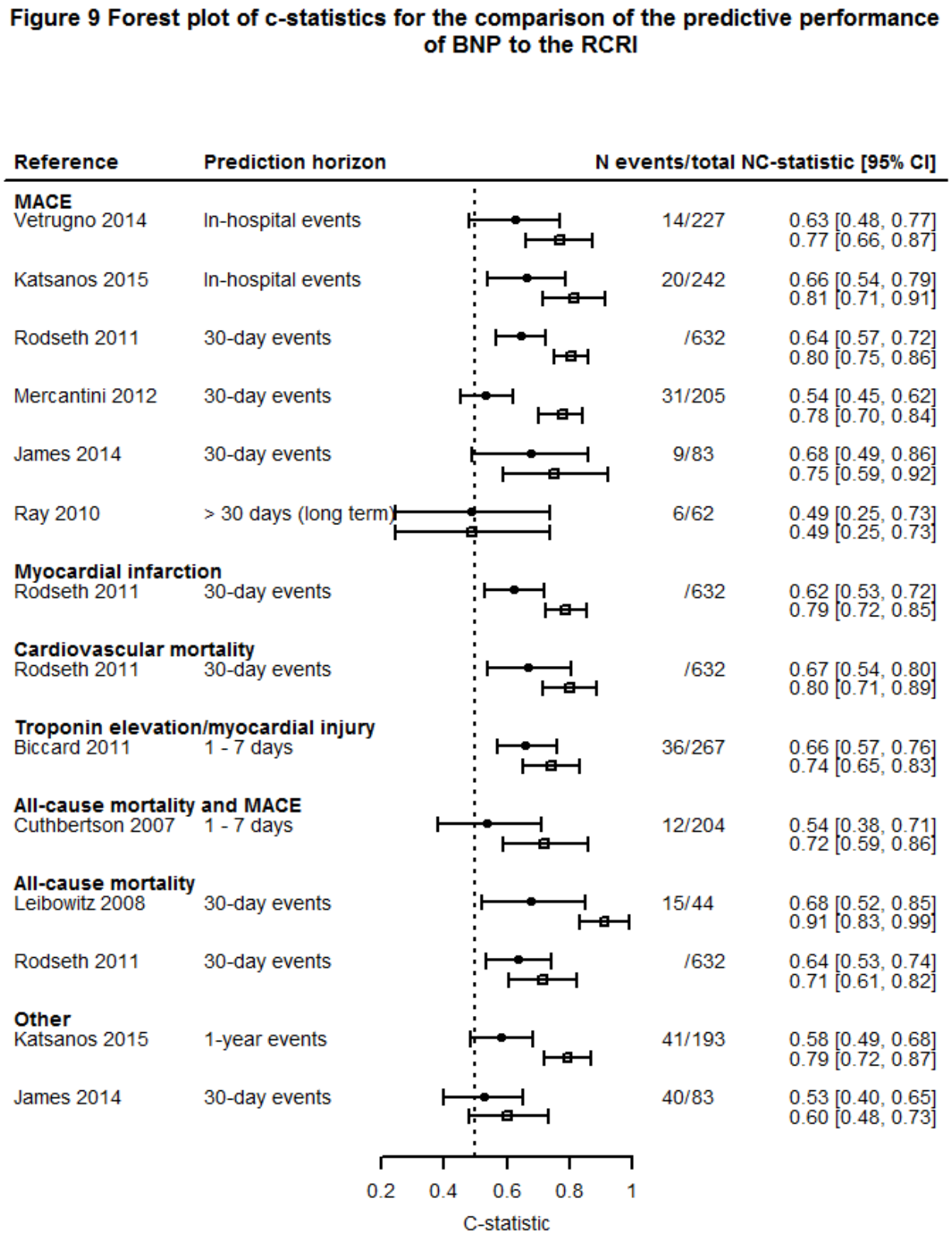
Figure 8. (Continued)



Brain natriuretic peptide (BNP)

As mentioned before, BNP is released by cardiomyocytes due to myocardial stretch and used in clinical practice as a marker for heart failure (Yancy 2013). We included 10 articles that compared the predictive ability of BNP to the RCRI over 14 different analyses. Rodseth et al reported predictions for BNP and RCRI alone using four different outcomes (Rodseth 2011), and Katsanos et al used two different outcomes (i.e. MACE and all-cause mortality; Figure 9; Katsanos 2015). Predictions were made for seven different outcome categories, i.e. MACE (n = 6), myocardial infarction (n = 1), all-cause mortality (n = 2), a combination of the latter two (n = 1), cardiovascular mortality (n = 1), troponin elevation (n = 1) and other (noncardiac) outcomes (n = 2). The number of included patients was low (i.e. less than 50) resulting in wide confidence intervals. The delta c-statistic was 0.15 (0.0 to 0.24) in favour of BNP compared to the predictive discriminative performance of the RCRI to predict MACE (6 studies, n = 2301, unknown number of MACE). For one study, the number of outcomes was not reported (Rodseth 2011). Surgical specialties were orthopaedic, general, vascular and noncardiac surgery. The prediction horizon was in-hospital or 30-day MACE. None of the included studies reported on calibration or reclassification measures.

Figure 9. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents BNP alone.

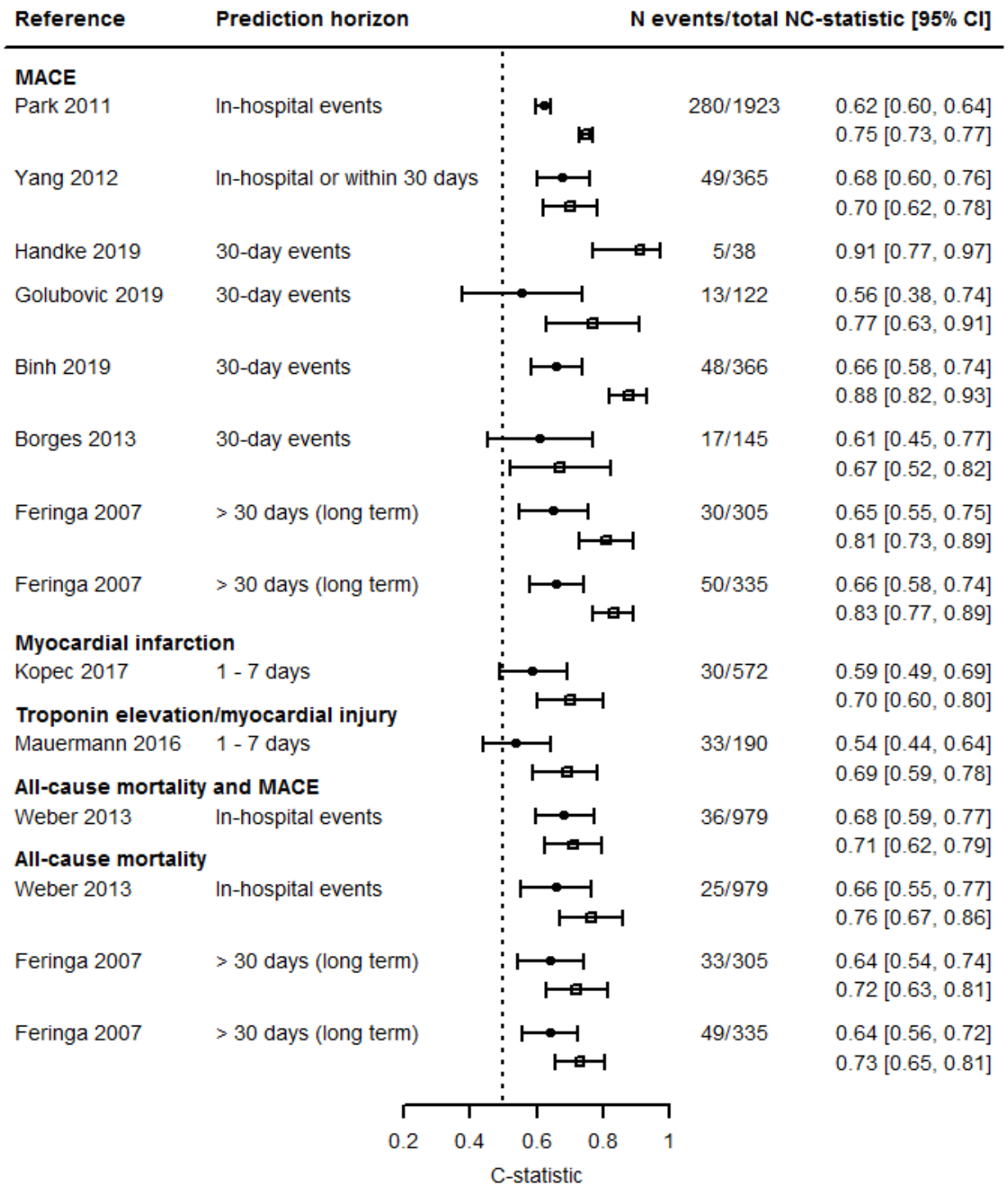


NT-proBNP

NT-proBNP is used as marker for heart failure in clinical practice (Yancy 2013). The predictive performance of NT-proBNP was compared to the RCRI alone in 15 validations over 11 included articles (Figure 10). Feringa et al reported four different analyses on two different outcomes (i.e. all-cause mortality and MACE) in two different patient populations (Feringa 2007). Weber et al reported prediction for two different outcomes (i.e. all-cause mortality and all-cause mortality and MACE) (Weber 2013). MACE was predicted in nine different validations, however the prediction horizon varied from in-hospital to long-term events in either vascular or noncardiac surgical patients. Six articles studied NT-proBNP on a continuous scale, one on a categorical scale (Biccard 2011), and three on a dichotomous scale. For one article, the method of handling NT-proBNP was unclear (Feringa 2007). The confidence intervals were wide and there was large heterogeneity between included studies due to the different study populations, outcome composition and prediction horizons. Using MACE as an outcome, the delta c-statistic was 0.15 (range 0.02 to 0.22) in favour of NT-proBNP (6 studies, n = 3256, 457 MACE) (Binh 2019; Borges 2013; Feringa 2007; Golubovic 2018; Park 2011; Yang 2012). In these studies, the surgical specialty was vascular and noncardiac surgery and the prediction horizons varied between in-hospital, 30-day and 6 months. None of the included studies reported on calibration or reclassification measures.

Figure 10. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents NT-proBNP alone. As Handke 2019 solely reported on the c-statistics for the additive model, no c-statistic for RCRI alone is provided for this study.

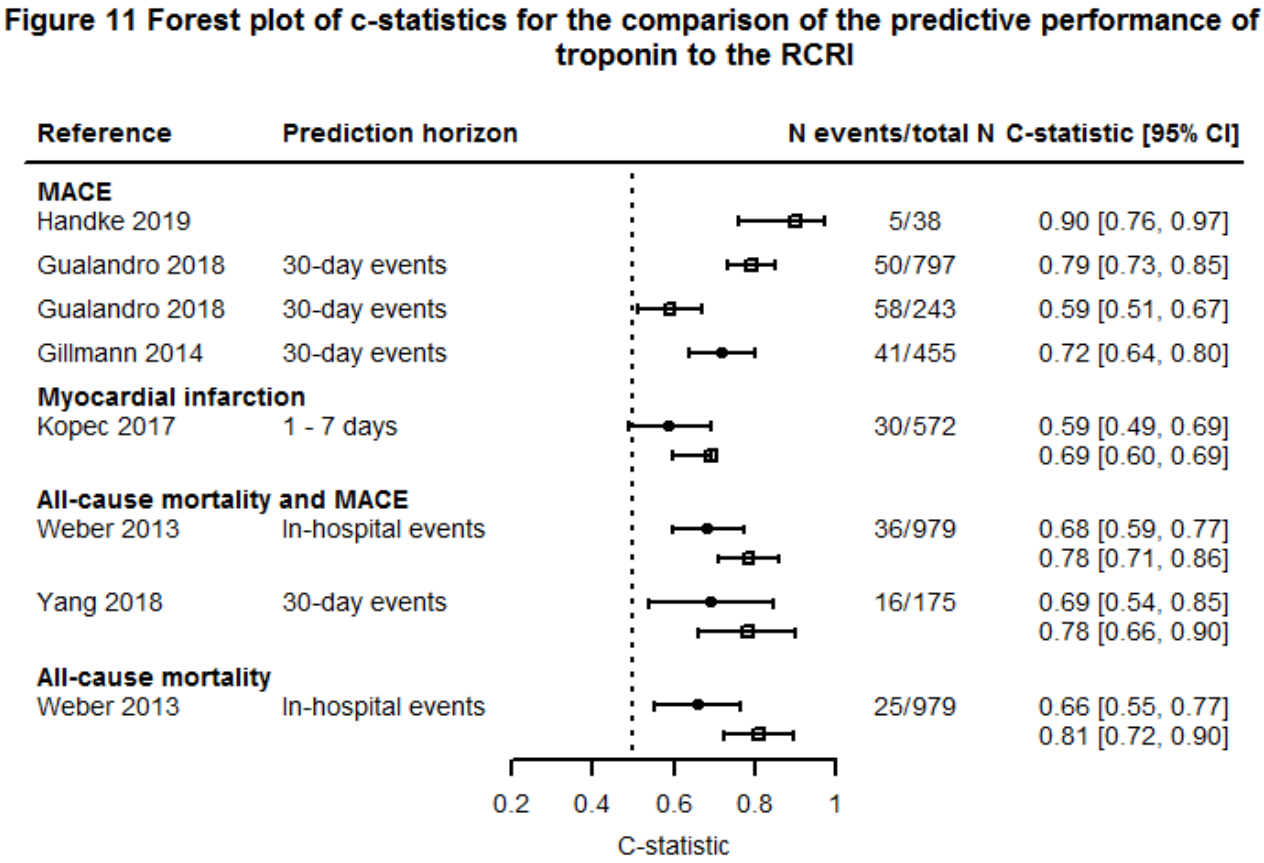
Figure 10 Forest plot of c-statistics for the comparison of the predictive performance of NT-proBNP to the RCRI



Troponin

Troponin is a protein released by cardiomyocytes in case of myocardial ischaemia (Mair 2018; Thygesen 2018). We included six articles reporting on eight validations (Figure 11). Gualandro et al predicted MACE using troponin in two different populations (i.e. vascular and nonvascular patients) (Gualandro 2018). Although the aim in that study was to compare the predictive performance of troponin to the RCRI, only the c-statistic for troponin alone was reported. Included patients underwent either vascular (n = 2) or noncardiac surgery (n = 4). For the prediction of all-cause mortality and MACE (2 studies, n = 1154, 52 events), higher c-statistics were observed for troponin alone compared to the RCRI (median delta c-statistic 0.09, range 0.09 to 0.10) (Weber 2013; Yang 2018). None of the included studies reported on calibration or reclassification measures.

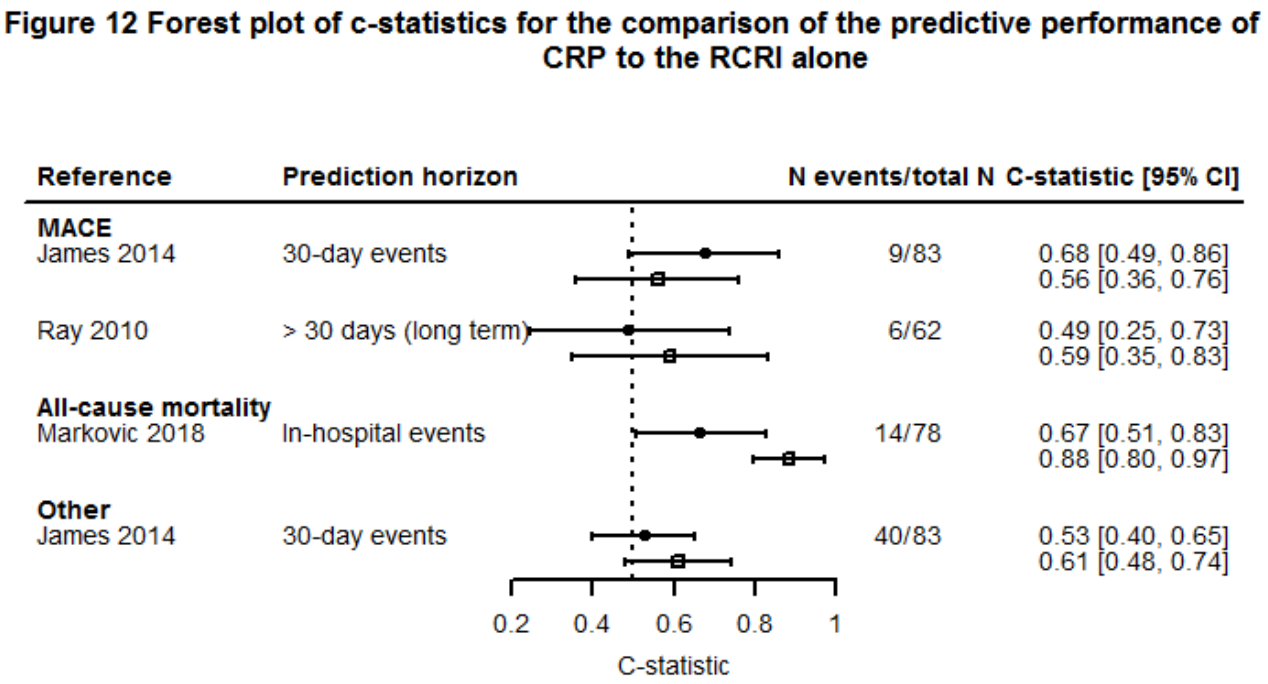
Figure 11. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents troponin alone. As Handke 2019 and Gualandro 2018 solely reported on the c-statistics for the additive model, no c-statistic for RCRI alone is provided for this study. Gillmann 2014 only reported c-statistics for RCRI alone.



C-reactive protein (CRP)

C-reactive protein (CRP) is a sensitive systemic marker of inflammation and tissue damage. The acute-phase response comprises the nonspecific physiological and biochemical responses of tissue damage, infection, inflammation and malignant neoplasia (Pepys 2003). Three articles compared the predictive ability of CRP to the RCRI (Figure 12). James et al made predictions for two different outcomes (i.e. MACE and postoperative complications) (James 2014). All included patients underwent noncardiac surgery except for patients included in the study Ray 2010, who underwent orthopaedic surgery. Two studies compared the predictive discriminative performance of CRP to the RCRI to predict MACE resulting in a delta c-statistic of -0.01 with a range of -0.12 to 0.10 (n = 306, 15 MACE) (James 2014; Ray 2010). None of the included studies reported on calibration or reclassification measures.

Figure 12. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents CRP alone.



Objective 3: Comparison of predictive value of prediction models to the RCRI

Study design and study population

Fifty-one articles compared the predictive ability of the RCRI to another prediction model, reporting on 79 validations of the RCRI with a unique outcome (Table 3). Most validations were based on cohort study data (n = 68, 86%). Retrospective study data were most common (n = 54, 68%). Included patients originated most commonly from Europe (36%) or North America (35%) and most frequently underwent noncardiac (47%) or vascular surgery (32%). The median number of included patients was higher for this objective compared to articles reporting on the added value or the predictive performance of biomarkers to the RCRI (median (IQR)): 941 (251 to 2284), 442 (223 to 1389) and 594 (227 to 52,066), respectively). The most frequently used prediction horizons were during hospital admission (18%) or 30 days (66%) after surgery. The outcome of interest was most often MACE (41%) followed by other outcomes (e.g. stroke, transient ischaemic attack (TIA), systemic embolism (20%), all-cause mortality (17%) and myocardial infarction or cardiac arrest (9%). The number of publications increased over time with most included articles in the 2018 to June 2020 period (Figure 4).

Composition of MACE

For included studies that used MACE (also in combination with all-cause mortality) as an outcome, all validations used a different definition meaning that the composition of MACE varied among the included validations (Table 4). We found 19 different composites for MACE. Similar to the articles reporting on the added value or the predictive performance of biomarkers to the RCRI, the most frequently used composite of MACE was myocardial infarction, i.e. in 26 out of 45 different definitions. The MACE definition also commonly included heart failure (42%), cardiac arrest (40%), cardiac death (24%) or stroke (20%).

Risk of bias and concern regarding applicability

We judged 44 (85%) articles that compared the predictive performance of the RCRI to other prediction models as having overall high risk of bias. Most articles scored as having low risk of bias for participants (n = 44, 85%). For predictors, 27 (52%) articles scored as having unclear risk of bias, for outcome 2 (4%) and for analyses 40 (77%) articles scored as having high risk of bias. Comparable to articles included in the other objectives, most articles had high concern regarding applicability (n = 44, 85%) (Figure 2; Figure 3). We observed no differences in the reasons for judgements of high or unclear of risk of bias and concern regarding applicability among the different objectives. Accordingly, more detailed information is described below under the subheading 'Risk of bias and concern regarding applicability' as part of the first objective.

Performance measures reported

Discrimination measures were reported in 50 (96%) articles mostly using a c-statistic (n = 48, 92%) (Table 5). Calibration was more often reported in articles that compared the predictive performance of other prediction models to the RCRI than articles that studied the added value or the comparison of the predictive ability of biomarker to the RCRI (42%, 20% and 29%, respectively). This was in particular by means of the calibration plot and observed/expected ratio. Reclassification measures were reported in five (10%) articles using a NRI.

Prediction models compared to the RCRI

An overview of prediction models for which the predictive performance was compared to the RCRI is presented in Table 9. Fifty-two articles compared the predictive ability of the RCRI to other prediction models. In these 52 studies, 27 (42%) addressed the development of a new prediction model, 14 (22%) updated the RCRI or another prediction model, and 24 (37%) addressed the validation of an existing prediction model.

For prediction models for which the predictive performance was compared head-to-head to the RCRI in at least three different studies, the study characteristics are described in further detail below. These prediction models were ACS-NSQIP-MICA, ACS-NSQIP-SRS, $CHADS_2$ score, Goldman index, Detsky index, $CHADS_2VASc$, R_2CHADS and Vascular Study Group of New England Cardiac Risk Index.

ACS-NSQIP-MICA

The ACS-NSQIP-MICA was developed in 2011 and provides a risk estimate of 30-day myocardial infarction or cardiac arrest (MICA) in patients undergoing noncardiac surgery. Data from the ACS-NSQIP was used for the development of the model (Gupta 2011). Predictions for MACE were made in four articles describing 11 validations. The delta c-statistic was reported in three studies (n = 1567, 95 MACE) and not different between both models (delta median c-statistic 0, range -0.09 to 0.04) (Cohn 2018; Fronczek 2019; Rutkowski 2019). One study showed poor calibration for both RCRI and ACS-NSQIP-MICA in a calibration plot with an intercept of 0.95 and 2.37 and slope of 0.29 and 0.70 for the RCRI and ACS-NSQIP-MICA, respectively (Fronczek 2019). Cohn 2018 reported on six validations (i.e. all elective noncardiac patients, patients with short (≤ 2 days) and long (> 2 days) hospital stay using both prediction horizons for in-hospital and 30-day events). Rutkowski 2019 presented three validations (i.e. patients undergoing elective craniotomy, deceased patients and surviving patients) and Fronczek 2019 and Glance 2018 reported on the validation in a vascular and noncardiac surgical population, respectively. Six articles (n = 243,896, unknown MICAs) predicted 30-day MICA in nine analyses, which resulted in higher predictive performance of the ACS-NSQIP-MICA compared to the RCRI alone (delta median c-statistic 0.11, range -0.05 to 0.39). In one study, the number of events was not reported (Gupta 2011). Calibration was poor for both scores, however calibration was better for the RCRI compared to the ACS-NSQIP-MICA (2 studies, n = 181,920, 1889 MICAs) (Alrezk 2017; Glance 2018). The Hosmer Lemeshow for the RCRI ranged from P = 0.018 to P < 0.001 and was P < 0.001 for the ACS-NSQIP-MICA. Calibration improved after recalibration of the NSQIP-MICA (Asuzu 2018; Glance 2018). Asuzu 2018 reported three validations among patients undergoing open procedures, laparoscopic procedures or all included procedures and Alrezk 2017 studied geriatric and non-geriatric patients. None of the included studies reported on reclassification measures. Information regarding the c-statistics is presented in Figure 13.

Figure 13. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents the ASC-NSQIP surgical risk score. As Cohn 2018 solely reported on the c-statistics for the RCRI, no c-statistic for NSQIP MICA is provided for this study.

Figure 13 Forest plot of c-statistics for the comparison of the predictive performance of ACS-NSQIP-MICA to the RCRI

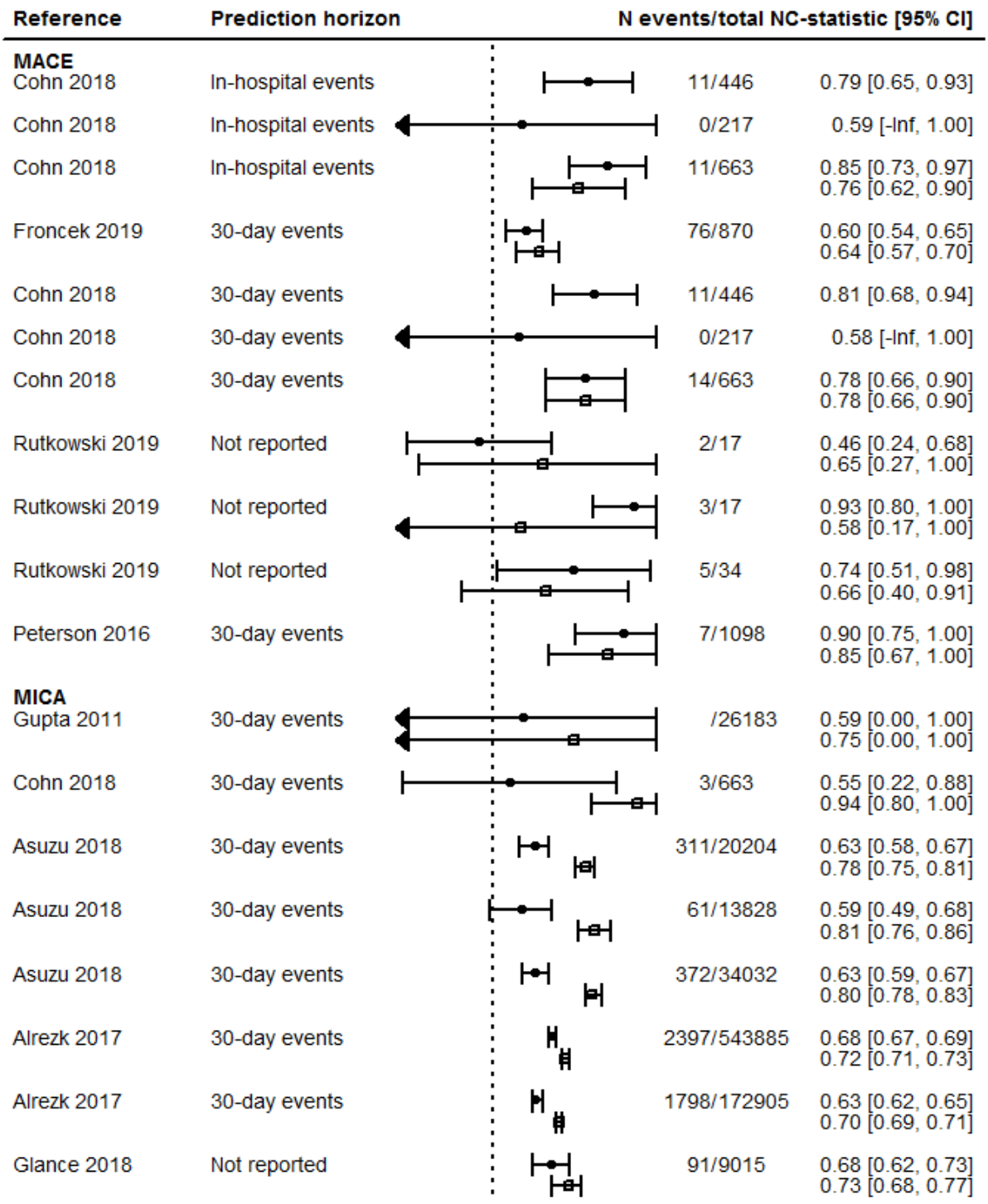
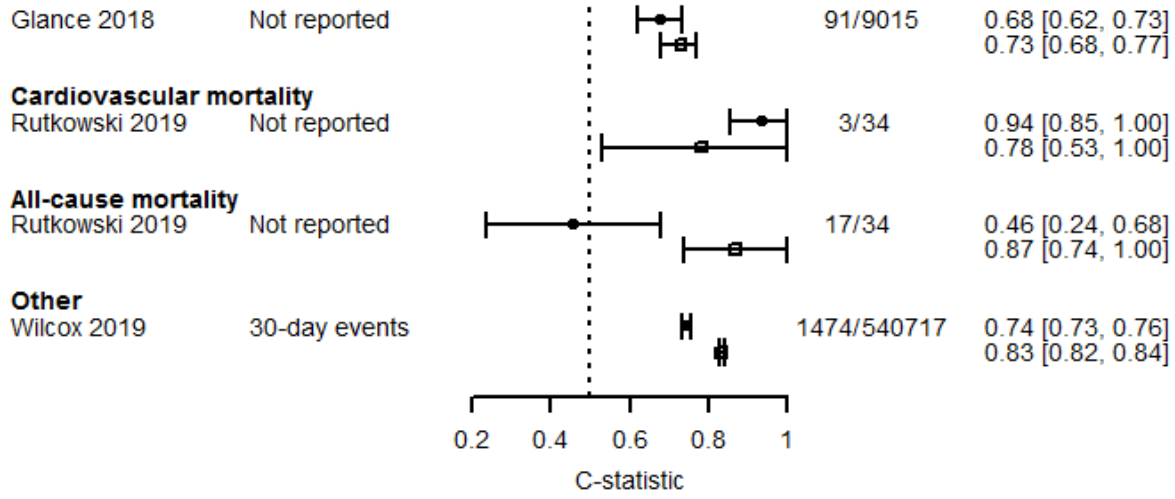


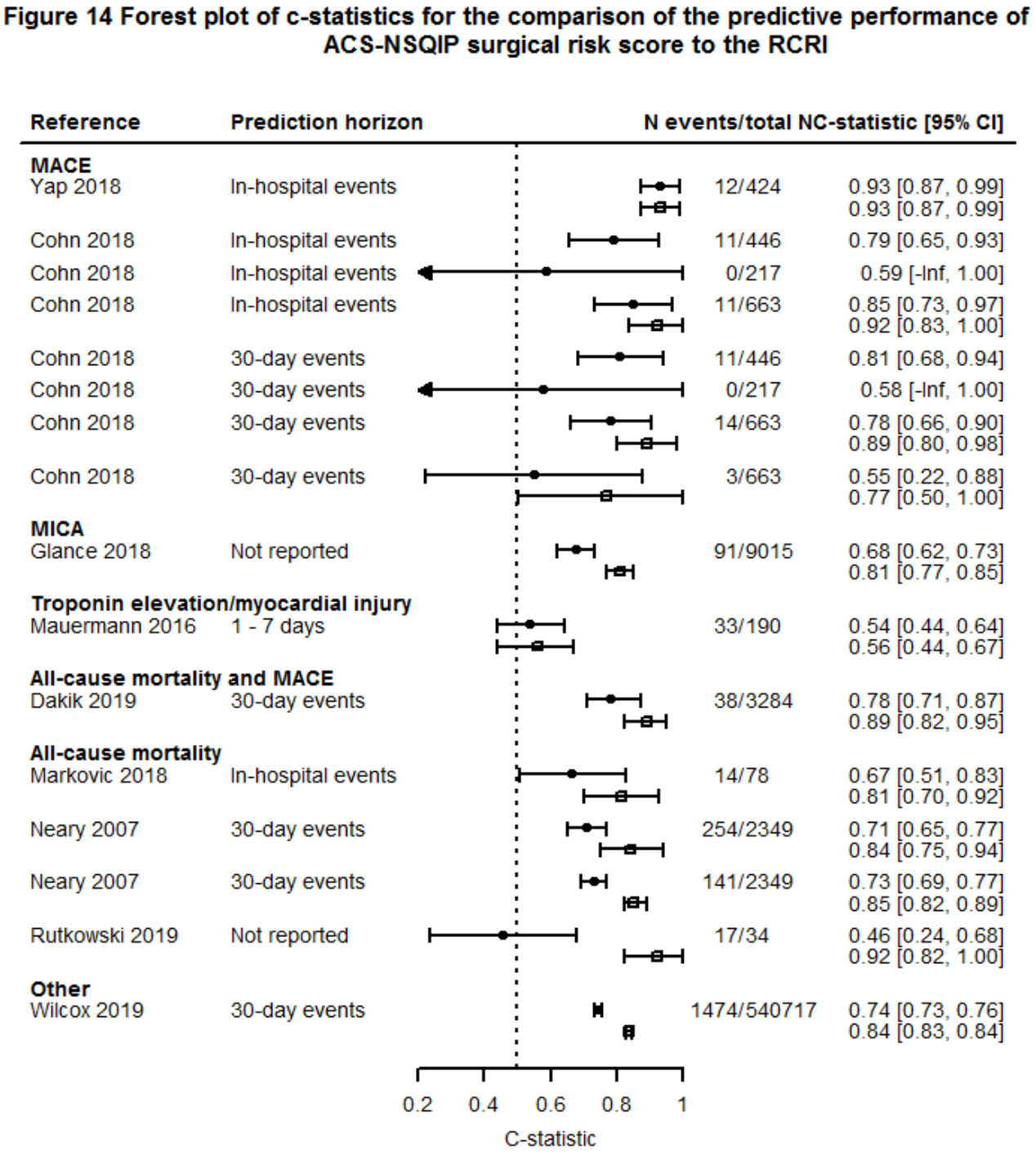
Figure 13. (Continued)



ACS-NSQIP surgical risk score (ACS-NSQIP-SRS)

The American College of Surgeons National Surgical Quality Improvement Program surgical risk score (ACS-NSQIP-SRS) is a decision-support tool based on multi-institutional clinical data, which can be used to estimate the risks of multiple outcomes (including myocardial infarction) for most operations (Bilimoria 2013). We included 10 articles reporting 18 different validations (Figure 14). Two studies compared the discriminative performance of the RCRI to the ACS-NSQIP-SRS for predicting MACE, resulting in a median delta c-statistic of 0.06 with a range of 0.00 to 0.11 in favour of the ACS-NSQIP-SRS (n = 1087, 26 MACE) (Cohn 2018; Yap 2018). To predict MICA (2 studies, n = 9678, 94 MICA), the ACS-NSQIP-SRS had a higher c-statistic compared to the RCRI (delta median c-statistic 0.18 with range 0.13 to 0.22) (Cohn 2018; Glance 2018). Calibration was reported in one study and showed poor calibration for the RCRI and acceptable calibration for the ACS-NSQIP-SRS (Hosmer Lemeshow RCRI: P < 0.001; ACS-NSQIP-SRS, P = 0.07). However, data from the NSQIP database was used in this study (Glance 2018). Using all-cause mortality as an outcome (3 studies, n = 2461, 155 deaths), the ACS-NSQIP-SRS had a higher discriminative performance compared to the RCRI (median delta c-statistic 0.14, range 0.11 to 0.15) (Markovic 2018; Neary 2007; Rutkowski 2019). One article predicted the 30-day risk of stroke in a large cohort originating from the NSQIP registry, showing better predictive performance for the ACS-NSQIP-SRS compared to the RCRI (delta c-statistic 0.10; Wilcox 2019). None of the included studies reported on reclassification measures.

Figure 14. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents the NSQIP surgical risk score.

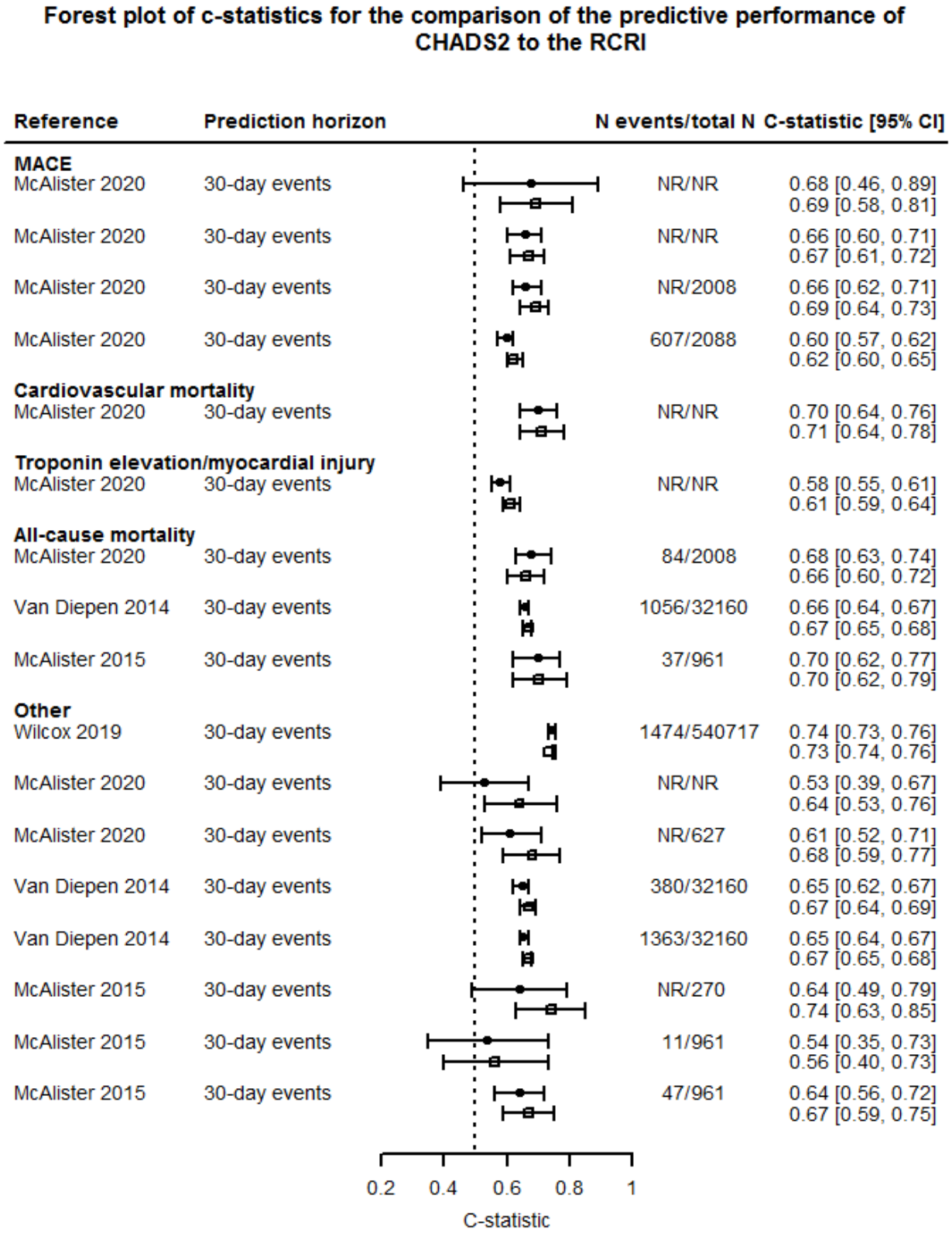


CHADS$_2$

The CHADS$_2$ is a combination of two existing risk scores to predict stroke in patients diagnosed with atrial fibrillation. CHADS$_2$ is an acronym for its risk factors and their scoring. The score is calculated adding one point each for any of the following: recent congestive heart failure, hypertension, age 75 years or older and diabetes mellitus, and two points for a history of stroke or TIA (Gage 2001). Four articles reported on 17 validations of which nine were described by McAlister et al (McAlister 2020). Eight of these validations reported on varying outcomes including MACE, all-cause mortality, vascular death, stroke, myocardial injury, congestive heart failure and nonfatal cardiac arrest in a noncardiac surgical population derived from the VISION study (Devereaux

2017). The other validation by McAlister et al was in patients undergoing only high-risk surgery to predict all-cause mortality and stroke (delta c-statistic 0.07) (McAlister 2015). The predictive performance in terms of the c-statistics are presented in Figure 15. $CHADS_2$ was compared to the RCRI to predict 30-day all-cause mortality in three studies (n = 35,129, 1177 deaths), resulting in a median delta c-statistic of 0.00 (range -0.02 to 0.01) and a median NRI of 0.07 (range 0.01 to 0.12) (McAlister 2015; McAlister 2020; van Diepen 2014). Using stroke as an outcome, the median delta c-statistic was 0.02 (range -0.01 to 0.11; 4 studies, n = unknown, unknown events) with NRI 0.05 (range -0.06 to 0.17; 2 studies, n = 33,121, 391 events) in favour of $CHADS_2$ (McAlister 2015; McAlister 2020; van Diepen 2014; Wilcox 2019). Three studies (n = 33,748, unknown events) compared the $CHADS_2$ to the RCRI to predict all-cause mortality or stroke resulting in a median delta c-statistic of 0.03 (range 0.02 to 0.07) and a median NRI of 0.31 (range 0.14 to 0.35) (McAlister 2015; McAlister 2020; van Diepen 2014). None of the included studies reported on calibration measures.

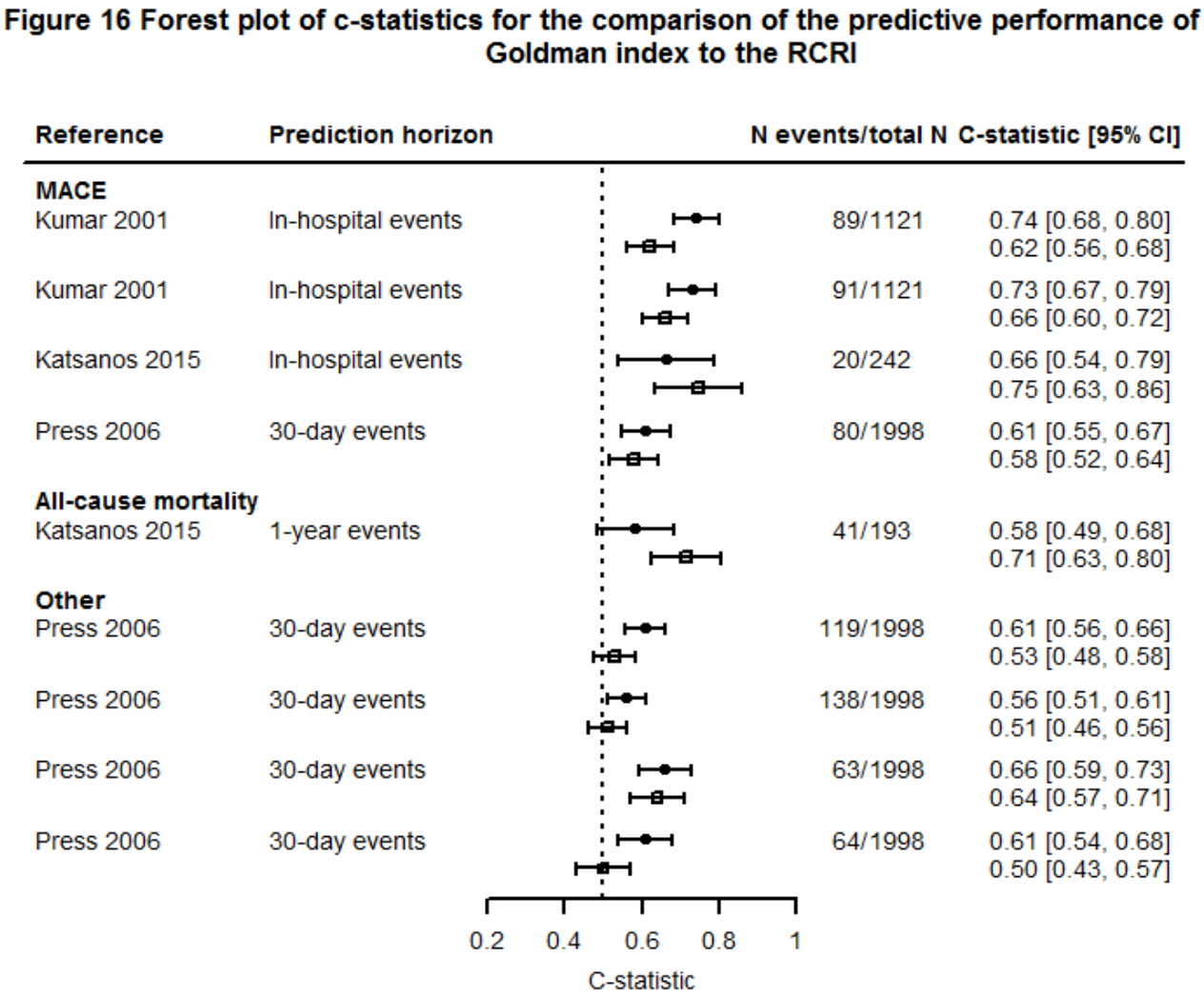
Figure 15. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents the CHADS2.



Goldman index

The Goldman index represents a multivariable approach to estimate cardiac risk in patients undergoing noncardiac procedures (Goldman 1977). The model was developed in 1977 and can be considered as a previous version of the RCRI. The RCRI and Goldman index were validated in three articles reporting on eight validations (Figure 16). Press et al reported on predictions of five different outcomes (i.e. MACE and four noncardiac outcomes) in patients undergoing vascular surgery (Press 2006). No difference in c-statistic was found, which could be explained by the fact that both models were not originally developed to predict noncardiac outcomes. Katsanos et al compared the RCRI to the Goldman index to predict in-hospital MACE and one-year all-cause mortality in patients undergoing orthopaedic surgery (Katsanos 2015), and Pantoja Muñoz et al used both models to predict in-hospital MACE (Pantoja 2014). For the latter, only sensitivity and specificity measures were reported and therefore the data were not sufficient to be presented in a forest plot. Three studies (n = 3361 patients, 191 MACE) compared the discriminative performance of the Goldman index to the RCRI, which resulted in a median delta c-statistic of -0.03 with a range of -0.07 to 0.08 in favour of the RCRI (Katsanos 2015; Kumar 2001; Press 2006). Reclassification or calibration were not reported in any of the included studies.

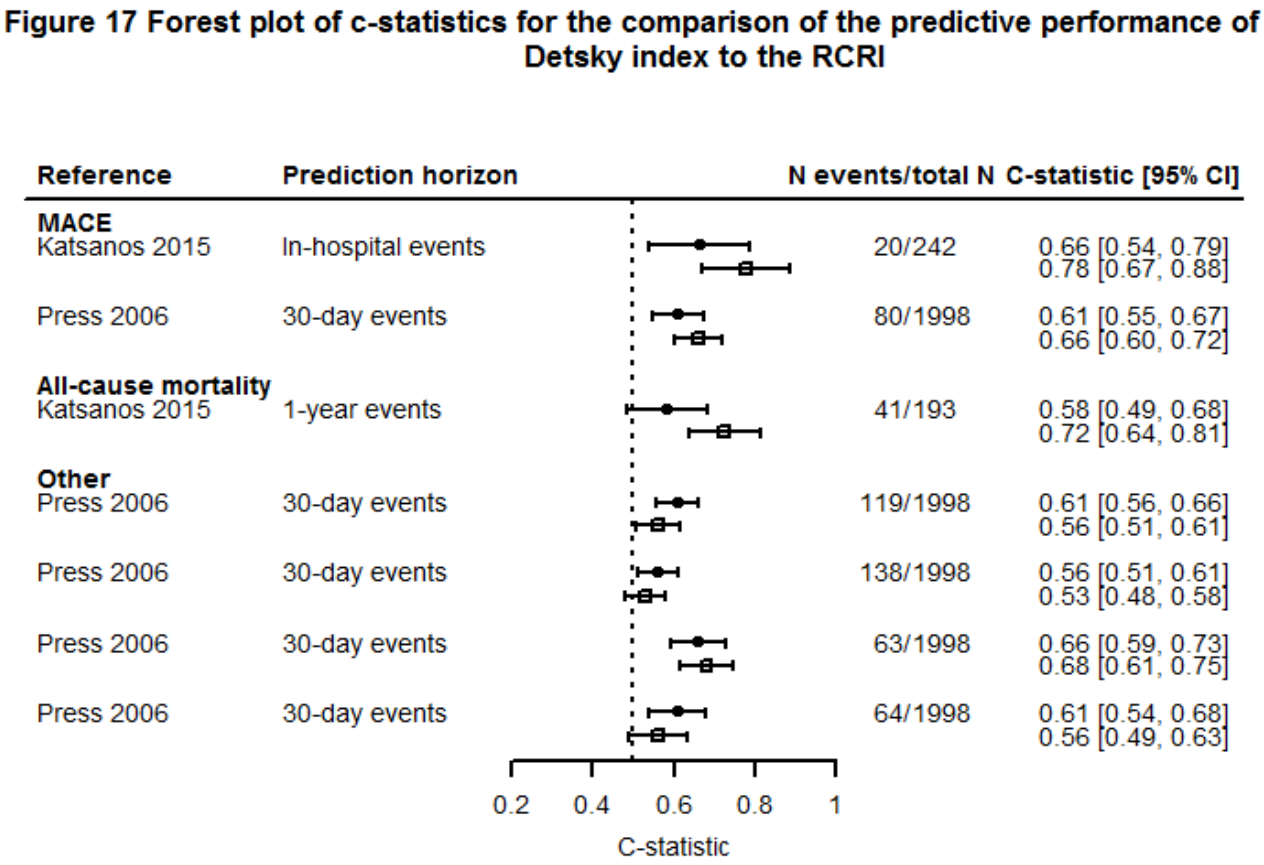
Figure 16. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents the Goldman index.



Detsky index

The Detsky index is a modified version of an index that was previously generated by Goldman in 1977 (Detsky 1986). This model was developed in 1986 and revised to the RCRI by Lee et al in 1999 (Lee 1999). The same articles that were identified for the Goldman index also compared the discriminative performance of the Detsky index to the RCRI, resulting in a median delta c-statistic of 0.05 with a range of -0.07 to 0.11 in favour of the Detsky index (Figure 17) (Katsanos 2015; Kumar 2001; Press 2006). Again, reclassification or calibration were not reported in any of the included studies.

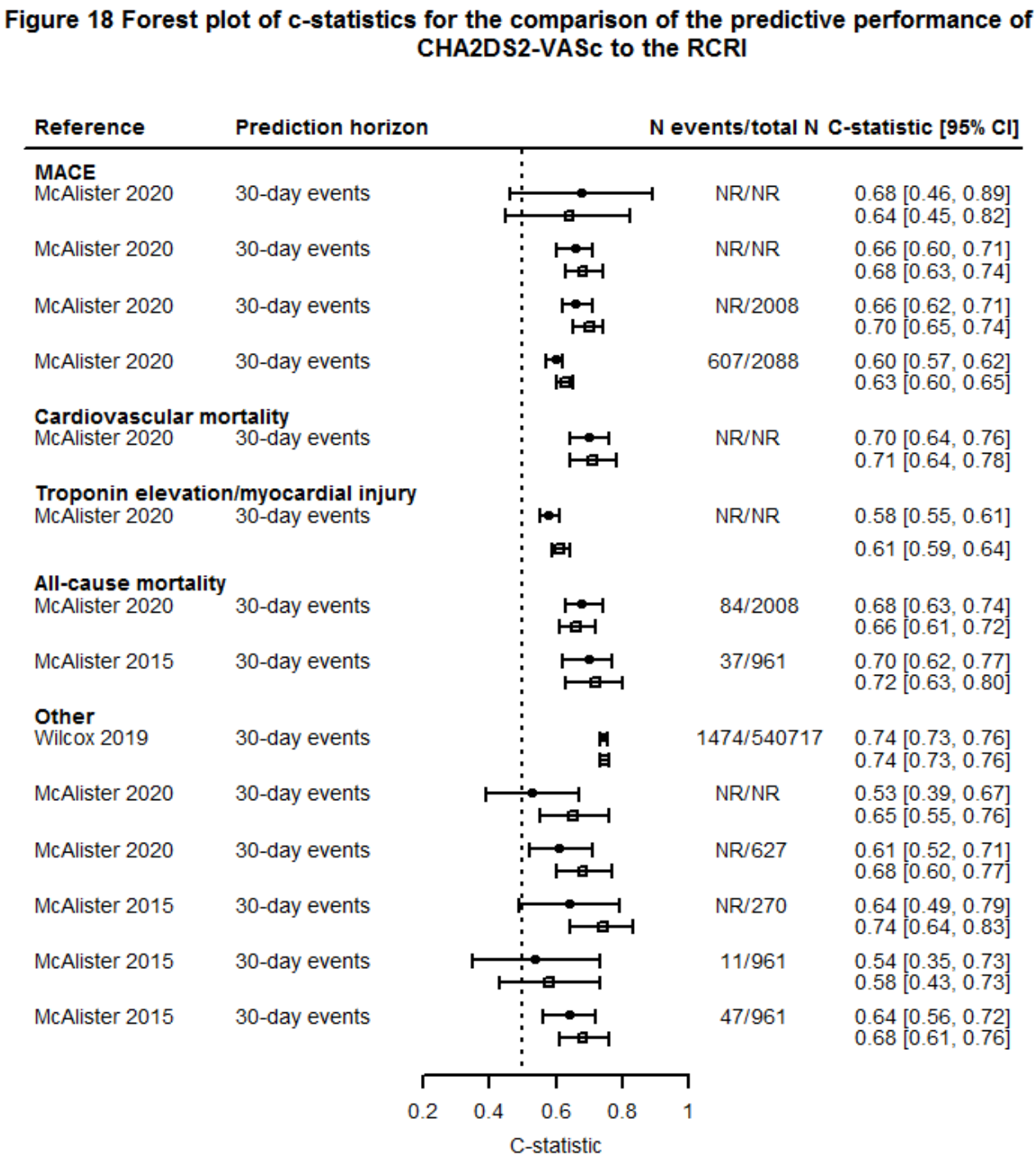
Figure 17. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents the Detsky index.



CHA_2DS_2-VASc

In 2010, the $CHADS_2$ was updated and additional new risk factors were incorporated. For the CHA_2DS_2-VASc, one point is assigned to congestive heart failure/left ventricular dysfunction, hypertension, age between 65 and 74 years, diabetes mellitus, vascular disease (prior myocardial infarction, peripheral artery disease or aortic plaque) and sex category, and two points for age ≥ 75 years and history of stroke, TIA or thromboembolism (Lip 2010). Similar articles were identified that reported on the validation of the $CHADS_2$ (McAlister 2015; McAlister 2020; Wilcox 2019). Comparison of the predictive performance of the CHA_2DS_2-VASc to the RCRI is presented in Figure 18. $CHADS_2$-VASc was compared to the RCRI to predict 30-day all-cause mortality in two studies (n = 2969, 121 deaths), resulting in a median delta c-statistic of 0.00 (range -0.02 to 0.02) and a median NRI of 0.09 (range 0.01 to 0.17) (McAlister 2015; McAlister 2020). Using stroke as an outcome, the median delta c-statistic was 0.04 (range 0.00 to 0.12; 3 studies, n = unknown, unknown events) with a NRI of 0.05 (range -0.06 to 0.17; 1 study, n = 961, 11 events) in favour of $CHADS_2$-VASc (McAlister 2015; McAlister 2020; Wilcox 2019). Two studies (n = 1588, unknown events) compared the $CHADS_2$-VASc to the RCRI to predict all-cause mortality or stroke, resulting in a median delta c-statistic of 0.04 (range 0.01 to 0.07) and a median NRI of 0.30 (range 0.14 to 0.35) (McAlister 2015; McAlister 2020). None of the included studies reported on calibration measures.

Figure 18. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents the CHA_2DS_2-VASc.



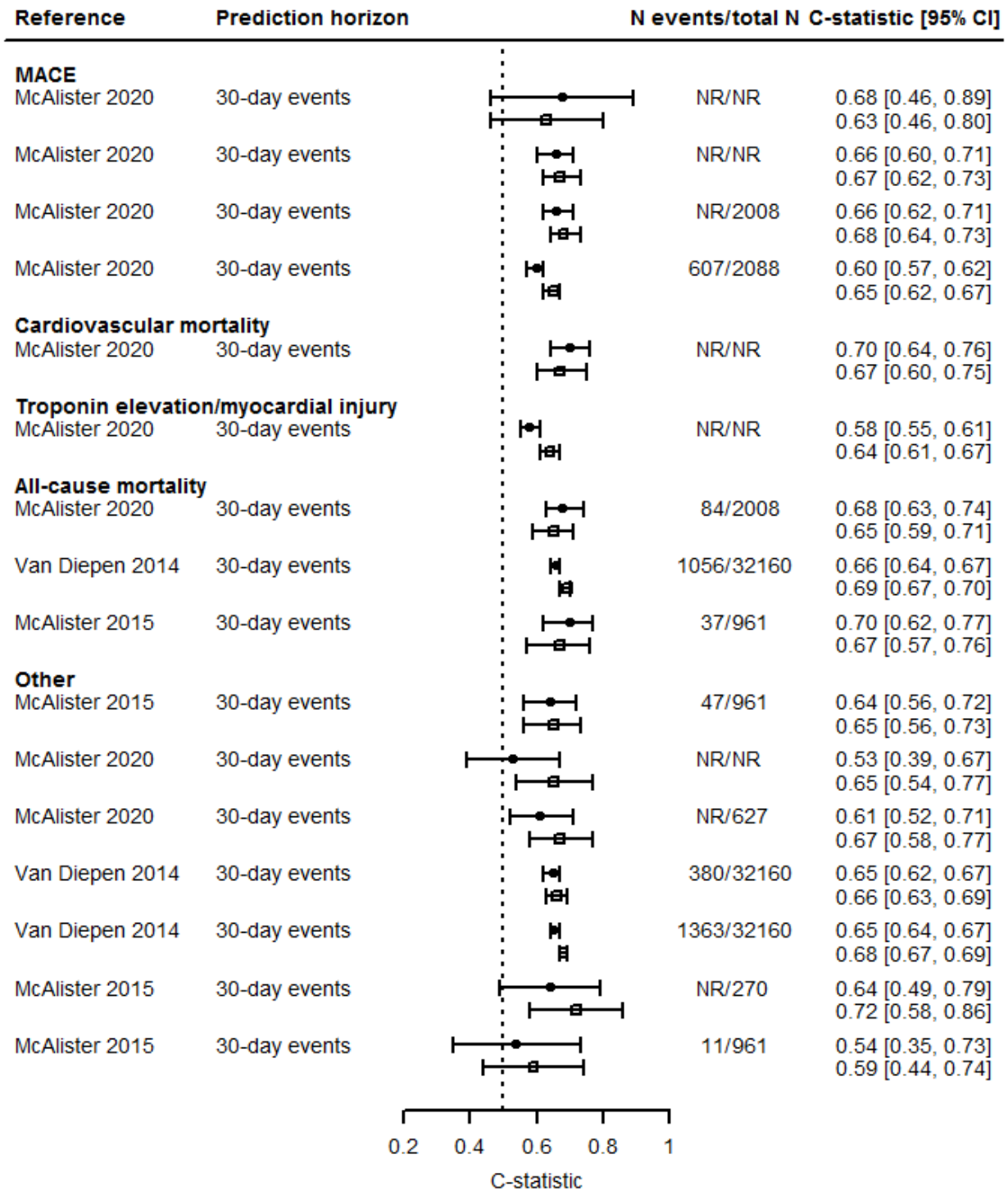
R_2CHADS_2

A new update of the $CHADS_2$ was published in 2013. In this version, two points were added to the $CHADS_2$ score for creatinine clearance < 60 mL/min to designate the R_2CHADS_2. The outcome to be predicted was stroke (both ischaemic and haemorrhagic) and systemic embolism (Piccini 2013). The model was compared to the RCRI by three different articles describing 16 validations (McAlister 2015; McAlister 2020; van Diepen 2014). In three different validations, Van Diepen et al predicted all-cause mortality, the composite of stroke, TIA and systemic embolism, and the combination of all these outcomes in a noncardiac surgical population (van Diepen 2014). Comparison of the predictive

performance of the R_2CHADS_2 to the RCRI is shown in Figure 19. R_2CHADS_2 was compared to the RCRI to predict MACE in one study resulting in a delta c-statistic of 0.02 and a NRI of 0.21 (McAlister 2020). All-cause mortality was predicted in three studies (n = 35,129, 1177 deaths) and resulted in a median delta c-statistic of -0.03 (range -0.03 to 0.03) and a total NRI of 0.03 (range -0.09 to 0.13) in favour of R_2CHADS_2. For the prediction of stroke, the median delta c-statistic was 0.05 with a range of 0.01 to 0.12 (3 studies, n = unknown, unknown events) and the NRI was -0.06 with a range of -0.14 to 0.01 (2 studies, n = 33,121, 391 events) (McAlister 2015; McAlister 2020; van Diepen 2014). Three studies reported on the comparison of R_2CHADS_2 to the RCRI to predict all-cause mortality or stroke (n = 33,748, unknown events), which resulted in a median delta c-statistic of 0.03 with a range of 0.01 to 0.06 and a median NRI of 0.17 with a range of 0.11 to 0.44 (McAlister 2015; McAlister 2020; van Diepen 2014). None of the included studies reported on calibration measures.

Figure 19. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents the R_2CHADS_2.

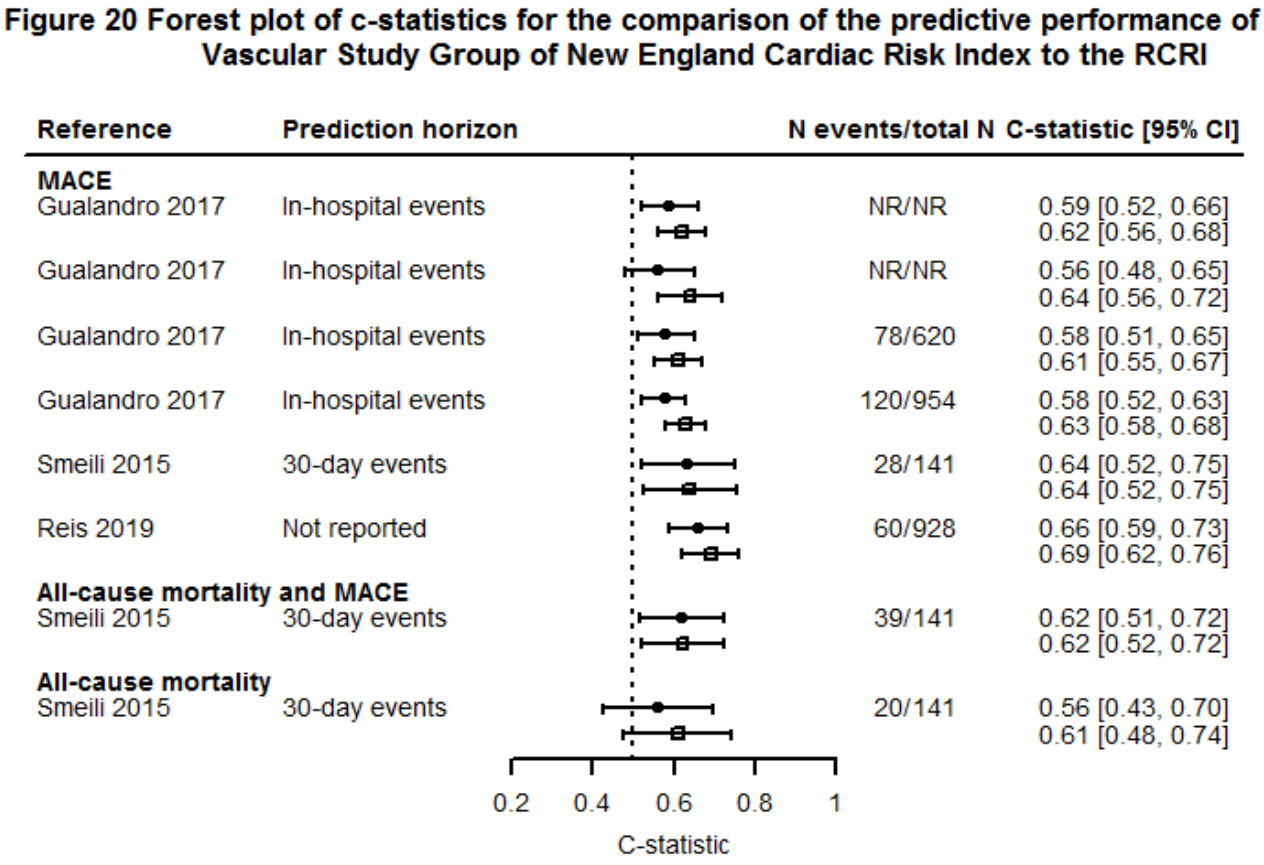
Figure 19 Forest plot of c-statistics for the comparison of the predictive performance of R2CHADS2 to the RCRI



Vascular Study Group of New England Cardiac Risk Index (VSG-CRI)

In response to the fact that the RCRI does not accurately predict cardiac events in vascular surgery patients, a new prediction model was developed to predict a composite cardiac outcome of in-hospital myocardial infarction (MI), clinically significant new arrhythmia or congestive heart failure (CHF). The model was developed in patients undergoing a broad range of vascular surgery, i.e. carotid endarterectomy, open abdominal aortic aneurysm repair, endovascular abdominal aortic aneurysm repair and lower extremity bypass (Bertges 2010). Eight validations were reported by three articles in vascular surgical patients (Avena 2015; Gualandro 2018; Reis 2019). Comparison of the discriminative performance of the VSG-CRI to the RCRI is presented in Figure 20. Three studies (n = 2023, 208 MACE) compared the VSG-CRI to the RCRI resulting in a delta c-statistic of 0.03 with a range of 0.00 to 0.05 (Avena 2015; Gualandro 2018; Reis 2019). The surgical specialty in all studies was vascular surgery. The prediction horizon was in-hospital MACE, but in one study the prediction horizon was not reported. None of the included studies reported on calibration or reclassification measures.

Figure 20. Per article, two c-statistics with confidence intervals are presented. The upper (filled circle) represents the RCRI alone and the lower (open square) represents the Vascular Study Group of New England Cardiac Risk Index.



DISCUSSION

Summary of main results

We screened 3962 studies resulting in a final inclusion of 107 studies. In general, over the three objectives, 'concern regarding applicability' and 'risk of bias' were rated as high in at least one domain in 78% and 90% of the included studies, respectively, the latter particularly in the analysis domain. Furthermore, the composition of predicted outcomes was very heterogeneous, especially for major adverse cardiac events (MACE) for which 80 different definitions were reported. Also the number of included patients and outcome events was relatively low in the majority of the studies. We deemed pooling of the results (delta c-statistic) impossible due to large heterogeneity in various aspects; i.e. in the (composition of the) used outcomes, the scale by which the biomarker was added to the model (i.e. dichotomous, continuous or categorical) and in the patient populations (e.g. vascular and noncardiac surgery).

In total, 51 articles reported on the *added value* of predictors to the Revised Cardiac Risk Index (RCRI) in 62 outcome validations. We identified 69 unique predictors that were added to the RCRI, which were derived from blood (29%), imaging (33%) or other types of predictors such as age, anaemia or six-metre walking test (38%). Addition of N-terminal pro-B type natriuretic peptide (NT-proBNP), troponin or a combination of both improved the RCRI model for the prediction of MACE with a median delta c-statistic

ranging from 0.04 to 0.22, 0.06 to 0.33 and 0.10 to 0.34 for NT-proBNP, troponin and their combination, respectively, as compared to the c-statistic for the RCRI alone. The total net reclassification index (NRI) ranged from 0.09 to 0.22 and 0.26 to 1.22 in favour of troponin and NT-proBNP, respectively, as compared to the classification of the RCRI alone. Data on (improved) calibration of the biomarkers when added to the RCRI was not reported. For the prediction of myocardial infarction, the median delta c-statistic range when NT-proBNP was added to the RCRI was 0.06 to 0.07 and 0.06 to 0.11 for the prediction of all-cause mortality and MACE combined. For BNP and copeptin, the data were not sufficient to provide median results on their added predictive performance, for any of the outcomes.

The predictive performance of biomarkers alone was *compared* to the RCRI in 51 articles reporting on 89 validations. Sixty unique biomarkers were identified that were compared to the RCRI. Predictors were derived from blood (38%), imaging (30%) or other types of characteristics such as the American Society of Anesthesiologists classification (ASA), functional capacity or ankle-to-arm-index (32%). Regarding ASA, predictions were similar to the RCRI for each of the studied outcomes (median delta c-statistics -0.02, 0.02 and 0.05 for MACE, myocardial infarction and all-cause mortality, respectively). In studies different from those identified in objective 1, the median delta c-statistic was 0.15 and 0.12 in favour of BNP and NT-proBNP alone, respectively, when compared to the RCRI, for the prediction of MACE. For C-reactive protein (CRP), the predictive performance was similar to the RCRI in predicting MACE. For other biomarkers and outcomes, no summary results could be given due to insufficient data. Only one study reported on calibration and none on reclassification measures.

For the third objective, in 52 articles we found 65 different *prediction models that were compared* to the RCRI. In these 52 studies, 27 (42%) addressed the development of a new prediction model, 14 (22%) updated the RCRI or another prediction model and 24 (37%) reported on the validation of an existing prediction model. None of the prediction models that were compared to the RCRI showed better predictive performance for the prediction of MACE compared to the RCRI. For the prediction of myocardial infarction and cardiac arrest, the ACS-NSQIP-MICA had a higher median delta c-statistic of 0.11 (range -0.05 to 0.39) compared to the RCRI. Using all-cause mortality as an outcome, the predictive performance of the ACS-NSQIP surgical risk score was higher compared to the RCRI (median delta c-statistic 0.15, range 0.12 to 0.47). The predictive performance was not better for the $CHADS_2$, CHA_2DS_2-VASc, R_2CHADS_2, Goldman index, Detsky index or Vascular Study Group of New England Cardiac Risk Index compared to the RCRI for any of the validated outcomes. Only one study reported on calibration measures; reclassification measures were reported in three studies.

Certainty of the evidence

There is currently no official GRADE guidance available for grading summarised results of prognostic model studies. Therefore, we did not perform rating of the certainty of evidence (Kreuzberger 2020).

Limitations of the included studies

We rated risk of bias as 'high' in at least one domain in 96 (90%) of all included studies. The reasons for judgements of high risk of bias were mainly the inappropriate in- or exclusion of participants, low numbers of events, not reporting of relevant performance measures at all or without uncertainty measures. TRIPOD recommends reporting of both discrimination and calibration measures in all prediction model papers (Collins 2015; Moons 2015). Discrimination was reported in most studies, however calibration measures were not. Evaluation of calibration is highly important since the model predictions are actually used to inform patients and physicians to make decisions (Van Calster 2019). In addition, none of the included articles used proper methods for handling of missing data. Only four studies (4%) reported on handling of missing data by assumption of normal values (n = 2, e.g. in case of missing postoperative creatinine measurement), last measurement carried forward or mean imputation. We judged concerns regarding applicability to be 'high' in 84 (79%) of all included studies, mainly due to strict in- and exclusion criteria and the use of other outcomes than the outcome that was used in the development study, i.e. MACE. Many included articles, for example, reported predictions for other cardiac complications, noncardiac complications and all-cause mortality.

Finally, meta-analyses of the predictive performance measures (including c-statistics) were not possible due to extreme clinical and methodological heterogeneity across studies. This heterogeneity included a wide variety in biomarkers and prediction models added or compared to the RCRI, outcome definitions and prediction horizons, and there was no uniformity in the scales by which the predictor was added/compared to the RCRI (i.e. continuous, categorical or dichotomous).

Limitations of the review

Several limitations should be addressed. Firstly, we excluded articles for which the full text was not available (4%). This may have led to an underestimation of the number of predictors that are added or compared to the RCRI. Secondly, we encountered missing data for many of the included studies especially in the predictive performance measures. However, we did not contact study authors for additional information (e.g. on performance measures) as we anticipated that this would not result in different conclusions, given the expectation that this information would not be available to them in any case. The main reason why pooling of the results was not possible was less the lack of data than the extreme heterogeneity and high risk of bias in the majority of the included studies. Thirdly, we did not extract clinical utility measures such as decision curves or net benefit since almost none of the papers reported these measures.

Currently, there is no established standard for assessing the likelihood of publication bias in research on prognostic models. In addition, publication bias could also not be assessed due to the low number of included papers reporting on a particular biomarker. However, many studies in this research field have measured biomarkers and collected the items of the RCRI and/or other prediction models, but have not published results on their predictive performance.

Applicability of findings to clinical practice and policy

In more than half of the included articles, the outcome of interest was MACE. The definition of MACE, however, varied greatly: we found 80 different definitions. One reason for this heterogeneity could be the fact that many studies included, for example, atrial

fibrillation or myocardial ischaemia (or myocardial injury after noncardiac surgery (MINS)) in the MACE definition, whereas others did not. As the incidence of these outcomes is much higher than the occurrence of a myocardial infarction (MI) or (fatal) cardiac arrest, comparison of these studies is complicated, which could explain the reported model calibration inconsistencies of the RCRI or extended RCRI across studies. In addition, some studies added the occurrence of stroke and/or pulmonary embolism as components of MACE. Hence, the aetiology of such complications is, in essence, different from the aetiology of cardiac complications such as myocardial infarction. Recently, guidance on standardised definitions of cardiovascular endpoints has come out as part of the 'Standardized Endpoint for Perioperative Medicine' (StEP) initiative (Beattie 2020; Myles 2016). In this guidance paper, MACE was described as a composite outcome including cardiac death, myocardial infarction, nonfatal cardiac arrest and coronary revascularisation within 30 days of the index surgery. Cardiac death is defined as death with a vascular cause and included those deaths after a myocardial infarction, nonfatal cardiac arrest and cardiac revascularisation procedure. Myocardial infarction is defined in accordance with the fourth universal definition of myocardial infarction. Cardiac arrest is defined as successful resuscitation from either documented or presumed ventricular fibrillation, sustained ventricular tachycardia, asystole or pulseless electrical activity requiring cardiopulmonary resuscitation, pharmacological therapy or cardiac defibrillation. Finally, coronary revascularisation is defined as percutaneous coronary intervention or coronary artery bypass graft surgery within 30 days of the index surgery (Beattie 2020). Unfortunately, none of the included studies used MACE as defined in the StEP guidance paper. Adherence to guidelines, such as StEP but also such as reporting guidelines for prediction model papers (TRIPOD), is recommended when designing new studies to enhance comparability between studies, enhance meta-analysis of multiple studies and thus improve the generalisability of study and review results to a broader patient population (Beattie 2020; Collins 2015; Moons 2015). In addition, studies should consider calibration and clinical utility measures to assess its impact on clinical practice (Collins 2015; Moons 2015).

Furthermore, the original RCRI development paper based the diagnosis of MI on serial CK/CK-MB measurements, while (high-sensitivity) troponin measurements are currently used (Lee 1999). As troponin assays are more sensitive, more MIs are detected resulting in a higher incidence of MI compared to the data used to develop the RCRI model. This could lead to substantial miscalibration in the more recent validation studies, resulting in underestimation of risk by the RCRI. Therefore, the Canadian Cardiovascular Society updated the RCRI risk estimates based on external validation studies that were published in the past 15 years, systematically monitored perioperative troponin measurements and reported event rates for the various RCRI scores (Duceppe 2017).

Besides the variety in predicted outcomes, we identified a large amount of different biomarkers and other prediction models added or compared to the RCRI. Most biomarkers and prediction models that were added or compared to the RCRI were only studied once, meaning that selecting promising predictors from the existing literature is currently not possible. The focus of the current studies in the literature was mainly on the (incremental) predictive accuracy of cardiac biomarkers such as NT-proBNP or high-sensitivity troponins, however the superiority of other biomarker(s) cannot be ruled out as the available evidence is currently not sufficient. Extra complexity in the comparison of different studies arises when biomarkers are studied on a different scale (i.e. continuous, categorical or dichotomous) or using different thresholds. Imaging biomarkers might in turn be exposed to the subjective interpretation of the assessor.

In addition, we found 51 articles that compared the predictive performance of a single biomarker to the RCRI. However, treatment decisions are normally based on information from multiple predictors and, therefore, making predictions based on a single biomarker is less relevant (Moons 1999; Moons 2009; Riley 2019). Subsequently, demonstrating incremental value in model performance by *adding* a certain biomarker to the RCRI is more challenging than *comparing* the RCRI model to a single biomarker. Due to the substantial miscalibration and the explained variance of the RCRI model itself, improvement of predictive performance by the addition of a biomarker may be harder than assessing the predictive performance of a single biomarker, which may be optimally modelled in the dataset under investigation (Moons 2015; Riley 2019; Steyerberg 2009).

The RCRI has been externally validated in numerous and therefore very heterogeneous patient populations, ranging from a broad variety of noncardiac surgical procedures to specific surgical procedures such as posterior lumbar decompressions or kidney transplants. Furthermore, populations with specific characteristics (e.g. patients with a history of ischaemic heart disease or known atrial fibrillation) have been studied. The RCRI has only moderate predictive performance in vascular surgery patients, probably due to the presence of its items in high-risk patients (Ford 2010). This implies that the predictive performance of prediction models could vary in different populations, which should be taken into account when implementing such models in clinical practice.

Agreements and disagreements with other studies or reviews

To our knowledge, this is the first systematic review that provides a comprehensive overview of all biomarkers and prediction models that have been added or compared to the RCRI to improve risk prediction in patients undergoing noncardiac surgery. However, there is one individual patient data meta-analysis including data from six studies comparing the predictive performance of BNP to the RCRI in vascular surgical patients (Rodseth 2011). They found higher c-statistics for BNP compared to the RCRI (0.62, 95% CI 0.55 to 0.69 and 0.81, 95% CI 0.75 to 0.86). However, the authors attribute this difference to the fact that the RCRI was derived from a population of predominantly noncardiac and nonvascular surgery patients. Therefore, they recommended that further research should be undertaken to determine whether the RCRI improves pre-operative risk stratification in patients primarily risk stratified using BNP (Rodseth 2011). In addition, the findings from this review are in line with international guidelines on cardiac risk assessment in patients undergoing noncardiac surgery, that recommend considering (NT-pro)BNP and troponin for further preoperative risk stratification in high-risk patients (Duceppe 2017; Kristensen 2014).

AUTHORS' CONCLUSIONS

Implications for practice

A large number of studies have externally validated the Revised Cardiac Risk Index (RCRI) with the aim of improving its predictive performance by adding biomarkers or by comparing its predictive accuracy to biomarkers or other prediction models. The studies included in this review suggest that the predictive performance of the RCRI in predicting major adverse cardiac events (MACE) is improved when N-terminal pro-B type natriuretic peptide (NT-proBNP), troponin, or the combination of both, are added. Furthermore, other studies included in this review have indicated that BNP and NT-proBNP, when used in isolation, may even have a higher discriminative performance than the RCRI. There was insufficient evidence of a difference between the predictive accuracy of the RCRI and other prediction models in predicting MACE. However, the ACS-NSQIP-MICA and ACS-NSQIP surgical risk scores outperformed the RCRI in predicting myocardial infarction and cardiac arrest, and all-cause mortality, respectively. Nevertheless, the results cannot be interpreted as conclusive due to high risk of bias in a majority of the studies. We also deemed pooling to be impossible due to heterogeneity in outcomes, prediction horizons, biomarkers and studied populations. Furthermore, we scored risk of bias and concern regarding applicability as high in the majority of studies and reporting of predictive performance measures was poor, particularly on calibration measures.

Implications for research

Future research on the added prognostic value of biomarkers to existing prediction models for the preoperative prediction of in-hospital adverse outcomes of patients undergoing noncardiac surgery should focus on biomarkers that demonstrated good predictive accuracy (i.e. diagnosis of myocardial infarction or heart failure) to assess their predictive value in the perioperative setting. In addition, research using omics data could be useful to identify new biomarkers for this purpose. Such new biomarkers should be compared to novel biomarkers with so far insufficient evidence compared to established ones such as NT-proBNP or troponins. Adherence to recent guidance for prediction studies is recommended, such as TRIPOD and PROBAST, and the use of standardised outcome definitions (StEP) is highly recommended to improve generalisability and comparability between studies. This would facilitate individual patient data meta-analyses, as well as comparison of different prediction models to the RCRI. Besides the identification of patients at risk of adverse outcomes by the use of the RCRI or other prediction models, future studies should also focus on prophylactic measures to optimise high-risk patients in order to prevent such postoperative adverse outcomes.

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CHARACTERISTICS OF STUDIES

Characteristics of included studies *[ordered by study ID]*

Adar 2019

Study characteristics	
General information	Objective • Biomarkers compared Journal • *Heart & Lung* Country • Turkey Study design • Prospective cohort study
Participants	Number of included patients • 714 Surgical specialty

Adar 2019 *(Continued)*

- Orthopaedic surgery

Age

- Mean 70.4 years

Male sex

- 35%

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- 12.9%

History of congestive heart failure

- Not reported

History of cerebrovascular accidents

- 5.9%

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: Aortic arch calcification • Objective: biomarker compared • Category: imaging • Scale: categorical • Threshold: Grade > 1, grade > 2 • Assay/device: Curix HT 1.000G Plus, Agfa, Mortsel, Belgium
Outcome	Outcome category • MACE Full outcome definition

Adar 2019 *(Continued)*

	• Acute coronary syndrome (STEMI, non-STEMI, UAP), decompensated heart failure, new onset atrial fibrillation, stroke and cardiac death Prediction horizon • 30-day events
Analysis	Number of outcomes • 33 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: Only orthopaedic patients were included and patients with malignancy and previous cardiac surgery were excluded. In addition, patients from 18 years onwards were eligible. Domain 2: Predictors • Unclear Justification: No information on the definition of the individual RCRI predictor definitions. Domain 3: Outcome • High Justification: Although outcome is MACE, it also includes stroke, atrial fibrillation and unstable angina pectoris. Overall judgement • High Justification: Only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing orthopaedic surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.

Adar 2019 *(Continued)*

Domain 2: Predictors	Unclear	No information on the definition of the individual RCRI predictor definitions.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes and no information on handling missing data.
Overall judgement	No	Low number of outcomes and no information on handling missing data and no information on the definition of the individual RCRI predictor definitions. However, patient selection was appropriate and outcome definitions were clearly defined and assessed.

Ahn 2013

Study characteristics	
General information	Objective • Added value biomarkers • Biomarkers compared Journal • *Journal of American College of Cardiology* Country • Republic of Korea Study design • Retrospective cohort study
Participants	Number of included patients • 239 Surgical specialty • Noncardiac surgery Age • Median 69 years (IQR 62 to 75) Male sex • 52.3% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 13% History of ischaemic heart disease • Not reported

Ahn 2013 *(Continued)*

History of congestive heart failure

- 3.3%

History of cerebrovascular accidents

- 10.9%

Elevated creatinine

- Not reported

0 RCRI factors

- 43.9%

1 RCRI factor

- 41%

2 RCRI factors

- 11.7%

3 or more RCRI factors

- 3.3%

Predictors	Predictor 1: Coronary artery calcium scores (CACS) • Objective: added value, biomarker compared • Category: imaging • Scale: dichotomous • Threshold: 113 CACS • Assay/device: Brilliance 64, Philips Healthcare, Best, the Netherlands Predictor 2: Multi-vessel disease • Objective: added value • Category: imaging • Scale: categorical • Threshold: significant stenosis (50% luminal diameter narrowing) in 1, 2 or 3 vessels • Assay/device: Brilliance 64, Philips Healthcare, Best, the Netherlands Predictor 3: Coronary artery calcium scores (CACS) + multi-vessel disease • Objective: added value • Category: imaging • Scale: categorical • Threshold: not applicable • Assay/device: Brilliance 64, Philips Healthcare, Best, the Netherlands
Outcome	Outcome category • MACE Full outcome definition

Ahn 2013 *(Continued)*

	• Cardiac death, acute coronary syndrome (nonfatal myocardial infarction and unstable angina), pulmonary oedema, ventricular fibrillation, ventricular tachycardia with haemodynamic compromise, and complete heart block Prediction horizon • 30-day events
Analysis	Number of outcomes • 19 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Domain 2: Predictors • Low Domain 3: Outcome • Low Overall judgement: • Low Patient selection was appropriate; predictor and outcome definitions were clearly defined and comparable to the definitions used in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Patients with severe cardiac morbidities such as previous myocardial infarction, severe heart failure or severe valvular disease were excluded from the analysis.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.

Ahn 2013 *(Continued)*

Domain 4: Analysis	No	Small number of outcomes. No information on how missing data were handled.
Overall judgement	No	Patients with severe cardiac morbidities were excluded from the analysis. In addition, there was a small number of outcomes and no information on handling of missing data. However, predictor and outcome definitions were clearly reported and assessed.

Ahn 2020

Study characteristics	
General information	Objective • Added biomarkers • Biomarkers compared Journal • *Journal of Cardiovascular Computed Tomography* Country • Republic of Korea Study design • Prospective cohort study
Participants	Number of included patients • 206 Surgical specialty • Noncardiac surgery Age • Mean 69.2 years (SD 8.7) Male sex • 52.9% High-risk surgery • 14.1% Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 35% History of congestive heart failure • 12.6% History of cerebrovascular accidents

Ahn 2020 *(Continued)*

- 28.2%

Elevated creatinine

- 16%

0 RCRI factors

- 51.9%

1 RCRI factor

- 35.4%

2 RCRI factors

- 11.2%

3 or more RCRI factors

- 1.5%

Predictors	Predictor 1: Dobutamine stress test • Objective: added biomarker, biomarker compared • Category: imaging • Scale: dichotomous • Threshold: abnormal if there is ischaemia during stress or fixed wall motion abnormalities • Assay/device: Vivid E9 apparatus (GE Healthcare, Waukesha, WI) Predictor 2: Coronary artery stenosis • Objective: added biomarker, biomarker compared • Category: imaging • Scale: dichotomous • Threshold: 50% • Assay/device: Brilliance 64 multidetector scanner (Philips Healthcare, Best, the Netherlands) Predictor 3: Coronary artery calcium scores • Objective: added biomarker, biomarker compared • Category: imaging • Scale: dichotomous • Threshold: 203 • Assay/device: Brilliance 64 multidetector scanner (Philips Healthcare, Best, the Netherlands) Predictor 4: Coronary artery calcium scores + significant coronary artery stenosis ≥ 50% • Objective: added biomarker

Ahn 2020 *(Continued)*

	• Category: imaging • Scale: dichotomous • Threshold: not applicable • Assay/device: Brilliance 64 multidetector scanner (Philips Healthcare, Best, the Netherlands)
Outcome	Outcome category • MACE Full outcome definition • Cardiovascular death, nonfatal myocardial infarction, myocardial injury after noncardiac surgery (MINS), pulmonary oedema, nonfatal stroke and systemic embolism Prediction horizon • 30-day events
Analysis	Number of outcomes • 24 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: Patients with at least 1 RCRI factor were included, patients were excluded if they had active cardiac conditions including recent MI, decompensated heart failure, more than moderate valvular heart disease and significant arrhythmia. Domain 2: Predictors • Unclear Justification: No information on the definition of the individual RCRI predictor definitions. Domain 3: Outcome • High Justification: MACE includes MINS and pulmonary embolism and stroke Overall judgement • High Justification: Only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study

Ahn 2020 *(Continued)*

Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 2: Predictors	Unclear	No information on the definition of the individual RCRI predictor definitions.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Small number of outcomes. No information on how missing data were handled.
Overall judgement	No	No information on the definition of the individual RCRI predictor definitions. In addition, the number of outcomes was low and there was no information on handling missing data. However, patient selection was appropriate and outcomes were clearly defined and assessed.

Alrezk 2017

Study characteristics	
General information	Objective • Prediction model compared Journal • *Journal of the American Heart Association* Country • USA Study design • Prospective existing registry
Participants	Number of included patients • 172,905 Surgical specialty • Noncardiac surgery Age • Mean 74.1 years (SD 6.9) Male sex • Not reported High-risk surgery

Alrezk 2017 *(Continued)*

	• Not reported Insulin-dependent diabetes mellitus • 7.3% History of ischaemic heart disease • Not reported History of congestive heart failure • 1.1% History of cerebrovascular accidents • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: GSCRI Objective: Prediction model compared • Category: prediction model • Scale: continuous • Threshold: not applicable • Assay/device: not applicable Predictor 2: ACS-NSQIP-MICA • Objective: prediction model compared • Category: prediction model • Scale: continuous • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Myocardial infarction and cardiac arrest (MICA)

Alrezk 2017 *(Continued)*

	Full outcome definition • Not applicable Prediction horizon • 30-day events
Analysis	Number of outcomes • 1798 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Not applicable Domain 2: Predictors • Low Justification: Not applicable Domain 3: Outcome • High Justification: Outcome is different from MACE in the development study Overall judgement • High Justification: Patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.

Alrezk 2017 *(Continued)*

Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	Clear methodology and appropriate number of outcomes.
Overall judgement	Yes	Appropriate patient selection and number of outcomes, clear predictor and outcome definitions and study methodology.

Archan 2010

Study characteristics	
General information	Objective • Biomarkers compared, prediction model compared Journal • *Journal of Cardiothoracic and Vascular Anesthesia* Country • USA Study design • Retrospective cohort study
Participants	Number of included patients • 225 Surgical specialty • Vascular surgery Age • Mean 73.8 years (SD 9) Male sex • 85.8% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 74.2% History of congestive heart failure • 10.2% History of cerebrovascular events

Archan 2010 *(Continued)*

	• 17.8% Elevated creatinine • Not reported 0 RCRI factors • 0% 1 RCRI factor • 43.1% 2 RCRI factors • 34.7% 3 or more RCRI factors • 22.2%
Predictors	Predictor 1: Age Objective: biomarker compared • Category: patient characteristic • Scale: continuous • Threshold: not applicable • Assay/device: not applicable Predictor 2: Glasgow Aneurysm Risk score (GAS) • Objective: prediction model compared • Category: prediction model • Scale: unclear • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition • Cardiac death, nonfatal myocardial infarction, unstable angina, now onset or worsening of chronic heart failure or coronary revascularisation Prediction horizon • In-hospital events
Analysis	Number of outcomes • 14 Handling missing data

Archan 2010 *(Continued)*

	• No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: not applicable Domain 2: Predictors • Low Justification: not applicable Domain 3: Outcome • High Justification: Outcome is different from MACE in the development study Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Other (more advanced) performance measures could have been calculated and reported including confidence intervals and/or standard error; low number of outcomes.
Overall judgement	No	Appropriate patient selection and clearly defined predictors and outcomes. However, the number of outcomes was low and other performance measures should have been calculated with confidence intervals and/or standard error.

Asuzu 2018

Study characteristics	
General information	Objective • Prediction model compared Journal • *Surgery* Country • USA Study design • Prospective existing registry
Participants	Number of included patients • 34,032 Surgical specialty • General surgery Age • Not reported Male sex • Not reported High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor

Asuzu 2018 *(Continued)*

	• Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: Weighted RCRI score • Objective: prediction model compared • Category: prediction model • Scale: continuous • Threshold: not applicable • Assay/device: not applicable Predictor 2: ASC-NSQIP-MICA • Objective: prediction model compared • Category: prediction model • Scale: continuous • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Myocardial infarction and cardiac arrest Full outcome definition • Not applicable Prediction horizon • 30-day events
Analysis	Number of outcomes • 372 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No

Asuzu 2018 *(Continued)*

PROBAST: Applicability	Domain 1: Participant selection • High Justification: patients were eligible if they underwent a single procedure, were > 18 years and had a lower incidence of comorbidities Domain 2: Predictors • Low Justification: not applicable Domain 3: Outcome • High Justification: outcome does not match outcome of the development study Overall judgement • High Justification: only a selected group of patients was used. Predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing general surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Patients with missing data were excluded from the analyses (> 50%), however they did provide the right performance measures.
Overall judgement	No	Appropriate patient selection and clearly defined predictors and outcomes. However, handling of missing data was inappropriate as > 50% of patients were excluded from the analysis.

Avena 2015

Study characteristics	
General information	Objective • Prediction model compared Journal

Avena 2015 *(Continued)*

	• *Arquivos Brasileiros de Cardiologia* Country • Brazil Study design • Prospective cohort study
Participants	Number of included patients • 141 Surgical specialty • Vascular surgery Age • 66 years Male sex • 65% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 39.7% History of congestive heart failure • 54.6% History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 4.3% 1 to 2 factors • 44.7% 3 or more RCRI factors • 51%
Predictors	Predictor 1: Vascular study group of New England cardiac risk index (VSG-CRI) Objective: prediction model compared

Avena 2015 *(Continued)*

	• Category: prediction model • Scale: categorical • Threshold: 0 to 4 = low; 5 to 6 = moderate; > 6 = high risk • Assay/device: not applicable
Outcome	Outcome category • All-cause mortality; MACE; all-cause mortality and MACE Full outcome definition • MACE was defined as nonfatal myocardial infarction, decompensated heart failure, significant arrhythmia and stroke Prediction horizon • 30-day events
Analysis	Number of outcomes • 39 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: included patients have very high incidence of comorbidities Domain 2: Predictors • Unclear Justification: no information on predictor definitions Domain 3: Outcome • High Justification: outcome does not match outcome of the development study Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Avena 2015 *(Continued)*

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information on predictor definitions
Domain 3: Outcome	Unclear	No standardised definition of composite outcomes; no information how outcomes were assessed.
Domain 4: Analysis	No	Low number of outcomes; no estimate reported; no handling of missing data.
Overall judgement	No	Patient selection was appropriate. However, predictors and outcomes definitions were unclear. In addition, the number of outcomes was low, no performance measures were reported and no information on handling of missing data.

Bae 2012

Study characteristics	
General information	Objective • Added biomarkers Journal • *International Journal of Cardiology* Country • Republic of Korea Study design • Cohort study (prospective/retrospective unclear)
Participants	Number of included patients • 428 Surgical specialty • Vascular surgery Age • Not reported Male sex • Not reported High-risk surgery • Not reported

Bae 2012 *(Continued)*

	Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 50.5% 1 RCRI factor • 33.2% 2 RCRI factors • 13.1% 3 or more RCRI factors • 3.3%
Predictors	Predictor 1: Fragmented QRS complex (fQRS) • Objective: added biomarker • Category: imaging • Scale: dichotomous • Threshold: not applicable • Assay/device: 12-lead resting ECG
Outcome	Outcome category • MACE Full outcome definition • Myocardial ischaemia or scar, as detected by myocardial perfusion single photon emission computed tomography (SPECT) Prediction horizon • Not reported
Analysis	Number of outcomes • 87 Handling missing data

Bae 2012 *(Continued)*

	• No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Unclear Justification: patients underwent noncardiac vascular surgery and no information is reported on baseline characteristics of included patients Domain 2: Predictors • Unclear Justification: no information was provided how the items of the RCRI were interpreted and defined Domain 3: Outcome • High Justification: outcome does not match outcome of the development study Overall judgement • High Justification: no information on baseline characteristics of included patients was reported. There was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information was provided how the items of the RCRI were interpreted and defined.
Domain 3: Outcome	Unclear	No information on how the SPECT images were assessed and how the outcome was determined based on the SPECT.
Domain 4: Analysis	No	Low number of outcomes and no information on the handling of missing data.
Overall judgement	No	Patient selection was appropriate. However, predictors and outcomes definitions were unclear. In addition, the number of outcomes was low and no information on handling of missing data.

Bae 2013

Study characteristics	
General information	Objective • Added biomarkers Journal • *American Journal of Cardiology* Country • Republic of Korea Study design • Retrospective cohort study
Participants	Number of included patients • 467 Surgical specialty • Vascular surgery Age • Mean 69.4 years (SD 9.5) Male sex • 86% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 15.2% History of congestive heart failure • 6.2% History of cerebrovascular events • 14.1% Elevated creatinine • 8% 0 RCRI factors • 46.9% 1 RCRI factor

Bae 2013 *(Continued)*

	• 35.3% 2 RCRI factors • 12.4% 3 or more RCRI factors • 5.4%
Predictors	Predictor 1: Fragmented QRS complex (fQRS) • Objective: added biomarker • Category: imaging • Scale: dichotomous • Threshold: not applicable • Assay/device: Philips TraceMasterVue ECG management system, Philips 12-leas algorithm, Andover, Massachusetts
Outcome	Outcome category • MACE Full outcome definition • Death, myocardial infarction, congestive heart failure, and percutaneous coronary intervention before noncardiac vascular surgery during index hospitalisation Prediction horizon • In-hospital events
Analysis	Number of outcomes • 38 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patients underwent vascular surgery and underwent SPECT before being considered for inclusion Domain 2: Predictors • High

Bae 2013 *(Continued)*

	Justification: for some items, no information on the definition was provided. High-risk surgery was not inserted into the RCRI and the definition of diabetes was different compared to the development paper Domain 3: Outcome • High Justification: outcome does not match outcome of the development study Overall judgement • High Justification: patient selection was appropriate. However, no/unclear information on predictor definitions for some items and other predictors of the original RCRI were not included or had a different definition. Furthermore, outcome definition was different compared to the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	No	For some items, no information on the definition was provided. High-risk surgery was not inserted into the RCRI and the definition of diabetes was different compared to the development paper.
Domain 3: Outcome	Unclear	No information how the outcomes were assessed and if the assessors were blinded for predictor values.
Domain 4: Analysis	No	Low number of outcomes and no information on the handling of missing data.
Overall judgement	No	Patient selection was appropriate. However, there was no information on how outcomes were assessed. Prediction definitions were unclear or were different compared to definitions used in the RCRI development study. In addition, the number of outcomes was low, no performance measures were reported and no information on handling of missing data.

Biccard 2011

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Anaesthesia* Country • South Africa Study design

Biccard 2011 *(Continued)*

	• Prospective cohort study
Participants	Number of included patients • 267 Surgical specialty • Vascular surgery Age • Median 61 years (IQR = 50 to 69, range = 20 to 86) Male sex • 62% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 34% History of congestive heart failure • 4% History of cerebrovascular events • 27% Elevated creatinine • 3% 0 RCRI factors • 35% 1 to 2 RCRI factors • 54% 3 or more RCRI factors • 11%
Predictors	Predictor 1: BNP • Objective: added biomarker, biomarker compared • Category: blood • Scale: dichotomous, categorical • Threshold: 69 pg/mLand tertiles • Assay/device: Advia Centaur Xp (Siemens Medical, Deerfield, IL, USA)
Outcome	Outcome category

Biccard 2011 *(Continued)*

	• Troponin elevation Full outcome definition • Not applicable Prediction horizon • Within 3 postoperative days
Analysis	Number of outcomes • 36 Handling missing data • No missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • High Justification: patients underwent vascular surgery; no age limit was provided Domain 2: Predictors • Unclear Justification: no information on the definition of the individual RCRI predictor definitions Domain 3: Outcome • High Justification: outcome assessed is troponin elevation and not MACE as defined in the development study Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Post hoc decision to exclude a selective group of patients.

Biccard 2011 *(Continued)*

Domain 2: Predictors	Unclear	No information on the definition of the individual RCRI predictor definitions.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Very low number of events; calibration not assessed; limited information on discrimination.
Overall judgement	No	Inappropriate exclusion of a selective group of patients, predictor definitions were not reported and the number of events was low and no calibration measures were assessed. However, outcome definitions were clearly defined and assessed.

Biccard 2012

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Anaesthesia* Country • Not applicable Study design • Individual patient data meta-analysis
Participants	Number of included patients • 850 Surgical specialty • Vascular surgery Age • Mean 65.3 years (SD 12.1 years) Male sex • 66% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 38.5%

Biccard 2012 *(Continued)*

	History of congestive heart failure • 7.5% History of cerebrovascular events • 7.1% Elevated creatinine • 3.3% 0 RCRI factors • 37.6% 1 to 2 RCRI factors • 56% 3 or more RCRI factors • 6.4%
Predictors	Predictor 1: BNP or NT-proBNP • Objective: added biomarker, biomarker compared • Category: blood • Scale: dichotomous • Threshold: screening cut-off value BNP 30, NT-proBNP 851; optimal discriminatory point BNP 116, NT-proBNP 532 pg/ml • Assay/device: several assays as this is an IPD meta-analysis
Outcome	Outcome category • MACE Full outcome definition • Cardiac death and nonfatal myocardial infarction Prediction horizon • 30-day events
Analysis	Number of outcomes • 75 Handling missing data • No information on handling missing data Discrimination reported? • No Calibration reported? • Yes Reclassification reported?

Biccard 2012 *(Continued)*

	• No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: patients underwent vascular surgery, no age limit was provided Domain 2: Predictors • Unclear Justification: no information on the definition of the individual RCRI predictor definitions Domain 3: Outcome • Unclear Justification: no clear definition of the outcome measure MACE Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was not clearly defined
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Unclear	Almost no information reported about participants.
Domain 2: Predictors	Unclear	No information on the definition of the individual RCRI predictor definitions.
Domain 3: Outcome	Unclear	No clear definition of the outcome measure MACE.
Domain 4: Analysis	No	Low number of outcomes (with no definition) and no information on the handling of missing data.
Overall judgement	No	There was no/limited information on participants included in the analysis, and on how predictors and outcomes were defined and assessed. In addition, the number of outcomes was low and there was no information on handling of missing data.

Binh 2019

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *The Surgeon*

Binh 2019 *(Continued)*

	Country • Vietnam Study design • Prospective cohort study
Participants	Number of included patients • 714 Surgical specialty • Noncardiac surgery Age • Median 64 years (IQR = 56 to 73) Male sex • 64% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 9.6% History of ischaemic heart disease • 7.1% History of congestive heart failure • 5.2% History of cerebrovascular events • 6.3% Elevated creatinine • 1.4% 0 RCRI factors • 74.3% 1 RCRI factor • 22.4% 2 RCRI factors • 2.7% 3 or more RCRI factors • 0.5%
Predictors	Predictor 1: NT-proBNP

Binh 2019 *(Continued)*

- Objective: added biomarker, biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Elecsys proBNP II assay, Roche Diagnostics GmbH, Mannheim, Germany

Predictor 2:

NT-proBNP + high creatinine (> 2 mg/L)

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable

Predictor 3:

NT-proBNP + high creatinine (> 2 mg/L) + ischaemic heart disease

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable

Predictor 4:

NT-proBNP + high creatinine (> 2 mg/L) + ischaemic heart disease+ congestive heart failure

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable

Outcome	Outcome category • MACE Full outcome definition • Myocardial infarction, pulmonary oedema, severe cardiac arrhythmias and cardiac death Prediction horizon • 30-day events
Analysis	Number of outcomes • 48 Handling missing data • No information on handling missing data Discrimination reported? • Yes

Binh 2019 *(Continued)*

	Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: not applicable Domain 2: Predictors • Low Justification: not applicable Domain 3: Outcome • Low Justification: not applicable Overall judgement: • Low Patient selection was appropriate; predictor and outcome definitions were clearly defined and comparable to the definitions used in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no information on handling missing data; only discrimination reported.
Overall judgement	No	Appropriate patient selection and predictors and outcomes were clearly defined. However, the number of outcome was low, there was no information on handling of missing data and only discrimination was reported as performance measure.

Boersma 2001

Study characteristics	
General information	Objective

Boersma 2001 *(Continued)*

	• Added biomarkers Journal • *JAMA* Country • Netherlands and Italy Study design • Prospective cohort study
Participants	Number of included patients • 1351 Surgical specialty • Vascular surgery Age • Not reported Male sex • 78% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • 5.3% History of cerebrovascular events • 8.8% Elevated creatinine • 4.1% 0 RCRI factors • 45% 1 RCRI factor • 38% 2 or more RCRI factors • 17%
Predictors	Predictor 1:

Boersma 2001 *(Continued)*

	Dobutamine stress echocardiography (DES) + betablocker use • Objective: added biomarker • Category: imaging • Scale: dichotomous • Threshold: worsening of ≥ 1 point during the stress test using a 5-point ordinal scale • Assay/device: not reported
Outcome	Outcome category • MACE Full outcome definition • Cardiac death or nonfatal myocardial infarction Prediction horizon • 30-day events
Analysis	Number of outcomes • 45 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: population very different from the development study; only high-risk patients included Domain 2: Predictors • Low Justification: Domain 3: Outcome • High Justification: outcome is cardiovascular death with myocardial infarction in this study and MACE in the development study Overall judgement • High Justification: only high-risk patients were included. Predictors were clearly defined. However, the outcome used was different compared to the development study.

Boersma 2001 *(Continued)*

Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Only patients with at least one cardiac risk factor had a DSE meaning that only high-risk patients were assessed.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes and no information on handling missing data.
Overall judgement	No	Only high-risk patients were included. Predictors and outcomes were clearly defined. However, the number of outcomes was low and there was no information on handling missing data.

Boersma 2005

Study characteristics	
General information	Objective • Added biomarkers Journal • *American Journal of Medicine* Country • Netherlands Study design • Retrospective cohort study
Participants	Number of included patients • 108,593 Surgical specialty • Noncardiac surgery Age • Not reported Male sex • 48.2% High-risk surgery • 27.1%

Boersma 2005 *(Continued)*

	Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 3.3% History of congestive heart failure • 1.3% History of cerebrovascular events • 0.5% Elevated creatinine • 1.7% 0 RCRI factors • 69.4% 1 RCRI factor • 26.6% 2 RCRI factors • 3.1% 3 or more RCRI factors • 0.9%
Predictors	Predictor 1: Type of surgery + laparoscopic procedure + emergency surgery • Objective: added biomarker • Category: patient characteristic • Scale: categorical • Threshold: type of surgery = 4 categories according to the American Heart Association • Assay/device: not applicable Predictor 2: Type of surgery + type of surgery + laparoscopic procedure + emergency surgery + age • Objective: added biomarker • Category: patient characteristic • Scale: categorical • Threshold: type of surgery = 4 categories according to the American Heart Association • Assay/device: not applicable
Outcome	Outcome category • Cardiovascular mortality Full outcome definition

Boersma 2005 *(Continued)*

	• Deaths following myocardial infarction, cardiac arrhythmia, resuscitation, heart failure or stroke Prediction horizon • In-hospital or within 30 days
Analysis	Number of outcomes • 543 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: patients were included from 15 years onwards meaning that the percentage with comorbidities is much lower compared to development study Domain 2: Predictors • High Justification: ICD codes were used as RCRI predictor definitions and high-risk surgery was defined as retroperitoneal, intrathoracic or suprainguinal vascular procedures Domain 3: Outcome • High Justification: outcome is cardiovascular death in this study and MACE in the development study Overall judgement • High Justification: the inclusion criteria were broader compared to the development study. ICD codes were used as RCRI predictor definitions and outcome definition was different compared to the development study.
Notes	

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	No	ICD codes were used as RCRI predictor definitions.

Boersma 2005 *(Continued)*

Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	However, no confidence intervals or standard error for the c-statistics.
Overall judgement	No	Appropriate selection of patients and clearly defined outcomes with proper methodology. However, ICD codes were used as RCRI predictor definitions.

Borges 2013

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Arquivos Brasileiros de Cardiologia* Country • Brazil Study design • Prospective cohort study
Participants	Number of included patients • 145 Surgical specialty • Noncardiac surgery Age • Mean 65.7 years (SD 9.8 years) Male sex • 48.3% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 22.8% History of ischaemic heart disease • Not reported History of congestive heart failure • 17.9% History of cerebrovascular events

Borges 2013 *(Continued)*

	• 32.4% Elevated creatinine • 24.8% 0 RCRI factors • 0% 1 RCRI factor • 9% 2 RCRI factors • 58.6% 3 or more RCRI factors • 32.4%
Predictors	Predictor 1: NT-proBNP • Objective: added biomarker, biomarker compared • Category: blood • Scale: unclear • Threshold: 917 pg/ml • Assay/device: electrochemiluminescence sandwich immunoassay, Elecsys ProBNP, Roch Diagnostics
Outcome	Outcome category • MACE Full outcome definition • Vascular death, nonfatal myocardial infarction and nonfatal cardiac arrest Prediction horizon • 30-day events
Analysis	Number of outcomes • 17 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection

Borges 2013 *(Continued)*

	• High Justification: patients with at least one RCRI factor were eligible for inclusion Domain 2: Predictors • High Justification: definition of high-risk surgery is according to the American College of Cardiology/American Heart Association and no definition for ischaemic heart disease and congestive heart failure was reported. Domain 3: Outcome • Low Justification: not applicable Overall judgement • High Justification: only a selected group of patients was included. There was no/unclear information on predictor definitions or different predictor definitions were used. Outcome definition used was clearly defined and comparable to the RCRI development study outcome definition.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Patients with at least one RCRI factor were eligible for inclusion.
Domain 2: Predictors	No	Definition of high-risk surgery is according to the American College of Cardiology/American Heart Association and no definition for ischaemic heart disease and congestive heart failure was reported.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes and no information on how missing data were handled.
Overall judgement	No	Justification: only a selected group of patients was included. There was no/unclear information on predictor definitions or different predictor definitions were used. Outcome used was appropriate and clearly defined. However, the number of outcomes was low and there was no information on handling missing data.

Bronheim 2018

Study characteristics	
General information	Objective • Biomarkers compared Journal

Bronheim 2018 *(Continued)*

- *Spine*; *World Neurosurgery*

Country

- USA

Study design

- Prospective existing registry

Participants	Number of included patients • 52,066 Surgical specialty • Neurosurgery Age • Mean 56.4 years (SD 15.7 years) Male sex • 55.7% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 4.9% History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 81.9% 1 RCRI factor • 16.3% 2 RCRI factors • 1.7% 3 or more RCRI factors • 0.1%
Predictors	Predictor 1:

Bronheim 2018 *(Continued)*

	ASA • Objective: biomarker compared • Category: patient characteristic • Scale: categorical • Threshold: not reported • Assay/device: not applicable
Outcome	Outcome category • MACE; myocardial infarction; all-cause mortality; any noncardiac complication; unplanned intubation; pulmonary embolism; ventilated > 48 hours; acute renal failure; cerebrovascular accident/stroke with neurologic deficit; coma > 24 hours; sepsis; septic shock; reoperation; superficial surgical site infection; deep incisional surgical site infection; organ space surgical site infection; wound dehiscence; pneumonia; progressive renal insufficiency; urinary tract infection; peripheral nerve injury; bleeding transfusions; deep vein thrombosis/thrombophlebitis; readmission Full outcome definition • MACE was defined as cardiac arrest requiring CPR Prediction horizon • 30-day events
Analysis	Number of outcomes • Varying depending on outcome, ranging from 8 to 3399 events Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: patient underwent posterior lumbar decompression Domain 2: Predictors • Low Justification: Domain 3: Outcome • High Justification: the RCRI was not developed to predict noncardiac complications Overall judgement

Bronheim 2018 *(Continued)*

	• High Justification: only a selected group of patients was included. Predictors were clearly defined. However, many (noncardiac) outcomes were assessed and therefore different compared to the outcome used in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing neurosurgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Depending on the outcome, low number of outcomes. Only discrimination is reported and no other performance measures. Multiple testing issue. No information on handling missing data.
Overall judgement	No	Appropriate patient selection and outcomes and predictors were clearly defined. However, many outcomes were tested and there was no correction for multiple testing; only discrimination measures were reported and there was no information on handling missing data.

Brunelli 2010

Study characteristics	
General information	Objective • Prediction model compared Journal • *Annals of Thoracic Surgery* Country • Italy, Spain Study design • Prospective cohort study
Participants	Number of included patients • 1696 Surgical specialty • Thoracic surgery Age

Brunelli 2010 *(Continued)*

- Mean 65 years (SD 11.2 years)

Male sex

- 82%

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- 11%

History of congestive heart failure

- Not reported

History of cerebrovascular events

- 4%

Elevated creatinine

- 3.3%

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

Not reported

Predictors	Predictor 1: Thoracic RCRI, including serum creatinine, cerebrovascular disease, cardiac ischaemia, pneumonectomy • Objective: prediction model compared • Category: prediction model • Scale: categorical • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition

Brunelli 2010 *(Continued)*

	• Acute myocardial infarction (diagnosed by electrocardiogram changes and increased serum troponin level), pulmonary oedema (confirmed by consistent findings at chest X-ray), ventricular fibrillation or primary cardiac arrest, complete heart block and any cardiac-related death Prediction horizon • In hospital or within 30 days
Analysis	Number of outcomes • 57 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: very selective group of patients included Domain 2: Predictors • Low Justification: not applicable Domain 3: Outcome • Low Justification: not applicable • High Justification: only a selected group of patients was included. However, predictors and outcomes were clearly defined and comparable as used in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing thoracic surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.

Brunelli 2010 *(Continued)*

Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of events; no information on missing data and calibration.
Overall judgement	No	Appropriate patient selection and clearly defined predictors and outcomes. However, the number of outcomes was low and there was no information on missing data and no calibration was reported.

Bryce 2012

Study characteristics	
General information	Objective • Prediction model compared Journal • *European Journal of Vascular & Endovascular Surgery* Country • United Kingdom Study design • Prospective cohort study
Participants	Number of included patients • 106 Surgical specialty • Vascular surgery Age • Median 73 years (IQR 66 to 77 years) Male sex • 83% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • 12% History of cerebrovascular events

Bryce 2012 *(Continued)*

- 21%

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: Glasgow aneurysm score • Objective: prediction model compared • Category: prediction model • Scale: continuous • Threshold: not applicable • Assay/device: not applicable Predictor 2: V(p)-POSSUM score • Objective: prediction model compared • Category: prediction model • Scale: continuous • Threshold: not applicable • Assay/device: not applicable Predictor 3: Vascular biochemical and haematological outcome model • Objective: prediction model compared • Category: prediction model • Scale: continuous • Threshold: not applicable • Assay/device: not applicable Predictor 4: Preoperative risk score of the estimation of physiological ability and surgical stress score • Objective: prediction model compared

Bryce 2012 *(Continued)*

	• Category: prediction model • Scale: continuous • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • All-cause mortality; MACE; cardiovascular death Full outcome definition • MACE was defined as nonfatal myocardial infarction and cardiac death. Cardiac death was defined as death secondary to myocardial infarction, cardiogenic shock or intractable dysrhythmia. Prediction horizon • 30-day events
Analysis	Number of outcomes • 9 Handling missing data • No missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: most RCRI predictor definitions not reported Domain 3: Outcome • High Justification: outcome different from the development study Overall judgement • High Justification: patient selection was appropriate. However, there was no/unclear information on predictor definitions. In addition, the outcome used was different from MACE in the development study.
Notes	

Bryce 2012 *(Continued)*

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	Most predictor definitions not reported including RCRI definition factors.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Very low sample size; calibration not assessed.
Overall judgement	No	Appropriate patient selection and clearly defined outcome. However, there was no/unclear information on predictor definitions. In addition, the sample size was low and calibration was not assessed.

Canbolat 2018

Study characteristics	
General information	Objective • Prediction model compared Journal • *Bratislava Medical Journal* Country • Turkey Study design • Retrospective cohort study
Participants	Number of included patients • 278 Surgical specialty • General surgery Age • Median 53.5 years (range = 20 to 75 years) Male sex • 71.6% High-risk surgery • Not reported Insulin-dependent diabetes mellitus

Canbolat 2018 *(Continued)*

	• Not reported History of ischaemic heart disease • 3.2% History of congestive heart failure • 0% History of cerebrovascular events • 0% Elevated creatinine • Not reported 0 RCRI factors • 80.2% 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: NSQIP surgical risk score • Objective: prediction model compared • Category: prediction model • Scale: categorical • Threshold: according to estimated risk probability for perioperative myocardial infarction or cardiac arrest: < 1 % low risk; 1% to 5 % medium risk and ≥ 5 % high risk • Assay/device: not applicable
Outcome	Outcome category • All-cause mortality; MACE Full outcome definition • MACE was defined as acute coronary syndrome (ACS), congestive heart failure, complete heart block and cardiac arrest Prediction horizon • In-hospital and 30-day events
Analysis	Number of outcomes • 5 MACE, 18 deaths Handling missing data • No information on handling missing data

Canbolat 2018 *(Continued)*

	Discrimination reported? • No Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Unclear Justification: not sure if patients who underwent liver transplantation were involved in the original study. Domain 2: Predictors • Unclear Justification: no definition of RCRI factors was reported Domain 3: Outcome • High Justification: outcome different from the development study Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing general surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No definition of RCRI factors was reported.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Very low sample size, no information on missing data, no information on discrimination and limited information on calibration.
Overall judgement	No	Appropriate patient selection and clearly defined outcome. However, there was no/unclear information on predictor definitions. In addition, the sample size was low and calibration was not assessed.

Carabini 2014

Study characteristics	
General information	Objective • Biomarkers compared Journal • *Spine* Country • USA Study design • Retrospective cohort study
Participants	Number of included patients • 547 Surgical specialty • General surgery Age • Median 53.5 years (range = 20 to 75 years) Male sex • 71.6% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 72.4% 1 RCRI factor • 22.9%

Carabini 2014 *(Continued)*

	2 RCRI factors • 4.4% 3 or more RCRI factors • 0.4%
Predictors	Predictor 1: Age + surgical complexity • Objective: biomarker compared • Category: patient characteristic • Scale: unclear • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition • New arrhythmia requiring treatment with vasoactive medication infusion, cardioversion, pacing or defibrillation, myocardial infarction and troponin elevation Prediction horizon • Not reported
Analysis	Number of outcomes • 49 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: no definition of RCRI factors were reported Domain 3: Outcome

Carabini 2014 *(Continued)*

	• High Justification: outcome different from the development study Overall judgement • High Justification: appropriate patient selection. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing general surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information on predictor definitions.
Domain 3: Outcome	Unclear	Time horizon is unclear; limited information on outcome measurement.
Domain 4: Analysis	No	Low sample size and complete-case analysis but only 3 patients excluded because of missing data.
Overall judgement	No	Appropriate patient selection. However, predictors definitions and outcome assessments were unclear. In addition, the sample size and number of outcomes was low.

Che 2018

Study characteristics	
General information	Objective • Prediction model compared Journal • *Clinical Interventions in Aging* Country • China Study design • Prospective cohort study
Participants	Number of included patients • 1202 Surgical specialty

Che 2018 *(Continued)*

- Noncardiac surgery

Age

- Mean 69.5 years (SD 5.3 years)

Male sex

- Not reported

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- 0%

1 RCRI factor

- 26.1%

2 RCRI factors

- 59.5%

3 or more RCRI factors

- 14.4%

Predictors	Number of included patients • 1202 Surgical specialty • Noncardiac surgery Age • Mean 69.5 years (SD 5.3 years) Male sex • Not reported High-risk surgery

Che 2018 *(Continued)*

	• Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 0% 1 RCRI factor • 26.1% 2 RCRI factors • 59.5% 3 or more RCRI factors • 14.4%
Outcome	Outcome category • MACE Full outcome definition • Cardiac death, nonfatal myocardial infarction, nonfatal cardiac arrest and heart failure Prediction horizon 30-day events
Analysis	Number of outcomes • 52 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported?

Che 2018 *(Continued)*

	• No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only participants with CAD were included Domain 2: Predictors • Low Justification: not applicable Domain 3: Outcome • High Justification: outcome different from the development study Overall judgement • High Justification: only a selected group of patients was included and the outcome definition was different compared to the development study. However, predictor definitions were clearly defined and comparable to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of events; 15% of participants excluded due to missing data.
Overall judgement	No	Appropriate patient selection and clearly defined predictors and outcomes. However, the number of outcomes was low and complete case analysis was performed.

Cho 2020

Study characteristics	
General information	Objective • Added biomarkers Journal • *Korean Circulation Journal*

Cho 2020 *(Continued)*

	Country • Republic of Korea Study design • Retrospective cohort study
Participants	Number of included patients • 26501 Surgical specialty • Noncardiac surgery Age • Not reported Male sex • Not reported High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: Atrial fibrillation

Cho 2020 *(Continued)*

	• Objective: added biomarkers • Category: patient characteristic • Scale: dichotomous • Threshold: not applicable • Assay/device: ECG
Outcome	Outcome category • All-cause mortality and MACE Full outcome definition • Composite of death, ischaemic stroke and myocardial infarction Prediction horizon • In-hospital or within 30 days
Analysis	Number of outcomes • 353 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Low Justification: Domain 3: Outcome • High Justification: MACE definition varies from definition of MACE in development cohort Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.

Cho 2020 *(Continued)*

Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Patients without cardiac evaluation were excluded (approximately 80% of sample).
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	However, no information on handling missing data, only c-statistic reported. No measures of calibration or reclassification.
Overall judgement	No	Only a selected group of patients were included in the analysis and no information on the handling of missing data. In addition, only discrimination was reported and no other performance measures. However, outcomes and predictors were clearly defined and assessed.

Choi 2010

Study characteristics	
General information	Objective • Added biomarkers Journal • *Heart* Country • Republic of Korea Study design • Prospective cohort study
Participants	Number of included patients • 2054 Surgical specialty • Noncardiac surgery Age • Median 68 years (IQR = 61 to 73 years) Male sex • 60.7% High-risk surgery

Choi 2010 *(Continued)*

- 41.1%

Insulin-dependent diabetes mellitus

- 3.5%

History of ischaemic heart disease

- 21.6%

History of congestive heart failure

- 3%

History of cerebrovascular events

- 9.3%

Elevated creatinine

- Not reported

0 RCRI factors

- 27%

1 RCRI factor

- 41.2%

2 RCRI factors

- 28.2%

3 or more RCRI factors

- 3.6%

Predictors	Predictor 1: NT-proBNP • Objective: added biomarkers • Category: blood • Scale: dichotomous • Threshold: 301 mg/L • Assay/device: not reported Predictor 2: CRP • Objective: added biomarkers • Category: blood • Scale: dichotomous • Threshold: 3.4 mg/L • Assay/device: not reported Predictor 3: NT-proBNP + CRP

Choi 2010 *(Continued)*

- Objective: added biomarkers
- Category: blood
- Scale: dichotomous
- Threshold: 301 and 3.4 mg/L, respectively
- Assay/device: not reported

Outcome	Outcome category • MACE; myocardial infarction; pulmonary oedema; cardiovascular death Full outcome definition • MACE was defined as myocardial infarction, development of pulmonary oedema or primary cardiovascular death. Cardiovascular death was defined as sudden death that could not be explained by any other than cardiovascular postoperative complications. Prediction horizon • In-hospital or within 30 days
Analysis	Number of outcomes • 291 MACE Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: patients were required to have ≥ 1 cardiovascular risk factor such as hypertension, diabetes, angina, history of revascularisation, heart failure or stroke, or abnormal preoperative electrocardiography with pathological Q wave or non-sinus rhythm. In addition patients with creatinine > 2.0 mg/dL were excluded from the analysis. Domain 2: Predictors • Low Justification: not applicable Domain 3: Outcome • Low Justification: not applicable Overall judgement • High

Choi 2010 *(Continued)*

	Justification: only a selected group of patients was included. However, predictors and outcomes were clearly defined and comparable as used in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Data were dichotomised for all predictors of interest; no information on the handling of missing data. No calibration or reclassification measures were reported.
Overall judgement	No	Appropriate patient selection and clearly defined predictors and outcomes. However, data were dichotomised, there was no information on the handling of missing data and no information on calibration and reclassification measures were reported.

Cohn 2018

Study characteristics	
General information	Objective • Prediction model compared Journal • *American Journal of Cardiology* Country • USA Study design • Retrospective cohort study
Participants	Number of included patients • 663 Surgical specialty • Noncardiac surgery Age • Mean 60.8 years (SD 14 years) Male sex

Cohn 2018 *(Continued)*

- 49.2%

High-risk surgery

- 15.7%

Insulin-dependent diabetes mellitus

- 2.3%

History of ischaemic heart disease

- 11.6%

History of congestive heart failure

- 2.3%

History of cerebrovascular events

- 3.9%

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: Reconstructed RCRI, defined as high-risk surgery, ischaemic heart disease, congestive heart failure, cerebrovascular disease, renal insufficiency (GFR < 30) Objective: prediction model compared • Category: prediction model • Scale: categorical • Threshold: not applicable • Assay/device: not applicable Predictor 2: ACS-NSQIP-MICA • Objective: prediction model compared • Category: prediction model • Scale: categorical • Threshold: not applicable • Assay/device: not applicable

Cohn 2018 *(Continued)*

	Predictor 3: ACS-NSQIP surgical risk score • Objective: added biomarkers • Category: prediction model • Scale: categorical • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE; myocardial infarction or cardiac arrest Full outcome definition • MACE was defined as myocardial infarction, cardiac arrest, complete heart block and pulmonary oedema Prediction horizon • In-hospital or within 30 days
Analysis	Number of outcomes • 14 MACE Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Unclear Justification: Eligibility criteria were not described Domain 2: Predictors • Unclear Justification: limited information on predictor definitions and measurement Domain 3: Outcome • Low Justification: not applicable Overall judgement

Cohn 2018 *(Continued)*

	• Unclear Justification: there was no information on eligibility criteria and predictor definitions. Outcome used was comparable to the outcome used in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Unclear	Eligibility criteria were not described.
Domain 2: Predictors	Unclear	Limited information on predictor definitions and measurement.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Very low number of events; no information about missing values; calibration not assessed.
Overall judgement	No	No information on eligibility criteria and predictor definitions. In addition, the number of events was low, there was no information on the handling of missing values and calibration measures were not reported. However, the outcome was clearly defined and assessed.

Cuthbertson 2007

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *British Journal of Anaesthesia* Country • United Kingdom Study design • Prospective cohort study
Participants	Number of included patients • 204 Surgical specialty • Noncardiac surgery Age • Mean 66 years (range = 28 to 79 years) Male sex

Cuthbertson 2007 *(Continued)*

	• 61% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 2 or more RCRI factors • 32%
Predictors	Outcome category • All-cause mortality and MACE Full outcome definition • All-cause mortality or troponin elevation Prediction horizon • Within the first 3 postoperative days
Outcome	Outcome category • All-cause mortality and MACE Full outcome definition • All-cause mortality or troponin elevation Prediction horizon • Within the first 3 postoperative days
Analysis	Number of outcomes

Cuthbertson 2007 *(Continued)*

	• 12 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: not applicable Domain 2: Predictors • Unclear Justification: no information on predictor definitions Domain 3: Outcome • High Justification: outcome different from the development study Overall judgement • High Justification: patient selection was appropriate. However, there was no/unclear information on predictor definitions. In addition, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on predictor definitions.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	The number of events was low; there was no information on handling missing data.
Overall judgement	No	Appropriate patient selection and outcomes definitions were clearly defined and assessed. However, there was no/unclear information on predictor defi-

Cuthbertson 2007 *(Continued)*

	nitions, the number of outcomes was low and no information on handling of missing data was reported.

Dakik 2019

Study characteristics	
General information	Objective • Prediction model compared Journal • *Journal of the American College of Cardiology* Country • Lebanon and USA Study design • Prospective cohort study
Participants	Number of included patients • 3284 Surgical specialty • Noncardiac surgery Age • Mean 62.5 years (SD 12.4 years) Male sex • 50.8% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 3.7% History of ischaemic heart disease • 28.7% History of congestive heart failure • 2.3% History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors

Dakik 2019 *(Continued)*

- 93.8%

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: AUB-HAS2 Cardiovascular Risk Index, which includes age > 75 years, history of heart disease, symptoms of angina or dyspnoea, haemoglobin < 12 mg/dl, vascular surgery and emergency surgery • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: NSQIP surgical risk score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • All-cause mortality and MACE Full outcome definition • All-cause mortality, ischaemic stroke and myocardial infarction Prediction horizon • 30-day events
Analysis	Number of outcomes • 38 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No

Dakik 2019 *(Continued)*

	Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: no information on how RCRI items were defined Domain 3: Outcome • High Justification: outcome different from the development study Overall judgement • High Justification: patient selection was appropriate. However, there was no/unclear information on predictor definitions. In addition, the outcome used was different from MACE in the development study.
Notes	

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on how RCRI items were defined.
Domain 3: Outcome	No	There was no routine troponin monitoring so some MIs could be missed.
Domain 4: Analysis	No	Low number of outcome; predictor selection for new prediction model based on significant univariable factors; only c-statistic was reported.
Overall judgement	No	Patient selection was appropriate. However, predictor definition were not reported/unclear. In addition, outcomes assessment was inappropriate, the number of outcomes was low and no calibration measures were reported.

Dakik 2020

Study characteristics	
General information	Objective • Prediction model compared Journal • *Journal of the American College of Cardiology*

Dakik 2020 *(Continued)*

	Country • Lebanon and USA Study design • Prospective existing registry
Participants	Number of included patients • 1,167,278 Surgical specialty • Noncardiac surgery Age • Mean 57 years (SD 17 years) Male sex • 42% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • 0.9% History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1:

Dakik 2020 *(Continued)*

	AUB-HAS2 Cardiovascular Risk Index, which includes age > 75 years, history of heart disease, symptoms of angina or dyspnoea, haemoglobin < 12 mg/dl, vascular surgery and emergency surgery • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • All-cause mortality and MACE Full outcome definition • All-cause mortality, ischaemic stroke and myocardial infarction Prediction horizon • 30-day events
Analysis	Number of outcomes • 25,034 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: also patients < 50 years are included and lower incidence of comorbidities are reported. This might be a more healthy population compared to the population of the development study. Domain 2: Predictors • Unclear Justification: no information on how RCRI items were defined Domain 3: Outcome • High Justification: outcome different from the development study Overall judgement • High

Dakik 2020 *(Continued)*

	Justification: patient selection was appropriate. However, there was no/unclear information on predictor definitions. In addition, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on how RCRI items were defined.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	No measures or calibration or reclassification were reported and no information on handling of missing data.
Overall judgement	No	Patient selection was appropriate and outcomes were clearly defined and assessed. However, there was no information on RCRI predictor definitions and no calibration and/or reclassification measures were reporting.

Datema 2010

Study characteristics	
General information	Objective • Added biomarkers, prediction model compared Journal • *Head and Neck* Country • Netherlands Study design • Retrospective cohort study
Participants	Number of included patients • 135 Surgical specialty • Head and neck surgery Age • Median 59 years (range = 24 to 83 years) Male sex • 59.3%

Datema 2010 *(Continued)*

	High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • 0.9% History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 57% 1 RCRI factor • 28.9% 2 RCRI factors • 11.1% 3 or more RCRI factors • 3%
Predictors	Predictor 1: Age • Objective: added biomarker • Category: patient characteristic • Scale: dichotomous • Threshold: ≥ 70 years • Assay/device: not applicable Predictor 2: Adult comorbidity evaluation (ACE-27) • Objective: prediction model compared • Category: prediction model • Scale: categorical • Threshold: grade 1: mild decompensation; grade 2: moderate decompensation; or grade 3: severe decompensation • Assay/device: not applicable

Datema 2010 *(Continued)*

	Predictor 3: Adult comorbidity evaluation (ACE-27) + age ≥ 70 years • Objective: prediction model compared • Category: prediction model • Scale: categorical • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition • Cardiac death, nonfatal myocardial infarction, heart failure and cardiac arrhythmias Prediction horizon • In-hospital events
Analysis	Number of outcomes • 23 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: not applicable Domain 2: Predictors • Low Justification: not applicable Domain 3: Outcome • Low Justification: not applicable Overall judgement: • Low

Datema 2010 *(Continued)*

	Patient selection was appropriate, predictor and outcome definitions were clearly defined and comparable to the definitions used in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing head and neck surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes and only c-statistic reported without any confidence intervals or standard errors.
Overall judgement	No	Appropriate patient selection and clearly defined predictors and outcomes. However, the number of outcomes was low and no calibration was reported.

Davis 2013

Study characteristics	
General information	Objective • Prediction model compared Journal • *Canadian Journal of Anaesthesia* Country • Canada Study design • Prospective cohort study
Participants	Number of included patients • 9519 Surgical specialty • Noncardiac surgery Age • Mean 66 years (SD = not reported) Male sex • 51.5%

Davis 2013 *(Continued)*

	High-risk surgery • 26.3% Insulin-dependent diabetes mellitus • 2.4% History of ischaemic heart disease • 18.5% History of congestive heart failure • 3% History of cerebrovascular events • 7.2% Elevated creatinine • 1.4% 0 RCRI factors • 55.4%% 1 RCRI factor • 33% 2 RCRI factors • 9.4% 3 or more RCRI factors • 2.1%
Predictors	Predictor 1: RCRI without insulin-dependent diabetes and preoperative creatinine > 2.0 mg/dL • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: RCRI without insulin-dependent diabetes and eGFR < 30 instead of preoperative creatinine > 2.0 mg/dL • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category

Davis 2013 *(Continued)*

	• MACE Full outcome definition • Myocardial infarction, pulmonary oedema or primary cardiac arrest Prediction horizon • In-hospital events
Analysis	Number of outcomes • 200 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: not applicable Domain 2: Predictors • Low Justification: not applicable Domain 3: Outcome • Low Justification: not applicable Overall judgement: • Low Patient selection was appropriate, predictor and outcome definitions were clearly defined and comparable to the definitions used in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.

Davis 2013 *(Continued)*

Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	Clear methodology and appropriate number of outcomes.
Overall judgement	Yes	Patient selection was appropriate; predictor and outcome definitions were clearly defined and comparable to the definitions used in the development study. In addition, methodology used was appropriate including the number of outcomes.

Dhillon 2018

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Anesthesia and Analgesia* Country • USA Study design • Prospective cohort study
Participants	Number of included patients • 100 Surgical specialty • Vascular surgery Age • Mean 61 years (SD 15.8) Male sex • 60% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure

Dhillon 2018 *(Continued)*

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- 31%

1 RCRI factor

- 43%

2 RCRI factors

- 21%

3 or more RCRI factors

- 5%

Predictors	Predictor 1: 6-minute walking test • Objective: added biomarker, biomarker compared • Category: patient characteristic • Scale: continuous • Threshold: not applicable • Assay/device: not applicable Predictor 2: METs • Objective: biomarker compared • Category: patient characteristic • Scale: unclear • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Troponin elevation Full outcome definition • Not applicable Prediction horizon • Postoperative day 1
Analysis	Number of outcomes • 17

Dhillon 2018 *(Continued)*

	Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: the definition of each predictor was not clarified Domain 3: Outcome • High Justification: the outcome is troponin elevation which is not similar to the outcome used in the RCRI development paper Overall judgement • High Justification: patient selection was appropriate. However, predictor definitions were unclear/not reported. Furthermore, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	The definition of the RCRI predictors was not clarified.
Domain 3: Outcome	No	Troponin was only measured on the morning of postoperative day 1 meaning that many outcomes could have been missed.
Domain 4: Analysis	No	Low number of outcomes and only c-statistics are reported; no measures of calibration or reclassification.
Overall judgement	No	Patient selection was appropriate. However, predictor definitions were not clear/not reported. In addition, outcome assessment was inappropriate, the

Dhillon 2018 *(Continued)*

	number of outcomes was low and no calibration/reclassification measures were reported.

Dillon 2011

Study characteristics	
General information	Objective • Biomarkers compared Journal • *Head and Neck* Country • USA Study design • Retrospective cohort study
Participants	Number of included patients • 92 Surgical specialty • Ear, nose, throat and dental surgery Age • Mean 66 years (SD 14) Male sex • 62% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 22% History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • 0% 0 RCRI factors

Dillon 2011 *(Continued)*

	• Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: Estimated blood loss + operation time • Objective: biomarker compared • Category: patient characteristic • Scale: continuous • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition • Myocardial infarction, arrhythmia and persistent hypertension necessitating treatment Prediction horizon • Not reported
Analysis	Number of outcomes • 23 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear

Dillon 2011 *(Continued)*

	Justification: there was no definition of the RCRI items; predictors compared are intraoperative predictors meaning that the model cannot be used preoperatively Domain 3: Outcome • Unclear Justification: no information on how the outcomes were assessed and whether predefined definitions were used; no reporting of event per individual item of the composite outcome Overall judgement • High Justification: patient selection was appropriate. However, predictor and outcome definitions were not clear/not reported and outcome assessment was inappropriate. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing ENT surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	There was no definition of the RCRI items; predictors compared are intraoperative predictors meaning that the model cannot be used preoperatively.
Domain 3: Outcome	Unclear	No information on how the outcomes were assessed and whether predefined definitions were used, no reporting of event per individual item of the composite outcome.
Domain 4: Analysis	No	Low number of outcomes; only c-statistic reported and not interpreted in the right way.
Overall judgement	No	Patient selection was appropriate. However, predictor and outcome definitions were unclear/not reported. There was no information on how outcomes were assessed. In addition, the number of outcomes was low and no calibration measures were reported.

Douville 2020

Study characteristics	
General information	Objective • Added biomarkers, prediction model compared Journal • *Circulation: Genomic and Precision Medicine* Country • USA Study design

Douville 2020 *(Continued)*

- Prospective cohort study

Participants	Number of included patients • 89,624 Surgical specialty • Noncardiac surgery Age • Median 55 years (IQR = 42 to 65) Male sex • 45% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: Polygenic risk score (CAD) • Objective: added biomarker • Category: blood • Scale: continuous • Threshold: not applicable

Douville 2020 *(Continued)*

	• Assay/device: Illumina Infinium CoreExome-24 Predictor 2: Preoperative model (age, admission type, composite RCRI, arrhythmia, fluid/electrolyte disorder, hypertension) • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: Preoperative model + Polygenic Risk Score (CAD) • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Troponin elevation Full outcome definition • Myocardial injury after noncardiac surgery (MINS) Prediction horizon • 30-day events
Analysis	Number of outcomes • 429 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low

Douville 2020 *(Continued)*

	Justification: However, patients might be healthier compared to the patients included in the development study Domain 2: Predictors • Low Justification: Domain 3: Outcome • High Justification: troponin elevation is not similar to the outcome MACE in the development study Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	No	Troponins are not routinely drawn on all patients, but rather drawn when a clinical suspicion of MINS exists.
Domain 4: Analysis	Yes	Clear methodology and appropriate number of outcomes.
Overall judgement	No	Appropriate patient selection, clearly defined predictors and proper methodology. However, outcomes could have been missed due to inappropriate outcome assessment.

Duceppe 2020

Study characteristics	
General information	Objective • Added biomarkers Journal • *Annals of Internal Medicine* Country • Canada, Hong Kong, Brazil, UK, South Africa, Australia, Malaysia, Poland, USA, Germany Study design

Duceppe 2020 *(Continued)*

	• Prospective cohort study
Participants	Number of included patients • 10,402 Surgical specialty • Noncardiac surgery Age • Mean 66 years (SD 11.1) Male sex • 50% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 14.7% History of congestive heart failure • 3.3% History of cerebrovascular events • 6.9% Elevated creatinine • Not reported 0 RCRI factors • 56.7% 1 RCRI factor • 30.6% 2 RCRI factors • 9.3% 3 or more RCRI factors • 3.4%
Predictors	Predictor 1: NT-proBNP • Objective: added biomarker • Category: blood • Scale: categorical • Threshold: < 100, 100 to 200, 200 to 1500, > 1500 pg/ml

Duceppe 2020 *(Continued)*

	• Assay/device: Roche immunoassay analysers (Roche Diagnostics)
Outcome	Outcome category • MACE; all-cause mortality and MACE Full outcome definition • MACE was defined as MINS (myocardial injury after noncardiac surgery) or vascular death; all-cause mortality and MACE were defined as all-cause mortality or myocardial infarction Prediction horizon • 30-day events
Analysis	Number of outcomes • 1269 MACE; 446 deaths or myocardial infarction Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: no definition for the RCRI items was reported Domain 3: Outcome • High Justification: composite outcome that is different from MACE in the development study. In addition, the severity of the composites is very different compared to MACE in the development study. Overall judgement • High Justification: patient selection was appropriate. However, there was no information on how predictors were defined. Furthermore, the outcome used was different from MACE in the development study.
Notes	—

Duceppe 2020 *(Continued)*

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No definition for the RCRI items was reported.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	Clear methodology and appropriate number of outcomes.
Overall judgement	Unclear	Patient selection was appropriate, outcome definitions were clearly defined and assessed and proper methodology was used. However, there was no/unclear information on predictor definitions.

Dunn 2019

Study characteristics	
General information	Objective • Prediction model compared Journal • *Surgery Research and Practice* Country • USA Study design • Retrospective cohort study
Participants	Number of included patients • 503 Surgical specialty • Kidney transplant surgery Age • Median 52 years (IQR = 42 to 61) Male sex • 58.4% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 28.4% History of ischaemic heart disease

Dunn 2019 *(Continued)*

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: ASC-NSQIP-MICA • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: PORT model • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Myocardial infarction and cardiac arrest Full outcome definition • Not applicable Prediction horizon • 30 days and one-year events

Dunn 2019 *(Continued)*

Analysis	Number of outcomes • 31 Handling missing data • No information on handling missing data Discrimination reported? • No Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only kidney transplants Domain 2: Predictors • High Justification: definition of ischaemic heart disease is different from the definition in the development study and no information on blinding Domain 3: Outcome • High Justification: outcome is myocardial infarction and cardiac arrest, which is different from the definition from the development study Overall judgement • High Justification: only a selected group of patients was included; predictor definitions were different from the predictor definitions used in the development study. In addition, outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing kidney transplant surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	No	Definition of ischaemic heart disease is different from the definition in the development study and no information on blinding.
Domain 3: Outcome	Unclear	No information on how myocardial infarction is defined/diagnosed.

Dunn 2019 *(Continued)*

Domain 4: Analysis	No	Low number of outcomes; complete case analyses; c-statistic was not provided for the RCRI alone; no information on calibration and reclassification.
Overall judgement	No	Patient selection was appropriate. However, predictors were defined differently compared to predictor definitions used in the development study. In addition, the number of outcomes was low, complete case analysis was performed and no calibration and reclassification was reported.

Ehlert 2016

Study characteristics	
General information	Objective • Biomarkers compared, prediction model compared Journal • *Journal of Vascular Surgery* Country • USA Study design • Prospective existing registry
Participants	Number of included patients • 6 different subgroups are evaluated Surgical specialty • Vascular surgery Age • Median 72 years (IQR = 65 to 77) Male sex • 73% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • < 1% History of cerebrovascular events

Ehlert 2016 *(Continued)*

- 5%

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: ASA • Objective: biomarker compared • Category: patient characteristic • Scale: categorical • Threshold: not applicable • Assay/device: not applicable Predictor 2: Modified frailty index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • All-cause mortality; Clavien Dindo Class IV complications Full outcome definition • Not applicable Prediction horizon • 30 days all-cause mortality and in-hospital Clavien Dindo Class IV complications
Analysis	Number of outcomes • Varies per outcome and patient population studied Handling missing data • No information on handling missing data

Ehlert 2016 *(Continued)*

	Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: only kidney transplants Domain 2: Predictors • High Justification: some of the definitions of the RCRI were not similar to the predictor definitions of the development study Domain 3: Outcome • High Justification: outcome was all-cause mortality or Clavien Dindo Class IV complications, which is different from the definition from the development study (MACE) Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	No	Some of the definitions of the RCRI were not similar to the predictor definitions of the development study.
Domain 3: Outcome	Yes	Clear (RCRI) outcomes definitions were described with appropriate assessment.
Domain 4: Analysis	No	Complete case analysis while there were missing data and only c-statistic without accuracy measures (CI or SE).
Overall judgement	No	Patient selection and outcome definitions/assessment was appropriate. However, different predictor definitions were used compared to predictor definitions in the development study. In addition, complete case analysis was performed and no calibration and/or reclassification was reported.

Farina-Castro 2020

Study characteristics	
General information	Objective • Biomarkers compared, prediction model compared Journal • *Journal of Vascular Surgery* Country • Spain Study design • Retrospective cohort study
Participants	Number of included patients • 244 Surgical specialty • Noncardiac surgery Age • Median 91 years (IQR = 90 to 93) Male sex • 39.3% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 5.7% 1 RCRI factor

Farina-Castro 2020 *(Continued)*

- 31.1%

2 RCRI factors

- 32.8%

3 or more RCRI factors

- 30.3%

Predictors	Predictor 1: ASA • Objective: biomarker compared • Category: patient characteristic • Scale: categorical • Threshold: not applicable • Assay/device: not applicable Predictor 2: S-MPM (surgical mortality probability model) • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: Charlson Comorbidity Index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 4: Reiss Index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • All-cause mortality; Comprehensive Complication Index ≥ 1 Full outcome definition

Farina-Castro 2020 *(Continued)*

	• Not applicable Prediction horizon • 30 days all-cause mortality and prediction horizon for Comprehensive Complication Index ≥ 1 was not reported
Analysis	Number of outcomes • 66 deaths and 179 complications Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only patients with age > 90 years were included Domain 2: Predictors • Unclear Justification: the definition of each item of RCRI was unclear Domain 3: Outcome • High Justification: outcome is all-cause mortality or Comprehensive Complication Index, which is different from the definition from the development study (MACE) Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	The definition of each item of RCRI was unclear.

Farina-Castro 2020 *(Continued)*

Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, complete case analysis and no information on calibration and reclassification.
Overall judgement	No	Patient selection and outcome definitions with their assessment was appropriate. However, there was no/unclear information on predictor definitions. In addition, the number of outcomes was low, complete case analysis was performed and no calibration and reclassification measures were reported.

Feringa 2007

Study characteristics	
General information	Objective • Biomarkers compared Journal • *Heart* Country • Netherlands Study design • Prospective cohort study
Participants	Number of included patients • 335 Surgical specialty • Vascular surgery Age • Mean 62.2 years (SD 12.4) Male sex • 76.4% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 49.3% History of congestive heart failure • 17%

Feringa 2007 *(Continued)*

History of cerebrovascular events

- 16.7%

Elevated creatinine

- 6%

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: NT-proBNP • Objective: biomarker compared • Category: blood • Scale: unclear • Threshold: 319 ng/L • Assay/device: electrochemiluminescence immunoassay kit (Elycsys 2010, Roche, Mannheim, Germany) Predictor 2: Dobutamine stress echocardiography • Objective: biomarker compared • Category: imaging • Scale: dichotomous • Threshold: ischaemia was defined as new or worsening wall-motion abnormalities as indicated by an increase in regional wall motion score ≥ 1 grade with stress • Assay/device: not reported
Outcome	Outcome category • All-cause mortality; MACE Full outcome definition • MACE was defined as cardiac death or nonfatal myocardial infarction Prediction horizon • 6 months
Analysis	Number of outcomes • Not reported

Feringa 2007 *(Continued)*

	Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: patients underwent vascular surgery and high incidences of comorbidities Domain 2: Predictors • Low Justification: not applicable Domain 3: Outcome • High Justification: outcome is all-cause mortality or MACE, which is different to the definition from the development study (MACE) Overall judgement • High Justification: predictor definitions were clearly defined and comparable to definitions used in the development study. However, patient selection was inappropriate and the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Patients who underwent coronary artery revascularisation were excluded.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no information on the handling of missing data; no information how many outcomes have occurred for the 6-month outcome; no calibration or reclassification measures reported.
Overall judgement	No	Predictors and outcomes were clearly defined and assessed. However, patient selection was inappropriate, the number of outcomes was low. there was no

Feringa 2007 *(Continued)*

	information on missing data and no calibration or reclassification measures were reported.

Ferrante 2019

Study characteristics	
General information	Objective • Prediction model compared Journal • *International journal of Cardiology* Country • Italy Study design • Retrospective cohort study
Participants	Number of included patients • 889 Surgical specialty • Vascular surgery Age • Mean 69.9 years (SD 7.2) Male sex • 94% High-risk surgery • 100% Insulin-dependent diabetes mellitus • 0.9% History of ischaemic heart disease • 32.9% History of congestive heart failure • 1.6% History of cerebrovascular events • 12.3% Elevated creatinine • Not reported 0 RCRI factors

Ferrante 2019 *(Continued)*

	• Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: Prediction model made by the authors including dilated cardiopathy, ischaemic cardiopathy, cerebrovascular disease, peripheral artery disease • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: Prediction model made by the authors including previous MI, congestive heart failure and COPD • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition • Acute myocardial infarction or dysrhythmia or acute pulmonary oedema diagnosed by ECG, positive troponin and CK-MB, and echocardiography report when found Prediction horizon • Not reported
Analysis	Number of outcomes • 86 Handling missing data • No handling of missing data, complete case analysis Discrimination reported? • No Calibration reported?

Ferrante 2019 *(Continued)*

	• No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only AAA patients were included Domain 2: Predictors • High Justification: several RCRI items, including high creatinine value and congestive heart failure, had a different definition compared to the development paper Domain 3: Outcome • Low Justification: not applicable Overall judgement • High Justification: only a selected group of patients was included. Predictor definitions were defined differently from the predictor definitions in the development study. However, the outcome used was comparable to the development study.
Notes	

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	No	Several RCRI items, including high creatinine value and congestive heart failure, had a different definition compared to the development paper.
Domain 3: Outcome	Unclear	No information on how the endpoints were defined and assessed.
Domain 4: Analysis	No	Complete case analysis; low number of outcomes; no predictive performance measures were reported.
Overall judgement	No	Patient selection was appropriate. Furthermore, the number of outcomes was low, complete case analysis was performed and no predictive performance measures were reported.

Fisher 2008

Study characteristics	
General information	Objective

Fisher 2008 *(Continued)*

- Biomarkers compared

Journal

- *Anesthesia and Analgesia*

Country

- Canada

Study design

- Prospective cohort study

Participants	Number of included patients • 242 Surgical specialty • Noncardiac surgery Age • Median 66 years (range = 50 to 85 years) Male sex • 60% High-risk surgery • 37% Insulin-dependent diabetes mellitus • 3% History of ischaemic heart disease • 14% History of congestive heart failure • 4% History of cerebrovascular events • 5% Elevated creatinine • 2% 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 2 or more RCRI factors

Fisher 2008 *(Continued)*

	• 34%
Predictors	Predictor 1: All 4 pedal pulses absent or any palpated ankle-to-arm blood pressure index (AAI) • Objective: biomarkers compared • Category: patient characteristic • Scale: not applicable • Threshold: ≤ 0.9 • Assay/device: 5 MHx hand-held Doppler techniques (Nicolet Elite 5 mHz vascular model 110R Doppler, Nicolet Vascular, Golden, CO) Predictor 2: Doppler ankle to arm blood pressure index • Objective: biomarkers compared • Category: patient characteristic • Scale: dichotomous • Threshold: ≤ 0.9 on any of the 4 vessels • Assay/device: 5 MHx hand-held Doppler techniques (Nicolet Elite 5 mHz vascular model 110R Doppler, Nicolet Vascular, Golden, CO) Predictor 3: All 4 pedal pulses absent • Objective: biomarkers compared • Category: patient characteristic • Scale: dichotomous • Threshold: not applicable • Assay/device: 5 MHx hand-held Doppler techniques (Nicolet Elite 5 mHz vascular model 110R Doppler, Nicolet Vascular, Golden, CO) Predictor 4: Ankle to arm blood pressure index AAI ≥ 1.2 • Objective: biomarkers compared • Category: patient characteristic • Scale: dichotomous • Threshold: AAI ≥ 1.2 on any of the 4 vessels • Assay/device: 5 MHx hand-held Doppler techniques (Nicolet Elite 5 mHz vascular model 110R Doppler, Nicolet Vascular, Golden, CO)
Outcome	Outcome category • MACE Full outcome definition • Cardiac death, noncardiac death, nonfatal acute myocardial infarction, cardiogenic pulmonary oedema, primary cardiac arrest, ventricular fibrillation or complete heart block

Fisher 2008 *(Continued)*

	Prediction horizon • 7 days postoperatively
Analysis	Number of outcomes • 14 Handling missing data • No missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement: • Low Patient selected were generalisable to the patient population used in the RCRI development study. Predictor and outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.

Fisher 2008 *(Continued)*

Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no information on the handling of missing data; dichotomisation of AAI and RCRI; patients in which it was not possible to perform an AAI were excluded from the analysis
Overall judgement	No	Patient selection was appropriate. Predictors and outcomes were clearly defined and assessed. However, the number of outcomes was low and there was no information on handling of missing data and dichotomisation of predictors.

Fronczek 2019

Study characteristics	
General information	Objective • Prediction model compared Journal • *British Journal of Anaesthesia* Country • Poland Study design • Prospective cohort study
Participants	Number of included patients • 870 Surgical specialty • Vascular surgery Age • Mean 65.8 years (SD 8.5 years) Male sex • 80.9% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 15.2% History of ischaemic heart disease • 45.5% History of congestive heart failure

Fronczek 2019 *(Continued)*

- 11.1%

History of cerebrovascular events

- 10.7%

Elevated creatinine

- 1.1%

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: ASC-NSQIP-MICA • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: Recalibrated RCRI by Canadian Cardiovascular Society • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: Recalibrated ASC-NSQIP-MICA after logistic recalibration • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE

Fronczek 2019 *(Continued)*

	Full outcome definition • Nonfatal MI, nonfatal cardiac arrest or cardiac death Prediction horizon • 30-day events
Analysis	Number of outcomes • 76 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patients selected were generalisable to the patients included in the RCRI development studies Domain 2: Predictors • Low Justification: predictor definitions were clearly defined/assessed and comparable to the predictor definitions used in the RCRI development study Domain 3: Outcome • Low Justification: predictor definitions were clearly defined/assessed and comparable to the predictor definitions used in the RCRI development study Overall judgement: • Low Patient selected were generalisable to the patient population used in the RCRI development study. Predictor and outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement

Fronczek 2019 *(Continued)*

Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	No information on handling missing data and low number of outcomes.
Overall judgement	No	Patient selection was appropriate. Predictors and outcomes were clearly defined and assessed. However, the number of outcomes was low and there was no information on handling of missing data.

Gillmann 2014

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Critical Care Medicine* Country • Germany Study design • Prospective cohort study
Participants	Number of included patients • 455 Surgical specialty • Vascular surgery Age • Median 70 years (SD = not reported) Male sex • 80% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 38%

Gillmann 2014 *(Continued)*

	History of congestive heart failure • 8% History of cerebrovascular events • 22% Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 or more RCRI factors • 90% 2 or more RCRI factors • 49% 3 or more RCRI factors • 21%
Predictors	Predictor 1: High-sensitivity troponin T • Objective: added biomarker, biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Roche Diagnostics, Mannheim, Germany
Outcome	Outcome category • MACE Full outcome definition • Myocardial infarction (both spontaneous or due to ischaemic dysbalance), cardiovascular death, any new rise of cardiac troponin measurements prompted by clinical suspicion for acute coronary syndrome Prediction horizon • 30-day events
Analysis	Number of outcomes • 41 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported?

Gillmann 2014 *(Continued)*

	• No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selected were generalisable to the patient population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on RCRI predictor definitions Domain 3: Outcome • High Justification: the outcome definition MACE is different from the definition in the development study as it includes troponin elevation Overall judgement • High Justification: patient selection was appropriate, there was no/unclear information on predictor definitions/assessments and outcome definition was different compared to the RCRI development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on RCRI predictor definitions.
Domain 3: Outcome	No	Outcome definition is unclear and no information on the assessment of outcomes and blinding of assessors.
Domain 4: Analysis	No	Low number of outcomes; no information on missing data; exclusion of patients without blood samples; no calibration measures.
Overall judgement	No	Patient selection was appropriate. However, predictor and outcomes definitions were unclear and there was no information on predictor and outcome assessments. In addition, the number of outcomes was low, there was no information on missing data and no calibration was reported.

Glance 2018

Study characteristics	
General information	Objective

Glance 2018 *(Continued)*

- Prediction model compared

Journal

- *Anesthesiology*

Country

- USA

Study design

- Prospective existing registry

Participants	Number of included patients • 9015 Surgical specialty • Noncardiac surgery Age • < 65 years 60%, 65 to 74 years 23.7%, 75 to 84 years 13.4%, > 84 years 2.9% Male sex • 43.2% High-risk surgery • 31.2% Insulin-dependent diabetes mellitus • 6.1% History of ischaemic heart disease • 0.8% History of congestive heart failure • 0.5% History of cerebrovascular events • 6.5% Elevated creatinine • 2.3% 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors

Glance 2018 *(Continued)*

	• Not reported
Predictors	Predictor 1: ACS-NSQIP surgical risk score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: ACS-NSQIP-MICA • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Myocardial infarction and cardiac arrest Full outcome definition • Not applicable Prediction horizon • Not reported
Analysis	Number of outcomes • 91 Handling missing data • Assumption of normal value if missing Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selected were generalisable to the patient population used in the RCRI development study Domain 2: Predictors

Glance 2018 *(Continued)*

	• Unclear Justification: there is no information on predictor definitions and measurement Domain 3: Outcome • High Justification: MICA (myocardial infarction and cardiac arrest) differs from outcome used in development study Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	There is no information on predictor definitions and measurement.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes and exclusion of patients due to missing values or assumption of normal value in case of missing creatinine values. However, discrimination and calibration measures were appropriately reported.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, there was no/unclear information on predictor definitions/assessment. Furthermore, the number of outcomes was low and inappropriate exclusion of patients with missing values.

Golubovic 2018

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared, prediction model compared Journal • *BioMed Research International*; *Medical Principles and Practice* Country • Serbia Study design

Golubovic 2018 *(Continued)*

- Prospective cohort study

Participants	Number of included patients • 122 Surgical specialty • Vascular surgery Age • Mean 67 years (SD 4.5) Male sex • 77% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 15.6% History of ischaemic heart disease • 21.3% History of congestive heart failure • Not reported History of cerebrovascular events • 26.2% Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: V-POSSUM • Objective: added biomarker, biomarker compared • Category: prediction model • Scale: not applicable • Threshold: not applicable

Golubovic 2018 *(Continued)*

- Assay/device: not applicable

Predictor 2:

NT-proBNP

- Objective: added biomarkers, biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: chemiluminescence enzyme immunoassay technology (CLEIA) (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany)

Predictor 3:

High-sensitivity troponin I

- Objective: added biomarkers
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Magtration5 technology on a PATHFAST Immunoanalyser (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany)

Predictor 4:

V-POSSUM + NT-proBNP

- Objective: added biomarker
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: chemiluminescence enzyme immunoassay technology (CLEIA) (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany)

Predictor 5:

NT-proBNP + high-sensitivity troponin I

- Objective: added biomarkers, biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: chemiluminescence enzyme immunoassay technology (CLEIA) and Magtration5 technology on a PATHFAST Immunoanalyser (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany)

Predictor 6:

V-POSSUM + high-sensitivity troponin I

- Objective: added biomarker, biomarker compared
- Category: prediction model

Golubovic 2018 *(Continued)*

- Scale: not applicable
- Threshold: not applicable
- Assay/device: Magtration5 technology on a PATHFAST Immunoanalyser (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany)

Predictor 7:

V-POSSUM + NT-proBNP + high-sensitivity troponin I

- Objective: added biomarker, biomarker compared
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: chemiluminescence enzyme immunoassay technology (CLEIA) and Magtration5 technology on a PATHFAST Immunoanalyser (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany)

Predictor 8:

High-sensitivity troponin I + high-sensitivity CRP

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Magtration5 technology on a PATHFAST Immunoanalyser (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany) and immunoturbidimetry method on a Beckman Coulter AU 680 analyser (Beckman Coulter Inc., Brea, CA, USA)

Predictor 9:

High-sensitivity troponin I + CK-MB

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Magtration5 technology on a PATHFAST Immunoanalyser (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany) and immunoturbidimetry method on a Beckman Coulter AU 680 analyser (Beckman Coulter Inc., Brea, CA, USA)

Predictor 10:

NT-proBNP + high-sensitivity troponin I + high-sensitivity CRP

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: chemiluminescence enzyme immunoassay technology (CLEIA) and Magtration5 technology on a PATHFAST Immunoanalyser (Mitsubishi Chemical Europe GmbH, Düsseldorf, Germany) and immunoturbidimetry method on a Beckman Coulter AU 680 analyser (Beckman Coulter Inc., Brea, CA, USA)

Golubovic 2018 *(Continued)*

Outcome	Outcome category • MACE Full outcome definition • Acute myocardial infarction, cardiac arrhythmia, pulmonary oedema, acutely decompensated heart failure and cardiac arrest Prediction horizon • 30-day events and 90-day events
Analysis	Number of outcomes • 13 within 30 days and 29 within 90 days Handling missing data • Assumption of normal value if missing Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: no information on RCRI predictor definitions Domain 3: Outcome • High Justification: definition of MACE varies from the development cohort (includes cardiac arrhythmias) Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement

Golubovic 2018 *(Continued)*

Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information on RCRI predictor definitions.
Domain 3: Outcome	Unclear	No information how the individual items of the composite outcome were defined and whether blinding occurred.
Domain 4: Analysis	No	Low number of events, dichotomisation of continuous variable and no information on handling missing data.
Overall judgement	No	Patient selection was appropriate. There was no/unclear information on how predictors were defined/assessed. However, the number of outcomes was low and there was no information on missing data and no calibration was reported.

Gualandro 2017

Study characteristics	
General information	Objective • Added biomarkers, prediction model compared Journal • *Journal of Vascular Surgery* Country • Switzerland and Brazil Study design • Prospective cohort study
Participants	Number of included patients • 954 Surgical specialty • Vascular surgery Age • Median 70 years (IQR = 63 to 76) Male sex • 72% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 12%

Gualandro 2017 *(Continued)*

History of ischaemic heart disease

- 40%

History of congestive heart failure

- 16%

History of cerebrovascular events

- 24%

Elevated creatinine

- Not reported

0 RCRI factors

- 14.6%

1 RCRI factor

- 35.3%

2 RCRI factors

- 29.9%

3 or more RCRI factors

- 20.2%

Predictors	Predictor 1: Anaemia • Objective: added biomarker • Category: blood • Scale: dichotomous • Threshold: 12 g/L for women, 13 g/L for men • Assay/device: not specified Predictor 2: Smoking • Objective: added biomarkers • Category: patient characteristic • Scale: dichotomous • Threshold: smoking status included current and former smokers • Assay/device: not applicable Predictor 3: Vascular Study Group of New England Cardiac Risk Index (VSG-score) • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable

Gualandro 2017 *(Continued)*

	• Assay/device: not applicable Predictor 4: Vascular Study Group of New England Cardiac Risk Index (VSG-score) + anaemia • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition • Cardiac arrest, perioperative myocardial infarction, clinically relevant arrhythmia and acute heart failure (AHF) Prediction horizon • In-hospital events
Analysis	Number of outcomes • 120 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: patients in which no preoperative cardiologic consultation was performed were excluded Domain 2: Predictors • Low Justification: Predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • Low

Gualandro 2017 *(Continued)*

	Justification: Outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement: • Low Patient selection was inappropriate and not generalisable to the patient population used in the RCRI development study. However, predictor and outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	However, no information on the handling of missing data.
Overall judgement	Yes	Patient selection was appropriate. Predictors and outcomes were clearly defined and assessed. Study methodology was appropriate and clear.

Gualandro 2018

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *American Heart Journal* Country • Switzerland and Brazil Study design • Prospective cohort study
Participants	Number of included patients • 243 Surgical specialty • Vascular surgery Age

Gualandro 2018 *(Continued)*

- Median 68 years (IQR = 62 to 74)

Male sex

- 73%

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- 39%

History of congestive heart failure

- 16%

History of cerebrovascular events

- 25%

Elevated creatinine

- Not reported

0 RCRI factors

- 10%

1 RCRI factor

- 35%

2 RCRI factors

- 35%

3 or more RCRI factors

- 20%

Predictors	Predictor 1: High-sensitivity troponin T • Objective: added biomarker, biomarker compared • Category: blood • Scale: continuous, dichotomous • Threshold: > 14 ng/L • Assay/device: Elecsys, Roche diagnostics, Mannheim, Germany Predictor 2: High-sensitivity troponin I • Objective: added biomarker, biomarker compared • Category: blood • Scale: continuous, dichotomous

Gualandro 2018 *(Continued)*

	• Threshold: > 13 ng/L • Assay/device: ARCHITECT high-sensitivity STAT Troponin I assay, Abbott Laboratories Predictor 3: Sensitive cardiac troponin I • Objective: biomarker compared • Category: blood • Scale: continuous, dichotomous • Threshold: > 13 ng/L • Assay/device: s-cTnI, Siemens Ultra, Advia Centaur immunoassay system
Outcome	Outcome category • MACE Full outcome definition • Cardiac arrest, perioperative myocardial infarction, clinically relevant arrhythmia and acute heart failure (AHF) Prediction horizon 30-day events
Analysis	Number of outcomes • 58 Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selected were generalisable to the patient population used in the RCRI development study Domain 2: Predictors • Unclear Justification: unclear what definitions for the RCRI has been used Domain 3: Outcome • Low

Gualandro 2018 *(Continued)*

	Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement • Unclear Patient selected were generalisable to the patient population used in the RCRI development study. Outcomes definitions were clearly defined and comparable to definitions used in the RCRI development study. However, there was no information on the definition of predictors and their assessment.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	Unclear what definitions for the RCRI has been used.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; exclusion of patients (> 50%) without preoperative troponin; no measures of calibration or reclassification reported.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, predictors definitions were not clear/reported. Furthermore, the number of outcomes was low, inappropriate exclusion of patients with missing data and no calibration/reclassification measures were reported.

Gupta 2011

Study characteristics	
General information	Objective • Prediction model compared Journal • *Circulation* Country • USA Study design • Prospective existing registry
Participants	Number of included patients • 26,183 Surgical specialty

Gupta 2011 *(Continued)*

- Noncardiac surgery

Age

- Not reported

Male sex

- Not reported

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: ACS-NSQIP-MICA • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Myocardial infarction and cardiac arrest Full outcome definition

Gupta 2011 *(Continued)*

	• Not applicable Prediction horizon • 30-day events
Analysis	Number of outcomes • Not reported Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: no information on how the RCRI predictors were defined Domain 3: Outcome • High Justification: outcome is myocardial infarction and cardiac arrest, which is not the outcome for which the RCRI is developed Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on how the RCRI predictors were defined.

Gupta 2011 *(Continued)*

Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Number of outcomes is not reported; calibration and discrimination was reported. Development of a new model was reported and validated in a new model. However, no calibration plot was reported for the NSQIP-MICA model in the validation set and no information on the confidence intervals or standard errors was reported.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, predictor definitions were not clear/reported. Furthermore, the number of outcomes was not reported and inappropriate reporting of performance measures.

Handke 2019

Study characteristics	
General information	Objective • Biomarkers compared Journal • *Anesthesia and Analgesia* Country • Germany Study design • Prospective cohort study
Participants	Number of included patients • 38 Surgical specialty • Noncardiac surgery Age • Mean 69 years (SD 8.2 years) Male sex • 82% High-risk surgery • 42% Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported

Handke 2019 *(Continued)*

History of congestive heart failure

- 3%

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- 0%

1 RCRI factor

- 11%

2 RCRI factors

- 45%

3 or more RCRI factors

- 45%

Predictors	Predictor 1: High-sensitivity troponin T • Objective: biomarker compared • Category: blood • Scale: dichotomous • Threshold: 14 pg/ml • Assay/device: Cobas E4111, Roche Diagnostics, Mannheim, Germany Predictor 2: NT-proBNP • Objective: biomarker compared • Category: blood • Scale: dichotomous • Threshold: 300 ng/ml • Assay/device: Immulite, Siemens Health care Diagnostics, Erlangen, Germany Predictor 3: eGFR (KDIGO stage ≥ 3) • Objective: biomarker compared • Category: blood • Scale: dichotomous • Threshold: 60 ml/min • Assay/device: not applicable

Handke 2019 *(Continued)*

	Predictor 4: Presepsin • Objective: biomarker compared • Category: blood • Scale: dichotomous • Threshold: 184 pg/ml • Assay/device: noncompetitive immunoassay on the PATHFAST analyzer (LSI Medience, Tokyo, Japan)
Outcome	Outcome category • MACE Full outcome definition • Cardiovascular death, myocardial infarction, myocardial ischaemia or stroke Prediction horizon • 30-day events
Analysis	Number of outcomes • 5 Handling missing data • In case of missing laboratory values, last measurement carried forward Discrimination reported? • No Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only included participants with coronary artery disease Domain 2: Predictors • Unclear Justification: no information on how the RCRI predictors were defined Domain 3: Outcome • High Justification: outcome definition of MACE is different from the outcome in the development study as it includes e.g. stroke and myocardial ischaemia Overall judgement • High

Handke 2019 *(Continued)*

	Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on how the RCRI predictors were defined.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of included patients and outcomes, dichotomisation of continuous variables, no predictive performance measures reported that compared the RCRI with predictors.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, predictors definitions were not clear/reported. Furthermore, the number of outcomes was low, dichotomisation of continuous variables and inappropriate reporting of performance measures.

Handke 2020

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *European Journal of Anaesthesiology* Country • Germany Study design • Prospective cohort study
Participants	Number of included patients • 233 Surgical specialty • Noncardiac surgery Age • Median 69 years (IQR = 65 to 75 years) Male sex

Handke 2020 *(Continued)*

- 80%

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- 15%

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- 2%

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- 22%

1 RCRI factor

- 54%

2 RCRI factors

- 19%

3 or more RCRI factors

- 5%

Predictors	Predictor 1: High-sensitivity troponin T • Objective: added biomarker • Category: blood • Scale: not reported • Threshold: not applicable • Assay/device: Cobas E4111, Roche Diagnostics, Mannheim, Germany Predictor 2: NT-proBNP • Objective: added biomarker • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Immulite, Siemens Health care Diagnostics, Erlangen, Germany

Handke 2020 *(Continued)*

Predictor 3:

Presepsin

- Objective: added biomarker, biomarker compared
- Category: blood
- Scale: dichotomous
- Threshold: 184 pg/ml
- Assay/device: noncompetitive immunoassay on the PATHFAST analyser (LSI Medience, Tokyo, Japan)

Predictor 4:

High-sensitivity troponin T + NT-proBNP

- Objective: added biomarker
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Cobas E4111, Roche Diagnostics, Mannheim, Germany and Immulite, Siemens Health care Diagnostics, Erlangen, Germany

Predictor 5:

High-sensitivity troponin T + presepsin

- Objective: added biomarker
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Cobas E4111, Roche Diagnostics, Mannheim, Germany and noncompetitive immunoassay on the PATHFAST analyser (LSI Medience, Tokyo, Japan)

Predictor 6:

NT-proBNP + presepsin

- Objective: added biomarker
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Immulite, Siemens Health care Diagnostics, Erlangen, Germany and noncompetitive immunoassay on the PATHFAST analyser (LSI Medience, Tokyo, Japan)

Predictor 7:

NT-proBNP + high-sensitivity troponin T + presepsin

- Objective: added biomarker
- Category: blood
- Scale: continuous
- Threshold: not applicable

Handke 2020 *(Continued)*

	Assay/device: Immulite, Siemens Health care Diagnostics, Erlangen, Germany and Cobas E4111, Roche Diagnostics, Mannheim, Germany and noncompetitive immunoassay on the PATHFAST analyser (LSI Medience, Tokyo, Japan)
Outcome	Outcome category • MACE Full outcome definition • Cardiovascular death, myocardial infarction, myocardial ischaemia or stroke Prediction horizon • 30-day events
Analysis	Number of outcomes • 23 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only included participants with coronary artery disease Domain 2: Predictors • Unclear Justification: no information on how the RCRI predictors were defined Domain 3: Outcome • High Justification: outcome definition of MACE is different from the outcome in the development study Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Handke 2020 *(Continued)*

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on how the RCRI predictors were defined.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of events and dichotomisation of continuous predictors.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, predictors definitions were not clear/reported. Furthermore, the number of outcomes was low and dichotomisation of continuous variables.

Hwang 2015

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Circulation-Cardiovascular Imaging* Country • Republic of Korea Study design • Retrospective cohort study
Participants	Number of included patients • 844 Surgical specialty • Noncardiac surgery Age • Median 67 years (IQR = 58 to 73 years) Male sex • 62.4% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 2.7%

Hwang 2015 *(Continued)*

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- 20.5%

1 RCRI factor

- 59%

2 RCRI factors

- 18.6%

3 or more RCRI factors

- 1.9%

Predictors	Predictor 1: Duke Jeopardy score • Objective: added biomarker, biomarker compared • Category: imaging • Scale: dichotomous • Threshold: > 0 • Assay/device: Aquilion 64; Toshiba Medical Systems, Tokyo, Japan and SOMATOM Definition Flash; Siemens Medical Solution, Forchheim, Germany Predictor 2: Segment involvement score • Objective: added biomarker, biomarker compared • Category: imaging • Scale: dichotomous • Threshold: > 3 • Assay/device: Aquilion 64; Toshiba Medical Systems, Tokyo, Japan and SOMATOM Definition Flash; Siemens Medical Solution, Forchheim, Germany Predictor 3: Duke Jeopardy score + segment involvement score • Objective: added biomarker • Category: imaging

Hwang 2015 *(Continued)*

	• Scale: dichotomous • Threshold: not applicable • Assay/device: Aquilion 64; Toshiba Medical Systems, Tokyo, Japan and SOMATOM Definition Flash; Siemens Medical Solution, Forchheim, Germany
Outcome	Outcome category • MACE Full outcome definition • Myocardial infarction, pulmonary oedema or cardiac death Prediction horizon • 30-day events
Analysis	Number of outcomes • 25 Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • High Justification: coronary CTA was performed when the patient had not been evaluated for coronary artery disease, had > 1 clinical cardiovascular risk factors or taking cardiovascular medications, and had no contraindication for CT, such as renal failure, any potential of pregnancy, contraindications to β-blockade or nitroglycerin. Patients with previous revascularisation were excluded. Domain 2: Predictors • High Justification: pulmonary oedema was used for item in RCRI of congestive heart failure, definition of other items were not reported and no statement was made on how the CTA results were assessed. Domain 3: Outcome • Low Justification: outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study Overall judgement • High

Hwang 2015 *(Continued)*

	Justification: only a selected group of patients was included. Some predictor definitions were different compared to the RCRI development study and others were not defined at all. However, outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Coronary CTA was performed when the patient had not been evaluated for coronary artery disease, had > 1 clinical cardiovascular risk factors or taking cardiovascular medications, and had no contraindication for CT, such as renal failure, any potential of pregnancy, contraindications to β-blockade or nitroglycerin. Patients with previous revascularisation were excluded.
Domain 2: Predictors	No	Pulmonary oedema was used for item in RCRI of congestive heart failure, definition of other items were not reported and no statement was made on how the CTA results were assessed.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, no handling of missing data and dichotomisation of predictor data. No calibration reported.
Overall judgement	No	Outcome was clearly defined and assessed. However, patient selection was inappropriate. Predictor definitions were defined differently compared to the definitions used in the RCRI development study. Furthermore, the number of outcomes was low, dichotomisation of continuous variables and inappropriate reporting of performance measures.

James 2014

Study characteristics	
General information	Objective • Biomarkers compared Journal • *British Journal of Anaesthesia* Country • United Kingdom Study design • Prospective cohort study
Participants	Number of included patients • 83 Surgical specialty

James 2014 *(Continued)*

- Noncardiac surgery

Age

- Median 68 years (IQR = 63 to 75 years)

Male sex

- Not reported

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 or 1 RCRI factor

- 34%

2 or 3 RCRI factors

- 66%

Predictors	Predictor 1: ASA • Objective: biomarker compared • Category: patient characteristic • Scale: categorical • Threshold: not applicable • Assay/device: not applicable Predictor 2: BNP • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Architect i2000SR, Abbott Diagnostics, USA

James 2014 *(Continued)*

Predictor 3:

CRP

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Architect c16000, Abbott Diagnostics, USA

Predictor 4:

eGFR

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Roche diagnostics
- eGFR was calculated from age and serum creatinine with adjustment for ethnicity using the modification of diet in renal disease equation

Predictor 5:

Anaerobic threshold

- Objective: biomarker compared
- Category: patient characteristics
- Scale: continuous
- Threshold: 10.6 ml/min*kg
- Assay/device: cardiopulmonary exercise testing

Predictor 6:

Peak VO2

- Objective: biomarker compared
- Category: patient characteristics
- Scale: continuous
- Threshold: 14 ml/min*kg
- Assay/device: cardiopulmonary exercise testing

Outcome	Outcome category • MACE; postoperative complications Full outcome definition • MACE was defined as myocardial infarction, cardiogenic pulmonary oedema, cardiac arrest or complete heart block. Postoperative complications were defined as pneumonia, wound infection, paralytic ileus, acute kidney injury, myocardial infarction, anastomotic leak, cardiogenic pulmonary oedema, haemorrhage, limb ischaemia, urinary tract infection, stroke/transient ischaemic attack, cardiac arrest, other Prediction horizon

James 2014 *(Continued)*

	• 30-day events
Analysis	Number of outcomes • 9 MACE, 40 postoperative complications Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: no information on how the RCRI predictors were defined Domain 3: Outcome • Low Justification: Overall judgement: • Unclear Patient selected were generalisable to the patient population used in the RCRI development study. Outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study. However, this was not the case for predictors.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Patients unsuitability for CPET (cardiopulmonary exercise testing) were not included.
Domain 2: Predictors	Unclear	No information on how the RCRI predictors were defined.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.

James 2014 *(Continued)*

Domain 4: Analysis	No	Low number of outcomes and no handling of missing data; calibration and re-classification were not reported.
Overall judgement	No	Outcomes were clearly defined and assessed. However, patient selection was inappropriate, there was no/unclear information on predictor definitions and assessments. Furthermore, the number of outcomes was low and there was no information on missing data and no calibration was reported.

Jarai 2011

Study characteristics	
General information	Objective • Added biomarkers Journal • *American Journal of Cardiology* Country • Austria Study design • Prospective cohort study
Participants	Number of included patients • 198 Surgical specialty • Vascular surgery Age • Mean 69 years (SD 9 years) Male sex • 78.8% High-risk surgery • 82.3% Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • 5.1% History of cerebrovascular events

Jarai 2011 *(Continued)*

	• 17.7% Elevated creatinine • 0% 0 RCRI factors • 64.1% 1 or more RCRI factors • 35.9%
Predictors	Predictor 1: Copeptin • Objective: added biomarker • Category: blood • Scale: dichotomous • Threshold: 14 mg/dL • Assay/device: chemiluminescence assay (Brahms AG, Hennigsdorf, Germany) Predictor 2: NT-proBNP + copeptin • Objective: added biomarker • Category: blood • Scale: dichotomous • Threshold: 280 pg/mL and 14 mg/dL, respectively • Assay/device: chemiluminescence assay (Brahms AG, Hennigsdorf, Germany)
Outcome	Outcome category • MACE Full outcome definition • Cardiac death, nonfatal myocardial infarction and emergent coronary artery revascularisation Prediction horizon • 24 to 30 months after surgery
Analysis	Number of outcomes • 40 Handling missing data • No information on handling missing data Discrimination reported? • No Calibration reported? • No

Jarai 2011 *(Continued)*

	Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • High Justification: preoperative creatinine was deleted from the model as all patients with creatinines > 1.4 were excluded Domain 3: Outcome • High Justification: the outcome definition differed from the MACE definition in the development study Overall judgement • High Justification: patient selected were generalisable to the patient population used in the RCRI development study. There was no/unclear information on predictor definitions and outcome definition was different compared to the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Excluded were patients with acute coronary syndromes or evidence of myocardial ischaemia on stress tests (n = 4), decompensated heart failure (n = 2), aortic stenosis (n 2), atrial fibrillation (n = 17), kidney dysfunction (serum creatinine 1.4 mg/dl; n = 26), reduced left ventricular function (left ventricular ejection fraction 40%; n = 10)
Domain 2: Predictors	No	Preoperative creatinine was deleted from the model as all patients with creatinines > 1.4 were excluded
Domain 3: Outcome	No	Independent cardiologist had access to all available documents and clinical charts of each patient.
Domain 4: Analysis	No	Low number of outcomes, dichotomisation of predictors and no handling of missing data.
Overall judgement	No	Patient selection and outcome and predictor definitions/assessments were inappropriate. In addition, the number of outcomes was low, there was no information on the handling of missing data and predictors were dichotomised.

Karkos 2002

Study characteristics

Karkos 2002 *(Continued)*

General information	Objective • Added biomarkers, biomarkers compared Journal • *Journal of Vascular Surgery* Country • Greece Study design • Retrospective cohort study
Participants	Number of included patients • 77 Surgical specialty • Vascular surgery Age • Mean 71.9 years (SD 7.1 years) Male sex • 76.6% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 1% History of ischaemic heart disease • 58% History of congestive heart failure • 10% History of cerebrovascular events • 18% Elevated creatinine • 6% 0 RCRI factors • 0% 1 RCRI factor • 27.3% 2 RCRI factors • 53.2%

Karkos 2002 *(Continued)*

	3 of more RCRI factors • 19.4%
Predictors	Predictor 1: Left ventricular ejection fraction • Objective: added biomarker, biomarker compared • Category: imaging • Scale: dichotomous • Threshold: 50% • Assay/device: resting LVEF was routinely estimated with MUGA scan, and any evidence of disturbances in phase and wall images were noted as evidence of myocardial wall motion abnormality. MUGA scan was performed with a standard ECG-gated equilibrium technique after in vivo labelling of red blood cells with 600-MBq technetium-99m pertechnetate after stannous pyrophosphate priming (4 mg stannous fluoride and 6.8 mg sodium medronate reconstituted in 6 mL to 2 mL of this are administered for priming). Predictor 2: Wall abnormalities • Objective: added biomarker, biomarker compared • Category: imaging • Scale: dichotomous • Threshold: presence or absence • Assay/device: resting LVEF was routinely estimated with MUGA scan, and any evidence of disturbances in phase and wall images were noted as evidence of myocardial wall motion abnormality Predictor 3: Left ventricular ejection fraction + wall abnormalities • Objective: added biomarker, biomarker compared • Category: imaging • Scale: dichotomous • Threshold: not applicable • Assay/device: resting LVEF was routinely estimated with MUGA scan, and any evidence of disturbances in phase and wall images were noted as evidence of myocardial wall motion abnormality
Outcome	Outcome category • MACE Full outcome definition • Myocardial infarction, congestive heart failure, ventricular tachyarrhythmia, unstable angina Prediction horizon • 30-day events
Analysis	Number of outcomes • 11 Handling missing data

Karkos 2002 *(Continued)*

	• No information on handling missing data Discrimination reported? • No Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement: • Low Patient selected were generalisable to the patient population used in the RCRI development study. Predictor and outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Only patients undergoing the MUGA scan were included over a 4-year period.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; dichotomisation of predictors; no handling of missing data; no reporting of appropriate performance measures
Overall judgement	No	Inappropriate exclusion of patients without a MUGA scan. In addition, the number of outcomes was low, dichotomisation of prediction, no information

Karkos 2002 *(Continued)*

	on handling missing data and no reporting of appropriate performance measures. However, predictors and outcomes were clearly defined and assessed.

Katsanos 2015

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared, prediction model compared Journal • *Journal of Cardiovascular Medicine* Country • Greece Study design • Prospective cohort study
Participants	Number of included patients • 242 Surgical specialty • Orthopaedic surgery Age • Median 80 years (IQR = 74 to 85 years) Male sex • 25% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 5.4% History of ischaemic heart disease • 16.5% History of congestive heart failure • 11.2% History of cerebrovascular events • 19% Elevated creatinine • Not reported 0 RCRI factors

Katsanos 2015 *(Continued)*

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 of more RCRI factors

- Not reported

Predictors	Predictor 1: BNP • Objective: added biomarker, biomarker compared • Category: blood • Scale: dichotomous, continuous • Threshold: 149 ng/mL • Assay/device: chemiluminescent immunoassay - automated analyser (Architect 16200, Abbott laboratories, Illinois, USA) Predictor 2: Goldman index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: Fleisher/Eagle index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 4: Detsky index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable

Katsanos 2015 *(Continued)*

	Predictor 5: Functional capacity index • Objective: biomarker compared • Category: patient characteristic • Scale: continuous • Threshold: not applicable • Assay/device: simple questionnaire about everyday activities that determine the functional capacity of patients
Outcome	Outcome category • MACE; all-cause mortality Full outcome definition • MACE was defined as cardiac death, myocardial infarction and acute heart failure Prediction horizon • In-hospital events and 1-year events, respectively
Analysis	Number of outcomes • 20 MACE, 41 deaths Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: unclear what definitions for each of the RCRI predictors were used Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement:

Katsanos 2015 *(Continued)*

	• Unclear Patient selected were generalisable to the patient population used in the RCRI development study. Outcome definition was clearly defined/assessed and comparable to the definitions used in the RCRI development study. However, there was no/unclear information on predictor definitions.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing orthopaedic surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	Unclear what definitions for each of the RCRI predictors were used.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, dichotomisation of predictors and no handling of missing data.
Overall judgement	No	Appropriate patient selection and outcomes were clearly defined and assessed. However, predictor definitions were unclear/not reported, number of outcomes was low, dichotomisation of predictors and no information on handling missing data.

Kaw 2019

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Journal of Cardiothoracic and Vascular Anesthesia* Country • USA Study design • Retrospective cohort study
Participants	Number of included patients • 368 Surgical specialty • Noncardiac surgery Age • Not reported

Kaw 2019 *(Continued)*

Male sex

- Not reported

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 of more RCRI factors

- Not reported

Predictors	Predictor 1: Estimated metabolic equivalents (METS) • Objective: added biomarker, biomarker compared • Category: patient characteristic • Scale: continuous • Threshold: not applicable • Assay/device: not applicable Predictor 2: METS + positive stress test • Objective: added biomarker • Category: patient characteristic/imaging • Scale: not applicable • Threshold: not applicable • Assay/device: non-pharmacological (treadmill) stress test

Kaw 2019 *(Continued)*

	Predictor 3: METSe + positive stress test with no false negatives • Objective: added biomarker • Category: patient characteristic/imaging • Scale: not applicable • Threshold: not applicable • Assay/device: non-pharmacological (treadmill) stress test Predictor 4: Positive stress test • Objective: biomarker compared • Category: imaging • Scale: dichotomous • Threshold: not applicable • Assay/device: non-pharmacological (treadmill) stress test Predictor 5: Positive stress test with no false negatives • Objective: biomarker compared • Category: imaging • Scale: dichotomous • Threshold: not applicable • Assay/device: non-pharmacological (treadmill) stress test
Outcome	Outcome category • All-cause mortality and MACE; MACE; all-cause mortality; respiratory failure Full outcome definition • All-cause mortality and MACE was defined as myocardial infarction, congestive heart failure and mortality. MACE was defined as arrhythmia Prediction horizon • In-hospital and 30-day events for all-cause mortality and MACE, in-hospital events for MACE and respiratory failure and 1-year events for all-cause mortality
Analysis	Number of outcomes • 23 all-cause mortality and MACE, 21 MACE, 16 deaths, 11 respiratory failure Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported?

Kaw 2019 *(Continued)*

	• No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only patients who underwent preoperative stress testing were included which seems to be less healthy compared to development population Domain 2: Predictors • Unclear Justification: no information on how the RCRI items were defined and on how the predictors added/compared were assessed Domain 3: Outcome • High Justification: outcome differs from outcome in development study Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on how the RCRI items were defined and on how the predictors added/compared were assessed.
Domain 3: Outcome	No	No information on how endpoints were defined apart from ICD-codes and no information on blinding.
Domain 4: Analysis	No	Low number of outcomes and no information on handling missing outcomes.
Overall judgement	No	Patient selection was appropriate. However, outcome assessment was through ICD codes and there was no information on blinding. Predictor definitions were unclear/not reported, number of outcomes was low and no information on handling missing data.

Kertai 2005

Study characteristics	
General information	Objective

Kertai 2005 *(Continued)*

- Prediction model compared

Journal

- *Archives of Internal Medicine*

Country

- The Netherlands

Study design

- Retrospective cohort study

Participants	Number of included patients • 1537 Surgical specialty • Vascular surgery Age • Not reported Male sex • Not reported High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 of more RCRI factors

Kertai 2005 *(Continued)*

	• Not reported
Predictors	Predictor 1: RCRI with redefined high-risk surgery • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: low risk (carotid endarterectomy), low-intermediate risk (infrainguinal bypass surgery), high-intermediate risk (abdominal and thoracoabdominal aortic surgery) and high-risk (acute abdominal aortic aneurysm surgery) Predictor 2: RCRI with redefined high-risk surgery + clinical characteristics • Objective: added biomarker • Category: prediction model compared • Scale: not applicable • Threshold: not applicable • Assay/device: advanced age, type 2 (non–insulin-dependent) diabetes mellitus, chronic pulmonary disease, hypertension, beta-blocker and statin use, ischaemic heart disease and cerebrovascular disease
Outcome	Outcome category • All-cause mortality Full outcome definition • Not applicable Prediction horizon • In-hospital and 30-day events
Analysis	Number of outcomes • 103 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low

Kertai 2005 *(Continued)*

	Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • High Justification: outcome is all-cause mortality Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clear methodology and appropriate number of outcomes.
Domain 4: Analysis	Yes	Clear methodology and appropriate number of outcomes.
Overall judgement	Yes	Patient selection was appropriate, predictor and outcome definitions were clearly defined and comparable to the definitions used in the development study. In addition, methodology used was appropriate including the number of outcomes.

Kopec 2017

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Anesthesia & Analgesia* Country • USA

Kopec 2017 *(Continued)*

	Study design • Prospective cohort study
Participants	Number of included patients • 572 Surgical specialty • Noncardiac surgery Age • 64.9 years (SD 10.7 years) Male sex • 62.1% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 14.3% History of ischaemic heart disease • 56.4% History of congestive heart failure • 12.1% History of cerebrovascular events • 14% Elevated creatinine • Not reported 0 RCRI factors • 30.8% 1 RCRI factor • 43.9% 2 RCRI factors • 20.4% 3 of more RCRI factors • 4.9%
Predictors	Predictor 1: High-sensitivity troponin T • Objective: added biomarker, biomarker compared • Category: blood

Kopec 2017 *(Continued)*

- Scale: dichotomous
- Threshold: 14 ng/L
- Assay/device: Roche Diagnostics, Indianapolis, IN, USA

Predictor 2:

NT-proBNP

- Objective: added biomarker, biomarker compared
- Category: blood
- Scale: dichotomous
- Threshold: 300 ng/L
- Assay/device: Roche Diagnostics, Indianapolis, IN, USA

Predictor 3:

High-sensitivity troponin T +NT-proBNP

- Objective: added biomarker, biomarker compared
- Category: blood
- Scale: not applicable
- Threshold: not applicable
- Assay/device: Roche Diagnostics, Indianapolis, IN, USA

Predictor 4:

ASA

- Objective: biomarker compared
- Category: patient characteristic
- Scale: categorical
- Threshold: not applicable
- Assay/device: not applicable

Outcome	Outcome category • Myocardial infarction Full outcome definition • Not applicable Prediction horizon • Within 3 days after surgery
Analysis	Number of outcomes • 30 Handling missing data • Complete case analysis Discrimination reported? • Yes

Kopec 2017 *(Continued)*

	Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: the definition of each item of RCRI was unclear Domain 3: Outcome • High Justification: outcome is myocardial infarction, which is different from the MACE definition in the development study Overall judgement • High Justification: patient selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Only patients with known coronary artery disease or multiple risk factors for coronary artery disease were included.
Domain 2: Predictors	Unclear	The definition of each item of RCRI was unclear.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, patients with missing biomarker data were excluded and dichotomisation of predictor information.
Overall judgement	No	Patient selection was inappropriate and predictor definitions were unclear/not reported. In addition, the number of outcomes was low, inappropriate exclusion of patients with missing data and dichotomisation of predictors. However, outcomes were clearly defined and assessed.

Kumar 2001

Study characteristics	
General information	Objective • Prediction model compared Journal • *Journal of General Internal Medicine* Country • USA Study design • Prospective cohort study
Participants	Number of included patients • 1121 Surgical specialty • Noncardiac surgery Age • 66 years (SD 8.5 years) Male sex • 99% High-risk surgery • 37% Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • 25% History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported

Kumar 2001 *(Continued)*

	2 RCRI factors • Not reported 3 of more RCRI factors • Not reported
Predictors	Predictor 1: DVAMC (new prediction model) • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: Goldman index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: Detsky index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 4: Ashton • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 5: DVAMC + type of surgery • Objective: prediction model compared • Category: prediction model

Kumar 2001 *(Continued)*

	• Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 6: Detsky index + type of surgery • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition • Cardiac death, myocardial infraction, pulmonary oedema, cardiac arrest, and nonfatal ventricular tachycardia and ventricular fibrillation Prediction horizon • In-hospital events
Analysis	Number of outcomes • 91 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: all included patients had known or suspected cardiac disease Domain 2: Predictors • High Justification: different definitions of RCRI items compared to development study Domain 3: Outcome • Low

Kumar 2001 *(Continued)*

	Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement • High Justification: only a selected group of patients was included; predictor definitions were different compared to definitions used in the RCRI development study. However, outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	All included patients had known or suspected cardiac disease.
Domain 2: Predictors	No	Different definitions of RCRI items compared to development study.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcome, no information on handling missing data and no measures on calibration.
Overall judgement	No	Outcome was clearly defined and assessed. However, patient selection was inappropriate. Predictor definitions were defined differently compared to the definitions used in the RCRI development study. Furthermore, the number of outcomes was low, no information on handling missing data and inappropriate reporting of performance measures.

Leibowitz 2008

Study characteristics	
General information	Objective • Biomarkers compared Journal • *Cardiology* Country • Israel Study design • Prospective cohort study
Participants	Number of included patients • 44 Surgical specialty

Leibowitz 2008 *(Continued)*

- Noncardiac surgery

Age

- 77 years (SD 11.8 years)

Male sex

- Not reported

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 of more RCRI factors

- Not reported

Predictors	Predictor 1: BNP • Objective: biomarker compared • Category: blood • Scale: continuous and dichotomous • Threshold: 175, 330 and 386 pg/mL • Assay/device: ADVIA-Centaur BNP assay (Bayer Health-Care)
Outcome	Outcome category • All-cause mortality and MACE Full outcome definition

Leibowitz 2008 *(Continued)*

	• All-cause mortality, acute coronary syndrome and development/worsening of congestive heart failure Prediction horizon • 30-day events
Analysis	Number of outcomes • 15 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: patients were included if they had a clinical history of congestive heart failure on physical examination or known ejection fraction < 40% or severe aortic stenosis Domain 2: Predictors • Unclear Justification: the definition of each item of RCRI was unclear Domain 3: Outcome • High Justification: composition of MACE is very different from the definition of MACE in the development study Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Patients were included if they had a clinical history of congestive heart failure on physical examination or known ejection fraction < 40% or severe aortic stenosis.
Domain 2: Predictors	Unclear	The definition of each item of RCRI was unclear.

Leibowitz 2008 *(Continued)*

Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no information on the handling of missing data; no information on calibration measures.
Overall judgement	No	Outcome was clearly defined and assessed. However, patient selection was inappropriate. Predictor definitions were unclear/not reported. Furthermore, the number of outcomes was low, no information on handling missing data and inappropriate reporting of performance measures.

Makary 2010

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared, prediction model compared Journal • *Journal of the American College of Surgeons* Country • USA Study design • Prospective cohort study
Participants	Number of included patients • 594 Surgical specialty • Surgical specialty not specified Age • Not reported Male sex • 39.7% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • 6.3%

Makary 2010 *(Continued)*

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- 68.5%

1 RCRI factor

- 22.5%

2 RCRI factors

- 7.1%

3 of more RCRI factors

- 2.1%

Predictors	Predictor 1: Frailty • Objective: added biomarker • Category: patient characteristic • Scale: categorical • Threshold: not applicable • Assay/device: age-associated decline in 5 domains, each domain yields 1 point: shrinking (weight loss) defined as unintended weight loss > 10 pounds, decreased grip strength, exhaustion, low physical activity, slowed walking speed Predictor 2: ASA • Objective: biomarker compared • Category: patient characteristic • Scale: categorical • Threshold: not applicable • Assay/device: not applicable Predictor 3: ASA + frailty • Objective: biomarker compared • Category: patient characteristic • Scale: not applicable • Threshold: not applicable • Assay/device: frailty was defined as age-associated decline in 5 domains, each domain yields 1 point: shrinking (weight loss) defined as unintended weight loss > 10 pounds, decreased grip strength, exhaustion, low physical activity, slowed walking speed

Makary 2010 *(Continued)*

	Predictor 4: Eagle score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 5: Eagle score + frailty • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: frailty was defined as age-associated decline in 5 domains, each domain yields 1 point: shrinking (weight loss) defined as unintended weight loss > 10 pounds, decreased grip strength, exhaustion, low physical activity, slowed walking speed
Outcome	Outcome category • Surgical complications; discharge to a nursing facility Full outcome definition • Not applicable Prediction horizon • 30-day events; in-hospital events
Analysis	Number of outcomes • 34 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: not specified what type of surgery the patients underwent and patients with previous stroke were excluded from the analysis Domain 2: Predictors

Makary 2010 *(Continued)*

	• Unclear Justification: the definition of each item of RCRI was unclear Domain 3: Outcome • High Justification: outcome includes surgical complications and presumably this also involves noncardiac complications, which differs from the MACE definition from the development study Overall judgement • High Justification: the type of surgery was not specified and inappropriate exclusion of patients with stroke. In addition, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Not specified what type of surgery the patients underwent and patients with previous stroke were excluded from the analysis.
Domain 2: Predictors	Unclear	The definition of each item of RCRI was unclear.
Domain 3: Outcome	No	No outcome definitions and no information on blinding.
Domain 4: Analysis	No	No information on the number of outcomes, how missing data were handled and no reporting of calibration measures.
Overall judgement	No	Patient selection was inappropriate. Predictor and outcome definitions were unclear/not reported. Furthermore, the number of outcomes was low, no information on handling missing data and inappropriate reporting of performance measures.

Markovic 2018

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared, prediction model compared Journal • E*uropean Geriatric Medicine*; *Aging Clinical and Experimental Research* Country • Serbia Study design • Prospective cohort study

Markovic 2018 *(Continued)*

Participants	Number of included patients • 78 Surgical specialty • Noncardiac surgery Age • 72 years (SD 6.9 years) Male sex • 47.4% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 7.7% History of ischaemic heart disease • 32.0% History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 20.5% 1 RCRI factor • 47.4% 2 RCRI factors • 18.0% 3 of more RCRI factors • 14.1%
Predictors	Predictor 1: Survivin • Objective: added biomarker, biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Quantikine Human Survivin ELISA Kit, R&D systems, Minneapolis, MM, USA

Markovic 2018 *(Continued)*

Predictor 2:

Heart-type fatty acid binding protein (H-FABP)

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: HFABP, Reagents Randox, Crumlin, UK

Predictor 3:

High-sensitivity CRP

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: cRP Latex, and Beckmann Coulter, Nyon, Switzerland

Predictor 4:

Survivin + high-sensitivity CRP

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Quantikine Human Survivin ELISA Kit, R&D systems, Minneapolis, MM, USA and CRP Latex, and Beckmann Coulter, Nyon, Switzerland

Predictor 5:

Survivin + H-FABP

- Objective: biomarker compared
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: HFABP, Reagents Randox, Crumlin, UK and CRP Latex, and Beckmann Coulter, Nyon, Switzerland

Predictor 6:

ASA

- Objective: added biomarkers, biomarker compared
- Category: patient characteristic
- Scale: categorical
- Threshold: not applicable
- Assay/device: not applicable

Markovic 2018 *(Continued)*

Predictor 7:

ASA + SORT + ACS-NSQIP surgical risk score

- Objective: added biomarkers
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: not applicable

Predictor 8:

ACS-NSQIP surgical risk score

- Objective: prediction model compared
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: not applicable

Predictor 9:

SORT

- Objective: prediction model compared
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: not applicable

Predictor 10:

ASA + SORT

- Objective: prediction model compared
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: not applicable

Predictor 11:

ASA + ACS-NSQIP surgical risk score

- Objective: prediction model compared
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: not applicable

Outcome	Outcome category • All-cause mortality

Markovic 2018 *(Continued)*

	Full outcome definition • Not applicable Prediction horizon • In-hospital events
Analysis	Number of outcomes • 14 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • High Justification: outcome is all-cause mortality and not MACE Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.

Markovic 2018 *(Continued)*

Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no information on the handling of missing data; multiple testing issue; no information on calibration/reclassification measures.
Overall judgement	No	Patient selection was appropriate. Predictors and outcomes were clearly defined and assessed. However, the number of outcomes was low, multiple comparisons were reported, there was no information on missing data and no calibration was reported.

Mauermann 2016

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Anesthesia & Analgesia* Country • Switzerland Study design • Prospective existing RCT
Participants	Number of included patients • 190 Surgical specialty • Noncardiac surgery Age • 72 years (SD 8 years) Male sex • 76% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 8% History of ischaemic heart disease • 75%

Mauermann 2016 *(Continued)*

History of congestive heart failure

- 4%

History of cerebrovascular events

- 12%

Elevated creatinine

- Not reported

0 RCRI factors

- 53%

1 RCRI factor

- 37%

2 RCRI factors

- 8%

3 of more RCRI factors

- 2%

Predictors	Predictor 1: Copeptin • Objective: added biomarker, biomarker compared • Category: blood • Scale: dichotomous • Threshold: 9.6 pmol/L; 14 pmol/L • Assay/device: Thermo Fisher Scientific Clinical Diagnostics BRAHMS GmbH, Henningsdorf, Germany Predictor 2: Age + sex + copeptin • Objective: added biomarker • Category: blood; patient characteristic • Scale: not applicable • Threshold: not applicable • Assay/device: Thermo Fisher Scientific Clinical Diagnostics BRAHMS GmbH, Henningsdorf, Germany Predictor 3: NT-proBNP • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Elecsys, Roche Diagnostics, Rotkreuz, Switzerland

Mauermann 2016 *(Continued)*

	Predictor 4: ACS-NSQIP MICA • Objective: prediction model compared • Category: prediction model • Scale: dichotomous • Threshold: 1.52% • Assay/device: not applicable
Outcome	Outcome category • Troponin elevation Full outcome definition • Cardiac troponin T level ≥ 0.03 µg/L without evidence of an alternative explanation of troponin elevation Prediction horizon • First or second postoperative day
Analysis	Number of outcomes • 33 Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: no information on RCRI predictor definition Domain 3: Outcome • High Justification: outcome is myocardial injury (MINS) and not MACE
Notes	—

Mauermann 2016 *(Continued)*

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Only high-risk patients, i.e. patients with a history of coronary artery disease or patients having two risk factors for coronary artery disease were included.
Domain 2: Predictors	Unclear	No information on RCRI predictor definition.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, complete case analysis and dichotomisation of predictors.
Overall judgement	No	Outcome was clearly defined and assessed. However, patient selection was inappropriate as only high-risk patients were included. Predictor definitions were unclear/not reported. Furthermore, the number of outcomes was low, dichotomisation of continuous variables and complete case analysis was performed.

McAlister 2015

Study characteristics	
General information	Objective • Prediction model compared Journal • *Journal of Thrombosis and Haemostasis* Country • Canada, USA, Spain, Brazil, Colombia, Malaysia, Hong Kong, South Africa, India, England, Peru, France, Australia Study design • Prospective cohort study
Participants	Number of included patients • 961 Surgical specialty • Noncardiac surgery Age • Median 76 years (IQR not reported) Male sex • 54.5% High-risk surgery

McAlister 2015 *(Continued)*

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- 20.5%

Elevated creatinine

- Not reported

0-1 RCRI factors

- 64.6%

2 RCRI factors

- 20.7%

3 of more RCRI factors

- 14.7%

Predictors	Predictor 1: $CHADS_2$ • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: $CHADS_2$-Vasc • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: R_2CHADS_2 • Objective: prediction model compared • Category: prediction model

McAlister 2015 *(Continued)*

	• Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Stroke, all-cause mortality, stroke or all-cause mortality Full outcome definition • Not applicable Prediction horizon • 30-day events
Analysis	Number of outcomes • 47 Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • High Justification: all patients had preoperative history of AF Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • High Justification: outcome is composite of stroke and all-cause mortality and not MACE Overall judgement • High Justification: predictors were clearly defined and comparable as used in the development study. However, only a selected group of patients were included and the outcome used was different from MACE in the development study.
Notes	—

McAlister 2015 *(Continued)*

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, complete case analysis and no calibration measures reported.
Overall judgement	No	Patient selection was appropriate. Predictors and outcomes were clearly defined and assessed. However, the number of outcomes was low, complete case analysis was reported and no calibration was reported.

McAlister 2020

Study characteristics	
General information	Objective • Prediction model compared Journal • *Anesthesia* Country • Canada, USA, Spain, Brazil, Colombia, Malaysia, Hong Kong, South Africa, India, England, Peru, France, Australia Study design • Prospective cohort study
Participants	Number of included patients • 2088 Surgical specialty • Noncardiac surgery Age • Mean 73.6 years (SD 10.1 years) Male sex • 59% High-risk surgery • Not reported

McAlister 2020 *(Continued)*

	Insulin-dependent diabetes mellitus • 18% History of ischaemic heart disease • 44% History of congestive heart failure • Not reported History of cerebrovascular events • 23% Elevated creatinine • Not reported 0 to 1 RCRI factors • 63.7% 2 RCRI factors • 22.4% 3 of more RCRI factors • 13.9%
Predictors	Predictor 1: $CHADS_2$ • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: $CHADS_2$-Vasc • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: R_2CHADS_2 • Objective: prediction model compared • Category: prediction model • Scale: not applicable

McAlister 2020 *(Continued)*

	• Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE, stroke, all-cause mortality, stroke or all-cause mortality, cardiovascular mortality, troponin elevation (MINS), congestive heart failure, nonfatal cardiac arrest Full outcome definition • MACE was defined as cardiovascular mortality, stroke, MINS due to ischaemia, heart failure or nonfatal cardiac arrest. MACE was also included as a secondary outcome excluding MINS from this definition. Prediction horizon • 30-day events
Analysis	Number of outcomes • 607 MACE; 84 deaths; number of other outcomes were not reported Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • High Justification: all patients had preoperative history of AF Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • High Justification: MACE outcome also includes stroke and troponin elevation (MINS) and is therefore different from the MACE definition in the development study Overall judgement • High Justification: predictors were clearly defined and comparable as used in the development study. However, only a selected group of patients were included and the outcome used was different from MACE in the development study.

McAlister 2020 *(Continued)*

Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Complete case analysis and categorisation of prediction models.
Overall judgement	No	Patient selection was appropriate. Predictors and outcomes were clearly defined and assessed. However, complete case analysis was reported and categorisation of prediction models.

McIlroy 2014

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *British Journal of Anaesthesia* Country • Australia and Hong Kong Study design • Prospective cohort study
Participants	Number of included patients • 238 Surgical specialty • Noncardiac surgery Age • Not reported Male sex • Not reported High-risk surgery • Not reported

McIlroy 2014 *(Continued)*

	Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 of more RCRI factors • Not reported
Predictors	Predictor 1: RH-PAT index (endothelial function) • Objective: added biomarker, biomarker compared • Category: patient characteristic • Scale: continuous • Threshold: not applicable • Assay/device: EndoPAT 2000 device
Outcome	Outcome category • Troponin elevation (MINS), all-cause mortality and MACE Full outcome definition • All-cause mortality and MACE was defined the composite of coronary artery intervention or all-cause mortality within 30 days of surgery or troponin ≥ 0.04 mg/L within 3 days of surgery Prediction horizon • Within 3 days after surgery; 30-day events
Analysis	Number of outcomes • 35 troponin elevations; 38 MACE or deaths Handling missing data

McIlroy 2014 *(Continued)*

- Complete case analysis

Discrimination reported?

- Yes

Calibration reported?

- No

Reclassification reported?

- Yes

PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on predictor definition of the RCRI items Domain 3: Outcome • High Justification: outcome is troponin elevation (MINS) or all-cause mortality and MACE, which is different from the MACE definition in the development study Overall judgement: • Unclear Patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on predictor definition of the RCRI items.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, complete case analysis and no reporting of calibration measures.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, prediction definitions were unclear/not reported. In addition, the number of outcomes was low, complete case analysis was performed and no calibration was reported.

Mercantini 2012

Study characteristics	
General information	Objective • Biomarkers compared Journal • *World Journal of Surgery* Country • Italy Study design • Prospective cohort study
Participants	Number of included patients • 205 Surgical specialty • General surgery Age • Mean 64.1 years (range = 18 to 93 years) Male sex • 46.3% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 16.7% History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 54.1% 1 RCRI factor

Mercantini 2012 *(Continued)*

	• 39.7% 2 RCRI factors • 6.2% 3 of more RCRI factors • Not reported
Predictors	Predictor 1: BNP • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: point of care Triage BNP test (Biosite, San Diego, CA, USA)
Outcome	Outcome category • MACE Full outcome definition • Angina pectoris, ST elevation myocardial infarction, non-ST elevation myocardial infarction, troponin elevation, cardiogenic dyspnoea with findings of heart failure, acute arrhythmia, hypertensive event and cardiac death Prediction horizon • 30-day events
Analysis	Number of outcomes • 31 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear

Mercantini 2012 *(Continued)*

	Justification: no information on predictor definition of the RCRI items and for history of ischaemic disease, another definition was used Domain 3: Outcome • High Justification: MACE definition is highly different from the MACE definition in the development study Overall judgement: • Low Patient selected were generalisable to the patient population used in the RCRI development study. However, no/unclear information on predictor definitions for some items and other predictors of the original RCRI were not included or had a different definition. In addition, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on predictor definition of the RCRI items and for history of ischaemic disease, another definition was used.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, no information on handling missing data and no reporting of calibration/reclassification measures.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, no/unclear information on predictor definitions for some items and other predictors of the original RCRI were not included or had a different definition. In addition, the number of outcomes was low and there was no information on missing data and no calibration was reported.

Moodley 2013

Study characteristics	
General information	Objective • Prediction model compared Journal • *South African Medical Journal* Country • South Africa Study design

Moodley 2013 *(Continued)*

	• Prospective cohort study
Participants	Number of included patients • 788 Surgical specialty • Vascular surgery Age • Mean 58.3 years (SD 14.2 years) Male sex • 65% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 34.9% History of congestive heart failure • 4.7% History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 of more RCRI factors • Not reported
Predictors	Predictor 1: SAVS-CRI (South African Vascular Surgery Cardiac Risk Index) • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable

Moodley 2013 *(Continued)*

	• Assay/device: not applicable
Outcome	Outcome category • All-cause mortality and MACE Full outcome definition • All-cause mortality or perioperative troponin elevation Prediction horizon • 30-day events
Analysis	Number of outcomes • 136 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Low Justification: Domain 3: Outcome • High Justification: outcome used in this study is highly different from the MACE definition in the development study Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Moodley 2013 *(Continued)*

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	Clear methodology and appropriate number of outcomes.
Overall judgement	Yes	Patient selection was appropriate, predictor and outcome definitions were clearly defined and comparable to the definitions used in the development study. In addition, methodology used was appropriate including the number of outcomes.

Neary 2007

Study characteristics	
General information	Objective • Prediction model compared Journal • *British Journal of Surgery* Country • United Kingdom Study design • Prospective cohort study
Participants	Number of included patients • 2349 Surgical specialty • Noncardiac surgery Age • Mean 47 years (SD not reported) Male sex • 52.5% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported

Neary 2007 *(Continued)*

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- 45.6%

1 RCRI factor

- 44.9%

2 RCRI factors

- 7.7%

3 of more RCRI factors

- 1.9%

Predictors	Predictor 1: POSSUM • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: ACS-NSQIP surgical risk score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: Biochemistry and Haematology Outcome Models • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable

Neary 2007 *(Continued)*

	• Assay/device: not applicable
Outcome	Outcome category • All-cause mortality Full outcome definition • Not applicable Prediction horizon • 30-day events
Analysis	Number of outcomes • 141 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: inclusion of emergency surgery patients and broad range in ages Domain 2: Predictors • Unclear Justification: predictor definitions not described Domain 3: Outcome • High Justification: outcome was all-cause mortality and not MACE Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement

Neary 2007 *(Continued)*

Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	Predictor definitions not described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	Adequate sample size, no information on missing data but likely there were no missing data because of the prospective nature of the study.
Overall judgement	Unclear	Patient selection was appropriate. Outcome definition was clearly defined/assessed and clear study methodology used was used with appropriate the number of outcomes. However, there was no/unclear information on predictor definitions.

Noordzij 2006

Study characteristics	
General information	Objective • Added biomarkers Journal • *American Journal of Cardiology* Country • The Netherlands Study design • Retrospective cohort study
Participants	Number of included patients • 28,457 Surgical specialty • Noncardiac surgery Age • Median 60.1 years (IQR = 49.1 to 71.2 years) Male sex • Not reported High-risk surgery • 43.4% Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease

Noordzij 2006 *(Continued)*

	• 2.7% History of congestive heart failure • 0.6% History of cerebrovascular events • Not reported Elevated creatinine • 0.6% 0 RCRI factors • 95% 1 RCRI factor • 4.3% 2 RCRI factors • 0.6% 3 of more RCRI factors • 0.1%
Predictors	Predictor 1: ECG abnormalities • Objective: added biomarkers • Category: imaging • Scale: dichotomous • Threshold: not applicable • Assay/device: not applicable Predictor 2: Age • Objective: added biomarker • Category: patient characteristic • Scale: not reported • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Cardiovascular death Full outcome definition • Not applicable Prediction horizon • 30-day events

Noordzij 2006 *(Continued)*

Analysis	Number of outcomes • 199 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only patients at high risk for CAD included Domain 2: Predictors • High Justification: predictor definitions very different from the development study Domain 3: Outcome • High Justification: outcome was cardiovascular death and not MACE Overall judgement • High Justification: only a selected group of patients was included; predictors of the original RCRI were not included or had a different definition. In addition, the outcome definition used was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	No	Predictor definitions very different from the development study.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	No information on handling of missing data and calibration/reclassification not assessed.

Noordzij 2006 *(Continued)*

Overall judgement	No	Patient selection was appropriate and outcomes was clearly defined and assessed. Predictor definitions were defined differently compared to the definitions used in the RCRI development study. Furthermore, there was no information on handling of missing data and inappropriate reporting of performance measures.

Pandey 2015

Study characteristics	
General information	Objective • Added biomarkers Journal • *American Journal of Cardiology* Country • USA Study design • Prospective existing registry
Participants	Number of included patients • 1568 Surgical specialty • Noncardiac surgery Age • Median 70 years (IQR = 62 to 77 years) Male sex • 64.2% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • 11.6% History of cerebrovascular events • 29% Elevated creatinine

Pandey 2015 *(Continued)*

	• 9.3% 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 of more RCRI factors • Not reported
Predictors	Predictor 1: History of preoperative stable angina • Objective: added biomarkers • Category: patient characteristic • Scale: dichotomous • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Myocardial infarction or cardiac arrest Full outcome definition • Not applicable Prediction horizon • 30-day events
Analysis	Number of outcomes • 87 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only participants with recent myocardial infarction were included

Pandey 2015 *(Continued)*

	Domain 2: Predictors • Unclear Justification: no information on predictor definitions Domain 3: Outcome • High Justification: outcome was different from the MACE definition used in the development study Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on predictor definitions.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no information on handling missing data; no reporting of calibration/reclassification measures.
Overall judgement	No	Patient selection was appropriate and outcomes was clearly defined and assessed. Predictor definitions were unclear/not reported. Furthermore, the number of outcomes was low, there was no information on handling of missing data and inappropriate reporting of performance measures.

Pantoja 2014

Study characteristics	
General information	Objective • Prediction model compared Journal • *Revista Colombiana de Anestesiologia* Country • Cuba Study design • Cohort study

Pantoja 2014 *(Continued)*

Participants	Number of included patients • 88 Surgical specialty • Noncardiac surgery Age • 39 to 45 years = 20.5% and 50 to 69 years = 30.5% Male sex • 59% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • 30.7%
Predictors	Predictor 1: Goldman index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable

Pantoja 2014 *(Continued)*

	Predictor 2: Detsky index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition • Cardiac arrhythmias, ST-T changes, cardiorespiratory arrest, angina pectoris, acute heart failure, cardiogenic death Prediction horizon • In-hospital events
Analysis	Number of outcomes • 56 Handling missing data • No information on handling missing data Discrimination reported? • No Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on how the RCRI predictors were defined, when the model was used Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study

Pantoja 2014 *(Continued)*

	Overall judgement: • Unclear Patient selected were generalisable to the patient population used in the RCRI development study. Outcome definition was clearly defined/assessed and comparable to the definitions used in the RCRI development study. However, there was no/unclear information on predictor definitions.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on how the RCRI predictors were defined and when the model was used.
Domain 3: Outcome	Unclear	No definitions for each of the composite outcomes and no information whether the assessors were blinded for the predictor variables.
Domain 4: Analysis	No	Low number of outcomes, complete case analysis, only sensitivity and specificity reported and no performance measures on discrimination, calibration and reclassification.
Overall judgement	No	Patient selection was appropriate. However, outcome and predictor definitions were unclear/not reported. In addition, the number of outcomes was low, complete case analysis was performed and inappropriate reporting on performance measures.

Park 2011

Study characteristics	
General information	Objective • Biomarkers compared Journal • *Sunhwangi* Country • Republic of Korea Study design • Prospective cohort study
Participants	Number of included patients • 1923 Surgical specialty • Noncardiac surgery

Park 2011 *(Continued)*

Age

- Median 68 years (IQR = 61 to 73 years)

Male sex

- 61.6%

High-risk surgery

- 42.3%

Insulin-dependent diabetes mellitus

- 3.5%

History of ischaemic heart disease

- 22.7%

History of congestive heart failure

- 3.2%

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 of more RCRI factors

- Not reported

Predictors	Predictor 1: NT-proBNP • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Elecsys pro-BNP reagent kit (Roche Diagnostics, Indianapolis, In, USA) Predictor 2: Left ventricular ejection fraction • Objective: biomarker compared • Category: imaging

Park 2011 *(Continued)*

- Scale: continuous
- Threshold: not applicable
- Assay/device: 2-D transthoracic echocardiography (Vivid 7, GE Medical Systems, Milwaukee, CA, USA)

Predictor 3:

Regional wall motion index

- Objective: biomarker compared
- Category: imaging
- Scale: continuous
- Threshold: not applicable
- Assay/device: 2-D transthoracic echocardiography (Vivid 7, GE Medical Systems, Milwaukee, CA, USA)

Predictor 4:

Left atrial volume index

- Objective: biomarker compared
- Category: imaging
- Scale: continuous
- Threshold: not applicable
- Assay/device: 2-D transthoracic echocardiography (Vivid 7, GE Medical Systems, Milwaukee, CA, USA)

Predictor 5:

E/E' (transmitral early diastolic velocity/tissue Doppler mitral annular early diastolic velocity)

- Objective: biomarker compared
- Category: imaging
- Scale: continuous
- Threshold: not applicable
- Assay/device: 2-D transthoracic echocardiography (Vivid 7, GE Medical Systems, Milwaukee, CA, USA)

Outcome	Outcome category • MACE Full outcome definition • Myocardial infarction, development of pulmonary oedema or primary cardiovascular death Prediction horizon • In-hospital events
Analysis	Number of outcomes • 280 Handling missing data • Complete case analysis Discrimination reported? • Yes

Park 2011 *(Continued)*

	Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only patients referred for cardiac testing were included in this study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement • High Justification: only a selected group of patients was included, that was not generalisable to the patient population used in the RCRI development study. However, predictors and outcomes were clearly defined/assessed and comparable as used in the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Patients without an echocardiography, with moderate to severe valvular stenosis and with a preoperative creatinine ≥ 2.0 mg/dL were excluded. Patients underwent echocardiography at the discretion of the physician or if they had 2 or more of the following cardiovascular risk factors: diabetes mellitus, hypertension, aged 65 years and older, current smoking status or hypercholesterolaemia.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	However, no information on handling missing data and no reporting of calibration and reclassification measures.
Overall judgement	No	Patient selection was inappropriate resulting in a more high-risk population compared to the RCRI development study. However, predictor and outcome definitions were clearly defined and assessed. In addition, methodology used was appropriate, although there was no information on the handling of missing data and no reporting of calibration/reclassification measures.

Parmar 2010

Study characteristics	
General information	Objective • Biomarkers compared, prediction model compared Journal • *Vascular & Endovascular Surgery* Country • United Kingdom Study design • Retrospective cohort study
Participants	Number of included patients • 334 Surgical specialty • Vascular surgery Age • Mean 70 years (SD 9.9 years) Male sex • 67% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 5.5% History of ischaemic heart disease • 34% History of congestive heart failure • 7.8% History of cerebrovascular events • 45% Elevated creatinine • 7.8% 0 RCRI factors • Not reported 1 RCRI factor

Parmar 2010 *(Continued)*

	• Not reported 2 RCRI factors • Not reported 3 of more RCRI factors • Not reported
Predictors	Predictor 1: ASA • Objective: biomarker compared • Category: patient characteristic • Scale: categorical • Threshold: not applicable • Assay/device: not applicable Predictor 2: Eagle score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: P-POSSUM • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 4: Age > 80 years old + ischaemic heart disease • Objective: biomarker compared • Category: patient characteristic • Scale: dichotomous • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition

Parmar 2010 *(Continued)*

	• Myocardial infarction, coronary revascularisation, sudden death and left ventricular failure Prediction horizon • 30-day events
Analysis	Number of outcomes • 18 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: all patients were started on statins and beta-blockade was initiated if not contraindicated. Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement • High Justification: only a selected group of patients was included, that was not generalisable to the patient population used in the RCRI development study. However, predictors and outcomes were clearly defined/assessed and comparable as used in the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	All patients were started on statins and beta-blockade was initiated if not contraindicated.

Parmar 2010 *(Continued)*

Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no information on the handling of missing data; a new prediction model was developed based on univariable analysis; no reporting of calibration/reclassification measures.
Overall judgement	No	Predictors and outcomes were clearly defined and assessed. However, patient selection was inappropriate, as all patients were initiated on drug therapy. In addition, the number of outcomes was low and there was no information on missing data and no calibration was reported.

Peterson 2016

Study characteristics	
General information	Objective • Prediction model compared Journal • *American Journal of Cardiology* Country • USA Study design • Retrospective cohort study
Participants	Number of included patients • 1098 Surgical specialty • Orthopaedic surgery Age • Mean 63 years (SD 11 years) Male sex • 40% High-risk surgery • 0% Insulin-dependent diabetes mellitus • 2.8% History of ischaemic heart disease • 12.3%

Peterson 2016 *(Continued)*

	History of congestive heart failure • 3% History of cerebrovascular events • 5.3% Elevated creatinine • 1% 0 RCRI factors • 80.6% 1 RCRI factor • Not reported 2 RCRI factors • Not reported 2 or more RCRI factors • 19.4%
Predictors	Outcome category • Myocardial infarction and cardiac arrest Full outcome definition • Not applicable Prediction horizon • 30-day events
Outcome	Outcome category • Myocardial infarction and cardiac arrest Full outcome definition • Not applicable Prediction horizon • 30-day events
Analysis	Number of outcomes • 7 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No

Peterson 2016 *(Continued)*

	Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • High Justification: definition of MACE is different to the definition of MACE in the RCRI development study Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing orthopaedic surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no handling of missing data; no reporting of calibration measures.
Overall judgement	No	Patient selection was appropriate. Predictors and outcomes were clearly defined and assessed. However, the number of outcomes was low and there was no information on missing data and no calibration was reported.

Press 2006

Study characteristics	
General information	Objective

Press 2006 *(Continued)*

- Biomarkers compared, prediction model compared

Journal

- *Archives of Internal Medicine*

Country

- USA

Study design

- Retrospective cohort study

Participants	Number of included patients • 1998 Surgical specialty • Vascular surgery Age • Mean 72.4 years (SD 8.7 years) Male sex • 57.1% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 7.5% History of ischaemic heart disease • 57.8% History of congestive heart failure • 7.2% History of cerebrovascular events • 45.9% Elevated creatinine • 4% 0 RCRI factors • 19.6% 1 RCRI factor • 46.6% 2 RCRI factors • 26.8% 3 or more RCRI factors

Press 2006 *(Continued)*

- 7%

Predictors	Predictor 1: ASA • Objective: biomarker compared • Category: patient characteristic • Scale: categorical • Threshold: not applicable • Assay/device: not applicable Predictor 2: Goldman index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: Detsky index • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 4: Score by Halm et al • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 5: Score by Tu et al • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category

Press 2006 *(Continued)*

	• MACE, all-cause mortality or nonfatal stroke, noncardiac complications, minor neurological complications, wound complications Full outcome definition • MACE was defined as myocardial infarction, unstable angina, congestive heart failure and ventricular tachycardia. Noncardiac complications included mechanical ventilatory assistance, postoperative pneumonia, sepsis, renal failure, deep venous thrombosis or pulmonary embolism, and gastrointestinal tract bleeding. Minor neurological complications included transient ischaemic attack (TIA), cranial nerve palsy, and seizure and wound complications included wound bleeding or haematoma or infection. Prediction horizon • 30-day events
Analysis	Number of outcomes • 80 MACE Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: No information on predictor definitions Domain 3: Outcome • Low Justification: concern regarding applicability is low for outcome MACE, but high for the other validated outcomes Overall judgement: • Unclear Patients selected were generalisable to the patient population used in the RCRI development study. Outcome definition was clearly defined/assessed and comparable to the definitions used in the RCRI development study. However, there was no/unclear information on predictor definitions.
Notes	—

Press 2006 *(Continued)*

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information on predictor definitions.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no handling of missing data; only c-statistics reported. Many models are compared to each other without adjustment for multiple testing.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, there was no/unclear information on predictor definitions. In addition, the number of outcomes was low and there was no information on missing data, multiple testing issue and no calibration was reported.

Ray 2010

Study characteristics	
General information	Objective • Biomarkers compared Journal • *European Journal of Clinical Investigation* Country • Australia Study design • Prospective cohort study
Participants	Number of included patients • 62 Surgical specialty • Orthopaedic surgery Age • Not reported Male sex • Not reported High-risk surgery

Ray 2010 *(Continued)*

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- 82%

1 RCRI factor

- 14%

2 RCRI factors

- 3%

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: Platelet CD40 ligand • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: phycoerythrin (PE)-labelled CD154 (BD Biosciences, San Jose, CA, USA) Predictor 2: Platelet factor V/Va • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: isothiocyanate-labelled antibody against human factor V and Va (American Diagnostica, Stamford, CT, USA) Predictor 3:

Ray 2010 *(Continued)*

	Platelet P-selectin • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: CD62P PE (BD Biosciences, San Jose, CA, USA) Predictor 4: High-sensitivity CRP • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Beckman Coulter, Brea, CA, USA Predictor 5: BNP • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Triage BNP; Biosite, San Diego, CA, USA Predictor 6: sCD40L • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: R&D Systems Inc, Minneapolis, MN, USA
Outcome	Outcome category • MACE Full outcome definition • Cardiac death, nonfatal myocardial infarction, unstable angina, clinically evident heart failure and new arrhythmia Prediction horizon • 6 weeks after surgery
Analysis	Number of outcomes • 6 Handling missing data

Ray 2010 *(Continued)*

	• No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on RCRI predictor definitions Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement: • Unclear Patient selected were generalisable to the patient population used in the RCRI development study. Outcome definition was clearly defined/assessed and comparable to the definitions used in the RCRI development study. However, there was no/unclear information on predictor definitions.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing orthopaedic surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information on RCRI predictor definitions.
Domain 3: Outcome	Unclear	No outcome definitions were provided.
Domain 4: Analysis	No	Low number of outcomes, no information on the handling of missing data and no reporting on calibration/reclassification measures.
Overall judgement	No	Patient selection was appropriate. However, predictor and outcome definitions were unclear/not reported. In addition, the number of outcomes was low, there was no information on missing data and no calibration was reported.

Reis 2019

Study characteristics	
General information	Objective • Prediction model compared Journal • *Seminars in Cardiothoracic and Vascular Anesthesia* Country • Portugal Study design • Retrospective cohort study
Participants	Number of included patients • 928 Surgical specialty • Vascular surgery Age • Not reported Male sex • Not reported High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor

Reis 2019 *(Continued)*

	• Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: Vascular Surgery Group Cardiac Risk Index (VSG-CRI) • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: Vascular Quality Initiative Cardiac Risk Index (VQI-CRI) • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: South African Vascular Surgical Cardiac Risk Index (SAVS-CRI) • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 4: New model - coronary artery disease, atrial fibrillation, diabetes mellitus, mechanical ventilation and heart rate ordinal • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition

Reis 2019 *(Continued)*

	• Cardiac arrhythmias, MI, cardiogenic pulmonary oedema, acute heart failure and cardiac arrest Prediction horizon • Not reported
Analysis	Number of outcomes • 60 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on RCRI predictor definitions Domain 3: Outcome • High Justification: although MACE was used as the outcome, it was different from the MACE outcome used in the development study Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.

Reis 2019 *(Continued)*

Domain 2: Predictors	Unclear	No information on RCRI predictor definitions.
Domain 3: Outcome	Unclear	No information on how the outcomes were determined, what definitions were used and what prediction horizon was used.
Domain 4: Analysis	No	Low number of outcomes and no information on handling missing data.
Overall judgement	No	Patient selection was appropriate. However, predictor and outcome definitions were unclear/not reported including their assessment. In addition, the number of outcomes was low and there was no information on missing data.

Rodseth 2011

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Journal of the American College of Cardiology* Country • Unknown due to inclusion of patients from multiple studies Study design • Individual patient data meta-analysis
Participants	Number of included patients • 623 Surgical specialty • Vascular surgery Age • Mean 65.3 years (SD 12.1 years) Male sex • 66% High-risk surgery • 25.5% Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 38.5% History of congestive heart failure • 7.5%

Rodseth 2011 *(Continued)*

	History of cerebrovascular events • 17.1% Elevated creatinine • 3.3% 0 RCRI factors • 37.6% 1 -2 RCRI factors • 56% 3 or more RCRI factors • 6.4%
Predictors	Predictor 1: BNP • Objective: added biomarker, biomarker compared • Category: blood • Scale: continuous; categorical • Threshold: screening: 30 ng/mL, general optimal: 116 ng/mL, diagnostic: 372 ng/mL • Assay/device: multiple different assays due to inclusion of patients from different studies
Outcome	Outcome category • MACE, all-cause mortality, cardiovascular death, myocardial infarction Full outcome definition • MACE was defined as myocardial infarction and cardiac death Prediction horizon • 30-day events
Analysis	Number of outcomes • Not reported Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low

Rodseth 2011 *(Continued)*

	Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on RCRI predictor definitions Domain 3: Outcome • Unclear Justification: no clear definition of the outcome measure MACE, which could be different among the included studies + outcome is different compared to development study Overall judgement • Unclear Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information on RCRI predictor definitions.
Domain 3: Outcome	Unclear	No clear definition of the outcome measure MACE, which could be different among the included studies.
Domain 4: Analysis	No	Low number of outcomes, no information on the handling of missing data and no reporting of calibration measures
Overall judgement	No	Patient selection was appropriate. However, predictor and outcome definitions were unclear/not reported including their assessment. In addition, the number of outcomes was low, there was no information on missing data and no reporting calibration measures.

Rohde 2001

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *American Journal of Cardiology* Country

Rohde 2001 *(Continued)*

	• USA Study design • Prospective cohort study
Participants	Number of included patients • 570 Surgical specialty • Noncardiac surgery Age • Mean 66 years (SD 10 years) Male sex • 40% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • 5% History of cerebrovascular events • 13% Elevated creatinine • Not reported 0 RCRI factors • 0% 1 -2 RCRI factors • 39.8% 3 or more RCRI factors • 60.2%
Predictors	Predictor 1: Abnormal echocardiography • Objective: added biomarker, biomarker compared • Category: imaging • Scale: dichotomous

Rohde 2001 *(Continued)*

- Threshold: the presence of any degree of systolic dysfunction, or moderate to severe LV hypertrophy, or moderate to severe mitral regurgitation, or aortic gradient > 20 mm Hg
- Assay/device: not reported

Predictor 2:

Any degree of systolic dysfunction on echocardiography

- Objective: biomarker compared
- Category: imaging
- Scale: categorical
- Threshold: normal function (1), mild (2), moderate (3) or severe systolic dysfunction (4)
- Assay/device: not reported

Predictor 3:

Any degree of systolic dysfunction or moderate to severe left ventricular hypertrophy on echocardiography

- Objective: biomarker compared
- Category: imaging
- Scale: categorical
- Threshold: normal function (1), mild (2), moderate (3) or severe systolic dysfunction (4); normal thickness and mild hypertrophy (1) or moderate to severe hypertrophy (2)
- Assay/device: not reported

Outcome	Outcome category • MACE Full outcome definition • Myocardial infarction, cardiogenic pulmonary oedema, ventricular fibrillation or primary cardiac arrest, and sustained complete heart block Prediction horizon • In-hospital events
Analysis	Number of outcomes • 44 Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No

Rohde 2001 *(Continued)*

PROBAST: Applicability	Domain 1: Participant selection • High Justification: only patients who underwent preoperative TTE were included in the analysis Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement • High Justification: only a selected group of patients was included, that was not generalisable to the patient population used in the RCRI development study. However, predictors and outcomes were clearly defined/assessed and comparable as used in the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Only patients who underwent preoperative TTE were included in the analysis.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, no information on the handling of missing data and no reporting on calibration/reclassification measures.
Overall judgement	No	Predictors and outcomes was clearly defined and assessed. However, patient selection was inappropriate, the number of outcomes was low, no information on handling of missing data and inappropriate reporting of performance measures.

Rohrig 2004

Study characteristics	
General information	Objective • Biomarkers compared, prediction model compared Journal

Rohrig 2004 *(Continued)*

	• *Anesthesia and Analgesia* Country • Germany Study design • Retrospective cohort study
Participants	Number of included patients • 29,437 Surgical specialty • Noncardiac surgery Age • Not reported Male sex • 50.6% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 to 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: ASA • Objective: biomarker compared

Rohrig 2004 *(Continued)*

- Category: patient characteristic
- Scale: categorical
- Threshold: not applicable
- Assay/device: not applicable

Predictor 2:

Model 1 – age, male gender, coronary bypass/PTCA, valvular heart disease, arrhythmia, arterial hypertension, carotid stenosis, hypervolaemia, chronic renal failure, emergency surgery, neurosurgery, major vascular surgery, haematopoietic/lymphatic surgery and gastrointestinal surgery

- Objective: prediction model compared
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: not applicable

Predictor 3:

Model 2 – age, ASA, neurosurgery, thoracic surgery, major vascular surgery, haematopoietic/lymphatic surgery and gastrointestinal surgery

- Objective: prediction model compared
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: not applicable

Outcome	Number of outcomes • 5249 Handling missing data • No information on handling missing values Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
Analysis	Number of outcomes • 5249 Handling missing data • No information on handling missing values Discrimination reported? • Yes

Rohrig 2004 *(Continued)*

	Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • High Justification: the RCRI was not developed to predict intraoperative events and the outcome is very different from the MACE outcome used in the development study Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	Clear methodology and appropriate number of outcomes.
Overall judgement	Yes	Patient selection was appropriate, predictor and outcome definitions were clearly defined and comparable to the definitions used in the development study. In addition, methodology used was appropriate including the number of outcomes.

Rutkowski 2019

Study characteristics	
General information	Objective • Prediction model compared Journal • *Journal of Clinical Neuroscience* Country • USA Study design • Retrospective case-control study
Participants	Number of included patients • 34 Surgical specialty • Neurosurgery Age • Mean 59 years Male sex • 82% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 to 2 RCRI factors • Not reported

Rutkowski 2019 *(Continued)*

	3 or more RCRI factors • Not reported
Predictors	Predictor 1: ACS-NSQIP-MICA • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: ACS-NSQIP-Cardiac death score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: ACS-NSQIP-Death score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 4: ACS-NSQIP-Cardiac complications score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 5: Karnofsky performance score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable

Rutkowski 2019 *(Continued)*

	Predictor 6: ASA • Objective: biomarker compared • Category: patient characteristic • Scale: categorical • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE, cardiovascular mortality, all-cause mortality Full outcome definition • MACE was defined as shock, arrest and/or unstable arrhythmia resulting in pulseless electrical activity Prediction horizon • Not reported
Analysis	Number of outcomes • 5 MACE Handling missing data • No information on handling missing values Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only patients who underwent craniotomy were included Domain 2: Predictors • High Justification: craniotomy was considered as high-risk surgery, however this procedure is not considered high-risk in the RCRI predictor definitions. No definition was provided for history of ischaemic heart disease and congestive heart failure. Domain 3: Outcome • High Justification: MACE definition was different from its definition used in the development study Overall judgement

Rutkowski 2019 *(Continued)*

- High

Justification: only a selected group of patients was included, there was no/unclear information on some predictor definitions and other had different definitions compared to the RCRI development study. In addition, outcome definition used was different compared to the RCRI development study.

Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	This study was a case-control study, which is not the appropriate design for prediction research.
Domain 2: Predictors	No	Craniotomy was considered as high-risk surgery, however this procedure is not considered high-risk in the RCRI predictor definitions. No definition was provided for history of ischaemic heart disease and congestive heart failure.
Domain 3: Outcome	Unclear	No information on the definition, how it was determined and whether it was blinded.
Domain 4: Analysis	No	Low number of events; no reporting of calibration/reclassification measures; use of a case-control design is not appropriate for prediction research analysis.
Overall judgement	No	This study was a case-control study, which is not the appropriate design for prediction research. Predictor definitions were defined differently compared to the definitions used in the RCRI development study. Outcome definitions with their assessment were unclear/not reported. Furthermore, the number of outcomes was low and inappropriate reporting of performance measures.

Sabate 2011

Study characteristics	
General information	Objective • Prediction model compared Journal • *British Journal of Anaesthesia* Country • Spain Study design • Prospective cohort study
Participants	Number of included patients • 3387 Surgical specialty • Noncardiac surgery

Sabate 2011 *(Continued)*

	Age • Median 67 years (10th to90th percentile: 47 to 81 years) Male sex • 48.3% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 4.8% History of ischaemic heart disease • 8.5% History of congestive heart failure • 6.6% History of cerebrovascular events • 6.6% Elevated creatinine • 6.7% 0 RCRI factors • 75.4% 1 RCRI factor • 17.9% 2 RCRI factors • 4.6% 3 or more RCRI factors • 2.1%
Predictors	Outcome category • MACE Full outcome definition • Nonfatal cardiac arrest, acute myocardial infarction, congestive heart failure, new cardiac arrhythmia, angina, stroke, cardiovascular death and cerebrovascular death Prediction horizon • In-hospital events
Outcome	Outcome category • MACE Full outcome definition

Sabate 2011 *(Continued)*

	• Nonfatal cardiac arrest, acute myocardial infarction, congestive heart failure, new cardiac arrhythmia, angina, stroke, cardiovascular death and cerebrovascular death Prediction horizon • In-hospital events
Analysis	Number of outcomes • 146 Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • High Justification: definition of IHD and CHF are unclear and definition of high-risk surgery is different Domain 3: Outcome • High Justification: MACE definition also includes cerebrovascular events and is therefore different from its definition used in the development study Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, no/unclear information on predictor definitions for some items and other predictors of the original RCRI were not included or had a different definition. In addition, outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.

Sabate 2011 *(Continued)*

Domain 2: Predictors	No	Definition of IHD and CHF are unclear and definition of high-risk surgery is different.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	Clear methodology and appropriate number of outcomes.
Overall judgement	No	Patient selection was appropriate, outcome definitions with their assessment were clearly defined and comparable to the definitions used in the development study. In addition, methodology used was appropriate including the number of outcomes. However, no/unclear information on predictor definitions for some items and other predictors of the original RCRI were not included or had a different definition.

Saito 2012

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Heart and Vessels* Country • Japan Study design • Retrospective cohort study
Participants	Number of included patients • 200 Surgical specialty • Noncardiac surgery Age • Median 69.5 years (SD 12.3 years) Male sex • 73.5% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 8% History of ischaemic heart disease

Saito 2012 *(Continued)*

- 45%

History of congestive heart failure

- 5%

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: E/E' • Objective: added biomarker, biomarker compared • Category: imaging • Scale: dichotomous • Threshold: 15 • Assay/device: transthoracic echocardiography using Sonos 5500 (Philips Medical Systems, Andover, MA, USA) or SSD 5500 (Aloka, Mitaka, Tokyo, Japan)
Outcome	Outcome category • MACE Full outcome definition • Fatal or nonfatal arrhythmia, acute myocardial infarction, ischaemic heart events and heart failure Prediction horizon • In-hospital events
Analysis	Number of outcomes • 11 Handling missing data • No information on handling missing data Discrimination reported? • No

Saito 2012 *(Continued)*

	Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on RCRI predictor definitions Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement: • Unclear Patients selected were generalisable to the patient population used in the RCRI development study. Outcome definition was clearly defined/assessed and comparable to the definitions used in the RCRI development study. However, there was no/unclear information on predictor definitions.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Only those who underwent TTE were eligible for study participation.
Domain 2: Predictors	Unclear	No/unclear information on RCRI predictor definitions.
Domain 3: Outcome	Unclear	Outcome definitions for, among others, myocardial infarction and heart failure are not clear and no information on blinding.
Domain 4: Analysis	No	Low number of outcomes; no predictive performance measures are reported; no information on handling of missing data.
Overall judgement	No	Patient selection was inappropriate as only a selected group of high-risk patients were included. Predictor and outcome definitions were unclear/not reported including their assessment. Furthermore, the number of outcomes was low, no information on the handling of missing data and inappropriate reporting of performance measures.

Scholz 2019

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Journal of Leukocyte Biology* Country • Germany Study design • Prospective cohort study
Participants	Number of included patients • 714 Surgical specialty • Noncardiac surgery Age • Median 69 years (IQR 63 to 75 years) Male sex • 80% High-risk surgery • 42% Insulin-dependent diabetes mellitus • 15% History of ischaemic heart disease • 100% History of congestive heart failure • 2% History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 21% 1 RCRI factor • 54%

Scholz 2019 *(Continued)*

	2 RCRI factors • 20% 3 or more RCRI factors • 5%
Predictors	Predictor 1: Regulatory T cells • Objective: added biomarker, biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: FACSVerse; BD Biosciences, Heidelberg, Germany Predictor 2: NT-proBNP + high-sensitivity troponin • Objective: added biomarker • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Immulite, Siemens Healthcare Diagnostics, Erlangen, Germany; Cobas E4111, Roche Diagnostics, Mannheim, Germany Predictor 3: NT-proBNP + high-sensitivity troponin + regulatory T-cells • Objective: added biomarker • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: FACSVerse; BD Biosciences, Heidelberg, Germany; Immulite, Siemens Healthcare Diagnostics, Erlangen, Germany; Cobas E4111, Roche Diagnostics, Mannheim, Germany Predictor 4: Regulatory T cells + age + sex +ASA + history of PCI + creatinine • Objective: biomarker compared • Category: prediction model • Scale: continuous • Threshold: not applicable • Assay/device: FACSVerse; BD Biosciences, Heidelberg, Germany
Outcome	Outcome category • MACE Full outcome definition

Scholz 2019 *(Continued)*

	• Cardiovascular death, myocardial infarction, myocardial ischaemia, myocardial injury after noncardiac surgery (MINS), and embolic or thrombotic stroke Prediction horizon • 30-day events
Analysis	Number of outcomes • 84 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • High Justification: all included patients had coronary artery disease Domain 2: Predictors • Unclear Justification: no information on how the RCRI items were defined Domain 3: Outcome • High Justification: outcome also includes troponin elevation (MINS), which is not included in the original RCRI outcome definition Overall judgement • High Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information on how the RCRI items were defined.

Scholz 2019 *(Continued)*

Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcome and no information on missing data.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, predictor definitions were unclear/not reported. Furthermore, the number of outcomes was low and there was no information on missing data.

Schouten 2006

Study characteristics	
General information	Objective • Added biomarkers Journal • *Journal of Vascular Surgery* Country • The Netherlands Study design • Retrospective cohort study
Participants	Number of included patients • 500 Surgical specialty • Vascular surgery Age • Mean 70 years (SD 9.5 years) Male sex • 86% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • 5%

Schouten 2006 *(Continued)*

	History of cerebrovascular events • 15% Elevated creatinine • 6% 0 RCRI factors • 0% 1 RCRI factor • 41% 2 RCRI factors • 33% 3 or more RCRI factors • 26%
Predictors	Predictor 1: AAA size • Objective: added biomarker • Category: imaging • Scale: continuous • Threshold: not applicable • Assay/device: assessment based on a CTA scan Predictor 2: AAA size + age • Objective: added biomarker • Category: imaging • Scale: continuous • Threshold: not applicable • Assay/device: assessment based on a CTA scan
Outcome	Outcome category • MACE Full outcome definition • Cardiovascular death and nonfatal myocardial infarction Prediction horizon • 30-day events
Analysis	Number of outcomes • 31 Handling missing data

Schouten 2006 *(Continued)*

	• No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on blinding in retrospective study and no information on the definition of CHF and IHD Domain 3: Outcome • High Justification: outcome is composite of cardiovascular death and nonfatal myocardial infarction which differs from outcome in development study Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information on blinding in retrospective study and no information on the definition of CHF and IHD.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, no information on handling missing values and no reporting of calibration/reclassification measures.

Schouten 2006 *(Continued)*

Overall judgement	No	Outcome was clearly defined and assessed. Patient selection was appropriate. Predictor definitions were unclear/not reported. Furthermore, the number of outcomes was low, no information on the handling of missing data and inappropriate reporting of performance measures.

Schrimpf 2015

Study characteristics	
General information	Objective • Added biomarkers Journal • *PLOS One* Country • Germany Study design • Prospective cohort study
Participants	Number of included patients • 477 Surgical specialty • Vascular surgery Age • Median 70 years (IQR 63 to 75 years) Male sex • 79.9% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 37.8% History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine

Schrimpf 2015 *(Continued)*

	• Not reported 0 RCRI factors • 10.7% 1 RCRI factor • 40.5% 2 RCRI factors • 28.3% 3 or more RCRI factors • 20.5%
Predictors	Predictor 1: Copeptin • Objective: added biomarker • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: BRAHMS Kryptor Assay (Thermo Fisher scientific, Waltham, MA, USA)
Outcome	Outcome category • MACE Full outcome definition • Myocardial infarction, cardiac death and any new rise of cardiac troponin prompted by suspicion for an acute coronary syndrome Prediction horizon • 30-day events
Analysis	Number of outcomes • 41 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low

Schrimpf 2015 *(Continued)*

	Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on RCRI predictor definitions Domain 3: Outcome • High Justification: composite endpoint of MACE is very different from the outcome used in the development study Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information on RCRI predictor definitions.
Domain 3: Outcome	Unclear	Individual items of MACE composite are not reported; no information on blinding.
Domain 4: Analysis	No	Low number of outcomes; no information on handling missing outcome; no reporting on calibration/reclassification measures.
Overall judgement	No	Patient selection was appropriate. However, predictor and outcome definitions were unclear/not reported including their assessment. Furthermore, the number of outcomes was low, no information on the handling of missing data and inappropriate reporting of performance measures.

Scorcu 2020

Study characteristics	
General information	Objective • Prediction model compared Journal • *Monaldi Archives for Chest Disease* Country

Scorcu 2020 *(Continued)*

	• Italy Study design • Prospective cohort study
Participants	Number of included patients • 4600 Surgical specialty • Noncardiac surgery Age • Mean 63 years (SD 13 years) Male sex • Not reported High-risk surgery • 7.1% Insulin-dependent diabetes mellitus • 4.6% History of ischaemic heart disease • 8.1% History of congestive heart failure • 3.5% History of cerebrovascular events • 4.9% Elevated creatinine • 4.1% 0 RCRI factors • 77% 1 RCRI factor • 18% 2 RCRI factors • 5% 3 or more RCRI factors • 2%
Predictors	Predictor 1: Updated Cardiac Risk Score (UCRS) - high-risk surgery, preoperative estimate glomerular filtration rate < 30 ml/min/1.73 m2, age ≥ 75 years and history of heart failure

Scorcu 2020 *(Continued)*

- Objective: prediction model compared
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: not applicable

Outcome	Outcome category • MACE Full outcome definition • Death due to cardiovascular causes, cardiac arrest, acute myocardial infarction, acute heart failure, type 2 second-degree atrioventricular block or complete atrioventricular block requiring cardiac pacing, and stroke Prediction horizon • 30-day events
Analysis	Number of outcomes • 82 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • High Justification: definitions of high-risk surgery and ischaemic heart disease were different from the development study Domain 3: Outcome • Low Justification: although stroke was included in the outcome definition, it is only a small contribution to the number of events Overall judgement: • High

Scorcu 2020 *(Continued)*

	Patients selected were generalisable to the patient population used in the RCRI development study. Outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study. However, no/unclear information on predictor definitions for some items and other predictors of the original RCRI were not included or had a different definition.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	No	Definition of high-risk surgery and ischaemic heart disease were different from the development study.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, no information on the handling of missing data and no reporting of calibration/reclassification measures.
Overall judgement	No	Patient selection was appropriate and outcome was clearly defined and assessed. However, predictor definitions were defined differently compared to the definitions used in the RCRI development study. Furthermore, the number of outcomes was low, no information on handling missing data and inappropriate reporting of performance measures.

Scrutinio 2014

Study characteristics	
General information	Objective • Added biomarkers, prediction model compared Journal • *Annals of Vascular Surgery* Country • Italy Study design • Prospective cohort study
Participants	Number of included patients • 411 Surgical specialty • Vascular surgery Age

Scrutinio 2014 *(Continued)*

- Mean 70.2 years (SD 9.4 years)

Male sex

- 78.8%

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- 16.8%

History of ischaemic heart disease

- 27.7%

History of congestive heart failure

- 4.4%

History of cerebrovascular events

- 17.8%

Elevated creatinine

- 9.5%

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: NT-proBNP • Objective: added biomarker • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: not reported Predictor 2: High-sensitivity CRP • Objective: added biomarker • Category: blood • Scale: continuous

Scrutinio 2014 *(Continued)*

- Threshold: not applicable
- Assay/device: Dimension RxL immunoassay (Siemens Healthcare Diagnostics, Glasgow, DE)

Predictor 3:

NT-proBNP+ high-sensitivity CRP

- Objective: added biomarker
- Category: blood
- Scale: continuous
- Threshold: not applicable
- Assay/device: Dimension RxL immunoassay (Siemens Healthcare Diagnostics, Glasgow, DE)

Predictor 4:

New developed prediction model including insulin therapy for diabetes, open surgery and the highest tertiles of fibrinogen (> 377 mg/dL), hs-CRP (> 3.2 mg/L) and NT-proBNP (> 221 ng/L)

- Objective: prediction model compared
- Category: prediction model
- Scale: not applicable
- Threshold: not applicable
- Assay/device: not applicable

Outcome	Outcome category • All-cause mortality and MACE Full outcome definition • Composite of death, acute coronary syndromes, acute pulmonary oedema within 30 days of surgery and postoperative myocardial damage Prediction horizon • 30-day events
Analysis	Number of outcomes • 74 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • Yes Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low

Scrutinio 2014 *(Continued)*

	Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement: • Low Patient selected were generalisable to the patient population used in the RCRI development study. Predictor and outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes and no information on handling missing data.
Overall judgement	No	Patient selection was appropriate. Predictors and outcomes were clearly defined and assessed. However, the number of outcomes was low and there was no information on missing data.

Sheth 2015

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *BMJ* Country

Sheth 2015 *(Continued)*

- Canada, USA, China, South Africa, Malaysia, India, Poland

Study design

- Prospective cohort study

Participants	Number of included patients • 955 Surgical specialty • Noncardiac surgery Age • Mean 69.7 years (SD 8.5 years) Male sex • 61% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 32% History of congestive heart failure • 4% History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 34% 1 RCRI factor • 43% 2 RCRI factors • 19% 3 or more RCRI factors • 6%
Predictors	Predictor 1: Coronary CT angiography • Objective: added biomarker, biomarker compared

Sheth 2015 *(Continued)*

- Category: imaging
- Scale: categorical; dichotomous
- Threshold: normal - no evidence of coronary atherosclerosis; non-obstructive coronary artery disease - evidence of at least one coronary artery plaque with a < 50% stenosis; obstructive coronary artery disease - at least one coronary artery plaque with a ≥ 50% stenosis; or extensive obstructive disease — ≥ 50% stenosis in two coronary arteries including the proximal left anterior descending artery, ≥ 50% stenosis in three coronary arteries, or ≥ 50% stenosis in the left main coronary
- Assay/device: the protocol used for coronary CT angiography is reported in Appendix 1 of the original research paper.

Outcome	Outcome category • MACE Full outcome definition • Cardiac death or nonfatal myocardial infarction Prediction horizon • 30-day events
Analysis	Number of outcomes • 74 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • High Justification: many exclusion criteria including persistent atrium fibrillation, patients with previous stent implantation. However, they could not have done it differently as these exclusions were due to CTA measurements. Domain 2: Predictors • Unclear Justification: no information for each of the RCRI predictor definitions Domain 3: Outcome • High Justification: outcome MACE differs from the definition of MACE in the development study Overall judgement • High

Sheth 2015 *(Continued)*

	Justification: only a selected group of patients was included, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	No information for each of the RCRI predictor definitions.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no information on handling missing outcome; no reporting on calibration measures.
Overall judgement	No	Patient selection was appropriate. Outcome was clearly defined and assessed. However, predictor definitions were unclear/not reported. Furthermore, the number of outcomes was low, no information on the handling of missing data and inappropriate reporting of performance measures.

Stonelake 2015

Study characteristics	
General information	Objective • Biomarkers compared, prediction model compared Journal • *Annals of Medicine and Surgery* Country • United Kingdom Study design • Retrospective cohort study
Participants	Number of included patients • 86 Surgical specialty • General surgery Age • Median 63 years (range 19 to 86 years) Male sex • 50%

Stonelake 2015 *(Continued)*

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- Not reported

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- Not reported

History of cerebrovascular events

- Not reported

Elevated creatinine

- Not reported

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

Not reported

Predictors	Predictor 1: ASA • Objective: biomarker compared • Category: patient characteristic • Scale: categorical • Threshold: not applicable • Assay/device: not applicable Predictor 2: POSSUM • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3:

Stonelake 2015 *(Continued)*

	P-POSSUM • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 4: CR-POSSUM • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • All-cause mortality Full outcome definition • Not applicable Prediction horizon • 30-day events
Analysis	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: no information on each of the RCRI predictor definitions Domain 3: Outcome • High Justification: outcome is all-cause mortality and not MACE
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on each of the RCRI predictor definitions Domain 3: Outcome

Stonelake 2015 *(Continued)*

	• High Justification: outcome is all-cause mortality and not MACE Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Exclusion of some surgical procedure as described in figure 1 seems inappropriate.
Domain 2: Predictors	Unclear	No information on each of the RCRI predictor definitions.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, no information on handling missing data and no reporting of performance measures, only percentages.
Overall judgement	No	Outcome was clearly defined and assessed. However, patient selection was inappropriate and predictor definitions were unclear/not reported. Furthermore, the number of outcomes was low, no information on the handling of missing data and inappropriate reporting of performance measures.

Subramaniam 2011

Study characteristics	
General information	Objective • Prediction model compared Journal • *Annals of Vascular Surgery* Country • Israel and USA Study design • Retrospective cohort study
Participants	Number of included patients • 922 Surgical specialty

Subramaniam 2011 *(Continued)*

- Vascular surgery

Age

- Mean 65.8 years (SD 11 years)

Male sex

- 75.2%

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- 9.1%

History of ischaemic heart disease

- 46.2%

History of congestive heart failure

- 7.5%

History of cerebrovascular events

- 12.5%

Elevated creatinine

- 5.3%

0 RCRI factors

- Not reported

1 RCRI factor

- Not reported

2 RCRI factors

- Not reported

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: LTSS - age > 65 years, diabetes mellitus, history of cerebrovascular disease, history of ischaemic heart disease, history of congestive heart failure, ST-depression on preoperative ECG and renal insufficiency • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • All-cause mortality Full outcome definition

Subramaniam 2011 *(Continued)*

	• Not applicable Prediction horizon • 6 months, 1 year and 3 years after surgery
Analysis	Number of outcomes • 63 deaths after 6 months; 106 after 1 year and 238 after 3 years Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Unclear Justification: definition of ischaemic heart disease and congestive heart failure unclear and probable exclusion of high-risk surgery Domain 3: Outcome • High Justification: outcome is all-cause mortality and not MACE. In addition, outcomes were assessed at 6 months and at 1 and 3 years after surgery, whereas the RCRI has a prediction horizon of 30 days Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.

Subramaniam 2011 *(Continued)*

Domain 2: Predictors	Unclear	Definition of ischaemic heart disease and congestive heart failure unclear and probable exclusion of high-risk surgery.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, no handling of missing data and no reporting on calibration measures.
Overall judgement	No	Patient selection was appropriate. Outcome was clearly defined and assessed. However, predictor definitions were unclear/not reported. Furthermore, the number of outcomes was low, no information on the handling of missing data and inappropriate reporting of performance measures.

Valentijn 2012

Study characteristics	
General information	Objective • Added biomarkers Journal • *American Journal of Cardiology* Country • The Netherlands Study design • Prospective cohort study
Participants	Number of included patients • 1172 Surgical specialty • Vascular surgery Age • Mean 68 years (SD 10 years) Male sex • 74% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 40.4%

Valentijn 2012 *(Continued)*

History of congestive heart failure

- 9.4%

History of cerebrovascular events

- 33.5%

Elevated creatinine

- 5.3%

0 to 1 RCRI factors

- 57.3%

1 RCRI factor

- Not reported

2 RCRI factors

- 27%

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: Aortic value function (aortic valve sclerosis) • Objective: added biomarker • Category: imaging • Scale: dichotomous • Threshold: defined by the presence of thickening and/or calcium of 1 cusp of a tricuspid valve not inducing stenosis (i.e. with a maximal velocity < 2.5 m/s) • Assay/device: portable Acuson Cypress ultrasound system (Acuson, A Siemens, Mountain View, California) with a 7V3c transducer or a portable Vivid-I ultrasound System (Vivid-I, GE Healthcare, Solingen, Germany) with a 3S-RS transducer Predictor 2: Aortic value function (aortic valve stenosis) • Objective: added biomarker • Category: imaging • Scale: dichotomous • Threshold: defined as a jet velocity > 2.5 m/s • Assay/device: portable Acuson Cypress ultrasound system (Acuson, A Siemens, Mountain View, California) with a 7V3c transducer or a portable Vivid-I ultrasound System (Vivid-I, GE Healthcare, Solingen, Germany) with a 3S-RS transducer
Outcome	Outcome category • All-cause mortality Full outcome definition • Not applicable Prediction horizon

Valentijn 2012 *(Continued)*

	• 4 years after surgery
Analysis	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • High Justification: some of the echocardiographies were performed in the 30 days after surgery Domain 3: Outcome • High Justification: outcome is all-cause mortality and not MACE
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • High Justification: some of the echocardiographies were performed in the 30 days after surgery Domain 3: Outcome • High Justification: outcome is all-cause mortality and not MACE Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, some predictors were measures after surgery and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	No	Some of the echocardiographies were performed in the 30 days after surgery.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.

Valentijn 2012 *(Continued)*

Domain 4: Analysis	No	Categorisation of predictors; no performance measures for additive predictive performance are reported; complete case analysis.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, some predictors were not preoperatively available. Furthermore, predictors were categorised, complete case analysis was performed and no reclassification measures were reported.

van Diepen 2014

Study characteristics	
General information	Objective • Prediction model compared Journal • *American Heart Journal* Country • Canada Study design • Retrospective cohort study
Participants	Number of included patients • 32160 Surgical specialty • Noncardiac surgery Age • Not reported Male sex • Not reported High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events

van Diepen 2014 *(Continued)*

- Not reported

Elevated creatinine

- Not reported

0 to 1 RCRI factors

- 73.4%

1 RCRI factor

- Not reported

2 RCRI factors

- 16.8%

3 or more RCRI factors

- 9.8%

Predictors	Predictor 1: $CHADS_2$ • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: $CHADS_2$-Vasc • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 3: R_2CHADS_2 • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Other; all-cause mortality Full outcome definition • Composite outcome of all-cause mortality, stroke, TIA or systemic embolism

van Diepen 2014 *(Continued)*

	Prediction horizon • 30-day events
Analysis	Number of outcomes • 1363 Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • High Justification: only patients with nonvalvular atrium fibrillation were included Domain 2: Predictors • High Justification: some definitions of the RCRI did not match the definitions used for this article Domain 3: Outcome • High Justification: outcome is composite of mortality, stroke, TIA and systemic embolism and not MACE Overall judgement • High Justification: only a selected group of patients was included which are not generalisable to the RCRI development cohort. No/unclear information on predictor definitions for some items and other predictors of the original RCRI were not included or had a different definition. Outcome definition was different compared to the RCRI development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	No	Some definitions of the RCRI did not match the definitions used for this article.
Domain 3: Outcome	Yes	some definitions of the RCRI did not match the definitions used for this article.

van Diepen 2014 *(Continued)*

Domain 4: Analysis	Yes	Clear methodology and appropriate number of outcomes.
Overall judgement	No	Patient selection was appropriate, outcome definitions were clearly defined and comparable to the definitions used in the development study. Methodology used was appropriate including the number of outcomes. However, some predictor definitions were defined differently compared to the definitions used in the RCRI development study.

van Klei 2007

Study characteristics	
General information	Objective • Added biomarkers Journal • *Annals of Surgery* Country • Canada and the Netherlands Study design • Prospective cohort study
Participants	Number of included patients • 2967 Surgical specialty • Noncardiac surgery Age • Mean 64.9 years (SD 9.2 years) Male sex • 56% High-risk surgery • 53.8% Insulin-dependent diabetes mellitus • 5.5% History of ischaemic heart disease • 10.5% History of congestive heart failure • 1.8% History of cerebrovascular events

van Klei 2007 *(Continued)*

- 4.1%

Elevated creatinine

- 2.7%

0 RCRI factors

- 31.6%

1 RCRI factor

- 42.6%

2 RCRI factors

- 19.8%

3 or more RCRI factors

- 6%

Predictors	Predictor 1: Left bundle branch block on ECG • Objective: added biomarker • Category: imaging • Scale: dichotomous • Threshold: not applicable • Assay/device: not reported Predictor 2: Right bundle branch block on ECG • Objective: added biomarker • Category: imaging • Scale: dichotomous • Threshold: not applicable • Assay/device: not reported Predictor 3: Male gender • Objective: added biomarker • Category: patient characteristic • Scale: dichotomous • Threshold: not applicable • Assay/device: not reported
Outcome	Outcome category • Myocardial infarction Full outcome definition • Not applicable

van Klei 2007 *(Continued)*

	Prediction horizon • In-hospital events
Analysis	Number of outcomes • 72 Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • High Justification: outcome is myocardial infarction and not MACE Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.

van Klei 2007 *(Continued)*

Domain 3: Outcome	No	Troponin, ECG and echocardiography were not measured in all patients, only on clinical indication.
Domain 4: Analysis	No	Low number of outcomes, complete case analysis and no reporting on calibration and reclassification measures.
Overall judgement	No	Patient selection was appropriate. Predictors were clearly defined and assessed. However, troponin, ECG and echocardiography were only measured on clinical indication. In addition, the number of outcomes was low, complete case analysis and no calibration was reported.

Vetrugno 2014

Study characteristics	
General information	Objective • Biomarkers compared Journal • *BMC Anesthesiology* Country • Italy Study design • Prospective cohort study
Participants	Number of included patients • 227 Surgical specialty • Orthopaedic surgery Age • Median 71 years (IQR 66 to 79 years) Male sex • 40% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported

Vetrugno 2014 *(Continued)*

	History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 72.7% 1 RCRI factor • 19.4% 2 RCRI factors • 4.4% 3 or more RCRI factors • 3.5%
Predictors	Predictor 1: BNP • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Bayer ADVIA Centaur Predictor 2: ASA • Objective: biomarker compared • Category: patient characteristic • Scale: categorical • Threshold: not applicable • Assay/device: not reported
Outcome	Outcome category • MACE Full outcome definition • New onset atrium fibrillation, flutter, acute heart failure or nonfatal/fatal myocardial infarction Prediction horizon • In-hospital events
Analysis	Number of outcomes • 14 Handling missing data

Vetrugno 2014 *(Continued)*

	• No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • High Justification: MACE outcome is different from the MACE definition used in the development study Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Exclusion criteria were atrial fibrillation, a recent history (within 6 months) of unstable coronary syndrome, or decompensate heart failure. Since severe aortic valve stenosis and impaired renal function are associated with increased serum levels of natriuretic peptides, patients with these preoperative diagnoses were also excluded.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	No	AV block counted as MACE, but this was not predefined.
Domain 4: Analysis	No	Low number of outcomes, complete case analysis and no reporting on calibration measures.
Overall judgement	No	Predictor definitions were clearly defined/reported and assessed. However, patient selection was inappropriate as only a selected group of patients were

Vetrugno 2014 *(Continued)*

included. Outcome definition was inconsistent with the MACE definition reported. Furthermore, the number of outcomes was low, complete case analysis and inappropriate reporting of performance measures.

Vilarino-Rico 2015

Study characteristics	
General information	Objective • Prediction model compared Journal • *Annals of Vascular Surgery* Country • Spain Study design • Prospective cohort study
Participants	Number of included patients • 385 Surgical specialty • Vascular surgery Age • Mean 67.8 years (SD 8.3 years) Male sex • 86.5% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • 26.7% History of congestive heart failure • Not reported History of cerebrovascular events • 17.3% Elevated creatinine • Not reported

Vilarino-Rico 2015 *(Continued)*

	0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: Halm score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: Tu score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition • Acute myocardial infarction, stroke, cardiovascular death (fatal stroke, fatal acute myocardial infarction, fatal congestive heart failure, sudden cardiac death and death due to ruptured aortic aneurysm Prediction horizon • During follow-up up to 5 years
Analysis	Number of outcomes • 92 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported?

Vilarino-Rico 2015 *(Continued)*

	• No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on individual RCRI predictor definitions Domain 3: Outcome • High Justification: MACE outcome is different from the MACE definition used in the development study Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information on individual RCRI predictor definitions.
Domain 3: Outcome	Unclear	No definitions were provided for the separate composite outcomes and no information on blinding.
Domain 4: Analysis	No	Low number of outcomes, complete case analysis and no reporting on calibration measures.
Overall judgement	No	Patient selection was appropriate. However, predictor and outcome definitions were unclear/not reported including their assessment. Furthermore, the number of outcomes was low, complete case analysis was performed and inappropriate reporting of performance measures.

Waterman 2016

Study characteristics

Waterman 2016 *(Continued)*

General information	Objective • Added biomarkers, prediction model compared Journal • *Journal of Arthroplasty* Country • USA Study design • Prospective existing registry
Participants	Number of included patients • 51,063 Surgical specialty • Orthopaedic surgery Age • Mean 67.1 years (SD 9.8 years) Male sex • 37% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported

Waterman 2016 *(Continued)*

	3 or more RCRI factors • Not reported
Predictors	Predictor 1: Total joint arthroplasty model (TJA) - risk score (age > 80, hypertension, history of cardiac disease) • Objective: added biomarker, prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: Total joint arthroplasty model (TJA) - individual risk factors (age > 80, hypertension, history of cardiac disease) • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Myocardial infarction or cardiac arrest Full outcome definition • Not applicable Prediction horizon • 30-day events
Analysis	Number of outcomes • 158 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low

Waterman 2016 *(Continued)*

	Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information on individual RCRI predictor definitions Domain 3: Outcome • High Justification: MACE outcome is different from the MACE definition used in the development study Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing orthopaedic surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information on individual RCRI predictor definitions.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	The analysis performed is not clear; no reporting on calibration measures; no information on handling missing data.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, predictor definitions were unclear/not reported including their assessment. Furthermore, the analysis performed is not clear, no information on handling missing data and inappropriate reporting of performance measures.

Weber 2013

Study characteristics	
General information	Objective • Biomarkers compared Journal • *European Heart Journal* Country

Weber 2013 *(Continued)*

	• Germany, Switzerland, Serbia, Spain Study design • Prospective cohort study
Participants	Number of included patients • 979 Surgical specialty • Noncardiac surgery Age • Mean 68 years (SD 8 years) Male sex • 54% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • 7.9% History of ischaemic heart disease • 25% History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • 28% 1 RCRI factor • 46% 2 RCRI factors • 19% 3 or more RCRI factors • 7%
Predictors	Predictor 1: NT-proBNP • Objective: biomarker compared

Weber 2013 *(Continued)*

	• Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Elecsys proBNP, Roche Diagnostics, Mannheim, Germany Predictor 2: High-sensitivity troponin T • Objective: biomarker compared • Category: blood • Scale: continuous • Threshold: not applicable Assay/device: Roche Diagnostics, Mannheim, Germany
Outcome	Outcome category • All-cause mortality and MACE Full outcome definition • All-cause mortality, acute myocardial infarction, cardiac arrest or ventricular fibrillation, cardio-pulmonary resuscitation, acute decompensated heart failure Prediction horizon • In-hospital events
Analysis	Domain 1: Participant selection • Low Justification: Domain 2: Predictors • Low Justification: Domain 3: Outcome • High Justification: MACE outcome is different from the MACE definition used in the development study
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: the authors state that they used the definitions by the original Lee paper, however the definition of CAD is different and others are not specified Domain 3: Outcome

Weber 2013 *(Continued)*

	• High Justification: MACE outcome is different from the MACE definition used in the development study Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Unclear	The authors state that they used the definitions by the original Lee paper, however the definition of CAD is different and others are not specified.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes; no information on handling missing outcomes; no calibration/reclassification measures were reported.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, predictor definitions were unclear/not reported including their assessment. Furthermore, the number of outcomes was low, no information on handling missing data and inappropriate reporting of performance measures.

Welten 2007

Study characteristics	
General information	Objective • Added biomarkers Journal • *European Journal of Vascular & Endovascular Surgery* Country • The Netherlands Study design • Retrospective cohort study
Participants	Number of included patients • 2642

Welten 2007 *(Continued)*

	Surgical specialty • Vascular surgery Age • Mean 66 years (SD 11 years) Male sex • 75% High-risk surgery • 79% Insulin-dependent diabetes mellitus • 15% History of ischaemic heart disease • 30% History of congestive heart failure • 5% History of cerebrovascular events • 31% Elevated creatinine • 6% 0 RCRI factors • 0% 1 RCRI factor • 51% 2 RCRI factors • 30% 3 or more RCRI factors • 18%
Predictors	Predictor 1: Type of surgery + age + history of hypertension (low, low-intermediate, high-intermediate and high risk of surgery; < 55, age 56 to 65, age 66 to 75 and > 70) • Objective: added biomarkers • Category: patient characteristics • Scale: not applicable • Threshold: not applicable Assay/device: not applicable
Outcome	Outcome category

Welten 2007 *(Continued)*

	• MACE Full outcome definition • Cardiac death, myocardial infarction, coronary revascularisation and heart failure Prediction horizon • 30-day events
Analysis	Number of outcomes • 287 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • High Justification: MACE outcome is different from the MACE definition used in the development study Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement

Welten 2007 *(Continued)*

Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	No measures of calibration/reclassification were reported and no information on handling missing data.
Overall judgement	No	Patient selection was appropriate. Predictors and outcomes were clearly defined and assessed. However, there was no information on missing data and no calibration/reclassification measures was reported.

Wijeysundera 2018

Study characteristics	
General information	Objective • Added biomarkers Journal • *Lancet* Country • Canada, UK, Australia and New Zealand Study design • Prospective cohort study
Participants	Number of included patients • 1401 Surgical specialty • Vascular surgery Age • Median 65 years (IQR 57 to 72 years) Male sex • 61% High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease

Wijeysundera 2018 *(Continued)*

- 12%

History of congestive heart failure

- 1%

History of cerebrovascular events

- 4%

Elevated creatinine

- Not reported

0 RCRI factors

- 45%

1 RCRI factor

- 45%

2 RCRI factors

- 8%

3 or more RCRI factors

- Not reported

Predictors	Predictor 1: Peak oxygen consumption • Objective: added biomarkers • Category: patient characteristic • Scale: not applicable • Threshold: not applicable • Assay/device: as measured during Cardiopulmonary Exercise Testing (CPET) Predictor 2: Anaerobic threshold • Objective: added biomarkers • Category: patient characteristic • Scale: not applicable • Threshold: not applicable • Assay/device: as measured during Cardiopulmonary Exercise Testing (CPET) Predictor 3: DASI • Objective: added biomarkers • Category: patient characteristic • Scale: not applicable • Threshold: not applicable • Assay/device: as measured using a questionnaire on functional capacity

Wijeysundera 2018 *(Continued)*

	Predictor 4: NT-proBNP • Objective: added biomarkers • Category: blood • Scale: continuous • Threshold: not applicable • Assay/device: Siemens Healthcare Diagnostics, Frimley, UK
Outcome	Outcome category • All-cause mortality or MACE; all-cause mortality Full outcome definition • All-cause mortality or myocardial infarction Prediction horizon • 30-day events; 1-year events
Analysis	Number of outcomes • 28 deaths or MACE Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: RCRI predictor definitions were not reported Domain 3: Outcome • High Justification: outcome used is different from the MACE definition used in the development study Overall judgement

Wijeysundera 2018 *(Continued)*

	• High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, there was no/unclear information on predictor definitions and outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing vascular surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	RCRI predictor definitions were not reported.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Complete case analysis, low number of outcomes and no reporting on calibration measures.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, predictor definitions were unclear/not reported including their assessment. Furthermore, the number of outcomes was low, complete case analysis and inappropriate reporting of performance measures.

Wilcox 2019

Study characteristics	
General information	Objective • Prediction model compared Journal • *Stroke* Country • USA Study design • Prospective existing registry
Participants	Number of included patients • 54,717 Surgical specialty • Noncardiac surgery Age • Not reported

Wilcox 2019 *(Continued)*

	Male sex • Not reported High-risk surgery • Not reported Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • Not reported 0 RCRI factors • Not reported 1 RCRI factor • Not reported 2 RCRI factors • Not reported 3 or more RCRI factors • Not reported
Predictors	Predictor 1: ACS-NSQIP surgical risk score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 2: ACS-NSQIP MICA • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable

Wilcox 2019 *(Continued)*

	Predictor 3: MASHOUR • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 4: $CHADS_2$-VASC • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable Predictor 5: $CHADS_2$ • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • Stroke Full outcome definition • Not applicable Prediction horizon • 30-day events
Analysis	Number of outcomes • 1474 Handling missing data • Missing data on outcome timing was imputed by median imputation Discrimination reported? • Yes Calibration reported? • No

Wilcox 2019 *(Continued)*

	Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • High Justification: different definition for ischaemic heart disease and unclear definition for high-risk surgery and congestive heart failure Domain 3: Outcome • High Justification: outcome is stroke and not MACE Overall judgement • High Justification: patients selected were generalisable to the patient population used in the RCRI development study. However, no/unclear information on predictor definitions for some items and other predictors of the original RCRI were not included or had a different definition. In addition, outcome definition was different compared to the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	No	Different definition for ischaemic heart disease and unclear definition for high-risk surgery and congestive heart failure.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	Yes	However, method of handling missing data was not appropriate and no reporting of calibration measures.
Overall judgement	No	Patient selection was appropriate. Outcome definitions were clearly defined and comparable to the definitions used in the development study. However, no/unclear information on predictor definitions for some items and other predictors of the original RCRI were not included or had a different definition. In addition, method of handling missing data was not appropriate and no reporting of calibration measures.

Wotton 2013

Study characteristics	
General information	Objective • Prediction model compared Journal • *Journal of Cardiothoracic Surgery* Country • United Kingdom Study design • Prospective cohort
Participants	Number of included patients • 703 Surgical specialty • Thoracic surgery Age • Median 68 years; < 55 years: 18%, 55 to 65 years: 25%, > 65 years: 57% Male sex • 57% High-risk surgery • 100% Insulin-dependent diabetes mellitus • Not reported History of ischaemic heart disease • Not reported History of congestive heart failure • Not reported History of cerebrovascular events • Not reported Elevated creatinine • 9% 0 RCRI factors • 0% 1 RCRI factor • 69%

Wotton 2013 *(Continued)*

	2 RCRI factors • 21% 3 or more RCRI factors • 9.5%
Predictors	Predictor 1: ThRCRI • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • All-cause mortality and MACE Full outcome definition • Pulmonary oedema, myocardial infarction, ventricular fibrillation arrest, supraventricular arrhythmia, atrial fibrillation and all-cause mortality Prediction horizon • 30-day events
Analysis	Number of outcomes • 34 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Unclear Justification: no information regarding the definition of some of the RCRI variables Domain 3: Outcome

Wotton 2013 *(Continued)*

	• High Justification: definition differs from outcome in development study (mainly because of addition of atrial fibrillation and all-cause mortality to the composite outcome)
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Although only patients undergoing thoracic surgery were included, participant selection was appropriate and the RCRI model can be applied in these patients.
Domain 2: Predictors	Unclear	No information regarding the definition of some of the RCRI variables.
Domain 3: Outcome	Yes	Clearly defined outcome definitions and appropriate adjudication of outcomes.
Domain 4: Analysis	No	Low number of outcomes, no information on handling missing outcomes, no information on blinding and no reporting on calibration measures.
Overall judgement	No	Patient selection was appropriate. Outcomes were clearly defined and assessed. However, predictor definitions were unclear/not reported including their assessment. Furthermore, the number of outcomes was low, no information on handling of missing data and inappropriate reporting of performance measures.

Yang 2012

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Korean Journal of Internal Medicine* Country • Republic of Korea Study design • Prospective cohort study
Participants	Number of included patients • 365 Surgical specialty • Vascular surgery Age • Median 67.1 years (SD 8.5 years)

Yang 2012 *(Continued)*

Male sex

- 91%

High-risk surgery

- Not reported

Insulin-dependent diabetes mellitus

- 3.8%

History of ischaemic heart disease

- Not reported

History of congestive heart failure

- 2.2%

History of cerebrovascular events

- Not reported

Elevated creatinine

- 2.5%

0 RCRI factors

- 40.3%

1 to 2 RCRI factors

- 51.8%

2 RCRI factors

- Not reported

3 or more RCRI factors

- 7.9%

Predictors	Predictor 1: Ischaemia on a thallium scan • Objective: added biomarkers • Category: imaging • Scale: dichotomous • Threshold: a positive result on the stress thallium scan was defined as a perfusion defect at any segment to any degree and significant perfusion defect as a large (≥ 3 walls), moderate to severely decreased, reversible defect on the stress thallium scan • Assay/device: not reported Predictor 2: NT-proBNP • Objective: added biomarker, biomarkers compared • Category: blood • Scale: dichotomous

Yang 2012 *(Continued)*

	• Threshold: 302 pg/mL • Assay/device: not reported
Outcome	Outcome category • MACE Full outcome definition • Primary cardiovascular death, myocardial infarction, development of aggravation of congestive heart failure Prediction horizon • In-hospital or 30-day events
Analysis	Number of outcomes • 49 Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • Low Justification: outcome definitions were clearly defined and comparable to the definitions used in the development study Overall judgement: • Low Patient selected were generalisable to the patient population used in the RCRI development study. Predictor and outcome definitions were clearly defined/assessed and comparable to the definitions used in the RCRI development study.

Yang 2012 *(Continued)*

Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Eligible patients needed to be referred to the cardiologist before surgery.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	No	The authors defined myocardial infarction solely as a rise in troponin and no information on blinding.
Domain 4: Analysis	No	Low number of outcomes, no information on handling missing data, no information on blinding and dichotomisation of the predictors.
Overall judgement	No	Predictor definitions were clearly defined/reported and assessed. However, patient selection was inappropriate as only a selected group of high-risk patients were included. Outcome definition was inappropriate as myocardial infarction was solely defined as a rise in troponin. Furthermore, the number of outcomes was low, no information on the handling of missing data and dichotomisation of predictors.

Yang 2018

Study characteristics	
General information	Objective • Added biomarkers, biomarkers compared Journal • *Annals of Laboratory Medicine* Country • Republic of Korea Study design • Prospective cohort study
Participants	Number of included patients • 175 Surgical specialty • Noncardiac surgery Age • Median 66 years (SD 12 years) Male sex • 51.4%

Yang 2018 *(Continued)*

High-risk surgery

- 56%

Insulin-dependent diabetes mellitus

- 2.9%

History of ischaemic heart disease

- 8.6%

History of congestive heart failure

- 3.4%

History of cerebrovascular events

- 10.3%

Elevated creatinine

- 6.9%

0 RCRI factors

- 33.1%

1 RCRI factor

- 51.4%

2 RCRI factors

- 11.4%

3 or more RCRI factors

- 4%

Predictors	Predictor 1: High-sensitivity troponin I • Objective: added biomarkers, biomarkers compared • Category: blood • Scale: dichotomous • Threshold: 53 ng/L • Assay/device: ARCHITECT STAT high-sensitivity troponin-I chemiluminescence immunoassay on an i2000 analyser (Abbott diagnostics, Abbott Park, IL, USA) Predictor 2: sST2 (soluble suppression of tumorigenicity-2) • Objective: added biomarker, biomarkers compared • Category: blood • Scale: dichotomous • Threshold: 182 ng/mL • Assay/device: Presage ST2 Assay (Critical Diagnostics, San Diego, CA, USA)

Yang 2018 *(Continued)*

	Predictor 3: High-sensitivity troponin I +sST2 • Objective: added biomarker, biomarkers compared • Category: blood • Scale: dichotomous • Threshold: 182 ng/mL • Assay/device: ARCHITECT STAT high-sensitive troponin-I chemiluminescence immunoassay on an i2000 analyser (Abbott diagnostics, Abbott Park, IL, USA) and Presage ST2 Assay (Critical Diagnostics, San Diego, CA, USA)
Outcome	Outcome category • All-cause mortality and MACE Full outcome definition • All-cause mortality, nonfatal cardiac arrest, myocardial infarction and acute decompensated heart failure Prediction horizon • 30-day events
Analysis	Number of outcomes • 16 Handling missing data • Complete case analysis Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • Yes
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • Unclear Justification: no information on how the composite outcomes were defined and whether assessors were blinded

Yang 2018 *(Continued)*

	Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome definitions were unclear/not reported including their assessment.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	No	Inappropriate exclusion of many patients: 150 who did not provide informed consent and 71 patients who could not undergo biomarker testing. Only 10% of the original sample was included in the study.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Unclear	No information on how the composite outcomes were defined and whether assessors were blinded
Domain 4: Analysis	No	Low number of outcomes, no information on handling missing outcomes, no information on blinding and dichotomisation of the predictors.
Overall judgement	No	Predictor definitions were clearly defined and assessed. However, patient selection was inappropriate as only a selected group of high-risk patients were included. Outcome definitions were unclear/not reported including their assessment. Furthermore, the number of outcomes was low, no information on the handling of missing data and dichotomisation of predictors.

Yap 2018

Study characteristics	
General information	Objective • Prediction model compared Journal • *Heart Asia* Country • Philippines Study design • Prospective cohort study
Participants	Number of included patients • 424 Surgical specialty • Noncardiac surgery

Yap 2018 *(Continued)*

	Age • Median 54.3 years (SD 16.3 years) Male sex • 37% High-risk surgery • 38% Insulin-dependent diabetes mellitus • 17% History of ischaemic heart disease • 13% History of congestive heart failure • 3% History of cerebrovascular events • Not reported Elevated creatinine • 8% 0 RCRI factors • 45% 1 RCRI factor • 42% 2 RCRI factors • 8% 3 or more RCRI factors • 5%
Predictors	Predictor 1: ACS-NSQIP surgical risk score • Objective: prediction model compared • Category: prediction model • Scale: not applicable • Threshold: not applicable • Assay/device: not applicable
Outcome	Outcome category • MACE Full outcome definition • Cardiac arrest, acute myocardial infarction and heart failure

Yap 2018 *(Continued)*

	Prediction horizon • In-hospital events
Analysis	Number of outcomes • 12 Handling missing data • No information on handling missing data Discrimination reported? • Yes Calibration reported? • No Reclassification reported? • No
PROBAST: Applicability	Domain 1: Participant selection • Low Justification: patient selection was appropriate and generalisable to the population used in the RCRI development study Domain 2: Predictors • Low Justification: predictor definitions were clearly defined and comparable to the definitions used in the development study Domain 3: Outcome • High Justification: outcome definition of MACE is different from the outcome used in the development study Overall judgement • High Justification: patient selection was appropriate and predictor definitions were clearly defined and comparable to definitions used in the development study. However, the outcome used was different from MACE in the development study.
Notes	—

Item	Authors' judgement	Support for judgement
Domain 1: Participant selection	Yes	Appropriate participant selection in which patients were selected in whom the RCRI model can be applied.
Domain 2: Predictors	Yes	Clear (RCRI) predictor definitions were described.
Domain 3: Outcome	Unclear	No composite outcome definitions and no information on blinding.

Yap 2018 *(Continued)*

Domain 4: Analysis	No	Low number of outcomes, no information on missing data and no calibration measures were reported.
Overall judgement	No	Patient selection was appropriate. Predictors were clearly defined and assessed. However, outcome definitions were unclear/not reported including their assessment. Furthermore, the number of outcomes was low, there was no information on missing data and no calibration was reported.

AAA: abdominal aortic aneurysm; AAI: ankle-to-arm blood pressure index; ACS-NSQIP: American College of Surgeons National Surgical Quality Improvement; AF: atrial fibrillation; ASA: American Society of Anesthesiologists; BNP: brain natriuretic peptide; CACS: Coronary artery calcium scores; CAD: coronary artery disease; CHF: congestive heart failure; COPD: chronic obstructive pulmonary disease; CPR: Cardiopulmonary resuscitation; CRP: C-reactive protein; CT: computed tomography; CTA: computed tomography angiography; DSE: dobutamine stress echocardiography; DVAMC: Durham Veterans Administration Hospital; ECG: electrocardiogram; eGFR: estimated glomerular filtration rate; ICD: International Classification of Diseases; IHD: ischaemic heart disease; IPD: individual patient data; IQR: interquartile range; LTSS: long term survival score; LVEF: left ventricular ejection fraction; MACE: major adverse cardiac events; MET: metabolic equivalents; MI: myocardial infarction; MICA: myocardial infarction or cardiac arrest; MINS: myocardial injury after noncardiac surgery; MUGA: multigated acquisition scan; NSQIP: National Surgical Quality Improvement; NT-proBNP: (NT-pro)brain natriuretic peptide; PCI: percutaneous coronary intervention; PTCA: percutaneous transluminal coronary angioplasty; RCRI: Revised Cardiac Risk Index; RCT: randomised controlled trial; SD: standard deviation; SORT: Surgical Outcome Risk Tool; SPECT: single photon emission computed tomography; STEMI: ST-elevation myocardial infarction; TTE: transthoracic echocardiography; UAP: unstable angina pectoris

Characteristics of excluded studies *[ordered by study ID]*

Study	Reason for exclusion
Abbott 2017	No prediction
Abbott 2019	No prediction
Abdelmalak 2018	No external validation of RCRI
Abdullah 2017	No prediction
Abdullaha 2018	No external validation of RCRI
Abelha 2009	No prediction
Abelha 2010	No prediction
Abelha 2012	No prediction
Ackland 2007	No prediction
Ackland 2010	Other prediction model
Ackland 2011	No prediction
Ackland 2018	No prediction
Agarwal 2013	No prediction
Albaladejo 2011	No prediction
Alcock 2012	No prediction

Study	Reason for exclusion
Alcock 2013	No prediction
Alvarez 2016	No prediction
Ambler 2014	No prediction
Andersson 2015	External validation only without added value or comparison
Anghelescu 2018	No external validation of RCRI
Arain 2016	No prediction
Armstrong 2017	No prediction
Azevedo 2017	No prediction
Bae 2014	No external validation of RCRI
Baer-Bositis 2018	No prediction
Bajaj 2013	No prediction
Bakker 2012	No prediction
Bakker 2013	No prediction
Barisione 2016	No prediction
Barrett 2007	No prediction
Batsis 2009	No prediction
Belmont 2014	No external validation of RCRI
Bertges 2010	No external validation of RCRI in the same cohort
Biccard 2007	No prediction
Biccard 2010	No prediction
Biccard 2012a	No external validation of RCRI
Biccard 2013	Non-original research (review, comment, guideline etc.)
Biccard 2014	Non-original research (review, comment, guideline etc.)
Biccard 2015	Non-original research (review, comment, guideline etc.)
Biteker 2011	No prediction
Biteker 2011a	No prediction
Biteker 2012	No prediction
Biteker 2014	No prediction

Study	Reason for exclusion
Biteker 2014a	No prediction
Bolliger 2009	No external validation of RCRI
Bolliger 2012	No prediction
Borges 2013a	No external validation of the RCRI
Butt 2009	No prediction
Calvillo-King 2010	No external validation of RCRI
Canter 2008	No external validation of RCRI
Cassagneau 2012	No external validation of RCRI
Chan 2018	Other prediction model
Chang 2019	No external validation of RCRI
Chen 2002	No external validation of RCRI
Christiansen 2017	No external validation of RCRI
Cicarelli 2001	External validation only without added value or comparison
Cloney 2017	No prediction
Cook 2017	No external validation of RCRI
Crowther 2018	No external validation of RCRI
Cullen 2020	No external validation of RCRI
Cuthbertson 2007a	No external validation of RCRI
Cuthbertson 2007b	No external validation of RCRI
Davies 2015	No prediction
Davies 2015a	No prediction
Davis 2018	No prediction
de Campos 2012	No external validation of RCRI
Dernellis 2006	Other prediction model
Devereaux 2011	External validation only without added value or comparison
de Virgilio 2009	No prediction
Dover 2013	External validation only without added value or comparison
Drake 2016	No external validation of RCRI

Study	Reason for exclusion
Drudi 2016	No external validation of RCRI
Duceppe 2018	No external validation of RCRI
Duceppe 2019	No external validation of RCRI
Edelmuth 2018	No external validation of RCRI
Ekeloef 2017	No prediction
Ekeloef 2020	No external validation of RCRI
Ekeloef 2020a	Postoperative biomarker was evaluated
Erol 2019	No prediction
Eyraud 2000	No external validation of RCRI
Faggiano 2012	No prediction
Fayad 2011	No external validation of RCRI
Feringa 2006	No prediction
Feringa 2006a	No prediction
Feringa 2007a	No external validation of RCRI
Feringa 2009	No prediction
Ferrante 2018	No external validation of the RCRI
Filipovic 2003	No prediction
Filipovic 2005	No external validation of RCRI
Flu 2009	No external validation of RCRI
Flu 2010	Other prediction model
Flu 2010a	No external validation of RCRI
Galal 2010	No prediction
Garcia 2009	External validation only without added value or comparison
Garcia 2013	No external validation of RCRI
Ghadri 2012	No external validation of RCRI
Ghazali 2017	No external validation of RCRI
Gibson 2007	No external validation of RCRI
Gillmann 2019	No external validation of RCRI

Study	Reason for exclusion
Go 2017	No external validation of RCRI
Goei 2009	No external validation of RCRI
Goh 2000	No external validation of RCRI
Gómez 2012	No prediction
Goodman 2015	No prediction
Gu 2018	No prediction
Gundes 2017	No prediction
Halm 2005	No prediction
Halm 2009	No prediction
Halm 2009a	No prediction
Hammill 2008	No prediction
Hansen 2016	No prediction
Hanss 2008	RCRI was part of the inclusion criteria
Harland 2020	No external validation of RCRI
Hawn 2013	No prediction
Hennis 2012	No external validation of RCRI
Hietala 2014	No prediction
Hirano 2014	No prediction
Hirpara 2019	No external validation of RCRI
Hoeks 2007	No prediction
Hoeks 2008	No prediction
Hoeks 2009	No prediction
Hoeks 2009a	No prediction
Hoeks 2010	No external validation of RCRI
Hofer 2018	Other prediction model
Hoftman 2013	External validation only without added value or comparison
Hokari 2015	Other prediction model
Holcomb 2016	No prediction

Study	Reason for exclusion
Holcomb 2016a	No prediction
Hollis 2016	No prediction
Huang 2017	No prediction
Jakobson 2014	No prediction
Kamber 2018	No external validation of RCRI
Kanakaraj 2017	Other prediction model
Karakas 2013	Non-original research (review, comment, guideline etc.)
Kazimierczak 2015	Other prediction model
Kerry 2011	Non-original research (review, comment, guideline etc.)
Kertai 2004	No prediction
Khambalia 2015	No prediction
Kikura 2008	No prediction
Kim 2013	No prediction
Kim 2016	No external validation of RCRI
Kim 2016a	No external validation of RCRI
Kim 2018	No external validation of RCRI
Kim 2019	No external validation of RCRI
Kistan 2018	No external validation of RCRI
Koh 2012	No prediction
Kougias 2013	No prediction
Kougias 2017	No prediction
Kronzer 2016	Non-original research (review, comment, guideline etc.)
Kronzer 2016a	No prediction
Kumar 2017	No prediction
Küpper 2015	Other prediction model
Ladha 2018	No external validation of RCRI
Lau 2013	No external validation of RCRI
Lee 1999	Development study, external validation only without added value or comparison

Study	Reason for exclusion
Leibowitz 2009	No prediction
Levitan 2016	No prediction
Li 2016	No external validation of RCRI
Licker 2011	Other prediction model
Licker 2013	No external validation of RCRI
Liem 2018	No external validation of RCRI
Lin 2005	No prediction
Lin 2016	Other prediction model
Lin 2017	No prediction
Lindenauer 2004	No prediction
Lindenauer 2005	No prediction
Liu 2013	No external validation of RCRI
Lo 2014	No prediction
Long 2016	No prediction
Lucreziotti 2007	No prediction
Lupei 2014	No prediction
Maas 2007	No external validation of RCRI
MacIntyre 2018	No prediction
Mahmoud 2016	No prediction
Mann 2020	No external validation of RCRI
Marinho 2018	No prediction
Marsman 2020	No external validation of RCRI
Marston 2013	No prediction
Martins 2011	No external validation of RCRI
Mases 2014	No prediction
Matsumoto 2016	No prediction
May 2019	No prediction
McIlroy 2015	No prediction

Study	Reason for exclusion
Meershoek 2020	No external validation of RCRI
Mendonca 2014	No prediction
Mitropoulos 2006	Other prediction model
Moitra 2011	No external validation of RCRI
Moodley 2015	No prediction
Moodley 2015a	No prediction
Mooney 2016	No prediction
Moran 2008	External validation only without added value or comparison
Moses 2018	Other prediction model
Mureddu 2017	Non-original research (review, comment, guideline etc.)
Nagayoshi 2012	No prediction
Nepogodiev 2015	Non-original research (review, comment, guideline etc.)
Noordzij 2010	No external validation of RCRI
Noordzij 2015	No external validation of RCRI
Nordling 2016	No external validation of RCRI
Nutt 2012	No external validation of RCRI
O'Neill 2016	No prediction
Oberweis 2015	No prediction
Ochroch 2006	No prediction
Oliveros 2005	No external validation of RCRI
Oscarsson 2009	No external validation of RCRI
Oscarsson 2009a	No external validation of RCRI
Oshin 2013	No prediction
Padayachee 2018	No prediction
Paladugu 2020	Non-original research (review, comment, guideline etc.)
Parente 2013	No prediction
Parikh 2020	No external validation of RCRI
Park 2018	No external validation of RCRI

Study	Reason for exclusion
Patel 2018	No prediction
Patorno 2015	No prediction
Patorno 2016	No prediction
Payne 2011	No external validation of RCRI
Payne 2013	External validation only without added value or comparison
Pereira 2016	No external validation of RCRI
Pili-Floury 2012	No external validation of RCRI
Pinho 2016	No prediction
Puelacher 2018	No prediction
Rajagopalan 2008	No external validation of RCRI
Rao 2012	External validation only without added value or comparison
Redman 2014	No prediction
Reeh 2016	No prediction
Reeve 2018	No prediction
Reis 2018	No external validation of RCRI
Richards 2015	No prediction
Richardson 2018	No external validation of RCRI
Rinfret 2004	No prediction
Rodriguez 2018	No prediction
Rodseth 2014	No external validation of RCRI
Rosenberg 2016	No prediction
Roshanov 2017	Non-original research (review, comment, guideline etc.)
Roxburgh 2011	No prediction
Sakuma 2010	No prediction
Salinas 2012	No prediction
Sankar 2014	Other prediction model
Sankar 2019	No external validation of RCRI
Schier 2012	No external validation of RCRI

Study	Reason for exclusion
Schier 2013	No prediction
Shalaeva 2016	No external validation of RCRI
Silva 2020	No prediction
Simeoni 2016	No prediction
Skaro 2016	No prediction
Smilowitz 2016	No prediction
Smilowitz 2018	No prediction
Smolock 2012	No prediction
Snowden 2010	No external validation of RCRI
Snowden 2013	No external validation of RCRI
Sousa 2016	No prediction
Stevens 2017	No prediction
Sunny 2018	External validation only without added value or comparison
Tao 2008	Other prediction model
Tashiro 2014	External validation only without added value or comparison
Tavakoli 2009	Other prediction model
Teixeira 2014	No prediction
Toda 2018	No prediction
Tong 2015	Wrong population
Toyonaga 2017	No external validation of RCRI
Valentijn 2013	No prediction
Valentijn 2013a	No prediction
van Kuijk 2009	No prediction
Vanniyasingam 2016	No external validation of RCRI
van Waes 2017	Postoperative biomarker measurement
Vanwagner 2012	No prediction
VanWagner 2014	No external validation of RCRI
Veiga 2012	No prediction

Study	Reason for exclusion
Venkatraghavan 2015	No prediction
Vetrugno 2018	Non-original research (review, comment, guideline etc.)
Waliszek 2011	No prediction
Ward 2006	No prediction
Warnakulasuriya 2017	No prediction
Weissman 2011	No external validation of RCRI
Widmer 2018	No prediction
Wijeysundera 2010	No prediction
Wijeysundera 2011	No prediction
Wijeysundera 2012	No prediction
Wijeysundera 2020	No external validation of RCRI
Wilson 2010	No external validation of RCRI
Xara 2015	No external validation of RCRI
Yun 2008	No external validation of RCRI
Yurtlu 2016	No prediction

RCRI: Revised Cardiac Risk Index

Characteristics of studies awaiting classification *[ordered by study ID]*

Alexander 2008

Notes	No full text available

Andreenko 2003

Notes	No full text available

Author unknown 2010

Notes	No full text available

Author unknown 2011

Notes	No full text available

Barbarash 2012

Notes	No full text available

Can 2018

Notes	No full text available

Caruso 2006

Notes	No full text available

Dobrushina 2012

Notes	No full text available

Domínguez 2014

Notes	No full text available

Faris 1999

Notes	No full text available

Ghorra 1999

Notes	No full text available

Gnocchi 2000

Notes	No full text available

Grabowska-Gawel 2004

Notes	No full text available

Kapma 2017

Notes	No full text available

Kavarana 2003

Notes	No full text available

Kertai 2003

Notes	No full text available

Khan 2010

Notes	No full text available

Khoronenko 2009

Notes	No full text available

Kim 2017

Notes	No full text available

Knaak 2020

Notes	No full text available

Kozlov 2016

Notes	No full text available

Kuznetsov 2018

Notes	No full text available

Law 2014

Notes	No full text available

Leo 2005

Notes	No full text available

Li 2016a

Notes	No full text available

Li 2018

Notes	No full text available

Macan 2004

Notes	No full text available

Martinez 2018

Notes	No full text available

Maruoka 2018

Notes	No full text available

Moodley 2018

Notes	No full text available

Mori 2014

Notes	No full text available

Peretich (year of publication unknown)

Notes	No full text available

Ray 2013

Notes	No full text available

Shevchenko 2005

Notes	No full text available

Stelzner 2003

Notes	No full text available

Sumin 2012

Notes	No full text available

Sumin 2013

Notes	No full text available

Vanzetto 1999

Notes	No full text available

Wolf 2001

Notes	No full text available

Wunderlich 2005

Notes	No full text available

Yamada 2019

Notes	No full text available

Yi 2015

Notes	No full text available

Zarich 2001

Notes	No full text available

Characteristics of ongoing studies *[ordered by study ID]*

CTRI/2019/02/017668

Study name	To predict 30-day in hospital mortality and morbidity using preoperative hand grip strength and comparing it with existing Revised Cardiac Risk Index and Modified Frailty Index
Starting date	February 2019
Contact information	Kompal Jain, Department of Anaesthesia and Intensive Care, Government Medical College and Hospital, Sector - 32, Chandigarh, India
Notes	To predict 30-day in hospital mortality and morbidity using preoperative hand grip strength and comparing it with existing Revised Cardiac Risk Index and Modified Frailty Index

NCT01280253

Study name	Preoperative biochemical predictors of outcome in patients with hip fracture
Starting date	January 2011
Contact information	Peter Bentzer, MD, PhD, Skane University Hospital
Notes	The objective of the study is to identify biochemical predictors of morbidity and mortality in patients suffering from hip fracture. Biochemical predictors include pro-brain natriuretic peptide, lactate, pro-calcitonin, adrenomedullin, copeptin, cystatin c. The predictive value of the potential markers will be compared to that of ASA, RCRI and POSSUM.

NCT02146560

Study name	TEAMS (Troponin Elevation After Major Surgery) Study (TEAMS)
Starting date	August 2014
Contact information	University Health Network, Toronto
Notes	This study will compare postoperative health-related quality of life of patients who did or did not experience perioperative myocardial injury (defined by troponin-I > 0.07 ng/ml) after noncardiac surgery. Clinically based risk stratification tools used in noncardiac surgery (e.g. Revised Cardiac Risk Index) are of moderate utility and assign patients only to broad risk categories. This study will examine the usefulness of pre-operative biomarkers (BNP, HbA1c and others) in supporting cardiac risk

NCT02146560 *(Continued)*

	stratification and will address the question: Is there a set of preoperative criteria that can accurately inform the decision to monitor troponin postoperatively?

NCT02860754

Study name	The prognostic capabilities of a preoperative six-minute walk test to independently inform cardiovascular risk after major noncardiac surgery
Starting date	August 2016
Contact information	Amal Bessissow, MD, McGill University Health Centre/Research Institute of the McGill University Health Centre
Notes	This prospective cohort study aims to determine whether the addition of the 6MWT to the RCRI score improves the risk prediction of postoperative cardiovascular outcomes after noncardiac surgery. In addition, this study will assess whether the patients' reported MET score corresponds to the determined MET score from the 6MWT distance completed.

NCT03016936

Study name	MET: REevaluation for Perioperative cArdIac Risk (MET-REPAIR)
Starting date	1 August 2017
Contact information	Giovanna Lurati Buse, PD Dr, University Hospital, Düsseldorf, Germany
Notes	Multicentre international prospective cohort study designed to answer the question: "In patients undergoing elevated risk noncardiac surgery, are METs estimated by questionnaire associated with perioperative major adverse cardiovascular events or cardiovascular mortality?" If so: 1. What is the optimal cut-off for METs estimated by questionnaire to predict perioperative major adverse cardiovascular events or cardiovascular mortality? 2. How does the optimal cut-off compare with the currently guideline-endorsed 4-MET cut-off? MET-REPAIR will examine the ability of MET estimated using a questionnaire to predict perioperative cardiovascular events correcting for preoperative risk factors, (e.g. comorbidity and type of surgery) and calculate the effect on risk stratification (net reclassification improvement) by the addition of METs estimated by questionnaire to established risk scores, such as the Revised Cardiac Risk Score (Lee-index) and the NSQIP MICA.

NCT03436238

Study name	Myocardial Injury in Noncardiac Surgery in Sweden (MINSS)
Starting date	15 May 2017
Contact information	Michelle Chew, Professor, Senior Consultant, Linkoeping University
Notes	The purpose of this multicentre, prospective, observational study is to identify robust biochemical markers that predict adverse cardiovascular outcomes and mortality in patients undergoing major abdominal surgery.

NCT03436238 *(Continued)*	Plasma levels of hsTnT, NTproBNP, copeptin, MR-proADM and CT-proET1 will be measured. Receiver operating curve analysis will be used to determine the optimal threshold of each biomarker in predicting mortality/MACCE. The net reclassification index will be used to assess if biomarkers confer added value to the RCRI for the classification of MACCE.

6MWT: six-minute walk test; ASA: American Society of Anesthesiologists; BNP: brain natriuretic peptide; MACCE: major adverse cardiac and cerebrovascular events; MET: metabolic equivalents; MICA: myocardial infarction or cardiac arrest; NSQIP: National Surgical Quality Improvement; POSSUM: Physiological and Operative Severity Score for the enUmeration of Mortality and morbidity; RCRI: Revised Cardiac Risk Index

ADDITIONAL TABLES

Table 1. Scoring of the Revised Cardiac Risk Index

Predictor	Definition	Point distribution
High-risk surgery	Intraperitoneal, intrathoracic, or suprainguinal vascular surgery	1
Ischaemic heart disease	History of myocardial infarction, positive exercise test, current complaint of ischaemic chest pain or use of nitrate therapy, or ECG with Q waves. Patients with prior CABG surgery or PTCA were included in this definition only if they had current complaints of chest pain that were presumed to be due to ischaemia.	1
History of congestive heart failure	History of congestive heart failure, pulmonary oedema, or paroxysmal nocturnal dyspnoea, physical examination showing bilateral rales or S3 gallop, or chest radiograph showing pulmonary vascular redistribution.	1
History of cerebrovascular disease	History of transient ischaemic attack or stroke.	1
Insulin therapy for diabetes mellitus	—	1
Preoperative serum creatinine > 2.0 mg/dL	—	1

Complication rates in patients with none of these predictors is 0.4%, with 1 point is 1.0%, 2 points is 7% and 3 or more points is 11%.
CSBG: coronary artery bypass graft; ECG: electrocardiogram; PTCA: percutaneous transluminal coronary angioplasty

Table 2. PICOTS for the objectives based on the CHARMS checklist

Population	Patients undergoing noncardiac surgery
Index Model	Revised Cardiac Risk Index (RCRI)
Comparator	Biomarker(s) added or compared to the RCRI; other prediction models compared to the RCRI
Outcome(s)	Postoperative occurrence of (in-hospital) major adverse cardiac events, all-cause mortality and other adverse outcomes
Timing	Time point of prognostication: before surgery Prediction horizon: in-hospital, but all time spans are included

Table 2. PICOTS for the objectives based on the CHARMS checklist *(Continued)*

Setting	To inform physicians of the patient's risk of developing in-hospital events after noncardiac surgery

Table 3. Study characteristics of included studies

	All validations	Added value of biomarkers	Comparison of biomarkers	Comparison of prediction models
N	172	62	89	79
Geographical area (%)				
Europe	51 (29.8)	22 (35.5)	24 (27.3)	28 (35.9)
North America	63 (36.8)	12 (19.4)	42 (47.7)	27 (34.6)
Asia	20 (11.7)	14 (22.6)	10 (11.4)	3 (3.8)
Africa	2 (1.2)	1 (1.6)	1 (1.1)	1 (1.3)
Australia	1 (0.6)	0 (0.0)	1 (1.1)	0 (0.0)
South America	5 (2.9)	1 (1.6)	1 (1.1)	4 (5.1)
Combination	29 (17.0)	12 (19.4)	9 (10.2)	15 (19.2)
Data collection (%)				
Prospective	124 (72.5)	44 (71.0)	66 (74.2)	25 (32.1)
Retrospective	41 (24.0)	15 (24.2)	18 (20.2)	54 (68.4)
Unclear	6 (3.5)	3 (4.8)	5 (5.6)	0 (0.0)
Study design (%)				
Cohort	130 (75.6)	57 (91.9)	57 (64.0)	68 (86.1)
Existing registry	35 (20.3)	2 (3.2)	26 (29.2)	9 (11.4)
Case-control	1 (0.6)	0 (0.0)	0 (0.0)	1 (1.3)
Existing RCT	1 (0.6)	1 (1.6)	1 (1.1)	1 (1.3)
Individual patient data meta-analysis	5 (2.9)	2 (3.2)	5 (5.6)	0 (0.0)
Surgical specialty (%)				
Noncardiac	77 (44.8)	36 (58.1)	30 (33.7)	37 (46.8)
Vascular	47 (27.2)	19 (30.2)	23 (25.6)	25 (31.6)
ENT and dental	2 (1.2)	1 (1.6)	1 (1.1)	1 (1.3)
General	5 (2.9)	0 (0.0)	2 (2.2)	4 (5.1)

Table 3. Study characteristics of included studies *(Continued)*

Neurological	25 (14.5)	0 (0.0)	24 (26.7)	1 (1.3)
Orthopaedic	8 (4.6)	3 (4.8)	5 (5.6)	5 (6.3)
Other	5 (2.9)	1 (1.6)	2 (2.2)	3 (3.8)
Not specified	3 (1.7)	2 (3.2)	2 (2.2)	3 (3.8)
Prediction horizon (%)				
Intraoperative events	1 (0.6)	0 (0.0)	1 (1.1)	1 (1.3)
1 to 7 days	7 (4.1)	6 (9.7)	7 (7.9)	1 (1.3)
In-hospital events	25 (14.5)	12 (19.4)	13 (14.6)	14 (17.7)
In-hospital or within 30 days	10 (5.8)	8 (12.9)	2 (2.2)	2 (2.5)
30-day events	109 (63.4)	29 (46.8)	59 (66.3)	52 (65.8)
> 30 days (long-term)	12 (7.0)	6 (9.7)	5 (5.6)	4 (5.1)
Not reported	8 (4.6)	1 (1.6)	2 (2.2)	5 (6.3)
Outcome (%)				
MACE	70 (40.7)	31 (50.0)	35 (39.3)	32 (40.5)
MICA	8 (4.7)	2 (3.2)	0 (0.0)	7 (8.9)
Myocardial infarction	5 (2.9)	3 (4.8)	3 (3.4)	0 (0.0)
Cardiovascular mortality	6 (3.5)	3 (4.8)	1 (1.1)	2 (2.5)
Troponin elevation/myocardial injury	6 (3.5)	5 (8.1)	4 (4.5)	3 (3.8)
All-cause mortality	22 (12.8)	6 (9.7)	10 (11.2)	13 (16.5)
All-cause mortality and MACE	15 (8.7)	8 (12.9)	7 (7.9)	6 (7.6)
Other	40 (23.3)	4 (6.5)	29 (32.6)	16 (20.3)
Number of participants (median (IQR))	922 (244 to 9267)	442 (223 to 1389)	594 (227 to 52066)	941 (251 to 2284)
Number of events (median (IQR))	49 (23 to 112)	38 (21 to 84)	39 (19 to 77)	64 (21 to 132)
Incidence (median (IQR))	0.06 (0.02 to 0.13)	0.09 (0.05 to 0.14)	0.06 (0.02 to 0.13)	0.06 (0.03 to 0.14)

RCT: randomised controlled trial; noncardiac: patients of multiple (noncardiac) surgical specialties were included in the analysis; ENT: ear, nose and throat; MACE: major adverse cardiac events; MICA: myocardial infarction and cardiac arrest; IQR: interquartile range

Table 4. Composites used to define major adverse cardiac events (MACE)

	Overall	Added value of biomarkers	Comparison of biomarkers	Comparison of prediction models
n	93	41	42	45
Cardiac death	28 (30.1)	14 (34.5)	16 (38.1)	11 (24.4)
Cardiovascular death	16 (17.2)	9 (22.0)	8 (19.0)	6 (13.3)
All cause mortality	17 (18.3)	9 (22.0)	8 (19.0)	6 (13.3)
Nonfatal myocardial infarction	22 (23.7)	11 (26.8)	12 (28.6)	8 (17.8)
Fatal myocardial infarction	1 (1.1)	0 (0.0)	1 (2.4)	0 (0.0)
Myocardial infarction (not specified)	44 (47.3)	22 (53.7)	23 (54.8)	18 (40.0)
Myocardial infarction (any)	66 (70.1)	33 (80.5)	35 (83.3)	26 (57.8)
Heart failure	33 (35.5)	12 (29.3)	17 (40.5)	19 (42.2)
Cardiac arrest	27 (29.0)	6 (14.6)	8 (19.0)	18 (40.0)
Complete heart block	7 (7.5)	2 (4.9)	4 (9.5)	3 (6.7)
Pulmonary oedema	18 (19.4)	8 (19.5)	9 (21.4)	8 (17.8)
Ventricular arrhythmia	12 (12.9)	4 (9.8)	8 (19.0)	7 (15.6)
Atrial arrhythmia	4 (4.3)	1 (2.4)	3 (7.1)	2 (4.4)
Arrhythmia, not specified	17 (18.3)	7 (17.1)	8 (19.0)	8 (17.8)
Revascularisation	6 (6.5)	4 (9.8)	3 (7.1)	2 (4.4)
Acute coronary syndrome	6 (6.5)	4 (9.8)	4 (9.5)	2 (4.4)
Unstable angina	8 (8.6)	2 (4.8)	6 (14.3)	4 (8.9)
Myocardial injury	15 (16.1)	10 (24.4)	10 (23.8)	4 (8.9)
Stroke	14 (15.1)	4 (9.5)	5 (11.9)	9 (20.0)
Hypertensive crisis	2 (2.2)	0 (0.0)	2 (4.8)	0 (0.0)
ST-T changes on ECG	1 (1.1)	0 (0.0)	0 (0.0)	1 (2.2)
Intraoperative hemodynamic adversity	1 (1.1)	0 (0.0)	1 (2.4)	1 (2.2)
Systemic embolism	1 (1.1)	1 (2.4)	1 (2.4)	0 (0.0)

Table 5. Reporting of performance measures in included studies

	All included studies	Added value to the RCRI	Comparison of biomarkers	Comparison of prediction models
N	107	51	51	52
Performance category (%)				
Discrimination	102 (95.3)	48 (94.1)	49 (96.1)	50 (96.2)
Calibration	39 (36.4)	10 (19.6)	15 (29.4)	22 (42.3)
Reclassification	23 (21.5)	18 (35.3)	2 (4.0)	5 (9.6)
C-statistic (%)	98 (91.6)	40 (78.4)	45 (88.2)	48 (92.3)
O/E (%)	22 (20.6)	6 (11.8)	12 (23.5)	8 (15.4)
Calibration plot (%)	14 (13.1)	4 (7.8)	1 (2.0)	10 (19.2)
Hosmer Lemeshow test (%)	7 (6.5)	1 (2.0)	3 (5.9)	7 (13.5)
IDI (%)	7 (6.5)	7 (13.7)	1 (2.0)	0 (0.0)
NRI (%)	22 (20.6)	17 (33.3)	2 (3.9)	5 (9.6)
Other reported measures (%)				
Sensitivity	41 (38.3)	6 (11.8)	27 (52.9)	14 (26.9)
Specificity	40 (37.4)	6 (11.8)	27 (52.9)	13 (25.0)
Negative predictive value	19 (17.8)	3 (5.9)	12 (23.5)	5 (9.6)
Positive predictive value	18 (16.8)	3 (5.9)	11 (21.6)	5 (9.6)
Accuracy	3 (2.8)	0 (0.0)	2 (3.9)	1 (1.9)

O/E: observed/expected ratio; IDI: integrated discrimination improvement; NRI: net reclassification improvement.
Discrimination includes the following performance measures: c-statistics/AUC, sensitivity, specificity, negative predictive value, positive predictive value, positive predictive value and accuracy.
Calibration includes O:E ratio, calibration plot and Hosmer Lemeshow test.
Reclassification includes IDI and NRI.

Table 6. Biomarkers/predictors added to the RCRI

	Number of studies	Derivation
NT-proBNP	13	Blood
Troponin	7	Blood
NT-proBNP + troponin	5	Blood
BNP	4	Blood

Table 6. Biomarkers/predictors added to the RCRI *(Continued)*

Copeptin	3	Blood
Coronary artery calcium score (CACS)	2	Imaging
CRP	2	Blood
fQRS of an ECG	2	Imaging
NT-proBNP + CRP	2	Blood
V-POSSUM	2	Other
V-POSSUM + NTproBNP	2	Blood
V-POSSUM + troponin	2	Blood
6 minute walking test	1	Other
Abdominal aortic aneurysm size	1	Other
Age	1	Other
Age + abdominal aortic aneurysm size	1	Other
Age + sex + copeptin	1	Other
Age > 70 years	1	Other
Anaerobic threshold	1	Other
Anaemia	1	Other
Angina pectoris	1	Other
ASA	1	Other
ASA + SORT + NSQIP-MICA	1	Other
Atrial fibrillation	1	Other
Copeptin + NT-proBNP	1	Blood
Coronary CT angiography	1	Imaging
Duke Activity Status Index	1	Other
ECG abnormalities	1	Imaging
Echocardiography	1	Imaging
Echocardiography + beta blockers	1	Imaging
EE ratio of echocardiography	1	Imaging
Frailty	1	Other

Table 6. Biomarkers/predictors added to the RCRI *(Continued)*

Jeopardy score	1	Imaging
Left bundle branch block on ECG	1	Imaging
Left ventricular ejection fraction	1	Imaging
Male sex	1	Other
Metabolic equivalent (METS)	1	Other
METS + positive stress test with no false negatives	1	Other
METS + stress test	1	Imaging
Multi vessel disease	1	Imaging
Multi vessel disease + CACS	1	Imaging
Peak oxygen	1	Other
Polygenic risk score for coronary artery disease	1	Other
Presepsin	1	Blood
Presepsin + NT-proBNP	1	Blood
Presepsin + troponin	1	Blood
Presepsin + troponin + NT-proBNP	1	Blood
Reactive hyperaemia peripheral arterial tonometry	1	Other
Regulatory T cells	1	Blood
Regulatory T cells + troponin + NT-proBNP	1	Blood
Right bundle branch block on ECG	1	Imaging
Segment involvement + Jeopardy score	1	Imaging
Segment involvement score	1	Imaging
Smoking	1	Other
ST2 + troponin	1	Blood
ST2 cardiac biomarker	1	Blood
Stenosis of CTA + CACS	1	Imaging
Stenosis on CTA	1	Imaging
Stress echocardiography	1	Imaging
Survivin	1	Blood

Table 6. Biomarkers/predictors added to the RCRI *(Continued)*

Thallium scan	1	Imaging
Total joint arthroplasty risk score	1	Other
Type of surgery	1	Other
Type of surgery + age	1	Other
Type of surgery + age + hypertension	1	Other
Valve sclerosis	1	Imaging
Valve stenosis	1	Imaging
V-POSSUM + troponin + NT-proBNP	1	Blood
Wall abnormalities on an echocardiography	1	Imaging

ASA: American Society of Anesthesiologists; BNP: brain natriuretic peptide; CRP: C-reactive protein; CT: computed tomography; E/e' ratio: ratio between early mitral inflow velocity and mitral annular early diastolic velocity; fQRS of an ECG: fragmented QRS of an electrocardiogram (ECG); NSQIP-MICA: National Surgical Quality Improvement Program score for the prediction of myocardial infarction and cardiac arrest; NT-prBNP: N-terminal prohormone of brain natriuretic peptide; SORT: Surgical Outcome Risk Tool; V-POSSUM: Vascular Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity

Table 7. Biomarkers/predictors for which the predictive performance was compared to the RCRI

	Number of studies	Derivation
ASA	14	Other
NT-proBNP	11	Blood
BNP	10	Blood
Troponin	6	Blood
CRP	3	Blood
Coronary artery calcium score (CACS)	2	Imaging
Dobutamine stress echocardiography	2	Imaging
EE ratio on an echocardiography	2	Imaging
Left ventricular ejection fraction	2	Imaging
METS	2	Other
NT-proBNP + troponin	2	Blood
Positive stress test	2	Imaging
Presepsin	2	Blood
6 minute walking test	1	Other

Table 7. Biomarkers/predictors for which the predictive performance was compared to the RCRI *(Continued)*

Abnormal echocardiography	1	Imaging
Age	1	Other
Age + surgical complexity	1	Other
Anaerobic threshold	1	Other
Ankle arm index	1	Other
Ankle arm index ≤ 0.9	1	Other
Ankle arm index ≥ 1.2	1	Other
Aortic arch calcification	1	Imaging
ASA + frailty	1	Other
CD40	1	Blood
Copeptin	1	Blood
Coronary artery stenosis	1	Imaging
Coronary CT angiography	1	Imaging
eGFR	1	Blood
Estimated blood loss + estimated surgical duration	1	Other
Estimated blood loss + estimated surgical duration + type of surgery	1	Other
Functional capacity	1	Other
H-FABP	1	Blood
H-FABP + survivin	1	Blood
High age + ischaemic heart disease	1	Other
Jeopardy score	1	Imaging
Karnofsky score	1	Other
KDIGO stage 3	1	Other
Left atrial volume index	1	Imaging
Left ventricular ejection fraction + wall motion abnormalities	1	Imaging
NT-proBNP + high creatinine	1	Blood
NT-proBNP + high creatinine + ischaemic heart disease	1	Blood
Peak VO2	1	Other

Table 7. Biomarkers/predictors for which the predictive performance was compared to the RCRI *(Continued)*

Pedal pulses absent on ankle arm index	1	Other
Platelet factor V	1	Blood
Platelet P-selectin	1	Blood
Positive stress test without false positives	1	Imaging
Reactive hyperaemia peripheral arterial tonometry	1	Other
Regional wall motion abnormalities	1	Imaging
Regulatory T cells	1	Blood
sCD40L	1	Blood
Segment involvement in echocardiography	1	Imaging
St2	1	Blood
Survivin	1	Blood
Survivin + CRP	1	Blood
Systolic dysfunction	1	Imaging
Systolic dysfunction + left hypertrophy	1	Imaging
Troponin + CK-MB	1	Blood
Troponin + CRP	1	Blood
Troponin + CRP + NT-proBNP	1	Blood
Wall motion abnormalities	1	Imaging

ASA: American Society of Anesthesiologists classification; BNP: brain natriuretic peptide; NT-proBNP: N-terminal prohormone of brain natriuretic peptide; CRP: C-reactive protein; E/e' ratio: ratio between early mitral inflow velocity and mitral annular early diastolic velocity; METS: metabolic equivalent; CD40: co-stimulatory protein found on antigen-presenting cells and is required for their activation; eGFR: estimated glomerular filtration rate; H-FABP; heart-type fatty acid binding protein; KDIGO stage 3: Kidney Disease Improving Global Outcomes stage 3 indicates severity of kidney injury; VO2: rate of oxygen consumption; St2: soluble interleukin 1 receptor like-1, protein that signals the presence and severity of adverse cardiac remodeling; CT scan: computed tomography scan

Table 8. C-statistics for the comparison of the predictive performance of ASA classification to the RCRI using outcomes other than cardiovascular

Author	Outcome	Prediction horizon	N events	N total	c-statistic RCRI	CI (95%) c-statistic RCRI	c-statistic ASA	CI (95%) c-statistic RCRI
Bronheim 2018	Any noncardiac complication	30 days	3399	52,066	0.62	(0.61 to 0.63)	0.77	(0.73 to 0.82)
Bronheim 2018	Unplanned intubation	30 days	111	52,066	0.84	(0.83 to 0.84)	0.74	(0.74 to 0.75)
Bronheim 2018	Pulmonary embolism	30 days	149	52,066	0.41	(0.4 to 0.42)	0.81	(0.81 to 0.82)
Bronheim 2018	Ventilated > 48 hours	30 days	65	52,066	0.85	(0.84 to 0.85)	0.74	(0.74 to 0.75)
Bronheim 2018	Acute renal failure	30 days	36	52,066	0.88	(0.88 to 0.89)	0.79	(0.78 to 0.79)
Bronheim 2018	Cerebrovascular accident	30 days	42	52,066	0.75	(0.74 to 0.75)	0.84	(0.84 to 0.84)
Bronheim 2018	Coma > 24 hours	30 days	8	52,066	0.90	(0.87 to 0.93)	0.65	(0.65 to 0.66)
Bronheim 2018	Sepsis	30 days	259	52,066	0.83	(0.82 to 0.83)	0.91	(0.9 to 0.91)
Bronheim 2018	Septic shock	30 days	50	52,066	0.85	(0.84 to 0.85)	0.76	(0.76 to 0.76)
Bronheim 2018	Reoperation	30 days	912	52,066	0.85	(0.85 to 0.86)	0.87	(0.86 to 0.87)
Bronheim 2018	Superficial surgical site infection	30 days	452	52,066	0.72	(0.71 to 0.72)	0.84	(0.84 to 0.85)
Bronheim 2018	Deep incisional surgical site infection	30 days	297	52,066	0.88	(0.88 to 0.88)	0.95	(0.95 to 0.95)
Bronheim 2018	Organ space surgical site infection	30 days	104	52,066	0.88	(0.87 to 0.88)	0.78	(0.77 to 0.78)
Bronheim 2018	Wound dehiscence	30 days	102	52,066	0.72	(0.71 to 0.72)	0.79	(0.79 to 0.8)
Bronheim 2018	Pneumonia	30 days	177	52,066	0.74	(0.73 to 0.74)	0.82	(0.82 to 0.83)
Bronheim 2018	Progressive renal insufficiency	30 days	35	52,066	0.85	(0.84 to 0.85)	0.81	(0.81 to 0.82)
Bronheim 2018	Urinary tract infection	30 days	558	52,066	0.74	(0.73 to 0.74)	0.83	(0.82 to 0.83)
Bronheim 2018	Peripheral nerve injury	30 days	21	52,066	0.07	(0.07 to 0.08)	0.51	(0.51 to 0.52)
Bronheim 2018	Bleeding transfusions	30 days	1621	52,066	0.71	(0.71 to 0.72)	0.80	(0.8 to 0.8)

Table 8. C-statistics for the comparison of the predictive performance of ASA classification to the RCRI using outcomes other than cardiovascular *(Continued)*

Bronheim 2018	Deep vein thrombosis/thrombophlebitis	30 days	165	52,066	0.71	(0.7 to 0.71)	0.78	(0.78 to 0.79)
Bronheim 2018	Readmission	30 days	NR	52,066	0.84	(0.83 to 0.84)	0.91	(0.9 to 0.91)
Ehlert 2016	Clavien Dindo class IV complications	In-hospital	800	5621	0.56	NR	0.55	NR
Ehlert 2016	Clavien Dindo class IV complications	In-hospital	541	15,354	0.59	NR	0.56	NR
Ehlert 2016	Clavien Dindo class IV complications	In-hospital	455	8367	0.56	NR	0.57	NR
Ehlert 2016	Clavien Dindo class IV complications	In-hospital	32	1833	0.56	NR	0.59	NR
Ehlert 2016	Clavien Dindo class IV complications	In-hospital	835	40,803	0.69	NR	0.56	NR
Farina-Castro 2020	Postoperative complications (CCI 0 vs CCI ≥ 1)	Not reported	179	244	0.69	(0.60 to 0.79)	0.65	(0.56 to 0.74)
James 2014	Surgical complications	30 days	40	83	0.53	(0.4 to 0.65)	0.60	(0.48 to 0.72)
Makary 2010	Surgical complications	30 days	34	594	0.72	NR	0.71	NR
Makary 2010	Discharge to a nursing facility	In-hospital	14	594	0.75	NR	0.78	NR
Press 2006	All-cause mortality or nonfatal stroke	30 days	64	1998	0.61	NR	0.53	NR
Press 2006	Noncardiac complications	30 days	63	1998	0.66	NR	0.62	NR
Press 2006	Minor neurological complications	30 days	138	1998	0.56	NR	0.53	NR
Press 2006	Wound complications	30 days	119	1998	0.61	NR	0.54	NR

NR: not reported

Table 9. Prediction models for which the predictive performance was compared to the RCRI

	Number of studies
NSQIP-MICA	10
NSQIP surgical risk score	9
CHADS2 score	4
Detsky index	4
Goldman index	4
CHADS2VASc	3
R2CHADS2 score	3
Vascular Study Group of New England Cardiac Risk Index	3
AUB-HAS2 Cardiovascular Risk Index	2
Charlson Index	2
Glasgow Aneurysm Risk score	2
Halm score	2
Individual items of the RCRI	2
POSSUM	2
P-POSSUM	2
RCRI without insulin use with low eGFR	2
Reiss Index	2
South African Vascular Surgical Cardiac Risk Index	2
Surgical Mortality Probability Model	2
Thoracic RCRI	2
Tu score	2
V-POSSUM	2
Adult Comorbidity Evaluation-27 score	1
Adult Comorbidity Evaluation-27 score + high age	1
Age + type of admission + RCRI + arrhythmia + electrolyte disorder + hypertension	1
Age + type of admission + RCRI + arrhythmia + electrolyte disorder + hypertension + polygenic risk score for coronary artery disease	1

Table 9. Prediction models for which the predictive performance was compared to the RCRI *(Continued)*

ANESCARDIOCAT	1
ASA + NSQIP surgical risk score	1
ASA + Surgical Outcome Risk Tool	1
Ashton	1
Biochemistry and Haematology Outcome Model	1
Coronary artery disease + atrium fibrillation + diabetes mellitus + mechanical ventilation + heart rate	1
CR-POSSUM	1
Detsky score + type of surgery	1
Dilated cardiomyopathy + ischaemic cardiopathy + CVA	1
Eagle score	1
Geriatric Sensitive Perioperative Cardiac Risk Index	1
Insulin use + open surgery + high fibrinogen + CRP + NT-proBNP	1
Long Term Survival Score	1
MASHOUR	1
Modified Frailty Index	1
Myocardial infarction + sex + insulin-dependent diabetes mellitus + low BMI + high age + atrium fibrillation	1
New model 1	1
New model 2	1
New model 3	1
NSQIP score "Death"	1
NT-proBNP + high creatinine + ischaemic heart disease + congestive heart failure	1
Patient Outcomes in Renal Transplant model	1
Preoperative risk score of the estimation of physiological ability + surgical stress score	1
RCRI with redefined high-risk surgery	1
RCRI with redefined high-risk surgery and clinical characteristics	1
RCRI without insulin use and creatinine > 2.0 mg/dL	1
Recalibrated NSQIP surgical risk score	1

Table 9. Prediction models for which the predictive performance was compared to the RCRI *(Continued)*

Recalibrated RCRI	1
Regulatory T cells + age + sex + ASA + previous PCI + creatinine	1
Surgical Outcome Risk Tool	1
Surgical risk score	1
TJA individual factors	1
TJA risk score	1
Updated Cardiac Risk Score	1
Vascular Biochemistry and Haematology Outcome Model	1
Vascular Quality Initiative Cardiac Risk Index	1
Vascular Study Group of New England Cardiac Risk Index + anaemia	1
V-POSSUM + troponin	1
V-POSSUM + troponin + NT-proBNP	1

ACE-27: adult comorbidity evaluation-27; ACS-NSQIP: American College of Surgeons National Surgical Quality Improvement Program; CHADS2 score: congestive heart failure, hypertension, age ≥ 75 years, diabetes mellitus, stroke (double weight); CHADS2VASc: CHADS2 added with vascular disease, age 65 to 74 years and sex; CR-POSSUM: POSSUM score for colorectal surgical patients; MICA: myocardial infarction and cardiac arrest; New model 1: age, sex, history of coronary revascularisation, aortic or mitral valve disease, arrhythmia, hypertension, carotid artery stenosis, hypovolaemia, chronic renal failure, emergency surgery, neurosurgery, thoracic surgery, major vascular surgery, haematopoietic/lymphatic surgery, gastro-intestinal surgery; New model 2: age, ASA, neurosurgery, thoracic surgery, major vascular surgery, haematopoietic/lymphatic surgery, gastro-intestinal surgery; New model 3: history of myocardial infarction, age > 70, insulin dependent diabetes mellitus, female, BMI < 18, operation time > 2.5 hours, atrium fibrillation, intraoperative hypotension; P-POSSUM: Portsmouth-POSSUM; POSSUM: Physiologic and Operative Severity Score for the enUmeration of Mortality and Morbidity; R2CHADS2: CHADS2 score added with renal failure (double weighted); SORT: Surgical Outcome Risk Tool; TJA: total joint arthroplasty; V-POSSUM: POSSUM for vascular surgical patients

APPENDICES

Appendix 1. MEDLINE Ovid search strategy

1 ("Revised Cardiac risk index" or RCRI or "Lee index" or "Lee-index" or "Lee's index" or "revised goldman index" or goldman or detsky or LCRI or RCI or "revised cardiac index" or "pre-operative variable*" or "preoperative variable*" or "revised cardiac risk" or "cardiac risk factor*").ti,ab,kf.

2 Reproducibility of Results/ or calibration/ or Area Under Curve/ or Validation Studies.pt. or (validat* or stratification or overfit* or overpredict* or underfit* or underpredict* or overestimation or underestimation or pooled or recalibration or re-calibration or calibration or discrimination or cohort or discriminate or c-statistic* or "c statistic*" or "Area under the curve*" or AUC or Indices or Algorithm or Multivariable or "added value" or incremental or "receiver operating curve" or roc or "receiver operating characteristic" or "c index" or "c-index" or "predictive accuracy" or "prognostic accuracy" or "reclassifi*" or "prognostic value" or "predictive value" or MACE).ti,ab,kf.

3 1 and 2

4 (exp animals/ not humans/) or (equine or cattle or bovine or canine or mice or mouse or rat or rats or guinea-pig* or dog).ti.

5 3 not 4

Appendix 2. Ovid Embase search strategy

1 ("Revised Cardiac risk index" or RCRI or "Lee index" or "Lee-index" or "Lee's index" or "revised goldman index" or goldman or detsky or LCRI or RCI or "revised cardiac index" or "pre-operative variable*" or "preoperative variable*" or "revised cardiac risk" or "cardiac risk factor*").ti,ab,kw.

2 reproducibility/ or validation study/ or validation process/ or calibration/ or area under the curve/ or (validat* or stratification or overfit* or overpredict* or underfit* or underpredict* or overestimation or underestimation or pooled or recalibration or re-calibration or calibration or discrimination or cohort or discriminate or c-statistic* or "c statistic*" or "Area under the curve*" or AUC or Indices or Algorithm or Multivariable or "added value" or incremental or "receiver operating curve" or roc or "receiver operating characteristic" or "c index" or "c-index" or "predictive accuracy" or "prognostic accuracy" or "reclassifi*" or "prognostic value" or "predictive value" or MACE).ti,ab,kw.

3 1 and 2

4 ((exp experimental organism/ or animal tissue/ or animal cell/ or exp animal disease/ or exp carnivore disease/ or exp bird/ or exp experimental animal welfare/ or exp animal husbandry/ or animal behavior/ or exp animal cell culture/ or exp mammalian disease/ or exp mammal/ or exp marine species/ or nonhuman/ or animal.hw.) not human/) or (equine or cattle or bovine or canine or mice or mouse or rat or rats or guinea-pig* or dog).ti.

5 3 not 4

6 limit 5 to (conference abstract or conference paper or "conference review")

7 5 not 6

Appendix 3. ClinicalTrials.gov and World Health Organization International Clinical Trials Registry platform (WHO-ICTRP) search strategy up to 27 July 2020

Clinicaltrials.gov

Advanced search

Condition or disease:

Other terms: RCRI OR revised cardiac risk index

Study type: all studies

Study results: all studies

WHO-ICTRP

RCRI OR revised cardiac risk index

Appendix 4. Data extraction form

General items	
Author	
Year	
Journal	
Study ID	
Validation ID	Example: if 1 study reports results using multiple outcomes, the first extraction (MACE) receives number studynumber-1 and the second (mortality) studynumber-2

(Continued)

Reviewer	
Validation details	If there are multiple outcomes, a single outcome per column. E.g. if both results for mortality and MACE are reported, extract data in two columns (i.e. one per outcome)
Type of study	Predesigned validation study: study is prospectively designed with the aim to validate the model
Was data collection prospective or retrospective?	
Participant selection	
Study design	
	Comment on study design
In- and exclusion criteria for the analyses	
Lower age limit	Enter number
Surgical specialty	Only information on eligibility criteria for surgical specialty
Surgical procedure if specified	Specify only when a particular surgical procedure is performed within a surgical specialty. E.g. some studies might only report patients undergoing AAA repair and not include patients undergoing other vascular procedures
Emergency surgery	Only information on eligibility criteria for emergency surgery
Other specific patient characteristics	e.g. patients undergoing vascular surgery **with COPD and heart failure**
Eligibility criteria for participants comparable to RCRI	≥ 50 years, non-emergent and non-cardiac procedures
Case mix	***For continuous variables: if reported extract mean and SD (other information is not needed), if these are not reported, extract median and IQR. If these are not reported specify any other information that is reported (e.g. a plot).***
Is case mix solely reported for 2 separate groups (e.g. for cases and non-cases)?	***If yes, extract numbers at the bottom of this DE table.***
If yes, specify which table.	
Age >70 years	**%**
Age	Mean
	SD
	Median

(Continued)

	IQR - 25th percentile
	IQR - 75th percentile
	If NR: other (specify)
Gender	% men
Type of procedure - thoracic	%
Type of procedure - orthopaedic	%
Type of procedure - vascular	%
Type of procedure - general/abdominal	%
Type of procedure - gynaecological/urological	
Type of procedure - other	%
High-risk procedure	%, more information tab High-risk surgical procedures
Similar definition used as in RCRI (intraperitoneal, intrathoracic or suprainguinal vascular procedures)	
If no, which definition has been used?	
Diabetes	%
Insulin dependent diabetes	%
History of ischaemic heart disease	%
History of myocardial infarction	% - part of definition of ischaemic heart disease
Patients with prior CABG or PTCA	% - part of definition of ischaemic heart disease
History of congestive heart failure	%
History of cerebrovascular disease	% both TIA and CVA
Serum creatinine > 2.0 mg/dL or > 177 µmol/L	%
Continue creatinine if no threshold reported	report mean (SD)
Renal insufficiency	%
Hypertension	%
Chronic medication use – beta blockers	% more information tab - Medication
Chronic medication use - calcium antagonists	% more information tab - Medication
Chronic medication use - diuretics	% more information tab - Medication

(Continued)

Chronic medication use - ACE of ARB	% more information tab - Medication
Chronic medication use - anticoagulation	% more information tab - Medication
Chronic medication use - platelet aggregation medication	% more information tab - Medication
Chronic medication use - nitrates	% more information tab - Medication
Chronic medication use – anti-hypertensives	%, report only if not specified in detail
Chronic medication use - cardiac medication	%, report only if not specified in detail
Smoking	% Never
	% Past
	% Current
	% Ever
	% not specified/other (specify)
Atrial fibrillation	%
RCRI	Mean
	SD
	Median
	IQR - 25th percentile
	IQR - 75th percentile
RCRI 0 factor	%
RCRI 1 factor	%
RCRI 2 factor	%
RCRI 3 factor	%
RCRI 4 factor	%
RCRI 5 factor	%
RCRI 3 or more	%
RCRI - other information/classification	
Study dates	
Start date recruitment period (dd-mm-yyyy)	If day is not reported enter 00. So July 2010 is 00-07-2010
End date recruitment period (dd-mm-yyyy)	

(Continued)

End date of follow up (dd-mm-yyyy)	
Follow-up time - median (days)	
Follow-up time - range (days) min	
Follow-up time - range (days) max	
Follow-up time - mean (days)	
Prediction horizon - category	In-hospital events/30-day/1-year/other
Follow-up time - other information (specify)	
Location	
Number of centres	
Location of centres - continent	
Location of centres - country	
Data collection in academic or peripheral hospital?	
Risk of Bias - Participant selection	Be strict on signalling questions, but less strict on risk of bias. If there is no information, answer 'No information' to the signalling question, but you might score Low risk of bias, if you think it didn't cause bias.
1. Were appropriate data sources used, e.g. cohort, RCT or nested case-control study data?	YES: Cohort, RCT, Case cohort, nested case-control PROBABLY YES registry or existing cohort studies. In case RCT data is used and treatment is accounted for, score Yes. NO: case-control, cross-sectional Consider scoring NO if data collection was not intended for research purposes.
2. Were all inclusions and exclusions based on characteristics of participants appropriate (e.g. comorbidities, treatment)?	The key issue is whether any inclusion or exclusion criteria, or the recruitment strategy, could have made the included study participants unrepresentative of the intended target population, e.g. selection of participants was based on the outcome at time of predictor measurement or specific subgroups are excluded that may alter the performance of the prediction model. This item is NOT on loss to follow-up or missing data, but rather on eligibility criteria and exclusions made before entrance in the cohort used for the validation. This is really about the people that were selected for the analyses (although, exclusion of people with missing data should be scored below in 'sample size and participant flow').
Risk of bias introduced by selection of participants	
Justification of bias rating	Justification is not always necessary when you score LOW (although it might be helpful), but is necessary when you score HIGH or UNCLEAR.

(Continued)

Applicability	
1. Were participants enrolled at a similar state of health compared to the development population?	
Concern that the included participants and setting do not match the review question	Studies might have reduced applicability to our review if they included a study population different from the original development study, e.g. if they included only young people, or a more diseased population with 50% diabetes or cancer (see separate file).
Justification of applicability rating	Justification is not always necessary when you score LOW (although it might be helpful), but is necessary when you score HIGH or UNCLEAR.
Predictors	
Actions to blind assessment of predictors for the outcome	
Actions to blind assessment of predictors for each other	
Was there a general statement that predictor definitions were the same as in the development study? If not, answer the following question for every predictor.	
For the following predictors: was the same definition used? If not, copy the definition in the box below. (if the same definition is used, you don't have to copy it)	
High-risk surgery intraperitoneal, intrathoracic, or suprainguinal vascular procedures	Yes/No/NR/NA Score NA if predictor was not included in the model
	Definition
Ischaemic heart disease history of myocardial infarction, positive exercise test, current complaint of ischaemic chest pain or use of nitrate therapy, or ECG with pathological Q waves. Patients with previous revascularisation (i.e. CABG or PCI or PTCA) were included in this definition only if they had current chest pain	Yes/No/NR/NA Score NA if predictor was not included in the model.
	Definition
History of congestive heart failure history of congestive heart failure, pulmonary oedema or paroxysmal nocturnal dyspnoea, physical examination showing bilateral rales or S3 gallop or chest radiograph showing pulmonary vascular redistribution	Yes/No/NR/NA Score NA if predictor was not included in the model.
	Definition
History of cerebrovascular disease history of transient ischaemic attack or stroke	Yes/No/NR/NA Score NA if predictor was not included in the model.
	Definition
Insulin therapy for the treatment of diabetes	Yes/No/NR/NA Score NA if predictor was not included in the model
	Definition
Preoperative creatinine > 2.0 mg/dl or > 177 µmol/L	Yes/No/NR/NA Score NA if predictor was not included in the model

(Continued)

	Definition
Were predictors deleted?	
If yes, which ones?	
Was the number of predictors or the individual predictors used for validation of the model?	
For each biomarkers that was added to the RCRI	
Which biomarker was added to the RCRI?	
How was the biomarker derived?	Blood derived/imaging/patient characteristic/prediction model/other
How was the biomarker added to the model?	Continuous/categorical/dichotomous
What threshold of the biomarker was used to define elevation?	Only insert the number, for patient characteristic use NA, if not reported use NR
Entity of the threshold	
Which assay/device was used?	
For each biomarkers that was compared to the RCRI	
Which biomarker alone was compared to the RCRI?	
How was the biomarker derived?	Blood derived/imaging/patient characteristic/prediction model/other
How was the biomarker added to the model?	Continuous/categorical/dichotomous
What threshold of the biomarker was used to define elevation?	Only insert the number, for patient characteristic use NA, if not reported use NR
Entity of the threshold	
Which assay/device was used?	
Risk of Bias - predictors	Be strict on signalling questions, but less strict on risk of bias. If there is no information, answer 'No information' to the signalling question, but you might score Low risk of bias, if you think it didn't cause bias.
1. Were predictors defined and assessed in a similar way for all participants?	
2. Were predictor assessments made without knowledge of outcome data?	
3a. Are all predictors available at the time the model is used?	Score No if it is stated that not all predictors were measured at baseline, or if not all predictors were available.
3b. Were predictors defined and assessed in the same way as in the original RCRI model?	Score Yes if it is stated that the same definitions were used. Score No if there is at least one definition different.

(Continued)

Risk of bias introduced by predictors or their assessment	
Justification of bias rating:	Justification is not always necessary when you score LOW (although it might be helpful), but is necessary when you score HIGH or UNCLEAR.
Applicability	
Concern that the definition, assessment or timing of assessment of predictors in the model do not match the review question	
Justification of applicability rating	Justification is not always necessary when you score LOW (although it might be helpful), but ís necessary when you score HIGH or UNCLEAR.
Outcome	
Is the outcome definition the same as the development study? RCRI: major cardiac complications This composite outcome included myocardial infarction, pulmonary oedema, ventricular fibrillation or primary cardiac arrest, and complete heart block. Myocardial infarction was diagnosed if CK-MB was > 5% of an elevated total CK or the peak CK-MB was > 3% of an elevated total CK in the presence of ECG changes consistent with ischaemia or infarction. Diagnosis of pulmonary oedema required a formal reading of a chest radiograph by a radiologist	
Outcome - main category	MACE/cardiovascular mortality/all-cause mortality/myocardial infarction/myocardial injury (troponin elevation)/Other
Outcome - full definition	Copy/paste information
Outcome - full definition - other information	
Outcome - measurement method	E.g. expert panel, death register
If a composite outcome was used, enter the relative or absolute frequency/distribution of each contributing outcome	Format: outcome number, outcome number. E.g. MI 250, stroke 302
Actions to blind outcome assessment for the predictors	
Risk of bias - Outcome	Be strict on signalling questions, but less strict on risk of bias. If there is no information, answer 'No information' to the signalling question, but you might score Low risk of bias, if you think it didn't cause bias.
1. Was the outcome determined appropriately?	
2. Was a prespecified or standard outcome definition used?	
3. Were predictors excluded from the outcome definition?	
3. Was the outcome defined and determined in a similar way for all participants?	Score Yes if it was stated that patients were diagnosed using a panel diagnosis.

(Continued)

4. Was the outcome determined without knowledge of predictor information?	
5. Was the time interval between predictor assessment and outcome determination appropriate?	
Risk of bias introduced by the outcome or its determination	You might score HIGH if outcomes were self-reported.
Justification of bias rating	Justification is not always necessary when you score LOW (although it might be helpful), but is necessary when you score HIGH or UNCLEAR.
Applicability	
Concern that the definition, assessment or timing of assessment of the outcome in the model does not match the review question	
Justification of applicability rating	Justification is not always necessary when you score LOW (although it might be helpful), but is necessary when you score HIGH or UNCLEAR.
Sample size and participant flow	
Number of participants included in the full cohort	Enter number
Number of events in the full cohort	Enter number
Number of participants included in the analysis	Enter number
Number of events included in the analysis	Enter number
Missing data	
Number of participants with any missing value	Enter number
Number of participants with missing data for outcome	Enter number
Number of participants with missing data for predictors	Enter number
Method used to account for missing data	
Type of missing data	
	Comment on missing data
Analysis	
How were predictors calculated	
	Comment on calculating predictors
Type of validation - Investigators Is this a validation by different investigators? Is there NO overlap between the researchers of the validation study and the development study?	Score YES if there was NO overlap, score NO if there was overlap between authors. Thomas H. Lee, MD, SM; Edward R. Marcantonio, MD, SM; Carol M. Mangione, MD, SM; Eric J. Thomas, MD, SM; Carisi A. Polanczyk, MD; E. Francis Cook, ScD; David J. Sugarbaker, MD; Magruder C. Donaldson, MD;

(Continued)

	Robert Poss, MD; Kalon K.L. Ho, MD, SM; Lynn E. Ludwig, MS, RN; Alex Pedan, PhD; Lee Goldman, MD, MPH
Risk of bias - analysis	Be strict on signalling questions, but less strict on risk of bias. If there is no information, answer 'No information' to the signalling question, but you might score Low risk of bias, if you think it didn't cause bias.
1. Were there a reasonable number of outcome events?	Yes: >=100 (ref: Vergouwe)
2. Were continuous and categorical predictors handled appropriately?	
3. Were all enrolled participants included in the analysis?	This question is on exclusions made after study entrance (e.g. participants with missing data were excluded, or people with short follow-up time were excluded), so not on eligibility criteria. Score YES if all enrolled participants were included in the analysis.
4. Were participants with missing data handled appropriately?	Yes: probabilistic imputation approach such as multiple imputation, or explicit mentioning of no missing data. Probably yes: single imputation Probably no: no information on missing data reported anywhere in the paper No: deterministic (e.g. mean) imputation, complete case analysis
5. Was selection of predictors based on univariable analysis avoided?	This is for development studies only.
6. Were any complexities in the data (e.g. censoring, competing risks) accounted for appropriately?	Score No if it was a multicentre study and this was not taken into account, or if it was a case-cohort/nested case-control study and this was not taken into account. Score Probably yes if you have no reason to believe there were any complexities in the data.
7. Were relevant model performance measures evaluated appropriately?	
8. Were model overfitting, underfitting, and optimism in model performance accounted for?	For development studies only A model extension, where new predictors are added to an existing model, would be assessed as new model development.
9. Do predictors and their assigned weights in the final model correspond to the results from the reported multivariable analysis?	For development studies only A model extension, where new predictors are added to an existing model, would be assessed as new model development.
Risk of bias introduced by the analysis	If it was a multicentre study and this was not taken into account you might score Low if there was protocolised data collection.
Justification of bias rating	Justification is not always necessary when you score LOW (although it might be helpful), but is necessary when you score HIGH or UNCLEAR.
Results	

(Continued)

Performance RCRI alone	
C-statistic - type	
C-statistic	
C-statistic - 95% CI Lower bound	
C-statistic - 95% CI Upper bound	
C-statistic - SE	
C-statistic - P value	Report only if confidence interval and/or SE is not reported
C-statistic - other information	Specify
Observed rate	%
Observed rate - 95% CI Lower bound	
Observed rate - 95% CI Upper bound	
Expected rate	%
Expected rate - 95% CI Lower bound	
Expected rate - 95% CI Upper bound	
Observed/expected	
Observed/expected - 95% CI Lower bound	
Observed/expected - 95% CI Upper bound	
Observed/expected - SE	
Observed/expected - P value	
Observed/expected - IQR Lower bound	
Observed/expected - IQR Upper bound	
Expected/observed	
Expected/observed - 95% CI Lower bound	
Expected/observed - 95% CI Upper bound	
Expected/observed - SE	
Expected/observed - P value	
Expected/observed - IQR Lower bound	
Expected/observed - IQR Upper bound	

(Continued)

Calibration plot - calibration table is available	If yes, mention which table in the article
Sensitivity	%
Specificity	%
Negative predictive value	%
Positive predictive value	%
In case sensitivity, specificity, negative predictive value or positive predictive value is reported, what threshold is used?	
Hosmere Lemeshow X2	
Hosmere Lemeshow X2 - P value	
Calibration - other	
Performance after updating - addition for each biomarker	
Which biomarker(s) is (are) added?	In case, multiple biomarkers are added at once, name all biomarkers
C-statistic - type	
C-statistic	
C-statistic - 95% CI Lower bound	
C-statistic - 95% CI Upper bound	
C-statistic - SE	
C-statistic - P value	Report only if confidence interval and/or SE is not reported
C-statistic - P value difference in c-statistic	
C-statistic - other information	Specify
Observed rate	%
Observed rate - 95% CI Lower bound	
Observed rate - 95% CI Upper bound	
Expected rate	%
Expected rate - 95% CI Lower bound	
Expected rate - 95% CI Upper bound	
Observed/expected	
Observed/expected - 95% CI Lower bound	

(Continued)

Observed/expected - 95% CI Upper bound	
Observed/expected - SE	
Observed/expected - P value	
Observed/expected - IQR Lower bound	
Observed/expected - IQR Upper bound	
Expected/observed	
Expected/observed - 95% CI Lower bound	
Expected/observed - 95% CI Upper bound	
Expected/observed - SE	
Expected/observed - P value	
Expected/observed - IQR Lower bound	
Expected/observed - IQR Upper bound	
Calibration plot - calibration table is available	If yes, mention which table in the article
Sensitivity	%
Specificity	%
Negative predictive value	%
Positive predictive value	%
Accuracy	%
In case sensitivity, specificity, negative predictive value or positive predictive value is reported, what threshold is used?	
Hosmer Lemeshow X2	
Hosmer Lemeshow X2 - P value	
IDI	
IDI - 95% CI lower bound	
IDI - 95% CI upper bound	
IDI - P value	Report only if confidence interval and/or SE is not reported
NRI - cases	
NRI - 95% CI lower bound - cases	

(Continued)

NRI - 95% CI upper bound - cases	
NRI – non-cases	
NRI - 95% CI lower bound – non-cases	
NRI - 95% CI upper bound – non-cases	
NRI - total	
NRI - 95% CI lower bound - total	
NRI - 95% CI upper bound - total	
NRI - category-free or thresholds	Category free NRI or thresholds were used?
NRI - if thresholds, which thresholds were used?	
NRI - table available with thresholds	If yes, mention which table in the article
NRI - other information	
Performance after updating - for each biomarker that is compared to the RCRI	
Which biomarker(s) is (are) compared to RCRI?	In case, multiple biomarkers are added at once, name all biomarkers
C-statistic - type	
C-statistic	
C-statistic - 95% CI Lower bound	
C-statistic - 95% CI Upper bound	
C-statistic - SE	
C-statistic - P value	Report only if confidence interval and/or SE is not reported
C-statistic - P value difference in c-statistic	
C-statistic - other information	Specify
Observed rate	%
Observed rate - 95% CI Lower bound	
Observed rate - 95% CI Upper bound	
Expected rate	%
Expected rate - 95% CI Lower bound	
Expected rate - 95% CI Upper bound	

(Continued)

Observed/expected	
Observed/expected - 95% CI Lower bound	
Observed/expected - 95% CI Upper bound	
Observed/expected - SE	
Observed/expected - P value	
Observed/expected - IQR Lower bound	
Observed/expected - IQR Upper bound	
Expected/observed	
Expected/observed - 95% CI Lower bound	
Expected/observed - 95% CI Upper bound	
Expected/observed - SE	
Expected/observed - P value	
Expected/observed - IQR Lower bound	
Expected/observed - IQR Upper bound	
Calibration plot - calibration table is available	If yes, mention which table in the article
Sensitivity	%
Specificity	%
Negative predictive value	%
Positive predictive value	%
Accuracy	%
In case sensitivity, specificity, negative predictive value or positive predictive value is reported, what threshold is used?	
Hosmer Lemeshow X2	
Hosmer Lemeshow X2 - P value	
IDI	
IDI - 95% CI lower bound	
IDI - 95% CI upper bound	
IDI - P value	Report only if confidence interval and/or SE is not reported

(Continued)

NRI - cases	
NRI - 95% CI lower bound - cases	
NRI - 95% CI upper bound - cases	
NRI – non-cases	
NRI - 95% CI lower bound – non-cases	
NRI - 95% CI upper bound – non-cases	
NRI - total	
NRI - 95% CI lower bound - total	
NRI - 95% CI upper bound - total	
NRI - category-free or thresholds	Category free NRI or thresholds were used?
NRI - if thresholds, which thresholds were used?	
NRI - table available with thresholds	If yes, mention which table in the article
NRI - other information	

Addition information	
Additional information regarding conflict of interest	E.g. funding of biomarker assay manufacturers
Comments	

Extra baseline table when characteristics are not reported for the whole population. Baseline characteristics for cases and non-cases were collected separately similar to the baseline characteristics previously reported in this data extraction form

HISTORY

Protocol first published: Issue 10, 2018

CONTRIBUTIONS OF AUTHORS

Lisette M Vernooij: protocol development, screening and selection of studies, development of data extraction form and data extraction, characteristics of studies, risk of bias assessment, statistical analysis, writing and drafting of the review, communication with and between authors.

Wilton A van Klei: medical and content input.

Karel G Moons: methodological, statistical and content input.

Toshihiko Takada: selection of studies, data extraction, risk of bias assessment.

Judith AR van Waes: selection of studies, data extraction, risk of bias assessment, medical and content input.

Johanna AAG Damen: screening and selection of studies, data extraction, risk of bias assessment, methodological, statistical and content input.

DECLARATIONS OF INTEREST

Lisette M Vernooij: none known.

Wilton A van Klei: none known.

Karel G Moons: none known.

Toshihiko Takada: none known.

Judith AR van Waes: none known.

Johanna A Damen: none known.

SOURCES OF SUPPORT

Internal sources

- No sources of support provided

External sources

- NIHR, UK

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DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Several differences between the protocol and review should be addressed:

- Initially, we aimed to identify all biomarkers that were compared or added to the RCRI to improve risk prediction. As we found many studies that compared the RCRI to a new or existing prediction model, we added a third aim that specifically focused on the comparison of the predictive performance of the RCRI to other prediction models.
- Conference proceedings for abstracts were eventually not searched, because the lack of information would not allow us to perform a risk of bias assessment.
- The review protocol stated that we would include studies reporting on patients of all ages, however we eventually selected studies including only adult patients (≥ 18 years). As the RCRI has been developed for patients ≥ 50 years, we do not expect to have missed studies that reported on patients < 18 years.
- In the protocol, we stated that PubMed would be searched to check for any comments or retractions, however we only searched the Retraction Watch Database for retractions. We used PubMed to identify new studies during the cross-referencing procedure.
- In contrast with the protocol, selection of studies based on full text assessment was performed in two stages. In the first step, one review author assessed whether the RCRI was mentioned in the 'Results' and/or 'Methods' section of the article. This was done by searching for the terms 'RCRI' or often used synonyms, i.e. 'revised Goldman index' and 'Lee index', or by searching where in the report the original paper was referenced. If this was not the case, these articles were excluded. The remaining studies were screened for inclusion in the review as planned. We planned to contact the original investigators to provide this missing information in case of any missing data about the predictive performance measures of the RCRI, extended RCRI and other prediction models. However, we concluded that contacting authors for missing information would not lead to different review findings as we encountered large heterogeneity in the study population, outcome definitions, prediction horizons and studied biomarkers or prediction models.
- We planned to perform a meta-analysis of the predictive performance of the RCRI model only as compared to the RCRI with the biomarker(s) added, across the various RCRI validation studies. However, this turned out to be impossible due to the low number of studies reporting on the added value of the same biomarker, and due to the differences in included study populations and in outcome definitions between these RCRI validation studies. Meta-analysis of the c-statistic was also planned for the studies that compared the RCRI to biomarkers alone (objective 2), where there were at least three studies reporting on the same biomarker for predicting a similar outcome (using a similar definition), with a similar prediction horizon and scale on how the biomarker was studied. As there was no set of studies fulfilling these criteria, meta-analysis of the c-statistic for objective 2 also turned out to be not possible. Finally, meta-analysis of the c-statistics was also not possible for objective 3 for the same reason. Instead, the performance measures (c-statistic) for RCRI models extended with biomarkers that were studied in at least three studies were presented in forest plots, without presenting a pooled estimate.

- Several subgroup analyses were planned, including vascular surgery patients versus other noncardiac surgery patients, elective versus emergency surgery, different prediction horizons and patients in different age categories. For the same reasons as mentioned above, meta-analysis in these subgroups was not possible. Again, we stratified the forest plots according to the subgroups based on outcome, and reported the prediction horizon in the plot.
- Sensitivity analyses excluding studies with high risk of bias (at least four domains judged to be 'high') and excluding unpublished studies and studies with missing data were planned but not performed due to the large heterogeneity between studies.
- We planned a summary of findings table using GRADE to present the body of evidence for the included prognostic studies. However, GRADE guidance for grading the certainty of results from prognostic model studies is currently not available.

INDEX TERMS

Medical Subject Headings (MeSH)

Bias; Biomarkers; *Heart Arrest; *Myocardial Infarction; Peptide Fragments; Predictive Value of Tests; Prognosis; Risk Assessment

MeSH check words

Adult; Humans