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Greater Mortality, Higher Readmission Rates, and Increased Length of Stay is Associated with Multimorbidity in Patients with Acute Coronary Syndrome: A Systematic Review

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Abstract

Objective: The aims of this systematic review were to determine the magnitude and impact of multimorbidity (≥ 2 chronic conditions) on mortality, length of stay, and rates of coronary intervention in patients with acute coronary syndrome (ACS) and to compare the prevalence of cardiovascular vs. non-cardiovascular multimorbidities.

Methods: Medline, PubMed, MedlinePlus, Embase, OVID, and CINAHL databases were searched for studies published between 2009 and 2019. Eight original studies enrolling patients with ACS and assessing cardiovascular and non-cardiovascular comorbid conditions met the inclusion criteria. Study quality was evaluated using the Crowe Critical Appraisal Tool.

Results: The most frequently examined cardiovascular multimorbidities included hypertension, diabetes, heart failure, atrial fibrillation, stroke/transient ischemic attack, coronary heart disease, and peripheral vascular disease; the most frequently examined non-cardiovascular multimorbidities included cancer, anemia, chronic obstructive pulmonary disease, renal disease, liver disease, and depression. The prevalence of multimorbidity in the ACS population is high (25%-95%). Patients with multimorbidities receive fewer evidence-based treatments, including coronary intervention and high-dose statins. Patients with multimorbidities experience higher in-hospital mortality (5%-13.9% vs. 2.6%-6.1%), greater average length of stay (5-9 days vs. 3-4

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days), and lower rates of revascularization (9%-14% vs. 39%-42%) than non-multimorbid patients. Women, despite being the minority in all sample populations, exhibited greater levels of multimorbidity than men.

Conclusions: Multimorbid ACS patients are at greater risk for worse outcomes than their non-multimorbid counterparts. Lack of consistent measurement makes interpretation of the impact of multimorbidity challenging and emphasizes the need for more research on multimorbidity's effects on post-discharge healthcare utilization.

Keywords

acute coronary syndrome; multimorbidity; cardiovascular disease; mortality; length of stay

Introduction

Multimorbidity is defined by the World Health Organization as the co-occurrence of two or more chronic conditions.[1] Multimorbidity affects health care system use, and the burden of multimorbidity will increase as the aging population increases over the next 10 years.[2] Approximately 40 million individuals in the United States over the age of 65 have cardiovascular disease (CVD), which remains the leading cause of morbidity and mortality.[3,4] The proportion of adults aged 65 and over is rapidly increasing and will reach approximately 19% of the U.S. population by 2030.[3] As individuals age, multimorbidity dyads (2 conditions) and triads (3 conditions) emerge, and many include cardiovascular risk factors.[5,6] There is a high prevalence (>50%) of three or more additional comorbidities for the six most frequently managed conditions in cardiovascular medicine (heart failure, stroke, hyperlipidemia, atrial fibrillation, ischemic heart disease, and hypertension).[7] Comorbidity is the occurrence of two other conditions in addition to the primary condition.[5] As the number (count) of comorbid conditions increases, the risk of poorer outcomes increases. Multimorbidity is also associated with polypharmacy, reduced quality of life, and higher mortality.[8]

In the United States, 5.5 million patients are evaluated for acute coronary syndrome (ACS) in emergency departments every year.[9] Approximately 720,000 Americans this year will have a new coronary event, defined as the first hospitalization for myocardial infarction (MI) or coronary heart disease (a type of CVD), and approximately 335,000 will have a recurrent event.[3] Acute coronary syndrome is a blanket term for a group of cardiovascular conditions including unstable angina (UA), non-ST segment elevation myocardial infarction (NSTEMI), and ST-segment elevation myocardial infarction (STEMI). Mortality rates from ACS have declined in the past decade, and people are living longer; hence, a highly heterogeneous cohort of complex multimorbid patients now require care.[10] The risk for ACS increases in those with multimorbidity compared to the non-multimorbid population.[11]

Given the frequency of multimorbidity in ACS and the rapidly aging population, it is imperative to determine the prevalence of multimorbidity in this population to better understand clinical presentation for ACS, improve chronic care management, and design pragmatic clinical trials to include patients with multimorbidity. To date, no systematic review of the prevalence of or outcomes from multimorbidity in patients with ACS has been

published. Therefore, the aims of this systematic review were to 1) determine the prevalence and effect of multimorbidity in patients with ACS on clinical outcomes, including short and long-term mortality, length of stay, and readmission and 2) determine the prevalence of cardiovascular and non-cardiovascular multimorbidity among patients with ACS.

Methods

Search Strategy and Study Selection

Articles were obtained by searching the Medline, PubMed, MedlinePlus, CINAHL, OVID, and Embase databases for articles published from January 2009 through August 2019. The following search terms were used: multimorbidity, multiple chronic conditions, multiple comorbidities, concurrent chronic conditions, acute coronary syndrome, myocardial infarction, ST-elevation myocardial infarction (STEMI), non-ST-elevation myocardial infarction (NSTEMI), and unstable angina (UA). The following conditions were classified as cardiovascular conditions: cardiac arrhythmias (atrial fibrillation and atrial flutter), cerebrovascular disease, peripheral vascular disease, peripheral artery disease, diabetes mellitus, hyperlipidemia, and coronary heart disease (including previous history of MI, coronary artery bypass grafting, or percutaneous intervention). Non-cardiovascular conditions were any other conditions, including chronic pulmonary obstructive disorder (COPD), renal disease, anemia, cancer, arthritis, and mental health conditions such as depression and anxiety.

Search limits were used in each database to restrict findings to the following inclusion criteria: 1) original research studies published between 2009-2019; 2) articles in English; 3) qualitative or quantitative research articles that examined multimorbidity in patients with ACS; 4) studies examining health outcomes (readmission, mortality, and length of stay) following ACS; and 5) study participants over age 18. We excluded studies that did not analyze multimorbidity. Case reports, abstracts, reviews, conference proceedings, editorials, or opinions were also excluded. Reference lists from the selected articles were reviewed to identify additional articles that did not appear in the database search. The selection process followed PRISMA guidelines (Figure 1). Only research published in the past 10 years was selected because older studies may be less generalizable to the present-day due to changes in the ACS patient population, anticoagulants, percutaneous treatments, and improved outcomes. Furthermore, a recent systematic review found that 79% of all studies with multimorbidity as the focus were published between 2013 and 2016.[12]

Data Extraction and Synthesis

The first author independently examined the titles and abstracts to determine eligibility for inclusion. Duplicate articles were removed. If the title and abstract appeared to be relevant, it was marked for full-text review by the last author. Articles marked as questionable by the rater were also marked for full-text review. If there was a disagreement on inclusion, a third author examined the paper, and the paper was included or excluded based on majority opinion. A systematic analysis of all articles was completed by two reviewers (K.B and H.D) using a data extraction form developed by the authors. The reviewers conducted the data extraction process independently. Means and standard deviations of continuous variables

were extracted to compute the mean prevalence of multimorbidity for all studies in the aggregate. Otherwise, data were summarized using descriptive statistics from each study.

Quality Appraisal

The Crowe Critical Appraisal Tool (CCAT) was used to assess the quality of research articles in this review.[13] The CCAT consists of eight categories: preliminaries, introduction, design, sampling, data collection, ethical matters, results, and discussion. Each category is scored on a 6-point scale ranging from 0 to 5. Total scores range from 0 to 40. A higher score indicates higher quality. No quality parameters have been established; however, the score is useful for comparison purposes. Two authors (K.B. and H.D.) independently assessed the methodological quality of each study and resolved disagreements through discussion until consensus was reached.

Search Outcomes

A total of 132 articles were identified in the initial search, and duplicate articles and studies based on the title and abstract screen were removed. No qualitative studies were found that met inclusion criteria. The full texts of 13 articles were reviewed; seven met inclusion criteria (Figure 1). A review of reference lists from the seven articles resulted in the identification of one additional eligible study. The final number of research articles included was eight.

Results

Study Characteristics

Study characteristics are summarized in Table 1. One study included patients with diabetes mellitus (DM) and STEMI. The remaining seven studies included patients with either ACS or a specific clinical subcategory (MI, STEMI, or UA). Seven of the studies were multicenter, and one was single center. Six of the studies were retrospective. Two studies were prospective cohort studies. Three of the six retrospective studies analyzed different variables and different time points from the large Worcester Heart Attack Study dataset. Four were U.S.-based studies. The five non-U.S.-based studies were from Australia (n = 2), England and Wales (n = 1), Switzerland (n = 1), and Poland (n = 1). All studies used medical records for data collection. Two used the International Classification of Disease (ICD) 9 or 10 codes.[14,15] One used a baseline interview in addition to medical records. As determined by the CCAT, the quality scores of the studies ranged from 30 to 38, indicating moderate to high quality (Table 1).

Conditions were assessed in multiple ways: simple counts (n = 6), a combination of the Elixhauser[16] and Charlson Comorbidity Indices[17] (n = 1), and the Charlson Comorbidity Index alone (n = 1). The prevalence of conditions ranged from one additional condition present in 16% to 57% of study populations[18] to four or more conditions in 0.02% to 36.8% of study populations.[8,15] The most common conditions considered were DM, renal disease, chronic obstructive pulmonary disease (COPD), hypertension (HTN), heart failure (HF), anemia, cerebrovascular disease, and cancer.[6,8,14,18–21]

Participant Characteristics

Study sample sizes ranged from 277 to 693,388[18,22]; only one of the studies included <1,000 subjects.[22] The mean age ranged from 61 to 79 years.[8,14] Five of the eight studies included data on race/ethnicity, and most subjects (81% to 97%) in those studies were Caucasian[8,15] and male (55%-95%).[5,8]

Prevalence of Multimorbidity

Overall multimorbidity ranged from 25%[18] to 95%[22], with a mean of 48% across studies (Figure 2). Seven out of eight studies reported that patients with a greater multimorbidity count and burden were more likely to be older, female, non-white, and widowed or single. Four studies examined the prevalence of multimorbidity by the categories of cardiovascular and non-cardiovascular multimorbidity. Two studies simply classified conditions as multimorbidity. One[6] only examined cardiovascular multimorbidity, while another[14] examined only non-cardiovascular multimorbidity. The prevalence of cardiovascular multimorbidity ranged from 33% to 69%, with a mean of 56%.[19,22,23] Non-cardiovascular multimorbidity varied from 1% to 53%, with a mean of 31%.[8,18]

Two studies report mixed multimorbidity, including both cardiovascular multimorbidity and non-cardiovascular multimorbidity (Figure 3).[18,20] One study[15] generated groupings by the presence and combination of cardiovascular conditions and non-cardiovascular conditions and obtained four groupings: 1) ≤2 cardiovascular conditions and no non-cardiovascular conditions (28%), 2) ≤2 cardiovascular conditions and ≥ 1 non-cardiovascular condition (21%), 3) ≥3 cardiovascular conditions and no non-cardiovascular conditions (20%), and 4) ≥3 cardiovascular conditions and ≥1 non-cardiovascular condition (31%). Hall et al.[18] reported three multimorbidity classes among patients: 1) high overall multimorbidity (class 1) with concomitant HTN, HF, and PVD was present in 7% (n = 47,839); 2) moderate overall multimorbidity (class 2) with concomitant HTN and PVD was present in 13% (n = 87,009); and 3) low overall multimorbidity (class 3) with high prevalence concomitant PVD was present in 62% (n = 433,215). The high multimorbidity class more often had NSTEMI (83.2%) than STEMI diagnoses compared with the moderate and low multimorbidity classes (71.6% and 57.6%, respectively).[18]

Prevalence of Multimorbidity Over Time

Multimorbidity prevalence changed over time in two studies. One study[6] found that the proportion of people with no comorbid conditions declined by half and the number of people with four or more comorbid conditions diagnosed previously more than doubled between 1990 and 2007 (3% to 7%, and 31% to 16%, $p < 0.05$, respectively). Hall et al.[18] reported that the percentage of people in the high and moderate multimorbidity classes (classes 1 and 2) was higher in the latter years of study, as compared to the earliest time points of study (class 1: 9.0% in 2011-2013 vs. 7.9% 2003-2006; class 2: 16.6% in 2011-2013 vs. 13.9% in 2003-2006). There was an associated 2% (95% CI 1.9%-2.3%) increase in the number of conditions per year.[18]

Females and Multimorbidity

Patients with higher levels of multimorbidity were more likely to be older and female, with women making up more than half of patients with greater multimorbidity across studies.[15,18,24] Women with multimorbidity were 42-93% more likely to receive no coronary intervention compared to males with the same number (count) of conditions (Table 2).[21] Women were overly represented in the high multimorbidity class compared to the moderate and low multimorbidity classes (40.5% vs. 38.5% and 33.1%, respectively).[18] Furthermore, women were reported to have higher representation in mixed multimorbidity (≥2 cardiovascular and ≥1 non-cardiovascular condition) groups than their male counterparts.[15]

Greater Mortality and Increased Length of Stay

All studies reported a poorer prognosis and most reported increased mortality for patients with multimorbidity (Table 3). Four studies reported a significant association with cumulative multimorbidity and in-hospital mortality compared to non-multimorbid patients.[14,19,20,22] Two studies reported a significant increase in 30-day mortality, with an increase in the highly multimorbid patient (≥4 conditions) compared to low or non-multimorbid patients (17% vs. 7.4% and 22.3% vs. 9%, respectively).[6,18] This effect remained at one year across studies. The average 1-year mortality across studies for multimorbid patients vs. their non-multimorbid counterparts was 37% vs. 13%.[6,18,22] One study[18] reported a 2.4-fold increased hazard of death for class 1 (high multimorbidity) compared with class 3 (low multimorbidity; hazard ratio [HR] 2.40; 95% CI 2.33-2.47) patients over the 8.4-year study period. Increased LOS[25] was also associated with multimorbidity, with median LOS days in multimorbid patients ranging from five to nine days compared with a LOS of three to four days in non-multimorbid patients.[14,20,22]

Coronary Interventions and Guideline-Directed Therapies

Half of the studies reviewed demonstrated that as multimorbidity (count) increased, rates of revascularization (percutaneous coronary intervention or CABG) decreased.[15,18,20–22,24] Revascularization rates for patients with high multimorbidity were significantly lower than for their no- or low-level multimorbidity counterparts (9%-14% vs. 39%-42%).[15,24] Three studies reported that multimorbid patients were less likely to receive evidence-based pharmacologic treatments.[15,18,19] For example, patients with ≥2 non-cardiovascular conditions (OR = .72, 95% CI) or ≥3 non-cardiovascular conditions (OR = .62, 95% CI) were significantly less likely to receive at least four of the six following medications during their ACS hospitalization: angiotensin-converting enzyme inhibitors or angiotensin two receptor blockers, anticoagulants, aspirins, beta-blockers, lipid-lowering agents, or thrombolytics.[24]

Readmission

Higher readmission rates were reported in multimorbid patients compared to non-multimorbid patients at seven- and thirty-days post-discharge (6.8% vs. 4.6% and 21.5% vs. 14.5%), respectively.[15]

Post-Discharge Outcomes

Three studies reported on post-discharge outcomes, including cardiac rehab attendance, medications at discharge and at one year post-discharge, and medication prescriptions at one year post-discharge. Canivall et al.[8] reported that cardiac rehab attendance at one year was decreased in multimorbid patients compared to non-multimorbid patients (32.4% vs. 72%; $p < 0.001$). Two studies examined statins or lipid-lowering agents at discharge and one year following discharge and found decreased rates of usage in multimorbid patients (Table 2).[18,23] Polypharmacy (>5 medications) at one year was also significantly increased in multimorbid patients compared to their non-multimorbid counterparts (81.4% vs. 59.1%, $p < 0.001$).[8]

Discussion

This review produced multiple findings. 1) There is an inconsistency in the way which multimorbidity is measured and characterized in the ACS population. 2) Multimorbidity is highly prevalent in the ACS population. 3) Multimorbidity has a large impact on mortality rates, LOS, and pharmacologic intervention. 4) Women have greater levels of multimorbidity. 5) There is sparse literature on clinical outcome measures other than mortality at one year. The studies included in this review were of moderate to high quality as assessed by the CCAT.

Assessment of Multimorbidity

Despite the high prevalence of multimorbidity in the ACS population, our findings suggested that there was a lack of consistency in the way multimorbidity was measured and characterized. Currently, there is no “gold standard” for measuring the rather complex phenomenon of multimorbidity. Multiple methods for assessing multimorbidity, ranging from simple counts to psychometrically sound indices, have been employed in health research. A simple count of comorbid conditions is the most straightforward approach; however, it does not account for the severity of a condition or impact across conditions. Similar challenges are faced with the use of administrative data (i.e., claims databases), given that the data do not account for the severity of diseases at time of initial diagnosis and prevent investigators from assessing outcomes such as symptom burden, functional status, and quality of life. Comorbidity indices vary across studies and are widely used, given the ease of application. The summary scores derived from the various indices, however, can pose a challenge to apply in clinical decision-making in the care of the ACS patient.[26] A relatively recent systematic review comparing measures of multimorbidity used with administrative data found that the most frequently employed measure is the Charlson Comorbidity Index, followed by the Elixhauser Index.[27] The authors concluded that the performance of a given comorbidity measure depends on the patient population and outcome of interest.[27] Future studies, using both administrative data and supplemental data sources such as electronic health records and self-report measures, may improve our understanding of multimorbidity burden in adults with ACS.

Prevalence of Multimorbidity

The accumulation of chronic conditions is the result of genetics, lifestyle factors, environmental factors, treatment of prior conditions (e.g., heart failure as a consequence of chemotherapy regimens), and aging itself, resulting in a heterogeneous population of older adults that requires management of multiple medical problems.[11] Multiple pathologies are prevalent among older adults; a recent systematic review revealed that 66% of older adults in ambulatory settings had multimorbidity.[28] Additionally, the higher prevalence of cardiovascular multimorbidity compared to non-cardiovascular multimorbidity may increase a patient's risk for adverse outcomes. Further study will be required to establish the contributions of CV and non-CV multimorbidity to the risk for an episode of ACS, as well as the contribution to poorer outcomes. In one study, 92% of the sample were found to have one or more concordant conditions (i.e., HF, HTN, arrhythmias, and/or DM) related to their ACS diagnosis.[21] This helps explain the finding of this review in the ACS population regarding the higher prevalence of cardiovascular conditions, such as HTN and DM, which are known ACS risk factors.

Women Have a Higher Prevalence of Multimorbidity

Our review found that sex is associated with multimorbidity. While most study populations in this review were predominantly male, women had a higher multimorbidity burden and were overly represented in both high and moderate multimorbidity groups across studies.[6,18,22,23] This finding coincides with previous literature that women who experience ACS are often older; hence, additional conditions are likely to be present.[29–31] However, our review found that, even when matched by age and condition (count), women still experienced lower levels of intervention. Future studies should focus on the influence of multimorbidity on sex differences in diagnostic testing, treatments, and outcomes.

Multimorbidity Negatively Impacts Inpatient Treatment

This review explored the effect of multimorbidity on clinical outcomes in patients with ACS. Patients with greater multimorbidity and burden have been shown to be at risk for increased risk of poor outcomes.[21] Clinically, patients with multimorbidity are more susceptible to increased rates of complications from ACS treatment, such as bleeding, owing to factors such as drug interactions and drug-disease interactions.[14] Patients with multimorbidity are less likely to receive guideline-indicated treatments.[18,24,32] During inpatient treatment, the studies reviewed revealed lower rates of revascularization, less frequent high-dose statin use, and decreased cardiac rehab referrals for patients as comorbidities increase.[18,24,33] Females in the studies reviewed were less likely than their multimorbidity-matched male counterparts to receive invasive treatments for ACS. This disparity warrants further investigation to determine the extent of the disparity and the impact on outcomes following ACS hospitalization.

Multimorbidity and Post-discharge Outcomes at 1 year

The increased risk of adverse outcomes continues as treatment progresses from the acute setting to post-discharge care.[23] After discharge, patients with multimorbidity frequently receive care from different specialists, which may impact the medical optimization and

achievement of secondary prevention targets.[2,23,34,35] Unfortunately, no studies reviewed measured health care use (emergency department visits and specialist visits) following discharge, and only one[8] measured polypharmacy (>5 medications), medications at one year, and cardiac rehab attendance. The benefits and risks of treatments and preventive drugs are unknown among patients with multimorbidity. This is frequently due to clinical guidelines that are based on scientific studies that focus on the primary/index disease and exclude or underrepresent multimorbid patients.[2,12,26,31,34,36–38] Future studies should employ a pragmatic design and focus on health care use following discharge for ACS for patients with multimorbidity.

Clinical Decision-Making

In the clinical arena, the likelihood of an ACS diagnosis is done using risk scores.[39] Examples include the Agency for Health Care Policy and Research (AHCPR) criteria[40] and the thrombolysis in myocardial infarction (TIMI) risk score[41] used for prognostication and therapeutic decision-making in the emergency department. While risk stratification, along with the clinical presentation, is useful in predicting a diagnosis and patient outcomes, assessment of multimorbidity may be useful in the future if further research confirms patterns of multimorbidity in patients with ACS. Pragmatic trials are needed to determine if the identification of multimorbidity phenotypes may improve risk stratification for clinical decision-making.

Limitations

Only studies published in English were included in this review. The impact of multimorbidity on patients with ACS published in non-English journals remains unknown. Most studies limited their outcomes to in-hospital, 30-day, and 1-year all-cause mortality, making it difficult to determine cardiovascular mortality and draw critical conclusions about overall vs. cardiovascular mortality. Only a few studies measured health care use post-discharge, which limits the ability to evaluate the impact of multimorbidity on secondary prevention measures such as cardiac rehab referrals, statin use, and follow-up of care (ED, specialist visits, clinic visits, and primary care visits). There were, however, large variations in sample sizes in the studies, and there was an inconsistency in the way in which multimorbidity was measured and characterized in the ACS population. This may limit generalizability of the findings.

Conclusions

Multimorbidity is ubiquitous in the ACS population, with cardiovascular multimorbidity being more prevalent than non-cardiovascular multimorbidity. Multimorbidity is associated with a poorer prognosis following ACS and with higher short- and long-term mortality. There is little research on the importance of mixed multimorbidity (cardiovascular and non-cardiovascular conditions), which warrants further study to understand the complex simultaneous interactions of various conditions and the role multimorbidity plays in the likelihood of developing ACS and subsequent outcomes. Further research is needed to determine the impact of specific combinations of multimorbidity “phenotypes” on both inpatient and outpatient health care utilization.

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References

1. World Health Organization. Multimorbidity. Geneva: World Health Organization; 2016.
2. Alfredsson J, Alexander KP. Multiple Chronic Conditions in Older Adults with Acute Coronary Syndromes. Clinics in Geriatric Medicine. 2016;32(2):291–303. [PubMed: 27113147]
3. Benjamin EJ, Virani SS, Callaway CW, et al. Heart Disease and Stroke Statistics-2018 Update: A Report From the American Heart Association. Circulation. 2018;137(12):e67–e492. [PubMed: 29386200]
4. Mozaffarian D, Benjamin EJ, Go AS, et al. Heart disease and stroke statistics--2015 update: a report from the American Heart Association. Circulation. 2015;131(4):e29–322. [PubMed: 25520374]
5. Chen H-Y, Saczynski JS, McManus DD, et al. The impact of cardiac and noncardiac comorbidities on the short-term outcomes of patients hospitalized with acute myocardial infarction: a population-based perspective. Clinical Epidemiology. 2013;5:439–448. [PubMed: 24235847]
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. Clinical Epidemiology. 2012;4:115–123. [PubMed: 22701091]
7. Arnett DK, Goodman RA, Halperin JL, Anderson JL, Parekh AK, Zoghbi WA. AHA/ACC/HHS strategies to enhance application of clinical practice guidelines in patients with cardiovascular disease and comorbid conditions: from the American Heart Association, American College of Cardiology, and US Department of Health and Human Services. Circulation. 2014;130(18):1662–1667. [PubMed: 25212466]
8. Canivell S, Muller O, Gencer B, et al. Prognosis of cardiovascular and non-cardiovascular multimorbidity after acute coronary syndrome. PloS one. 2018;13(4):e0195174. [PubMed: 29649323]
9. Alabas OA, Gale CP, Hall M, et al. Sex Differences in Treatments, Relative Survival, and Excess Mortality Following Acute Myocardial Infarction: National Cohort Study Using the SWEDEHEART Registry. J Am Heart Assoc. 2017;6(12).
10. Hall M, Dondo TB, Yan AT, et al. Association of Clinical Factors and Therapeutic Strategies With Improvements in Survival Following Non-ST-Elevation Myocardial Infarction, 2003-2013. Jama. 2016;316(10):1073–1082. [PubMed: 27574717]
11. Bell SP, Saraf AA. Epidemiology of Multimorbidity in Older Adults with Cardiovascular Disease. Clinics in Geriatric Medicine. 2016;32(2):215–226. [PubMed: 27113142]
12. Xu X, Mishra GD, Jones M. Evidence on multimorbidity from definition to intervention: An overview of systematic reviews. Ageing Research Reviews. 2017;37:53–68. [PubMed: 28511964]
13. Crowe M, Sheppard L, Campbell A. Comparison of the effects of using the Crowe Critical Appraisal Tool versus informal appraisal in assessing health research: a randomised trial. International Journal of Evidence-Based Healthcare. 2011;9(4):444–449. [PubMed: 22093394]
14. Ofori-Asenso R, Zomer E, Chin KL, et al. Prevalence and impact of non-cardiovascular comorbidities among older adults hospitalized for non-ST segment elevation acute coronary syndrome. Cardiovascular Diagnosis and Therapy. 2019;9(3):250–261. [PubMed: 31275815]
15. Tisminetzky M, Gurwitz JH, Miozzo R, et al. Impact of cardiac- and noncardiac-related conditions on adverse outcomes in patients hospitalized with acute myocardial infarction. J Comorb. 2019;9:2235042x19852499.
16. Elixhauser A, Steiner C, Harris DR, Coffey RM. Comorbidity measures for use with administrative data. Medical care. 1998;36(1):8–27. [PubMed: 9431328]
17. Charlson M, Szatrowski TP, Peterson J, Gold J. Validation of a combined comorbidity index. Journal of Clinical Epidemiology. 1994;47(11):1245–1251. [PubMed: 7722560]

18. Hall M, Dondo TB, Yan AT, et al. Multimorbidity and survival for patients with acute myocardial infarction in England and Wales: Latent class analysis of a nationwide population-based cohort. PLoS Med. 2018;15(3):e1002501. [PubMed: 29509764]
19. Chen HY, Saczynski JS, McManus DD, et al. The impact of cardiac and noncardiac comorbidities on the short-term outcomes of patients hospitalized with acute myocardial infarction: a population-based perspective. Clinical epidemiology. 2013;5:439–448. [PubMed: 24235847]
20. Tisminetzky M, Gurwitz J, McManus DD, et al. Multiple Chronic Conditions and Psychosocial Limitations in Patients Hospitalized with an Acute Coronary Syndrome. Am J Med. 2016;129(6):608–614. [PubMed: 26714211]
21. Worrall-Carter L, McEvedy S, Wilson A, Rahman MA. Impact of comorbidities and gender on the use of coronary interventions in patients with high-risk non-ST-segment elevation acute coronary syndrome. Catheterization and cardiovascular interventions : official journal of the Society for Cardiac Angiography & Interventions. 2016;87(4):E128–136. [PubMed: 26277889]
22. Hudzik B, Korzonek-Szlacheta I, Szkodzinski J, et al. Prognostic impact of multimorbidity in patients with type 2 diabetes and ST-elevation myocardial infarction. Oncotarget. 2017;8(61):104467–104477. [PubMed: 29262654]
23. Canivell S, Muller O, Gencer B, et al. Prognosis of cardiovascular and non-cardiovascular multimorbidity after acute coronary syndrome. PloS one. 2018;13(4):e0195174. [PubMed: 29649323]
24. Chen HY, Saczynski JS, McManus DD, et al. The impact of cardiac and noncardiac comorbidities on the short-term outcomes of patients hospitalized with acute myocardial infarction: a population-based perspective. Clinical Epidemiology. 2013;5:439–448. [PubMed: 24235847]
25. Renzi C, Kaushal A, Emery J, et al. Comorbid chronic diseases and cancer diagnosis: disease-specific effects and underlying mechanisms. Nature Reviews Clinical Oncology. 2019;16(12):746–761.
26. Tisminetzky M, Goldberg R, Gurwitz JH. Magnitude and Impact of Multimorbidity on Clinical Outcomes in Older Adults with Cardiovascular Disease: A Literature Review. Clinics in Geriatric Medicine. 2016;32(2):227–246. [PubMed: 27113143]
27. Sharabiani MT, Aylin P, Bottle A. Systematic review of comorbidity indices for administrative data. Medical Care. 2012;50(12):1109–1118. [PubMed: 22929993]
28. Ofori-Asenso R, Jakhu A, Curtis AJ, et al. A Systematic Review and Meta-analysis of the Factors Associated With Nonadherence and Discontinuation of Statins Among People Aged >/=65 Years. The Journals of Gerontology Series A, Biological sciences and medical sciences. 2018;73(6):798–805.
29. DeVon HA, Vuckovic K, Burke LA, et al. What's the Risk? Older Women Report Fewer Symptoms for Suspected Acute Coronary Syndrome than Younger Women. BioResearch open access. 2018;7(1):131–138. [PubMed: 30237934]
30. Fabbri E, An Y, Zoli M, et al. Aging and the Burden of Multimorbidity: Associations With Inflammatory and Anabolic Hormonal Biomarkers. The Journals of Gerontology: Series A. 2014;70(1):63–70.
31. Marengoni A, Roso-Llorach A, Vetrano DL, et al. Patterns of Multimorbidity in a Population-Based Cohort of Older People: Sociodemographic, Lifestyle, Clinical, and Functional Differences. The Journals of Gerontology: Series A. 2019.
32. Dondo TB, Hall M, Timmis AD, et al. Excess mortality and guideline-indicated care following non-ST-elevation myocardial infarction. European Heart Journal Acute Cardiovascular Care. 2017;6(5):412–420. [PubMed: 27142174]
33. Tisminetzky M, Gurwitz J, McManus DD, et al. Multiple Chronic Conditions and Psychosocial Limitations in Patients Hospitalized with an Acute Coronary Syndrome. The American Journal of Medicine. 2016;129(6):608–614. [PubMed: 26714211]
34. Bell SP, Saraf AA. Epidemiology of Multimorbidity in Older Adults with Cardiovascular Disease. Clinics in geriatric medicine. 2016;32(2):215–226. [PubMed: 27113142]
35. Gudnadottir GS, James SK, Andersen K, et al. Outcomes after STEMI in old multimorbid patients with complex health needs and the effect of invasive management. Am Heart J. 2019;211:11–21. [PubMed: 30831330]

36. Burke LA, Rosenfeld AG, Daya MR, et al. Impact of comorbidities by age on symptom presentation for suspected acute coronary syndromes in the emergency department. European journal of Cardiovascular Nursing : Journal of the Working Group on Cardiovascular Nursing of the European Society of Cardiology. 2017;16(6):511–521.

37. O'Neill DE, Southern DA, Norris CM, O'Neill BJ, Curran HJ, Graham MM. Acute coronary syndrome patients admitted to a cardiology vs non-cardiology service: variations in treatment & outcome. BMC health services research. 2017;17(1):354. [PubMed: 28511683]

38. Wiley JF, Chan YK, Ahamed Y, et al. Multimorbidity and the Risk of All-Cause 30-Day Readmission in the Setting of Multidisciplinary Management of Chronic Heart Failure: A Retrospective Analysis of 830 Hospitalized Patients in Australia. The Journal of Cardiovascular Nursing. 2018;33(5):437–445. [PubMed: 28107252]

39. Adarkwah CC, Jegan N, Heinzel-Gutenbrunner M, et al. Time-to-event versus ten-year-absolute-risk in cardiovascular risk prevention–does it make a difference? Results from the Optimizing-Risk-Communication (OptRisk) randomized-controlled trial. BMC Medical Informatics and Decision Making. 2016;16(1):152. [PubMed: 27899103]

40. Farkouh ME, Aneja A, Reeder GS, et al. Clinical risk stratification in the emergency department predicts long-term cardiovascular outcomes in a population-based cohort presenting with acute chest pain: primary results of the Olmsted county chest pain study. Medicine. 2009;88(5).

41. Antman EM, Cohen M, Bernink PJ, et al. The TIMI risk score for unstable angina/non–ST elevation MI: a method for prognostication and therapeutic decision making. Jama. 2000;284(7):835–842. [PubMed: 10938172]

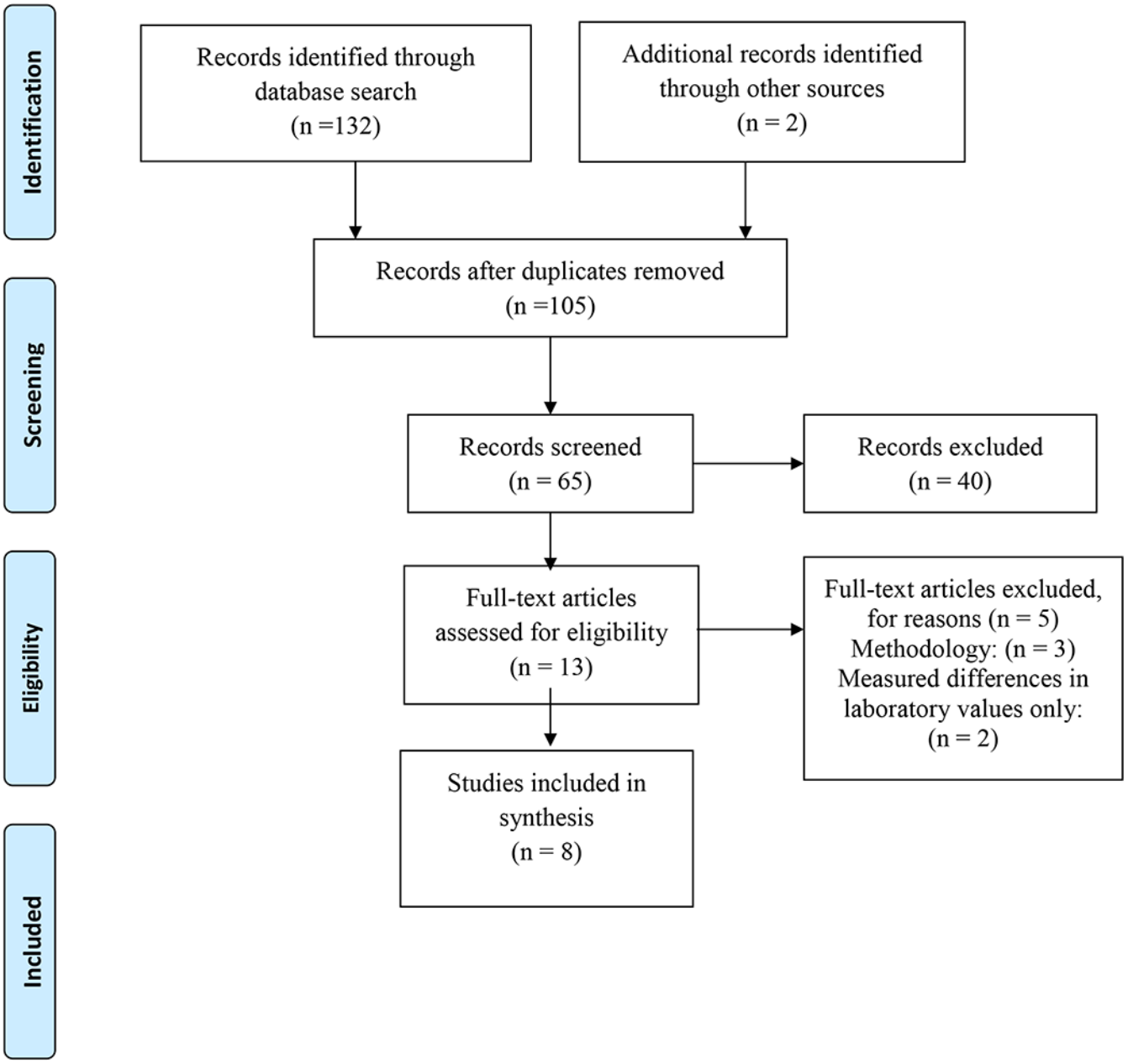

Figure 1.
Prisma Flow Diagram

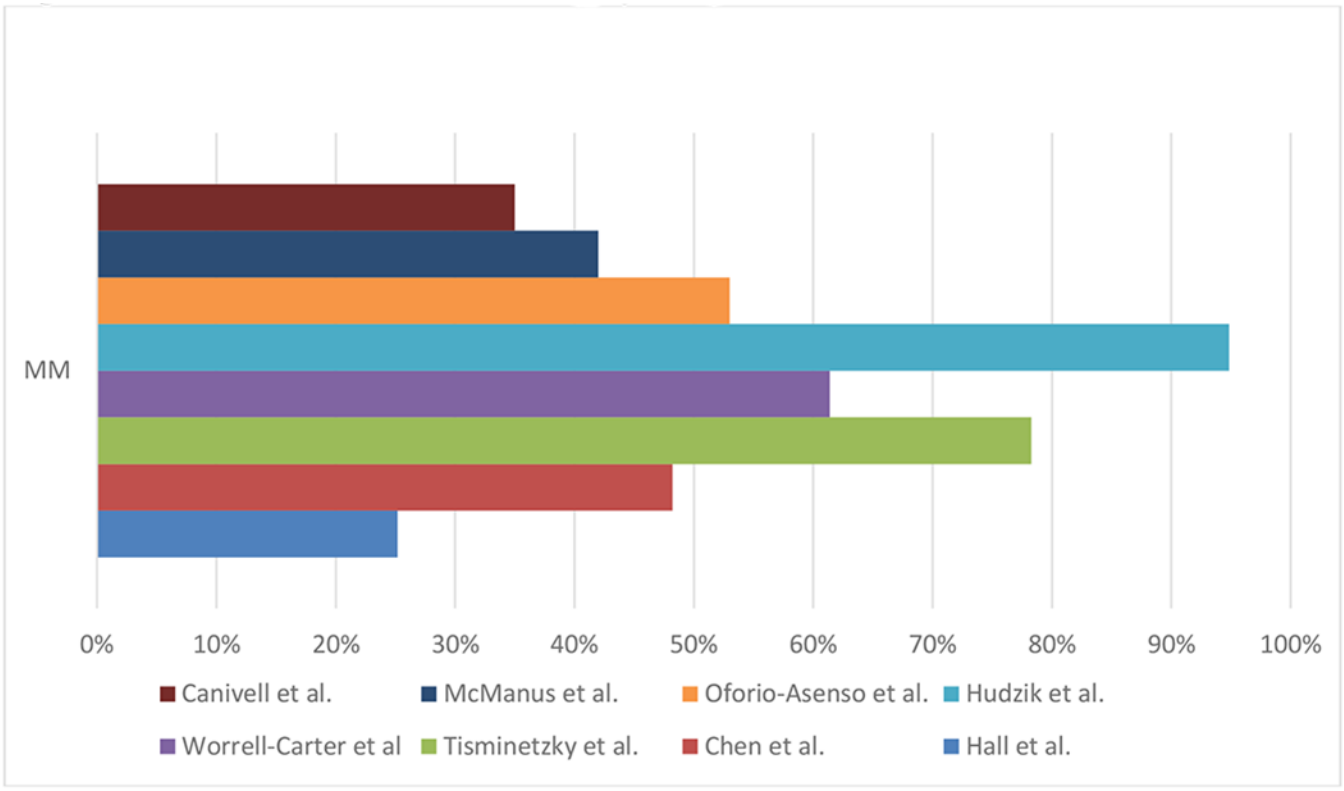

Figure 2.
Prevalence of multimorbidity by study
Abbreviations: MM = multimorbidity

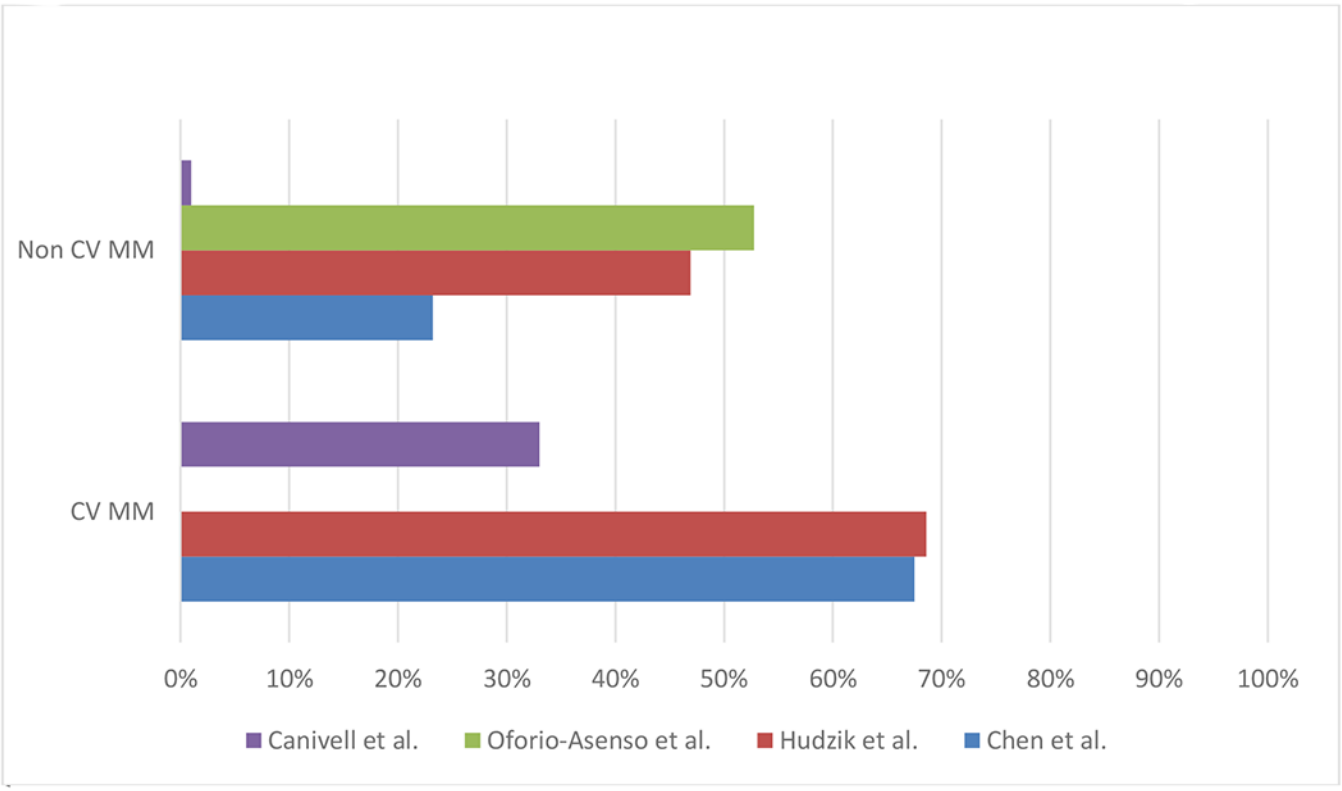

Figure 3.

Prevalence of Cardiovascular and Non-Cardiovascular Multimorbidity

[1]Oforio-Asenso et al. did not report CV MM.

Abbreviations: CV = cardiovascular; MM = multimorbidity.

Table 1.

Study Characteristics

Authors/Country	Study Design/Time Period	Purpose	Sample/Setting/Condition	Quality Score
Canivell et al. (2018),[8] Switzerland	Prospective cohort data collected from 2009-2014	Examine the prognosis of patients with CV and non-CV MM compared to patients without prior MM following ACS	N = 5,635 Mean Age: 67.7 years 79% Male 97.5% Caucasian Multiple hospitals in Switzerland, ACS	38/40
Hall et al. (2018),[18] England and Wales	Retrospective analysis of data collected in the *MINAP* database from January 2003-June 2013	Investigate MM phenotype clusters exist across a range of pre-existing long-term health conditions and study the association with long-term survival for patients hospitalized with AMI	N = 693,388 Mean Age: 70.7 years 65.5% male Race not reported All hospitals in the National Health Service in England and Wales AMI	37/40
Chen et al. (2013),[24] USA	Retrospective analysis of the *Worcester Heart Attack Study* with data collected in 2003, 2005, and 2007	Describe the prevalence of cardiac and noncardiac comorbidities in a community-based population of patients hospitalized with AMI	N = 2,972 Mean Age: 71 years 55% male 93% Caucasian All medical centers in Massachusetts AMI	38/40
McManus et al. (2012),[6] USA	Retrospective analysis of the *Worcester Heart Attack Study* with data collected between 1990-2007	Examine the overall and changing (1990-2007) frequency and impact on 30-day and 1-year death rates from multiple CV comorbidities	N = 9,581 Mean age: 70 years 57% male 93% Caucasian All medical centers in Massachusetts AMI	35/40
Tisminetzky et al. (2019),[15] USA	Multisite prospective cohort design with data collected between 2001-2011	Describe the prevalence of, and patient characteristics associated with, CV and non-CV multimorbidities in patients discharged from the hospital after ACS	N = 2,174 Mean age: 67 years 67% male 81% Caucasian Medical centers in Massachusetts and Georgia ACS	38/40
Worrall-Carter et al. (2015),[21] Australia	Retrospective cohort study of VAED) database analyzing data collected between June 2007-July 2009	Determine the impact of gender and comorbidity on use of coronary interventions in patients diagnosed with high-risk non-ST-segment elevation ACS	N = 16,771 Age Range: 15-59 (21%), 60-74 (32%), 75+ (48%) 62% male Race not reported All Victorian hospitals in Australia NSTEMI ACS	34/40
Hudzik et al. 2017, Poland	Retrospective cross-sectional analysis of data collected over a 12-month period	Determine the prognostic value of multiple comorbidities on long-term outcomes in patients with type II diabetes and STEMI	N = 277 Mean age: 63.5 years 58.8% male Race not reported Location not reported Patients with concurrent type II Diabetes and STEMI	31/40

Authors/Country	Study Design/Time Period	Purpose	Sample/Setting/Condition	Quality Score
Ofori-Aseno et al. 2019,[14] Australia	Retrospective cohort study of data collected between July 2013-December 2015	Examine the prevalence and impact of noncardiac comorbidities on the length of stay and mortality among older adults hospitalized for non-ST-segment elevation-ACS	N = 1,488, Mean age: 79.4 years 62% male, Race not reported Single-center (Alfred hospital) in Melbourne NSTEMI and UA	35/40

Abbreviations: ACS = acute coronary syndrome. AMI = acute myocardial infarction. CV = cardiovascular. MM = multimorbidity. NSTEMI = non-ST elevation myocardial infarction. STEMI = ST-elevation myocardial infarction. UA = unstable angina. VAED = The Victorian Admitted Episodes Data Set.

Table 2.

Clinical Outcomes Data by Study

Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
Canivell et al. (2018)[8]	Age-Sex adjusted HR (95% CI): No MM: 1.00 (ref) CV-MM: 1.87 (1.50-2.33) NONCVMM: 2.27 (1.11-4.63) CV and NONCVMM: 3.16 (1.82-5.50) *Measured as CV event	N/M	N/M	**Cardiac Rehab at 1 year:** No MM: 72% CV-MM:56.7% NONCVMM: 52.5% CV and NONCVMM: 32.4%. **Polypharmacy (>5) at 1 year:** No MM: 59.1% CV-MM: 79.5% NONCVMM: 83.9% CV and NONCVMM: 81.4%.	**High-Dose Statins at Discharge:** No MM: 71.7% CV-MM: 64.7% NONCVMM: 62.3% CV and NONCVMM: 55.9% ($p < 0.001$) **High-Dose Statins at 1-year:** No MM: 60.5% CV-MM:54.7% NONCVMM: 50.9% CV and NONCVMM: 41.4% ($p < 0.001$)
Hall et al. (2018)[18]	**30 Day:** Class 1: 17% Class 2: 10% Class 3: 7.4% ($p < 0.001$) **1 year:** Class 1: 39.8% Class 2: 21.4% Class 3: 14.4% ($p < 0.001$) **5 year:** Class 1: 57.4% Class 2: 34% Class 3: 22.4% ($p < 0.001$)	**Revascularization:** Class 1: 14.8% Class 2: 26.9% Class 3: 42.7% ($p < 0.001$) **Diuresis with Loop Diuretic** Class 1: 62.9% Class 2: 36.8% Class 3: 22% ($p < 0.001$)	N/M	N/M	**Statins at discharge:** Class 1: 80.6% Class 2: 58.9% Class 3: 85.2% ($p < 0.001$) **Beta-blocker at discharge:** Class 1: 74% Class 2: 80.9% Class 3: 85.2% ($p < 0.001$)
Chen et al. (2013)[5]	**In-Hospital** CVCM (0, 1, 2, 3+): 3.7%, 6.1%, 10.6%, 11.2%, 14.2% ($p < 0.001$) NONCVCM (0, 1, 2, 3+): 6.9%, 10.1%, 14.7%, 15.9% ($p < 0.001$)	**PCI:** **CVCM (0, 1, 2, 3, >4): 69.6%, 61.8%, 46.4%, 39.6%, 27.3%** ($p < 0.001$) NONCVCM (0, 1, 2, 3, >4): 60.6%, 41.4%, 29.2%, 19.9% ($p < 0.001$) **CABG:** CVCM (0, 1, 2, 3, >4): 4.7%, 6.8%, 6.4%, 6.8%, 2.9% ($p < 0.004$) NONCVCM (0, 1, 2, 3, >4): 6.2%, 6.3%, 3.2%, 2.7% ($p < 0.015$)	**LOS >3 days** CVCM (0, 1, 2, 3, 4+): 39.8%, 48.0%, 55.7%, 60.8%, 68.1% ($p < 0.001$) NONCVCM (0, 1, 2, 3, 4+): 47.8%, 58.3%, 68.6%, 70.7% ($p < 0.001$)	N/M	During hospitalization: Patients received an average of 4.2 of the 6 cardiac medications (b-blockers, ace or arbs, lipid-lowering agents, anticoagulants, aspirin, and thrombolytics)
McManus et al. (2012)[6]	**Mortality:** 30-day (0, 1, 2, 3, ≥4): 9.01%, 13.03%, 17.76%, 21.32%, 22.3%	N/M	N/M	N/M	N/M

Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
	1-year (0, 1, 2, 3, ≥4): 15.02%, 22.56%, 34.34%, 45.01%, 53.56%				
Tisminetzky et al. (2019)[15]	**In-Hospital** Group 1: 9.1%, Group 2: 14%, Group 3: 11.2% Group 4: 13.9%	**PCI:** Group 1: 59.9% Group 2: 41.7% Group 3: 56.6% Group 4: 42.2% (p < 0.001) **CABG:** Group 1: 7.7 Group 2: 4.5% Group 3: 7% Group 4: 4.8% (p < 0.01)	**Days (median):** Group 1: 4 Group 2: 5 Group 3: 4 Group 4: 5 (p < 0.01)	**Readmission** **7 days:** Group 1: 4.6% Group 2: 6.5% Group 3: 5.9% Group 4: 6.8% **30 days:** Group 1: 14.5% Group 2: 15.8% Group 3: 17.1% Group 4: 21.5%	**During hospitalization** **ACE-I/ARBs:** Group 1: 65.1% Group 2: 58.8% Group 3: 74.0% Group 4: 68.1% (p < 0.001) **Aspirin:** Group 1: 92.8% Group 2: 90.0% Group 3: 92.6% Group 4: 90.2% (p < 0.01) **Beta-Blockers:** Group 1: 90.5% Group 2: 86.1% Group 3: 90.1% Group 4: 89.6% (p < 0.01) **Lipid-Lowering agents:** Group 1: 70.5% Group 2: 63.2% Group 3: 77.9% Group 4: 75.3% (p < 0.001)
Worrall-Carter et al. (2015)[21]	N/M	**Angiogram** Female with (0, 1, 2, 3+) CM: 56%, 51%, 40%, 36% Male: 75%,71%, 61%, 50% **Stent** Female with (0, 1, 2, 3+) CM:11%, 10%, 5%, 4% Male: 19%, 17%, 9%, 5% **CABG** Female with (0, 1, 2, 3+) CM 2%, 3%, 7%, 10% Male with (0, 1, 2, 3+) CM: 5%, 8%, 17%, 18% **No Intervention** Female with (0, 1, 2, 3+) CM: 44%, 48%, 58%, 61% Male with (0, 1, 2, 3+) CM: 24%, 26%, 34%, 45%	N/M	N/M	N/M
Hudzik et al. (2017)[22]	**In hospital:** Group 1: 5.2% Group 2: 11.4% (p < 0.05) **1 year:** Group1: 8.6% Group 2: 19.9% (p < 0.05)	**Successful PCI:** Group 1: 89.9% Group 2: 84.0% (p = 0.4)	**Median days:** Group 1: 7.5 Group 2: 9 (p < 0.04)	N/M	N/M

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Citation	Mortality	Inpatient Treatment	Length of Stay	Management	Medications
Ofori-Aseno et al. (2019)[14]	**In hospital mortality for** (0, 1, 2+) NONCVCM: 4.4%, 5.5%, 10.6% **In hospital mortality**: the cohort 6.1%, UA 2.6%, and NSTEMI 7.1% (p = 0.003)	**PCI** (0, 1, 2+) NONCVCM: 30.9%, 23.2%, 11.9% (p < 0.001) **CABG** (0, 1, 2+) NONCVCM: 15.8%, 11.8%, 7.4% (p = 0.001)	**Median (IQR)** for (0, 1, 2+) NONCVCM: 3.83 (1.96-8.04), 4.40 (2.38-8.92), 5.83 (3.04-10.5)	N/M	N/M

Abbreviations: ACE = angiotensin-converting enzyme inhibitor. ARB angiotensin receptor blocker. CABG = coronary artery bypass graft. CV events were defined as the composite of incident myocardial infarction, ischemic stroke, transient ischemic attack, or cerebrovascular or CV mortality. CVMM = cardiovascular multimorbidity. IQR = interquartile ratio. MM = multimorbidity. N/M = not measured. PCI = percutaneous intervention.

Table 3.

Patient Outcomes and Limitations

Citation	Data Source	Outcome Findings	Study limitations
Canivell et al. (2018)[8]	Medical records	Multimorbid patients have a poorer prognosis, poorer control of CV risk factors, lower use of high-dose statins, lower attendance of cardiac rehab, and an increase in the risk of CV event at 1-yr. post ACS event	Classified patients according to the presence of multimorbidity(count), and not comorbidity Patients in the no multimorbidity group could still suffer from one of the CV or/and non-CV comorbidities No information on grade or severity of the different comorbidities
Hall et al. (2018)[18]	MINAP database	The prevalence of multimorbidity was high in AMI patients and conferred an accumulative increased risk of death. Patients in Class 1 (high multimorbidity) and Class 2 (moderate multimorbidity) had a 2.89 and 1.52 years loss in life expectancy	MINAP database doesn't have 100% case ascertainment; missing data could have biased estimates. Limited to all-cause mortality
Chen et al. (2013)[5]	Worcester heart attack study (ICD-9, medical records)	High prevalence of multiple CV and non-CV comorbidities in patients hospitalized with AMI. Multimorbidity was associated with a higher likelihood of dying during hospitalization and being hospitalized for a more prolonged period	Study population only from a metropolitan area. Majority of the population Caucasian. No information on income, education, and psychological factors included in study
McManus et al. (2012)[6]	Medical Records	In patients with AMI, the odds of having multiple CV comorbidities increased over time. Multimorbidity was associated with poor prognosis over the period of study	Majority of the study population Caucasian. Non-randomized study design. Physician thresholds for diagnosing several of the comorbid conditions studied may have changed over time
Tisminetzky et al. (2019)[15]	Medical records and baseline interview	CV and non-CV conditions are highly prevalent in patients hospitalized with MI Patients with both CV and non-CV conditions at greatest risk for developing adverse-in-hospital and short-term outcomes Patients with 1+ non-CV condition were less likely to be prescribed evidence-based medications and/or coronary intervention than those without non-CV conditions	Limited generalizability to other ethnic/racial groups >90% of the population Caucasian. No estimation of severity or duration of chronic conditions
Worrall-Carter et al. (2015)[21]	Dataset review derived from medical records	High prevalence of multimorbidity. Increasing multimorbidity with age. Higher rates of non-intervention in multimorbid females than their male counterparts. 28/30 comorbidities recorded were more prevalent (usually significantly) amongst patients who received no intervention	Potential underreporting of comorbidity, as comorbidity was classified based on coded diagnosis in the hospital record
Hudzik et al. (2017)[22]	Medical records	A majority of patients have at least 2 other CV comorbidities and/or two non-CV comorbidities Multimorbidity associate with greater 12-month all-cause mortality and risk of ACS event. Every additional comorbidity was associated with a 15% increase in relative risk of 12-month mortality and a 41% increase in relative risk of 12-month ACS event	Limited generalizability given study population is 100% of patients with type 2 DM and STEMI patients. Small sample size.
Ofori-Aseno et al. (2019)[14]	ICD-10 codes and medical records	Over half of patients hospitalized with NSTEMI had multiple non-CV comorbidities A higher burden of non-CV comorbidities was associated with increased LOS and decreased survival	Data collected as part of routine care. One sub-group analysis underpowered. Only use in-hospital data

Abbreviations: ACS = acute coronary syndrome, CV = cardiovascular, DM = diabetes mellitus, MI = myocardial infarction, NSTEMI = non-ST elevation myocardial infarction, LOS = length of stay, STEMI = ST-elevation myocardial infarction, UA = unstable angina