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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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Abstract:

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

Methods & 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% CI1.12-1.31) stable coronary artery disease (RR 1.38 95%CI 1.29-1.48) and HF (RR1.21 95%CI 1.13-1.29), but not CVA. A CCI score >2 significantly increased the risk of mortality in ACS (RR 2.52 95% CI 1.58-4.04), PCI (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 CV disease and should be incorporated into decision-making processes when counseling patients.

Keywords : Charlson comobidity 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 hospitalised 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 comorbidities. It remains unclear, however, 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 co-existing illnesses. Table 1 represent 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 cardiovascular diseases. 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

cardiovascular diseases; coronary heart disease, 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 Charlson co-morbidity index (CCI) in patients with coronary heart disease (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 cardiovascular disease.
2. Cardiovascular disease was defined by CHD (comprising of patients undergoing percutaneous coronary intervention or stable angina or acute coronary syndrome), or acute or chronic heart failure, or cerebrovascular disease.
3. Adverse outcomes included: mortality, 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 (MR, CSK) 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 risk ratios (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 (Supplementary Table 1). The primary analysis evaluated adverse outcomes with incremental increase in CCI and secondary analysis was performed by considering higher group of CCI score versus 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].

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] whilst 2 abstract studies[24, 26] were not clear in reporting the design. There were a total of 1,538,793 participants in 35 studies. 24 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.

17 studies[12-16, 19, 20, 22, 23, 25, 28, 29, 31, 34-36, 38, 42] reported individual CCI scores and 530,457 out of 1,538793 (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 coronary heart disease. 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 airways disease (COPD). Similarly, diabetes was the most prevalent co-morbidity in the patients with CVA

cohort. Hematological malignancies such lymphoma leukemia 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. 22 studies had less than 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 in described in Table 4.

Acute coronary syndrome (ACS)

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). 5 studies[17, 18, 31, 32, 36] were statistically pooled for the association between an incremental increase in CCI and mortality (Figure3A). 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). 3 studies, I^2=96% [11, 21, 31] compared patients with no co-morbidity (CCI score=0) versus patients with any co-morbidity (CCI score>0) showing that the presence of co-morbidity (CCI score>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 0-1 versus >1 showing a higher risk of death in patients with CCI score >1 (RR 2.26 95%CI 1.23-4.16, I^2=98%). 3 studies[21, 31, 37] demonstrated a more than two-fold rise in mortality in patients with CCI score >2 comparing to a score of 0-2. Only 1 study[16] compared CCI score 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 >3).

In an ACS registry (AMIS registry), Jeger *et al.*[22] reported an increase risk of MACE (a composite end point of re-infarction, CVA, and or death) over a one-year follow up period in patients with CCI score ≥2. In another study, Nunez *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

2 studies[14, 35] studied the relationship between incremental rise in CCI score and mortality in patients with stable coronary heart disease (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 comorbidities (CCI=0).

Patients undergoing PCI

Lastly, 5 studies[16, 20, 25, 38, 44]reported impact of CCI on long term survival in patients undergoing PCI, out of which 4 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 comorbidities 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 amongst 4 studies[13, 15, 26, 41]. Jong *et al.*[23] and Rodriguez-Pascual *et al.*[34] compared patients with CCI score 0-1 versus >1, and demonstrated that a CCI score >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 >2 with a CCI score of 0-2. For instance, 3 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 greater than 2. Patients with high burden of comorbidities (CCI score >4) were analyzed in 3 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%). 2 studies[27, 45] reported increased risk of death with higher co-morbid burden with hazard ratio >1 but it was unclear how they are related to CCI score. Both studies 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 increase risk of death (HR 1.39 95%CI 1.16-1.67) with growing burden of comorbidities.

Cerebrovascular accident (CVA):

A total of 4 studies analyzed the impact of CCI score on survival in patients with an acute CVA. Khawaja *et al*[24] reported a no significant increase 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 CV disease –two thirds of patients included in the analysis had at least one chronic condition. The most common CV comorbid conditions identified in patients with CHD were diabetes and history of prior myocardial infarction, whereas COPD 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 coronary heart disease, 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 CV disease.

CHD is the commonest cardiovascular disease affecting 1 in 7 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, hypertension or direct manifestations of coronary heart disease 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 comorbidities[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 presence of any co-morbidity compared to 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 hyperlipidemia, smoking and other related cardiovascular comorbidities such as hypertension, diabetes in patients with coronary heart disease are usually treated aggressively but there is growing evidence that non

cardiovascular disease burden may also contribute to increase risk of mortality [25, 31]. We report that CCI is not only a simple way of quantifying comorbid burden but also provides prognostic value in ascertaining outcomes. Clinicians often use risk assessment tools such GRACE, TIMI scores in determining the type of intervention, treatment plan and allocation of resources in managing patients with ACS. Although these models have been validated in the 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 comorbidities. Our study highlights the importance of taking into consideration of the overall co-morbid burden in such patients whilst making the therapeutic decisions. Furthermore, our study also demonstrates that comorbidity burden has prognostic value.

The prevalence of heart failure is increasing due to the aging population and better survival from acute cardiac events[50]. Our findings reinforce the hypothesis that heart failure patients with multiple comorbidities have worse outcomes[15]. Similarly, increasing comorbid 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 co-existing illnesses (Figure 5).

The mechanism by which the co-existing co-morbid burden influences outcomes in patients with cardiovascular disease is complex and multifactorial. Older and frailer patients with high burden of comorbidities 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, 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 comorbid burden as defined by CCI were less likely to receive coronary artery angiography and or/ revascularization following presentation with STEMI[54]. Similarly thrombolysis therapy in acute ischemic stroke is usually reserved for younger patients with no significant burden of comorbidities due to fear of less favorable outcomes such as bleeding complications in elderly patients with multiple comorbidities[55]. In the management of patients with chronic heart failure, the associated burden of comorbidities may limit the use of medications such as ACE inhibitors or spironolactone particularly in patients with severe chronic kidney disease[56] and beta-blockers in patients with coexisting severe COPD. Furthermore, patients with multiple chronic conditions are less likely to receive invasive therapies such as implantable cardioverter-defibrillators (ICD) or cardiac resynchronization therapy[57]. There is also growing evidence that increasing burden of comorbidities in patients with heart failure is associated with repeated hospitalization and poor outcomes[58, 59].

Provision of aggressive treatment strategies in patients with multi-morbidity can lead to higher incidence of complications and adverse outcomes. For example, Patients with leukemia are at higher risk of stent thrombosis[60] and those with liver dysfunction are at increase risk of bleeding complications post PCI and cardiac mortality[61]. Similarly, the presence of diabetes and hematological disorders has been shown to increase the risk of hemorrhagic transformation in patients with ischemic stroke[62, 63]. Consequently, the presence of co-existing 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 whilst 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 comorbidities on survival outcomes are presence of coexisting illness sharing the same pathophysiology and

adverse drug reactions (ADRs) due to polypharmacy. For example, 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 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 comorbid status, contemporary risk stratification tools such as GRACE, Cath PCI, Syntax are derived from datasets 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 re-classification 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 GRPI (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 counseling 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 cardiovascular disease 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 amongst individual cohorts of coronary heart disease 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 comorbidities in patients with cardiovascular disease and found that majority of patients in this cohort have significant burden of comorbidities.

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% confidence amongst 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 coronary heart disease, heart failure and CVA. Assessment of co-morbid burden using CCI provides a method of quantifying risk associated with comorbidities in patients with CV disease and

should be incorporated into decision making processes when counseling patients regarding risk and benefits of treatment in conjunction with allocation of resources.

Conflicts of interest: None

REFERENCES

1. Mendis S, Puska P, Norrving B., eds. Global atlas on cardiovascular disease prevention and control: Policies, strategies and interventions. Geneva: World Health Organization in collaboration with World Heart Federation and World Stroke Organization; 2011. Available from: http://www.who.int/cardiovascular_diseases/publications/atlas_cvd/en/.

2. Barnett K, Mercer SW, Norbury M, Watt G, Wyke S, Guthrie B, Epidemiology of multimorbidity and implications for health care, research, and medical education: a cross-sectional study. Lancet. 2012;**380**:37-43.

3. Wolff JL, Starfield B, Anderson G, Prevalence, expenditures, and complications of multiple chronic conditions in the elderly. Arch of intern Med. 2002;**162**:2269-76.

4. Alexander KP, Newby LK, Cannon CP, Armstrong PW, Gibler WB, Rich MW, et al. Acute coronary care in the elderly, part I Non–ST-segment–elevation acute coronary syndromes: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: In collaboration with the Society of Geriatric Cardiology. Circulation. 2007;**115**:2549-69.

5. Alexander KP, Newby LK, Armstrong PW, Cannon CP, Gibler WB, Rich MW, et al. acute coronary care in the elderly, Part II ST-segment–elevation myocardial infarction: a scientific statement for healthcare professionals from the American Heart Association Council on Clinical Cardiology: In collaboration with the Society of Geriatric Cardiology. Circulation. 2007;**115**:2570-89.

6. McManus DD, Nguyen HL, Saczynski JS, Tisminetzky M, Bourell P, Goldberg RJ, Multiple cardiovascular comorbidities and acute myocardial infarction: temporal trends (1990-2007) and impact on death rates at 30 days and 1 year.clin Epidemiol. 2012;**4**:115-123.

7. Charlson ME, Pompei P, Ales KL, MacKenzie CR, A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J chronic Dis. 1987;**40**:373-83.

8. Deyo RA, Cherkin DC, Ciol MA, Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol. 1992;**45**:613-9.

9. Deeks JJ, Higgins JP, Altman DG. Analysing data and undertaking meta-analyses. In: Higgins JPT, Green S, eds. Cochrane handbook for systematic reviews of interventions. John Wiley & Sons, 2011.

10. Ioannidis JP, Trikalinos TA, The appropriateness of asymmetry tests for publication bias in meta-analyses: a large survey. CMAJ. 2007;**176**:1091-6.

11. Bottle A, Sanders RD, Mozid A, Aylin P. Provider profiling models for acute coronary syndrome mortality using administrative data. Int J Cardiol. 2013;**168**:338-43.

12. Bar B, Hemphill JC, Charlson comorbidity index adjustment in intracerebral hemorrhage. Stroke. 2011;**42**:2944-6.

13. Chin MH, Goldman L, Gender differences in 1-year survival and quality of life among patients admitted with congestive heart failure. Med care. 1998;**36**:1033-46.

14. Chirinos JA, Veerani A, Zambrano JP, Schob A, Perez G, Mendez AJ, et al. Evaluation of comorbidity scores to predict all-cause mortality in patients with established coronary artery disease. Int J Cardiol. 2007;**117**:97-102.

15. Clarke B, Howlett J, Sapp J, Andreou P, Parkash R. The effect of comorbidity on the competing risk of sudden and nonsudden death in an ambulatory heart failure population. Can J Cardiol. 2011;**27**:254-61.

16. Eberli F, Valdes M, Menown I, Alhaddad I, Oldroyd K, Roffi M, Hildick-Smith D, Iosseliani D, Kapur K, Urban P. Comorbidities determine prognosis in patients undergoing coronary stenting: Results from two large registries evaluating biolimus-A9-eluting from biodegradable polymer stents. Eurointervention 2013;**9**:194.

17. Erickson SR, Cole E, Kline-Rogers E, Eagle KA. The addition of the Charlson Comorbidity Index to the GRACE Risk Prediction Index improves prediction of outcomes in acute coronary syndrome. Popul Health manag. 2014;**17**:54-9.

18. Fabbian F, Pala M, De Giorgi A, Manfredini F, Menegatti AM, Salmi R, et al. In-hospital mortality in patients with renal dysfunction admitted for myocardial infarction: the Emilia-Romagna region of Italy database of hospital admissions. Int Urol and Nephrol. 2013;**45**:769-75.

19. Goldstein LB, Samsa GP, Matchar DB, Horner RD. Charlson Index comorbidity adjustment for ischemic stroke outcome studies. Stroke. 2004;**35**:1941-5.

20. Hong YJ, Jeong MH, Abizaid A, Banning A, Bartorelli A, Dzavik V, et al. Sirolimus-eluting coronary stents in octogenarians: a 1-year analysis of the worldwide e-SELECT Registry. JACC: Cardiovasc Interv. 2011;**4**:982-91.

21. Huang Y-Y, Kung P-T, Chiu L-T, Tsai W-C. Related factors and incidence risk of acute myocardial infarction among the people with disability: A national population-based study. Res Dev Disabil. 2015;**36**:366-75.

22. Jeger R, Jaguszewski M, Nallamothu BN, Lüscher TF, Urban P, Pedrazzini GB, et al. Acute multivessel revascularization improves 1-year outcome in ST-elevation myocardial infarction: a nationwide study cohort from the AMIS Plus registry. Int J Cardiol. 2014;**172**:76-81.

23. Jong P, Vowinckel E, Liu PP, Gong Y, Tu JV. Prognosis and determinants of survival in patients newly hospitalized for heart failure: a population-based study. Arch Intern Med. 2002;**162**:1689-94.

24. Khawaja A, Boehme AK, Albright K, Kumar G, Arora K, Lyerly M, Harrigan M. The utility of Charlson Comorbidity Index in predicting short-term outcomes in patients with primary intracerebral hemorrhage. Stroke 2015;**46**:ATP326.

25. Mamas MA, Fath-Ordoubadi F, Danzi GB, Spaepen E, Kwok CS, Buchan I, et al. Prevalence and Impact of Co-morbidity Burden as Defined by the Charlson Co-morbidity Index on 30-Day and 1- and 5-Year Outcomes After Coronary Stent Implantation (from the Nobori-2 Study). Am J Cardiol. 2015;**116**:364-71.

26. Menendez-Colino R, Condorhuaman P, Diez-Sebastian J, Mauleon-Ladrero C, Paredes E, Ferrero-Martinez A, et al. One-year mortality related factors in older-old patients admitted with heart failure in six Spanish hospitals. European Geriatric Medicine. 2013;**4**:S32.

27. Munoz Rivas N. MM, Ortiz Alonso J, Nieto S, Audibert Mena L, Renieblas P, The role of comorbidities in elderly patients with heart failure: Implication on survival. European Journal of Heart Failure Supplements 2009, **8**(2), Abstract 1106.

28. Núñez JE, Núñez E, Fácila L, Bertomeu V, Llàcer À, Bodí V, et al. Prognostic value of Charlson comorbidity index at 30 days and 1 year after acute myocardial infarction. Revista Española de Cardiología (English Edition). 2004;**57**:842-9.

29. Oudejans I, Mosterd A, Zuithoff NP, Hoes AW. Comorbidity drives mortality in newly diagnosed heart failure: a study among geriatric outpatients. J Card Fail. 2012;**18**:47-52.

30. Montero P-BM, Conthe GP, Román SP, García AJ, Forteza-Rey J. [Morbidity from patients admitted for heart failure in the departments of internal medicine]. Rev Clin Esp. 2010;**210**:149-58.

31. Radovanovic D, Seifert B, Urban P, Eberli FR, Rickli H, Bertel O, et al. Validity of Charlson Comorbidity Index in patients hospitalised with acute coronary syndrome. Insights from the nationwide AMIS Plus registry 2002–2012. Heart. 2014;**100**:288-94.

32. Ramirez-Marrero M.A. Jimenez-Navarro M, De Teresa-Galvan E, De Mora-Martin M. The importance of the charlson index in risk stratification in patients admitted for acute coronary syndrome without ST-segment elevation. Eur J Cardiovasc Prev Rehabil.**18** (SUPPL. 1) (pp S113), 2011.

33. Ramirez-Marrero M, Roldan-Jimenez M, Delgado-Prieto J, Jimenez-Navarro M, de Mora-Martin M, Repercussion of complete percutaneous coronary revasculization on prognosis of elderly patients. Intensive care Med; 2013.**39**(ppS247).

34. Rodríguez-Pascual C, Vilches-Moraga A, Paredes-Galán E, Ferrero-Marinez AI, Torrente-Carballido M, Rodríguez-Artalejo F. Comprehensive geriatric assessment and hospital mortality among older adults with decompensated heart failure. Am Heart J. 2012;**164**:756-62.

35. Sachdev M, Sun JL, Tsiatis AA, Nelson CL, Mark DB, Jollis JG. The prognostic importance of comorbidity for mortality in patients with stable coronary artery disease. J Am Coll Cardiol. 2004;**43**:576-82.

36. Sanchis J, Núñez J, Bodí V, Núñez E, García-Alvarez A, Bonanad C, et al. Influence of Comorbid Conditions on One-Year Outcomes in non–ST-segment elevation acute coronary syndrome. Mayo Clin Proc; 2011: **86**:291-6.

37. Schmidt M, Jacobsen JB, Lash TL, Bøtker HE, Sørensen HT. 25 year trends in first time hospitalisation for acute myocardial infarction, subsequent short and long term mortality, and the prognostic impact of sex and comorbidity: a Danish nationwide cohort study. BMJ. 2012;**344**:e356.

38. Singh M, Rihal CS, Lennon RJ, Spertus JA, Nair KS, Roger VL. Influence of frailty and health status on outcomes in patients with coronary disease undergoing percutaneous revascularization. Circ Cardiovasc Qual Outcomes. 2011;4:**496**-502.

39. Subramanian U, Eckert G, Yeung A, Tierney WM. A single health status question had important prognostic value among outpatients with chronic heart failure. J Clin Epidemiol. 2007;**60**:803-11.

40. Teng T-HK, Katzenellenbogen JM, Thompson SC, Sanfilippo FM, Knuiman M, Geelhoed E, et al. Incidence of first heart failure hospitalisation and mortality in Aboriginal and non-Aboriginal patients in Western Australia, 2000–2009. Int J Cardiol. 2014;**173**:110-7.

41. Testa G, Cacciatore F, Galizia G, Della-Morte D, Mazzella F, Russo S, et al. Charlson Comorbidity Index does not predict long-term mortality in elderly subjects with chronic heart failure. Age and ageing. 2009;**38**:734-40.

42. Theuns DA, Schaer BA, Soliman OI, Altmann D, Sticherling C, Geleijnse ML et al. The prognosis of implantable defibrillator patients treated with cardiac resynchronization therapy: comorbidity burden as predictor of mortality. Europace. 2011;**13**:62-9.

43. Tuttolomondo A, Pedone C, Pinto A, Di Raimondo D, Fernandez P, Di Sciacca R, et al. Predictors of outcome in acute ischemic cerebrovascular syndromes: The GIFA study. Int J Cardiol. 2008;**125**:391-6.

44. Urban P, Abizaid A, Banning A, Bartorelli AL, Baux AC, Džavík V, et al. Stent thrombosis and bleeding complications after implantation of sirolimus-eluting coronary stents in an unselected worldwide population: a report from the e-SELECT (Multi-Center Post-Market Surveillance) registry. J Am Coll Cardiol. 2011;**57**:1445-54.

45. Van Wijk S, Bektas S, Muzzarelli S, Kiencke S, Maeder M, Estlinbaum W, et al. Impact of comorbidities on safety, tolerability and efficacy of intensified medical therapy in heart failure. Eur Heart J. 2013;**34**(suppl 1):P2742.

46. Mozaffarian D, Benjamin EJ, Go AS, Arnett DK, Blaha MJ, Cushman M, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;**131**:e29-322.

47. Taneva E, Bogdanova V, Shtereva N. Acute coronary syndrome, comorbidity, and mortality in geriatric patients. Ann N Y Acad Sci. 2004;**1019**:106-10.

48. Pollack CV, Sites FD, Shofer FS, Sease KL, Hollander JE. Application of the TIMI risk score for unstable angina and non‐ST elevation acute coronary syndrome to an unselected emergency department chest pain population. Acad Emerg Med. 2006;**13**:13-8.

49. Elbarouni B, Goodman SG, Yan RT, Welsh RC, Kornder JM, DeYoung JP, et al. Validation of the Global Registry of Acute Coronary Event (GRACE) risk score for in-hospital mortality in patients with acute coronary syndrome in Canada. Am heart J. 2009;**158**:392-9.

50. Mosterd A, Hoes AW. Clinical epidemiology of heart failure. Heart. 2007;**93**:1137-46.

51. Lee JH, Yang DH, Park HS, Cho Y, Jeong MH, Kim YJ, et al. Suboptimal use of evidence-based medical therapy in patients with acute myocardial infarction from the Korea Acute Myocardial Infarction Registry: prescription rate, predictors, and prognostic value. Am heart J. 2010;**159**:1012-9.

52. Passman R, Kimmel S. Do comorbidities influence the treatment of myocardial infarction?. J Gen Intern Med. 1997;**12**:73.

53. Zaman MJ, Stirling S, Shepstone L, Ryding A, Flather M, Bachmann M, et al. The association between older age and receipt of care and outcomes in patients with acute coronary syndromes: a cohort study of the Myocardial Ischaemia National Audit Project (MINAP). Euro Heart J. 2014;**35**:1551-8.

54. Patel N, Patel N, Thakkar B, Singh V, Arora S, Savani C, et al. Management strategies and outcomes of ST-segment elevation myocardial Infarction patients transferred after receiving fibrinolytic therapy in the United States. Clin Cardiol. 2016;**39**:9-18.

55. Bateman BT, Schumacher HC, Boden-Albala B, Berman MF, Mohr J, Sacco RL, et al. Factors associated with In-hospital mortality after administration of thrombolysis in acute ischemic stroke patients an analysis of the nationwide inpatient sample 1999 to 2002. Stroke. 2006;**37**:440-6.

56. Muzzarelli S, Maeder MT, Toggweiler S, Rickli H, Nietlispach F, Julius B, et al. Frequency and predictors of hyperkalemia in patients≥ 60 years of age with heart failure undergoing intense medical therapy. Am J Cardiol. 2012;**109**:693-8.

57. Green AR, Leff B, Wang Y, Spatz ES, Masoudi FA, Peterson PN, et al. Geriatric conditions in patients undergoing defibrillator implantation for

prevention of sudden cardiac death prevalence and impact on mortality. Circ Cardiovasc Qual Outcomes. 2016;**9**:23-30.

58. Braunstein JB, Anderson GF, Gerstenblith G, Weller W, Niefeld M, Herbert R, et al. Noncardiac comorbidity increases preventable hospitalizations and mortality among Medicare beneficiaries with chronic heart failure. J Am Coll Cardiol. 2003;**42**:1226-33.

59. Muzzarelli S, Leibundgut G, Maeder MT, Rickli H, Handschin R, Gutmann M, et al. Predictors of early readmission or death in elderly patients with heart failure. Am Heart J. 2010;**160**:308-14.

60. Sargsyan Z, Higgins C, Alexandrescu S, Ott DA, Jain SK. Acute promyelocytic leukemia as a cause of intracoronary drug-eluting–stent thrombosis. Tex Heart Inst J. 2012;**39**:416.

61. Tanaka S, Sakata R, Marui A, Furukawa Y, Kita T, Kimura T. Predicting long-term mortality after first coronary revascularization-The Kyoto model. Circ J. 2012;**76**:328-34.

62. Paciaroni M, Agnelli G, Corea F, Ageno W, Alberti A, Lanari A, et al. Early hemorrhagic transformation of brain infarction: rate, predictive factors, and influence on clinical outcome results of a prospective multicenter study. Stroke. 2008;**39**:2249-56.

63. Prodan C, Stoner J, Cowan L, Dale G. Lower coated-platelet levels are associated with early hemorrhagic transformation in patients with non-lacunar brain infarction. J Thromb Haemost. 2010;**8**:1185-90.

64. Kerr EA, Heisler M, Krein SL, Kabeto M, Langa KM, Weir D, et al. Beyond comorbidity counts: how do comorbidity type and severity influence diabetes

patients' treatment priorities and self-management? J Gen Intern Med. 2007;**22**:1635-40.

65. Turner BJ, Hollenbeak CS, Weiner M, Ten Have T, Tang SS. Effect of unrelated comorbid conditions on hypertension management. Ann Intern Med. 2008;**148**:578-86.

66. Silverberg DS, Wexler D, Iaina A, Schwartz D, editors. The interaction between heart failure and other heart diseases, renal failure, and anemia. Semin Nephrol; 2006: **26**:296-306.

67. Steg PG, James SK, Atar D, Badano LP, Lundqvist CB, Borger MA, et al. ESC Guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation. Euro Heart J. 2012;**33**:2569-619.

68. Amsterdam EA, Wenger NK, Brindis RG, Casey DE, Ganiats TG, Holmes DR, et al. 2014 AHA/ACC guideline for the management of patients with non–ST-elevation acute coronary syndromes: a report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines. J Am Coll Cardiol. 2014;**64**:e139-e228.

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Figure 1: Flow diagram of study selection

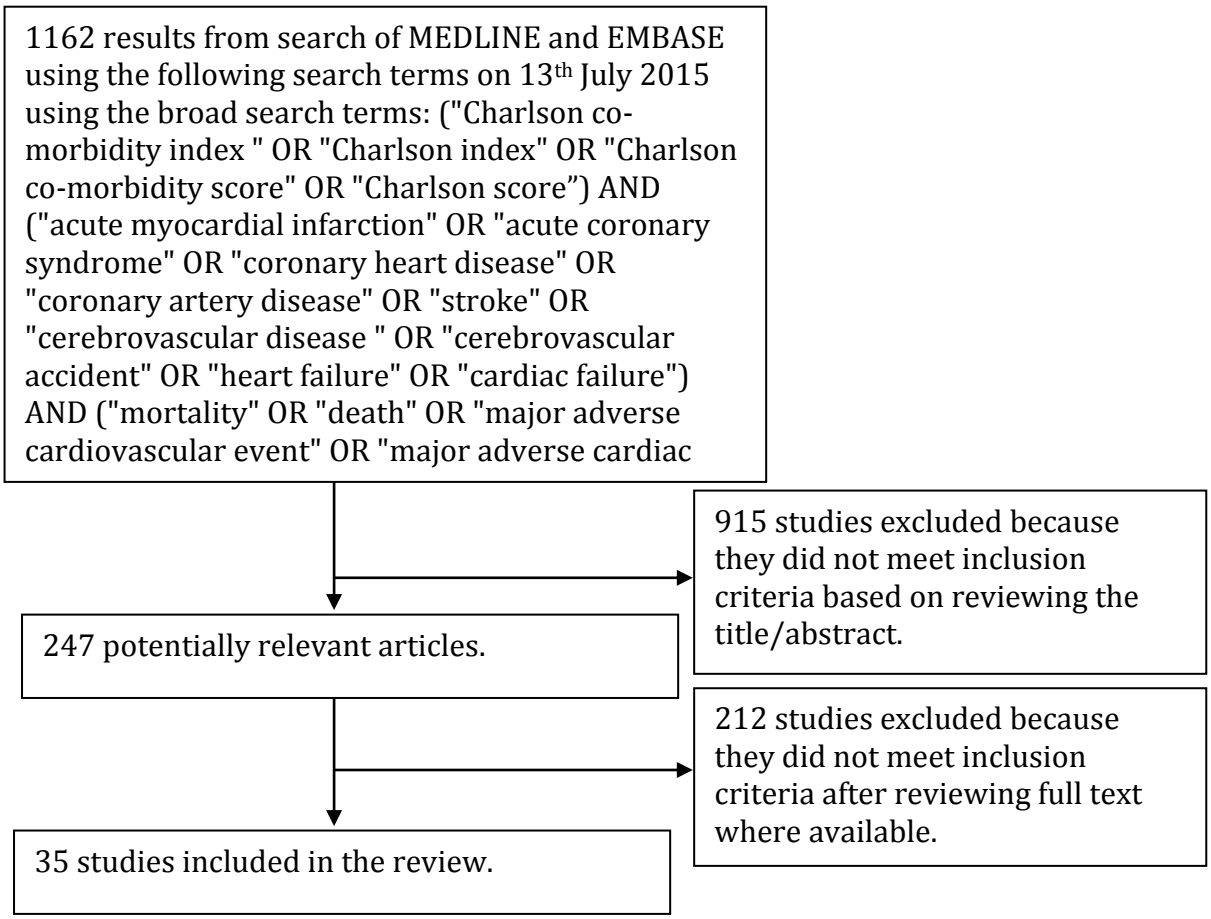

Figure 2: Charlson co-morbidity individual component distribution
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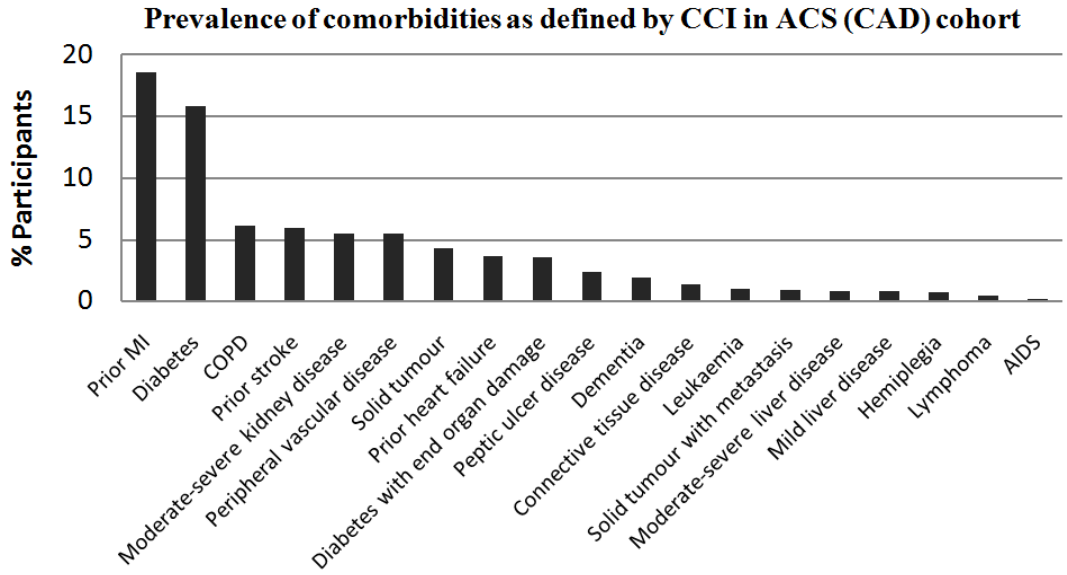

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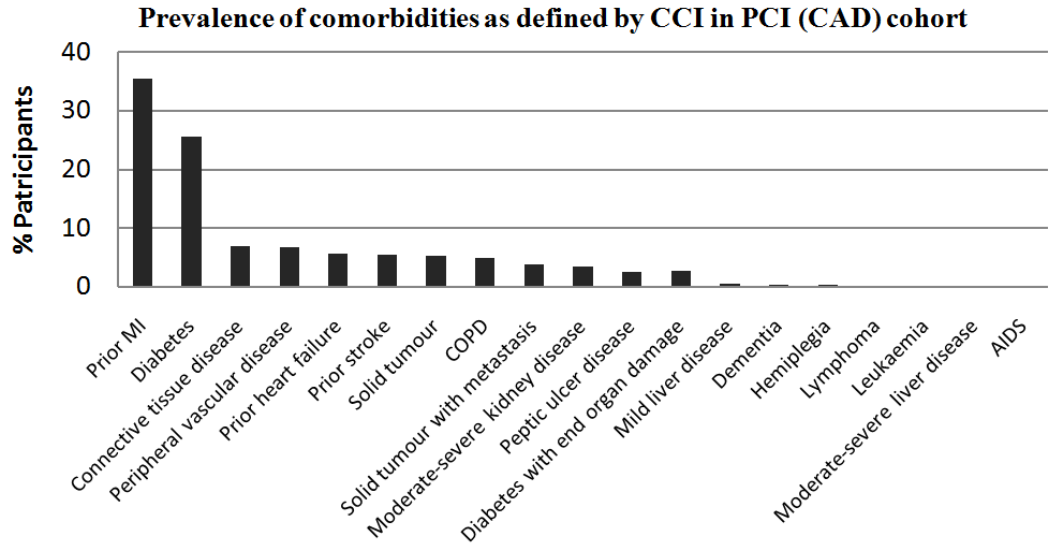

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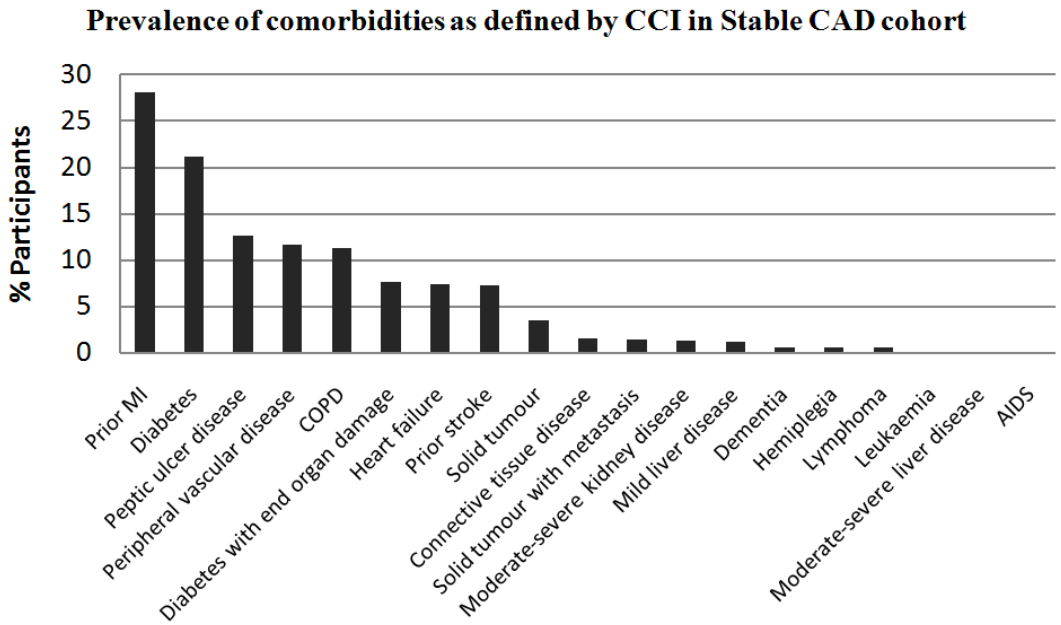

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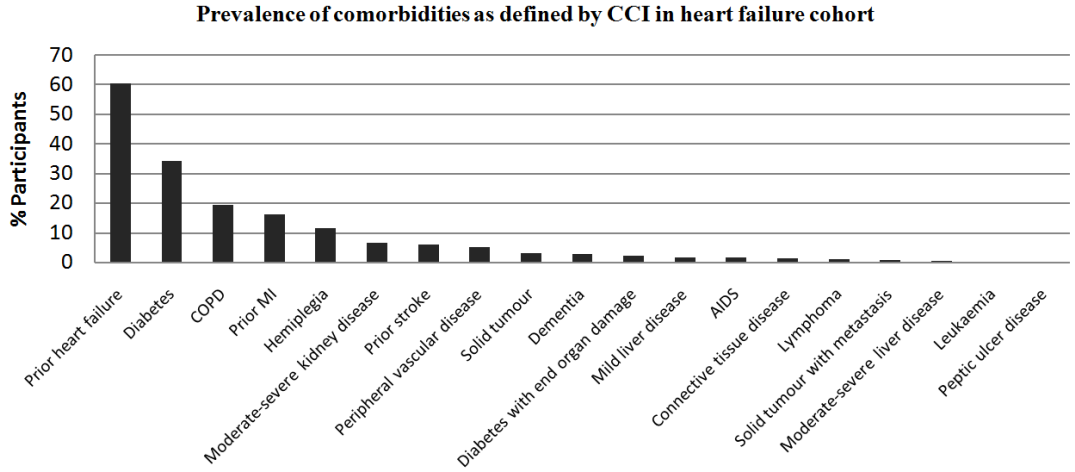

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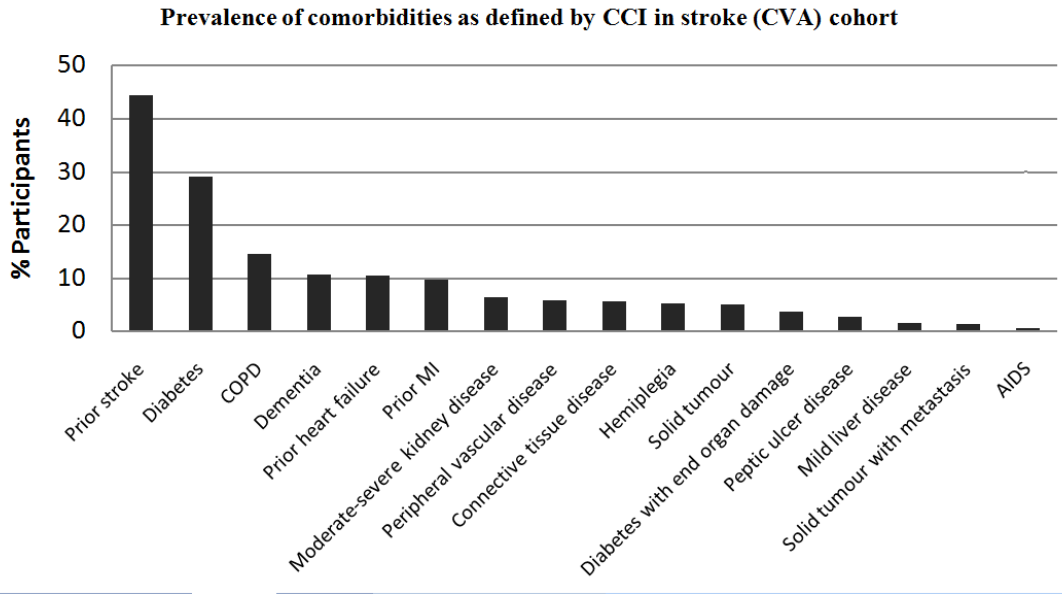
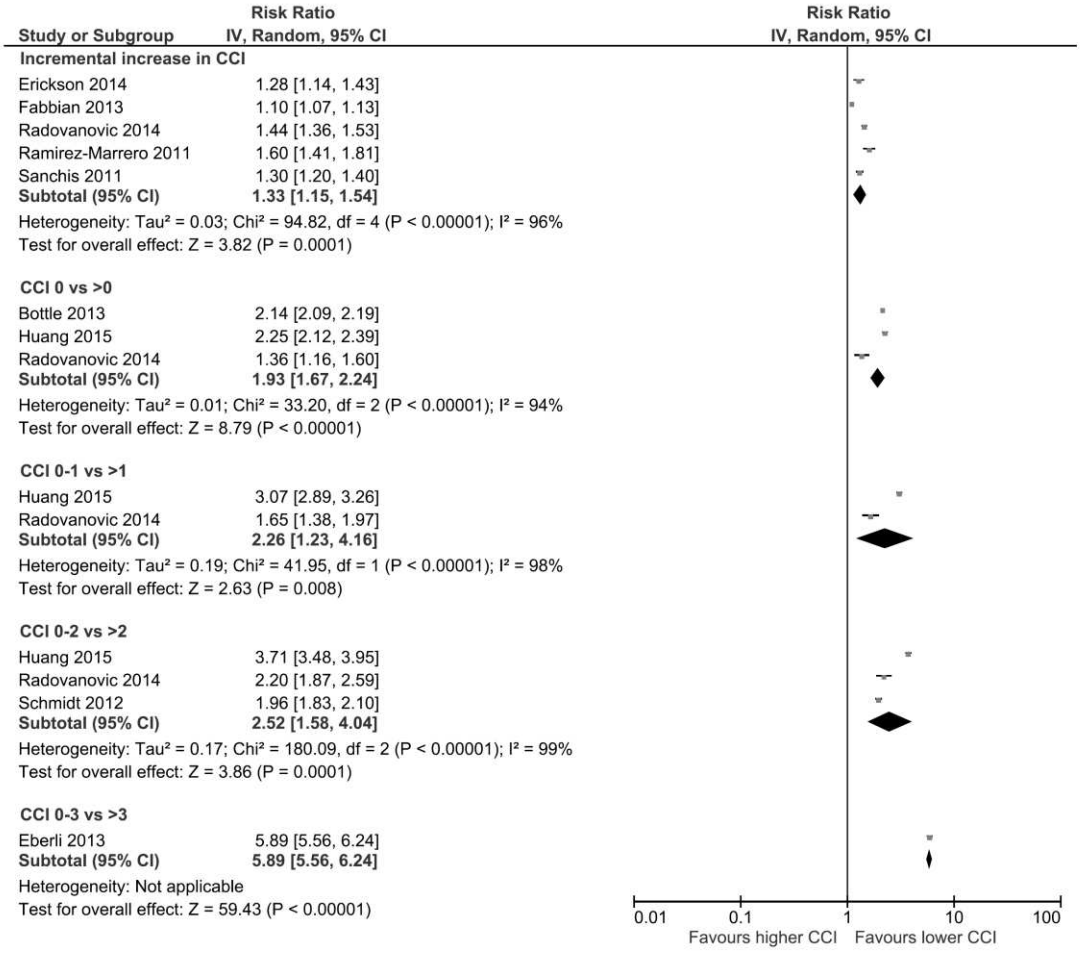
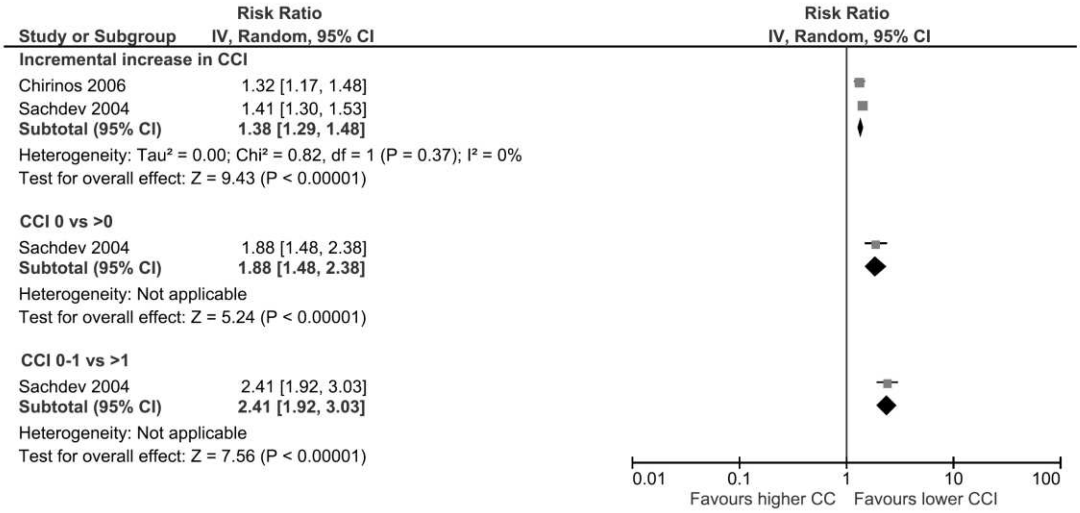


Figure 3: ACS patients, stable angina/stable coronary heart disease patients, and patients undergoing PCI and mortality according to CCI

A) Acute coronary syndrome



B) Stable angina/stable coronary heart disease



C) Patients undergoing PCI

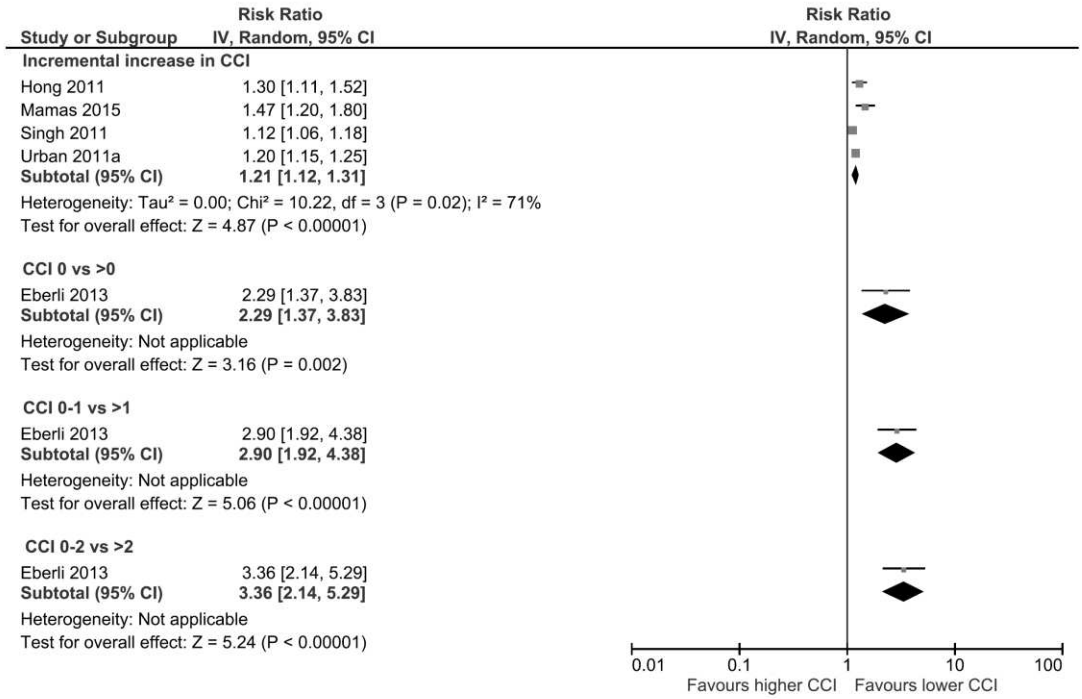


Figure 4: Heart failure patients and mortality according to CCI

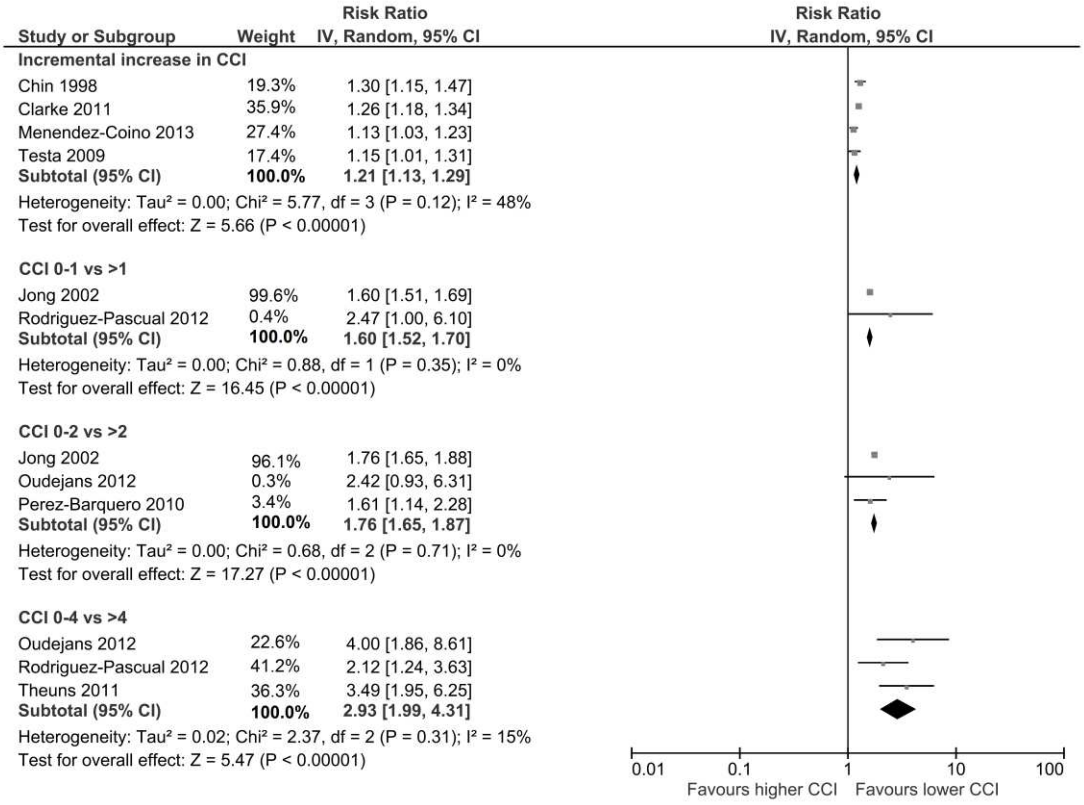


Figure 5: CVA patients and mortality according to CCI

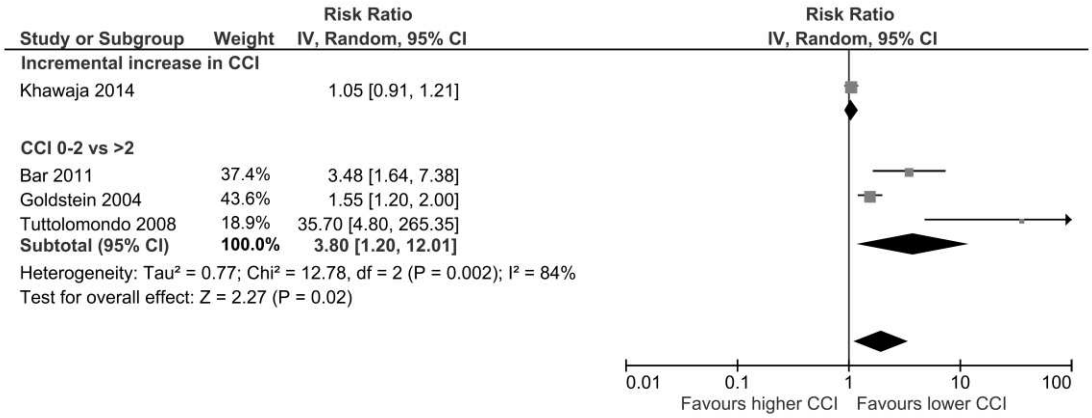


Table 1: Charlson co-morbidity index

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 2 if end-organ damage
Moderate to severe chronic kidney disease	2
Hemiplegia	2
Leukemia	2
Malignant lymphoma	2
Solid tumour	2 6 if metastatic
Liver disease	1 if mild 3 if moderate to severe
AIDS	6

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 to 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 to 2004; USA.	243.	88.(36%)	NA.	NA.	Patients with non-traumatic intra cerebral hemorrhage presented to hospital emergency department.
Chin 1998[13]	Prospective cohort study; 1993 to 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 to 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 to 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.	5,559.	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 to 2007; USA.	1,202.	NA.	64 years.	65%.	Participants from ACS registry from a large university hospital.
Fabbian 2013[18]	Retrospective cohort study; 1999 to 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 ischemic stroke Department of Veterans Affairs (VA) Stroke Study.
Hong 2011[20]	Prospective cohort study; 2006 to 2008; International.	675.	NA.	83 years.	58%.	Octogenarian participants from Sirolimus-eluting coronary stent (e-Select) registry.
Huang 2015[21]	Retrospective; 2002 to 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 to 2012; Switzerland.	1909.	NA.	65 years.	78%.	Participants from AMIS plus registry.

Jong 2002[23]	Retrospective; 1994 to 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 to 2013; USA.	383.	37.(9%)	NA.	NA.	Patients with primary intra cerebral haemorrhage.
Mamas 2015[25]	Post hoc-analysis of prospective registry; 2008 to 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 to 2007; Spain	270.	NA.	78 years.	42%.	Patients with chronic heart failure diagnosis.
Nunez 2004[28]	Prospective Cohort study; 2000 to 2003, Spain.	1,035.	481.(46%)	70 years.	70%.	Patients admitted with diagnosis of acute myocardial infarction.
Oudejans 2012[29]	Prospective cohort study; 2003 to 2007; Netherlands.	93.	0.	83 years.	37%.	Patients with diagnosis of heart failure.
Perez-Barquero 2010[30]	Retrospective cohort study; 2000 to 2001; Spain	2127.	NA.	77 years.	43%.	Patients admitted with heart failure to various hospitals in Spain.
Radovanovic 2014[31]	Prospective cohort study; 2002 to 2012; Switzerland.	29,620.	15 754.(51%)	64 years.	73%.	Participants from AMIS plus registry.
Ramirez-Marrero 2011[32]	Retrospective cohort study; 2004 to 2005; Spain	715.	NA.	66 years.	NA.	Patients admitted with diagnosis of NSTEACS.
Ramirez-Marrero 2013[33]	Retrospective cohort study; 2008 to 2009; Spain	146.	NA.	78 years.	63%.	Patients undergoing percutaneous coronary revascularization.
Rodriguez-Pascual 2012[34]	Prospective cohort study; 2006 to 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 to 1989; USA.	1,471.	810.(55%)	60 years.	72%.	All patients undergoing initial coronary angiography for symptoms of chronic CAD and found to have significant disease (≥75% stenosis) in one or more coronary arteries.
Sanchis 2011[36]	Prospective cohort study; 2002 to 2009; Spain.	1,017.	NA.	68 years.	66%.	Patients admitted with diagnosis of NSTEACS.
Schmidt 2012[37]	Retrospective cohort study; 1984 to 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	629.	NA.	75 years	69%	Patients undergoing PCI at the Mayo Clinic in

	to 2008; USA.					Rochester, USA.
Subramanian 2007[39]	Prospective cohort study; unclear; USA.	494.	NA.	68 years.	NA.	Participants from Veterans Affairs outpatients with diagnosis of CHF.
Teng 2014[40]	Prospective cohort study; 2000 to 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 to 2003; Italy.	1,268.	NA.	74 years.	43%.	Participants from 'Osservatorio Geriatrico Regione Campania' with and without heart failure.
Theuns 2011[42]	Prospective; 1999 to 2008; International.	463.	NA.	62 years.	75%.	Participants from two ICD registries from Rotterdam and Basel.
Tuttolomondo 2008[43]	Retrospective; 1988 to 1998; Italy.	1,878.	0.	77 years.	49%.	Participants from GIFA registry.
Urban 2011[44]	Prospective cohort study; 2006 to 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 versus symptom-guided therapy.

NA=not available or not reported.

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 ≥70 years, prior congestive heart failure, chronic pulmonary disease, Charlson Co-morbidity Index score, third heart sound, serum sodium ≤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, One year all cause and cardiac mortality by unclear method.	Unclear.	None
Erickson 2014[17]	No, Retrospective.	Yes, Six months 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	Yes, None.	Unclear.

		thrombosis.		
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 days and one-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 $p<0.05$.
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.
Nunez 2004[28]	Yes, Prospective.	Yes, 30 days 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.
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 was 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 six months, one 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 31–365 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 presence of 2 of 3 following criteria: prolonged (>20 minutes) ischemic chest pain and elevation of cardiac biomarkers (creatinine kinase-MB or relative index) more than 2 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 was 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, COPD, neurological disease, CHF, and CCI.
Theuns 2011[42]	Yes, Prospective.	Yes, The data collected from two prospective ICD registries from Rotterdam and Basel. Patient followed up at out-patient clinics.	Yes, None.	Adjusted for age.
Tuttolomondo 2008[43]	Yes, Prospective.	Yes, Demographic data and follow up was 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.

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 -0: 8,370/151,577 (5.5%), CCI >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-1: OR 1.78 (0.86- 3.70), CCI-2: OR 2.34 (0.98-5.61), CCI-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 one year mortality: CCI-0: 18/2,041 (0.9%), CCI-1: 28/2,162 (1.3%), CCI-2: 18/776 (2.3%), CCI≥3: 25/578 (4.3%). Cardiac mortality: CCI-0: 14/2,041 (0.7%), CCI-1: 13/2,162 (0.6%), CCI-2: 9/776 (1.2%), CC I≥3: 14/578 (2.4%).
Erickson 2014[17]	ACS (CAD)	Incremental increase in CCI.	Inpatient and 6 months mortality and post discharge cardiac event or procedure.	Inpatient death with CCI: OR 1.28 (1.14-1.43). 6 month death with CCI: OR 1.55 (1.41-1.72). 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 versus high CCI ≥2.	1-year mortality.	1 year mortality with low CCI score 0-1: 88/551 (16%), 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). 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 days and 1-year mortality.	CCI-0: 30 days mortality 1,397/15,020 (9.3%); one-year mortality 4,025/15,020 (26.8%). CCI-1: 30 days mortality 1,348/12,602 (10.7%); one-year mortality 3,907/12,602 (31.0%). CCI-2: 30 days mortality 895/6485 (13.8%); one-year mortality 2,555/6485 (39.4%). CCI-3: 30 days mortality 864/4,595 (18.8%); one-year mortality 2325/4,595 (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). 1-year: cardiac death OR 1.46 (1.30-1.65), MACE OR 1.32 (1.23-1.42). 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).
Nunez 2004[28]	ACS (CAD)	CCI score and risk compared to CCI 0.	Time to death or reinfarction to a maximum of 30 days and 1-year.	Risk of death or reinfarction at 30 days: CCI-1: HR 1.00, CCI-2: HR 1.69 (1.10-2.59), CCI-3: HR 1.78 (1.08- 2.92), CCI-4: HR 1.57 (0.87-2.83). Risk of death or reinfarction at 1 year: CCI-1: HR 1.00, CCI-2: HR 1.62 (1.18- 2.23), CCI-3: HR 2.00 (1.39-2.89), CCI-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 0-2: HR 1.00. CCI 3-4: HR 1.5 (0.7-2.9), CCI >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 1-2: 76/1,528, CCI ≥3: 48/599.
Radovanovic 2014[31]	ACS (CAD)	Incremental rise in CCI and risk compared to CCI=0.	In hospital mortality and 1 year mortality assessed using data from AMIS plus registry.	In hospital mortality compared to CCI=0: CCI=1 OR 1.36 (1.16-1.60), CCI=2 OR 1.65 (1.38-1.97), CCI≥3 OR 2.20 (1.86-2.57). 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 0: 95/810 (11.7%), CCI 1: 58/378 (15.3%), CCI ≥2: 88/283 (31.1%). 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: aHR1.3 (1.2-1.4).
Schmidt 2012[37]	ACS (CAD).	CCI=0 (normal) versus ≥3 (very severe).	30 days and 31-365 days mortality.	30 days mortality: RR 1.96 (1.83-2.11). 31-365 days 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). 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 cutoff.	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 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 <2 versus CCI >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). 1 year stent thrombosis: HR 1.2 (1.1-1.4). 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).