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REVIEW

# Impact of co-morbid burden on mortality in patients with coronary heart disease, heart failure, and cerebrovascular accident: a systematic review and meta-analysis

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**Aims** We sought to investigate the prognostic impact of co-morbid burden as defined by the Charlson Co-morbidity Index (CCI) in patients with a range of prevalent cardiovascular diseases.

**Methods and results** We searched MEDLINE and EMBASE to identify studies that evaluated the impact of CCI on mortality in patients with cardiovascular disease. A random-effects meta-analysis was undertaken to evaluate the impact of CCI on mortality in patients with coronary heart disease (CHD), heart failure (HF), and cerebrovascular accident (CVA). A total of 11 studies of acute coronary syndrome (ACS), 2 stable coronary disease, 5 percutaneous coronary intervention (PCI), 13 HF, and 4 CVA met the inclusion criteria. An increase in CCI score per point was significantly associated with a greater risk of mortality in patients with ACS [pooled relative risk ratio (RR) 1.33; 95% CI 1.15–1.54], PCI (RR 1.21; 95% CI 1.12–1.31), stable coronary artery disease (RR 1.38; 95% CI 1.29–1.48), and HF (RR 1.21; 95% CI 1.13–1.29), but not CVA. A CCI score of >2 significantly increased the risk of mortality in ACS (RR 2.52; 95% CI 1.58–4.04), PCI (RR 3.36; 95% CI 2.14–5.29), HF (RR 1.76; 95% CI 1.65–1.87), and CVA (RR 3.80; 95% CI 1.20–12.01).

**Conclusion** Increasing co-morbid burden as defined by CCI is associated with a significant increase in risk of mortality in patients with underlying CHD, HF, and CVA. CCI provides a simple way of predicting adverse outcomes in patients with cardiovascular disease and should be incorporated into decision-making processes when counselling patients.

**Keywords** Charlson Co-morbidity Index • Cardiovascular disease • Mortality

## Introduction

Cardiovascular disease (CVD) is a major cause of morbidity and mortality, accounting for 30% of all-cause mortality worldwide.[1] Given the incidence of CVD and co-morbidity burden increases with age,[2] a significant proportion of patients with CVD are older with multiple co-morbidities. This affects disease progression and clinical outcomes and can influence clinical decision-making.[3–5] Cardiovascular co-morbidities such as hypertension, diabetes, atrial fibrillation, heart failure, and stroke have an independent association with increased mortality in patients hospitalized with acute myocardial infarction with increasing numbers of these co-morbidities particularly associated with poor outcomes.[6]

While previous studies have mainly focused on cardiovascular co-morbid conditions, patients with CVD often have a broad spectrum of non-cardiovascular co-morbidities. It remains unclear, however,

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**Table 1 Charlson co-morbidity index**

| Variable | Points |
|---|---|
| Myocardial infarction | 1 |
| Congestive heart failure | 1 |
| Peripheral vascular disease | 1 |
| Cerebrovascular disease | 1 |
| Dementia | 1 |
| Chronic obstructive pulmonary disease | 1 |
| Connective tissue disease | 1 |
| Peptic ulcer disease | 1 |
| Diabetes mellitus | 1 if uncomplicated<br>2 if end-organ damage |
| Moderate to severe chronic kidney disease | 2 |
| Hemiplegia | 2 |
| Leukaemia | 2 |
| Malignant lymphoma | 2 |
| Solid tumour | 2<br>6 if metastatic |
| Liver disease | 1 if mild<br>3 if moderate to severe |
| AIDS | 6 |

how clustering of multiple cardiovascular and or non-cardiovascular chronic conditions influences clinical outcomes. Therefore, there is a need to understand the impact of co-morbid burden, rather than focusing on individual co-morbid conditions on clinical outcomes in patients with prevalent CVD.[2]

The Charlson Co-morbidity Index (CCI) is a recognized measure of co-morbid burden[7] and quantifies the prognostic impact of 22 co-morbid conditions based on their number and individual prognostic impact by means of a score.[8] It is a useful tool for estimating prognosis in patients with multiple coexisting illnesses. *Table 1* represents the variables. Although various studies have evaluated the prognostic value of CCI in predicting outcomes in different cohorts of patients with CVD, there is no systematic review of the literature that evaluates the prognostic value of CCI on mortality across a range of CVDs. In this systematic review, we sought to investigate the prevalence, and prognostic impact, of co-morbidity defined by the CCI score in patients with three major CVDs; coronary heart disease (CHD), heart failure, and cerebrovascular accident (CVA).

# Methods

## Study inclusion criteria

We included primary studies that evaluated the prognostic impact of co-morbid burden defined by CCI in patients with CHD, acute or chronic heart failure, and CVA. Studies were considered for inclusion and detailed review if their abstract potentially met all three of the following criteria:

(1) Primary studies evaluating the impact of co-morbidity defined by CCI on adverse outcomes in patients with CVD.
(2) CVD was defined by CHD [comprising of patients undergoing percutaneous coronary intervention (PCI) or stable angina or acute coronary syndrome (ACS)], or acute or chronic heart failure, or cerebrovascular disease.
(3) Adverse outcomes included mortality and major adverse cardiac events (MACE) at any length of follow-up.

We excluded studies that did not have results on outcomes defined by CCI score, but there was no restriction on the basis of language of study. We also excluded expert opinion and editorial reviews. We included conference abstracts to minimize publication bias.

## Search strategy

We searched MEDLINE and EMBASE on July 2015 using the broad search terms: ('Charlson co-morbidity index' OR 'Charlson index' OR 'Charlson co-morbidity score' OR 'Charlson score') AND ('acute myocardial infarction' OR 'acute coronary syndrome' OR 'coronary heart disease' OR 'coronary artery disease' OR 'stroke' OR 'cerebrovascular disease' OR 'cerebrovascular accident' OR 'heart failure' OR 'cardiac failure') AND ('mortality' OR 'death' OR 'major adverse cardiovascular event' OR 'major adverse cardiac event' OR 'cardiovascular disease'). The search results were reviewed by two independent investigators (M.R. and C.S.K.) for studies that met the inclusion criteria, and relevant reviews were identified. Additional studies were retrieved by checking the bibliographies of included studies and relevant reviews.

## Data extraction

Data were extracted from each study into preformatted tables generated in Microsoft Word. Data collected included year, country, number of participants, mean age of participants, percentage of male participants, participant inclusion criteria, follow-up assessment, lost to follow-up, and results of association between CCI and outcomes. With regards to quality assessment, we documented the design of the study, reliable method of ascertainment of outcomes, >10% loss to follow-up, and if there was any adjustment for potential confounders.

## Data analysis

Meta-analysis for estimated pooled risk ratios (RR) was performed by the inverse variance method using a random-effects model on the software RevMan 5.3 (Nordic Cochrane Centre, København, Denmark). To reduce the risk of confounding associated with crude estimates, where available, we chose to pool the results from the most adjusted model, whereby results were expressed as pooled relative RR with accompanying 95% confidence intervals (CI). Statistical heterogeneity was assessed using the $I^2$ statistic, with values of 30–60% representing a moderate level of heterogeneity.[9] For $I^2 > 50\%$, we performed sensitivity analysis by systematic exclusion of studies and evaluated the effect on $I^2$ estimates (see Supplementary material online, *Table S1*). The primary analysis evaluated adverse outcomes with incremental increase in CCI, and secondary analysis was performed by considering higher group of CCI score vs. lower group of CCI score. In the final analysis, we excluded studies by the same research group over the same time period where there was the potential that the same participants were studied more than once. Where there were similar study participants, we chose the study with the largest sample size or highest adverse outcome event rate. We evaluated publication bias through Funnel plots and Egger's test where there were >10 studies in the analysis and no evidence of statistical heterogeneity as the power to detect publication bias was low for meta-analyses of 10 or fewer studies.[10]

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**Table 2** Study design and characteristics of participants

| Study ID | Study design; Year; Country | No. of Participants | Participants with CCI = 0 (%) | Mean age | % Male | Description of participants |
|---|---|---|---|---|---|---|
| Bottle 2013[11] | Retrospective cohort study; 2006–2009; UK | 288 550 | 15 177 (5%) | 42% of admissions >75 years of age | 61% | Participants were emergency admissions for ACS in England |
| Bar 2011[12] | Retrospective cohort study; 2001–2004; USA | 243 | 88 (36%) | NA | NA | Patients with non-traumatic intra-cerebral haemorrhage presented to hospital emergency department |
| Chin 1998[13] | Prospective cohort study; 1993–1994; USA | 257 | 48 (18%) | Full cohort 41% >70 years of age | Full cohort 47% | Participants were admitted with congestive heart failure to the Brigham and Women's Hospital |
| Chirinos 2006[14] | Prospective cohort study; 1998–2000; USA | 305 | 70 (22%) | 64 years | 100% | Male veterans undergoing coronary angiography at Miami Veterans Administration Medical Centre |
| Clarke 2011[15] | Retrospective cohort study; 1998–2004; Canada | 824 | NA | 64 years | 69% | Consecutive patients followed at a tertiary care specialty ambulatory heart failure clinic |
| Eberli 2013[16] | Prospective registries; NA; international | 5559 | 2041 (36%) | NA | NA | Participants from e-Biomatrix PMR and PMS registries evaluating the efficacy and safety of biolimus-A9-eluting stent |
| Erickson 2014[17] | Retrospective cohort study; 1999–2007; USA | 1202 | NA | 64 years | 65% | Participants from ACS registry from a large university hospital |
| Fabbian 2013[18] | Retrospective cohort study; 1999–2009; Italy | 88 014 | NA | 71 years | 48% | Participants from database of Emilia-Romagna region, Italy who presented with first event of myocardial infarction |
| Goldstein 2004[19] | Prospective cohort study; 1995–1997; USA | 960 | 212 (22%) | 68 years | NA | Participants admitted with ischaemic stroke, Department of Veterans Affairs (VA) Stroke Study |
| Hong 2011[20] | Prospective cohort study; 2006–2008; international | 675 | NA | 83 years | 58% | Octogenarian participants from Sirolimus-eluting coronary stent (e-Select) registry |
| Huang 2015[21] | Retrospective; 2002–2011; Taiwan | 798 328 | 315 556 (39%) | 45% ≥65 years | 57% | Participants with disabilities from the National Health Insurance Research Database published by the Ministry of Health and Welfare in Taiwan |
| Jeger 2014[22] | Retrospective; 2005–2012; Switzerland | 1909 | NA | 65 years | 78% | Participants from AMIS plus registry |
| Jong 2002[23] | Retrospective; 1994–1997; Canada | 38 702 | 15 020 (38%) | 85% ≥65 years | 49% | Participants from Canadian institute for health information database admitted with first diagnosis of heart failure |
| Khawaja 2014[24] | NA; 2008–2013; USA | 383 | 37 (9%) | NA | NA | Patients with primary intra cerebral haemorrhage |
| Mamas 2015[25] | *Post hoc* analysis of prospective registry; 2008–2013; international | 3 067 | 787 (25%) | 64 years | 78% | Participants were in the Nobori 2 study who underwent Nobori biolimus-eluting stent implantation |
| Menendez-Colino 2013[26] | NA; Spain | 652 | NA | 85 years | NA | Patients admitted with heart failure in six Spanish hospitals |
| Munoz-Rivas 2009[27] | Retrospective cohort study; 2005–2007; Spain | 270 | NA | 78 years | 42% | Patients with chronic heart failure diagnosis |
| Núñez 2004[28] | Prospective cohort study; 2000–2003, Spain | 1035 | 481 (46%) | 70 years | 70% | Patients admitted with diagnosis of acute myocardial infarction |
| Oudejans 2012[29] | Prospective cohort study; 2003–2007; Netherlands | 93 | 0 | 83 years | 37% | Patients with diagnosis of heart failure |



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| | | | | | | |
|---|---|---|---|---|---|---|
| Perez-Barquero 2010[30] | Retrospective cohort study; 2000–2001; Spain | 2127 | NA | 77 years | 43% | Patients admitted with heart failure to various hospitals in Spain |
| Radovanovic 2014[31] | Prospective cohort study; 2002–2012; Switzerland | 29 620 | 15 754 (51%) | 64 years | 73% | Participants from AMIS plus registry |
| Ramirez-Marrero 2011[32] | Retrospective cohort study; 2004–2005; Spain | 715 | NA | 66 years | NA | Patients admitted with diagnosis of non-ST-elevation acute coronary syndromes |
| Ramirez-Marrero 2013[33] | Retrospective cohort study; 2008–2009; Spain | 146 | NA | 78 years | 63% | Patients undergoing percutaneous coronary revascularization |
| Rodriguez-Pascual 2012[34] | Prospective cohort study; 2006–2009 | 581 | 121 (20%) | 86 years | 33% | Patients admitted to an acute geriatric unit with decompensated heart failure |
| Sachdev 2004[35] | Prospective cohort study; 1985–1989; USA | 1471 | 810 (55%) | 60 years | 72% | All patients undergoing initial coronary angiography for symptoms of chronic CAD and found to have significant disease ($\geq$75% stenosis) in one or more coronary arteries |
| Sanchis 2011[36] | Prospective cohort study; 2002–2009; Spain | 1017 | NA | 68 years | 66% | Patients admitted with diagnosis of non-ST-elevation acute coronary syndromes |
| Schmidt 2012[37] | Retrospective cohort study; 1984–2009; Denmark | 234 331 | 164 937 (70%) | 75 years | 62% | Patients from nationwide Danish cohort registry admitted with myocardial infarction |
| Singh 2011[38] | Prospective cohort study; 2005–2008; USA | 629 | NA | 75 years | 69% | Patients undergoing PCI at the Mayo Clinic in Rochester, NY, USA |
| Subramanian 2007[39] | Prospective cohort study; unclear; USA | 494 | NA | 68 years | NA | Participants from Veterans Affairs outpatients with diagnoses of congestive heart failure |
| Teng 2014[40] | Prospective cohort study; 2000–2009; Australia | 17 379 | 105 (0.6%) | 70 years | 58% | Participants were Aboriginal and non-Aboriginal patient with first heart failure hospitalization |
| Testa 2009[41] | Prospective cohort study; 1992–2003; Italy | 1268 | NA | 74 years | 43% | Participants from 'Osservatorio Geriatrico Regione Campania' with and without heart failure |
| Theuns 2011[42] | Prospective; 1999–2008; international | 463 | NA | 62 years | 75% | Participants from two ICD registries from Rotterdam and Basel |
| Tuttolomondo 2008[43] | Retrospective; 1988–1998; Italy | 1878 | 0 | 77 years | 49% | Participants from GIFA registry |
| Urban 2011[44] | Prospective cohort study; 2006–2008; international | 15 147 | NA | 62 years | 75% | Participants from Sirolimus-Eluting Coronary Stent implantation study (e-Select) registry |
| Van Wijk 2013[45] | *Post hoc* analysis of RCT; unclear; international | 499 | NA | NA | NA | Participants from heart failure study randomized to intensified NT-proBNP-guided vs. symptom-guided therapy |

NA, not available or not reported.



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# Results

## Description of included studies

A total of 35[11–45] studies met the inclusion criteria. The process of study selection is shown in *Figure 1*. The details of the studies' design and participants are described in *Table 2*. The included studies comprised 14 retrospective cohort studies,[11,12,15,17,18,21–23,27,30,32,33,37,43] 17 prospective cohort studies,[13,14,16,19,20,28,29,31,34–36,38–42] 1 *post hoc* analysis of registry,[25] and 1 *post hoc* analyses of RCT,[45] while 2 abstract studies[24,26] were not clear in reporting the design. There were a total of 1 538 793 participants in 35 studies. Twenty-four studies reported a mean age of 71 years and 62% male. The study size varied from 93 participants[31] to 798 328 participants.[21] The follow-up time ranged from 30 days to 5 years.

Seventeen studies[12–16,19,20,22,23,25,28,29,31,34–36,38,42] reported individual CCI scores and 530 457 out of 1 538 793 (35%) patients had no co-morbidities (CCI = 0). The prevalence of each co-morbid condition in each of the cardiovascular conditions/events studied is presented in *Figure 2*. Diabetes and a history of previous myocardial infarction were the two most common conditions present in patients with CHD. Approximately 10% of the patients with heart failure had previous history of myocardial infarction (only reported in 6 studies out of the total 13) and 12% had a history of chronic obstructive pulmonary disease. Similarly, diabetes was the most prevalent co-morbidity in the patients with CVA cohort. Haematological malignancies such as lymphoma leukaemia and AIDS were the least frequent co-morbid conditions across all the cohorts studied.

## Quality assessment of included studies

The quality of studies included is described in *Table 3*. There was no loss to follow-up for 13 of the included studies. Twenty-two studies had <10% loss to follow-up. The largest absolute loss to follow-up was reported by Radovanovic *et al.* as they excluded 1091 patients from final results due to unavailability of CCI data.[31] Just over half of the studies[12–14,18,19,21,24,25,29,35–37,39–42,44,45] (18 out of 35) reported estimates of associations adjusted for potential confounders.

## Results of included studies

The characteristics of patients included in the studies and association of CCI score on outcomes are described in *Table 4*.

### Acute coronary syndrome

A total of 11 studies[11,17,18,21,22,28,32,33,36,37] evaluated the impact of co-morbidity in 1 154 408 patients admitted with ACS; however, only 5 studies[11,21,28,31,37] reported on patients with no co-morbidity (37% of patients had CCI = 0). Five studies[17,18,31,32,36] were statistically pooled for the association between an incremental increase in CCI and mortality (*Figure 3A*). Among patients with ACS, the risk of death was significantly greater with incremental increase in CCI score (RR 1.33; 95% CI 1.15–1.54). Three studies ($I^2$ = 96%)[11,21,31] compared patients with no co-morbidity (CCI score of 0) vs. patients with any co-morbidity (CCI score of >0) showing that the presence of co-morbidity (CCI score of >0) resulted in almost twice the risk of death (RR 1.93; 95% CI 1.67–2.24). Radovanovic *et al.*[31] and Huang *et al.*[21] also analysed the impact of CCI score of 0–1 vs. >1 showing a higher risk of death in patients

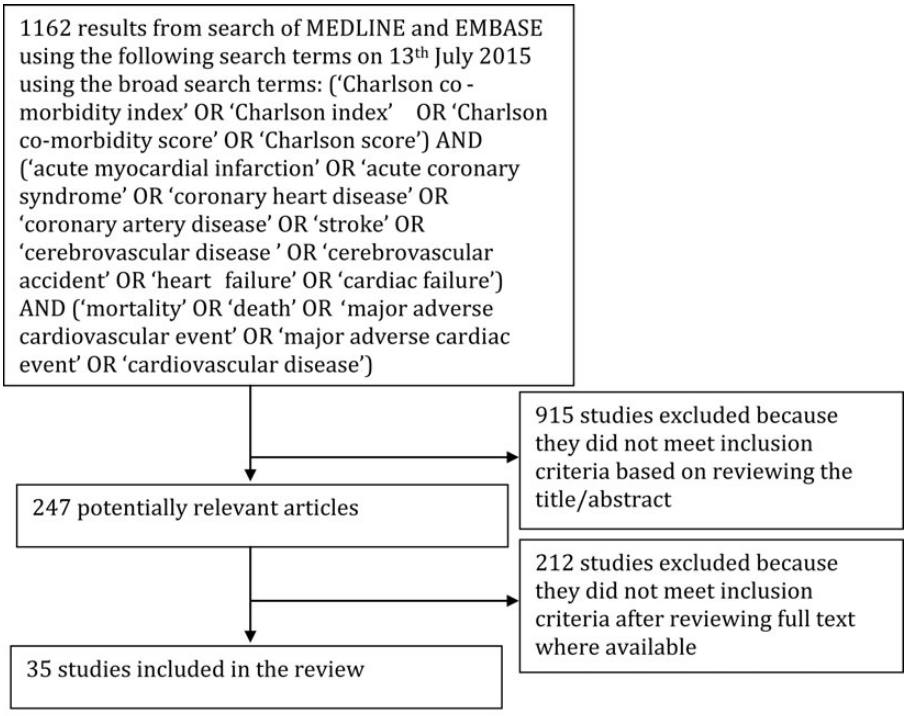


**Figure 1** Flow diagram of study selection.

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with CCI score of >1 (RR 2.26; 95% CI 1.23–4.16; $I^2 = 98\%$). Three studies[21,31,37] demonstrated a more than two-fold rise in mortality in patients with a CCI score of >2 comparing with a score of 0–2. Only one study[16] compared CCI score of 0–3 vs. >3, which reported higher mortality (RR 5.89; 95% CI 5.56–6.24) in patients with more co-morbidities (CCI score of >3).

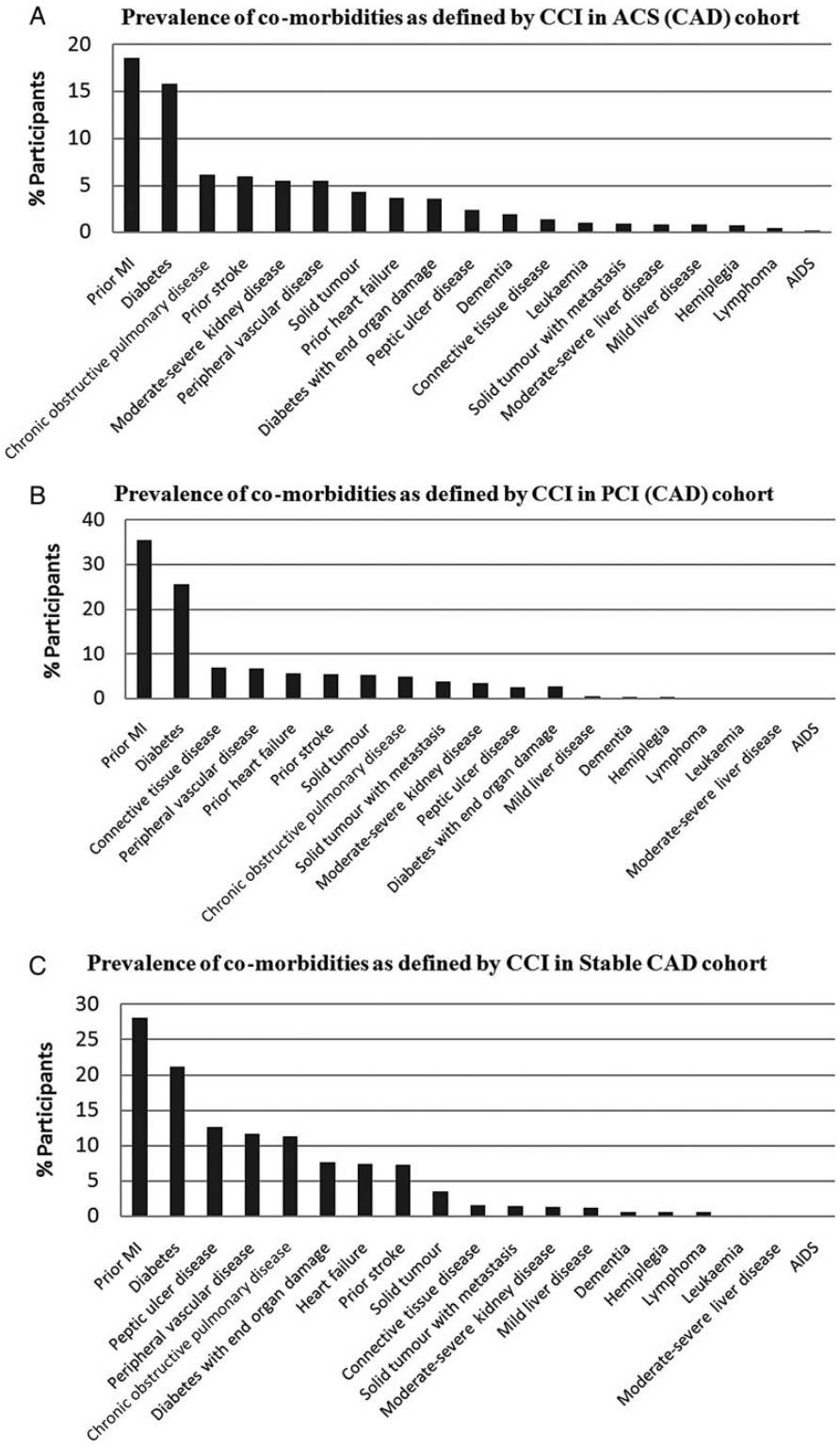


**Figure 2** Charlson co-morbidity individual component distribution.

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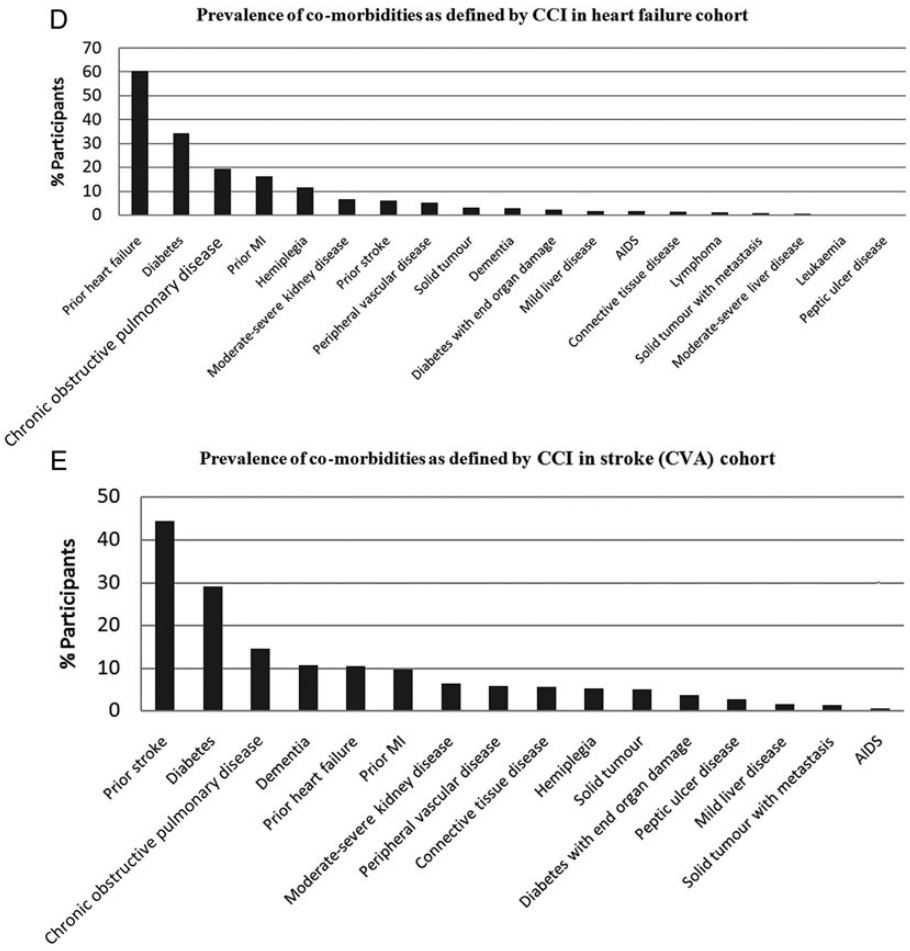


**Figure 2** Continued.

In an ACS registry (AMIS registry), Jeger *et al.*[22] reported an increased risk of MACE (a composite endpoint of re-infarction, CVA, and/or death) over a 1-year follow-up period in patients with CCI score of ≥2. In another study, Núñez *et al.*[28] demonstrated that a higher CCI score was an independent predictor of mortality or acute myocardial infarction at 30 days and 1 year.

### Stable coronary heart disease

Two studies[14,35] studied the relationship between incremental rise in CCI score and mortality in patients with stable CHD (*Figure 3B*), suggesting that incremental increases in CCI score were associated with worse outcomes (RR 1.38; 95% CI 1.29–1.48; $I^2 = 0\%$). Sachdev *et al.*[35] also reported that patients with a CCI score of 0 have better long-term survival (RR 1.88; 95% CI 1.48–2.38). They also reported that almost half of the patients (49%) included in the cohort were disease free and had no co-morbidities (CCI = 0).

### Patients undergoing percutaneous coronary intervention

Lastly, five studies[16,20,25,38,44] reported impact of CCI on long-term survival in patients undergoing PCI, out of which four indicated that mortality increases with each point rise in CCI score (RR 1.21; 95% CI 1.12–1.31; $I^2 = 71\%$) (*Figure 3C*). Only Mamas *et al.*[25] reported about patients with no co-morbidities in their study.

### Heart failure

A total of 13 studies reported the influence of co-morbidity in 63 609 patients with an underlying diagnosis of heart failure. An increased risk of mortality (RR 1.21; 95% CI 1.13–1.29; $I^2 = 48\%$) was observed per point increase in CCI score among four studies.[13,15,26,41] Jong *et al.*[23] and Rodriguez-Pascual *et al.*[34] compared patients with CCI score of 0–1 vs. >1 and demonstrated that a CCI score of >1 was associated with an increased risk of death (RR 1.60; 95% CI 1.52–1.70; $I^2 = 0\%$). Similar trends were observed in studies that compared a CCI score of >2 with a CCI score of 0–2. For instance, three studies[23,29,30] reported an increased risk of death (RR 1.76; 95% CI 1.65–1.87; $I^2 = 0\%$) in patients with CCI score of >2. Patients with high burden of co-morbidities (CCI score of >4) were analysed in three studies,[29,34,42] which showed almost three-fold increase in relative risk of mortality (RR 2.93; 95% CI 1.99–4.31; $I^2 = 15\%$). Two studies[27,45] reported increased risk of death with higher co-morbid burden with hazard ratio of >1, but it was unclear how they are related to CCI score. Both studies

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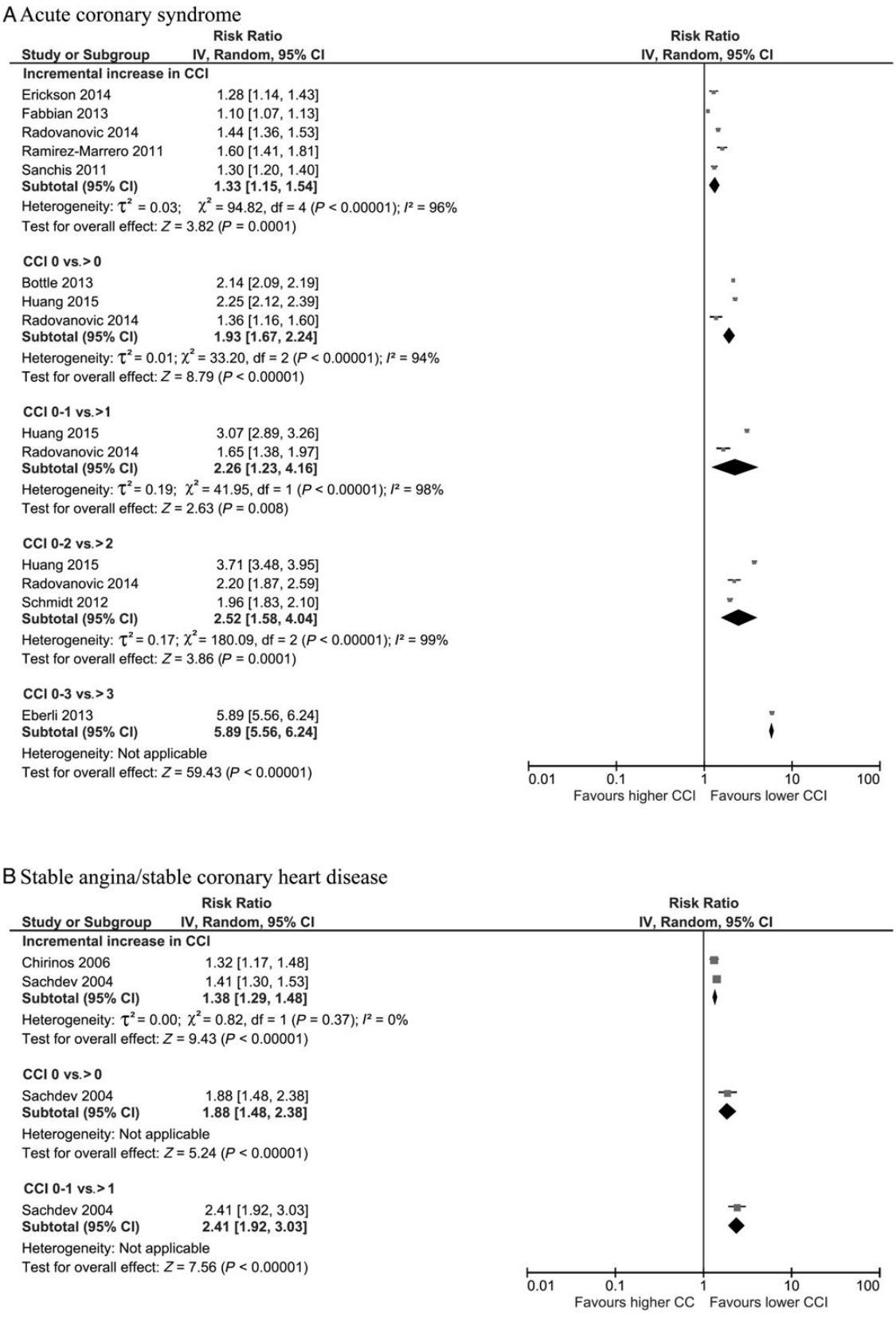


**Figure 3** Acute coronary syndrome patients, stable angina/stable coronary heart disease patients, and patients undergoing percutaneous coronary intervention and mortality according to Charlson Co-morbidity Index. (*A*) Acute coronary syndrome. (*B*) Stable angina/stable coronary heart disease. (*C*) Patients undergoing PCI.

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**Table 3 Quality of included studies**

| Study ID | Prospective study design | Reliable ascertainment of outcomes | Less than 10% loss to follow-up | Use of adjustments for potential confounders |
|---|---|---|---|---|
| Bottle 2013[11] | No; retrospective | Yes; death from death certificates from the Office for National Statistics | Unclear | None |
| Bar 2011[12] | Yes; prospective | Unclear; outcome assessed using modified Rankin scale out to 12 months by unclear methods | Unclear | Adjusted for presence of IVH, infratentorial ICH, and use of early DNACPR orders |
| Chin 1998[13] | Yes; prospective | Yes; death from chart review, survey of families, and search of the National Death Index | Yes; 7 patients discharged quickly and unreachable, 5 too sick for interview | White ethnicity, age $\geq$70 years, prior congestive heart failure, chronic pulmonary disease, Charlson Co-morbidity Index score, third heart sound, serum sodium $\leq$135, EF $<$0.50, diabetes, respiratory rate $>$30/min, cardiomegaly on admission chest radiograph |
| Chirinos 2006[14] | Yes; prospective | Yes; patients' interview and review of hospital electronic records | Yes; 9 patients were lost to follow-up | Multivariate analysis adjustments for age, left ventricular ejection fraction, congestive heart failure, and number of coronary artery territories involved with haemodynamically significant lesions |
| Clarke 2011[15] | No; retrospective | Yes; electronic database, review of medical notes, clinic visits, and review of death certificates | Yes; none | None |
| Eberli 2013[16] | Yes; prospective | Unclear; 1-year all-cause and cardiac mortality by unclear method | Unclear | None |
| Erickson 2014[17] | No; retrospective | Yes; 6-month post-discharge all-cause mortality or secondary cardiovascular events or revascularization procedures | Yes; none | None |
| Fabbian 2013[18] | No; retrospective | Yes; in-hospital mortality for myocardial infarction | Yes; none | Chronic kidney disease |
| Goldstein 2004[19] | Yes; prospective | Yes; death at discharge and 1-year mortality | Yes; none | Initial stroke severity |
| Hong 2011[20] | Yes; prospective | Yes; followed up at 30, 180, and 360 days by telephone communication, office visit, or by contacts with primary physicians or referring cardiologists for 1-year mortality, stent thrombosis | Yes; none | Unclear |
| Huang 2015[21] | No; retrospective | Yes; data collected from National Health Insurance Research Database and the National Disability Registration Database of Taiwan | Yes; none | Adjusted (Model A); variables unclear |
| Jeger 2014[22] | No; retrospective | Yes; data collected from AMIS plus registry | Yes; 161 lost to follow-up | None |
| Jong 2002[23] | No; retrospective. | Yes; 30-day and 1-year mortality ascertained by linking the database with Ontario registered person database | Yes; none | None |
| Khawaja 2014[24] | Unclear | Unclear; primary outcomes of modified Rankin scale of 4–6, death and poor discharge disposition (any disposition other than home or inpatient rehabilitation) assessed by unclear methods | Unclear | Adjusted for baseline ICH score |
| Mamas 2015[25] | Yes; prospective | Yes; data was collected into a Web-based data management system and an independent clinical events committee adjudicated all events | No; 326 lost to follow-up at 5 years | Adjusted for baseline demographic and lesion characteristic variables with a *P*-value of $<$0.05 |
| Menendez-Colino 2013[26] | Unclear | Unclear; mortality at 12 months; unclear follow-up methods | Yes; 25 patients | Unclear |
| Munoz-Rivas 2009[27] | No; retrospective | Unclear | Unclear | Unclear |
| Núñez 2004[28] | Yes; prospective | Yes; 30-day and 1-year mortality or reinfarction at outpatient follow-up and telephonic contact | Yes; none | None |
| Oudejans 2012[29] | Yes; prospective | Yes; all-cause mortality within 3 years; follow-up information obtained from hospital information system or from patient's general practitioners | Yes; 1 patient was lost to follow-up | Age, gender, LVEF, and NT-proBNP |



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| | | | | |
|---|---|---|---|---|
| Perez-Barquero 2010[30] | No; retrospective | Unclear; in-hospital mortality by unclear follow-up methods | Unclear | Unclear |
| Radovanovic 2014[31] | Yes; prospective | Yes; data collected from AMIS plus registry | No; 1091 patients' CCI data were not available | None |
| Ramirez-Marrero 2011[32] | No; retrospective | Unclear | Yes; none | None |
| Ramirez-Marrero 2013[33] | No; retrospective | Yes; cardiovascular mortality during follow-up | Yes; none | None |
| Rodriguez-Pascual 2012[34] | Yes; prospective | Unclear; mortality | Unclear | None |
| Sachdev 2004[35] | Yes; prospective | Yes; patients were followed up at 6 months, 1 year, and then annually by a mailed questionnaire, with telephone backup, as well as a National Death Index search for non-responders through December 2000 | Yes; none | Adjusted for age, unclear if other variables were adjusted |
| Sanchis 2011[36] | Yes; prospective | Yes; data collected from admission records and follow-up | Yes; 4 patients did not complete follow-up | Adjusted for variables with $P < 0.05$ but variables unclear |
| Schmidt 2012[37] | No; retrospective | Yes; standardized incidence rate of myocardial infarction and 30-day and 31- to 365-day mortality by sex | Unclear | Age and sex |
| Singh 2011[38] | Yes; prospective | Yes; all-cause mortality during follow-up; the second main outcome was MI defined as the presence of 2 of 3 following criteria: prolonged (>20 min) ischaemic chest pain and elevation of cardiac biomarkers (creatinine kinase-MB or relative index) more than two times upper limit of normal, or electrocardiographic changes (ST/T-wave changes or new Q waves) | Yes; 2% participants lost to follow-up | None |
| Subramanian 2007[39] | Yes; prospective | Yes; 5-year mortality during follow-up data obtained from Veterans Integrated Health Systems Technology Architecture databases | Yes; 35 patients were excluded for missing values | Adjusted; variables unclear |
| Teng 2014[40] | Yes; prospective | Yes; data were collected from the Hospital Morbidity Data Collection, which is linked to the Mortality register | Unclear | Adjusted; variables unclear |
| Testa 2009[41] | Yes; prospective | Yes; all subjects were contacted at home or in their institution and examined by physicians trained to administer a questionnaire | Yes; 35 patients were unreachable and 9 did not have social support | Age, sex, heart rate, systolic blood pressure, diastolic blood pressure, social support, drugs number, MMSE, BADL, NYHA, CAD, chronic obstructive pulmonary disease, neurological disease, congestive heart failure, and CCI |
| Theuns 2011[42] | Yes; prospective | Yes; the data collected from two prospective ICD registries from Rotterdam and Basel; patient followed up at outpatient clinics | Yes; none | Adjusted for age |
| Tuttolomondo 2008[43] | Yes; prospective | Yes; demographic data and follow-up were collected from GIFA registry | Yes; none | None |
| Urban 2011[44] | Yes; prospective | Yes; the data collected from the e-Select registry where patients were followed up at 30, 180, and 360 days by telephone communication or office visit by contacts with primary physicians or referring cardiologist | Unclear | Adjusted for variables with entry *P*-value of 0.10 and stay criterion of 0.15; unclear exact variables |
| Van Wijk 2013[45] | Yes; prospective | Yes; clinically followed up for 18 months with recording of hospitalization, mortality, and adverse events up to 5 years | Unclear | Adjusted; variables unclear |



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**Table 4** Follow-up and results of the association between Charlson Co-morbidity Index and outcome

| Study ID | Type of population (CAD, HF, CVA) | Definition of CCI | Outcome and duration of follow-up | Results demonstrating association between CCI and outcome |
|---|---|---|---|---|
| Bottle 2013[12] | ACS (CAD) | Charlson score 0 vs. >0 | 30-day mortality | 30-day mortality: CCI score 0: 8370/151 577 (5.5%); CCI score >0: 20 999/177 792 (11.8%) |
| Bar 2011[11] | Stroke (CVA) | Incremental rise in CCI from 0 to >3 | 12-month functional outcome according to modified Rankin scale | CCI score 1: OR 1.78 (0.86–3.70); CCI score 2: OR 2.34 (0.98–5.61); CCI score 3: OR 3.48 (1.64–7.37) |
| Chin 1998[13] | HF | Incremental increase in CCI | Time to mortality | Mortality per CCI point to max of 4 points: HR 1.3 (1.1–1.4) |
| Chirinos 2006[14] | Stable CAD | Incremental increase in modified CCI | All-cause mortality during 58-month follow-up | Odds of mortality with incremental increase in modified CCI score: OR 1.32 (1.17–1.48) |
| Clarke 2011[15] | Heart failure (HF) | Incremental increase in CCI | Time to mortality with follow-up of mean of 4.4 years | Overall mortality by per unit increase in CCI: HR 1.26 (1.19–1.35) |
| Eberli 2013[16] | PCI (CAD) | Mortality by different CCI score | 1-year mortality and cardiac mortality | Overall 1-year mortality: CCI score 0: 18/2041 (0.9%); CCI score 1: 28/2162 (1.3%); CCI score 2: 18/776 (2.3%); CCI score ≥3: 25/578 (4.3%)<br>Cardiac mortality: CCI score 0: 14/2041 (0.7%); CCI score 1: 13/2162 (0.6%); CCI score 2: 9/776 (1.2%); CCI score ≥3: 14/578 (2.4%) |
| Erickson 2014[17] | ACS (CAD) | Incremental increase in CCI | Inpatient and 6-month mortality and post-discharge cardiac event or procedure | Inpatient death with CCI: OR 1.28 (1.14–1.43)<br>6-month death with CCI: OR 1.55 (1.41–1.72)<br>Post-discharge cardiac event or procedure CCI: 1.21 (1.12–1.31) |
| Fabbian 2013[18] | ACS (CAD) | Incremental increase in CCI | In-hospital mortality from MI | In-hospital mortality for MI with CCI without renal dysfunction: OR 1.101 (1.069–1.134) |
| Goldstein 2004[19] | Stroke (CVA) | Low CCI 0–1 vs. high CCI ≥2 | 1-year mortality | 1-year mortality with low CCI score 0–1: 88/551 (16%)<br>High CCI score ≥2: 106/429 (26%) |
| Hong 2011[20] | PCI (CAD) | Incremental rise in CCI on outcomes | Time to mortality or stent thrombosis with follow-up up to 1-year | Every 1-point increment in CCI on death: HR 1.3 (1.1–1.5)<br>Every 1-point increment on stent thrombosis: HR 1.5 (1.3–1.8) |
| Huang 2015[21] | ACS (CAD) | Risk for each CCI score | Time to acute myocardial infarction | Adjusted model A (unclear variables): CCI score 1: HR 2.25 (2.12–2.39); CCI score 2: HR 3.07 (2.89–3.26); CCI score 3: HR 3.71 (3.48–3.95); CCI score ≥4: HR 5.89 (5.56–6.25) |
| Jeger 2014[22] | ACS (CAD) | Charlson score ≥2 | 1-year MACE | 1-year MACE with CCI score ≥2: OR 1.42 (1.05–1.92) |
| Jong 2002[23] | Heart failure (HF) | CCI score and mortality rate | 30-day and 1-year mortality | CCI score 0: 30-day mortality 1397/15 020 (9.3%); 1-year mortality 4025/15 020 (26.8%)<br>CCI score 1: 30-day mortality 1348/12 602 (10.7%); 1-year mortality 3907/12 602 (31.0%)<br>CCI score 2: 30-day mortality 895/6485 (13.8%); 1-year mortality 2555/6485 (39.4%)<br>CCI score 3: 30-day mortality 864/4595 (18.8%); 1-year mortality 2325/4595 (50.6%) |
| Khawaja 2014[24] | Stroke (CVA) | Incremental increase in CCI score | Death at unclear follow-up | Death and CCI score: OR 1.05 (0.91–1.21) |
| Mamas 2015[25] | PCI (CAD) | Incremental increase in CCI score | 30-day, 1-year, and 5-year cardiac death and MACE | 30-day: cardiac death: OR 1.47 (1.20–1.80); MACE: OR 1.27 (1.11–1.44)<br>1-year: cardiac death: OR 1.46 (1.30–1.65); MACE: OR 1.32 (1.23–1.42)<br>5-year: cardiac death: OR 1.38 (1.24–1.53); MACE: OR 1.29 (1.22–1.36) |
| Menendez-Colino 2013[26] | Heart failure (HF) | CCI score and mortality | Time to mortality with follow-up maximum of 12 months | CCI score: HR 1.13 (1.04–1.24) |
| Munoz-Rivas 2009[27] | Heart failure (HF) | Incremental increase in CCI | Survival | Survival with incremental CCI: HR 1.46 (1.21–5.07) |



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| Núñez 2004[28] | ACS (CAD) | CCI score and risk compared with CCI score 0 | Time to death or reinfarction to a maximum of 30 days and 1 year | Risk of death or reinfarction at 30 days: CCI score 1: HR 1.00; CCI score 2: HR 1.69 (1.10–2.59); CCI score 3: HR 1.78 (1.08–2.92); CCI score 4: HR 1.57 (0.87–2.83)<br>Risk of death or reinfarction at 1 year: CCI score 1: HR 1.00; CCI score 2: HR 1.62 (1.18–2.23); CCI score 3: HR 2.00 (1.39–2.89); CCI score 4: HR 2.24 (1.50–3.36) |
| Oudejans 2012[29] | Heart failure (HF) | CCI score 0–2 vs. 3–4 or ≥4 | Time to mortality to a maximum of 3 years | 3-year mortality: CCI score 0–2: HR 1.00; CCI score 3–4: HR 1.5 (0.7–2.9); CCI score >4: HR 4.0 (1.9–8.8) |
| Perez-Barquero 2010[30] | Heart failure (HF) | CCI score 1–2 vs. ≥3 | In-hospital mortality | In-hospital mortality: CCI score 1–2: 76/1528; CCI score ≥3: 48/599 |
| Radovanovic 2014[31] | ACS (CAD) | Incremental rise in CCI and risk compared with CCI score 0 | In-hospital mortality and 1-year mortality assessed using data from AMIS plus registry | In-hospital mortality compared with CCI score 0: CCI score 1: OR 1.36 (1.16–1.60); CCI score 2: OR 1.65 (1.38–1.97); CCI score ≥3: OR 2.20 (1.86–2.57)<br>1-year mortality per CCI point: age-adjusted mortality: OR 1.44 (1.36–1.53) |
| Ramirez-Marrero 2011[32] | ACS (CAD) | Higher CCI treated as incremental | In-hospital mortality and median follow-up of 24 months | In-hospital mortality: OR 1.6 (1.4–1.8); long-term mortality: OR 1.3 (1.2–1.5); readmission for HF: OR 1.2 (1.04–1.3); MACE during follow-up: OR 1.1 (1–1.2) |
| Ramirez-Marrero 2013[33] | ACS (CAD) | Highest CCI score | Cardiovascular mortality during follow-up of 36 months | CCI and long-term mortality: OR 1.72 (1.09–2.71) |
| Rodriguez-Pascual 2012[34] | Heart failure (HF) | CCI score | Mortality | Mortality by CCI score: 0–1: 5/121; 2–4: 17/227; ≥5: 26/194 |
| Sachdev 2004[35] | Stable CAD | CCI scores of 0, 1, and ≥2 | Time to mortality during follow-up period of almost 11 years | CCI score 0: 95/810 (11.7%); CCI score 1: 58/378 (15.3%); CCI score ≥2: 88/283 (31.1%)<br>Incremental increase in modified CCI: HR 1.41 (1.30–1.53) |
| Sanchis 2011[36] | ACS (CAD) | Incremental increase in CCI per point | Time to mortality to a maximum of 1 year | Per point increase in CCI: HR 1.3 (1.2–1.4) |
| Schmidt 2012[37] | ACS (CAD) | CCI score 0 (normal) vs. ≥3 (very severe) | 30-day and 31- to 365-day mortality | 30-day mortality: RR 1.96 (1.83–2.11)<br>31- to 365-day mortality: RR 3.89 (3.58–4.24) |
| Singh 2011[38] | PCI (CAD) | Incremental increase in CCI per point | Time to mortality or myocardial infarction during median follow-up of 35 months | Death during follow-up: HR 1.12 (1.06–1.18)<br>Death/MI during follow-up: HR 1.05 (1.01–1.10) |
| Subramanian 2007[39] | Heart failure (HF) | Incremental increase in 3 points of CCI | Time to mortality at follow-up of up to 5 years | 5-year all-cause mortality: HR 1.39 (1.16–1.67) |
| Teng 2014[40] | Heart failure (HF) | CCI unclear if incremental or cut-off | 1-year mortality | 1-year mortality with CCI: <55 years: HR 1.38 (1.26–1.51); ≥55 years: HR 1.20 (1.18–1.22) |
| Testa 2009[41] | Heart failure (HF) | Incremental increase in CCI score | Time to mortality to a maximum follow-up of 12 years | 12-year mortality with CCI: HR 1.15 (1.01–1.31) |
| Theuns 2011[42] | Heart failure (HF) | CCI score >5 | Time to all-cause mortality during a median follow-up of 30.5 months | All-cause mortality: HR 3.49 (2.06–6.60) |
| Tuttolomondo 2008[43] | Stroke (CVA) | CCI score <2 vs. CCI score >2 | In-hospital mortality | In-hospital mortality: OR 35.7 (4.8–265.2) |
| Urban 2011[44] | PCI (CAD) | Incremental increase in CCI per point | Time to death, stent thrombosis, and major bleeding at maximum of 1 year | 1-year death: HR 1.2 (1.1–1.2)<br>1-year stent thrombosis: HR 1.2 (1.1–1.4)<br>1-year major bleeding: HR 1.1 (1.0–1.2) |
| Van Wijk 2013[45] | Heart failure (HF) | Incremental increase in CCI score | Hospital-free survivals during follow-up period | CCI score: HR 2.47 (1.27–4.83) |



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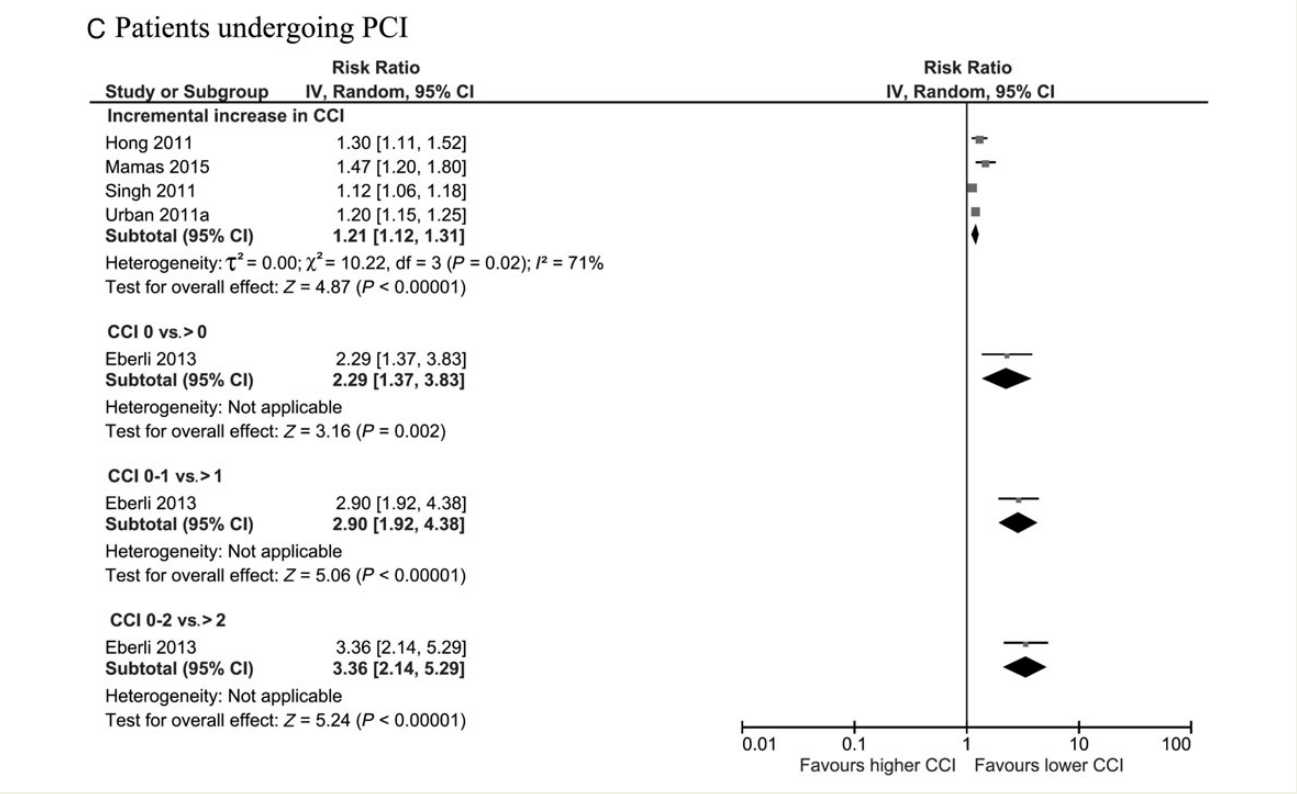


**Figure 3** Continued.

were only available in abstract form and, therefore, not included in the final meta-analysis. More interestingly, Subramanian *et al.*[39] assessed the impact of incremental increase in CCI per 3 points in heart failure patients over 5 years, reporting increased risk of death (HR 1.39; 95% CI 1.16–1.67) with growing burden of co-morbidities.

### Cerebrovascular accident

A total of four studies analysed the impact of CCI score on survival in patients with an acute CVA. Khawaja *et al.*[24] reported a no significant increased risk of death with incremental increase in CCI score (RR 1.05; 95% CI 0.91–1.21). However, higher CCI score (>2) had significant impact on mortality (RR 3.80; 95% CI 1.20–12.01; $I^2 = 84\%$) when compared with low CCI score (0–2).

## Discussion

In this study, we evaluated the prevalence and prognostic impact of co-morbidities as defined by CCI in patients with CHD, heart failure, and CVA. We observed a significant burden of co-morbidity in patients with CVD—two-thirds of patients included in the analysis had at least one chronic condition. The most common cardiovascular co-morbid conditions identified in patients with CHD were diabetes and history of prior myocardial infarction, whereas chronic obstructive pulmonary disease and kidney disease were the most frequent non-cardiovascular conditions. To our knowledge, this is the first study to systematically show the impact of co-morbid burden as defined by CCI on survival in patients with CHD, heart failure, and CVA. We found that the presence of co-morbidities had a significant incremental prognostic impact in patients with a broad range of CVDs.

CHD is the commonest CVD affecting one in seven people in USA[46] and UK every year. Patients with CHD are likely to have higher number of coexisting illnesses either in the form of prevalent cardiovascular risk factors such as diabetes and hypertension or in the form of direct manifestations of CHD such as prior myocardial infarction or heart failure. For instance, in one study, diabetes, hypertension, and heart failure were found to be most frequently encountered coexisting illnesses in patients admitted with ACS and 68% of the participants had at least three co-morbidities.[47] The rising burden of co-morbidity has been reported to have inverse relationship with survival outcomes in patients with CHD. In our analysis, incremental rise in CCI was associated with significant increase in mortality and the risk of death was almost doubled with the presence of any co-morbidity compared with the patients with no co-morbidity (*Figure 3A*). This has important clinical implications in this cohort of patients as the prevalent cardiovascular risk factors such as hyperlipidaemia, smoking, and other related cardiovascular co-morbidities such as hypertension and diabetes in patients with CHD are usually treated aggressively, but there is growing evidence that non-CVD burden may also contribute to increased risk of mortality.[25,31] We report that CCI is not only a simple way of quantifying co-morbid burden but also provides prognostic value in ascertaining outcomes. Clinicians often use risk assessment tools such as GRACE and TIMI scores in determining

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the type of intervention, treatment plan, and allocation of resources in managing patients with ACS. Although these models have been validated in predicting the adverse events,[48,49] the clinical data incorporated in these models do not take into account the co-morbid burden of the patients. Previous studies have suggested that the performance of such risk models improves when co-morbidity scores such as CCI are added to the risk scores[17] and may help in better allocations of resources and developing robust treatment pathways for patients with multiple co-morbidities. Our study highlights the importance of taking into consideration of the overall co-morbid burden in such patients while making the therapeutic decisions. Furthermore, our study also demonstrates that co-morbidity burden has prognostic value.

The prevalence of heart failure is increasing due to the ageing population and better survival from acute cardiac events.[50] Our findings reinforce the hypothesis that heart failure patients with multiple co-morbidities have worse outcomes.[15] Similarly, increasing co-morbid burden is associated with a worse prognosis in patients after an acute cerebrovascular event. We observed that the risk of death was almost four-fold greater in patients with two or more coexisting illnesses (*Figures 4* and *5*).

The mechanism by which the coexisting co-morbid burden influences outcomes in patients with CVD is complex and multifactorial. Older and frailer patients with high burden of co-morbidities are more likely to be treated conservatively following a cardiovascular event.[51,52] For instance, a large national ACS registry reported an incremental reduction in provision of evidence-based treatments such as aspirin, statins, angiotensin-converting enzyme (ACE) inhibitors, and reperfusion therapy to the older multi-morbid patients.[53] In another recent analysis of 18 814 patients, Patel *et al.* identified that patients with higher co-morbid burden as defined by CCI were less likely to receive coronary artery angiography and/or revascularization following presentation with ST-segment elevation myocardial infarction.[54] Similarly, thrombolysis therapy in acute ischaemic stroke is usually reserved for younger patients with no significant burden of co-morbidities due to fear of less favourable outcomes such as bleeding complications in elderly patients with multiple co-morbidities.[55] In the management of patients with chronic heart failure, the associated burden of co-morbidities may limit the use of medications such as ACE inhibitors or spironolactone, particularly in patients with severe chronic kidney disease[56] and β-blockers in patients with coexisting severe chronic obstructive pulmonary disease. Furthermore, patients with multiple chronic conditions are less likely to receive invasive therapies such as implantable cardioverter-defibrillators or cardiac resynchronization therapy.[57] There is also growing evidence that increasing burden of co-morbidities in patients with heart failure is associated with repeated hospitalization and poor outcomes.[58,59]

Provision of aggressive treatment strategies in patients with multimorbidity can lead to higher incidence of complications and adverse outcomes. For example, patients with leukaemia are at higher risk of stent thrombosis[60] and those with liver dysfunction are at increased

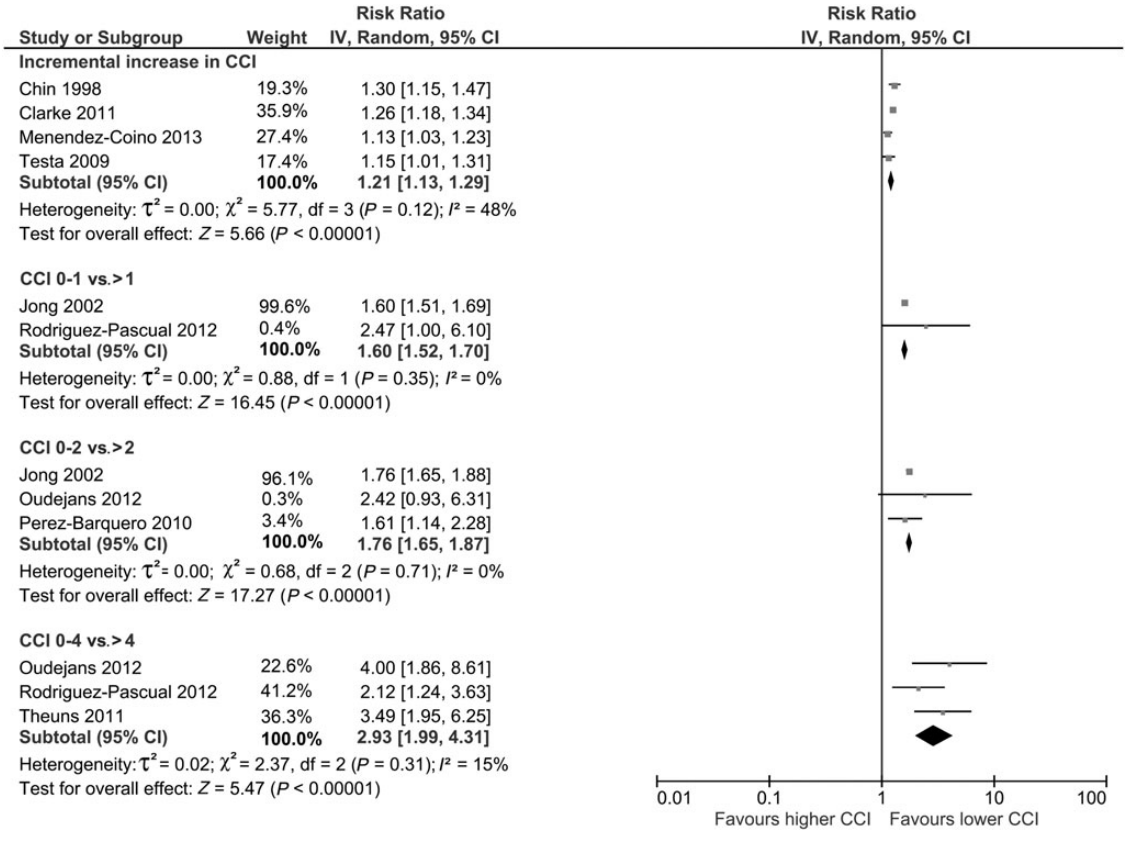


**Figure 4** Heart failure patients and mortality according to Charlson Co-morbidity Index.

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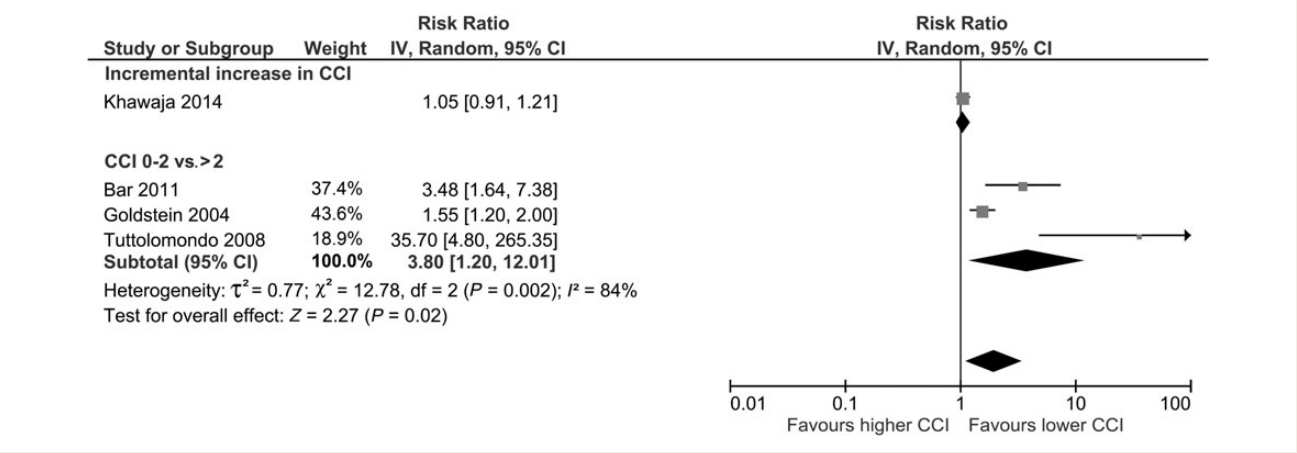


**Figure 5** Cerebrovascular accident patients and mortality according to Charlson Co-morbidity Index.

risk of bleeding complications post-PCI and cardiac mortality.[61] Similarly, the presence of diabetes and haematological disorders has been shown to increase the risk of haemorrhagic transformation in patients with ischaemic stroke.[62,63] Consequently, the presence of coexisting diseases may drive poor outcomes in patients with CHD due to reduced scope of treatment options and increased risk of complications. Hence, clinicians may be reserved in deciding treatment strategies while managing patients with multi-morbidity due to the challenge of finding a balance between risk and benefit of an intervention.[64,65]

Other factors that may be responsible for deleterious effect of co-morbidities on survival outcomes are the presence of coexisting illness sharing the same pathophysiology and adverse drug reactions due to polypharmacy. For example, the presence of anaemia results in low cardiac output state and has been reported to have synergetic impact on the mortality in patients with chronic heart failure.[66]

Our findings have important implications in the management of patients with CHD, heart failure, and cerebrovascular disease. Treatment options such as medical therapies, PCI, surgical revascularization, device therapies, and thrombolysis are now readily available to wider spectrum of patients. Although international guidelines[67,68] advocate a comprehensive assessment of patients taking into account their co-morbid status, contemporary risk stratification tools such as GRACE, Cath PCI, and Syntax are derived from data sets based on patient's characteristics, procedural demographics, and cardiovascular risk factors and do not take into account patients' co-morbid burdens. Our analysis shows that CCI score has prognostic value in our cohort of patients and using CCI alongside these risk models can help physicians to ascertain outcomes and better resource allocation. For instance, the addition of CCI to the Mayo Clinic Risk Score for PCI increased net reclassification index by 34% and improved the c-statistic for the model significantly.[38] Erickson *et al.*[17] also tested the risk prediction of GRACE model by adding CCI and observed a significant improvement in predicting outcomes in ACS patients. Another study reported improved discriminative performance of GRACE Risk Prediction Index score when added with CCI in predicting future cardiac-related events post-myocardial infarction.[17] Therefore, the assessment of co-morbid status and its impact on long-term survival should be integrated into the counselling of the patients before deciding the choice of treatment in conjunction with traditional risk assessment.

Our study has several strengths and limitations. To our knowledge, this is the first review on impact of co-morbidity defined by CCI on major CVD such as CHD, heart failure, and cerebrovascular disease. We were able to analyse the impact of per unit rise in CCI in our cohort of patients demonstrating that rise in CCI score has inverse relationship with survival. We were also able to evaluate the impact of CCI among individual cohorts of CHD namely stable angina, ACS, and those undergoing PCI and found a uniform negative impact of rising CCI score across all cohorts. Additionally, we also studied the prevalence of co-morbidities in patients with CVD and found that majority of patients in this cohort have significant burden of co-morbidities.

Our study was limited by the incomplete reporting of original studies and was reliant on the published data available. We were not able to evaluate the impact of individual components of CCI on mortality, as this was not consistently reported across all studies. Furthermore, the studies included in our review were mainly observational, which have their own inherent limitations and may be subject to selection biases and unmeasured confounders. Another limitation is that we found significant heterogeneity in several analyses. This may be because many of the studies are large with very narrow confidence intervals leading to statistical heterogeneity when there is little overlap in 95% CI among the studies. However, all the studies, in general, report estimates that are consistently significant and favour increased events with higher CCI score. The statistical heterogeneity arises from differences in each study in terms of population evaluated and study methodology, which leads to variation in estimates for the prognostic value of CCI.

## Conclusion

Our study shows that co-morbid burden defined by CCI is significant across a broad range of cardiovascular conditions and has significant impact on survival in patients with CHD, heart failure,

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and CVA. Assessment of co-morbid burden using CCI provides a method of quantifying risk associated with co-morbidities in patients with CVD and should be incorporated into decision-making processes when counselling patients regarding risk and benefits of treatment in conjunction with allocation of resources.

## Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

**Conflict of interest**: none declared.

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