Contribution of Cardiac and Extra-Cardiac Disease Burden to Risk of Cardiovascular Outcomes Varies by Ejection Fraction in Heart Failure

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Aims: Patients with heart failure (HF) often have multiple comorbidities that contribute to the risk of adverse cardiovascular (CV) and non-CV outcomes. We assessed the relative contribution of cardiac and extra-cardiac disease burden and demographic factors to CV outcomes in HF patients with reduced (HFrEF) or preserved (HFpEF) left ventricular ejection fraction (LVEF).

Methods and Results: We utilized data from the CHARM trial, which enrolled heart failure patients across the ejection fraction spectrum. We decomposed the previously validated MAGGIC risk score into cardiac (*LVEF, NYHA class, SBP, time since HF diagnosis, HF medication use*), extra-cardiac (*BMI, creatinine, DM, COPD, smoker*), and demographic (*age, gender*) categories, and calculated subscores for each patient representing the burden of each component. Cox proportional hazards models were used to estimate the population attributable risk (PAR) associated with each component to the outcomes of death, CV death, HF, myocardial infarction, and stroke relative to patients with the lowest risk score. PAR for each component were depicted across the spectrum of LVEF

In 2675 chronic heart failure patients from North America (HFrEF [LVEF≤40%]: 1589, HFpEF [LVEF>40%]: 1086) with data available for calculation of the MAGGIC score, the highest risk of death and CV death was attributed to cardiac burden. This was especially evident in HFrEF patients (PAR: 76%: cardiac disease vs. 58% extra-cardiac disease, $p<0.05$). Conversely, in HFpEF patients, extra-cardiac burden accounted for a greater proportion of risk for death than cardiac burden (PAR: 15%: cardiac disease vs. 49% extra-cardiac disease, $p<0.05$). For heart failure hospitalization, the contribution of both cardiac and extra-cardiac burden was comparable in HFpEF patients (PAR: 42%: cardiac disease vs. 53% extra-cardiac disease, p=NS). In addition, demographic burden was especially high in HFpEF patients, with 62% of deaths attributable to demographic characteristics.

Conclusion: In North American heart failure patients enrolled in the CHARM trials, the relative contribution of cardiac and extra-cardiac disease burden to CV outcomes and death differed depending on LVEF. The high risk of events attributable to non-cardiac disease burden may help explain why cardiac disease modifying medication proven to be efficacious in HFrEF patients have not proven beneficial in HFpEF.

Keywords: comorbidity, HFpEF, heart failure, CHARM, population attributable risk

Introduction

Patients with heart failure (HF) are often burdened with multiple comorbidities[1,2], and HF patients with e.g. diabetes[3], COPD[4,5], or anemia[5,6] bear a worse prognosis than similar HF patients without these conditions. Despite the consensus that extra-cardiac diseases affect the prognosis and treatment of HF patients[2,7], very little is known about the cumulative burden of multiple extra-cardiac comorbidities[5,8,9]. Although most heart failure intervention trials have focused on therapies aimed at the cardiovascular system, it is believed that extra-cardiac diseases

also influence CV outcomes in HF patients[2,5,9]. While several therapies have proven efficacious for patients with heart failure and reduced ejection fraction (HFrEF)[10–13], no therapy has been found to reduce morbidity and mortality in patients with preserved ejection fraction (HFpEF)[14–17].

It has been proposed that a greater demographic and co-morbid burden in HFpEF patients may explain why medications with predominantly cardiac effects will not affect mortality and morbidity outcomes to a significant degree[18]. Thus, estimating the contribution of disease burden to CV outcomes in both types of HF patients may help predict the maximal achievable risk reduction of treatments aimed at decreasing the cardiac or extra-cardiac disease burden. We utilized a HF risk score for mortality - the MAGGIC risk score - as an externally validated framework to discern the relative contribution of demographic, cardiac and extra-cardiac disease burden to clinically important CV morbidity and mortality outcome[19] in the broad spectrum of heart failure patients with both HFrEF and HFpEF enrolled in the CHARM program. Population Attributable Risk (PAR) for each of demographic, cardiac and extra-cardiac disease burden were visualized continuously across the LVEF spectrum

Methods

We utilized data from the previously reported CHARM trials[10]. In summary, 7599 chronic heart failure patients, NYHA class II-IV, were randomized to receive either placebo or candesartan (target dose 32 mg) in addition to optimal medical heart failure therapy. Patients were enrolled in the CHARM-Alternative[20] or CHARM-Added[21] trials if their LVEF was 40% or less, and in the CHARM-Preserved[15] trial if their LVEF was greater than 40%. Patients were followed for a

median of 38 months. All CV events during follow-up were adjudicated by an independent endpoints committee, who classified events according to pre-specified criteria[22].

Calculation of burden

To discern and quantify each risk component – demographic, cardiac and extra-cardiac – from the total risk profile of each patient, we utilized the externally validated MAGGIC risk score,[19] based on 39372 HF patients from 30 cohort trials (including the CHARM trial), with a median follow-up of 2.5 years. The MAGGIC model derived an optimal model for predicting death in both HFrEF and HFpEF patients, with thirteen variables identified as being highly significant, and an integer risk score created using model estimates of the predictive strength of each variable. A higher score was associated with increased risk of mortality (www.heartfailurerisk.org).

Definition of demographic, cardiac and extra-cardiac disease burden

In this analysis, we utilized all 13 baseline risk factors identified in the MAGGIC score, which were collected in the CHARM trial from patients recruited from North America only (n=2743). Data for calculation of the MAGGIC score was possible in 2675 patients (98%).

We grouped the 13 variables into 3 sub-categories each representing *demographic* (age, gender), *cardiac* risk factors or disease (LVEF, NYHA class, systolic blood pressure, HF hospitalization within 18 months, no beta-blocker use, no ACE inhibition), and *extra-cardiac* risk factors or disease (BMI, diabetes, COPD, creatinine, current smoker). Using the MAGGIC integer score, the sum of each sub-component reflected the total burden of either demographic, cardiac or extra-cardiac disease and was calculated individually for all patients. A total maximum score of

57 points was obtainable across all categories (cardiac disease burden; 0-26, extra-cardiac burden; 0-19, demographic burden; 0-16).

Statistical Analysis

All baseline characteristics pertaining to the risk categories were summarized as counts (%), mean ± SD, median [IQR], or as geometric mean±95% confidence intervals (CI), due to right-skewed distribution (creatinine). Restricted cubic spline models were used to depict the mean levels of demographic, cardiac disease and extra-cardiac disease burden across the LVEF spectrum. As burden was related to LVEF, LVEF was omitted from the cardiac disease burden component in this analysis only. Using time-to-event data for outcomes of all-cause death, CV death, HF hospitalization, fatal and non-fatal MI, fatal and non-fatal stroke, Cox proportional hazard modeling was used to estimate the Population Attributable Risk (PAR) for each component with respect to each of the examined outcomes. The PAR is summarized as percent (±95% confidence intervals), and estimates the hypothetical reduction of incidence rates if all patients had no burden in a specific sub-component (e.g. cardiac disease burden=0). Attributable risks may add up to greater than 100%. Combined attributable risks are calculated by multiplication. For example, attributable risks of 70% and 60% would produce a combined attributable risk of 1-(1-0.70)*(1-0.60) = 88%. Because risks are multiplicative, they are displayed graphically on a log scale so that relative importance can be seen visually. Non-significant negative PAR estimates were considered as 0. The Cox proportional hazards models were adjusted for all categories (demographic, cardiac and extra-cardiac) and analyses were stratified according to HF group (HFrEF vs. HFpEF) as well as continuously across the LVEF spectrum. In order to estimate the PAR for each component as a function of continuous LVEF, we used Cox proportional hazards models including interaction terms between that component

and LVEF (modeled using both linear and quadratic terms), while adjusting for the other two categories. For any value of LVEF, we then estimated the average additional risk experienced by the actual study patients relative to a hypothetical population with the same LVEF value but who possessed zero points for that score component. PAR estimates of cardiac and extra-cardiac categories stratified to HFrEF and HFpEF were compared using the delta method under the assumption of independence, resulting in potentially conservative p-values. Risk of CV outcomes and progressive extra-cardiac burden was analyzed using Cox proportional hazard spline models adjusted for each category of cardiac disease and demographic burden.

Results

Baseline characteristics and risk distribution

A total of 2675 patients from North America with baseline data available for calculation of the MAGGIC score were included in this study. The median follow-up time was 37 months. The 2675 included patients from North America differed from the original CHARM cohort at baseline by having higher incidences of hypertension, prior coronary procedures, diabetes, COPD/asthma, and active smoking, but fewer prior HF hospitalizations and males. By construction, each unit increase of the MAGGIC score should correspond to an increased event rate of 1.11. Similarly, the observed relationship with overall mortality in CHARM was HR=1.12 (1.10-1.13), $p<0.001$ for every integer point increase of the MAGGIC score (C statistic: 0.70). The HR for other outcomes examined were: CV death HR=1.12 (1.10-1.13), HF hospitalization HR=1.08 (1.07-1.10), myocardial infarction (MI) HR=1.07 (1.04-1.09), and stroke HR=1.04 (1.01-1.07). Baseline risk factors that were used to calculate the MAGGIC score

are listed in Table 1. The median[IQR] MAGGIC score in this sub-population of CHARM was 22[10, 33], range 2-43. The total score of all 3 categories was higher in the HFrEF group compared to the HFpEF group. The greater score in HFrEF patients was mostly due to a progressively higher burden of cardiac risk factors in patients with lower LVEF ($p<0.001$), with extra-cardiac burden only slightly increasing as LVEF decreased ($p<0.001$). Conversely, demographic burden was greater among patients with higher LVEF ($p<0.001$; Table 1 and Figure S1). The ratio of cardiac:extra-cardiac risk factors was much higher in patients with lower LVEF (Figure 1). As LVEF increased, so did the contribution of demographic risk factors, making it the biggest contributor of all categories in patients with higher LVEF.

Association between progressive extra-cardiac disease burden and CV outcomes

The risk of HF hospitalization and CV death increased in a linear fashion with higher extra-cardiac comorbid burden, irrespective of LVEF (Figure 2A-B; both $p<0.001$). Similar analyses were carried out for outcomes of MI and stroke, which all showed a significantly positive relationship with increasing extra-cardiac burden, irrespective of LVEF (data not shown).

Relative contribution of demographic, cardiac and extra-cardiac disease burden to CV outcomes across the LVEF spectrum

In patients with lower LVEF, the contribution of cardiac disease burden to all-cause death, CV death, and HF was greater than extra-cardiac disease burden. In contrast, in patients with higher LVEF extra-cardiac disease burden contributed more to all outcomes examined – death, CV death, HF, MI, stroke - compared to cardiac disease burden, cardiac disease burden having a non-significant contribution to outcomes of MI and stroke (cardiac disease burden: MI HR=1.0 [0.96-1.04], p=0.91; stroke HR=0.98 [0.93-1.02], p=0.29). In patients with higher LVEF the demographic component contributed with the greatest risk of death and stroke (Figures 3A-E).

PARs with confidence intervals (HFrEF vs. HFpEF and HFrEF vs. HFmrEF vs. HFpEF) are listed in Supplemental material (Table 1S and 4S), as are estimates of PAR with renal function grouped as a cardiac risk factor as sensitivity analysis (Table 2S), and PAR without renal function, but with all patients from the CHARM programme [n=7599](Table 3S).

Discussion

We found that in a broad spectrum of heart failure patients from North America the distribution of cardiac, extra-cardiac, and demographic risk factors differed by ejection fraction. Using the pre-defined MAGGIC risk factors, patients with lower LVEF had relatively more cardiovascular risk factors and minimally greater extra-cardiac risk factors. Conversely, the demographic burden was higher in patients with higher LVEF. There was a clear association between the incremental burden of extra-cardiac disease and risk of CV outcomes, irrespective of LVEF. Cardiac disease burden contributed most to outcomes of death and HF hospitalization in patients with lower LVEF, whereas extra-cardiac burden contributed more than cardiac burden to death, HF hospitalization, MI, and stroke in patients with higher LVEF.

In contrast to studies that reported crude prevalence rates of comorbidity [9,18], in this analysis we were able to account for the cumulative contribution of multiple diseases, as well as how these change with ejection fraction. Because cardiac risk factors were more prevalent in patients with lower LVEF, the ratio of cardiac to extra-cardiac risk factors was much higher in these patients, a finding which is consistent with the higher rates of adverse CV events HFrEF patients experienced, compared to HFpEF patients, in registries[9] and in the CHARM[15,20,21] and DIG[23,24] trials which included both HF populations. The finding that extra-cardiac risk factors

were at least as prevalent in lower LVEF patients compared to higher LVEF patients was also reported in a non-selective ambulatory cohort of US veterans with HF.[9]

In a large Medicare registry with chronic heart failure patients, a cumulative number of non-cardiac comorbidities were associated with increased risk of hospitalization for HF[8]. We also noted a linear relationship between the burden of extra-cardiac disease and HF hospitalization, as well as for the outcomes of CV death, MI and stroke. Our study adds clarity by exploring several adjudicated CV outcomes, and using selected risk factors that were validated from the MAGGIC risk score. Our finding of strong associations between extra-cardiac burden and CV outcomes suggests that extra-cardiac disease burden does indeed influence different CV outcomes, and that there is no upper threshold where incremental burden does not translate into a higher incidence of these outcomes.

The CHARM data allowed us to model the relative contributions of demographic, cardiac, and extra-cardiac disease burden across the entire LVEF spectrum, making these estimates applicable to all chronic HF patients, irrespective of how HF patients are sub-grouped (e.g. HF with mid-range EF[7], HFpEF with systolic impairment[25]). A key finding from this study is the clarification of the relative contributions of modifiable (cardiac and extra-cardiac disease) and non-modifiable (demographics) categories to outcomes across the LVEF range. Our finding in HFrEF patients that cardiac disease burden was the greatest contributor to death, CV death, and HF hospitalization, would suggest that modifying the cardiac disease burden might translate into benefits in these outcomes. In contrast, HFpEF patients had a non-significant contribution from cardiac disease burden to death and CV death in our study. In HFrEF outcome trials such as MERIT-HF[13], CONSENSUS[26], and PARADIGM-HF[27] that tested cardiac disease modifying treatments (beta-blockers, ACE inhibition, angiotensin-neprilysin inhibition), death, CV death,

and HF progression was reduced compared to placebo. In contrast, HFpEF patients treated with ACE inhibition, angiotensin receptor blocker, or mineralocorticoid-receptor antagonist in the PEP-CHF (Perindopril for elderly people with chronic heart failure trial)[28], I-PRESERVE (Irbesartan in heart failure with preserved systolic function)[16], CHARM-Preserved (Effects of candesartan in patients with chronic heart failure and preserved left-ventricular ejection fraction)[15], and TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist)[14] trials, did not have decreased risk of death or CV death. Our findings may help explain why cardiac disease-modifying treatments have not proven successful in alleviating the CV burden in HFpEF patients. The contribution of cardiac disease burden to CV outcomes may be relatively small, limiting the potential benefit of therapies that predominantly affect cardiovascular disease burden in patients with higher LVEF. Although we cannot infer that changing comorbid burden changes outcomes, these data may aid in the planning of future trials by quantifying what modifiable categories are contributing most to CV outcomes and death at a given LVEF range. To our knowledge, this is the first analysis that quantifies how the relative contribution of comorbidity and demographic factors influences risk in a cardiovascular population, and to show how this varies across the ejection fraction spectrum. As a method, this approach may prove useful beyond heart failure.

Some limitations of this analysis should be noted. Data from the CHARM study constituted ~19% of the total data used for development of the MAGGIC score, although the score was designed to assess the risk of death. In addition, because CHARM was a clinical trial with specific inclusion and exclusion criteria, caution needs to be exercised when extrapolating these findings to other heart failure populations. Specifically, the comorbid status of the CHARM population, may differ from that found in other heart failure populations. These

considerations should also be noted with the MAGGIC risk factors that were identified using patients from 31 cohort studies, 6 of which were randomized clinical trials. Although we confined our analysis to patients from North America in order to include creatinine, which was only measured in this subset, a sensitivity analysis including all patients in the CHARM programme (n=7599) from the entire program (with renal function omitted from analysis), yielded comparable results as our primary analysis suggesting that our results are not unique to North American patients.

The PAR estimates of the cardiac, extra-cardiac, or demographic categories to outcomes examined are depicted without confidence intervals. Confidence intervals are provided in the Supplemental material, and visual interpretation of the figures should be undertaken with this caveat.

The relative contribution of cardiac, extra-cardiac, and demographic risk factors to CV outcomes is highly dependent on the arbitrary grouping of risk factors into the categories. While estimates were affected by a different grouping, the overall differences between patients across the LVEF spectrum did not change.

In conclusion, the relative distribution and burden of cardiac, extra-cardiac disease, and demographics differs in HF patients depending on their LVEF. These data may help explain why cardiac disease modifying medication proven to be efficacious in patients with heart failure with reduced ejection fraction have not demonstrated the same benefits in HF patients with preserved ejection fraction.

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Conflict of Interest: none declared.

Declaration of Helsinki: This study complies with the Declaration of Helsinki, and the research protocol was approved by all relevant ethics committees and informed consent was obtained from the subjects (or their legally authorized representative).

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Legends

Figure 1. The distribution of MAGGIC risk score across the LVEF spectrum with all risk factors included.

Figure 2A-B. Risk of heart failure hospitalization (panel A) and CV death (panel B) with progressive extra-cardiac comorbid disease burden.

Figure 3A. Population Attributable Risks in outcome of death.

Figure 3B. Population Attributable Risks in outcome of CV death.

Figure 3C. Population Attributable Risks in outcome of HF hospitalization

Figure 3D. Population Attributable Risks in outcome of MI.

Figure 3E. Population Attributable Risks in outcome of stroke.