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Prediction models for hospital readmissions in patients with heart disease: a systematic review and meta-analysis

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Prediction models for hospital readmissions in patients with heart disease: a systematic review and meta-analysis.

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Abstract

Objective: To describe the discrimination and calibration of clinical prediction models, identify characteristics that contribute to better predictions, and investigate predictors that are associated with unplanned hospital readmissions.

Design: Systematic review and meta-analysis.

Data source: Medline, EMBASE, ICTPR (for study protocols), and Web of Science (for conference proceedings) were searched up to 25 August 2020.

Eligibility criteria for selecting studies: Studies were eligible if they reported on 1) hospitalized adult patients with acute heart disease; 2) a clinical presentation of prediction models with c-statistic; 3) unplanned hospital readmission within six months.

Primary and secondary outcome measures: Model discrimination for unplanned hospital readmission within six months measured using concordance (c) statistics and model calibration. Meta-regression and sub-group analyses were performed to investigate predefined sources of heterogeneity. Outcome measures from models reported in multiple independent cohorts and similarly defined risk predictors were pooled.

Results: Sixty studies describing 81 models were included: 43 models were newly developed, and 38 were externally validated. Included populations were mainly heart failure (HF) patients (n=29). The average age ranged between 56.5 and 84 years. The incidence of readmission ranged from 3% till 43%. Risk of bias was high in almost all studies. The c-statistic was <0.7 in 72 models, between 0.7-0.8 in 16 models and >0.8 in 5 models. The study population, data source and number of predictors were significant moderators for the discrimination. Calibration was reported for 27 models. Only the GRACE-score had adequate discrimination in independent cohorts (0.78, 95% CI 0.63-0.86). Eighteen predictors were pooled.

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Conclusion: Some promising models require updating and validation before use in clinical practice. The lack of independent validation studies, high risk of bias and low consistency in measured predictors limit their applicability.

Trial registration: Prospero, CRD42020159839

Key words: heart disease, meta-analysis, patient readmission, risk assessment, systematic review.

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Article summary

Strengths and limitations of this study

- Largest investigation of unplanned hospital readmission risk to date, including 81 unique prediction models in the systematic review.
- Independent and standardized procedures for study selection, data collection and risk of bias assessment.
- High risk of bias in current prediction models and unexplained heterogeneity between models limit recommendations for using prediction model in clinical practice.

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Introduction

Hospital readmissions in patients with acute heart disease are associated with a high burden on patients, healthcare and costs.[1] The identification of high-risk hospitalized patients is important to provide timely interventions.

Numerous systematic reviews have previously investigated the prediction of unplanned hospital readmissions in several populations.[2-11] While some have included hospitalized patients in general[10,11], others have focused specifically on patients with heart failure (HF)[2,4-7,9] or acute myocardial infarction (AMI).[3,8] The conclusion is generally the same, the discrimination is poor to adequate, and there is little consistency in the type of predictors included in the models.

The clinical applicability of risk prediction models in daily practice is currently limited. Statistical models are often not presented in a clinically useful way or models based on administrative data are considered.[3] These models therefore cannot be readily used in daily practice. In addition, prediction models are often developed for a very specific population, which asks from clinicians to be familiar with several models. Furthermore, patients may belong to multiple populations because of cardiac comorbidities.

We believe that the state of the art on risk prediction can be improved if more knowledge is available on the performance of clinical risk prediction models and risk predictors across different populations of patients with heart disease. Although heterogeneity in models and predictors is often considered as a limitation, it can inform effect moderators on how predictions can be improved.[12] For example, perhaps we can identify predictors who demonstrate a consistent association with hospital readmission regardless of the underlying disease. If this can be identified, a more general prediction model could be developed that is relevant for the heterogeneous group of patients on cardiac care units. This might contribute to

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the early recognition and onset of preventive interventions in patients with heart disease at risk of readmission.

We therefore performed a systematic review and meta-analysis on clinical risk prediction models for the outcome unplanned hospital readmission in patients hospitalized for acute heart disease. Our aim was to describe the discrimination and calibration of clinical prediction models, identify characteristics that contribute to better predictions, and to investigate predictors that are consistently associated with hospital readmissions.

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Methods

A protocol was registered in PROSPERO (CRD42020159839). The results are reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[13]

Eligibility criteria

Studies were eligible if 1) the study population included hospitalized adult patients with (symptoms of) heart disease; 2) a prediction model with c-statistic was reported; 3) a clinically useful presentation of the model with risk factors was reported; 4) the outcome was unplanned hospital readmissions within six months; 5) the study design was appropriate, i.e. (nested) case-control study, (prospective and retrospective) cohort study, database and registry study, or secondary analysis of a trial; 6) they were reported in English.

Information sources

A search strategy was designed with an information specialist (PROSPERO protocol and Supplemental Text 1). We searched the Medline, EMBASE, WHO ICTPR search portal (for study protocols), and Web of Science (for conference proceedings) databases up to 25 August 2020 without any restrictions for eligible studies. We searched for full text manuscripts of the identified protocols. After selecting the full text manuscripts, we screened references lists and prospective citations (using Google Scholar) for additional eligible studies.

Study selection

Three reviewers were involved in the study selection process. Each reviewer independently screened two thirds of the titles, abstracts and full-text articles of potentially relevant references identified in the literature search. Disagreements were resolved through consensus. Sixteen authors were contacted and six delivered data for readmission when a composite outcome was used. Two authors were also contacted when data was reported combining multiple patient

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populations. However, no additional data was provided for the population with heart disease and these studies were excluded.

Data extraction

Data extraction was performed based on the 'Critical Appraisal and Data Extraction for Systematic Reviews' checklist using standardized forms in the Distiller Systematic Review Software (see Supplemental Text 2 for the data items).[14] One reviewer collected the data and the second reviewer verified the extracted data. Disagreements were resolved through consensus. Eight authors were contacted and two delivered data to resolve uncertainties or missing data.

Risk of bias

The PROBAST tool[15] was used to assess the risk of bias (RoB) for the participants, predictors, outcome and analysis for each model. One author assessed the RoB as low, high or unclear, and the second author verified the extracted data and RoB conclusion. Disagreements were resolved through consensus. In addition, the applicability of the included studies based on our research question was assessed for the participants, predictors and outcome domains and rated as low concerns, high concerns or uncertain concerns regarding applicability.

Summary measures

The discrimination of the prediction models were described using the concordance (c)-statistic. Missing standard errors were derived from the sample data.[16] The calibration was described using the number of observed and expected events, the calibration slope, calibration in large, or the Hosmer-Lemeshow test.

The association between risk predictors and hospital readmission was described using regression coefficients. Missing standard errors for the coefficients were considered missing completely at random and were not imputed. A complete case analysis was performed.

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Synthesis of results and analyses

Meta-analyses using random-effects models, with the Hartung-Knapp modification, were performed to describe the distribution of the between-study variance of the different prediction models and their predictors. Because we considered that there would be substantial heterogeneity, conclusions were not based on the precision of the pooled estimates.

The c-statistic from each model was pooled and a meta-regression was performed to investigate the moderation effect of age and the number of predictors on the discrimination. A subgroup analysis was performed to investigate the moderation effect of the different patient populations, design, outcome definition, and endpoint. The c-statistic of the validated model was used if available; otherwise the c-statistic from the development phase was used.

The c-statistics of specific prediction models that were evaluated in multiple studies were pooled for the endpoint 30 days follow-up.

Coefficients of predictors that were similarly defined in at least five studies were pooled for the endpoint 30 days follow-up. The patient populations were defined as subgroups to explore consistency and heterogeneity (I^2, tau) in the effect estimates.

Analyses were performed using the 'metan' package in STATA 15 IC and the 'metamisc package' in Rstudio.

Public and patient involvement

Because of the design of the study and because we did not collect primary date, we did not involve patients or the public in the design, conduct, or reporting of our research.

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Results

A total of 8588 abstracts were reviewed and 60 studies describing 81 separate models were included (Figure 1). Table 1 provides an overview of the included studies and models, which were published between 2001 and 2020. The majority of the studies (n=40) was performed in the United States. The data sources used were mostly retrospective cohort studies (n=15), hospital databases (n=13) and registries (n=13). Included populations were mainly HF patients (n=29), surgical patients (n=14) and patients with an AMI or acute coronary syndrome (n=10). The average age was between 56.5 and 84 years. The sample size of development cohorts ranged from 182 till 193,899 patients and of the validation cohorts between 104 and 321,088 patients. The outcome of interest was mostly all-cause readmission (n=41) and measured on 30 days (n=55). The incidence of readmission per study ranged from 3% till 43%.

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Table 1. Study characteristics

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Moretti et al.[17]	EuroHeart PCI score	Hospital database	NA	Ext	-	1192	ACS	71 (7)	30d		4.7
Asche et al.[18]	NR	Retrospective cohort	Yes	Split	2446	612	AMI	65 (15)	30d	8.9	
Cediel et al.[19]	TARRACO Risk Score	Retrospective cohort	Yes	No	611	401	AMI type 2, ischemia	D: 78 [17] V: 60 [21]	30d	2.6	
		Retrospective cohort	Yes	No	611	401	AMI type 2, ischemia	D: 78 [17] V: 60 [21]	180d	7.9	
Chotechuang et al.[20]	GRACE	Retrospective cohort	NA	Ext	-	152	AMI	60.5 (6.3)	30d		5.3
	GRACE	Retrospective cohort	NA	Ext	-	152	AMI	60.5 (6.3)	180d		9.2
Hilbert et al.[21]	AMI decision tree	Registry	Yes	Ext	10848	10701	AMI	NR	30d	20.6	19.7
Dodson et al.[22]	SILVER-AMI 30-day readmission calculator	Prospective cohort	Yes	Split	2004	1002	AMI	81.5 (5.0)	30d	18.2	
Kini et al.[23]	NR	Registry	Yes	Split	60742	26107	AMI	76.5 (8.0)	90d	27.5	
Nguyen et al.[24]	AMI READMITS score	Retrospective cohort	Yes	Split	661	165	AMI	65.5 (12.8)	30d	13	
	Full-stay AMI model	Retrospective cohort	Yes	Split	661	165	AMI	65.5 (12.8)	30d	13	
	CMS AMI administrative model	Retrospective cohort	NA	Ext	-	826	AMI	65.5 (12.8)	30d		13

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Krumholz et al.[25]	CMS AMI administrative model	Registry	Yes	Split, Ext	100465	321088	AMI	78.7 (8.0)	30d	18.9	20.0 (Ext) NR (split)
	CMS AMI medical model	Registry	Yes	Split	130944	130944	AMI	76.2 (7.3)	30d	20	
Rana et al.[26]	Elixhauser index	Hospital database	NA	Ext	-	1660	AMI	67.9	30d		6.3
	HOSPITAL score	Hospital database	NA	Ext	-	1660	AMI	67.9	30d		6.3
Atzema et al.[27]	AFTER Part 2 scoring system	Retrospective cohort	Yes	Split	2343	1167	Arrhythmia, AF	D: 68.6 (14.7) V: 68.3 (15.1)	30d	7	7.6
Lahewala et al.[28]	CHADS2	Administrative	NA	Ext	-	116450	Arrhythmia, AF	<75	30d		15.8
	CHADS2	Administrative	NA	Ext	-	116450	Arrhythmia, AF	<75	90d		25.1
	CHA2DS-VASc	Administrative	NA	Ext	-	116450	Arrhythmia, AF	65-74	30d		15.8
	CHA2DS-VASc	Administrative	NA	Ext	-	116450	Arrhythmia, AF	65-74	90d		25.1
Benuzillo et al.[29]	CRSS	Hospital database	Yes	Boot, Ext	2589	896 (Ext) 500 (Boot)	CABG	66.7 (9.9)	30d	9.1	8.2 (Ext) 9.1 (Boot)
Deo et al.[30]	30-days CABG Readmission Calculator	Administrative	Yes	Boot	155054	1000	CABG	65.4 (10.4)	30d	12.5	
Engoren et al.[31]	NR	Hospital database	Yes	Split	2644	2711	CABG	NR	30d	7.6	8
Lancey et al.[32]	NR	Registry	Yes	Split	2341	2520	CABG	64.5 (10.5)	30d	8.8	9.5
Rosenblum et al.[33]	The STS PROM score	Hospital database	NA	Ext	-	21719	CABG	63.5 (10.7)	30d		9.3

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Zitser-Gurevich et al.[34]	NR	Prospective cohort	Yes	Split	2266,5	2266,5	CABG	65-74	30d	13.3	
	NR	Prospective cohort	Yes	Split	2266,5	2266,5	CABG	65-74	100d	24.1	
Zywot et al.[35]	CABG Risk Scale	Administrative	Yes	Ext	126519	94318	CABG	D: 70-74 V: 70-74	30d	23	21
Ahmad et al.[36]	CMS HF administrative model	Prospective cohort	NA	Ext	-	183	HF	61 [18]	30d		22.4
Amarasingham et al.[37]	ADHERE	Hospital database	NA	Ext	-	1372	HF	56.5	30d		24.1
	CMS HF administrative model	Hospital database	NA	Ext	-	1372	HF	56.5	30d		24.1
	Tabak mortality score	Hospital database	NA	Ext	-	1372	HF	56.5	30d		24.1
Au et al.[38]	Administrative Claims Model: HF 30-day mortality	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
	Charlson Comorbidity Score	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
	CMS HF administrative model	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
	LACE	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
Bardhan et al.[39]	NR	Hospital database	Yes	No	40983	-	HF	69.2 (15.7)	30d	7	

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size Dev.	Sample size Val.	Population	Average age	Outcome	Readmission (%) Dev.	Readmission (%) Val.
Betihavas et al.[40]	NR	RCT secondary analysis	Yes	Boot	280	200	HF	74 [64 - 81]	28d	18	
Cox et al.[41]	CMS HF administrative model	Hospital database	No	Ext	-	1454	HF	75 (12)	30d		21.5
	CMS HF medical model	Hospital database	No	Ext	-	1454	HF	75 (12)	30d		21.5
Delgado et al.[42]	15-day CV readmission risk score	Prospective cohort	Yes	Boot	1831	500	HF	72.4 (12.1)	15d	7.1	
	30-day CV readmission risk score	Prospective cohort	Yes	Boot	1831	500	HF	72.4 (12.1)	30d	13.9	
Formiga et al.[43]	CMS HF medical model	Hospital database	NA	Ext	-	719	HF	78.1 (9)	30d		7.6
	CMS HF medical model	Hospital database	NA	Ext	-	719	HF	78.1 (9)	90d		14.4
Frizzell et al.[44]	CMS HF administrative model	Registry	NA	External	-	56477	HF	80 [2]	30d		21.2
Hammill et al.[45]	CMS HF administrative model	Registry	NA	Ext	-	24163	HF	81	30d		21.9
Hilbert et al.[21]	HF decision tree	Registry	Yes	Ext	39682	38409	HF	NR	30d	25.5	25.2
Hummel et al.[46]	CMS HF medical model	Prospective cohort	NA	Ext	-	1807	HF	79.8 (7.6)	30d		27

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size Dev.	Sample size Val.	Population	Average age	Outcome	Readmission (%) Dev.	Readmission (%) Val.
Huynh et al.[47]	NR	Prospective cohort	Yes	Ext	430	1046	HF	D: 75 [19] V: 67 [17]	30d	21	24
Ibrahim et al.[48]	HOSPITAL score	Retrospective cohort	NA	Ext	-	692	HfpEF	68.3 (11.8)	30d		27.3
	LACE / LACE+ index	Retrospective cohort	NA	Ext	-	692	HfpEF	68.3 (11.8)	30d		27.3
Keenan et al.[49]	CMS HF administrative model	Registry	Yes	Split, Ext.	28319	845291	HF	79.9 (7.8)	30d	23.6	23.7 (Ext) NR (Split)
	CMS HF medical model	Registry	Yes	Split, Ext.	64329	64329	HF	75-84	30d	23.7	
Kitamura et al.[50]	FIM	Retrospective cohort	NA	Ext	-	113	HF	80.5 (6.7)	90d		20.4
Leong et al.[51]	30-day HF readmission risk score	Retrospective cohort	Yes	Split	888	587	HF	D: 70.0 (12.7) V: 69.1 (12.8)	30d	9.9	
Li et al.[52]	NR	Retrospective cohort	Yes	Split	51783	25887	HF	D: 84 [12] V: 84[11]	30d	24.2	
Lim et al.[53]	NR	Registry	Yes	No	4566	-	HF	70.5 (12.0)	30d	6.6 (car) 13 (all)	
Reed et al.[54]	AH model	Administrative	Yes	Split	NR	NR	HF	NR	30d	NR	
	CMS HF administrative model	Administrative	NA	Split	-	NR	HF	NR	30d		NR
	Hasan	Administrative	NA	Split	-	NR	HF	NR	30d		NR
	LACE	Administrative	NA	Split	-	NR	HF	NR	30d		NR
	PARR-30	Administrative	NA	Split	-	NR	HF	NR	30d		NR

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Salah et al.[55]	ELAN-HF score	Prospective cohort secondary analysis	Yes	No	1301	-	HF	74 [16]	180d	36.1	
Sudhakar et al.[56]	CMS HF medical model	Hospital database	NA	Ext	-	1046	HF	65.2 (16.6)	30d		35.3
Tan et al.[57]	NR	Hospital database	Yes	Split	246	104	HF	D: 67.7 (12.3) V: 69.0 (12.9)	90d	24.5	11.7
Wang et al.[58]	NR	Hospital database	Yes	No	4548	-	HF	68.5 [27.6]	30d	25.1	
Wang et al.[59]	LACE	Retrospective cohort	NA	Ext	-	253	HF	56.6 (11.5)	30d		24.5
Yazdan-Ashoori et al.[60]	CMS HF administrative model	Prospective cohort	NA	Ext	-	378	HF	73.1 (13.1)	30d		26
	LACE	Prospective cohort	NA	Ext	-	378	HF	73.1 (13.1)	30d		26
Disdier Moulder et al.[61]	NR	Prospective cohort	Yes	No	258		HF, ACS, NR	70.5 [23]	30d	17	
	NR	Prospective cohort	Yes	No	258		HF, ACS, NR	70.5 [23]	180d	38	
Raposeiras-Roubín et al.[62]	GRACE	Retrospective cohort	NA	Ext	-	4229	HF, ACS	68.2 [18.7]	30d		2.6
Burke et al.[63]	HOSPITAL score	Retrospective cohort	NA	Ext	-	HF: 3189 AMI: 767	HF, AMI	65.8 (16.8)	30d		HF: 18.2 AMI: 17.4
Minges et al.[64]	NR	Registry	Yes	Split	193899	194179	HF, PCI	65+	30d	11.4	
Pack et al.[65]	NR	Administrative	Yes	Split	30826	7706	HVD	64.9 (12.2)	90d	12.8	

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Oliver-McNeil et al.[66]	ICD Readmission-Risk Score	Registry	Update	Ext	182	-	ICD	69 (11)	30d		17.6
Wasfy et al.[67]	Pre-PCI model	Registry	Yes	Split	24052	12008	NR	64.8 (12.5)	30d	10.4	
Barnett et al.[68]	NR	Registry	Update	Ext	19964	19964	Surgical	65.3 (12.4)	30d	11.4	
Brown et al.[69]	STS Augmented Clinical Model	Prospective cohort	Update	Boot	1046	NR	Surgical	65.4 (9.8)	30d	NR	
	STS 30-day Readmission Model	Prospective cohort	NA	Ext	-	1194	Surgical	73.3 (10.1)	30d		NR
Espinoza et al.[70]	30-day readmission score after cardiac surgery	Retrospective cohort	Yes	Split	2529	2567	Surgical	65.1 (11.5)	30d	11.9	
Ferraris et al.[71]	READMIT	Prospective cohort	Yes		2574		Surgical	63 (11)	30d	9.8	
Kilic et al.[72]	NR	Retrospective cohort	Yes	Split	3898	1295	Surgical	D:61.9 (14.7) V: 61.6 (15.1)	30d	10	11
Stuebe et al.[73]	NR	Hospital database	Yes	No	4800		Surgical	60-69	30d	12	
Tam et al.[74]	NR	Retrospective cohort	Yes	Boot	63336	NR	Surgical	66.2 (10.7)	30d	11.3	
Khera et al.[75]	TAVR 30-Day Readmission Risk Model	Administrative	Yes	Boots, Ext	39305	40 (Boot) 885 (Ext)	TAVR	D: 81.3	V: 81.7	30d	16.2	16.2 (Boot) 18.9 (Ext)
Sanchez et al.[76]	NR	Registry	Yes	Split	6903	3442	TAVR	D: 81.1 (7.9)	V: 81.3 (7.9)	30d	9.8	10.7

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Abbreviations:

ACS: acute coronary syndrome, AF: atrial fibrillation, AH: Adventist hositals, Boot: bootstrapping, CABG: coronary artery bypass grafting, Car: cardiac-related, CMS=centers for Medicare and Medicaid services, CRSS: CABG Readmission Risk Score, d: days, Dev: development, Ext: external validation, Fim: motor and cognitive Functional Independence Measure, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HVD: heart valve disease, ICD: implantable cardioverter defibrillator, NA: not applicable, NR: not reported, PARR-30: Patients at Risk of Re-admission within 30-days, PCI: percutaneous coronary intervention, SD: standard deviation, Split: random split, TAVR: transcatheter aortic valve replacement, Val: validation

Legend: Age is reported as mean (SD), median [IQR] or average age as reported in the study.

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Risk of bias

Figure 2 summarizes the RoB and applicability assessment (Supplemental Table 1). The overall RoB was high in 98.9% of the models and only one study[22] showed low RoB in all four domains.

For the domain participants, 82.4% of studies was assessed as high RoB because most studies performed retrospective data analyses or used data from existing sources with large number of candidate predictors that were originally developed for other purposes, e.g. administrative databases or registries. The domain predictors was assessed as high RoB in 27.5% of the models, 24.2% as low RoB and 48.4% as unclear RoB. For the domain outcome, 41.8%, 34.1% and 24.2% were assessed as high, low and unclear RoB respectively.

The domain analysis was assessed as high RoB in 97.8%. Most studies did not use appropriate statistics for the development or validation of prediction models.

The domains participants and predictors were assessed as low concerns regarding applicability in all studies. For the domain outcome, 70.3% of studies used all-cause readmission as the outcome of interest and were therefore assessed as low concerns regarding applicability.

Prediction models

A total of 43 new models were developed for patients with HF (n=15), undergoing surgical procedures (n=12), AMI (n=9), transcatheter aortic valve replacement (TAVR) (n=2), a mixed sample with HF and coronary syndromes (n=2), arrhythmias (n=1), valvular disease (n=1), while one study did not specify the sample (table 1). The c-statistic was lower than 0.6 in five models, between 0.6 and 0.7 in 24 models, between 0.7 and 0.8 in six models, and between 0.8 and 0.9 in two models. In six models, the c-statistic was only reported for a validation cohort (table 2).

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A total of 38 separate models were externally validated for patients with HF (n=26), AMI (n=4), surgical patients (n=3), acute coronary syndrome (n=2), arrhythmias (n=2), mixed sample with HF and coronary syndromes (n=1). The discrimination was lower than 0.6 in sixteen models, between 0.6 and 0.7 in fifteen models, between 0.7 and 0.8 in five models, and between 0.8 and 0.9 in two models (Table 2).

The discrimination of six models was evaluated in multiple independent cohorts and was pooled in meta-analyses (Figure 3, Supplemental Figures 1-6): the CMS AMI administrative model[24,25] (0.65, 95% CI 0.56-0.73); the CMS HF administrative model[36-38,41,44,45,49,54,60] (0.60, 95% CI 0.58-0.62); the CMS HF medical model[41,43,46,49,56] (0.60, 95% CI 0.58-0.62); the HOSPITAL score[26,48,63] (0.64, 95% CI 0.58-0.70); the GRACE score[20,62] (0.78, 95% CI 0.63-0.86); and the LACE score[38,48,54,59,60] (0.62, 95% CI 0.53-0.70).

On average, models for AMI patients had the best discrimination (0.67, n=16), followed by TAVR patients (0.65, n=2), HF patients (0.64, n=45), and surgical patients (0.63, n=17). The discrimination was highest in studies using secondary analysis (0.70, n=2) and retrospective cohort studies (0.69, n=23), and was lowest in studies using registries (0.61, n=17) and hospital databases (0.61, n=18). The discrimination decreased when the number of predictors increased (beta -0.002, n=90). There were no moderation effects based on the average age of the sample, outcome definition and endpoint of the prediction (Supplemental Figures 7–8 and Supplemental Table 2).

The calibration was reported for 27 models using multiple measures and could not be pooled (Table 2).

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Table 2. Model discrimination and calibration

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Moretti et al.[17]	EuroHeart PCI score	ACS	16	External	0.59 (0.48 - 0.71)	NA	
Asche et al.[18]	NR	AMI	19	Development, random split	0.74, NR	NA	
Cediel et al.[19]	TARRACO Risk Score	AMI type 2, ischemia	7	Development (30d)	0.71 (0.61 - 0.82)	NA	
		AMI type 2, ischemia	7	Development (180d)	0.71 (0.64 - 0.78)	NA	
Burke et al.[63]	HOSPITAL score	AMI	7	External	0.66 (0.61 - 0.71)	HLT	p=0.49
Chotechuang et al.[20]	GRACE	AMI	9	External (30d)	0.77 (0.65 - 0.88)	NA	
	GRACE	AMI	9	External (180d)	0.63 (0.49 - 0.77)	NA	
Hilbert et al.[21]	AMI decision tree	AMI	44	Development, External	0.65 (0.64 - 0.66), 0.61 (0.61 - 0.62)	NA	
Dodson et al.[22]	SILVER-AMI 30-day readmission calculator	AMI	10	Development, random split	0.65, 0.63	HLT	p>0.05, p=0.05
Kini et al.[23]	NR	AMI	12	Development, random split	NR, 0.66	Slope, in large, plot	0.973 (p=0.330), -0.038 (p=0.221)
Nguyen et al.[24]	AMI READMITS score	AMI	7	Development, random split	0.75 (0.70 - 0.80), 0.73 (0.71 - 0.74)	Plot, Plot	
	Full-stay AMI model	AMI	10	Development, random split	0.78 (0.74 - 0.83), 0.75 (0.74 - 0.76)	Plot	
	CMS AMI administrative model	AMI	32	External	0.74 (0.69 - 0.74)	Plot	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Krumholz et al.[25]	CMS AMI administrative model	AMI	32	Development, external, random split	0.63, 0.63, 0.62	In large, slope	
	CMS AMI medical model	AMI	45	Development, random split	0.58, 0.59	NA	0, 1 / 0.015, 0.997/ 0.015, 0.983
Rana et al.[26]	Elixhauser index	AMI	30	External	0.53 (0.42 - 0.65)	NA	
	HOSPITAL score	AMI	7	External	0.60 (0.47 - 0.73)	NA	
Atzema et al.[27]	AFTER Part 2 scoring system	Arrhythmia, AF	12	Development	0.69, NR	NA	
Lahewala et al.[28]	CHADS2	Arrhythmia, AF	5	External (30d)	0.64	NA	
	CHADS2	Arrhythmia, AF	5	External (90d)	0.63	NA	
	CHA2DS-VASc	Arrhythmia, AF	9	External (30d)	0.65	NA	
	CHA2DS-VASc	Arrhythmia, AF	9	External (90d)	0.63	NA	
Benuzillo et al.[29]	CRSS	CABG	5	Development, bootstrapping	0.63, 0.63	HLT	7.13 (p=0.52), 9.31 (p=0.32)
Deo et al.[30]	30-days CABG Readmission Calculator	CABG	20	Development	0.65	NA	
Engoren et al.[31]	NR	CABG	6	Development, random split	0.68 (0.64 - 0.72), 0.68 (0.64 - 0.68)	NA	
Lancey et al.[32]	NR	CABG	8	Development, random split	0.64, 0.57	NA	
Rosenblum et al.[33]	The STS PROM score	CABG	40	External	0.59 (0.57 - 0.60)	NA	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Zitser-Gurevich et al.[34]	NR	CABG	17	Development, external (30d)	0.63, 0.66/0.63	HLT	7.91 (p=0.44)
	NR	CABG	13	Development (100d)	0.65	HLT	6.76 (p=0.56)
Zywot et al.[35]	CABG Risk Scale	CABG	27	Development, external	NR, 0.70	Plot	
Ahmad et al.[36]	CMS HF administrative model	HF	37	External	0.66 (0.57 - 0.76)	HLT	p=0.19
Amarasingham et al.[37]	ADHERE	HF	3	External	0.56 (0.54 - 0.59)	NA	
	CMS HF administrative model	HF	37	External	0.66 (0.63 - 0.68)	NA	
	Tabak mortality score	HF	18	External	0.61 (0.59 - 0.64)	NA	
Au et al.[38]	Administrative Claims Model: HF 30-day mortality	HF	17	External	0.58 (0.58 - 0.59)	NA	
	Charlson Comorbidity Score	HF	32	External	0.55 (0.55- 0.56)	NA	
	CMS HF administrative model	HF	37	External	0.59 (0.59 - 0.60)	NA	
	LACE	HF	18	External	0.58 (0.58 - 0.59)	NA	
Bardhan et al.[39]	NR	HF	30	Development	0.56	NA	
Betihavas et al.[40]	NR	HF	7	Development, bootstrapping	NR, 0.80	NA	
Burke et al.[63]	HOSPITAL score	HF	7	External	0.67 (0.65 - 0.70)	HLT	p=0.10

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Cox et al.[41]	CMS HF administrative model	HF	37	External	0.61	NA	
	CMS HF medical model	HF	20	External	0.60	NA	
Delgado et al.[42]	15-day CV readmission risk score	HF	5	Development, bootstrapping	0.65, 0.63	Plot	
	30-day CV readmission risk score	HF	11	Development, bootstrapping	0.66, 0.64	Plot	
Formiga et al.[43]	CMS HF medical model	HF	19	External (30d)	0.65 (0.57 - 0.72)	NA	
	CMS HF medical model	HF	19	External (90d)	0.62 (0.56 - 0.68)	NA	
Frizzell et al.[44]	CMS HF administrative model	HF	37	External	0.60	NA	
Hammill et al.[45]	CMS HF administrative model	HF	37	External	0.59	Plot	
Hilbert et al.[21]	HF decision tree	HF	44	Development, External	0.59 (0.58 - 0.60), 0.58 (0.58 - 0.59)	NA	
Hummel et al.[46]	CMS HF medical model	HF	28	External	0.61	NA	
Huynh et al.[47]	NR	HF	12	Development, external (30d)	0.82 (0.76 - 0.87), 0.73 (0.69 - 0.77)	NA	
	NR	HF	12	Development, external (90d)	NR, 0.65	NA	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Ibrahim et al.[48]	HOSPITAL score	HfpEF	7	External	0.60 (0.55 - 0.64)	NA	
	LACE	HfpEF	18	External	0.55 (0.50 - 0.60)	NA	
	LACE+ index	HfpEF	24	External	0.57 (0.52 - 0.62)	NA	
Keenan et al.[49]	CMS HF administrative model	HF	37	Development, external, random split	0.60, 0.60, 0.61	In large, slope	0, 1 / 0.02, 1.01/ 0.09, 1.05
	CMS HF medical model	HF	30	Development, random split	0.58, 0.61	In large, slope	0, 1 / 0, 1
Kitamura et al.[50]	FIM	HF	13	External	0.78	NA	
Leong et al.[51]	30-day HF readmission risk score	HF	7	Development, random split	0.76, 0.76	NA	
Li et al.[52]	NR	HF	10	Development, random split	0.63 (0.62 - 0.63) 0.63 (0.62 - 0.63)	HLT, plot	0.15 (p>0.005)
Lim et al.[53]	NR	HF	13	Development	0.68 (car), 0.62 (all)	HLT	27.5 (p=0.001) (car) 8.0 (p=0.429) (all)
Reed et al.[54]	AH model	HF	14	Development, random split	0.86 (0.85 - 0.86), 0.85 (0.84 - 0.86)	NA	
	CMS HF administrative model	HF	37	Random split	0.55 (0.54 - 0.56) 0.55 (0.54 - 0.57)	NA	
	Hasan	HF	9	Random split	0.80 (0.79 - 0.81) 0.80 (0.80 - 0.82)	NA	
	LACE	HF	18	Random split	0.75 (0.74 - 0.81) 0.74 (0.73 - 0.76)	NA	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Reed et al.[54] (continued)	PARR-30	HF	10	Random split	0.82 (0.81 - 0.83) 0.81 (0.80 - 0.82)	NA	
Salah et al.[55]	ELAN-HF score	HF	10	Development	0.60 (0.56 - 0.64)	NA	
Sudhakar et al.[56]	CMS HF medical model	HF	20	External	0.61 (0.57-0.64) ≥65y: 0.59 (0.53-0.64) Random patient-level: 0.58 (0.50-0.65)	NA	
Tan et al.[57]	NR	HF	3	Random split	0.73	HLT, plot	p=0.62
Wang et al.[58]	NR	HF	12	Development	0.65	NA	
Wang et al.[59]	LACE	HF	18	External	0.56 (0.48 - 0.64)	NA	
Yazdan-Ashoori et al.[60]	CMS HF administrative model	HF	37	External	0.61 (0.55 - 0.67)	NA	
	LACE	HF	18	External	0.59 (0.52 - 0.65)	HLT	p=0.73
Disdier Moulder et al.[61]	NR	HF, ACS, NR	4	Development (30d)	0.68	NA	
	NR	HF, ACS, NR	5	Development (180d)	0.69	NA	
Raposeiras-Roubín et al.[62]	GRACE	HF, ACS	9	External	0.74 (0.73-0.80)	HLT	p=0.14
Minges et al.[64]	NR	HF, PCI	35	Development, random split	0.67, 0.66	NA	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Pack et al.[65]	NR	HVD	28	Development, random split	0.67 (full dev.)/ 0.65 (nomogram), 0.67 (full val.)	Harrell's E, O:E, Harrell's E, plot	0.1%, 1.9%, 1.6%
Oliver-McNeil et al.[66]	ICD Readmission-Risk Score	ICD	4	Update, External	0.69 (0.58 - 0.79)	HLT, plot	3.44 (p=0.49)
Wasfy et al.[67]	Pre-PCI model	NR	23	Development, random split	0.68, 0.67	HLT, plot	p=0.59
Barnett et al.[68]	NR validation	Surgical	15	External	0.59	NA	
	NR update	Surgical	18	Update	0.60 (0.59 - 0.62)	NA	
Brown et al.[69]	STS Augmented Clinical Model	Surgical	27	Update (bootstrap), random split, external (bootstrap)	0.66 (0.61 - 0.72), 0.56, 0.47 (0.42 - 0.53)	HLT	p=1.0
	STS 30-day Readmission Model	Surgical	21	Update (bootstrap), random split, external (bootstrap)	0.66 (0.62 - 0.71), 0.58, 0.47 (0.41 - 0.52)	HLT	p=0.492
Espinoza et al.[70]	30-day readmission score after cardiac surgery	Surgical	5	Development, random split	0.66 (0.63 - 0.70), 0.64 (0.61 - 0.67)	NA	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Ferraris et al.[71]	READMIT	Surgical	9	Development	0.70	HLT	5.966 (p=0.651)
Kilic et al.[72]	NR	Surgical	15	Development, random split	NR, 0.64	HLT, plot	p=0.45, p=0.57
Stuebe et al.[73]	NR	Surgical	7	Development	0.63	NA	
Tam et al.[74]	NR	Surgical	29	Development, bootstrapping	0.63, 0.65	Plot	
Khera et al.[75]	TAVR 30-Day Readmission Risk Model	TAVR	11	Development, random split, external	NR, 0.63, 0.69	HLT, RMSE, RMSE, plot	p=0.33, 0.978, 0.928
Sanchez et al.[76]	NR	TAVR	10	Development, random split	0.61, 0.60	HLT	p=0.749, p=0.403

Abbreviations: ACS: acute coronary syndrome, AF: atrial fibrillation, AH: Adventist hospitals, CABG: coronary artery bypass grafting, Car: cardiac-related, CMS=centers for Medicare and Medicaid services, CRSS: CABG Readmission Risk Score, d: days, dev: development, Fim: motor and cognitive Functional Independence Measure, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HLT: Hosmer-Lemeshow test, HVD: heart valve disease, ICD: implantable cardioverter defibrillator, NA: not applicable, NR: not reported, O:E: observed:expected, PARR-30: Patients at Risk of Re-admission within 30-days, PCI: percutaneous coronary intervention, plot: calibration plot, TAVR: transcatheter aortic valve replacement, val: validation.

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Predictors

A total of 766 predictor values were estimated in the included models. The median number of predictors per model was 15 (IQR=9–28). The predictors were mostly situated in the domains medical comorbidities (n=211), disease and hospital characteristics (n=128), demographic data (n=128), laboratory values (n=97), and medical history characteristics (n=51). Age (n=47), the presence of diabetes (n=26), insurance status (n=24), length of stay (n=28), and gender (n=23) were the most prevalent predictors. There was little consistency in the definition of predictors, and most studies did not report how they were measured.

Only 18 predictors were similarly defined in multiple studies and could be pooled for the outcome readmission at 30 days (Figure 4, Supplemental Table 3 and Supplemental Figures 9–26). The coefficients of four predictors demonstrated a consistent and significant association across the different samples: chronic obstructive pulmonary disease (COPD), history of HF, and valvular disease. The coefficients of eleven predictors demonstrated an overall significant association, i.e. age, female gender, arrhythmias, chronic lung disease, diabetes mellitus, cerebrovascular disease, cardiovascular accident, anemia, peripheral vascular disease, urgent admission, and infection, but this was not consistent across the samples and the prediction intervals were not significant. The effect of these predictors was mostly smaller in the HF samples.

The coefficients for most predictors could not be pooled because they had different definitions, cutoff values or reference categories. However, renal disease, including dialysis, a longer length of stay, creatinine, NT-proBNP, and previous hospital admissions demonstrated a consistent association with readmissions.

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Discussion

In this systematic review, we included 60 studies that reported the results from 81 separate clinical risk prediction models and 766 risk predictors for unplanned readmission in patients with acute heart disease. No clinical model demonstrated good discrimination (i.e. c-statistic > 0.8) in independently externally validated cohorts, regardless of the underlying patient populations. GRACE was the only model that demonstrated adequate discrimination in multiple cohorts in patients with acute coronary syndromes[20,62] and HF[62], but the RoB was high. There was little consistency in the measurement of risk predictors.

The results of our review are in line with previous systematic reviews which have mainly focused on samples of patients with HF, AMI or focused on generic prediction models. All reviews confirm that the discrimination is generally low. Our review confirms the importance of previous HF[4,5] and previous hospital admissions[5,7] as consistent predictors for the risk of readmission. In addition two prevalent comorbidities, COPD and valve disease were also consistent predictors across the different populations. Other reviews also identified the importance of age, gender, comorbidities and certain laboratory values. These were also significant in our review but the association was not always consistent across the different populations or heterogeneously measured making comparisons difficult. As a result, no clinical risk prediction model or set of predictors that is relevant for different populations of heart disease could be identified.

Our review focused specifically on prediction models with a clinical presentation that can be used in daily practice, e.g. risk scores or nomograms. These simple models do not consider interactions between predictor values or nonlinear link functions in their predictions. This may partially explain the poor discrimination.[77] Using web applications or electronic patient records to run more complex prediction algorithms can likely offer a solution for future models. A recent systematic review observed an average c-statistic of 0.74 for models based using

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electronic patient records and machine learning algorithms.[10] Our review included eleven studies[20,22,28,33,35,56,60,62,69,74,75] that developed or validated electronic tools for risk prediction and their discrimination ranged between 0.59 and 0.77. However, these electronic tools were mostly derived from score charts and nomograms.

There are also concerns about the generalizability of the prediction models. The median age of patients included in the samples was 68 years (IQR=65–75). However, older and frail patients suffer more multimorbidity and geriatric syndromes, and the distribution of predictor and outcome values will also be different than in younger samples. It is therefore unlikely that the majority of the current models will hold their value in daily clinical practice where there is a high prevalence of older patients. Only eight studies[18,22,25,27,47,49,52,76] included one or more geriatric risk factors (e.g. physical performance, dementia) as predictors for readmission. The performance of models including geriatric conditions was similar to models without these conditions. This might be explained by the relative young mean age of the samples in our review. Mahmoudi et al.[10] reported that functional and frailty status are important predictors, but were only included in a small number of studies. Frailty was not identified in any of the models in our review. It might be valuable to examine the additive value of these predictors in prediction models for patients with heart disease.

We observed high RoB in almost all clinical risk prediction models (98.8%). This was mainly because the calibration was lacking or not fully reported (e.g. only p-value of Hosmer-Lemeshow test). Furthermore, most studies performed retrospective data analyses or used data from existing sources. However, our results demonstrate that studies using these data sources had the lowest c-statistic, and that the c-statistic decreased when more predictors were tested. Databases often have missing data, misclassification bias, and random measurement error, which likely explains their average poor performance.[78] Only the SILVER-AMI study[22]

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demonstrated low RoB on all domains. However, their readmission risk calculator for older AMI patients only discriminated modestly (c-statistic = 0.65).

Our review included many recent published studies that were not included in previous reviews and added some new perspective to the literature. Our results show the current state-of-the art of risk prediction in patients with acute heart disease. The timely identification of patients with acute heart disease at risk of readmission remains challenging with the prediction models identified in this systematic review. Therefore, further research in risk prediction remains important and some recommendations for further research can be derived from this review. First, consistency is needed in the definition and measurement of predictors. More homogeneity might improve the identification of important predictors and their effect on readmission. Second, the results suggest that multiple predictors are associated with readmissions regardless of the underlying population. Therefore, attention might be shifted from developing new risk prediction models to updating and externally validating existing prediction models in different populations with heart disease. Third, the applicability of current prediction models in daily practice is an important concern as most models had poor performance, were not replicated and had high RoB. More high-quality studies are needed that evaluate the discrimination, calibration and clinical usefulness. To limit the risk of bias as much as possible, future studies should adhere to the relevant reporting guidelines[79] and could use PROBAST[15] as a guidance to plan their study. Third, Fourth, more complex models integrated in electronic patient records may results in better predictions.

Limitations

Although we performed an extensive literature search, we might have missed some eligible studies, particularly those published in non-English languages. We were able to perform meta-analysis for predictors that were often (≥ 5 models) reported. However, it might be possible that some less frequently mentioned predictors (e.g. geriatric predictors) are a valuable addition

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in clinical practice. The review included a large number of results and statistical tests which may result in an inflated alpha error. The meta-regression identified that models with less predictors had a better discrimination, but this could also be explained by overfitting models; this could not be tested.

Conclusion

A large number of clinical models have recently been developed. Although some models are promising as they demonstrated adequate to good discrimination, no model can currently be recommended for clinical practice. The lack of independently validated studies, high risk of bias and low consistency in measured predictors limit their applicability. Model updating and external validation is urgently needed.

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Data statement section

All data relevant to the study are included in the article or uploaded as supplementary information.

Author contributions

Bastiaan Van Grootven and Patricia Jepma had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Bastiaan Van Grootven and Patricia Jepma contributed equally as first authors.

Concept and design: all authors; *Acquisition, analysis or interpretation of data*: Bastiaan Van Grootven, Patricia Jepma, Corinne Rijpkema, Mariska Leeflang, Joost Daams; *Drafting the manuscript*: Bastiaan Van Grootven, Patricia Jepma; *Critical revision of the manuscript*: all authors; *Analysis*: Bastiaan Van Grootven, Patricia Jepma; *Supervision:* Bianca Buurman.

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Conflict of interest

None declared.

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Figure legends

Figure 1. Flowchart

In total, 8592 records were screened and 60 studies with 81 prediction models were included.

Figure 2. PROBAST Risk of bias and applicability

The PROBAST tool[15] was used to assess the risk of bias for the participants, predictors, outcome and analysis for each model. Only one study demonstrated low risk of bias on all domains.

Figure 3. Meta-analysis of prediction models

Random-effect models were used to pool similar models reported in independent cohorts. For the HOSPITAL score, the discrimination for the HF and AMI samples were similar (0.65 and 0.64). For GRACE, the discrimination for the AMI and reinfarction samples were similar (0.77 and 0.74), and was higher for the HF sample (0.83). Only GRACE demonstrated adequate discrimination in external cohorts.

Figure 4. Predictors of unplanned hospital readmission

The plot provides an overview of the random-effects meta-analyses that were performed for predictors who were similarly defined for the outcome unplanned hospital readmission at 30 days follow-up. See Supplemental table 3 and Supplemental figures 9-26 for more details.

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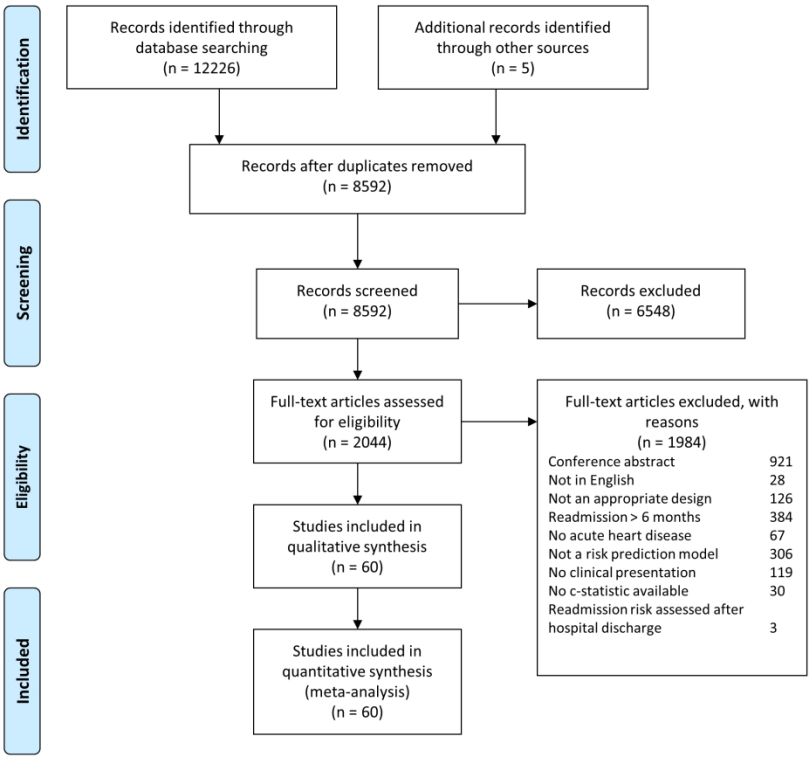
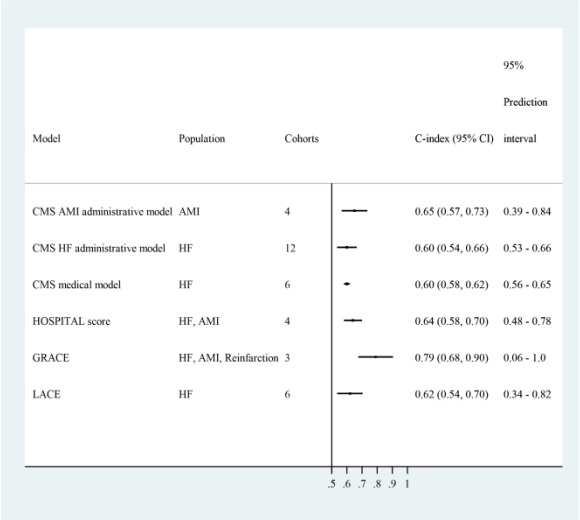


Flowchart
In total, 8592 records were screened and 60 studies with 81 prediction models were included.

190x275mm (300 x 300 DPI)

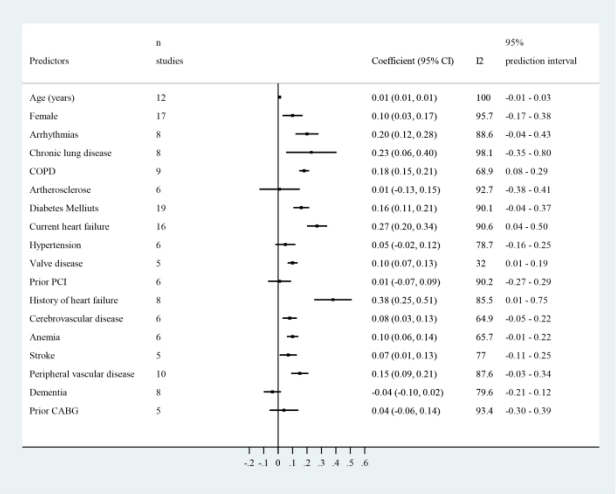
PROBAST Risk of bias and applicability
The PROBAST tool15 was used to assess the risk of bias for the participants, predictors, outcome and analysis for each model. Only one study demonstrated low risk of bias on all domains.

39x51mm (300 x 300 DPI)



Meta-analysis of prediction models
Random-effect models were used to pool similar models reported in independent cohorts. For the HOSPITAL score, the discrimination for the HF and AMI samples were similar (0.65 and 0.64). For GRACE, the discrimination for the AMI and reinfarction samples were similar (0.77 and 0.74), and was higher for the HF sample (0.83). Only GRACE demonstrated adequate discrimination in external cohorts.

338x190mm (300 x 300 DPI)



Predictors of unplanned hospital readmissionThe plot provides an overview of the random-effects meta-analyses that were performed for predictors who were similarly defined for the outcome unplanned hospital readmission at 30 days follow-up. See Supplemental table 2A and Supplemental figures 9-26 for more details.

338x190mm (300 x 300 DPI)

Supplemental materials

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Supplemental Text 1. Search string

Ovid MEDLINE(R) ALL 1946 to November 21, 2019
Search date: 25 August 2020

#	Searches	Results
1	exp "predictive value of tests"/ or roc curve/ or exp Decision Support Techniques/	321482
2	("signal to noise" or roc curve or reiver operating or predict*).ab,kf,ti.	1644590
3	(decision adj2 (aid? or model* or clinical* or support or system? or tool?)).ab,kf,ti.	56262
4	decision?.ab,kf,ti.	381353
5	logistic models/	139814
6	(logistic model* or regression).ab,kf,ti.	758909
7	5 or 6	814876
8	4 and 7	23040
9	or/1-3,8	1861041
10	patient readmission/	17534
11	((readmission or readmitted or re-admission or re-admitted) and (hospital* or prehospital*)).ab,kf,ti.	20747
12	((readmission or readmitted or re-admission or re-admitted) adj2 (patient? or client)).ab,kf,ti.	4515
13	(rehospitali?ation? or re-hospitali?ation? or rehospitali?ed or re-hospitali?ed).ab,kf,ti.	7834
14	or/10-13	35723
15	exp cardiovascular system/ or exp cardiovascular diseases/	3001695
16	(cardiac* or cardio* or myocard* or coronary or heart).ab,jw,kf,ti.	2161260
17	(diastolic or systolic or edema or dyspnea or renocardiac or Stenocardia* or angor or angina* or atherioscleros* or atheroscleros* or arteroscleros* or Arterioscleros* or Kounis syndrome or ST elevation or STEMI or valve* or aortic or stenosis or Leopard Syndrome or Noonan Syndrome with Multiple Lentigines or Multiple Lentigines Syndrome or Obstructive Subaortic Conus or Absent Right Atrioventricular Connection or arrhythmia* or sinus or sinoatrial or atria* or auricular or atrioventricular or ventricular or bradycardia or Bradyarrhythmia* or tachycardia* or fibrillation* or flutter* or Right Bundle Branch Block or Brugada or extrasystole* or (commotion adj1 cordis) or Auriculo-Ventricular Dissociation or Auriculo Ventricular Dissociation or Atrioventricular Dissociation or A-V Dissociation or AV Dissociation or syncope or (Andersen adj2 Tawil) or QT Syndrome or (jervell adj2 lange) or Prolonged QT Interval or (romano adj1 ward) or parasystole or Pre-Excitation or Preexcitation or (Lown adj2 Ganong) or Short PR-Normal QRS Complex Syndrome or Short PR Normal QRS Complex Syndrome or Wolff-Parkinson-White or WPW Syndrome or Idioventricular Rhythm or Torsade de Pointes).ab,hw,kf,ti.	1642025
18	or/15-17	4136701
19	(predict* adj3 risk?).ab,kf,ti.	57669
20	retrospective.ab,hw,kf,ti.	1006259
21	(admission or hospitali?ation or discharge).ab,hw,kf,ti.	529444
22	and/18-21	692
23	and/9,14,18	3482
24	(ISRCTN96643197 or ChiCTR1900026250 or NCT04008914 or NCT03791541 or NCT03300791 or "CTRI/2016/10/007411" or "CTRI/2014/06/004690" or NCT03949439 or NCT03905226 or NCT00344513 or NCT01755052 or NCT02041585).ab,kf,ti.	9
25	((OPERA or REIC or FIgARO or PREDIC or optimize-hf or ten-hms or tele-hf or readmits or silver-ami or dc promis or KorAHF) adj3 (trial or study)).ab,kf,ti.	118
26	or/22-25	4209

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Ovid Embase Classic+Embase <1947 to 2020 August 24>
Search date: 25 August 2020

#	Searches	Results
1	*predictive value/ or *receiver operating characteristic/ or exp *Decision Support system/	21786
2	("signal to noise" or roc curve or reiver operating or predict*).ab,kw,ti.	2224346
3	(decision adj2 (aid? or model* or clinical* or support or system? or tool?)).ab,kw,ti.	80866
4	decision?.ab,kw,ti.	531706
5	*logistic regression analysis/	1018
6	(logistic model* or regression).ab,kw,ti.	1107281
7	5 or 6	1107307
8	4 and 7	33059
9	or/1-3,8	2305864
10	*hospital readmission/	13570
11	((readmission or readmitted or re-admission or re-admitted) and (hospital* or prehospital*)).ab,kw,ti.	39681
12	((readmission or readmitted or re-admission or re-admitted) adj2 (patient? or client)).ab,kw,ti.	9596
13	(rehospitali?ation? or re-hospitali?ation? or rehospitali?ed or re-hospitali?ed).ab,kw,ti.	14392
14	or/10-13	56536
15	exp *cardiovascular system/	630584
16	(cardiac* or cardio* or myocard* or coronary or heart).ab,jw,kw,ti.	3123455
17	(diastolic or systolic or edema or dyspnea or renocardiac or Stenocardia* or angor or angina* or atherioscleros* or atheroscleros* or arteroscleros* or Arterioscleros* or Kounis syndrome or ST elevation or STEMI or valve* or aortic or stenosis or Leopard Syndrome or Noonan Syndrome with Multiple Lentigines or Multiple Lentigines Syndrome or Obstructive Subaortic Conus or Absent Right Atrioventricular Connection or arrhythmia* or sinus or sinoatrial or atria* or auricular or atrioventricular or ventricular or bradycardia or Bradyarrhythmia* or tachycardia* or fibrillation* or flutter* or Right Bundle Branch Block or Brugada or extrasystole* or (commotion adj1 cordis) or Auriculo-Ventricular Dissociation or Auriculo Ventricular Dissociation or Atrioventricular Dissociation or A-V Dissociation or AV Dissociation or syncope or (Andersen adj2 Tawil) or QT Syndrome or (jervell adj2 lange) or Prolonged QT Interval or (romano adj1 ward) or parasystole or Pre-Excitation or Preexcitation or (Lown adj2 Ganong) or Short PR-Normal QRS Complex Syndrome or Short PR Normal QRS Complex Syndrome or Wolff-Parkinson-White or WPW Syndrome or Idioventricular Rhythm or Torsade de Pointes).ab,hw,kw,ti.	2756334
18	or/15-17	4713190
19	(predict* adj3 risk?).ab,kw,ti.	90323
20	retrospective.ab,hw,kw,ti.	1280890
21	(admission or hospitali?ation or discharge).ab,hw,kw,ti.	1117031
22	and/18-21	991
23	and/9,14,18	6851
24	(ISRCTN96643197 or ChiCTR1900026250 or NCT04008914 or NCT03791541 or NCT03300791 or "CTRI/2016/10/007411" or "CTRI/2014/06/004690" or NCT03949439 or NCT03905226 or NCT00344513 or NCT01755052 or NCT02041585).ab,cn,kw,ti.	31
25	((OPERA or REIC or FIgARO or PREDIC or optimize-hf or ten-hms or tele-hf or readmits or silver-ami or dc promis or KorAHF) adj3 (trial or study)).ab,kw,ti.	285
26	or/22-25	8017

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Supplemental Text 2. Data items

The following data was collected in accordance with the CHARMS checklist (Critical Appraisal and Data Extraction for Systematic Reviews): citation, source of data, country, study design, setting, participant description, sample characteristics, study dates, outcome definition, follow-up, number and type of predictors, definition and method for measurement of predictors, timing of predictor measurement, handling of predictors in the modelling, number of participants and number of outcomes/events, calibration, discrimination, classification, methods used for testing model performance, final multivariable model results (regression coefficients, intercept, baseline survival, model performance), and model presentation.

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Supplemental Table 1. Risk of Bias

Study	Model	Risk of bias				Overall	Applicability			Overall
		Participants	Predictors	Outcome	Analysis	Risk of bias	Participants	Predictors	Outcome	applicability
Barnett et al.	Model validation	-	?	+	-	-	+	+	+	+
	Model update	-	?	+	-	-	+	+	+	+
Sanchez et al.	NR	-	?	?	-	-	+	+	+	+
Deo et al.	30-days CABG Readmission Calculator	-	-	-	-	-	+	+	?	?
Tan et al.	NR	-	-	-	-	-	+	+	-	-
Wang et al.	NR	-	?	?	-	-	+	+	+	+
Rosenblum et al.	The STS PROM score	-	?	-	-	-	+	+	+	+
Dodson et al.	SILVER-AMI 30-day readmission calculator	+	+	+	+	+	+	+	+	+
Lim et al.	NR	+	?	-	-	-	+	+	-	-
Kini et al.	NR	-	-	-	?	-	+	+	+	+
Nguyen et al.	AMI READMITS score	-	-	+	-	-	+	+	+	+
	Full-stay AMI model	-	-	+	-	-	+	+	+	+
	CMS AMI administrative model	-	?	+	-	-	+	+	+	+
Cediel et al.	TARRACO Risk Score	-	-	-	-	-	+	+	-	-
Brown et al.	STS 30-day Readmission Model	+	?	?	-	-	+	+	?	?
	STS Augmented Clinical Model	-	?	+	-	-	+	+	?	?
Khera et al.	TAVR 30-Day Readmission Risk Model	-	-	?	-	-	+	+	?	?
Tam et al.	NR	-	-	?	-	-	+	+	?	?
Atzema et al.	AFTER Part 2 scoring system	-	-	-	-	-	+	+	-	-
Stuebe et al.	NR	-	+	-	-	-	+	+	+	+
Huynh et al.	NR	-	-	?	-	-	+	+	+	+
Zywot et al.	CABG Risk Scale	-	?	?	-	-	+	+	+	+

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Supplemental Table 1. Risk of bias (continued)

Study	Model	Risk of bias				Overall Risk of bias	Applicability			Overall applicability
		Participants	Predictors	Outcome	Analysis		Participants	Predictors	Outcome	
Cox et al.	CMS HF medical model	-	+	+	-	-	+	+	+	+
	CMS HF administrative model	-	?	+	-	-	+	+	+	+
Zitser-Gurevich et al.	NR	?	+	+	-	-	+	+	+	+
Ahmad et al.	CMS HF administrative model	-	+	+	-	-	+	+	+	+
Minges et al.	NR	-	+	+	-	-	+	+	+	+
Pack et al.	NR	-	-	-	-	-	+	+	+	+
Benuzillo et al.	CRSS	-	-	+	-	-	+	+	+	+
Kitamura et al.	FIM	-	?	-	-	-	+	+	+	+
Lahewala et al.	CHADS2	-	?	+	-	-	+	+	+	+
	CHA2DS-VASc	-	?	+	-	-	+	+	+	+
Formiga et al.	CMS HF medical model	-	?	-	-	-	+	+	+	+
Leong et al.	30-day HF readmission risk score	-	+	-	-	-	+	+	-	-
Burke et al.	HOSPITAL score	-	-	-	-	-	+	+	+	+
Kilic et al.	NR	-	?	-	-	-	+	+	+	+
Moulder et al.	NR	+	+	-	-	-	+	+	+	+
Chotechuang et al.	GRACE	-	-	-	-	-	+	+	-	-
Yazdan-Ashoori et al.	LACE	?	?	+	-	-	+	+	+	+
	CMS HF administrative model	?	?	+	-	-	+	+	+	+
Oliver-McNeil et al.	ICD Readmission-Risk Score	-	?	-	-	-	+	+	+	+
Sudhakar et al.	CMS HF medical model	-	+	-	-	-	+	+	+	+
Raposeiras-Roubín et al.	GRACE	-	-	-	-	-	+	+	-	-
Betihavas et al.	NR	-	?	-	-	-	+	+	-	-
Lancey et al.	NR	-	?	-	-	-	+	+	+	+
Moretti et al.	EuroHeart PCI score	-	+	-	-	-	+	+	-	-
Hilbert et al.	HF decision tree	-	+	+	-	-	+	+	+	+
	AMI decision tree	-	+	+	-	-	+	+	+	+

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Supplemental Table 1. Risk of bias (continued)

Study	Model	Risk of bias				Overall Risk of bias	Applicability			Overall applicability
		Participants	Predictors	Outcome	Analysis		Participants	Predictors	Outcome	
Wang et al.	LACE	-	?	-	-	-	+	+	+	+
Rana et al.	HOSPITAL score	-	?	-	-	-	+	+	-	-
	Elixhauser index	-	?	-	-	-	+	+	-	-
Hummel et al.	CMS HF medical model	?	+	+	-	-	+	+	+	+
Salah et al.	ELAN-HF score	-	?	-	-	-	+	+	-	-
Wasfy et al.	Pre-PCI model	-	+	?	-	-	+	+	+	+
Engoren et al.	NR	-	?	+	-	-	+	+	+	+
Au et al.	Administrative Claims Model: HF 30-day mortality	-	?	?	-	-	+	+	?	?
	Charlson Comorbidity Score	-	?	?	-	-	+	+	?	?
	CMS HF administrative model	-	?	?	-	-	+	+	?	?
	LACE	-	?	?	-	-	+	+	?	?
Krumholz et al.	CMS AMI medical model	+	-	+	-	-	+	+	+	+
	CMS AMI administrative model	-	-	+	-	-	+	+	+	+
Amarasingham et al.	Tabak mortality score	-	?	?	-	-	+	+	+	+
	CMS HF administrative model	-	?	?	-	-	+	+	+	+
	ADHERE	-	?	?	-	-	+	+	+	+
Keenan et al.	CMS HF administrative model	-	-	+	-	-	+	+	+	+
	CMS HF medical model	+	-	-	-	-	+	+	+	+
Ferraris et al.	READMIT	?	+	+	-	-	+	+	+	+
Delgado et al.	15-day CV readmission risk score	?	+	-	-	-	+	+	-	-
	30-day CV readmission risk score	?	+	-	-	-	+	+	-	-
Espinoza et al.	30-day readmission score after cardiac surgery	+	?	?	-	-	+	+	+	+

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Supplemental Table 1. Risk of bias (continued)

Study	Model	Risk of bias				Overall Risk of bias	Applicability			Overall applicability
		Participants	Predictors	Outcome	Analysis		Participants	Predictors	Outcome	
Reed et al.	CMS HF administrative model	-	?	?	-	-	+	+	+	+
	PARR-30	-	?	?	-	-	+	+	+	+
	LACE	-	?	?	-	-	+	+	+	+
	Hasan	-	?	?	-	-	+	+	+	+
	AH model	-	?	?	-	-	+	+	+	+
Ibrahim et al.	HOSPITAL score	-	+	-	-	-	+	+	+	+
	LACE	-	+	-	-	-	+	+	+	+
	LACE+ index	-	+	-	-	-	+	+	+	+
Bardhan et al.	NR	-	-	-	-	-	+	+	-	-
Asche et al.	NR	-	?	-	-	-	+	+	?	?
Li et al.	NR	-	?	+	-	-	+	+	+	+
Hammill et al.	CMS HF administrative model	-	-	+	?	-	+	+	+	+
Frizzell et al.	CMS HF administrative model	-	-	+	-	-	+	+	+	+

Legend: the overall risk of bias assessment is located in the main paper.

Abbreviations: AH: Adventist hositals, CABG: coronary artery bypass grafting, CMS=centers for Medicare and Medicaid services, CRSS: CABG Readmission Risk Score, Fim: motor and cognitive Functional Independence Measure, HF: heart failure, ICD: implantable cardioverter defibrillator, NR: not reported, PARR-30: Patients at Risk of Re-admission within 30-days, PCI: percutaneous coronary intervention, TAVR: transcatheter aortic valve replacement

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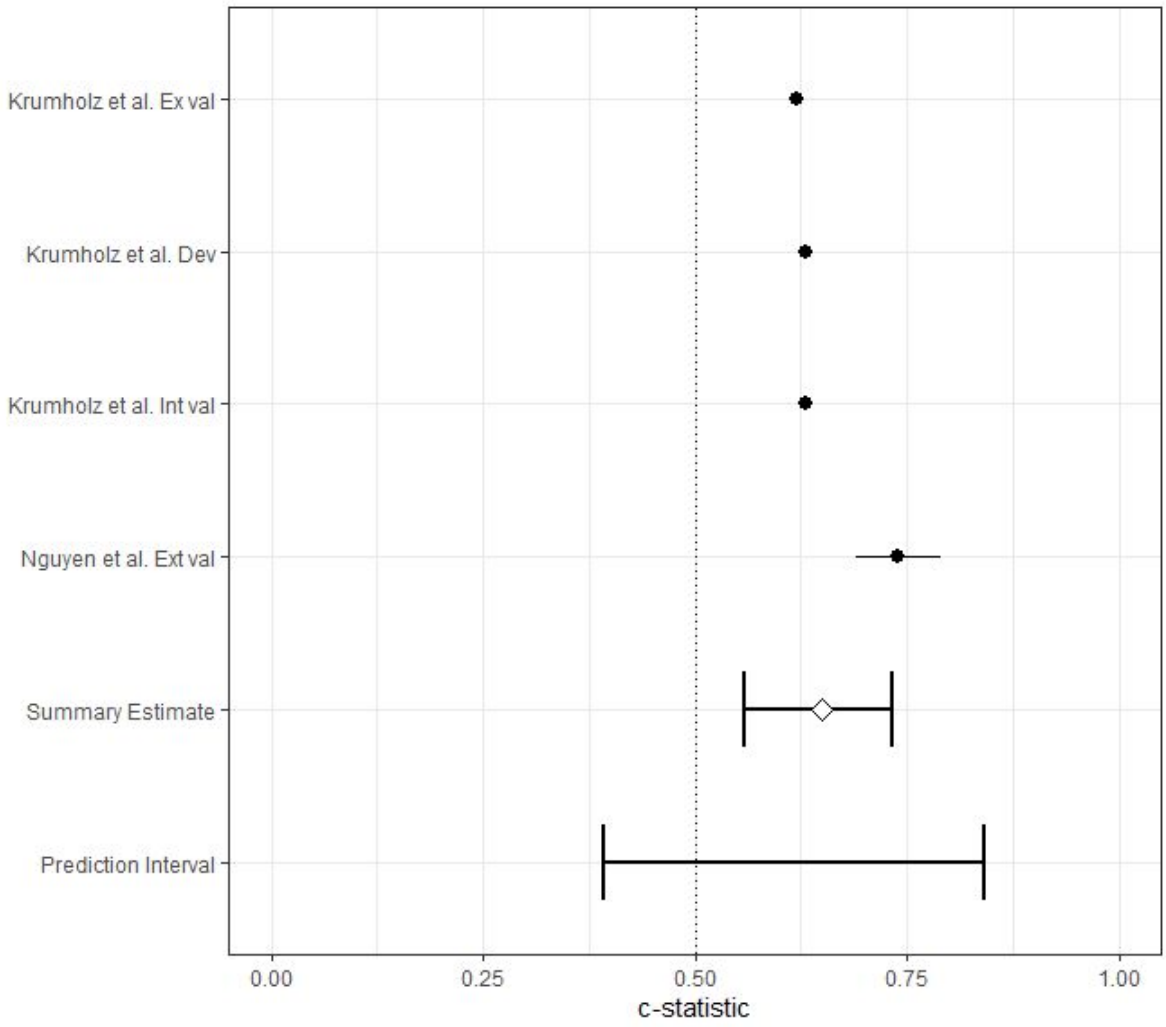
Supplemental Figure 1. Meta-analysis of CMS AMI administrative model



Legend: The CMS acute myocardial infarction (AMI) administrative model was evaluated in four independent cohorts in two studies: 0.65, 95% CI 0.56 to 0.73, 95% prediction interval 0.39 to 0.84. Standard errors were derived from the reported c-statistics, sample size and observed events. The readmission rate was missing for the internal validation cohort in the Krumholz et al. study, and this data was needed to derive the observed events. The development and validation cohort in the Krumholz et al. study were similar samples and we used the average readmission rate from these two cohorts to impute the missing readmission rate for the internal validation.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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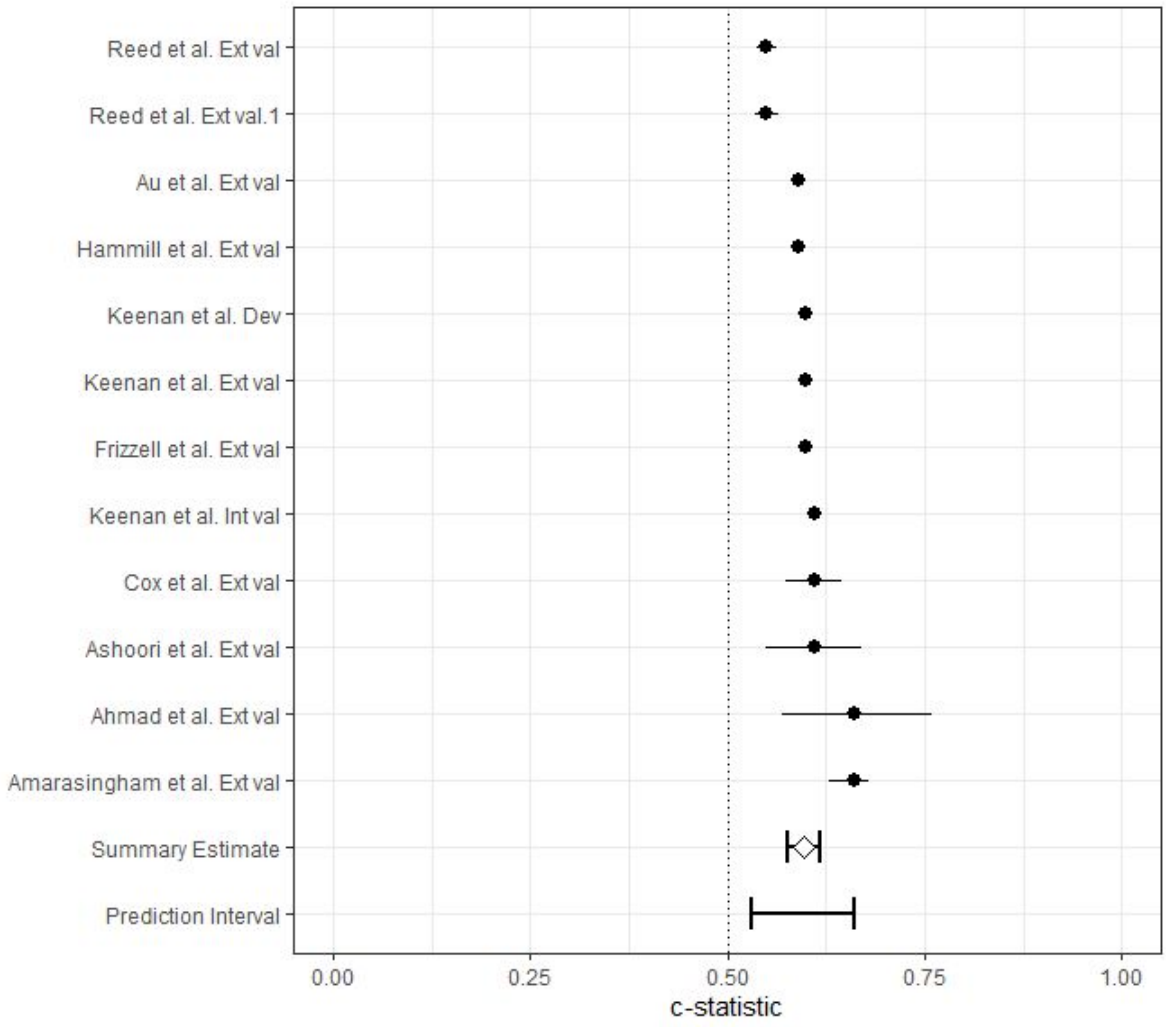
Supplemental Figure 2. Meta-analysis of CMS HF administrative model



Legend: The CMS heart failure (HF) administrative model was evaluated in twelve independent cohorts in nine studies: 0.60, 95% CI 0.58 to 0.62, 95% prediction interval 0.53 to 0.66. Standard errors were derived from the reported c-statistics, sample size and observed events. The readmission rate was missing for the internal validation cohort in the Keenan et al. study, and this data was needed to derive the observed events. The development and validation cohort in the Keenan et al. study were similar samples and we used the average readmission rate from these two cohorts to impute the missing readmission rate for the internal validation.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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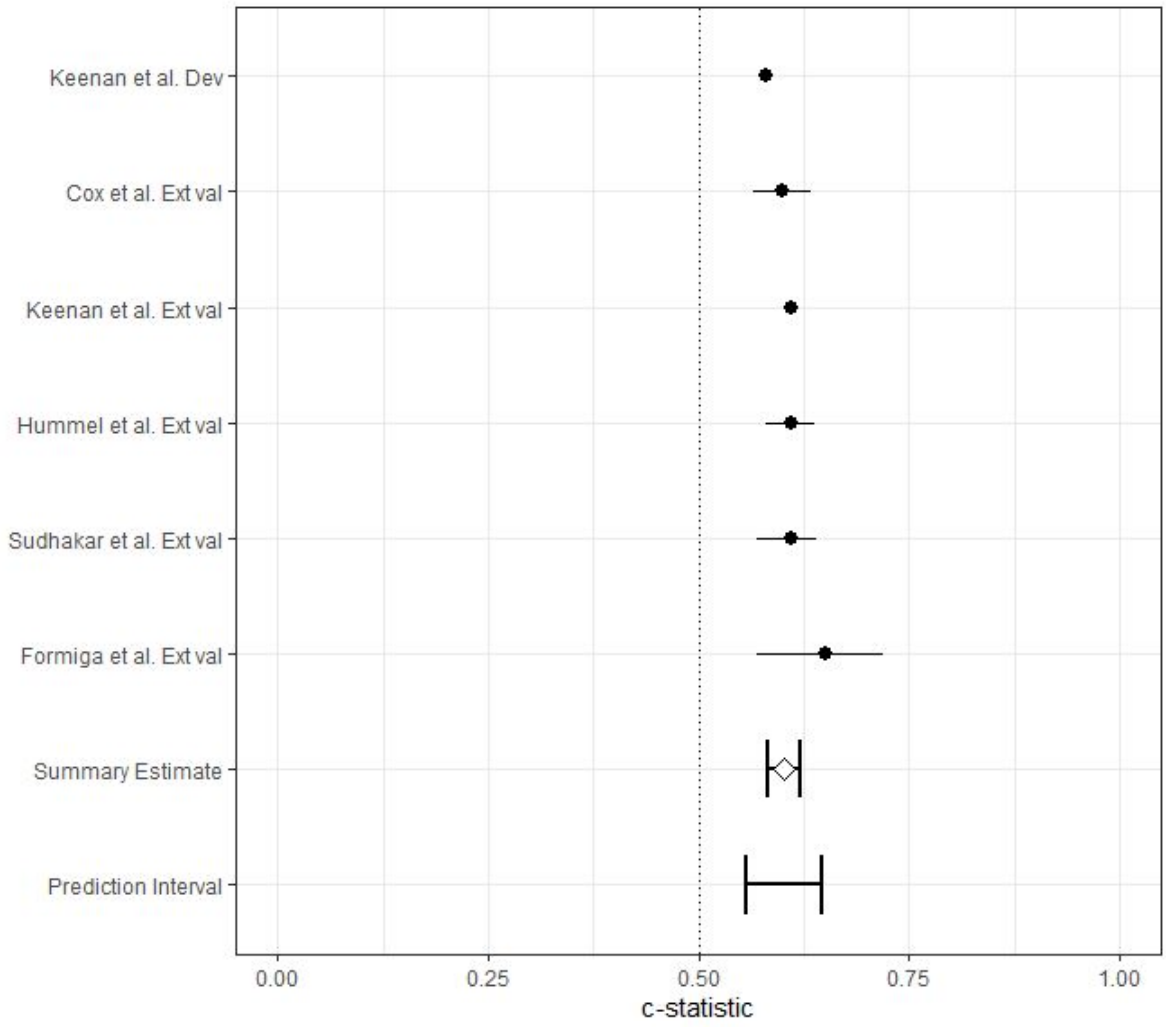
Supplemental Figure 3. Meta-analysis of CMS medical model



Legend: The CMS medical model was evaluated in six independent cohorts in five studies: 0.60, 95% CI 0.58 to 0.62, 95% prediction interval 0.56 to 0.65. Standard errors were derived from the reported c-statistics, sample size and observed events.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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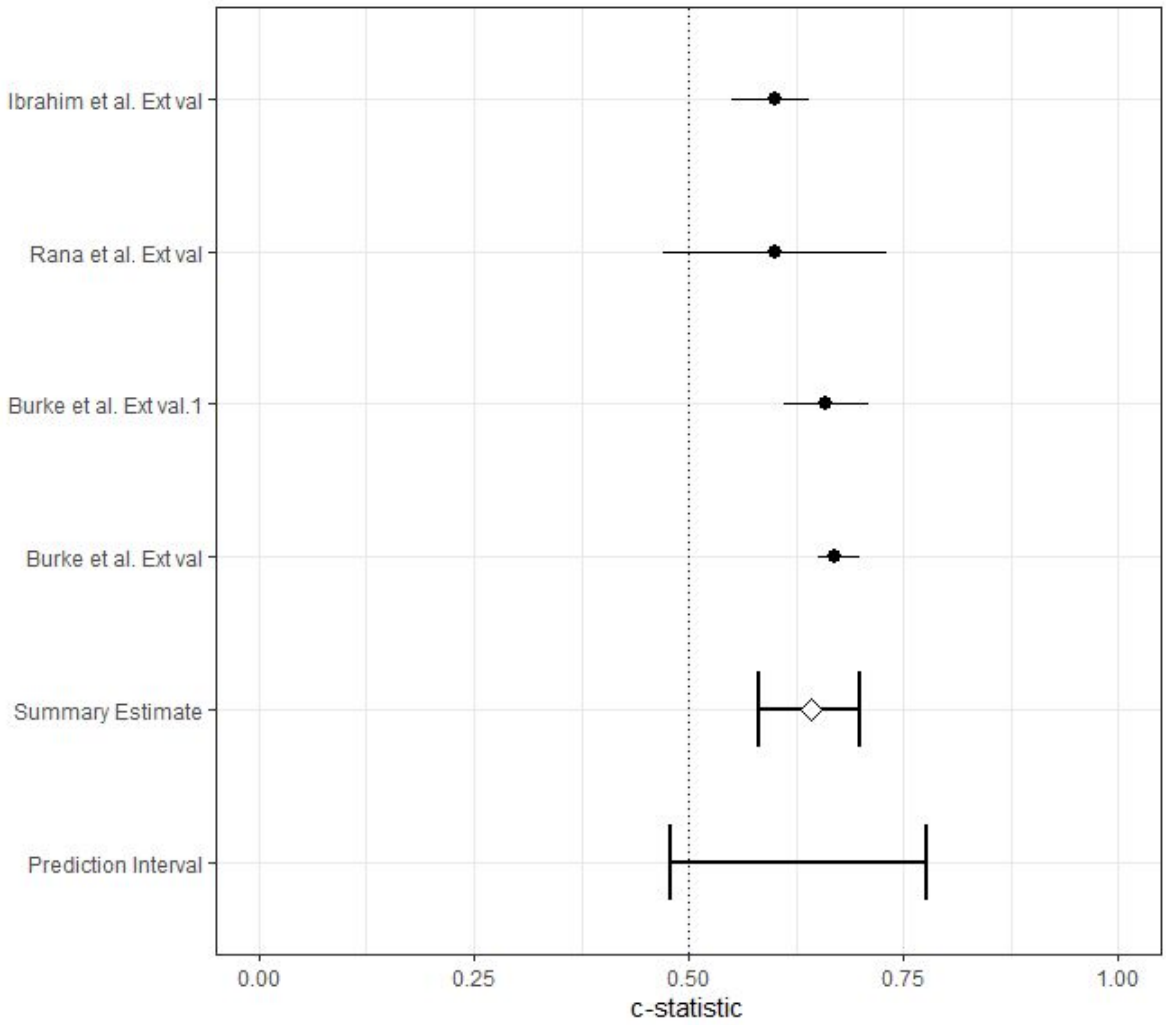
Supplemental Figure 4. Meta-analysis of HOSPITAL score



Legend: The HOSPITAL score was evaluated in four independent cohorts in three studies: 0.64, 95% CI 0.58 to 0.70, 95% prediction interval 0.48 to 0.78. Standard errors were derived from the reported c-statistics, sample size and observed events.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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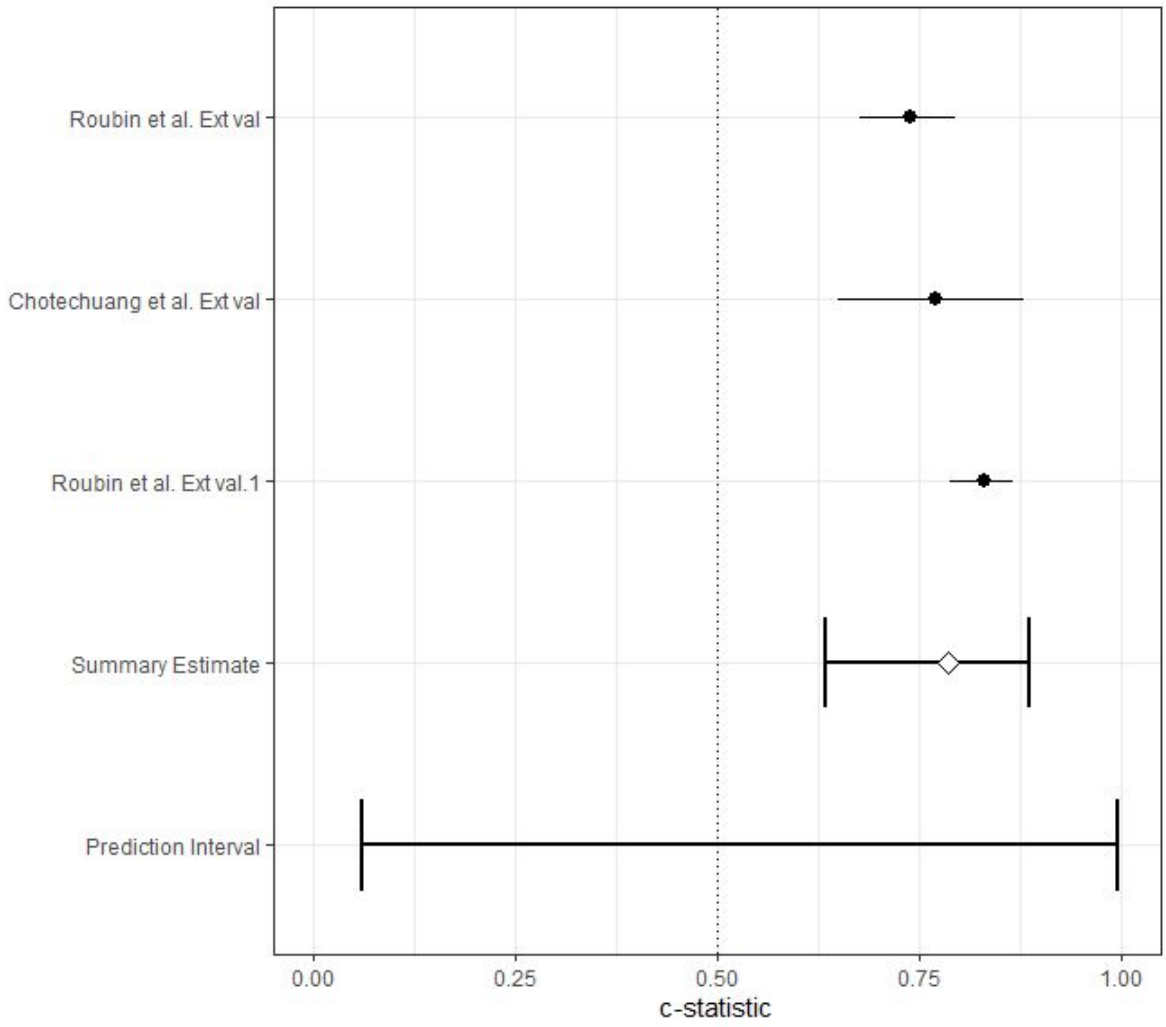
Supplemental Figure 5. Meta-analysis of GRACE



Legend: GRACE was evaluated in four independent cohorts in three studies: 0.79, 95% CI 0.63 to 0.86, 95% prediction interval 0.06 to 1.00. Standard errors were derived from the reported c-statistics, sample size and observed events.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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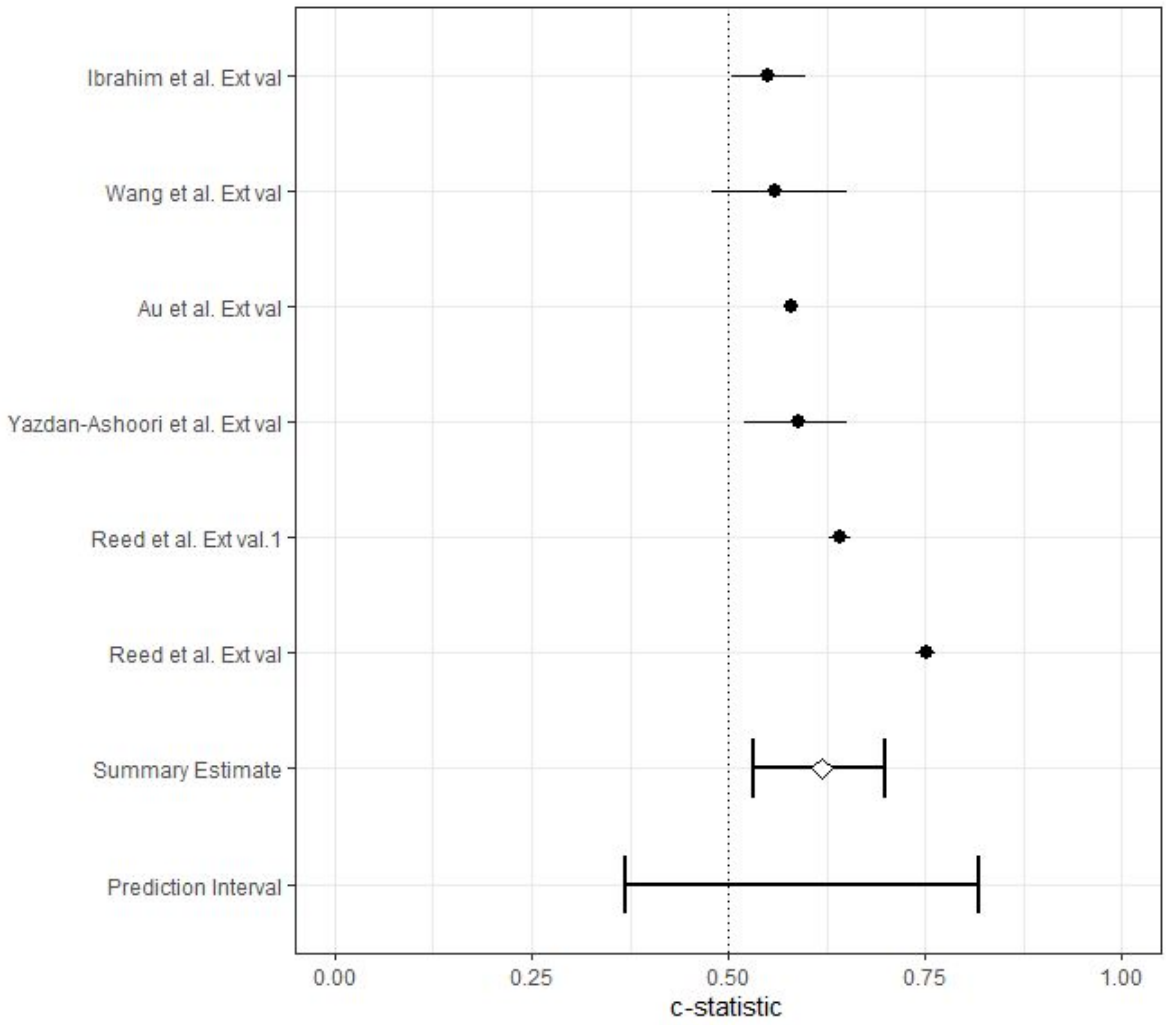
Supplemental Figure 6. Meta-analysis of LACE



Legend: LACE was evaluated in six independent cohorts in five studies: 0.62, 95% CI 0.53 to 0.70, 95% prediction interval 0.37 to 0.82. Standard errors were derived from the reported c-statistics, sample size and observed events.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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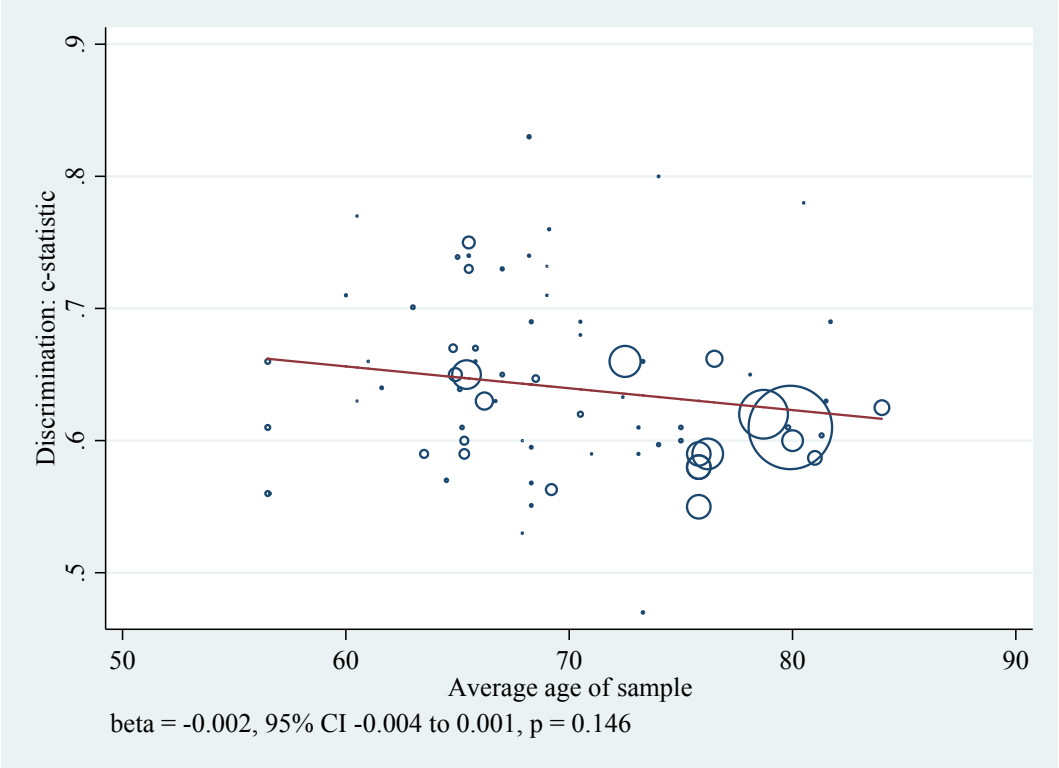
Supplemental Figure 7. Age as moderator



Legend: A meta-regression with average sample age as covariate was performed. The outcome was the discrimination (c-statistic). There is no association between the sample age and the discrimination.

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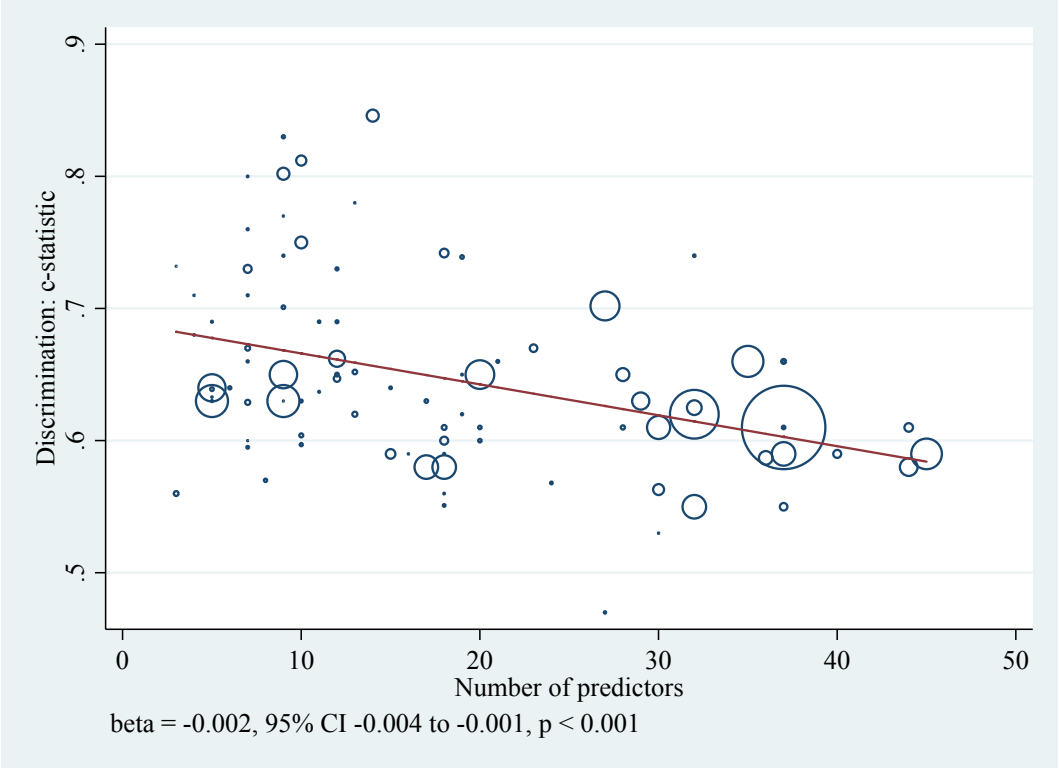
Supplemental Figure 8. Number of predictors as moderator



Legend: A meta-regression with the number of predictors as covariate was performed. The outcome was the discrimination (c-statistic). The discrimination increases with the number of predictors decreases. This association is significant.

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Supplemental Table 2. Subgroup analyses

Moderators	N	C-statistic	95% CI	Test for subgroup difference
Population				p = 0.835
- Surgical	17	0.627	0.605 – 0.649	
- TAVR	2	0.645	0.560 – 0.729	
- Heart failure	45	0.641	0.623 – 0.658	
- Acute myocardial infarction	16	0.671	0.644 – 0.697	
- Arrhythmias	5	0.640	0.630 – 0.649	
- Valve disease	1	0.650	0.641 – 0.659	
- ICD implantation	1	0.710	0.605 – 0.815	
- Reinfarction	1	0.740	0.681 – 0.799	
- Acute coronary syndrome	1	0.590	0.475 – 0.705	
- Mixed	3	0.660	0.656 – 0.664	
Data source				p = 0.014
- Registry	17	0.613	0.602 – 0.624	
- Administrative database	17	0.664	0.635 – 0.693	
- Hospital database	18	0.612	0.593 – 0.632	
- Prospective cohort	16	0.640	0.613 – 0.667	
- Retrospective cohort	23	0.682	0.653 – 0.710	
- Secondary analysis	2	0.695	0.497 – 0.894	
Endpoint				p = 0.589
- 15 days	1	0.633	0.539 – 0.727	
- 28 days	1	0.800	0.720 – 0.880	
- 30 days	78	0.642	0.631 – 0.654	
- 90 days	8	0.645	0.632 – 0.657	
- 100 days	1	0.652	0.626 – 0.678	
- 180 days	4	0.656	0.591 – 0.721	
Outcome definition				p = 0.144
- All cause	65	0.644	0.633 – 0.656	
- Cardiac related	18	0.676	0.628 – 0.723	

Legend: Subgroup analyses were performed. The outcome was the discrimination (c-statistic). The discrimination is moderator by the data source that was used in the study, but not by the population, outcome definition and endpoint.

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Supplemental Table 3. Summary of meta-analyses predictors

Predictor	Coefficient, 95% CI	Prediction interval
Age (years)	0.01, 0.00 - 0.01	-0.01 - 0.03
Female	0.10, 0.03 - 0.17	-0.17 - 0.38
Arrhythmias	0.20, 0.12 - 0.28	-0.04 - 0.43
Chronic lung disease	0.23, 0.05 - 0.40	-0.35 - 0.80
Chronic obstructive pumonary disease	0.18, 0.15 - 0.22	0.08 - 0.29
Artherosclerose	0.01, -0.13 - 0.15	-0.38 - 0.41
Diabetes mellitus	0.16, 0.11 - 0.22	-0.04 - 0.37
Current heart failure	0.27, 0.20 - 0.34	0.04 - 0.50
Hypertension	0.05, -0.02 - 0.12	-0.16 - 0.25
Valve disease	0.10, 0.06 - 0.13	0.01 - 0.19
Prior percutaneous coronary intervention	0.01, -0.07 - 0.09	-0.27 - 0.29
History of heart failure	0.38, 0.25 - 0.51	0.01 - 0.75
Cerebrovascular disease	0.08, 0.03 - 0.13	-0.05 - 0.22
Anemia	0.10, 0.06 - 0.14	-0.01 - 0.22
Stroke	0.07, 0.01 - 0.13	-0.11 - 0.25
Peripheral vascular disease	0.15, 0.09 - 0.21	-0.03 - 0.34
Dementia	-0.04, -0.10 - 0.02	-0.21 - 0.12
Prior Coronary Artery Bypass Graft	0.04, -0.06 - 0.14	-0.30 - 0.39

Legend: A meta-analyses was performed with the outcome 30 day unplanned hospital readmissions. The forest plots are detailed below. Please note that there are some small differences with the data reported in Figure 4 in the main manuscript. This is because of a difference in rounding the decimal points by the software.

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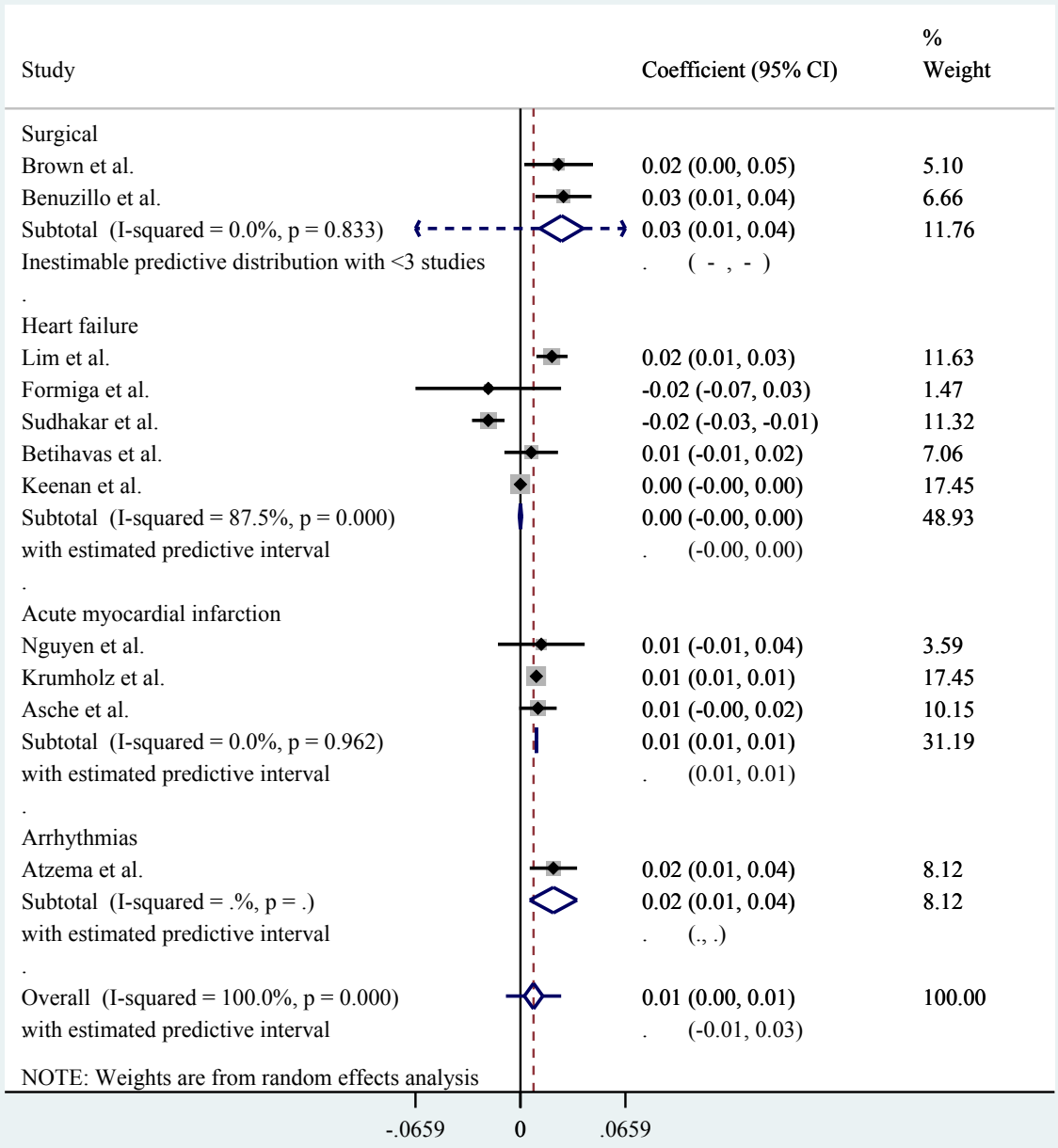
Supplemental Figure 9. Age as predictor



Legend: Two studies were not included in the analysis. One study had a missing standard error and one study reported transformed values. The values of their coefficients were: -0.001, and log(0,502).

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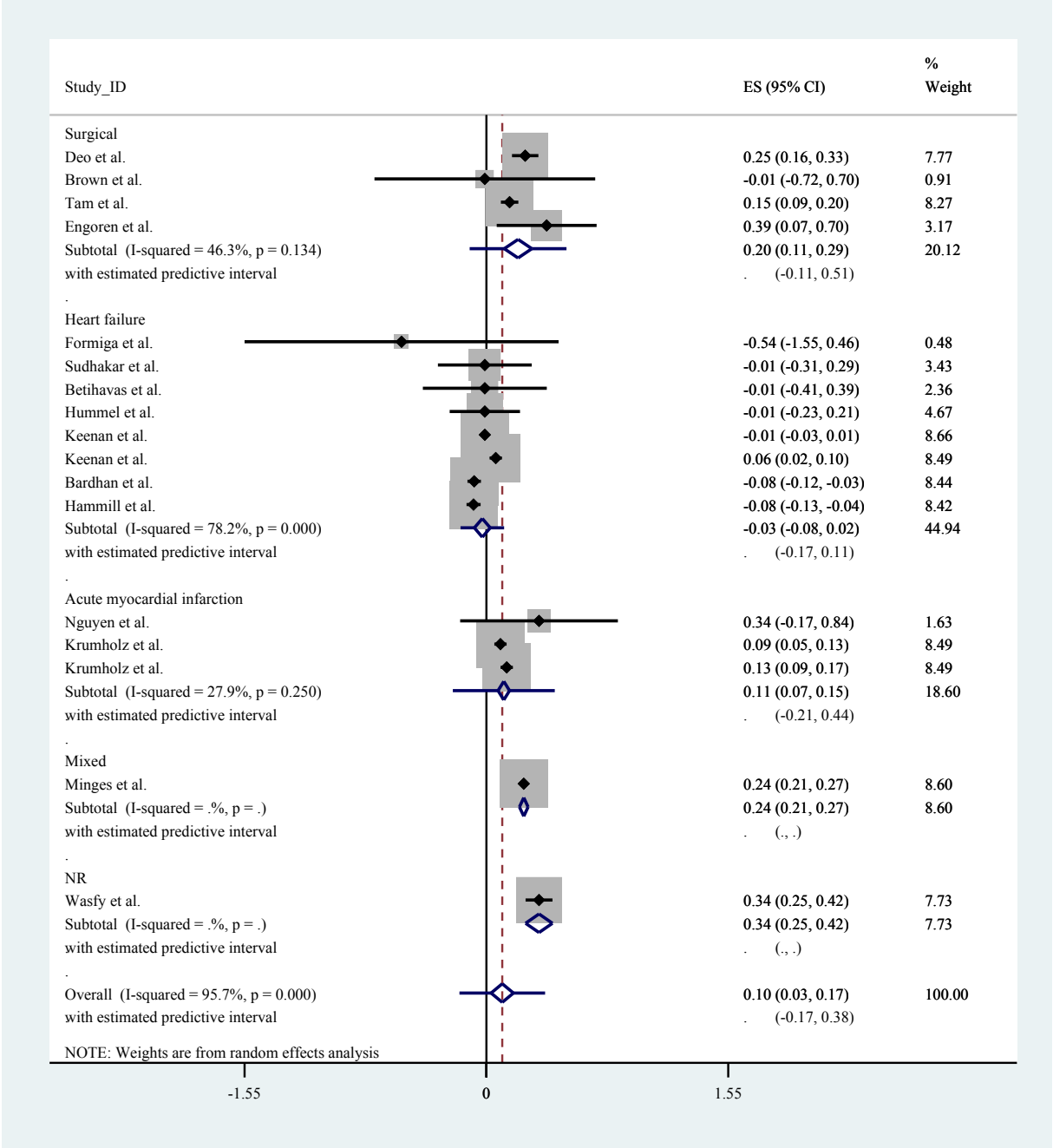
Supplemental Figure 10. Female as predictor



Legend: Two studies were not included in the analysis because the standard errors were missing. The values of their coefficients were: -0.28 and 0.206.

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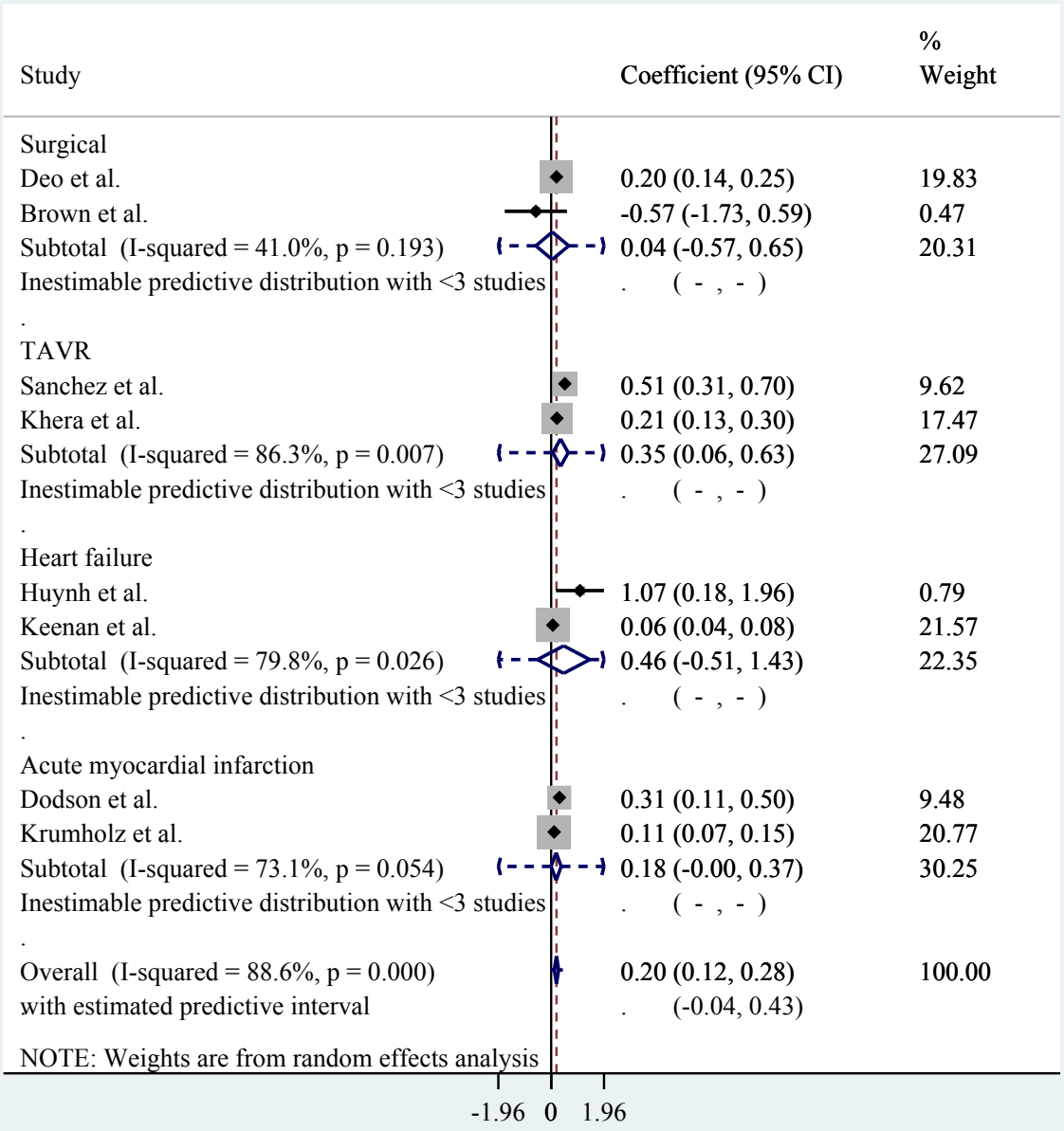
Supplemental Figure 1. Arrhythmias as predictor



Legend: There was no missing data in the analysis.

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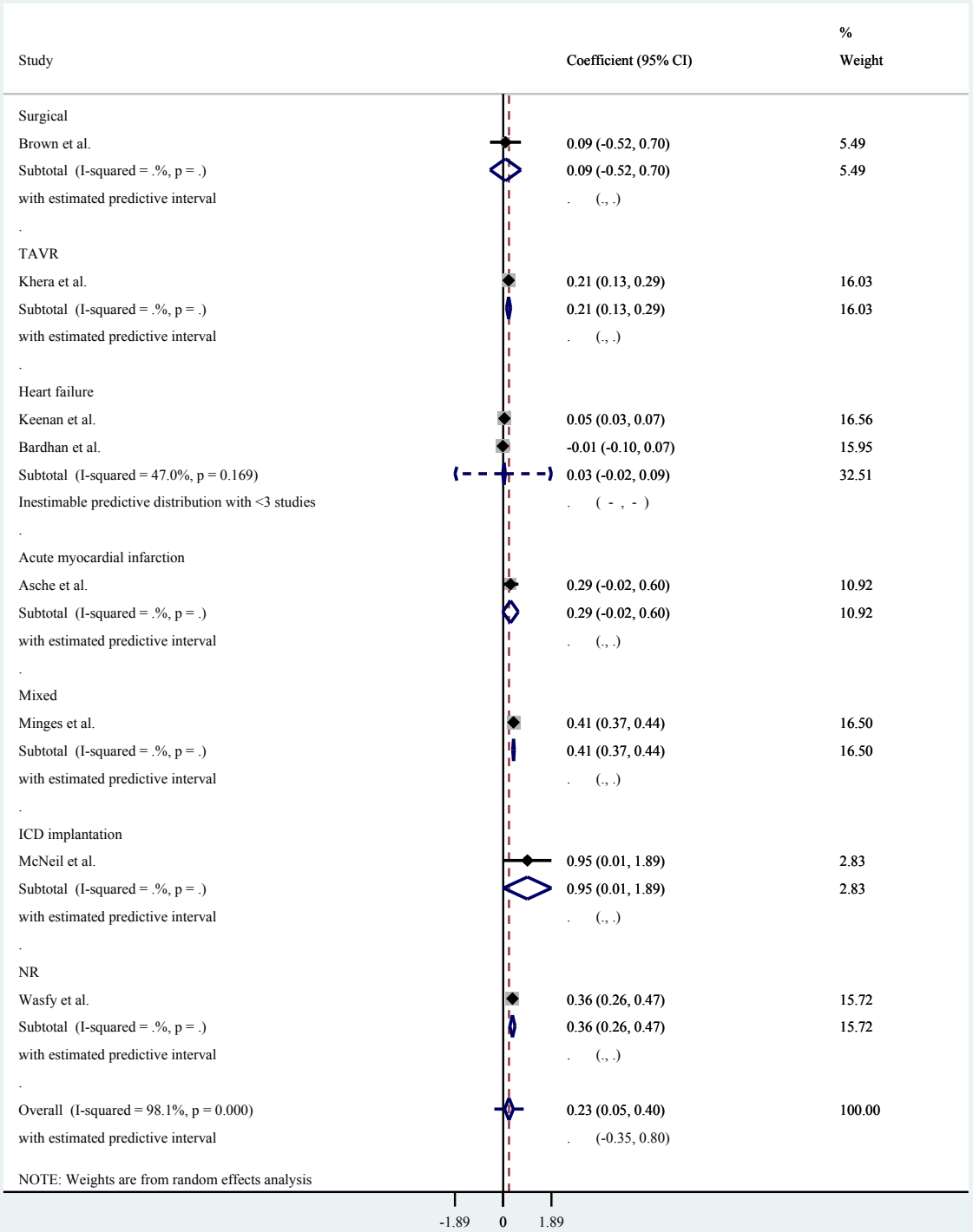
Supplemental Figure 12. Chronic lung disease as predictor



Legend: There was no missing data in the analysis.

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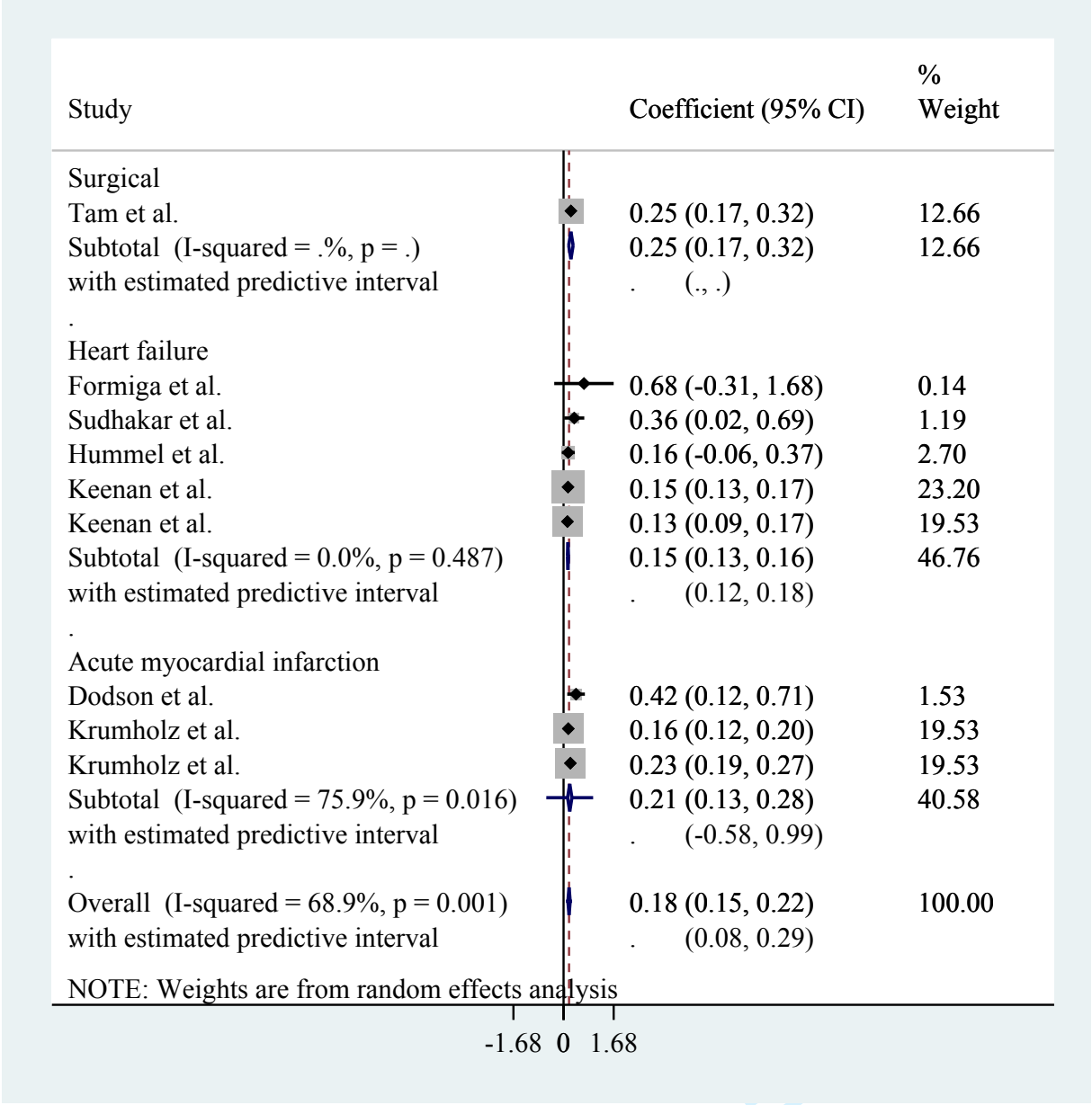
Supplemental Figure 13. Chronic Obstructive Pulmonary Disease as predictor



Legend: Two studies were not included in the analysis because the standard errors were missing. The values of their coefficients were: 0.053 and 0.677.

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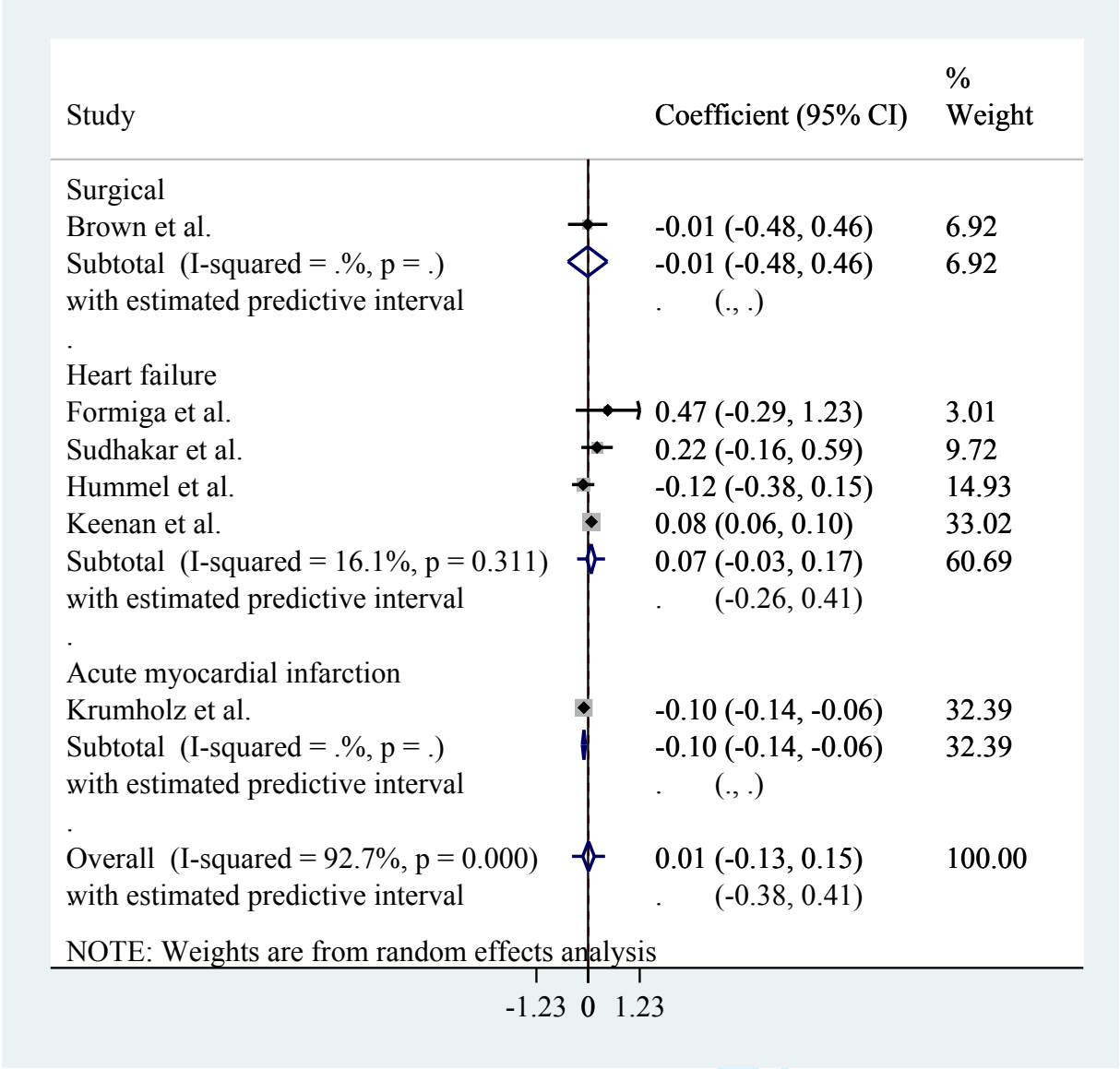
Supplemental Figure 14. Artherosclerose as predictor



Legend: One study was not included in the analysis because the standard error were missing. The values of their coefficient was: 0.11.

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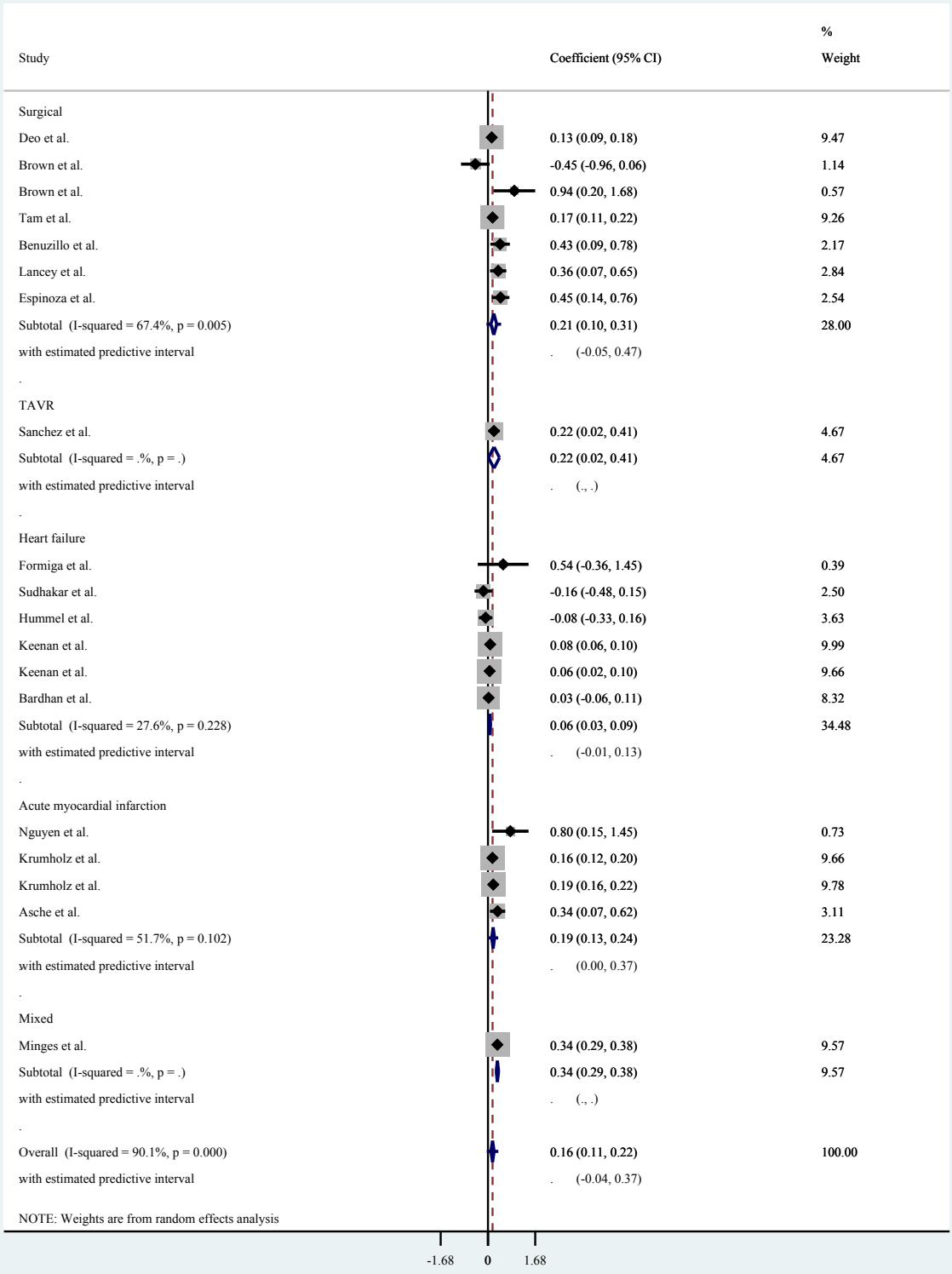
Supplemental Figure 15. Diabetes Mellitus as predictor



Legend: Two studies were not included in the analysis because the standard errors were missing. The values of their coefficients were: -0.068 and 0.639.

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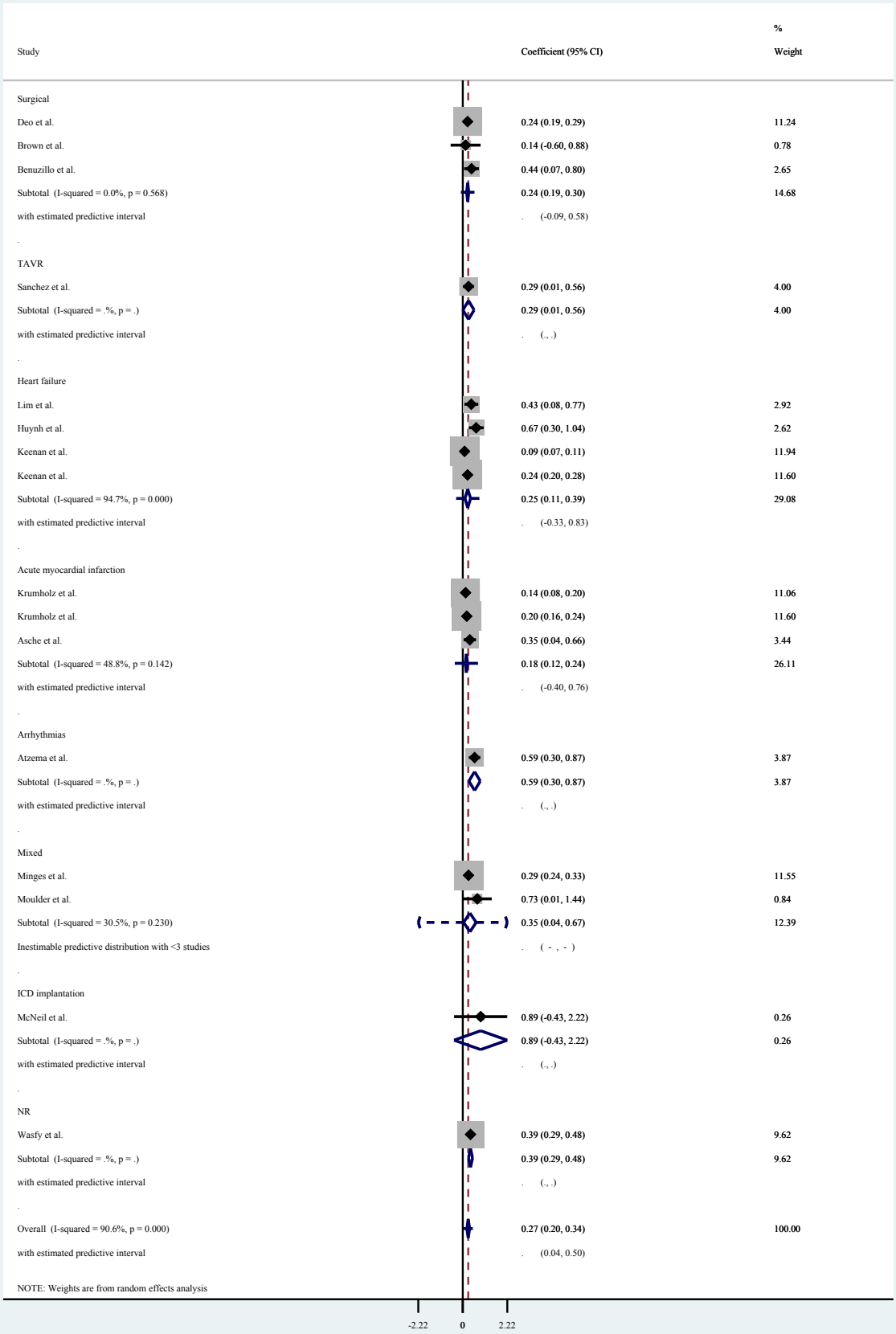
Supplemental Figure 16. Current heart failure as predictor



Legend: There was no missing data.

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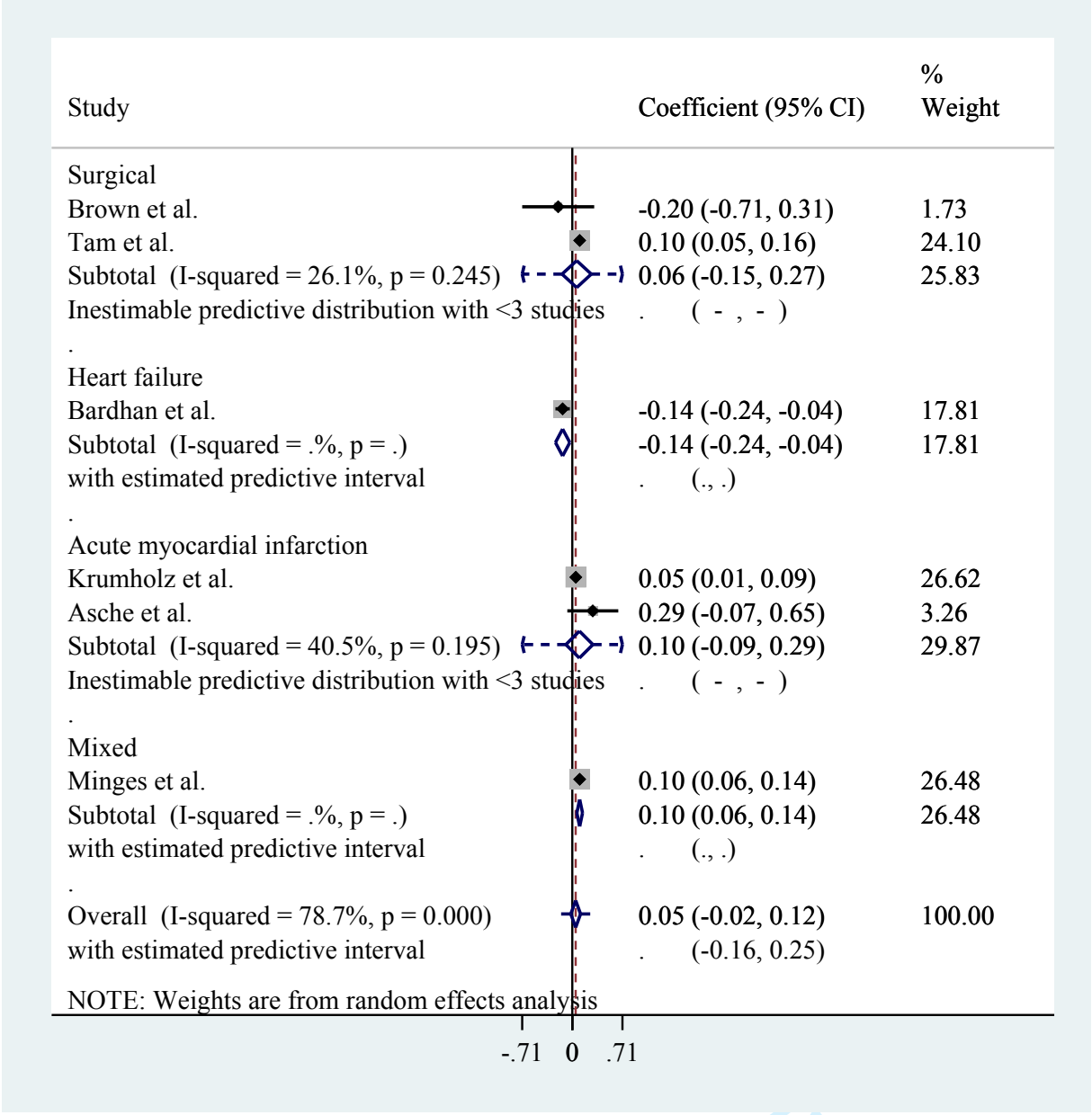
Supplemental Figure 17. Hypertension as predictor



Legend: One study was not included in the analysis because the standard error were missing. The values of their coefficient was: -0.28.

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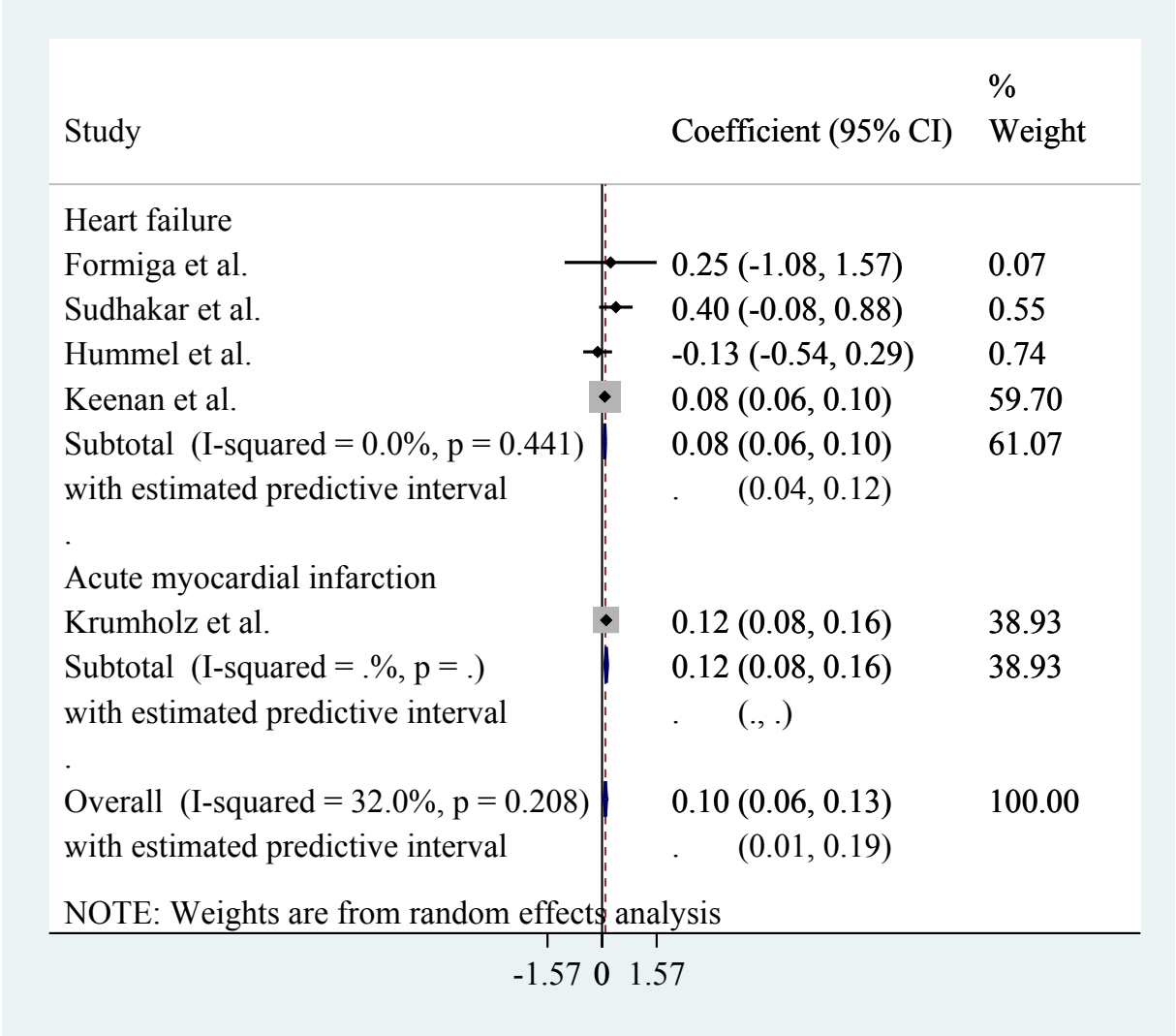
Supplemental Figure 18. Valve disease as predictor



Legend: There was nog missing data.

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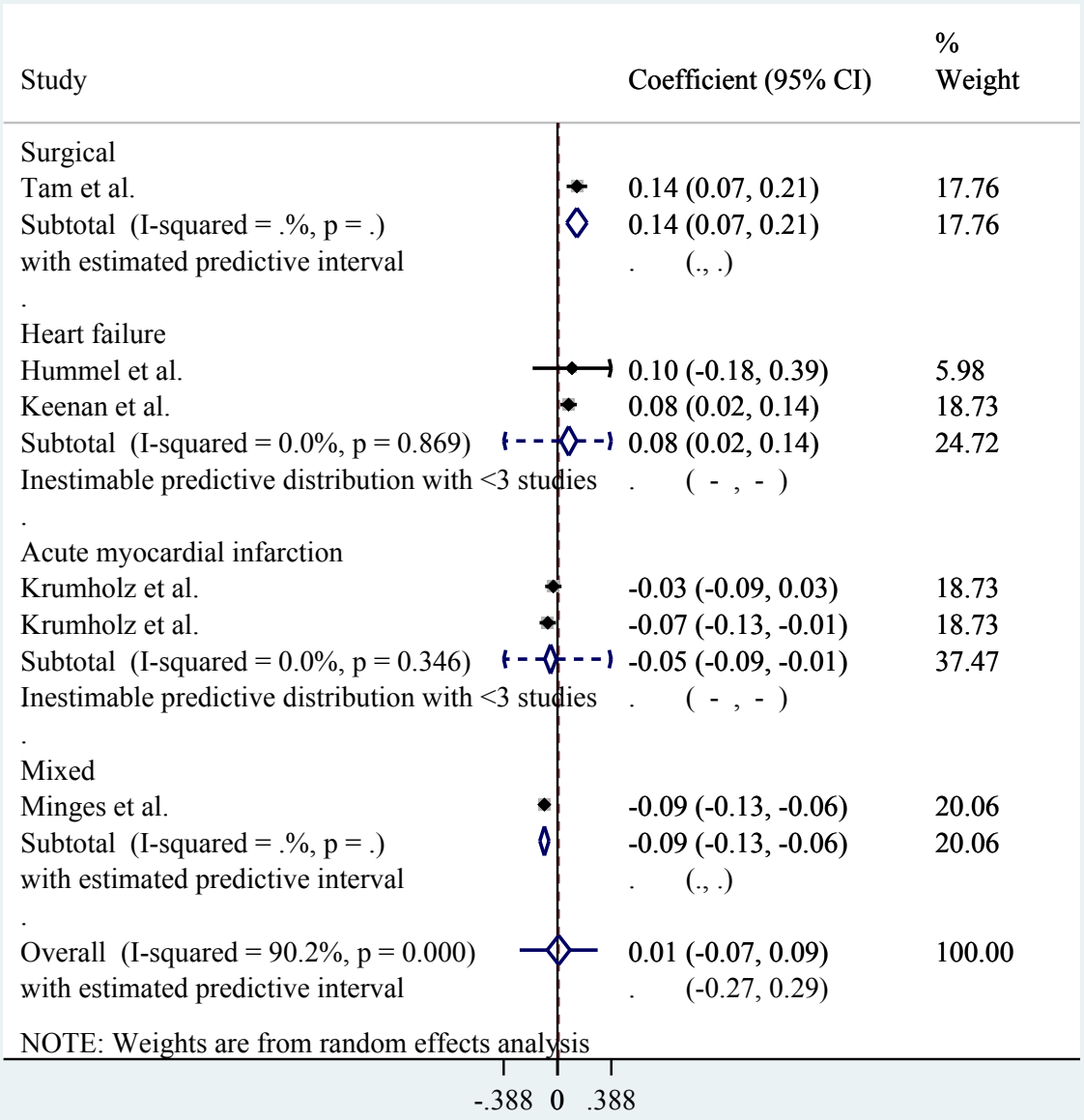
Supplemental Figure 19. Prior percutaneous coronary intervention as predictor



Legend: There was no missing data.

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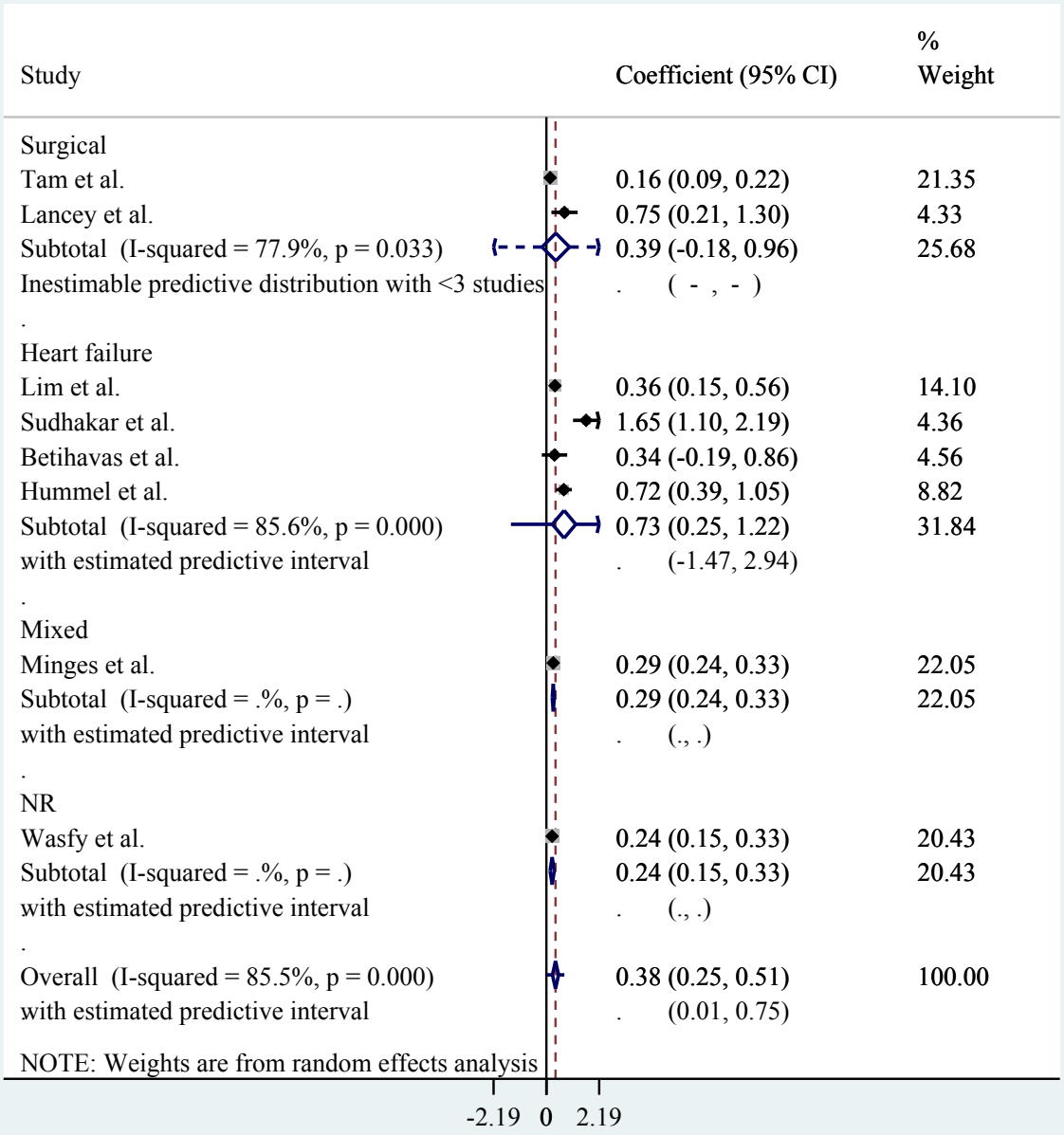
Supplemental Figure 20. History of heart failure as predictor



Legend: There was no missing data.

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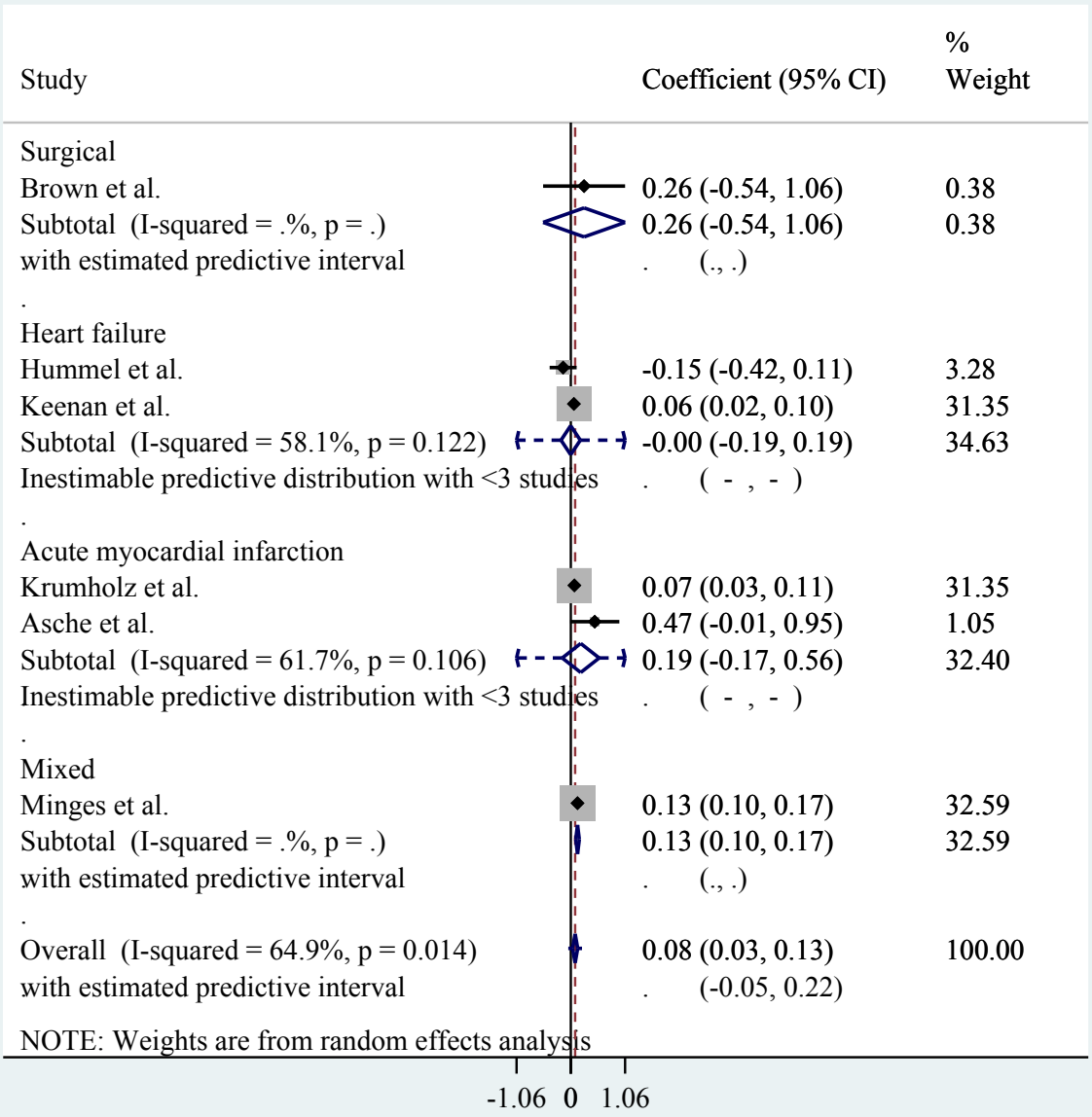
Supplemental Figure 21. Cerebrovascular disease as predictor



Legend: there was no missing data.

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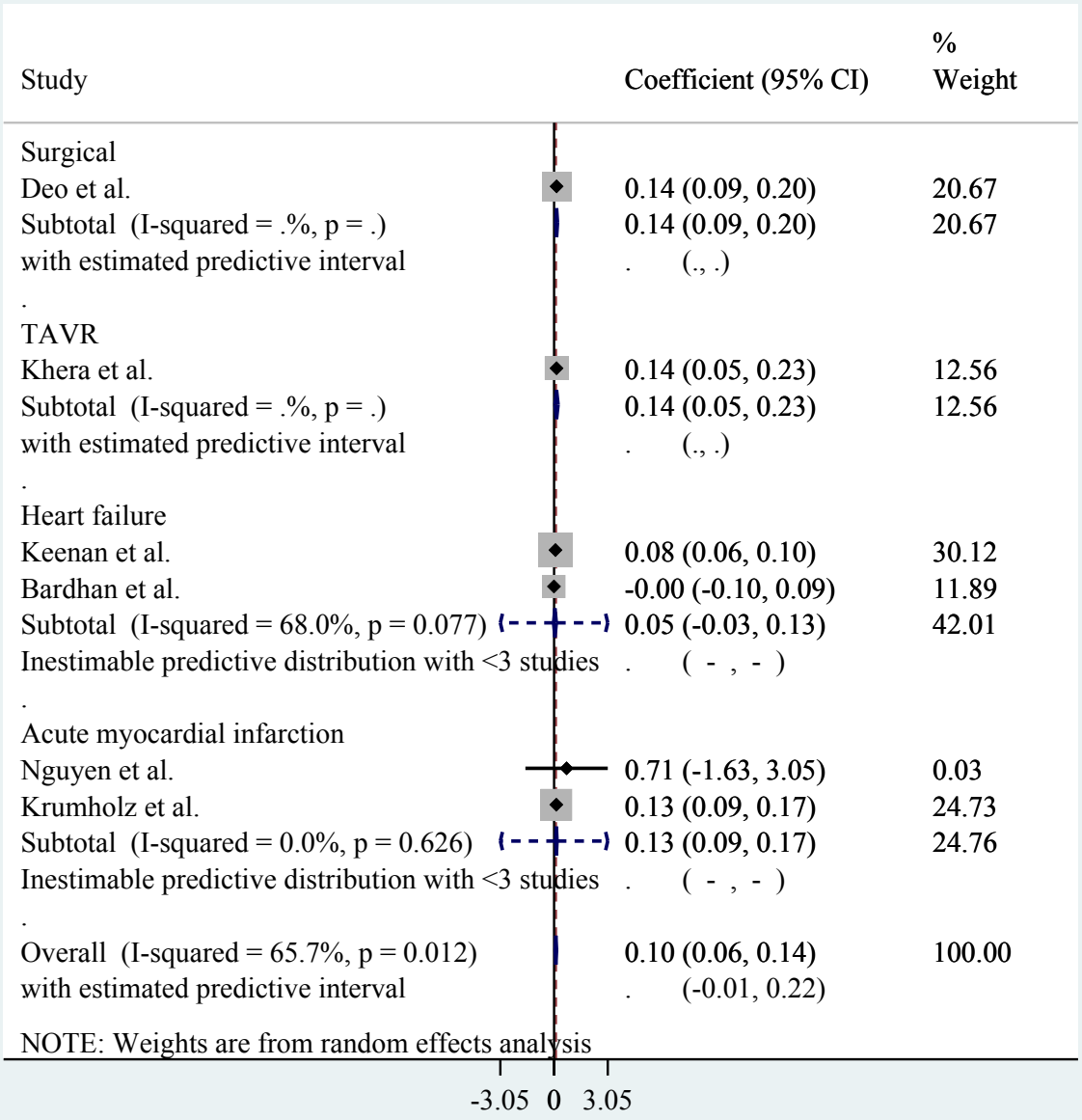
Supplemental Figure 22. Anemia as predictor



Legend: There was no missing data.

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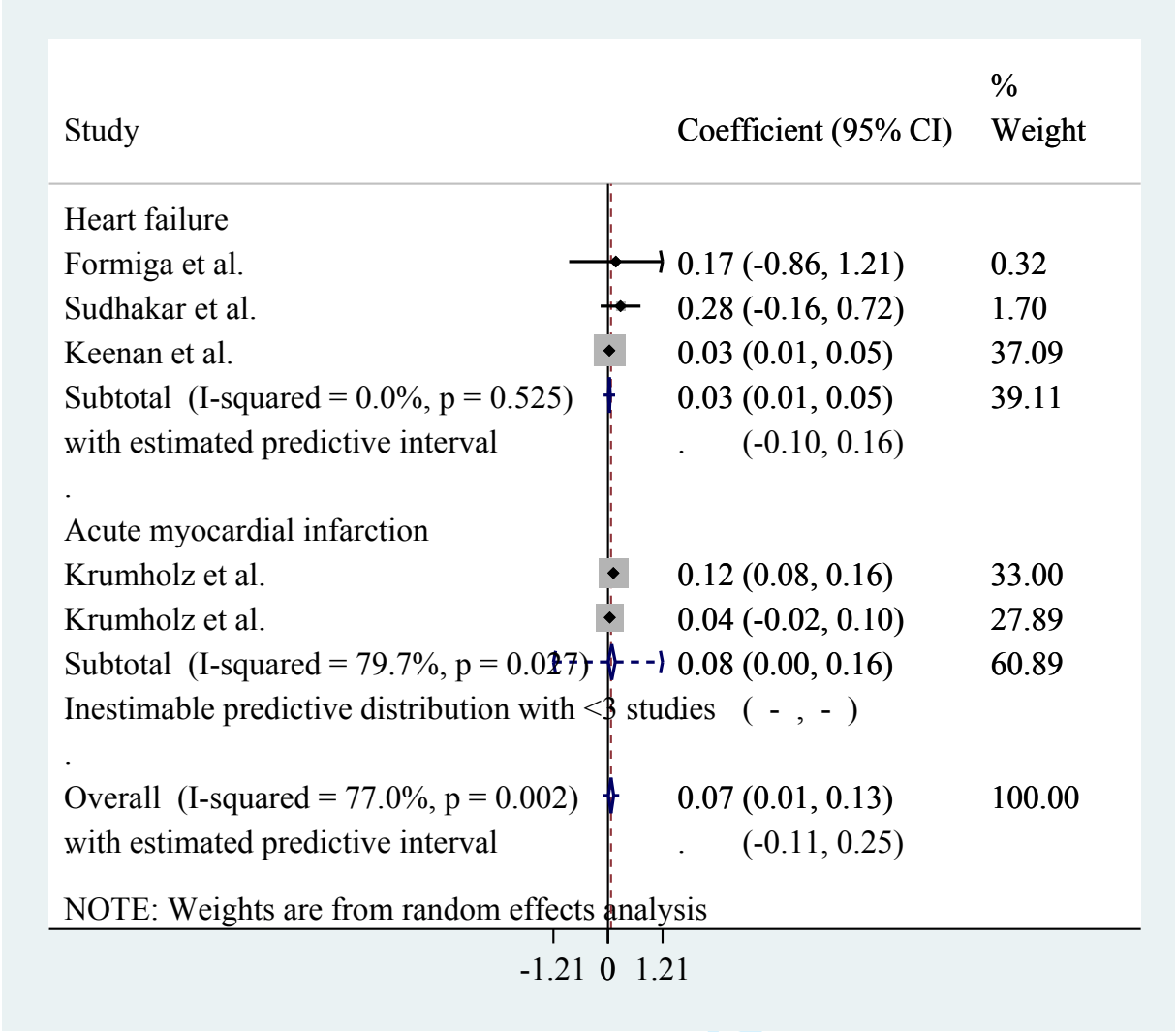
Supplemental Figure 23. Stroke as predictor



Legend: There was no missing data.

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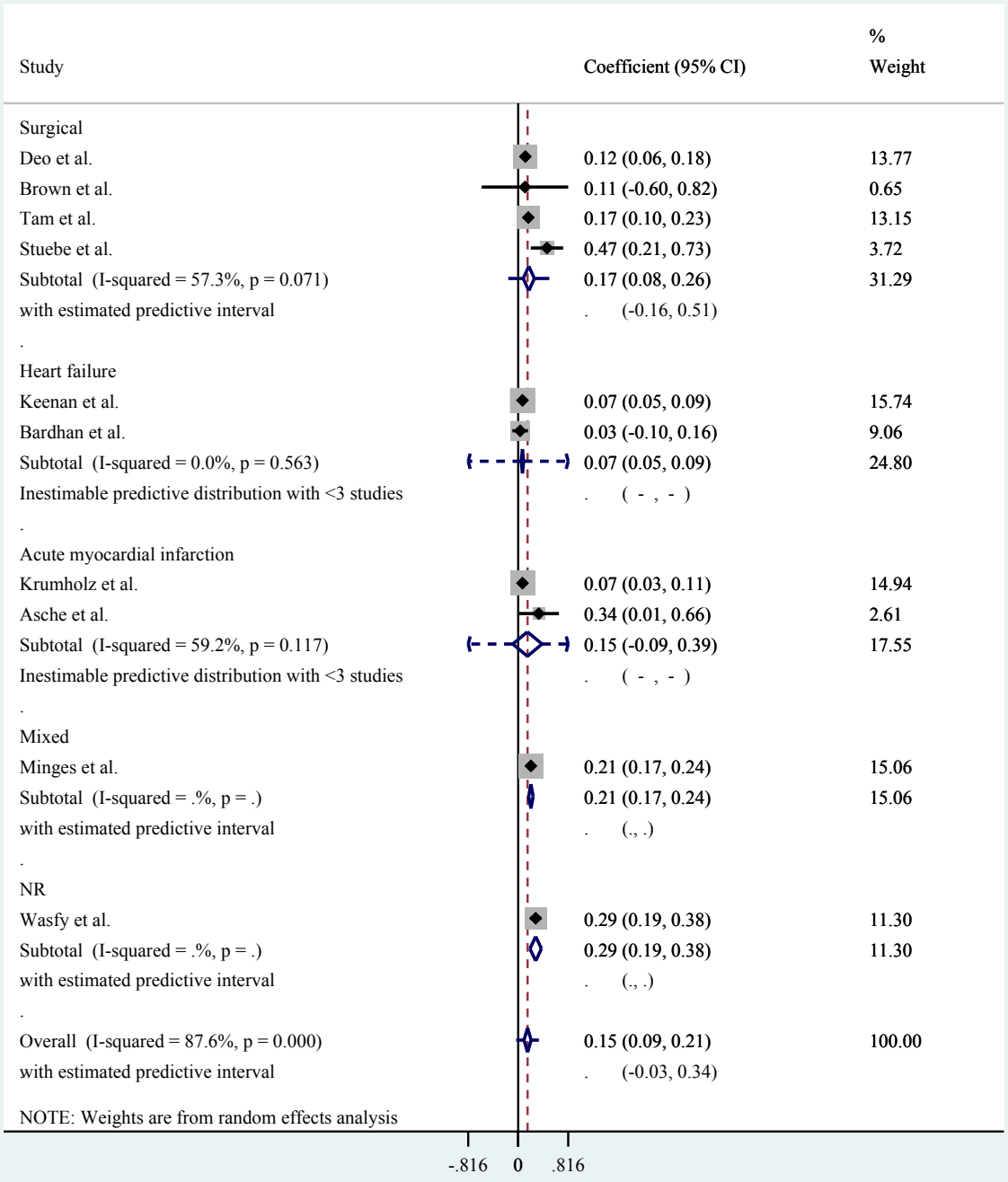
Supplemental Figure 24. Peripheral vascular disease as predictor



Legend: There was no missing data.

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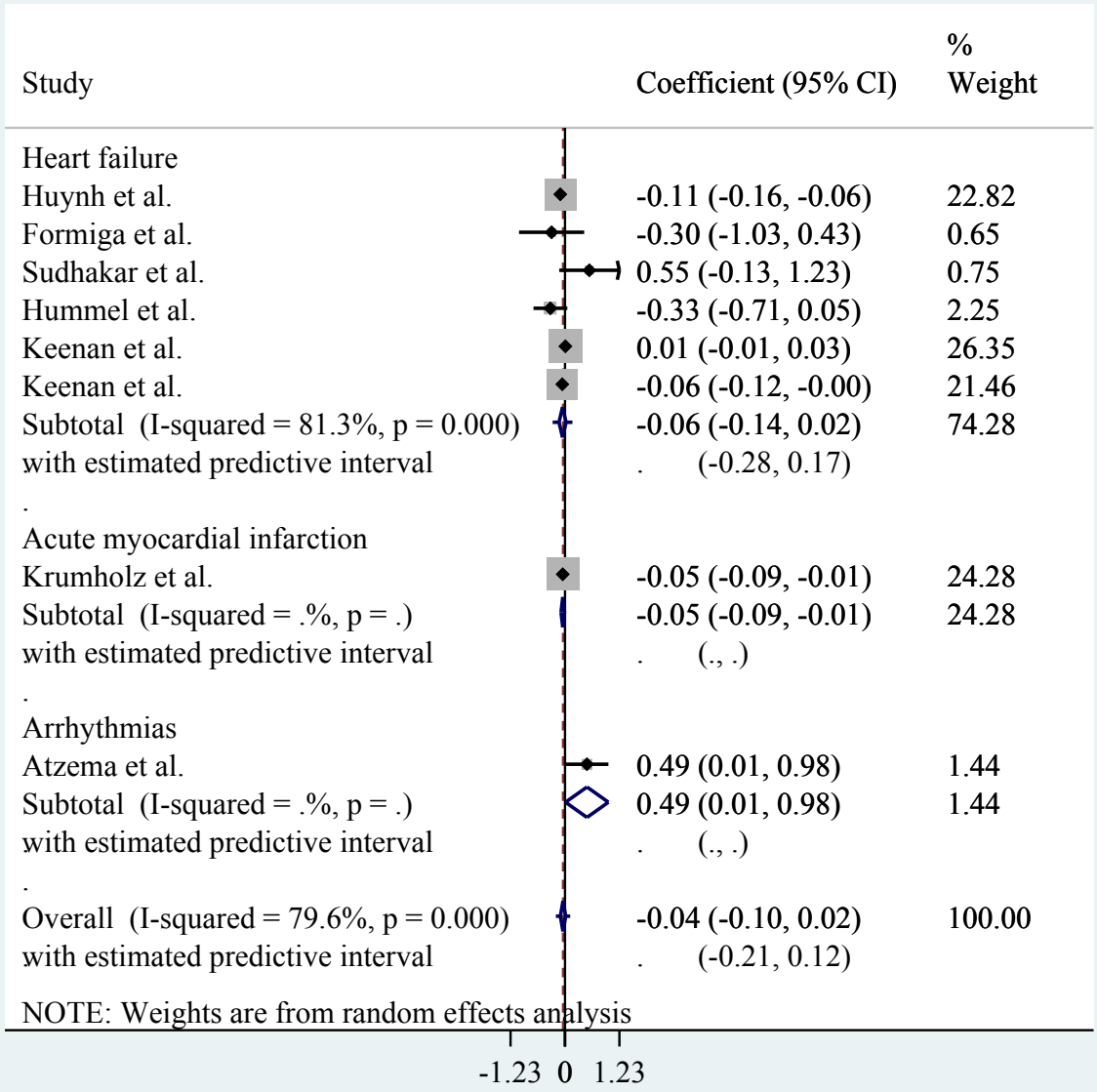
Supplemental Figure 25. Dementia as predictor



Legend: There was no missing data.

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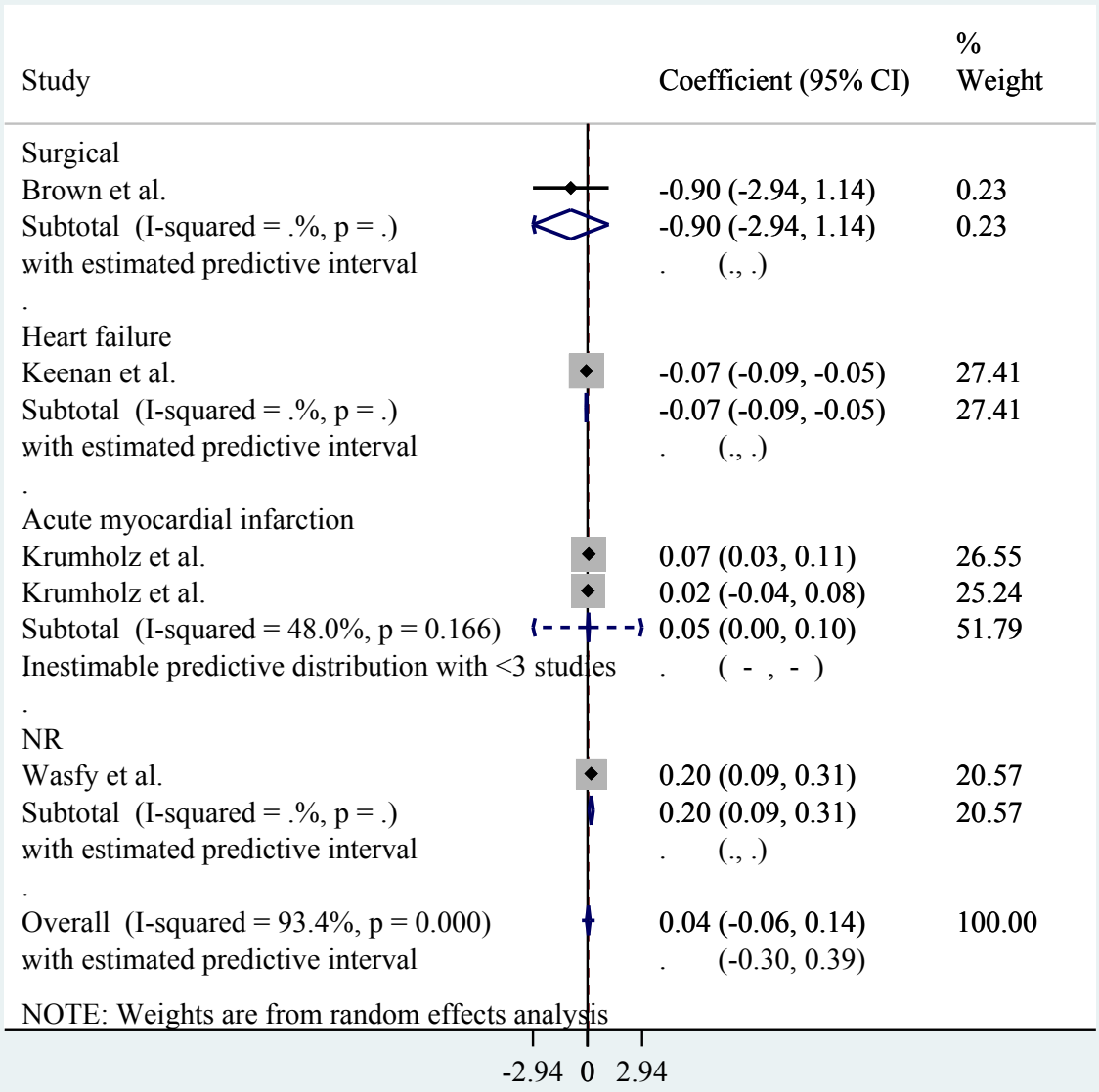
Supplemental Figure 26. Prior Coronary Artery Bypass Graft as predictor



Legend: There was no missing data.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Supp. Text 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7,8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8, Supp Text 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8

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PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-18, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	19, Fig 2, Supp. Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	19-29, Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	20, Fig 3 and 4, Supp. Table 3, Supp. Fig 1-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19, 20, 29 Supp. Table 2, Supp. Fig

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PRISMA 2009 Checklist

			7-26
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	30-32
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	32, 33
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	33
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	134

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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Secondary Subject Heading:	Research methods
Keywords:	CARDIOLOGY, Adverse events < THERAPEUTICS, Risk management < HEALTH SERVICES ADMINISTRATION & MANAGEMENT

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Prediction models for hospital readmissions in patients with heart disease: a systematic review and meta-analysis.

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Abstract

Objective: To describe the discrimination and calibration of clinical prediction models, identify characteristics that contribute to better predictions, and investigate predictors that are associated with unplanned hospital readmissions.

Design: Systematic review and meta-analysis.

Data source: Medline, EMBASE, ICTPR (for study protocols), and Web of Science (for conference proceedings) were searched up to 25 August 2020.

Eligibility criteria for selecting studies: Studies were eligible if they reported on 1) hospitalized adult patients with acute heart disease; 2) a clinical presentation of prediction models with c-statistic; 3) unplanned hospital readmission within six months.

Primary and secondary outcome measures: Model discrimination for unplanned hospital readmission within six months measured using concordance (c) statistics and model calibration. Meta-regression and sub-group analyses were performed to investigate predefined sources of heterogeneity. Outcome measures from models reported in multiple independent cohorts and similarly defined risk predictors were pooled.

Results: Sixty studies describing 81 models were included: 43 models were newly developed, and 38 were externally validated. Included populations were mainly heart failure (HF) patients (n=29). The average age ranged between 56.5 and 84 years. The incidence of readmission ranged from 3% till 43%. Risk of bias was high in almost all studies. The c-statistic was <0.7 in 72 models, between 0.7-0.8 in 16 models and >0.8 in 5 models. The study population, data source and number of predictors were significant moderators for the discrimination. Calibration was reported for 27 models. Only the GRACE-score had adequate discrimination in independent cohorts (0.78, 95% CI 0.63-0.86). Eighteen predictors were pooled.

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Conclusion: Some promising models require updating and validation before use in clinical practice. The lack of independent validation studies, high risk of bias and low consistency in measured predictors limit their applicability.

Trial registration: Prospero, CRD42020159839

Key words: heart disease, meta-analysis, patient readmission, risk assessment, systematic review.

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Article summary

Strengths and limitations of this study

- Largest investigation of unplanned hospital readmission risk to date, including 81 unique prediction models in the systematic review.
- Independent and standardized procedures for study selection, data collection and risk of bias assessment.
- High risk of bias in current prediction models and unexplained heterogeneity between models limit recommendations for using prediction model in clinical practice.

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Introduction

Hospital readmissions in patients with acute heart disease are associated with a high burden on patients, healthcare and costs.[1] The identification of high-risk hospitalized patients is important to provide timely interventions. Prediction models guide healthcare providers in daily practice to assess patients' probability of readmission within a certain time frame and include candidate variables identified by clinical perspectives, literature or data-driven approaches, e.g. using machine learning techniques.[2] Data are often collected from observational cohorts of intervention studies and subsequently analyzed to examine what set of predictors best predict the risk of readmission. The clinical applicability of risk prediction models in daily practice is currently limited. Statistical models are often not presented in a clinically useful way or models based on administrative data are considered.[3] These models therefore cannot be readily used in daily practice. In addition, prediction models are often developed for a very specific population, which asks from clinicians to be familiar with several models. Furthermore, patients may belong to multiple populations because of cardiac comorbidities. Numerous systematic reviews have previously investigated the prediction of unplanned hospital readmissions in several populations.[3-12] While some have included hospitalized patients in general[11,12], others have focused specifically on patients with heart failure (HF)[4-8,10] or acute myocardial infarction (AMI).[3,9] The conclusion is generally the same, the discrimination is poor to adequate, and there is little consistency in the type of predictors included in the models.

We believe that the state of the art on risk prediction can be improved if more knowledge is available on the performance of clinical risk prediction models and risk predictors across different populations of patients with heart disease. Although heterogeneity in models and predictors is often considered as a limitation, it can inform effect moderators on how predictions can be improved.[13] For example, perhaps we can identify predictors who demonstrate a consistent association with hospital readmission regardless of the underlying

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disease. If this can be identified, a more general prediction model could be developed that is relevant for the heterogeneous group of patients on cardiac care units. This might contribute to the early recognition and onset of preventive interventions in patients with heart disease at risk of readmission.

We therefore performed a systematic review and meta-analysis on clinical risk prediction models for the outcome unplanned hospital readmission in patients hospitalized for acute heart disease. Our aim was to describe the discrimination and calibration of clinical prediction models, identify characteristics that contribute to better predictions, and to investigate predictors that are consistently associated with hospital readmissions.

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Methods

A protocol was registered in PROSPERO (CRD42020159839). The results are reported following the PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) statement.[14]

Eligibility criteria

Studies were eligible if 1) the study population included hospitalized adult patients with (symptoms of) heart disease; 2) a prediction model with c-statistic was reported; 3) a clinically useful presentation of the model with risk factors was reported; 4) the outcome was unplanned hospital readmissions within six months; 5) the study design was appropriate, i.e. (nested) case-control study, (prospective and retrospective) cohort study, database and registry study, or secondary analysis of a trial; 6) they were reported in English.

Information sources

A search strategy was designed with an information specialist (PROSPERO protocol and Supplemental Text 1). We searched the Medline, EMBASE, WHO ICTPR search portal (for study protocols), and Web of Science (for conference proceedings) databases up to 25 August 2020 without any restrictions for eligible studies. We searched for full text manuscripts of the identified protocols. After selecting the full text manuscripts, we screened references lists and prospective citations (using Google Scholar) for additional eligible studies.

Study selection

Three reviewers were involved in the study selection process. Each reviewer independently screened two thirds of the titles, abstracts and full-text articles of potentially relevant references identified in the literature search. Disagreements were resolved through consensus. Sixteen authors were contacted and six delivered data for readmission when a composite outcome was used. Two authors were also contacted when data was reported combining multiple patient

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populations. However, no additional data was provided for the population with heart disease and these studies were excluded.

Data extraction

Data extraction was performed based on the 'Critical Appraisal and Data Extraction for Systematic Reviews' of prediction modelling studies checklist using standardized forms in the Distiller Systematic Review Software (see Supplemental Text 2 for the data items).[15] The checklist includes items on 11 relevant domains, including source of data, participants, outcomes, candidate predictors, sample size, missing data, model development, model performance, model evaluation, results, and interpretation. One reviewer collected the data and the second reviewer verified the extracted data. Disagreements were resolved through consensus. Eight authors were contacted and two delivered data to resolve uncertainties or missing data.

Risk of bias

The Prediction model Risk Of Bias ASsessment Tool (PROBAST) tool[16] was used to assess the risk of bias (RoB) for four 'quality' domains, i.e. the participants, predictors, outcome and analysis for each model. One author assessed the RoB as low, high or unclear, and the second author verified the extracted data and RoB conclusion. Disagreements were resolved through consensus. In addition, the applicability of the included studies based on our research question was assessed for three domains, i.e. participants, predictors and outcome domains and rated as low concerns, high concerns or uncertain concerns regarding applicability.

Summary measures

The discrimination of the prediction models were described using the concordance (c)-statistic. Missing standard errors were derived from the sample data.[17] The calibration was described using the number of observed and expected events, the calibration slope, calibration in large,

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or the Hosmer-Lemeshow test. A definition of the commonly used measures is described in box 1.

The association between risk predictors and hospital readmission was described using regression coefficients. Missing standard errors for the coefficients were considered missing completely at random and were not imputed. A complete case analysis was performed.

Synthesis of results and analyses

Meta-analyses using random-effects models, with the Hartung-Knapp modification, were performed to describe the distribution of the between-study variance of the different prediction models and their predictors. Because we considered that there would be substantial heterogeneity, conclusions were not based on the precision of the pooled estimates.

The c-statistic from each model was pooled and a meta-regression was performed to investigate the moderation effect of age and the number of predictors on the discrimination. A subgroup analysis was performed to investigate the moderation effect of the different patient populations, design, outcome definition, and endpoint. The c-statistic of the validated model was used if available; otherwise the c-statistic from the development phase was used.

The c-statistics of specific prediction models that were evaluated in multiple studies were pooled for the endpoint 30 days follow-up.

Coefficients of predictors that were similarly defined in at least five studies were pooled for the endpoint 30 days follow-up. The patient populations were defined as subgroups to explore consistency and heterogeneity (I^2, tau) in the effect estimates.

Analyses were performed using the 'metan' package in STATA 15 IC and the 'metamisc package' in Rstudio.

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Box 1. Definitions of commonly used measures

***Discrimination*:** Refers to the ability of a prediction model to discriminate between a patient with and without the outcome, e.g. readmission.

C-statistic: Is a measure of discrimination. For binary outcomes, the c-statistic is equivalent to the area under the curve: 1 indicates perfect discrimination, and 0.5 indicates that the models does not perform better than chance. Harrell's c-statistic is often used in survival models.

Calibration: Refers to the agreement between the predicted and the observed probability (or the outcome value for linear models). Calibration is expressed using different measures, e.g. calibration slope, calibration in large, hosmer-lemeshow test.

Calibration slope: The slope should be 1, a value < 1 indicates extreme predictions, and a value of > 1 indicates to moderate predictions.

Calibration in large: The value should be 0, a negative value indicates overestimation of the prediction, and a positive value indicates underestimation of the prediction.

Hosmer-Lemeshow test: This is a goodness-of-fit test for binary outcomes. A significant p-value, usually < 0.05, indicates poor goodness-of-fit.

Derivation/development cohort: A cohort of patients that is used to estimate the predictor values that are used in a prediction model to estimate a patients probability for an outcome.

Validation cohort: A cohort of patients that is used to evaluate how well the developed model performs (in terms of discrimination and calibration).

Internal validation: Estimates how well the performance of a model will be reproduced in the target population. Several techniques can be used, e.g. random-split sample, cross-validation, and bootstrapping techniques.

External validation: Evaluates how well a model performs in a new sample, and can consist of temporal validation (sample contains more recently treated patients), geographical

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validation (sample is from a different center) of a fully independent validation (validation by an independent team).

Public and patient involvement

Because of the design of the study and because we did not collect primary date, we did not involve patients or the public in the design, conduct, or reporting of our research.

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Results

A total of 8588 abstracts were reviewed and 60 studies describing 81 separate models were included (Figure 1). Table 1 provides an overview of the included studies and models, which were published between 2001 and 2020. The majority of the studies (n=40) was performed in the United States. The data sources used were mostly retrospective cohort studies (n=15), hospital databases (n=13) and registries (n=13). Included populations were mainly HF patients (n=29), surgical patients (n=14) and patients with an AMI or acute coronary syndrome (n=10). The average age was between 56.5 and 84 years. The sample size of development cohorts ranged from 182 till 193,899 patients and of the validation cohorts between 104 and 321,088 patients. The outcome of interest was mostly all-cause readmission (n=41) and measured on 30 days (n=55). The incidence of readmission per study ranged from 3% till 43%.

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Table 1. Study characteristics

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Moretti et al.[18]	EuroHeart PCI score	Hospital database	NA	Ext	-	1192	ACS	71 (7)	30d		4.7
Asche et al.[19]	NR	Retrospective cohort	Yes	Split	2446	612	AMI	65 (15)	30d	8.9	
Cediel et al.[20]	TARRACO Risk Score	Retrospective cohort	Yes	No	611	401	AMI type 2, ischemia	D: 78 [17] V: 60 [21]	30d	2.6	
		Retrospective cohort	Yes	No	611	401	AMI type 2, ischemia	D: 78 [17] V: 60 [21]	180d	7.9	
Chotechuang et al.[21]	GRACE	Retrospective cohort	NA	Ext	-	152	AMI	60.5 (6.3)	30d		5.3
	GRACE	Retrospective cohort	NA	Ext	-	152	AMI	60.5 (6.3)	180d		9.2
Hilbert et al.[22]	AMI decision tree	Registry	Yes	Ext	10848	10701	AMI	NR	30d	20.6	19.7
Dodson et al.[23]	SILVER-AMI 30-day readmission calculator	Prospective cohort	Yes	Split	2004	1002	AMI	81.5 (5.0)	30d	18.2	
Kini et al.[24]	NR	Registry	Yes	Split	60742	26107	AMI	76.5 (8.0)	90d	27.5	
Nguyen et al.[25]	AMI READMITS score	Retrospective cohort	Yes	Split	661	165	AMI	65.5 (12.8)	30d	13	
	Full-stay AMI model	Retrospective cohort	Yes	Split	661	165	AMI	65.5 (12.8)	30d	13	
	CMS AMI administrative model	Retrospective cohort	NA	Ext	-	826	AMI	65.5 (12.8)	30d		13

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Krumholz et al.[26]	CMS AMI administrative model	Registry	Yes	Split, Ext	100465	321088	AMI	78.7 (8.0)	30d	18.9	20.0 (Ext) NR (split)
	CMS AMI medical model	Registry	Yes	Split	130944	130944	AMI	76.2 (7.3)	30d	20	
Rana et al.[27]	Elixhauser index	Hospital database	NA	Ext	-	1660	AMI	67.9	30d		6.3
	HOSPITAL score	Hospital database	NA	Ext	-	1660	AMI	67.9	30d		6.3
Atzema et al.[28]	AFTER Part 2 scoring system	Retrospective cohort	Yes	Split	2343	1167	Arrhythmia, AF	D: 68.6 (14.7) V: 68.3 (15.1)	30d	7	7.6
Lahewala et al.[29]	CHADS2	Administrative	NA	Ext	-	116450	Arrhythmia, AF	<75	30d		15.8
	CHADS2	Administrative	NA	Ext	-	116450	Arrhythmia, AF	<75	90d		25.1
	CHA2DS-VASc	Administrative	NA	Ext	-	116450	Arrhythmia, AF	65-74	30d		15.8
	CHA2DS-VASc	Administrative	NA	Ext	-	116450	Arrhythmia, AF	65-74	90d		25.1
Benuzillo et al.[30]	CRSS	Hospital database	Yes	Boot, Ext	2589	896 (Ext) 500 (Boot)	CABG	66.7 (9.9)	30d	9.1	8.2 (Ext) 9.1 (Boot)
Deo et al.[31]	30-days CABG Readmission Calculator	Administrative	Yes	Boot	155054	1000	CABG	65.4 (10.4)	30d	12.5	
Engoren et al.[32]	NR	Hospital database	Yes	Split	2644	2711	CABG	NR	30d	7.6	8
Lancey et al.[33]	NR	Registry	Yes	Split	2341	2520	CABG	64.5 (10.5)	30d	8.8	9.5
Rosenblum et al.[34]	The STS PROM score	Hospital database	NA	Ext	-	21719	CABG	63.5 (10.7)	30d		9.3

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Zitser-Gurevich et al.[35]	NR	Prospective cohort	Yes	Split	2266,5	2266,5	CABG	65-74	30d	13.3	
	NR	Prospective cohort	Yes	Split	2266,5	2266,5	CABG	65-74	100d	24.1	
Zywot et al.[36]	CABG Risk Scale	Administrative	Yes	Ext	126519	94318	CABG	D: 70-74 V: 70-74	30d	23	21
Ahmad et al.[37]	CMS HF administrative model	Prospective cohort	NA	Ext	-	183	HF	61 [18]	30d		22.4
Amarasingham et al.[38]	ADHERE	Hospital database	NA	Ext	-	1372	HF	56.5	30d		24.1
	CMS HF administrative model	Hospital database	NA	Ext	-	1372	HF	56.5	30d		24.1
	Tabak mortality score	Hospital database	NA	Ext	-	1372	HF	56.5	30d		24.1
Au et al.[39]	Administrative Claims Model: HF 30-day mortality	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
	Charlson Comorbidity Score	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
	CMS HF administrative model	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
	LACE	Administrative	NA	Ext	59652	59652	HF	75.8 (12.7)	30d		15.9
Bardhan et al.[40]	NR	Hospital database	Yes	No	40983	-	HF	69.2 (15.7)	30d	7	

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size Dev.	Sample size Val.	Population	Average age	Outcome	Readmission (%) Dev.	Readmission (%) Val.
Betihavas et al.[41]	NR	RCT secondary analysis	Yes	Boot	280	200	HF	74 [64 - 81]	28d	18	
Cox et al.[42]	CMS HF administrative model	Hospital database	No	Ext	-	1454	HF	75 (12)	30d		21.5
	CMS HF medical model	Hospital database	No	Ext	-	1454	HF	75 (12)	30d		21.5
Delgado et al.[43]	15-day CV readmission risk score	Prospective cohort	Yes	Boot	1831	500	HF	72.4 (12.1)	15d	7.1	
	30-day CV readmission risk score	Prospective cohort	Yes	Boot	1831	500	HF	72.4 (12.1)	30d	13.9	
Formiga et al.[44]	CMS HF medical model	Hospital database	NA	Ext	-	719	HF	78.1 (9)	30d		7.6
	CMS HF medical model	Hospital database	NA	Ext	-	719	HF	78.1 (9)	90d		14.4
Frizzell et al.[45]	CMS HF administrative model	Registry	NA	External	-	56477	HF	80 [2]	30d		21.2
Hammill et al.[46]	CMS HF administrative model	Registry	NA	Ext	-	24163	HF	81	30d		21.9
Hilbert et al.[22]	HF decision tree	Registry	Yes	Ext	39682	38409	HF	NR	30d	25.5	25.2
Hummel et al.[47]	CMS HF medical model	Prospective cohort	NA	Ext	-	1807	HF	79.8 (7.6)	30d		27

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Huynh et al.[48]	NR	Prospective cohort	Yes	Ext	430	1046	HF	D: 75 [19] V: 67 [17]	30d	21	24
	NR	Prospective cohort	Yes	Ext	430	1046	HF	D: 75 [19] V: 67 [17]	90d	43	42
Ibrahim et al.[49]	HOSPITAL score	Retrospective cohort	NA	Ext	-	692	HfpEF	68.3 (11.8)	30d		27.3
	LACE / LACE+ index	Retrospective cohort	NA	Ext	-	692	HfpEF	68.3 (11.8)	30d		27.3
Keenan et al.[50]	CMS HF administrative model	Registry	Yes	Split, Ext.	28319	845291	HF	79.9 (7.8)	30d	23.6	23.7 (Ext) NR (Split)
	CMS HF medical model	Registry	Yes	Split, Ext.	64329	64329	HF	75-84	30d	23.7	
Kitamura et al.[51]	FIM	Retrospective cohort	NA	Ext	-	113	HF	80.5 (6.7)	90d		20.4
Leong et al.[52]	30-day HF readmission risk score	Retrospective cohort	Yes	Split	888	587	HF	D: 70.0 (12.7) V: 69.1 (12.8)	30d	9.9	
Li et al.[53]	NR	Retrospective cohort	Yes	Split	51783	25887	HF	D: 84 [12] V: 84[11]	30d	24.2	
Lim et al.[54]	NR	Registry	Yes	No	4566	-	HF	70.5 (12.0)	30d	6.6 (car) 13 (all)	
Reed et al.[55]	AH model	Administrative	Yes	Split	NR	NR	HF	NR	30d	NR	
	CMS HF administrative model	Administrative	NA	Split	-	NR	HF	NR	30d		NR
	Hasan	Administrative	NA	Split	-	NR	HF	NR	30d		NR
	LACE	Administrative	NA	Split	-	NR	HF	NR	30d		NR
	PARR-30	Administrative	NA	Split	-	NR	HF	NR	30d		NR

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Salah et al.[56]	ELAN-HF score	Prospective cohort secondary analysis	Yes	No	1301	-	HF	74 [16]	180d	36.1	
Sudhakar et al.[57]	CMS HF medical model	Hospital database	NA	Ext	-	1046	HF	65.2 (16.6)	30d		35.3
Tan et al.[58]	NR	Hospital database	Yes	Split	246	104	HF	D: 67.7 (12.3) V: 69.0 (12.9)	90d	24.5	11.7
Wang et al.[59]	NR	Hospital database	Yes	No	4548	-	HF	68.5 [27.6]	30d	25.1	
Wang et al.[60]	LACE	Retrospective cohort	NA	Ext	-	253	HF	56.6 (11.5)	30d		24.5
Yazdan-Ashoori et al.[61]	CMS HF administrative model	Prospective cohort	NA	Ext	-	378	HF	73.1 (13.1)	30d		26
	LACE	Prospective cohort	NA	Ext	-	378	HF	73.1 (13.1)	30d		26
Disdier Moulder et al.[62]	NR	Prospective cohort	Yes	No	258		HF, ACS, NR	70.5 [23]	30d	17	
	NR	Prospective cohort	Yes	No	258		HF, ACS, NR	70.5 [23]	180d	38	
Raposeiras-Roubín et al.[63]	GRACE	Retrospective cohort	NA	Ext	-	4229	HF, ACS	68.2 [18.7]	30d		2.6
Burke et al.[64]	HOSPITAL score	Retrospective cohort	NA	Ext	-	HF: 3189 AMI: 767	HF, AMI	65.8 (16.8)	30d		HF: 18.2 AMI: 17.4
Minges et al.[65]	NR	Registry	Yes	Split	193899	194179	HF, PCI	65+	30d	11.4	
Pack et al.[66]	NR	Administrative	Yes	Split	30826	7706	HVD	64.9 (12.2)	90d	12.8	

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Table 1. Study characteristics (continued)

Study	Model	Data source	Development	Validation	Sample size		Population	Average age	Outcome	Readmission (%)	
					Dev.	Val.				Dev.	Val.
Oliver-McNeil et al.[67]	ICD Readmission-Risk Score	Registry	Update	Ext	182	-	ICD	69 (11)	30d		17.6
Wasfy et al.[68]	Pre-PCI model	Registry	Yes	Split	24052	12008	NR	64.8 (12.5)	30d	10.4	
Barnett et al.[69]	NR	Registry	Update	Ext	19964	19964	Surgical	65.3 (12.4)	30d	11.4	
Brown et al.[70]	STS Augmented Clinical Model	Prospective cohort	Update	Boot	1046	NR	Surgical	65.4 (9.8)	30d	NR	
	STS 30-day Readmission Model	Prospective cohort	NA	Ext	-	1194	Surgical	73.3 (10.1)	30d		NR
Espinoza et al.[71]	30-day readmission score after cardiac surgery	Retrospective cohort	Yes	Split	2529	2567	Surgical	65.1 (11.5)	30d	11.9	
Ferraris et al.[72]	READMIT	Prospective cohort	Yes		2574		Surgical	63 (11)	30d	9.8	
Kilic et al.[73]	NR	Retrospective cohort	Yes	Split	3898	1295	Surgical	D:61.9 (14.7) V: 61.6 (15.1)	30d	10	11
Stuebe et al.[74]	NR	Hospital database	Yes	No	4800		Surgical	60-69	30d	12	
Tam et al.[75]	NR	Retrospective cohort	Yes	Boot	63336	NR	Surgical	66.2 (10.7)	30d	11.3	
Khera et al.[76]	TAVR 30-Day Readmission Risk Model	Administrative	Yes	Boots, Ext	39305	40 (Boot) 885 (Ext)	TAVR	D: 81.3 V: 81.7	30d	16.2	16.2 (Boot) 18.9 (Ext)

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Sanchez et al.[77]	NR	Registry	Yes	Split	6903	3442	TAVR	D: 81.1 (7.9) V: 81.3 (7.9)	30d	9.8	10.7

Abbreviations:

ACS: acute coronary syndrome, AF: atrial fibrillation, AH: Adventist Health Off-the-shelf model, Boot: bootstrapping, CABG: coronary artery bypass grafting, Car: cardiac-related, CMS=centers for Medicare and Medicaid services, CRSS: CABG Readmission Risk Score, d: days, Dev: development, Ext: external validation, Fim: motor and cognitive Functional Independence Measure, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HVD: heart valve disease, ICD: implantable cardioverter defibrillator, NA: not applicable, NR: not reported, PARR-30: Patients at Risk of Re-admission within 30-days, PCI: percutaneous coronary intervention, SD: standard deviation, Split: random split, TAVR: transcatheter aortic valve replacement, Val: validation

Legend: Age is reported as mean (SD), median [IQR] or average age as reported in the study.

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Risk of bias

Figure 2 summarizes the RoB and applicability assessment (Supplemental Table 1A). The overall RoB was high in 98.9% of the models and only one study[23] showed low RoB in all four domains.

For the domain participants, 82.4% of studies was assessed as high RoB because most studies performed retrospective data analyses or used data from existing sources with large number of candidate predictors that were originally developed for other purposes, e.g. administrative databases or registries. The domain predictors was assessed as high RoB in 27.5% of the models, 24.2% as low RoB and 48.4% as unclear RoB. For the domain outcome, 41.8%, 34.1% and 24.2% were assessed as high, low and unclear RoB respectively.

The domain analysis was assessed as high RoB in 97.8%. Most studies did not use appropriate statistics for the development or validation of prediction models. For example a description on how complexities in data were handled (e.g. competing risk of death) was often missing and relevant performance measures were incomplete (e.g. calibration).

The domains participants and predictors were assessed as low concerns regarding applicability in all studies. For the domain outcome, 70.3% of studies used all-cause readmission as the outcome of interest and were therefore assessed as low concerns regarding applicability.

Prediction models

A total of 43 new models were developed for patients with HF (n=15), undergoing surgical procedures (n=12), AMI (n=9), transcatheter aortic valve replacement (TAVR) (n=2), a mixed sample with HF and coronary syndromes (n=2), arrhythmias (n=1), valvular disease (n=1), while one study did not specify the sample (table 1). The c-statistic was lower than 0.6 in five models, between 0.6 and 0.7 in 24 models, between 0.7 and 0.8 in six models, and between 0.8

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and 0.9 in two models. In six models, the c-statistic was only reported for a validation cohort (Table 2).

A total of 38 separate models were externally validated for patients with HF (n=26), AMI (n=4), surgical patients (n=3), acute coronary syndrome (n=2), arrhythmias (n=2), mixed sample with HF and coronary syndromes (n=1). The discrimination was lower than 0.6 in sixteen models, between 0.6 and 0.7 in fifteen models, between 0.7 and 0.8 in five models, and between 0.8 and 0.9 in two models (Table 2).

The discrimination of six models was evaluated in multiple independent cohorts and was pooled in meta-analyses (Figure 3, Supplemental Figures 1-6): the CMS AMI administrative model[25,26] (0.65, 95% CI 0.56-0.73); the CMS HF administrative model[37-39,42,45,46,50,55,61] (0.60, 95% CI 0.58-0.62); the CMS HF medical model[42,44,47,50,57] (0.60, 95% CI 0.58-0.62); the HOSPITAL score[27,49,64] (0.64, 95% CI 0.58-0.70); the GRACE score[21,63] (0.78, 95% CI 0.63-0.86); and the LACE score[39,49,55,60,61] (0.62, 95% CI 0.53-0.70).

On average, models for AMI patients had the best discrimination (0.67, n=16), followed by TAVR patients (0.65, n=2), HF patients (0.64, n=45), and surgical patients (0.63, n=17). The discrimination was highest in studies using secondary analysis (0.70, n=2) and retrospective cohort studies (0.69, n=23), and was lowest in studies using registries (0.61, n=17) and hospital databases (0.61, n=18). The discrimination decreased when the number of predictors increased (beta -0.002, n=90). There were no moderation effects based on the average age of the sample, outcome definition and endpoint of the prediction (Supplemental Figures 7–8 and Supplemental Table 1B).

The calibration was reported for 27 models using multiple measures and could not be pooled (Table 2).

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Table 2. Model discrimination and calibration

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Moretti et al.[18]	EuroHeart PCI score	ACS	16	External	0.59 (0.48 - 0.71)	NA	
Asche et al.[19]	NR	AMI	19	Development, random split	0.74, NR	NA	
Cediel et al.[20]	TARRACO Risk Score	AMI type 2, ischemia	7	Development (30d)	0.71 (0.61 - 0.82)	NA	
		AMI type 2, ischemia	7	Development (180d)	0.71 (0.64 - 0.78)	NA	
Burke et al.[64]	HOSPITAL score	AMI	7	External	0.66 (0.61 - 0.71)	HLT	p=0.49
Chotechuang et al.[21]	GRACE	AMI	9	External (30d)	0.77 (0.65 - 0.88)	NA	
	GRACE	AMI	9	External (180d)	0.63 (0.49 - 0.77)	NA	
Hilbert et al.[22]	AMI decision tree	AMI	44	Development, External	0.65 (0.64 - 0.66), 0.61 (0.61 - 0.62)	NA	
Dodson et al.[23]	SILVER-AMI 30-day readmission calculator	AMI	10	Development, random split	0.65, 0.63	HLT	p>0.05, p=0.05
Kini et al.[24]	NR	AMI	12	Development, random split	NR, 0.66	Slope, in large, plot	0.973 (p=0.330), -0.038 (p=0.221)
Nguyen et al.[25]	AMI READMITS score	AMI	7	Development, random split	0.75 (0.70 - 0.80), 0.73 (0.71 - 0.74)	Plot, Plot	
	Full-stay AMI model	AMI	10	Development, random split	0.78 (0.74 - 0.83), 0.75 (0.74 - 0.76)	Plot	
	CMS AMI administrative model	AMI	32	External	0.74 (0.69 - 0.74)	Plot	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Krumholz et al.[26]	CMS AMI administrative model	AMI	32	Development, external, random split	0.63, 0.63, 0.62	In large, slope	
	CMS AMI medical model	AMI	45	Development, random split	0.58, 0.59	NA	0, 1 / 0.015, 0.997/ 0.015, 0.983
Rana et al.[27]	Elixhauser index	AMI	30	External	0.53 (0.42 - 0.65)	NA	
	HOSPITAL score	AMI	7	External	0.60 (0.47 - 0.73)	NA	
Atzema et al.[28]	AFTER Part 2 scoring system	Arrhythmia, AF	12	Development	0.69, NR	NA	
Lahewala et al.[29]	CHADS2	Arrhythmia, AF	5	External (30d)	0.64	NA	
	CHADS2	Arrhythmia, AF	5	External (90d)	0.63	NA	
	CHA2DS-VASc	Arrhythmia, AF	9	External (30d)	0.65	NA	
	CHA2DS-VASc	Arrhythmia, AF	9	External (90d)	0.63	NA	
Benuzillo et al.[30]	CRSS	CABG	5	Development, bootstrapping	0.63, 0.63	HLT	7.13 (p=0.52), 9.31 (p=0.32)
Deo et al.[31]	30-days CABG Readmission Calculator	CABG	20	Development	0.65	NA	
Engoren et al.[32]	NR	CABG	6	Development, random split	0.68 (0.64 - 0.72), 0.68 (0.64 - 0.68)	NA	
Lancey et al.[33]	NR	CABG	8	Development, random split	0.64, 0.57	NA	
Rosenblum et al.[34]	The STS PROM score	CABG	40	External	0.59 (0.57 - 0.60)	NA	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Zitser-Gurevich et al.[35]	NR	CABG	17	Development, external (30d)	0.63, 0.66/0.63	HLT	7.91 (p=0.44)
	NR	CABG	13	Development (100d)	0.65	HLT	6.76 (p=0.56)
Zywot et al.[36]	CABG Risk Scale	CABG	27	Development, external	NR, 0.70	Plot	
Ahmad et al.[37]	CMS HF administrative model	HF	37	External	0.66 (0.57 - 0.76)	HLT	p=0.19
Amarasingham et al.[38]	ADHERE	HF	3	External	0.56 (0.54 - 0.59)	NA	
	CMS HF administrative model	HF	37	External	0.66 (0.63 - 0.68)	NA	
	Tabak mortality score	HF	18	External	0.61 (0.59 - 0.64)	NA	
Au et al.[39]	Administrative Claims Model: HF 30-day mortality	HF	17	External	0.58 (0.58 - 0.59)	NA	
	Charlson Comorbidity Score	HF	32	External	0.55 (0.55- 0.56)	NA	
	CMS HF administrative model	HF	37	External	0.59 (0.59 - 0.60)	NA	
	LACE	HF	18	External	0.58 (0.58 - 0.59)	NA	
Bardhan et al.[40]	NR	HF	30	Development	0.56	NA	
Betihavas et al.[41]	NR	HF	7	Development, bootstrapping	NR, 0.80	NA	
Burke et al.[64]	HOSPITAL score	HF	7	External	0.67 (0.65 - 0.70)	HLT	p=0.10

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Cox et al.[42]	CMS HF administrative model	HF	37	External	0.61	NA	
	CMS HF medical model	HF	20	External	0.60	NA	
Delgado et al.[43]	15-day CV readmission risk score	HF	5	Development, bootstrapping	0.65, 0.63	Plot	
	30-day CV readmission risk score	HF	11	Development, bootstrapping	0.66, 0.64	Plot	
Formiga et al.[44]	CMS HF medical model	HF	19	External (30d)	0.65 (0.57 - 0.72)	NA	
	CMS HF medical model	HF	19	External (90d)	0.62 (0.56 - 0.68)	NA	
Frizzell et al.[45]	CMS HF administrative model	HF	37	External	0.60	NA	
Hammill et al.[46]	CMS HF administrative model	HF	37	External	0.59	Plot	
Hilbert et al.[22]	HF decision tree	HF	44	Development, External	0.59 (0.58 - 0.60), 0.58 (0.58 - 0.59)	NA	
Hummel et al.[47]	CMS HF medical model	HF	28	External	0.61	NA	
Huynh et al.[48]	NR	HF	12	Development, external (30d)	0.82 (0.76 - 0.87), 0.73 (0.69 - 0.77)	NA	
	NR	HF	12	Development, external (90d)	NR, 0.65	NA	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Ibrahim et al.[49]	HOSPITAL score	HfpEF	7	External	0.60 (0.55 - 0.64)	NA	
	LACE	HfpEF	18	External	0.55 (0.50 - 0.60)	NA	
	LACE+ index	HfpEF	24	External	0.57 (0.52 - 0.62)	NA	
Keenan et al.[50]	CMS HF administrative model	HF	37	Development, external, random split	0.60, 0.60, 0.61	In large, slope	0, 1 / 0.02, 1.01/ 0.09, 1.05
	CMS HF medical model	HF	30	Development, random split	0.58, 0.61	In large, slope	0, 1 / 0, 1
Kitamura et al.[51]	FIM	HF	13	External	0.78	NA	
Leong et al.[52]	30-day HF readmission risk score	HF	7	Development, random split	0.76, 0.76	NA	
Li et al.[53]	NR	HF	10	Development, random split	0.63 (0.62 - 0.63) 0.63 (0.62 - 0.63)	HLT, plot	0.15 (p>0.005)
Lim et al.[54]	NR	HF	13	Development	0.68 (car), 0.62 (all)	HLT	27.5 (p=0.001) (car) 8.0 (p=0.429) (all)
Reed et al.[55]	AH model	HF	14	Development, random split	0.86 (0.85 - 0.86), 0.85 (0.84 - 0.86)	NA	
	CMS HF administrative model	HF	37	Random split	0.55 (0.54 - 0.56) 0.55 (0.54 - 0.57)	NA	
	Hasan	HF	9	Random split	0.80 (0.79 - 0.81) 0.80 (0.80 - 0.82)	NA	
	LACE	HF	18	Random split	0.75 (0.74 - 0.81) 0.74 (0.73 - 0.76)	NA	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Reed et al.[55] (continued)	PARR-30	HF	10	Random split	0.82 (0.81 - 0.83) 0.81 (0.80 - 0.82)	NA	
Salah et al.[56]	ELAN-HF score	HF	10	Development	0.60 (0.56 - 0.64)	NA	
Sudhakar et al.[57]	CMS HF medical model	HF	20	External	0.61 (0.57-0.64) ≥65y: 0.59 (0.53-0.64) Random patient-level: 0.58 (0.50-0.65)	NA	
Tan et al.[58]	NR	HF	3	Random split	0.73	HLT, plot	p=0.62
Wang et al.[59]	NR	HF	12	Development	0.65	NA	
Wang et al.[60]	LACE	HF	18	External	0.56 (0.48 - 0.64)	NA	
Yazdan-Ashoori et al.[61]	CMS HF administrative model	HF	37	External	0.61 (0.55 - 0.67)	NA	
	LACE	HF	18	External	0.59 (0.52 - 0.65)	HLT	p=0.73
Disdier Moulder et al.[62]	NR	HF, ACS, NR	4	Development (30d)	0.68	NA	
	NR	HF, ACS, NR	5	Development (180d)	0.69	NA	
Raposeiras-Roubín et al.[63]	GRACE	HF, ACS	9	External	0.74 (0.73-0.80)	HLT	p=0.14
Minges et al.[65]	NR	HF, PCI	35	Development, random split	0.67, 0.66	NA	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Pack et al.[66]	NR	HVD	28	Development, random split	0.67 (full dev.)/ 0.65 (nomogram), 0.67 (full val.)	Harrell's E, O:E, Harrell's E, plot	0.1%, 1.9%, 1.6%
Oliver-McNeil et al.[67]	ICD Readmission-Risk Score	ICD	4	Update, External	0.69 (0.58 - 0.79)	HLT, plot	3.44 (p=0.49)
Wasfy et al.[68]	Pre-PCI model	NR	23	Development, random split	0.68, 0.67	HLT, plot	p=0.59
Barnett et al.[69]	NR validation	Surgical	15	External	0.59	NA	
	NR update	Surgical	18	Update	0.60 (0.59 - 0.62)	NA	
Brown et al.[70]	STS Augmented Clinical Model	Surgical	27	Update (bootstrap), random split, external (bootstrap)	0.66 (0.61 - 0.72), 0.56, 0.47 (0.42 - 0.53)	HLT	p=1.0
	STS 30-day Readmission Model	Surgical	21	Update (bootstrap), random split, external (bootstrap)	0.66 (0.62 - 0.71), 0.58, 0.47 (0.41 - 0.52)	HLT	p=0.492
Espinoza et al.[71]	30-day readmission score after cardiac surgery	Surgical	5	Development, random split	0.66 (0.63 - 0.70), 0.64 (0.61 - 0.67)	NA	

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Table 2. Model discrimination and calibration (continued)

Study	Model	Setting	Predictors, n	Cohort	Discrimination	Type calibration	Calibration
Ferraris et al.[72]	READMIT	Surgical	9	Development	0.70	HLT	5.966 (p=0.651)
Kilic et al.[73]	NR	Surgical	15	Development, random split	NR, 0.64	HLT, plot	p=0.45, p=0.57
Stuebe et al.[74]	NR	Surgical	7	Development	0.63	NA	
Tam et al.[75]	NR	Surgical	29	Development, bootstrapping	0.63, 0.65	Plot	
Khera et al.[76]	TAVR 30-Day Readmission Risk Model	TAVR	11	Development, random split, external	NR, 0.63, 0.69	HLT, RMSE, RMSE, plot	p=0.33, 0.978, 0.928
Sanchez et al.[77]	NR	TAVR	10	Development, random split	0.61, 0.60	HLT	p=0.749, p=0.403

Abbreviations: ACS: acute coronary syndrome, AF: atrial fibrillation, AH: Adventist Health Off-the-shelf model, CABG: coronary artery bypass grafting, Car: cardiac-related, CMS=centers for Medicare and Medicaid services, CRSS: CABG Readmission Risk Score, d: days, dev: development, Fim: motor and cognitive Functional Independence Measure, HF: heart failure, HFpEF: heart failure with preserved ejection fraction, HLT: Hosmer-Lemeshow test, HVD: heart valve disease, ICD: implantable cardioverter defibrillator, NA: not applicable, NR: not reported, O:E: observed:expected, PARR-30: Patients at Risk of Re-admission within 30-days, PCI: percutaneous coronary intervention, plot: calibration plot, TAVR: transcatheter aortic valve replacement, val: validation.

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Predictors

A total of 766 predictor values were estimated in the included models. The median number of predictors per model was 15 (IQR=9–28). The predictors were mostly situated in the domains medical comorbidities (n=211), disease and hospital characteristics (n=128), demographic data (n=128), laboratory values (n=97), and medical history characteristics (n=51). Age (n=47), the presence of diabetes (n=26), insurance status (n=24), length of stay (n=28), and gender (n=23) were the most prevalent predictors. There was little consistency in the definition of predictors, and most studies did not report how they were measured.

Only 18 predictors were similarly defined in multiple studies and could be pooled for the outcome readmission at 30 days (Figure 4, Supplemental Table 2A and Supplemental Figures 9–26). The coefficients of four predictors demonstrated a consistent and significant association across the different samples: chronic obstructive pulmonary disease (COPD), HF or history of HF, and valvular disease. The coefficients of eleven predictors demonstrated an overall significant association, i.e. age, female gender, arrhythmias, chronic lung disease, diabetes mellitus, cerebrovascular disease, cardiovascular accident, anemia, peripheral vascular disease, urgent admission, and infection, but this was not consistent across the samples and the prediction intervals were not significant. The effect of these predictors was mostly smaller in the HF samples.

The coefficients for most predictors could not be pooled because they had different definitions, cutoff values or reference categories. However, renal disease, including dialysis, a longer length of stay, creatinine, NT-proBNP, and previous hospital admissions demonstrated a consistent association with readmissions.

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Discussion

In this systematic review, we included 60 studies that reported the results from 81 separate clinical risk prediction models and 766 risk predictors for unplanned readmission in patients with acute heart disease. We found some promising prediction models, however, no clinical model demonstrated good discrimination (i.e. c-statistic > 0.8) in independently externally validated cohorts, regardless of the underlying patient populations. GRACE was the only model that demonstrated adequate discrimination in multiple cohorts in patients with acute coronary syndromes[21,63] and HF.[63] There was little consistency in the measurement of risk predictors.

The results of our review are in line with previous systematic reviews which have mainly focused on samples of patients with HF, AMI or focused on generic prediction models. All reviews confirm that the discrimination is generally low. Our review confirms the importance of previous HF[5,6] and previous hospital admissions[6,8] as consistent predictors for the risk of readmission. In addition two prevalent comorbidities, COPD and valve disease were also consistent predictors across the different populations. Other reviews also identified the importance of age, gender, comorbidities and certain laboratory values. These were also significant in our review but the association was not always consistent across the different populations or heterogeneously measured making comparisons difficult. As a result, no clinical risk prediction model or set of predictors that is relevant for different populations of heart disease could be identified.

Our review focused specifically on prediction models with a clinical presentation that can be used in daily practice, e.g. risk scores or nomograms. These simple models do not consider interactions between predictor values or nonlinear link functions in their predictions. This may partially explain the poor discrimination.[78] Using web applications or electronic patient records to run more complex prediction algorithms can likely offer a solution for future models. A

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recent systematic review observed an average c-statistic of 0.74 for models using electronic patient records and machine learning algorithms.[11] Our review included eleven studies[21,23,29,34,36,57,61,63,70,75,76] that developed or validated electronic tools for risk prediction and their discrimination ranged between 0.59 and 0.77. However, these electronic tools were mostly derived from score charts and nomograms.

There are also concerns about the generalizability of the prediction models. The median age of patients included in the samples was 68 years (IQR=65–75). However, older and frail patients suffer more multimorbidity and geriatric syndromes, and the distribution of predictor and outcome values will also be different than in younger samples. It is therefore unlikely that the majority of the current models will hold their value in daily clinical practice where there is a high prevalence of older patients. Only eight studies[19,23,26,28,48,50,53,77] included one or more geriatric risk factors (e.g. physical performance, dementia) as predictors for readmission. The performance of models including geriatric conditions was similar to models without these conditions. This might be explained by the relative young mean age of the samples in our review. Mahmoudi et al.[11] reported that functional and frailty status are important predictors, but were only included in a small number of studies. Frailty was not identified in any of the models in our review. It might be valuable to examine the additive value of these predictors in prediction models for patients with heart disease.

We observed high RoB in almost all clinical risk prediction models (98.8%). This was mainly because the calibration was lacking or not fully reported (e.g. only p-value of Hosmer-Lemeshow test). Furthermore, most studies performed retrospective data analyses or used data from existing sources. However, our results demonstrate that studies using these data sources had the lowest c-statistic, and that the c-statistic decreased when more predictors were tested. Databases often have missing data, misclassification bias, and random measurement error, which likely explains their average poor performance.[79] Only the SILVER-AMI study[23]

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demonstrated low RoB on all domains. However, their readmission risk calculator for older AMI patients only discriminated modestly (c-statistic = 0.65).

Our review show the current state-of-the art of risk prediction in patients with acute heart disease. The timely identification of patients with acute heart disease at risk of readmission remains challenging with the prediction models identified in this systematic review. Therefore, further research in risk prediction remains important and some recommendations for further research can be derived from this review. First, consistency is needed in the definition and measurement of predictors. More homogeneity might improve the identification of important predictors and their effect on readmission. Based on our insights, we believe that models could be improved by incorporating some key predictors, i.e. age, gender, comorbidity scores (or at least heart failure, COPD, cardiovascular disease, diabetes mellitus), admission status, readmission history, and the geriatric profile (e.g. functional status, cognitive status). Because there are a still a large number of potential predictors, a large sample size is needed to estimate the coefficients with sufficient precision, and to prevent against overfitting the models. Some selection of predictors may still be warranted, and penalized techniques (e.g. lasso regression) should be preferred over traditional selection based on p-values. Second, the results suggest that multiple predictors are associated with readmissions regardless of the underlying population. Therefore, attention might be shifted from developing new risk prediction models to updating and externally validating existing prediction models in different populations with heart disease. For example, the Adventist Health Off-the-shelf model[55] showed high discrimination rates in both the development (0.86) and validation cohort (0.85). External validation is recommended to examine the generalizability of this model in other settings. In addition, the AMI READMITS score[25], full-stay AMI readmission model[25], pre-PCI model[68], motor and cognitive Functional Independence Measure (FIM)[51], READMIT[72], 30-day readmission model of Huynh et al.[48], and the model of Engoren et al.[32] were examined in one

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study and showed reasonable c-statistics in the development (0.68 – 0.82) and validation cohorts (0.64 – 0.78). For these studies, model updating recalibration and external validation is recommended to improve the predictive performance and generalizability of these prediction models. Third, the applicability of current prediction models in daily practice is an important concern as most models had poor performance, were not replicated and had high RoB. More high-quality studies are needed that evaluate the discrimination, calibration and clinical usefulness. To limit the risk of bias as much as possible, future studies should adhere to the relevant reporting guidelines[80] and could use PROBAST[16] as a guidance to plan their study. Fourth, more complex models integrated in electronic patient records may results in better predictions.

Limitations

Although we performed an extensive literature search, we might have missed some eligible studies, particularly those published in non-English languages. We were able to perform meta-analysis for predictors that were often (≥ 5 models) reported. However, it might be possible that some less frequently mentioned predictors (e.g. geriatric predictors) are a valuable addition in clinical practice. The review included a large number of results and statistical tests which may result in an inflated alpha error. The meta-regression identified that models with less predictors had a better discrimination, but this could also be explained by overfitting models; this could not be tested.

Conclusion

A large number of clinical models have recently been developed. Although some models are promising as they demonstrated adequate to good discrimination, no model can currently be recommended for clinical practice. The lack of independently validated studies, high risk of bias and low consistency in measured predictors limit their applicability. Model updating and external validation is urgently needed.

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Data statement section

All data relevant to the study are included in the article or uploaded as supplementary information.

Contributorship Statement

Bastiaan Van Grootven and Patricia Jepma had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Bastiaan Van Grootven and Patricia Jepma contributed equally as first authors.

Concept and design: all authors; *Acquisition, analysis or interpretation of data*: Bastiaan Van Grootven, Patricia Jepma, Corinne Rijpkema, Mariska Leeflang, Joost Daams; *Drafting the manuscript*: Bastiaan Van Grootven, Patricia Jepma; *Critical revision of the manuscript*: all authors; *Analysis*: Bastiaan Van Grootven, Patricia Jepma; *Supervision:* Bianca Buurman.

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Conflict of interest

None declared.

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Figure legends

Figure 1. Flowchart

In total, 8592 records were screened and 60 studies with 81 prediction models were included.

Figure 2. PROBAST Risk of bias and applicability

The PROBAST tool[16] was used to assess the risk of bias for the participants, predictors, outcome and analysis for each model. Only one study demonstrated low risk of bias on all domains.

Figure 3. Meta-analysis of prediction models

Random-effect models were used to pool similar models reported in independent cohorts. For the HOSPITAL score, the discrimination for the HF and AMI samples were similar (0.65 and 0.64). For GRACE, the discrimination for the AMI and reinfarction samples were similar (0.77 and 0.74), and was higher for the HF sample (0.83). Only GRACE demonstrated adequate discrimination in external cohorts.

Figure 4. Predictors of unplanned hospital readmission

The plot provides an overview of the random-effects meta-analyses that were performed for predictors who were similarly defined for the outcome unplanned hospital readmission at 30 days follow-up. See Supplemental table 2A and Supplemental figures 9-26 for more details.

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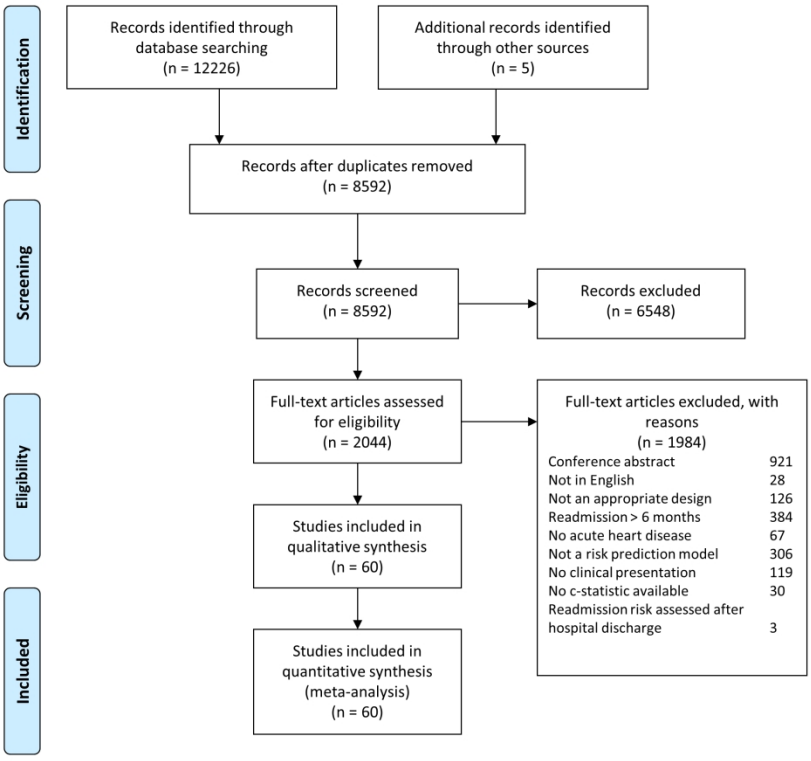
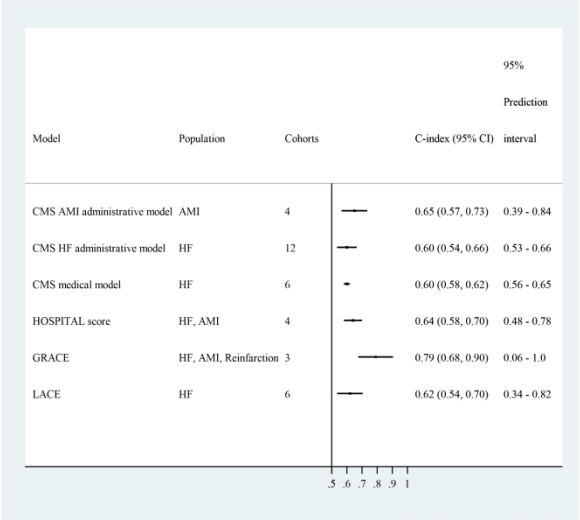


Flowchart
In total, 8592 records were screened and 60 studies with 81 prediction models were included.

190x275mm (300 x 300 DPI)

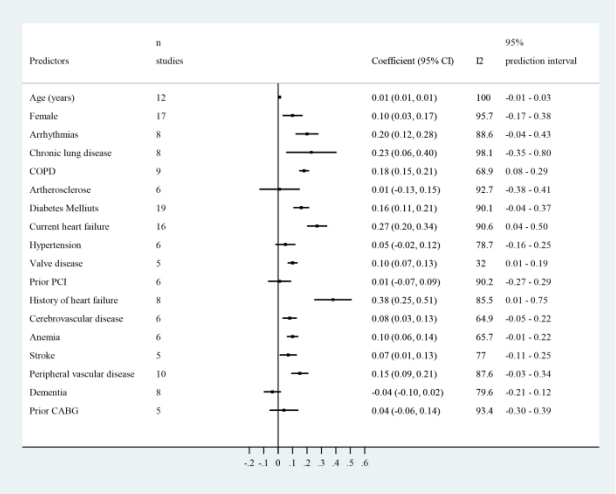
PROBAST Risk of bias and applicability
The PROBAST tool15 was used to assess the risk of bias for the participants, predictors, outcome and analysis for each model. Only one study demonstrated low risk of bias on all domains.

39x51mm (300 x 300 DPI)



Meta-analysis of prediction models
Random-effect models were used to pool similar models reported in independent cohorts. For the HOSPITAL score, the discrimination for the HF and AMI samples were similar (0.65 and 0.64). For GRACE, the discrimination for the AMI and reinfarction samples were similar (0.77 and 0.74), and was higher for the HF sample (0.83). Only GRACE demonstrated adequate discrimination in external cohorts.

338x190mm (300 x 300 DPI)



Predictors of unplanned hospital readmissionThe plot provides an overview of the random-effects meta-analyses that were performed for predictors who were similarly defined for the outcome unplanned hospital readmission at 30 days follow-up. See Supplemental table 2A and Supplemental figures 9-26 for more details.

338x190mm (300 x 300 DPI)

Supplemental materials

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Supplemental Text 1. Search string

Ovid MEDLINE(R) ALL 1946 to November 21, 2019
Search date: 25 August 2020

#	Searches	Results
1	exp "predictive value of tests"/ or roc curve/ or exp Decision Support Techniques/	321482
2	("signal to noise" or roc curve or reiver operating or predict*).ab,kf,ti.	1644590
3	(decision adj2 (aid? or model* or clinical* or support or system? or tool?)).ab,kf,ti.	56262
4	decision?.ab,kf,ti.	381353
5	logistic models/	139814
6	(logistic model* or regression).ab,kf,ti.	758909
7	5 or 6	814876
8	4 and 7	23040
9	or/1-3,8	1861041
10	patient readmission/	17534
11	((readmission or readmitted or re-admission or re-admitted) and (hospital* or prehospital*)).ab,kf,ti.	20747
12	((readmission or readmitted or re-admission or re-admitted) adj2 (patient? or client)).ab,kf,ti.	4515
13	(rehospitali?ation? or re-hospitali?ation? or rehospitali?ed or re-hospitali?ed).ab,kf,ti.	7834
14	or/10-13	35723
15	exp cardiovascular system/ or exp cardiovascular diseases/	3001695
16	(cardiac* or cardio* or myocard* or coronary or heart).ab,jw,kf,ti.	2161260
17	(diastolic or systolic or edema or dyspnea or renocardiac or Stenocardia* or angor or angina* or atherioscleros* or atheroscleros* or arteroscleros* or Arterioscleros* or Kounis syndrome or ST elevation or STEMI or valve* or aortic or stenosis or Leopard Syndrome or Noonan Syndrome with Multiple Lentigines or Multiple Lentigines Syndrome or Obstructive Subaortic Conus or Absent Right Atrioventricular Connection or arrhythmia* or sinus or sinoatrial or atria* or auricular or atrioventricular or ventricular or bradycardia or Bradyarrhythmia* or tachycardia* or fibrillation* or flutter* or Right Bundle Branch Block or Brugada or extrasystole* or (commotion adj1 cordis) or Auriculo-Ventricular Dissociation or Auriculo Ventricular Dissociation or Atrioventricular Dissociation or A-V Dissociation or AV Dissociation or syncope or (Andersen adj2 Tawil) or QT Syndrome or (jervell adj2 lange) or Prolonged QT Interval or (romano adj1 ward) or parasystole or Pre-Excitation or Preexcitation or (Lown adj2 Ganong) or Short PR-Normal QRS Complex Syndrome or Short PR Normal QRS Complex Syndrome or Wolff-Parkinson-White or WPW Syndrome or Idioventricular Rhythm or Torsade de Pointes).ab,hw,kf,ti.	1642025
18	or/15-17	4136701
19	(predict* adj3 risk?).ab,kf,ti.	57669
20	retrospective.ab,hw,kf,ti.	1006259
21	(admission or hospitali?ation or discharge).ab,hw,kf,ti.	529444
22	and/18-21	692
23	and/9,14,18	3482
24	(ISRCTN96643197 or ChiCTR1900026250 or NCT04008914 or NCT03791541 or NCT03300791 or "CTRI/2016/10/007411" or "CTRI/2014/06/004690" or NCT03949439 or NCT03905226 or NCT00344513 or NCT01755052 or NCT02041585).ab,kf,ti.	9
25	((OPERA or REIC or FIgARO or PREDIC or optimize-hf or ten-hms or tele-hf or readmits or silver-ami or dc promis or KorAHF) adj3 (trial or study)).ab,kf,ti.	118
26	or/22-25	4209

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Ovid Embase Classic+Embase <1947 to 2020 August 24>
Search date: 25 August 2020

#	Searches	Results
1	*predictive value/ or *receiver operating characteristic/ or exp *Decision Support system/	21786
2	("signal to noise" or roc curve or reiver operating or predict*).ab,kw,ti.	2224346
3	(decision adj2 (aid? or model* or clinical* or support or system? or tool?)).ab,kw,ti.	80866
4	decision?.ab,kw,ti.	531706
5	*logistic regression analysis/	1018
6	(logistic model* or regression).ab,kw,ti.	1107281
7	5 or 6	1107307
8	4 and 7	33059
9	or/1-3,8	2305864
10	*hospital readmission/	13570
11	((readmission or readmitted or re-admission or re-admitted) and (hospital* or prehospital*)).ab,kw,ti.	39681
12	((readmission or readmitted or re-admission or re-admitted) adj2 (patient? or client)).ab,kw,ti.	9596
13	(rehospitali?ation? or re-hospitali?ation? or rehospitali?ed or re-hospitali?ed).ab,kw,ti.	14392
14	or/10-13	56536
15	exp *cardiovascular system/	630584
16	(cardiac* or cardio* or myocard* or coronary or heart).ab,jw,kw,ti.	3123455
17	(diastolic or systolic or edema or dyspnea or renocardiac or Stenocardia* or angor or angina* or atherioscleros* or atheroscleros* or arteroscleros* or Arterioscleros* or Kounis syndrome or ST elevation or STEMI or valve* or aortic or stenosis or Leopard Syndrome or Noonan Syndrome with Multiple Lentigines or Multiple Lentigines Syndrome or Obstructive Subaortic Conus or Absent Right Atrioventricular Connection or arrhythmia* or sinus or sinoatrial or atria* or auricular or atrioventricular or ventricular or bradycardia or Bradyarrhythmia* or tachycardia* or fibrillation* or flutter* or Right Bundle Branch Block or Brugada or extrasystole* or (commotion adj1 cordis) or Auriculo-Ventricular Dissociation or Auriculo Ventricular Dissociation or Atrioventricular Dissociation or A-V Dissociation or AV Dissociation or syncope or (Andersen adj2 Tawil) or QT Syndrome or (jervell adj2 lange) or Prolonged QT Interval or (romano adj1 ward) or parasystole or Pre-Excitation or Preexcitation or (Lown adj2 Ganong) or Short PR-Normal QRS Complex Syndrome or Short PR Normal QRS Complex Syndrome or Wolff-Parkinson-White or WPW Syndrome or Idioventricular Rhythm or Torsade de Pointes).ab,hw,kw,ti.	2756334
18	or/15-17	4713190
19	(predict* adj3 risk?).ab,kw,ti.	90323
20	retrospective.ab,hw,kw,ti.	1280890
21	(admission or hospitali?ation or discharge).ab,hw,kw,ti.	1117031
22	and/18-21	991
23	and/9,14,18	6851
24	(ISRCTN96643197 or ChiCTR1900026250 or NCT04008914 or NCT03791541 or NCT03300791 or "CTRI/2016/10/007411" or "CTRI/2014/06/004690" or NCT03949439 or NCT03905226 or NCT00344513 or NCT01755052 or NCT02041585).ab,cn,kw,ti.	31
25	((OPERA or REIC or FIgARO or PREDIC or optimize-hf or ten-hms or tele-hf or readmits or silver-ami or dc promis or KorAHF) adj3 (trial or study)).ab,kw,ti.	285
26	or/22-25	8017

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Supplemental Text 2. Data items

The following data was collected in accordance with the CHARMS checklist (Critical Appraisal and Data Extraction for Systematic Reviews): citation, source of data, country, study design, setting, participant description, sample characteristics, study dates, outcome definition, follow-up, number and type of predictors, definition and method for measurement of predictors, timing of predictor measurement, handling of predictors in the modelling, number of participants and number of outcomes/events, calibration, discrimination, classification, methods used for testing model performance, final multivariable model results (regression coefficients, intercept, baseline survival, model performance), and model presentation.

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Supplemental Table 1A. Risk of Bias

Study	Model	Risk of bias				Overall Risk of bias	Applicability			Overall applicability
		Participants	Predictors	Outcome	Analysis		Participants	Predictors	Outcome	
Barnett et al.	Model validation	-	?	+	-	-	+	+	+	+
	Model update	-	?	+	-	-	+	+	+	+
Sanchez et al.	NR	-	?	?	-	-	+	+	+	+
Deo et al.	30-days CABG Readmission Calculator	-	-	-	-	-	+	+	?	?
Tan et al.	NR	-	-	-	-	-	+	+	-	-
Wang et al.	NR	-	?	?	-	-	+	+	+	+
Rosenblum et al.	The STS PROM score	-	?	-	-	-	+	+	+	+
Dodson et al.	SILVER-AMI 30-day readmission calculator	+	+	+	+	+	+	+	+	+
Lim et al.	NR	+	?	-	-	-	+	+	-	-
Kini et al.	NR	-	-	-	?	-	+	+	+	+
Nguyen et al.	AMI READMITS score	-	-	+	-	-	+	+	+	+
	Full-stay AMI model	-	-	+	-	-	+	+	+	+
	CMS AMI administrative model	-	?	+	-	-	+	+	+	+
Cediel et al.	TARRACO Risk Score	-	-	-	-	-	+	+	-	-
Brown et al.	STS 30-day Readmission Model	+	?	?	-	-	+	+	?	?
	STS Augmented Clinical Model	-	?	+	-	-	+	+	?	?
Khera et al.	TAVR 30-Day Readmission Risk Model	-	-	?	-	-	+	+	?	?
Tam et al.	NR	-	-	?	-	-	+	+	?	?
Atzema et al.	AFTER Part 2 scoring system	-	-	-	-	-	+	+	-	-
Stuebe et al.	NR	-	+	-	-	-	+	+	+	+
Huynh et al.	NR	-	-	?	-	-	+	+	+	+
Zywot et al.	CABG Risk Scale	-	?	?	-	-	+	+	+	+

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Supplemental Table 1. Risk of bias (continued)

Study	Model	Risk of bias				Overall Risk of bias	Applicability			Overall applicability
		Participants	Predictors	Outcome	Analysis		Participants	Predictors	Outcome	
Cox et al.	CMS HF medical model	-	+	+	-	-	+	+	+	+
	CMS HF administrative model	-	?	+	-	-	+	+	+	+
Zitser-Gurevich et al.	NR	?	+	+	-	-	+	+	+	+
Ahmad et al.	CMS HF administrative model	-	+	+	-	-	+	+	+	+
Minges et al.	NR	-	+	+	-	-	+	+	+	+
Pack et al.	NR	-	-	-	-	-	+	+	+	+
Benuzillo et al.	CRSS	-	-	+	-	-	+	+	+	+
Kitamura et al.	FIM	-	?	-	-	-	+	+	+	+
Lahewala et al.	CHADS2	-	?	+	-	-	+	+	+	+
	CHA2DS-VASc	-	?	+	-	-	+	+	+	+
Formiga et al.	CMS HF medical model	-	?	-	-	-	+	+	+	+
Leong et al.	30-day HF readmission risk score	-	+	-	-	-	+	+	-	-
Burke et al.	HOSPITAL score	-	-	-	-	-	+	+	+	+
Kilic et al.	NR	-	?	-	-	-	+	+	+	+
Moulder et al.	NR	+	+	-	-	-	+	+	+	+
Chotechuang et al.	GRACE	-	-	-	-	-	+	+	-	-
Yazdan-Ashoori et al.	LACE	?	?	+	-	-	+	+	+	+
	CMS HF administrative model	?	?	+	-	-	+	+	+	+
Oliver-McNeil et al.	ICD Readmission-Risk Score	-	?	-	-	-	+	+	+	+
Sudhakar et al.	CMS HF medical model	-	+	-	-	-	+	+	+	+
Raposeiras-Roubín et al.	GRACE	-	-	-	-	-	+	+	-	-
Betihavas et al.	NR	-	?	-	-	-	+	+	-	-
Lancey et al.	NR	-	?	-	-	-	+	+	+	+
Moretti et al.	EuroHeart PCI score	-	+	-	-	-	+	+	-	-
Hilbert et al.	HF decision tree	-	+	+	-	-	+	+	+	+
	AMI decision tree	-	+	+	-	-	+	+	+	+

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Supplemental Table 1. Risk of bias (continued)

Study	Model	Risk of bias				Overall Risk of bias	Applicability			Overall applicability
		Participants	Predictors	Outcome	Analysis		Participants	Predictors	Outcome	
Wang et al.	LACE	-	?	-	-	-	+	+	+	+
Rana et al.	HOSPITAL score	-	?	-	-	-	+	+	-	-
	Elixhauser index	-	?	-	-	-	+	+	-	-
Hummel et al.	CMS HF medical model	?	+	+	-	-	+	+	+	+
Salah et al.	ELAN-HF score	-	?	-	-	-	+	+	-	-
Wasfy et al.	Pre-PCI model	-	+	?	-	-	+	+	+	+
Engoren et al.	NR	-	?	+	-	-	+	+	+	+
Au et al.	Administrative Claims Model: HF 30-day mortality	-	?	?	-	-	+	+	?	?
	Charlson Comorbidity Score	-	?	?	-	-	+	+	?	?
	CMS HF administrative model	-	?	?	-	-	+	+	?	?
	LACE	-	?	?	-	-	+	+	?	?
Krumholz et al.	CMS AMI medical model	+	-	+	-	-	+	+	+	+
	CMS AMI administrative model	-	-	+	-	-	+	+	+	+
Amarasingham et al.	Tabak mortality score	-	?	?	-	-	+	+	+	+
	CMS HF administrative model	-	?	?	-	-	+	+	+	+
	ADHERE	-	?	?	-	-	+	+	+	+
Keenan et al.	CMS HF administrative model	-	-	+	-	-	+	+	+	+
	CMS HF medical model	+	-	-	-	-	+	+	+	+
Ferraris et al.	READMIT	?	+	+	-	-	+	+	+	+
Delgado et al.	15-day CV readmission risk score	?	+	-	-	-	+	+	-	-
	30-day CV readmission risk score	?	+	-	-	-	+	+	-	-
Espinoza et al.	30-day readmission score after cardiac surgery	+	?	?	-	-	+	+	+	+

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Supplemental Table 1. Risk of bias (continued)

Study	Model	Risk of bias				Overall Risk of bias	Applicability			Overall applicability
		Participants	Predictors	Outcome	Analysis		Participants	Predictors	Outcome	
Reed et al.	CMS HF administrative model	-	?	?	-	-	+	+	+	+
	PARR-30	-	?	?	-	-	+	+	+	+
	LACE	-	?	?	-	-	+	+	+	+
	Hasan	-	?	?	-	-	+	+	+	+
	AH model	-	?	?	-	-	+	+	+	+
Ibrahim et al.	HOSPITAL score	-	+	-	-	-	+	+	+	+
	LACE	-	+	-	-	-	+	+	+	+
	LACE+ index	-	+	-	-	-	+	+	+	+
Bardhan et al.	NR	-	-	-	-	-	+	+	-	-
Asche et al.	NR	-	?	-	-	-	+	+	?	?
Li et al.	NR	-	?	+	-	-	+	+	+	+
Hammill et al.	CMS HF administrative model	-	-	+	?	-	+	+	+	+
Frizzell et al.	CMS HF administrative model	-	-	+	-	-	+	+	+	+

Legend: the overall risk of bias assessment is located in the main paper.

Abbreviations: AH: Adventist hositals, CABG: coronary artery bypass grafting, CMS=centers for Medicare and Medicaid services, CRSS: CABG Readmission Risk Score, Fim: motor and cognitive Functional Independence Measure, HF: heart failure, ICD: implantable cardioverter defibrillator, NR: not reported, PARR-30: Patients at Risk of Re-admission within 30-days, PCI: percutaneous coronary intervention, TAVR: transcatheter aortic valve replacement

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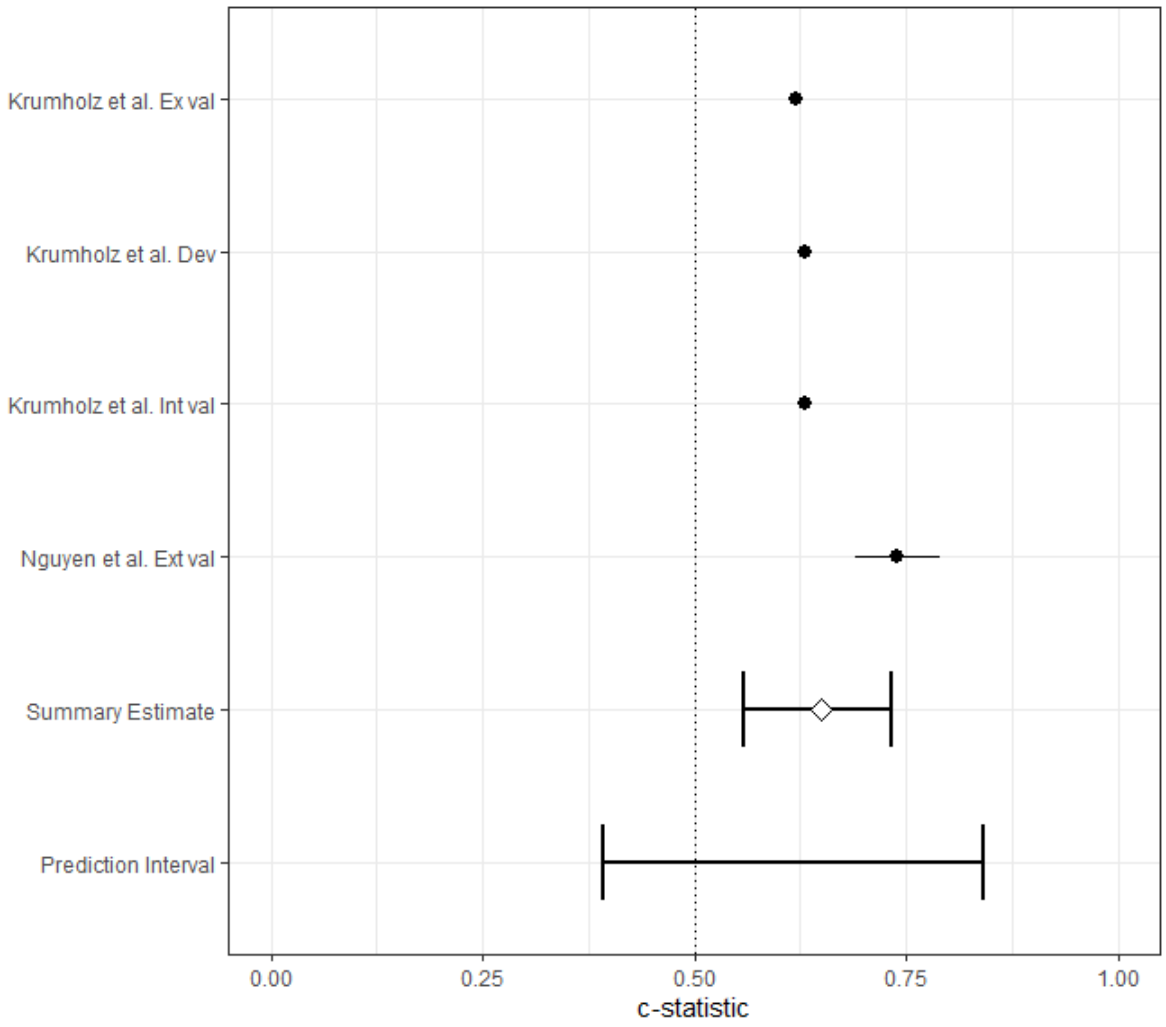
Supplemental Figure 1. Meta-analysis of CMS AMI administrative model



Legend: The CMS acute myocardial infarction (AMI) administrative model was evaluated in four independent cohorts in two studies: 0.65, 95% CI 0.56 to 0.73, 95% prediction interval 0.39 to 0.84. Standard errors were derived from the reported c-statistics, sample size and observed events. The readmission rate was missing for the internal validation cohort in the Krumholz et al. study, and this data was needed to derive the observed events. The development and validation cohort in the Krumholz et al. study were similar samples and we used the average readmission rate from these two cohorts to impute the missing readmission rate for the internal validation.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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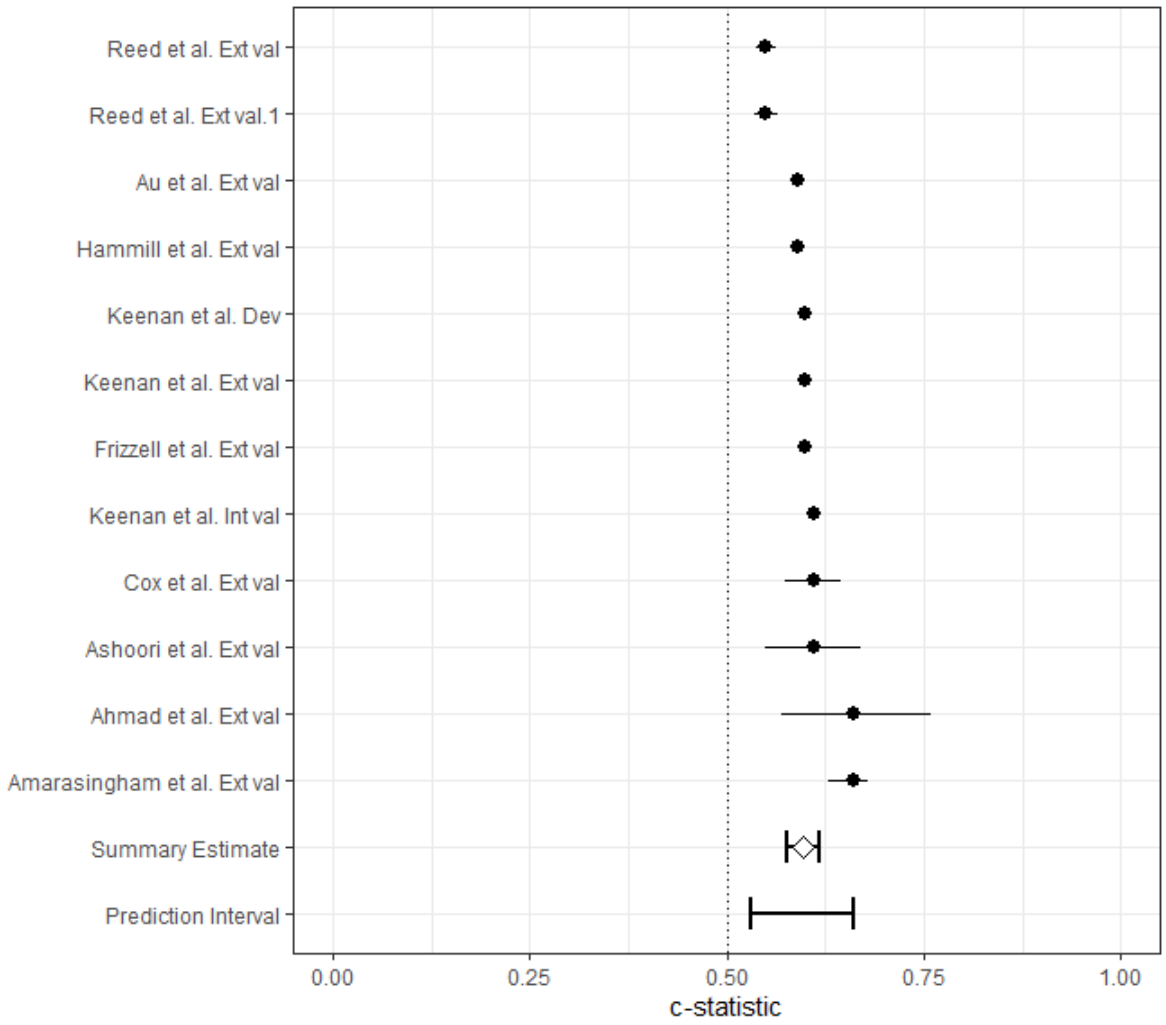
Supplemental Figure 2. Meta-analysis of CMS HF administrative model



Legend: The CMS heart failure (HF) administrative model was evaluated in twelve independent cohorts in nine studies: 0.60, 95% CI 0.58 to 0.62, 95% prediction interval 0.53 to 0.66. Standard errors were derived from the reported c-statistics, sample size and observed events. The readmission rate was missing for the internal validation cohort in the Keenan et al. study, and this data was needed to derive the observed events. The development and validation cohort in the Keenan et al. study were similar samples and we used the average readmission rate from these two cohorts to impute the missing readmission rate for the internal validation.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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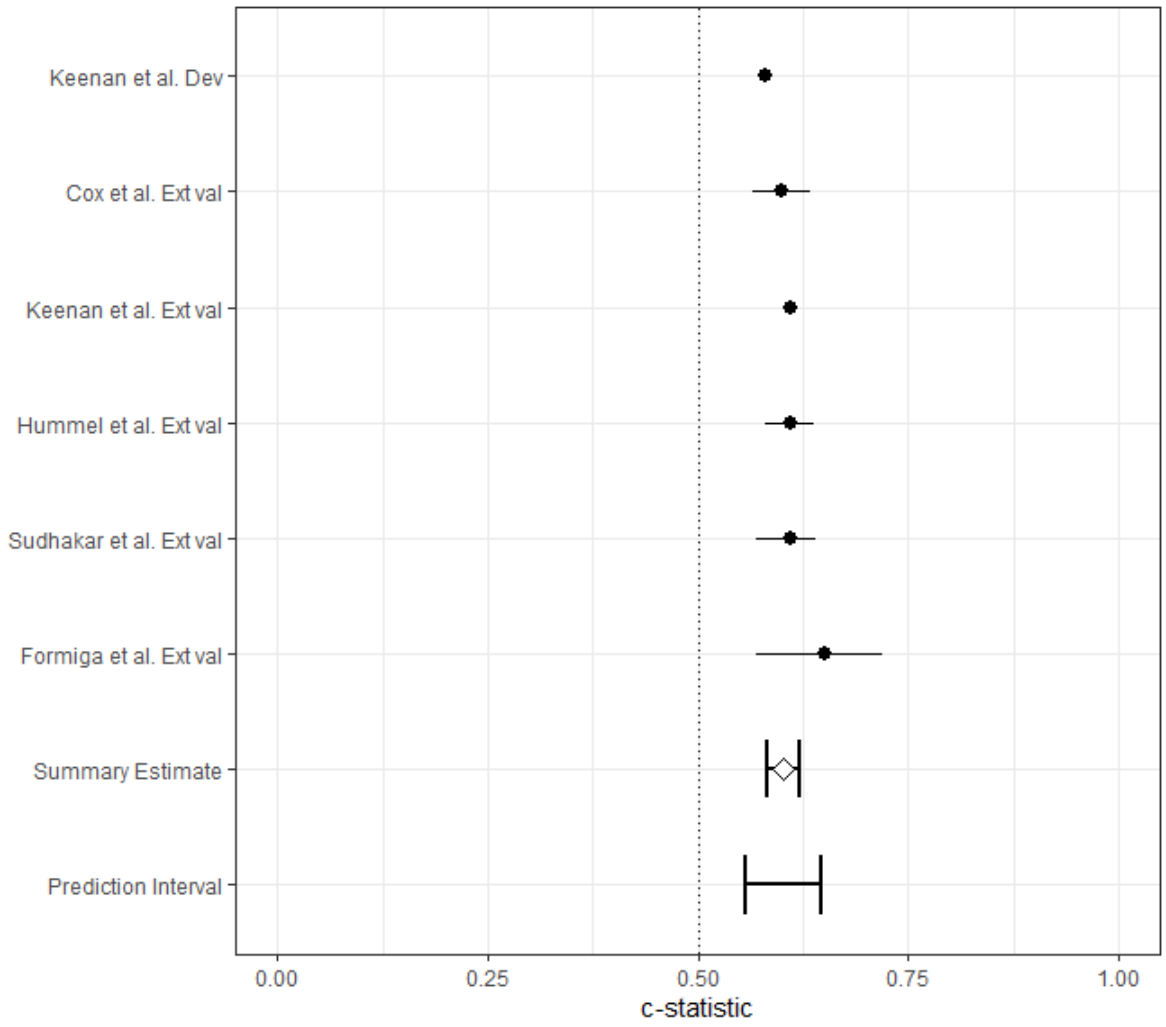
Supplemental Figure 3. Meta-analysis of CMS medical model



Legend: The CMS medical model was evaluated in six independent cohorts in five studies: 0.60, 95% CI 0.58 to 0.62, 95% prediction interval 0.56 to 0.65. Standard errors were derived from the reported c-statistics, sample size and observed events.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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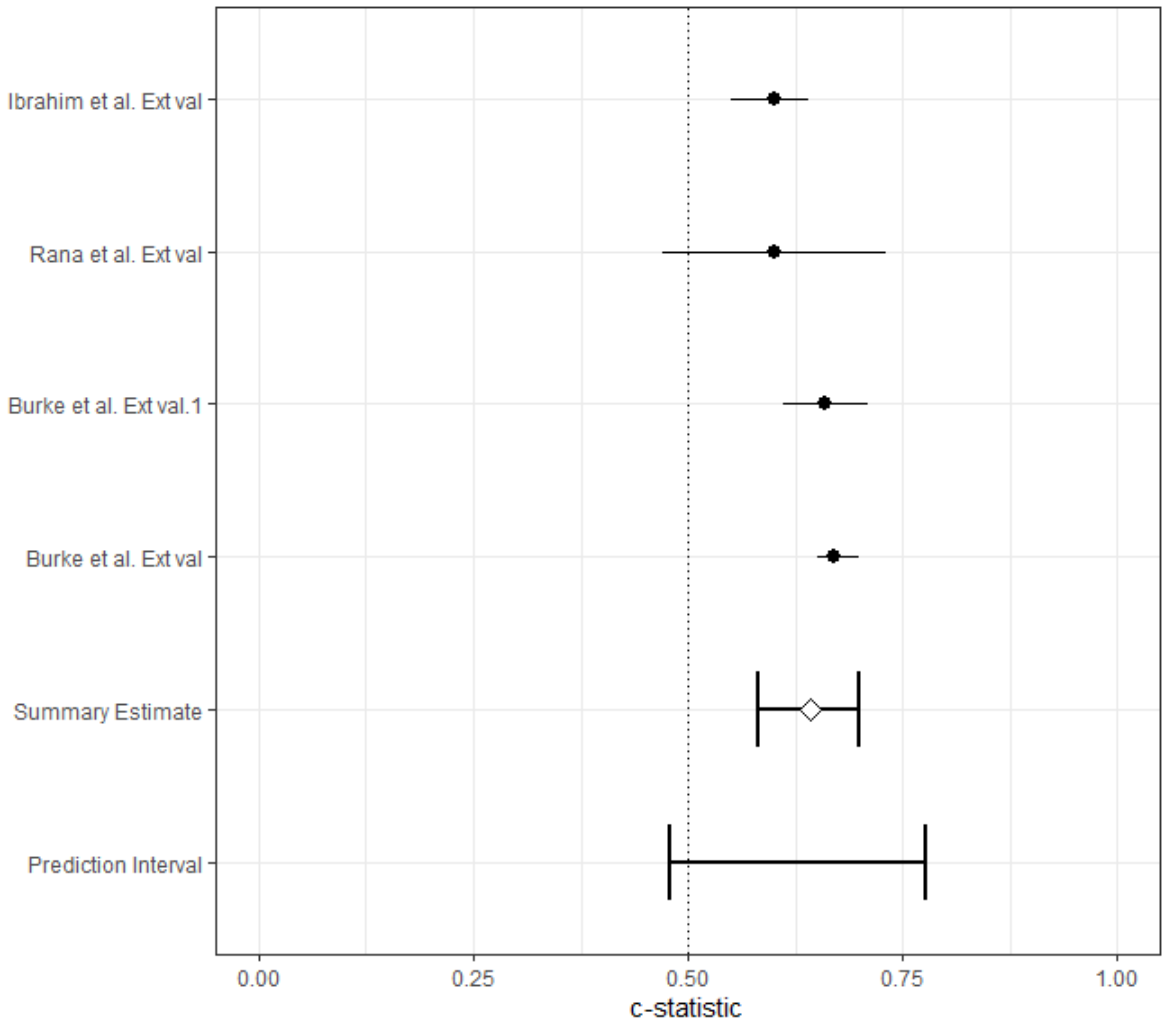
Supplemental Figure 4. Meta-analysis of HOSPITAL score



Legend: The HOSPITAL score was evaluated in four independent cohorts in three studies: 0.64, 95% CI 0.58 to 0.70, 95% prediction interval 0.48 to 0.78. Standard errors were derived from the reported c-statistics, sample size and observed events.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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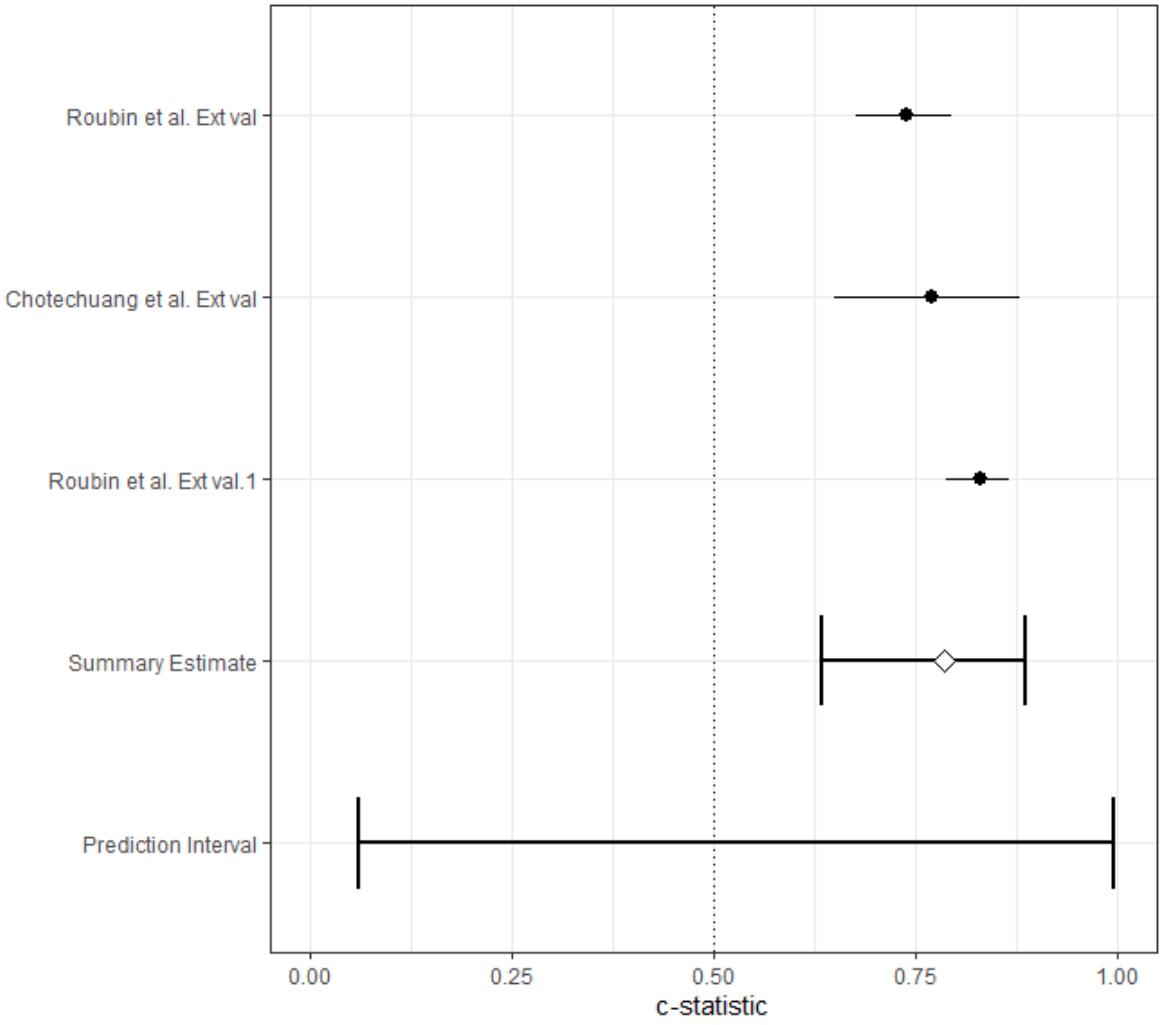
Supplemental Figure 5. Meta-analysis of GRACE



Legend: GRACE was evaluated in four independent cohorts in three studies: 0.79, 95% CI 0.63 to 0.86, 95% prediction interval 0.06 to 1.00. Standard errors were derived from the reported c-statistics, sample size and observed events.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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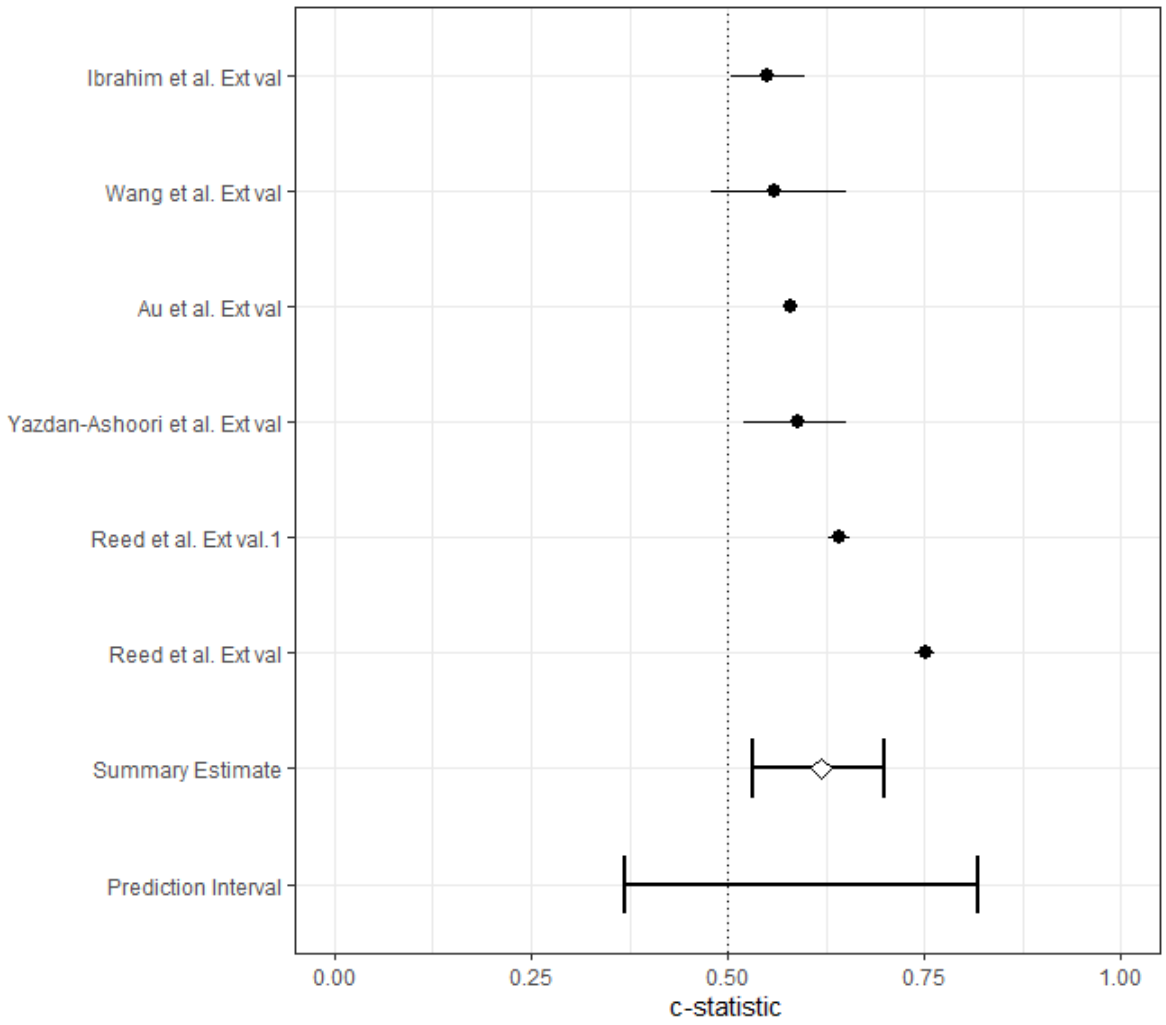
Supplemental Figure 6. Meta-analysis of LACE



Legend: LACE was evaluated in six independent cohorts in five studies: 0.62, 95% CI 0.53 to 0.70, 95% prediction interval 0.37 to 0.82. Standard errors were derived from the reported c-statistics, sample size and observed events.

Abbreviations: Ext val: external validation, Int val: internval validation, Dev: Development

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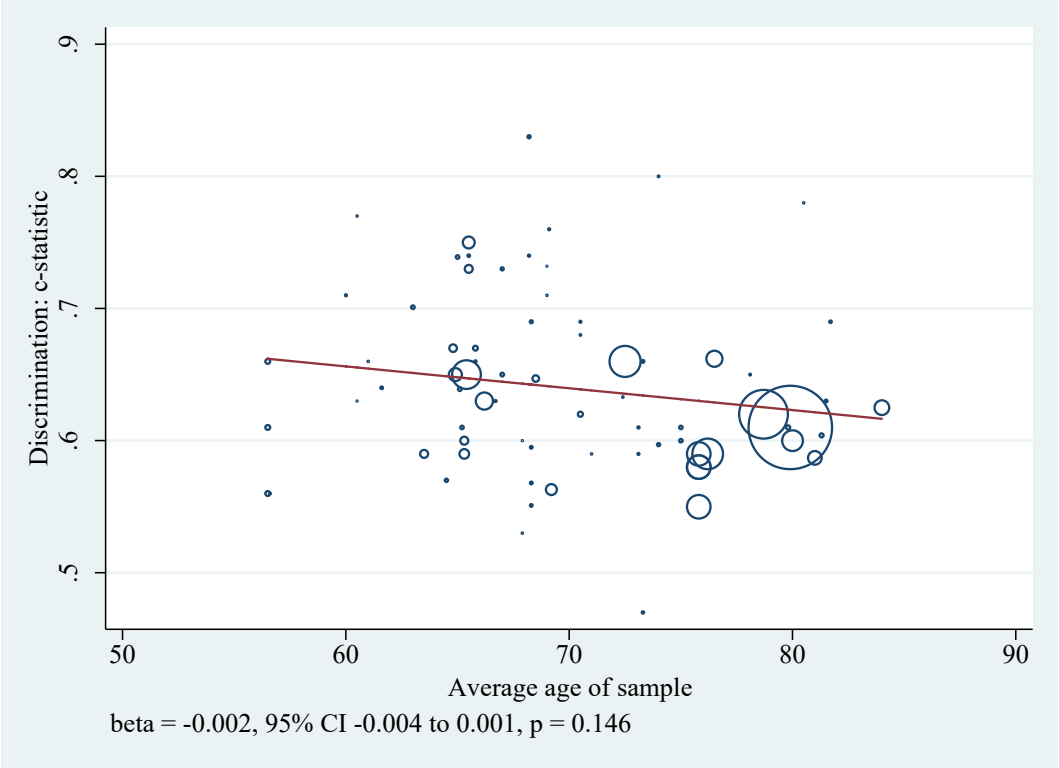
Supplemental Figure 7. Age as moderator



Legend: A meta-regression with average sample age as covariate was performed. The outcome was the discrimination (c-statistic). There is no association between the sample age and the discrimination.

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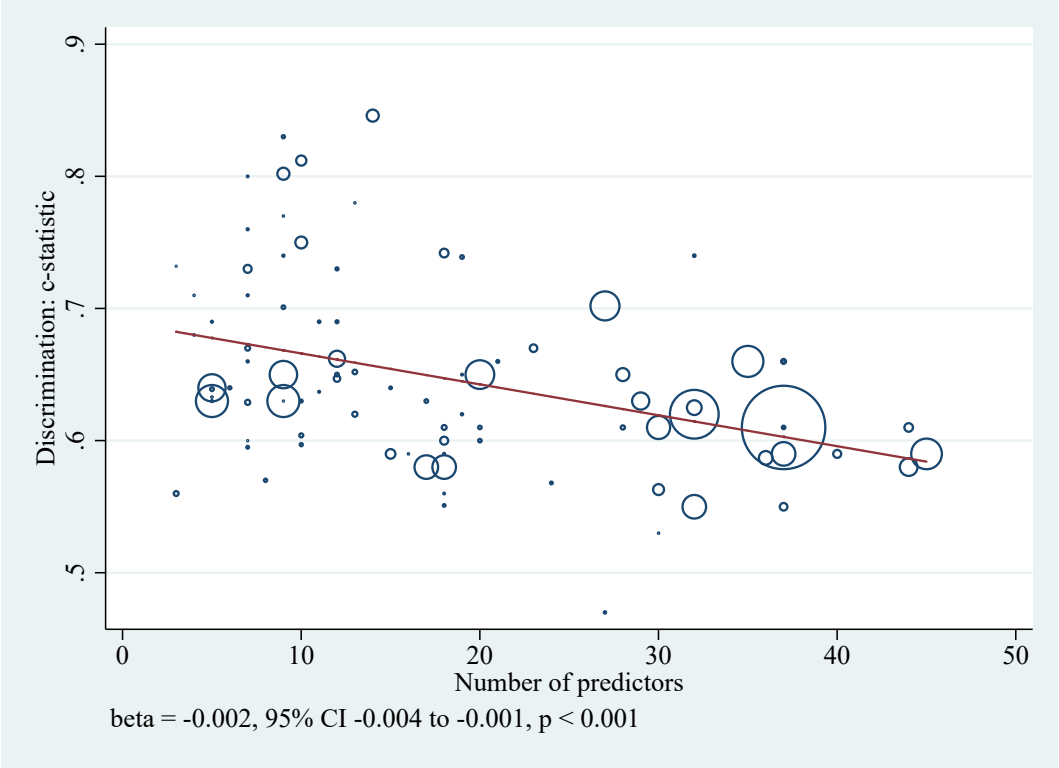
Supplemental Figure 8. Number of predictors as moderator



Legend: A meta-regression with the number of predictors as covariate was performed. The outcome was the discrimination (c-statistic). The discrimination increases with the number of predictors decreases. This association is significant.

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Supplemental Table 1B. Subgroup analyses

Moderators	N	C-statistic	95% CI	Test for subgroup difference
Population				p = 0.835
- Surgical	17	0.627	0.605 – 0.649	
- TAVR	2	0.645	0.560 – 0.729	
- Heart failure	45	0.641	0.623 – 0.658	
- Acute myocardial infarction	16	0.671	0.644 – 0.697	
- Arrhythmias	5	0.640	0.630 – 0.649	
- Valve disease	1	0.650	0.641 – 0.659	
- ICD implantation	1	0.710	0.605 – 0.815	
- Reinfarction	1	0.740	0.681 – 0.799	
- Acute coronary syndrome	1	0.590	0.475 – 0.705	
- Mixed	3	0.660	0.656 – 0.664	
Data source				p = 0.014
- Registry	17	0.613	0.602 – 0.624	
- Administrative database	17	0.664	0.635 – 0.693	
- Hospital database	18	0.612	0.593 – 0.632	
- Prospective cohort	16	0.640	0.613 – 0.667	
- Retrospective cohort	23	0.682	0.653 – 0.710	
- Secondary analysis	2	0.695	0.497 – 0.894	
Endpoint				p = 0.589
- 15 days	1	0.633	0.539 – 0.727	
- 28 days	1	0.800	0.720 – 0.880	
- 30 days	78	0.642	0.631 – 0.654	
- 90 days	8	0.645	0.632 – 0.657	
- 100 days	1	0.652	0.626 – 0.678	
- 180 days	4	0.656	0.591 – 0.721	
Outcome definition				p = 0.144
- All cause	65	0.644	0.633 – 0.656	
- Cardiac related	18	0.676	0.628 – 0.723	

Legend: Subgroup analyses were performed. The outcome was the discrimination (c-statistic). The discrimination is moderator by the data source that was used in the study, but not by the population, outcome definition and endpoint.

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Supplemental Table 2A. Summary of meta-analyses predictors

Predictor	Coefficient, 95% CI	Prediction interval
Age (years)	0.01, 0.00 - 0.01	-0.01 - 0.03
Female	0.10, 0.03 - 0.17	-0.17 - 0.38
Arrhythmias	0.20, 0.12 - 0.28	-0.04 - 0.43
Chronic lung disease	0.23, 0.05 - 0.40	-0.35 - 0.80
Chronic obstructive pumonary disease	0.18, 0.15 - 0.22	0.08 - 0.29
Artherosclerose	0.01, -0.13 - 0.15	-0.38 - 0.41
Diabetes mellitus	0.16, 0.11 - 0.22	-0.04 - 0.37
Current heart failure	0.27, 0.20 - 0.34	0.04 - 0.50
Hypertension	0.05, -0.02 - 0.12	-0.16 - 0.25
Valve disease	0.10, 0.06 - 0.13	0.01 - 0.19
Prior percutaneous coronary intervention	0.01, -0.07 - 0.09	-0.27 - 0.29
History of heart failure	0.38, 0.25 - 0.51	0.01 - 0.75
Cerebrovascular disease	0.08, 0.03 - 0.13	-0.05 - 0.22
Anemia	0.10, 0.06 - 0.14	-0.01 - 0.22
Stroke	0.07, 0.01 - 0.13	-0.11 - 0.25
Peripheral vascular disease	0.15, 0.09 - 0.21	-0.03 - 0.34
Dementia	-0.04, -0.10 - 0.02	-0.21 - 0.12
Prior Coronary Artery Bypass Graft	0.04, -0.06 - 0.14	-0.30 - 0.39

Legend: A meta-analyses was performed with the outcome 30 day unplanned hospital readmissions. The forest plots are detailed below. Please note that there are some small differences with the data reported in Figure 4 in the main manuscript. This is because of a difference in rounding the decimal points by the software.

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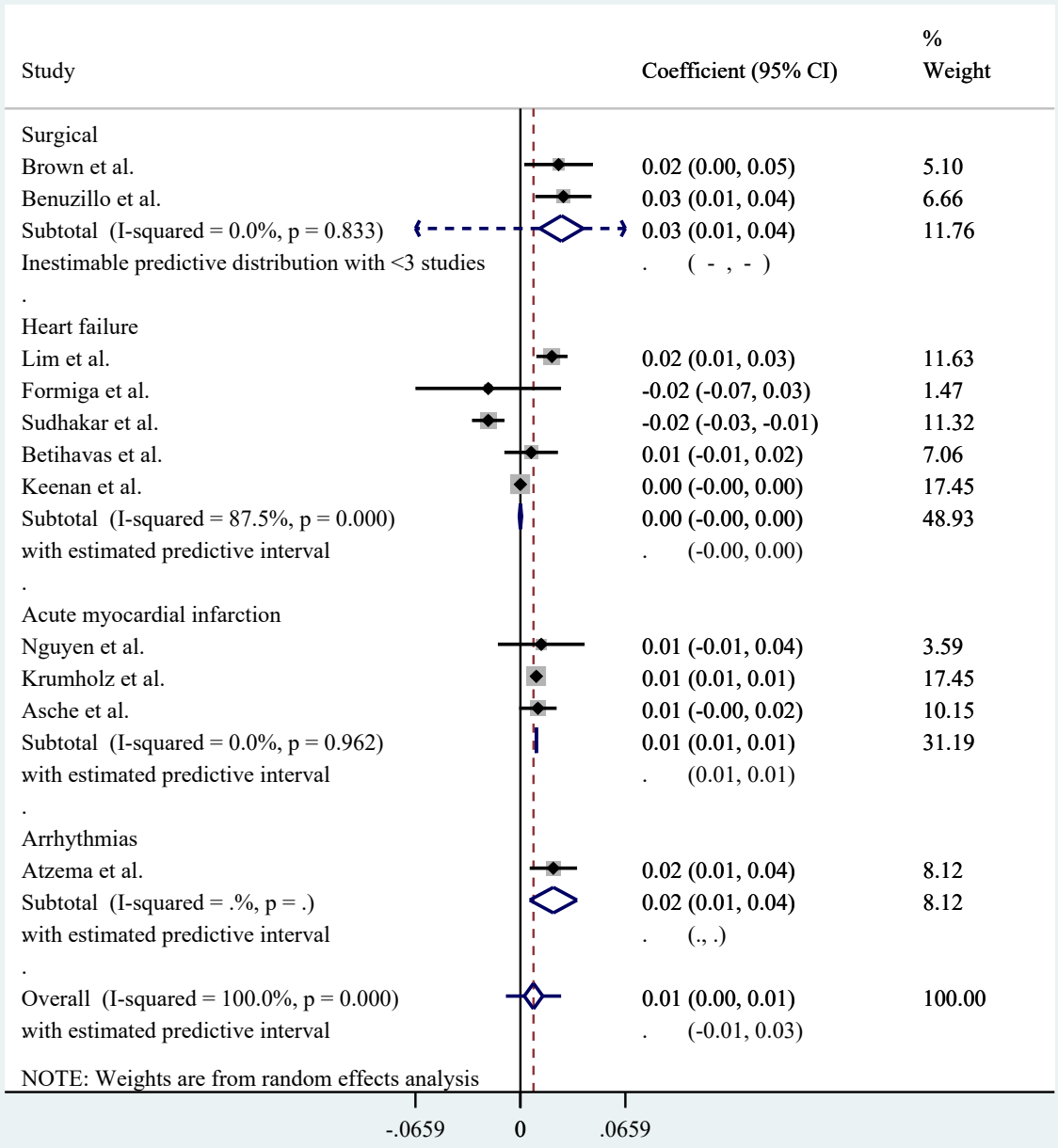
Supplemental Figure 9. Age as predictor



Legend: Two studies were not included in the analysis. One study had a missing standard error and one study reported transformed values. The values of their coefficients were: -0.001, and log(0,502).

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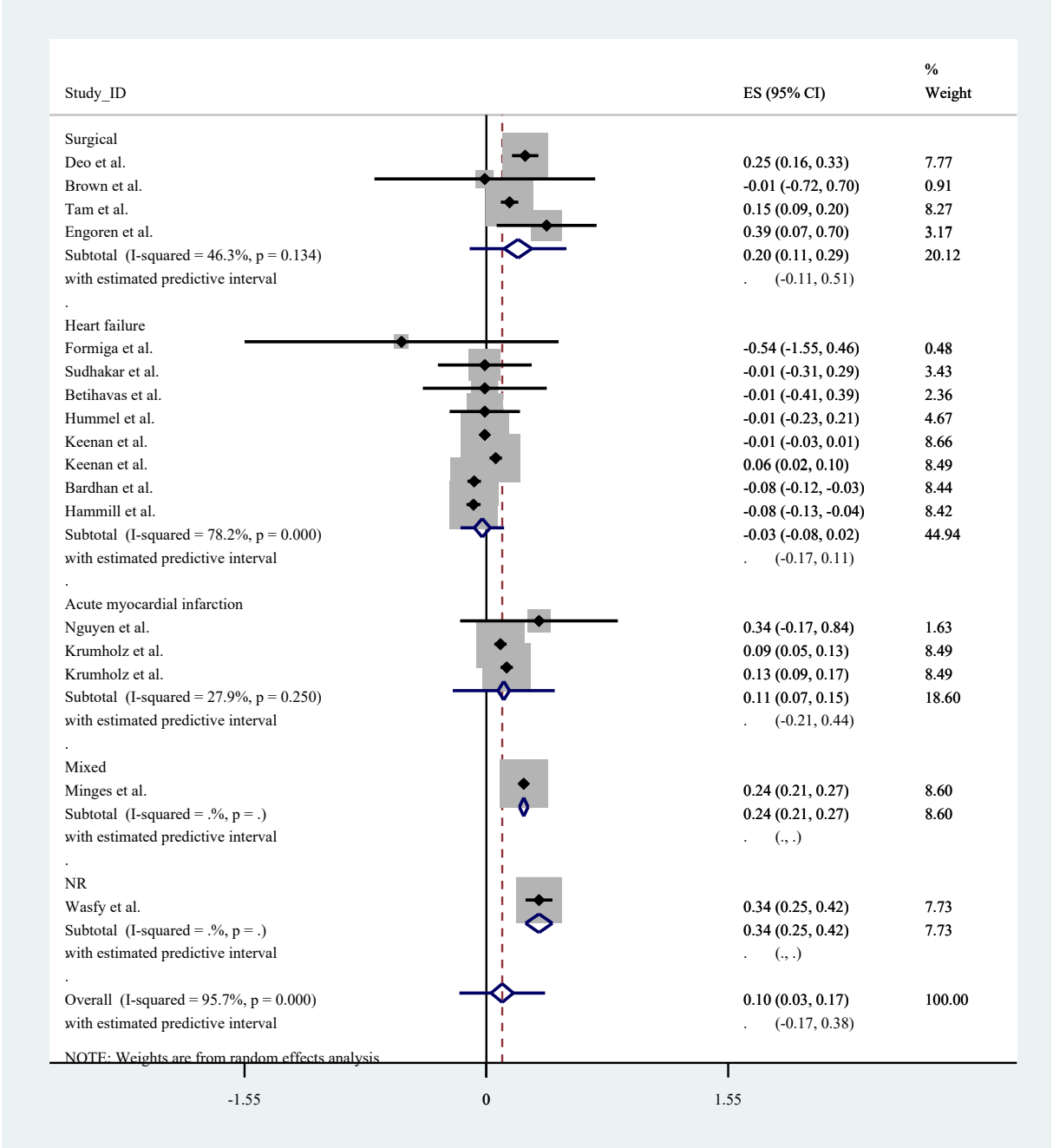
Supplemental Figure 10. Female as predictor



Legend: Two studies were not included in the analysis because the standard errors were missing. The values of their coefficients were: -0.28 and 0.206.

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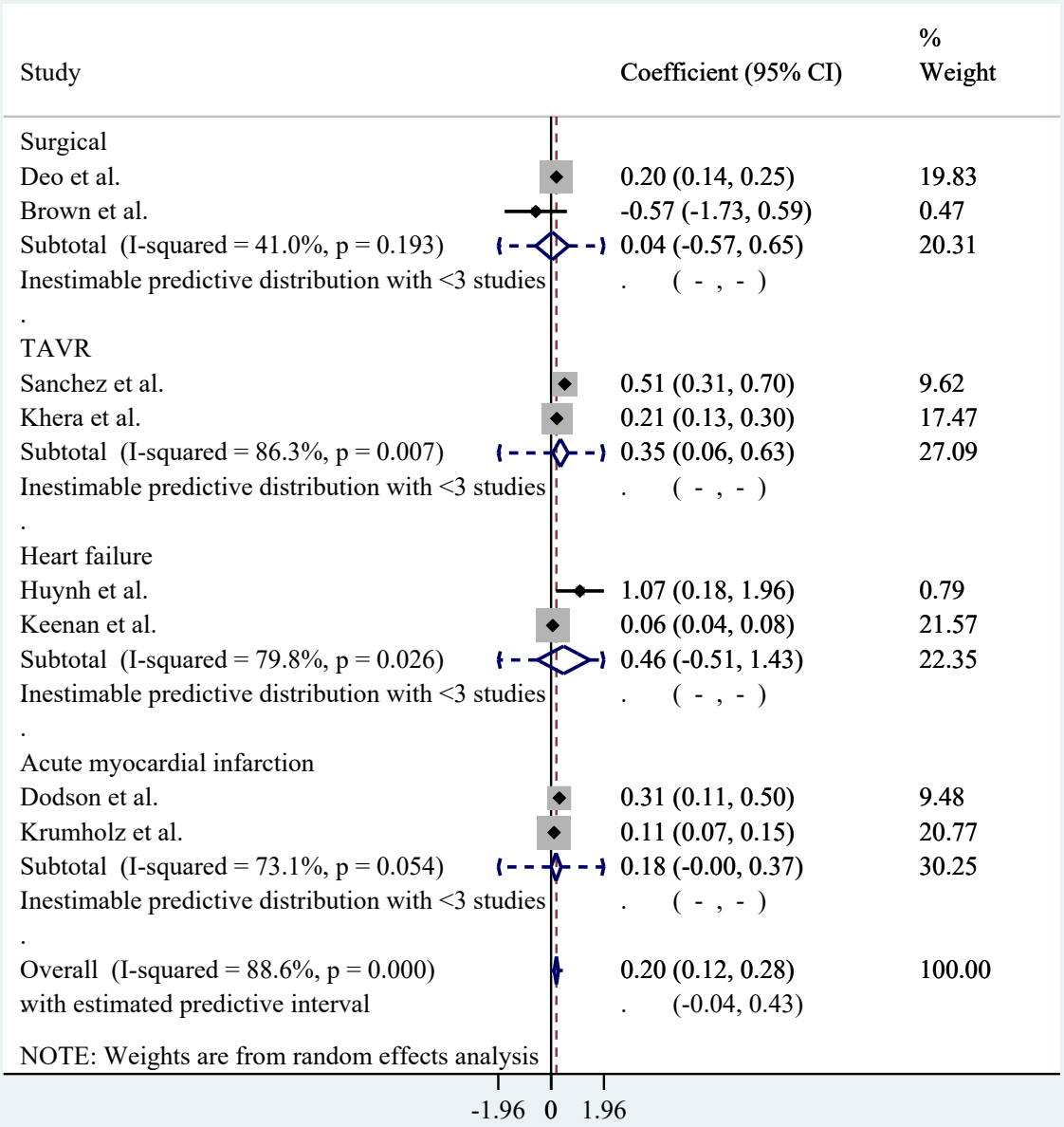
Supplemental Figure 1. Arrhythmias as predictor



Legend: There was no missing data in the analysis.

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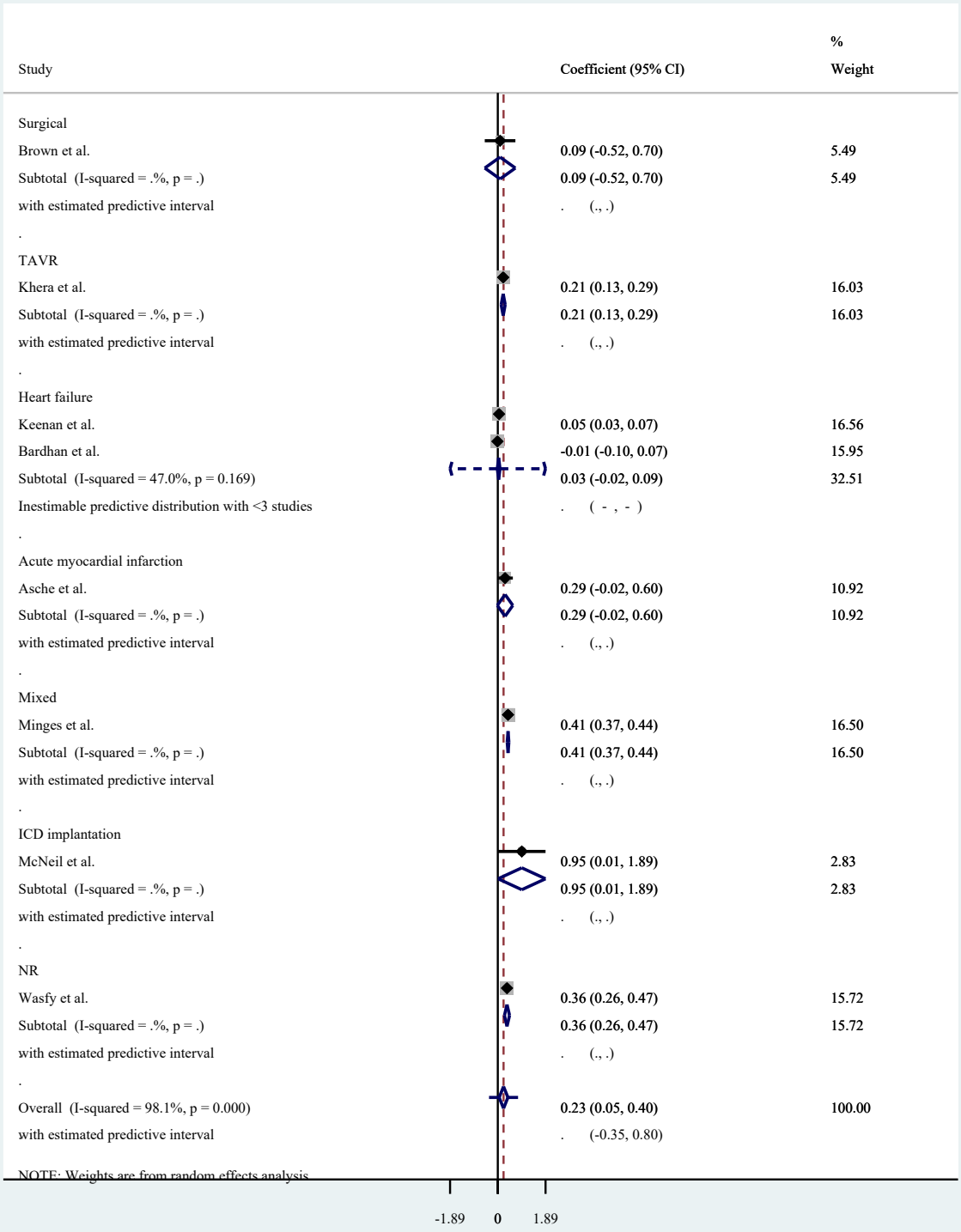
Supplemental Figure 12. Chronic lung disease as predictor



Legend: There was no missing data in the analysis.

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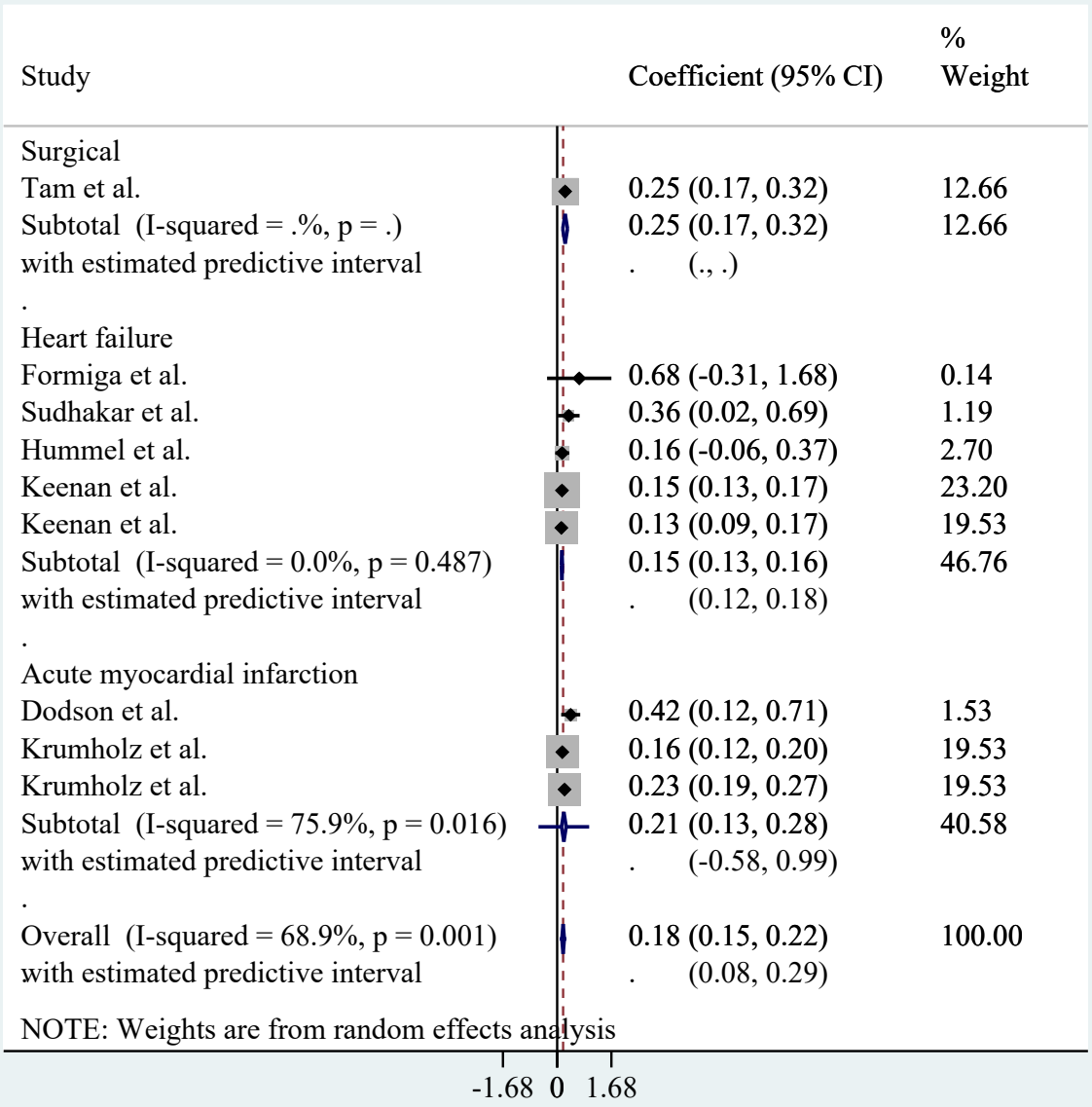
Supplemental Figure 13. Chronic Obstructive Pulmonary Disease as predictor



Legend: Two studies were not included in the analysis because the standard errors were missing. The values of their coefficients were: 0.053 and 0.677.

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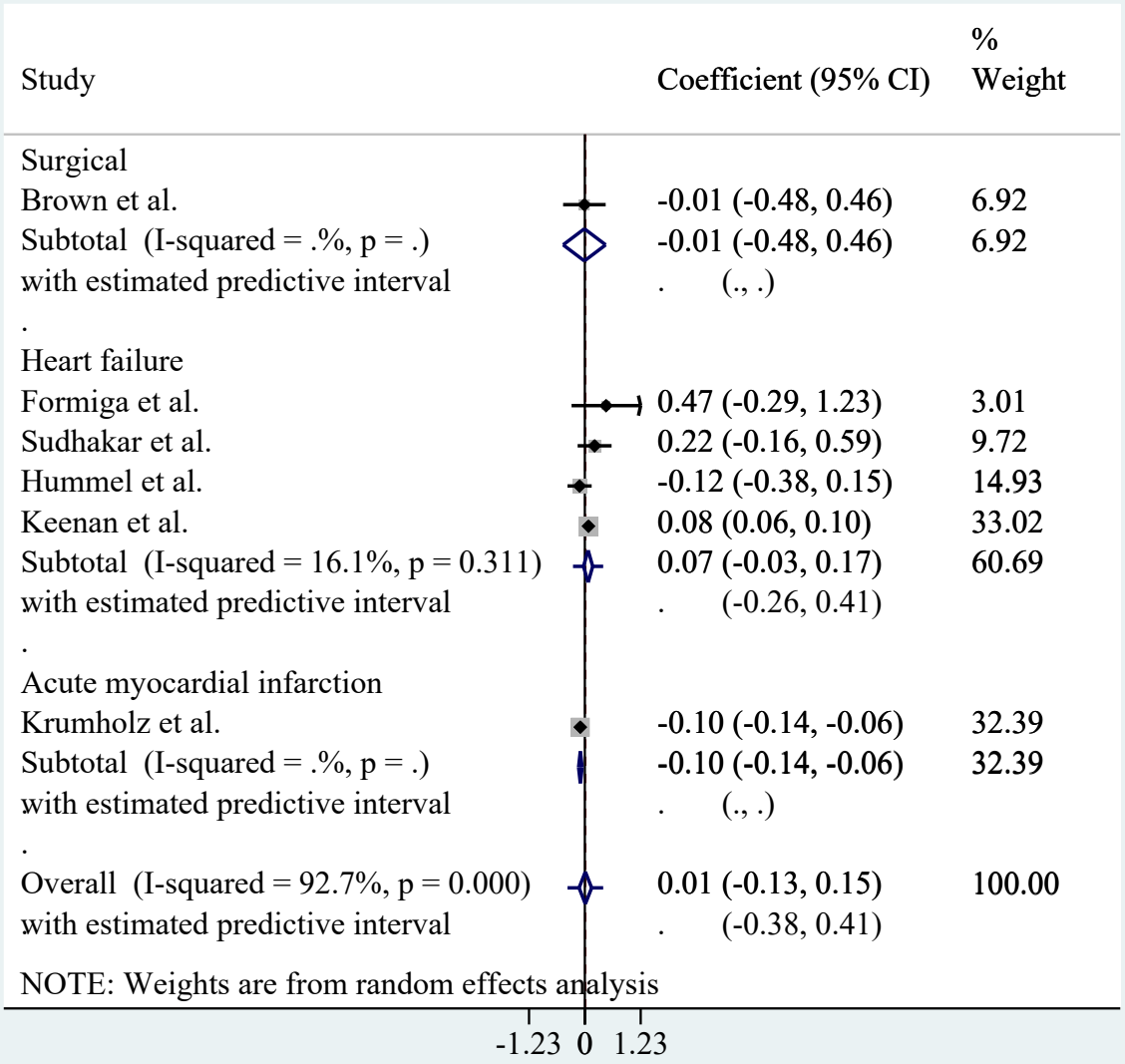
Supplemental Figure 14. Atherosclerosis as predictor



Legend: One study was not included in the analysis because the standard error were missing. The values of their coefficient was: 0.11.

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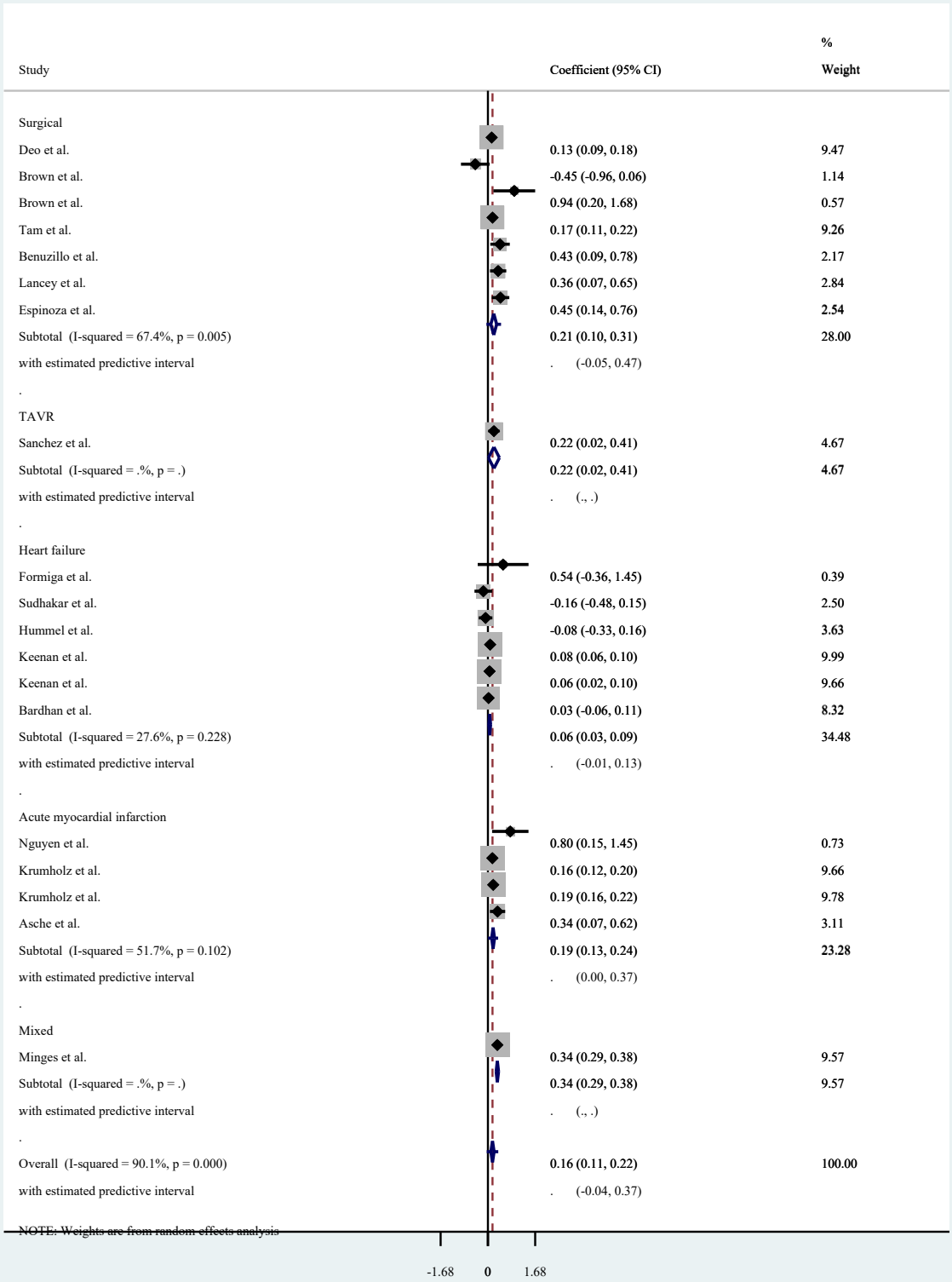
Supplemental Figure 15. Diabetes Mellitus as predictor



Legend: Two studies were not included in the analysis because the standard errors were missing. The values of their coefficients were: -0.068 and 0.639.

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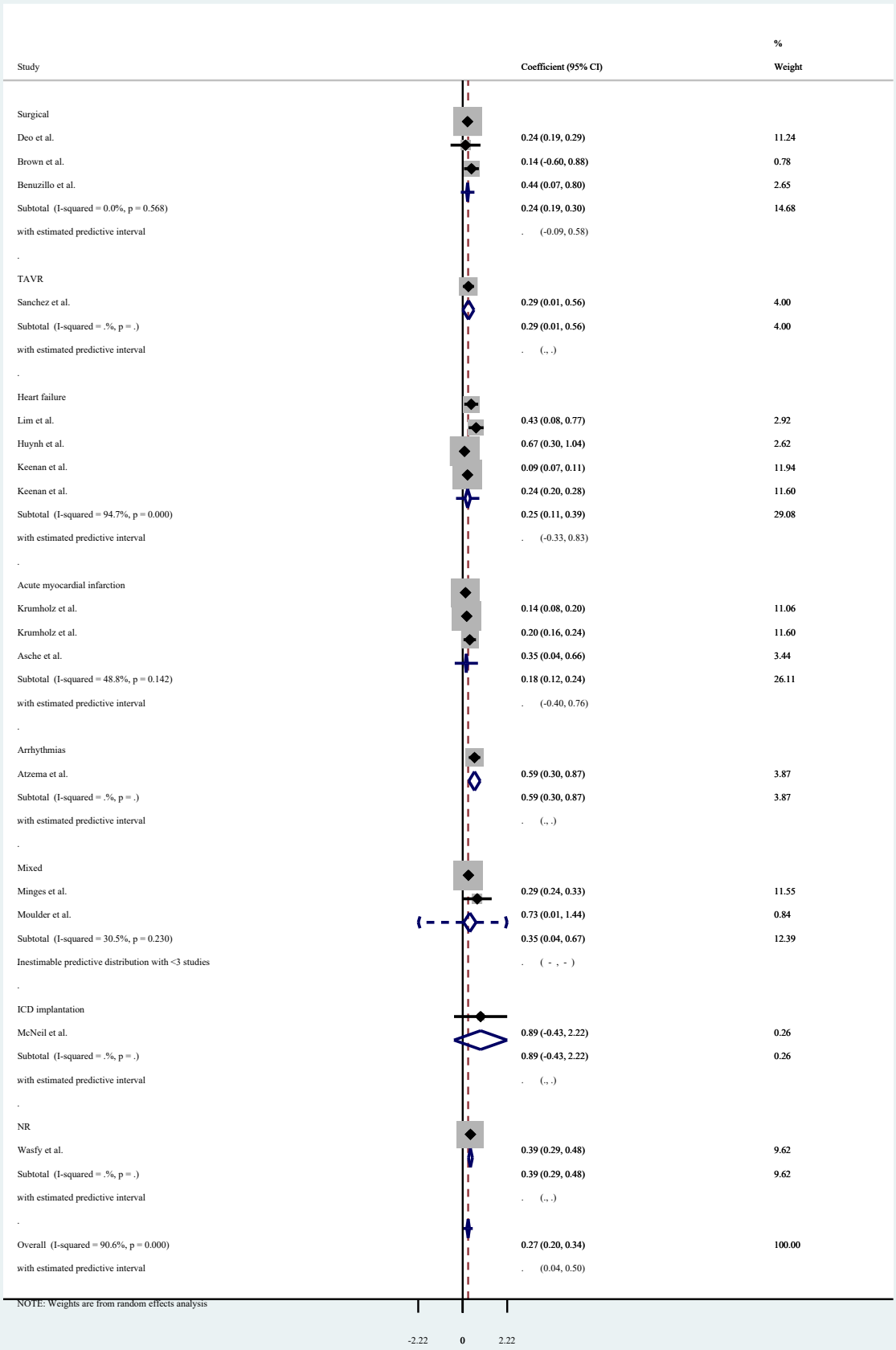
Supplemental Figure 16. Current heart failure as predictor



Legend: There was no missing data.

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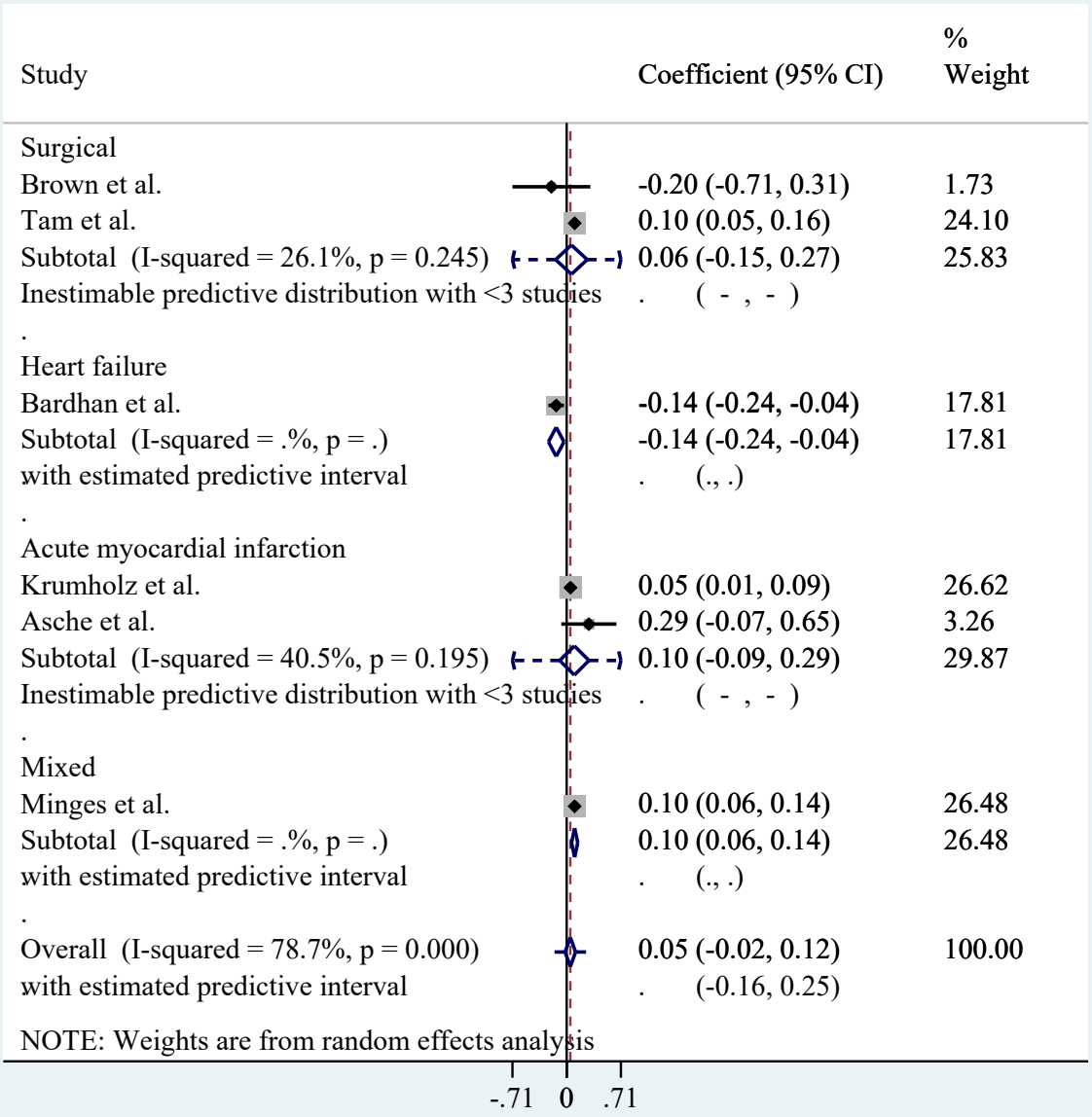
Supplemental Figure 17. Hypertension as predictor



Legend: One study was not included in the analysis because the standard error were missing. The values of their coefficient was: -0.28.

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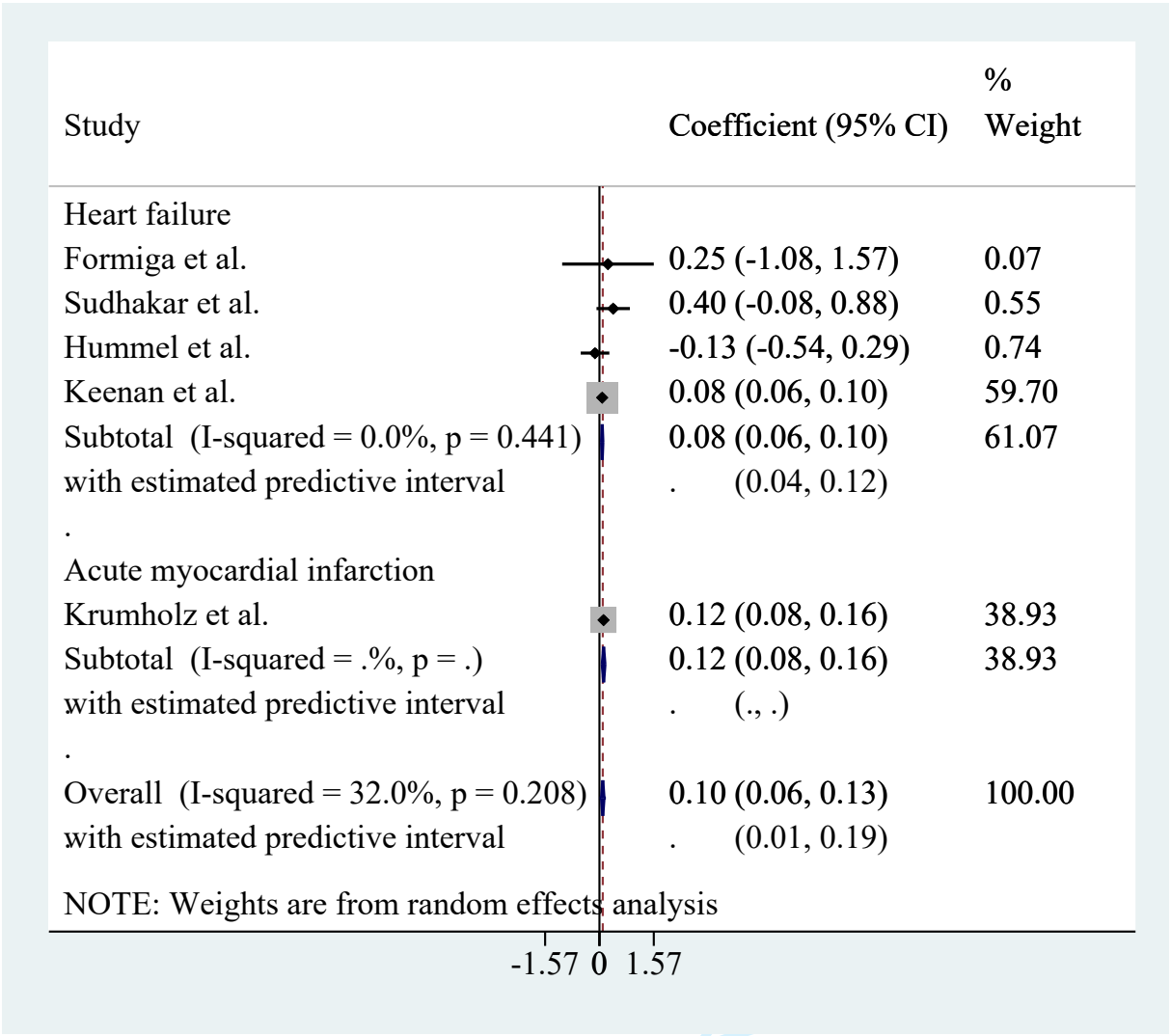
Supplemental Figure 18. Valve disease as predictor



Legend: There was nog missing data.

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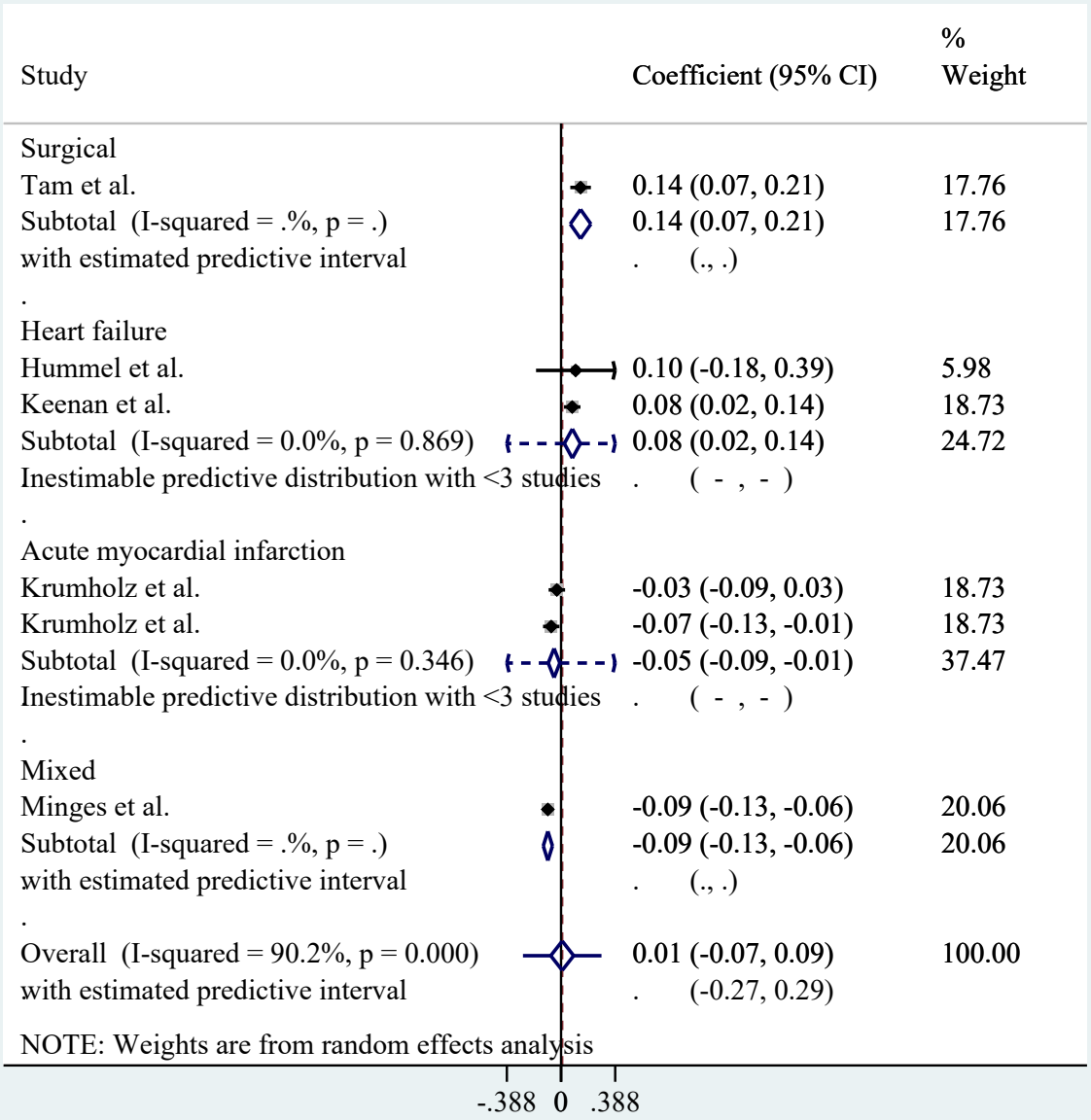
Supplemental Figure 19. Prior percutaneous coronary intervention as predictor



Legend: There was no missing data.

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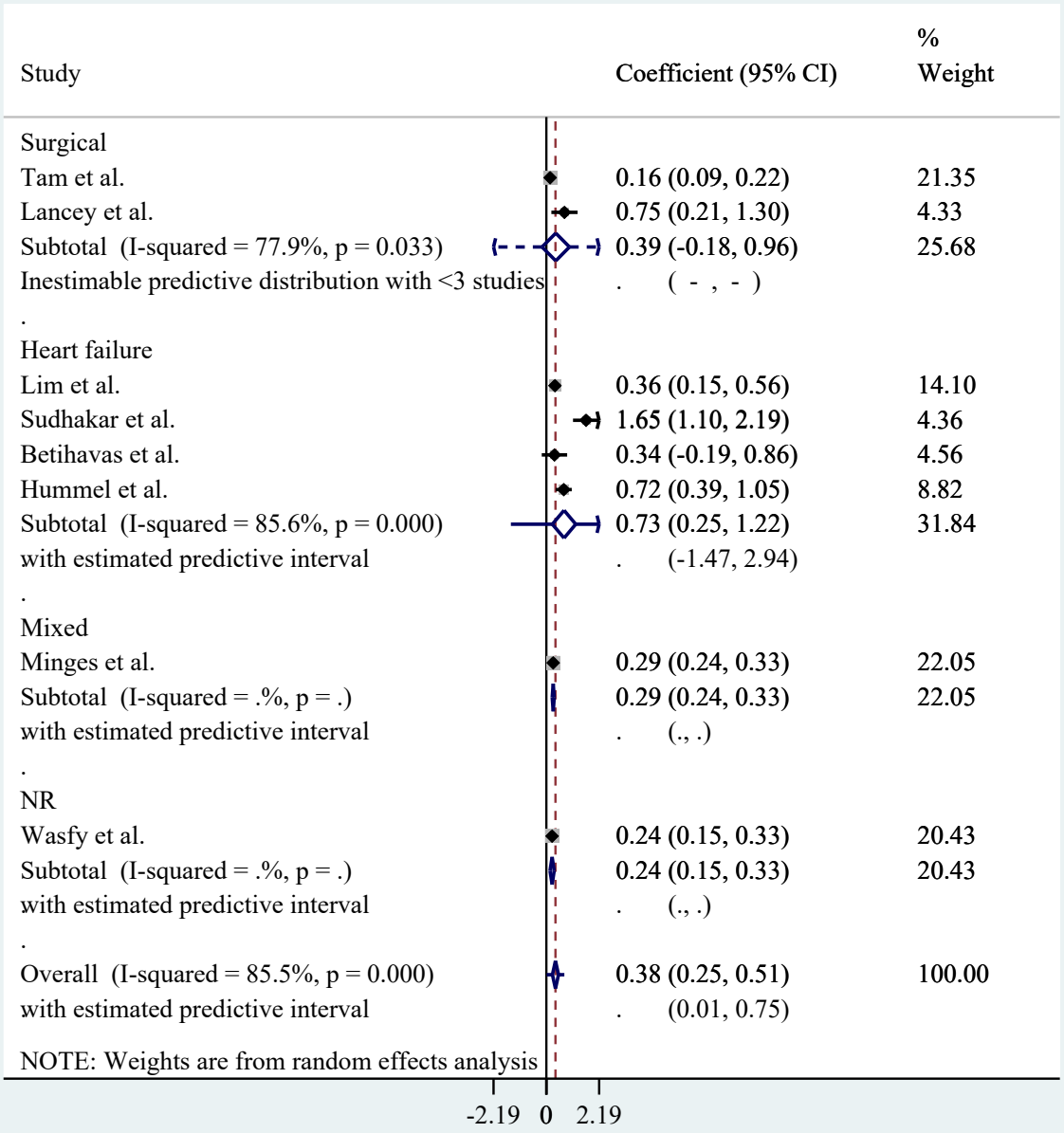
Supplemental Figure 20. History of heart failure as predictor



Legend: There was no missing data.

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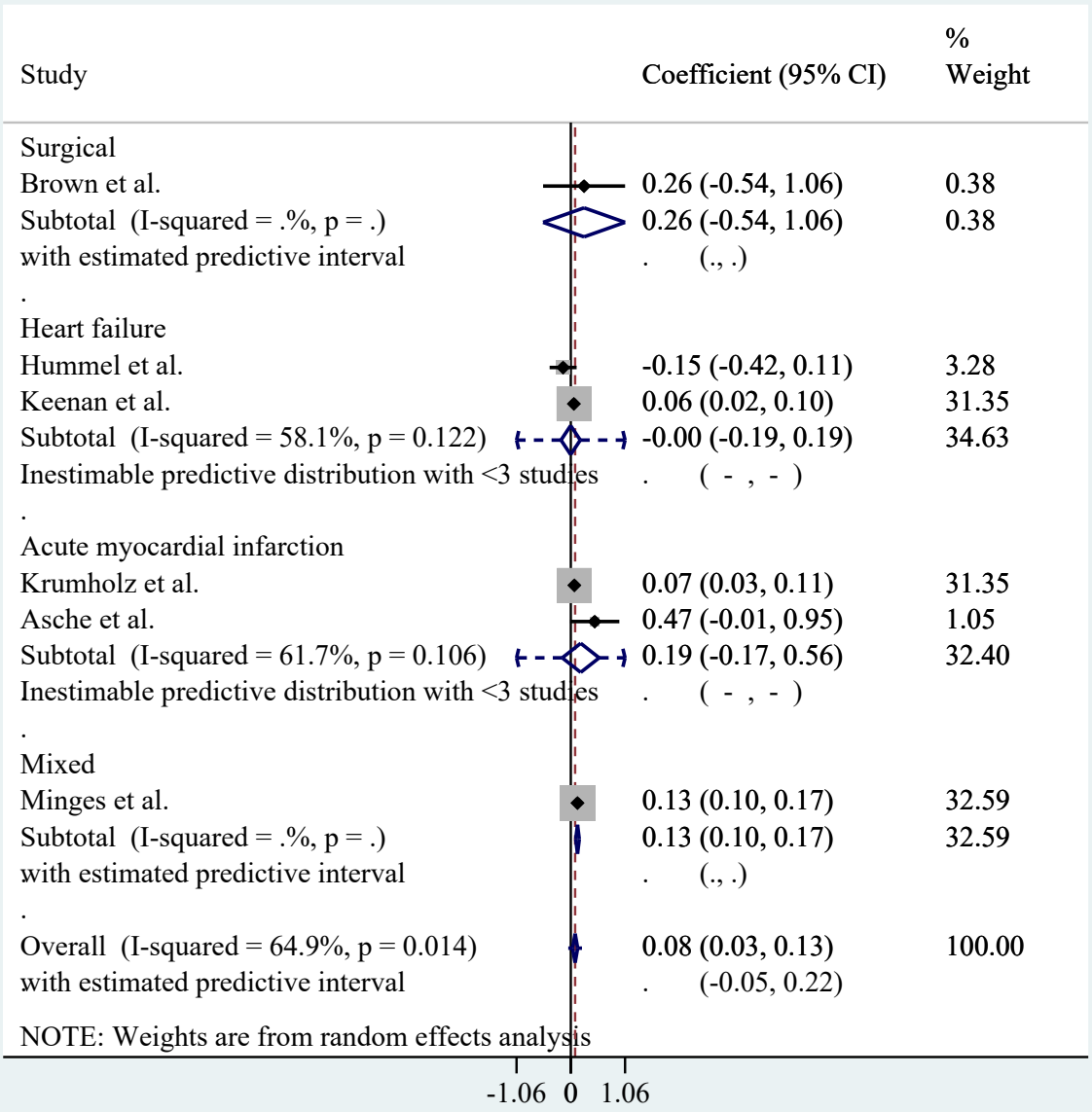
Supplemental Figure 21. Cerebrovascular disease as predictor



Legend: there was no missing data.

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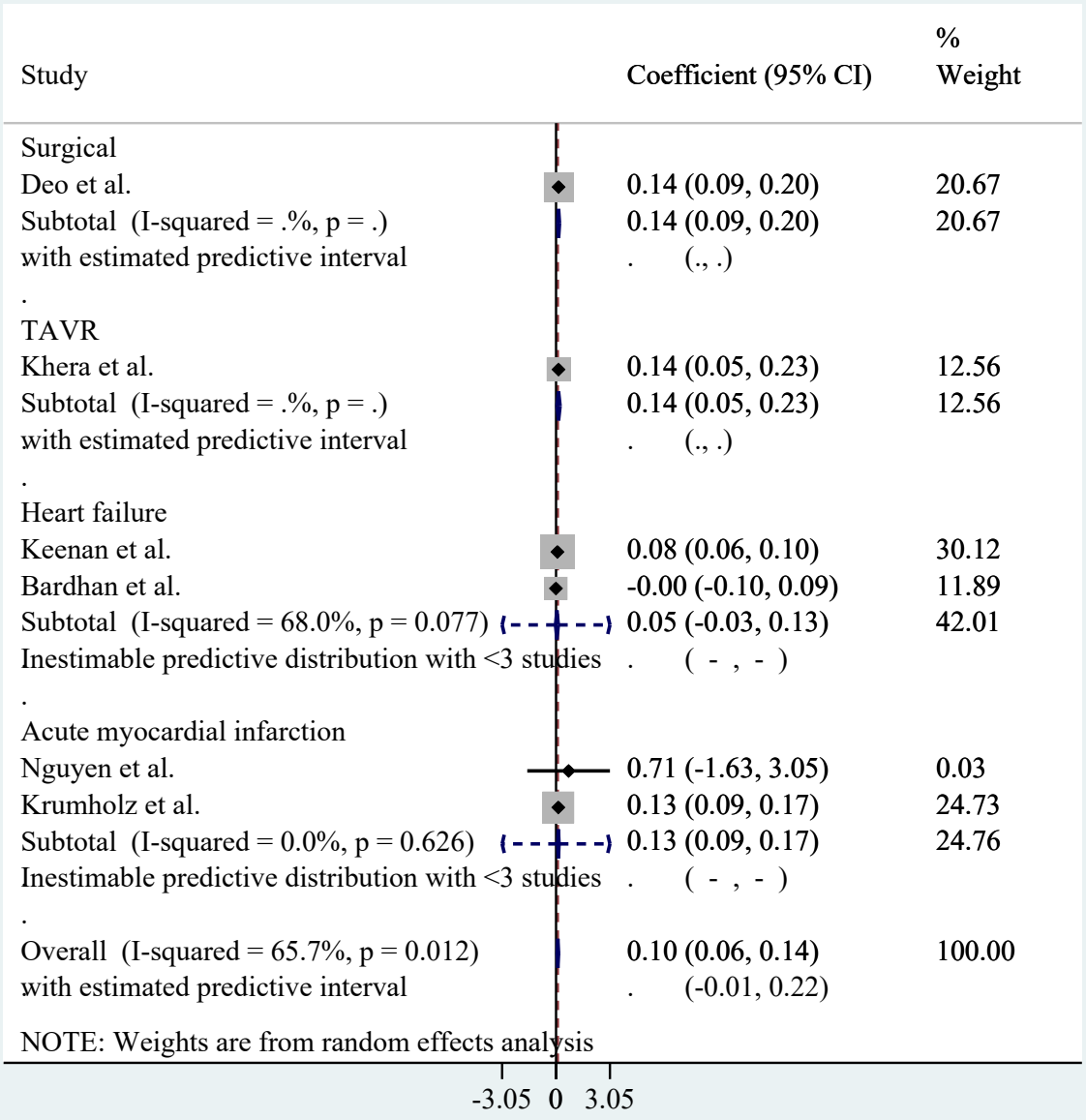
Supplemental Figure 22. Anemia as predictor



Legend: There was no missing data.

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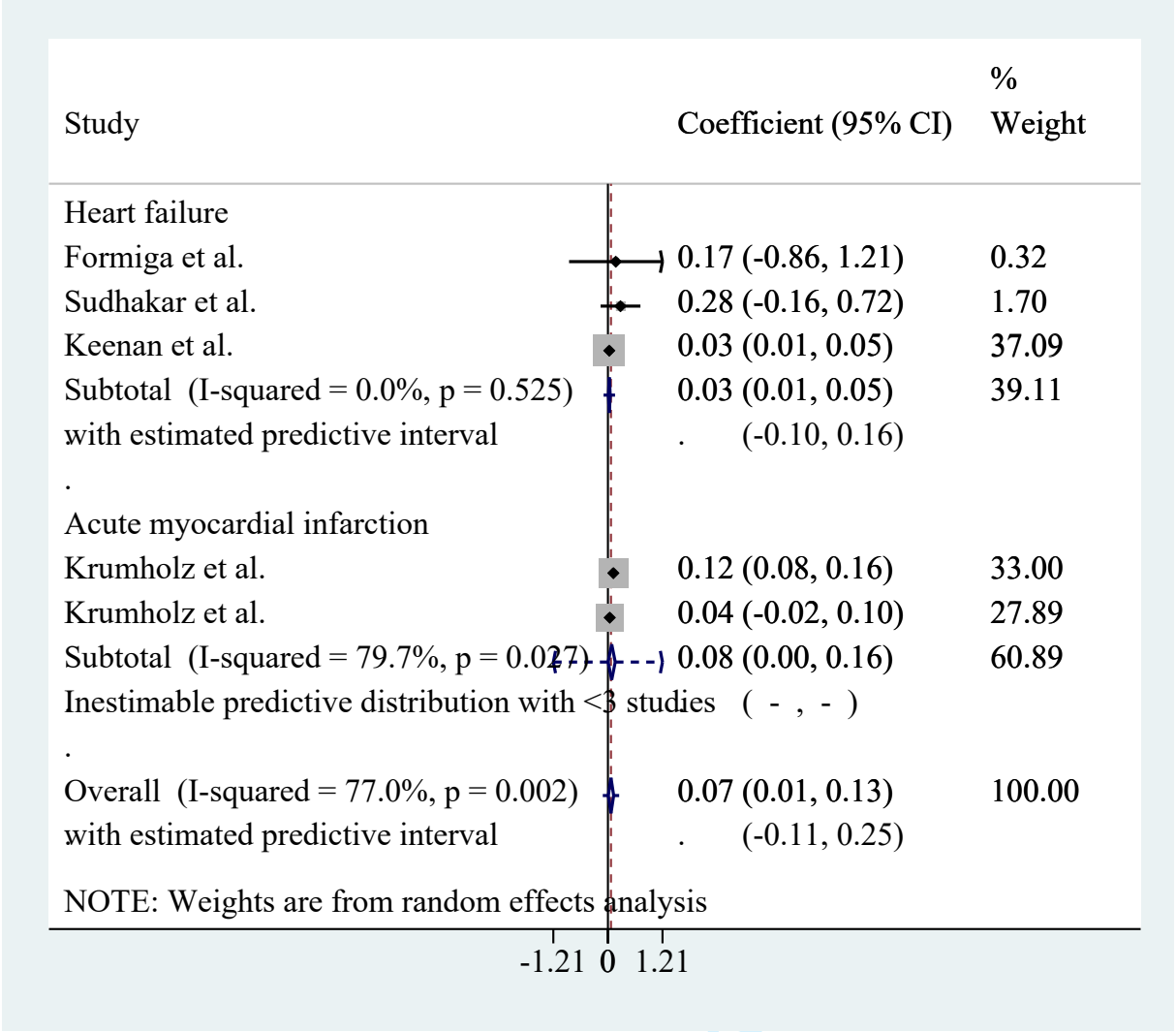
Supplemental Figure 23. Stroke as predictor



Legend: There was no missing data.

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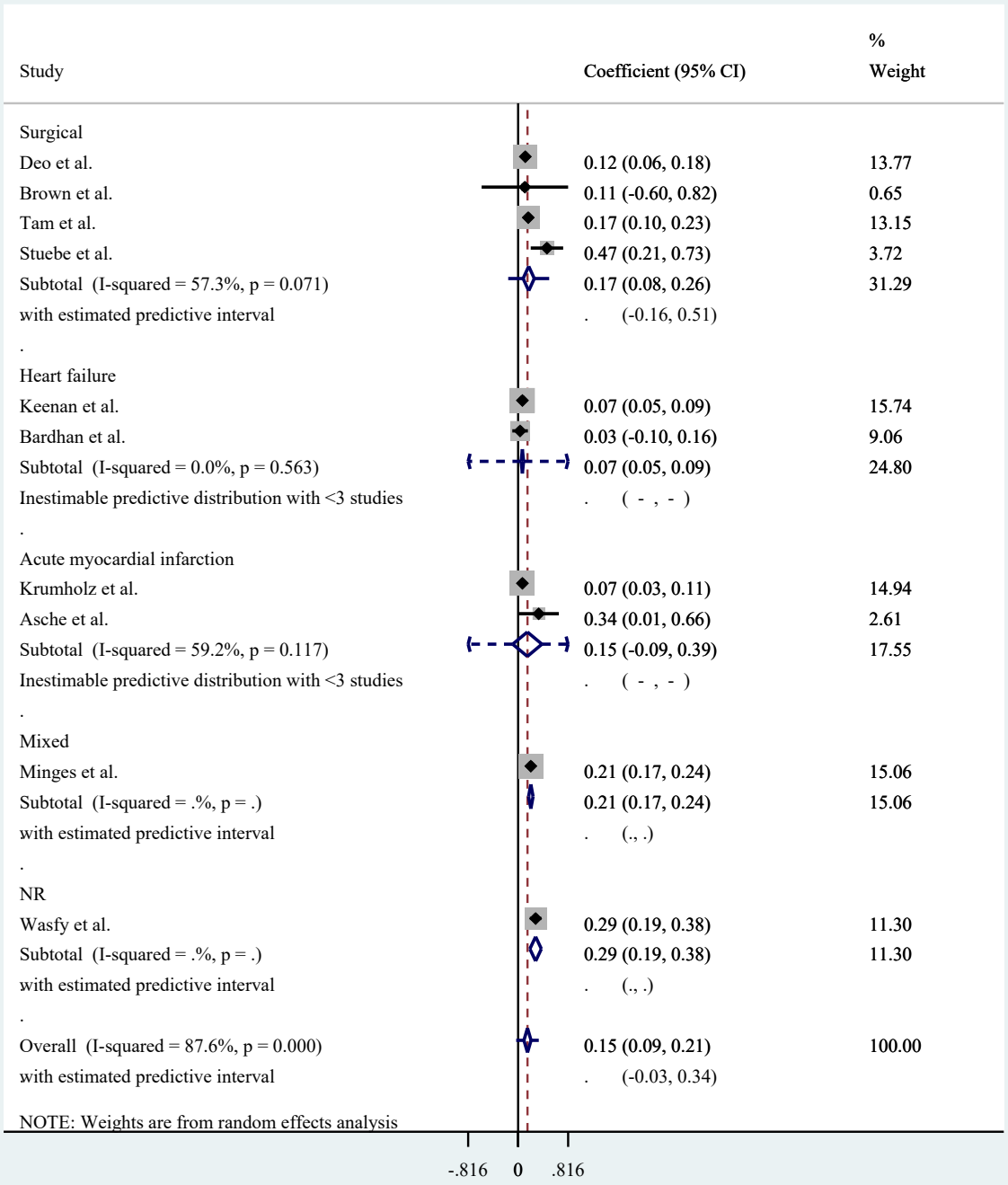
Supplemental Figure 24. Peripheral vascular disease as predictor



Legend: There was no missing data.

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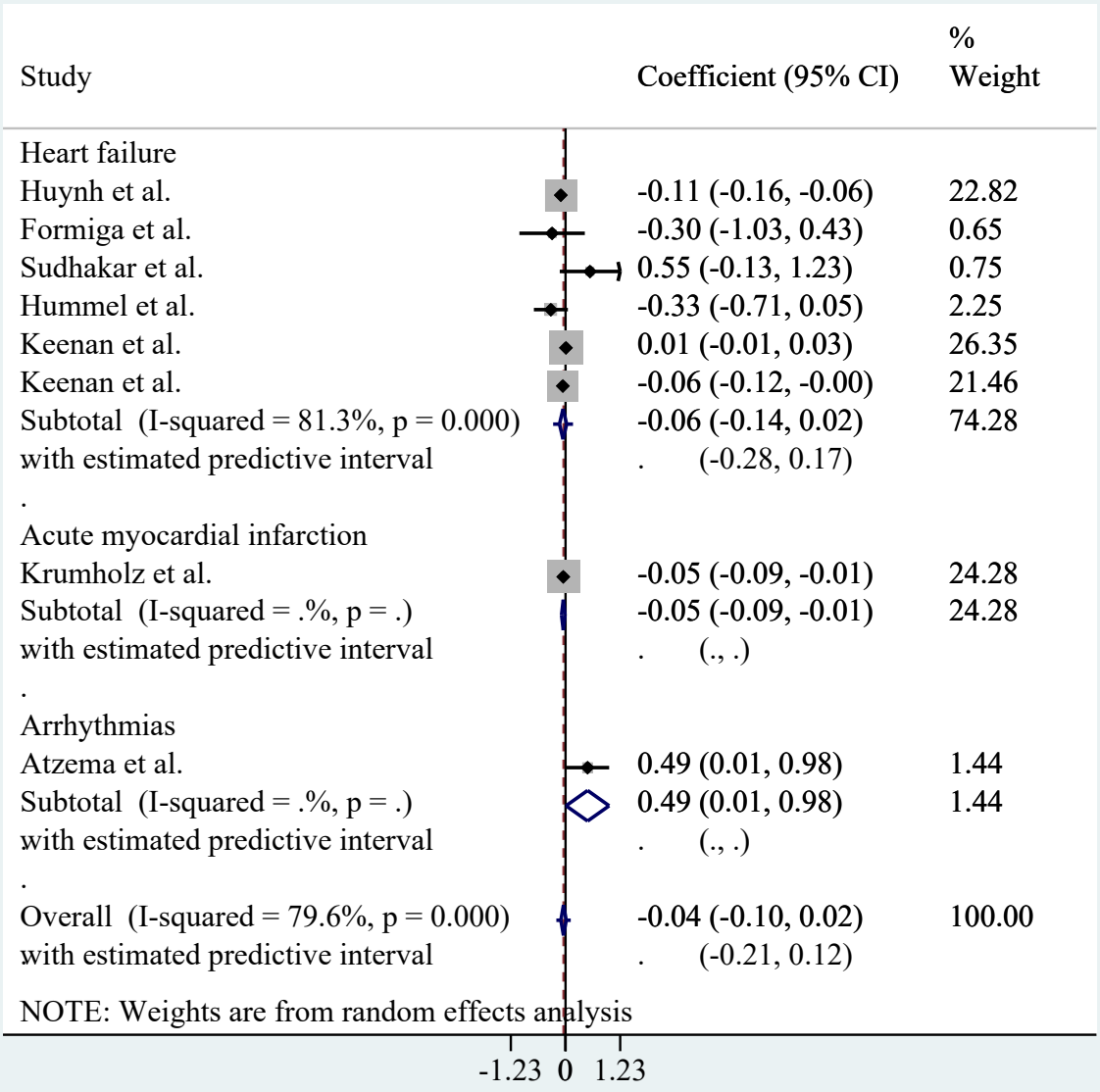
Supplemental Figure 25. Dementia as predictor



Legend: There was no missing data.

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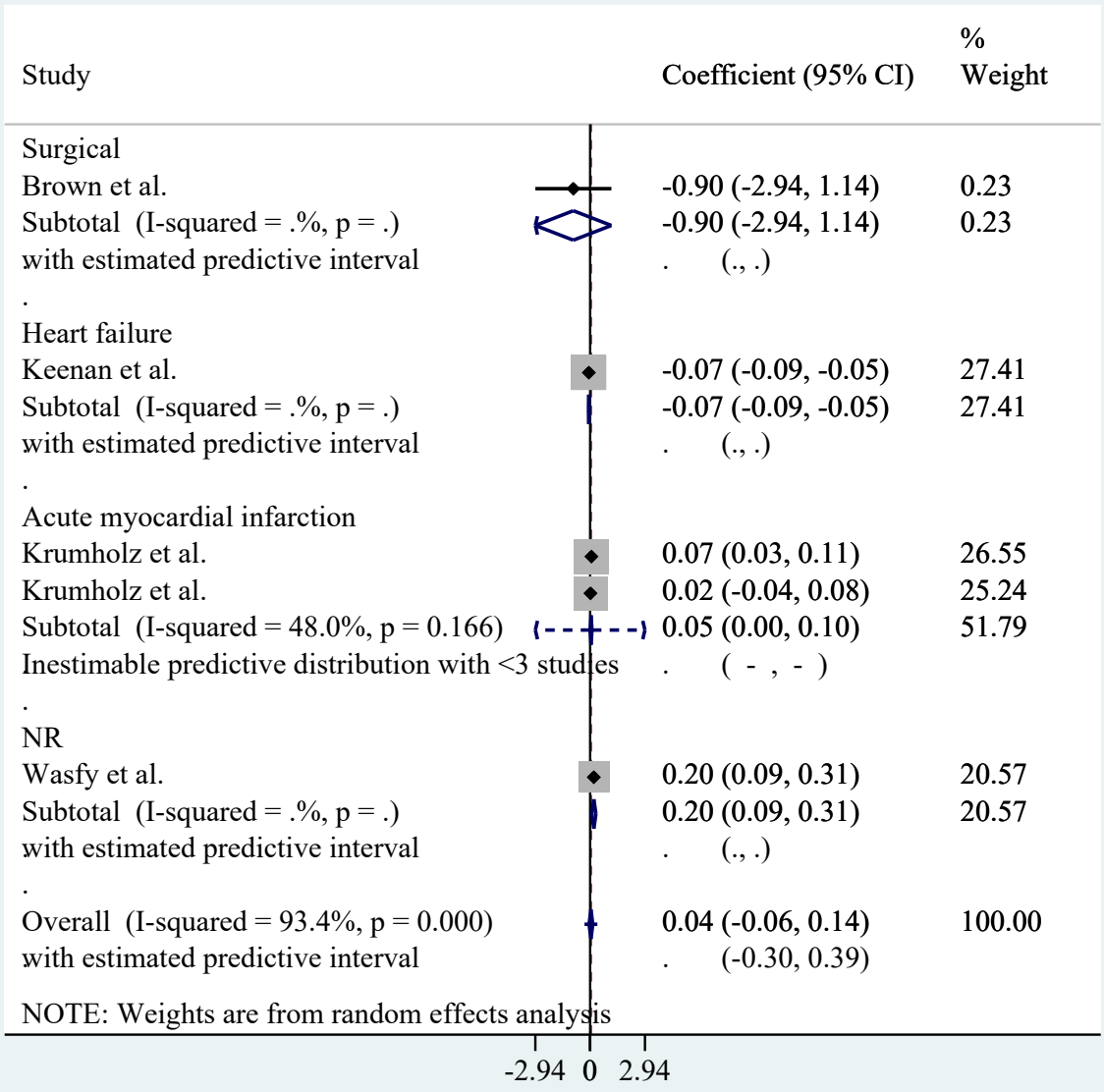
Supplemental Figure 26. Prior Coronary Artery Bypass Graft as predictor



Legend: There was no missing data.

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PRISMA 2009 Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7, Supp. Text 1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7,8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8, Supp Text 2
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8

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PRISMA 2009 Checklist

Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	9

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	NA
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	10, Fig 1
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	10-18, Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	19, Fig 2, Supp. Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	19-29, Table 2
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	20, Fig 3 and 4, Supp. Table 3, Supp. Fig 1-6
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	NA
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	19, 20, 29 Supp. Table 2, Supp. Fig

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PRISMA 2009 Checklist

			7-26
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	30-32
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	32, 33
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	33
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	134

From: Moher D, Liberati A, Tetzlaff J, Altman DG, The PRISMA Group (2009). Preferred Reporting Items for Systematic Reviews and Meta-Analyses: The PRISMA Statement. PLoS Med 6(6): e1000097. doi:10.1371/journal.pmed1000097

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