Temporal trends in mortality and readmission after acute heart failure: A systematic review and meta-regression in the past four decades

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Abbreviations:

AHF, acute heart failure

HF, heart failure

MeSH, medical subject headings

SBP, systolic blood pressure

HR, heart rate

EF, ejection fraction

RAASi, renin-angiotensin-aldosterone inhibitors

BB, Beta-Blocker

OR, odds ratio

CI, confidence interval

Abstract

Aims: Acute heart failure (AHF) is frequent and life-threatening disease. However, innovative AHF therapies have remained limited, and care is based on experts opinion. Temporal trends and benefits of long-term oral cardiovascular medications on AHF outcomes remain uncertain.

Methods and results: This study is registered with PROSPERO (CRD42018099885). A systematic review ranging from 1980 to 2017, searched AHF studies with more than 100 patients that reported death and/or readmission. Primary outcomes were temporal trends, assessed by meta-regression, for 30-day or one-year all-cause death and/or readmission rates. Secondary outcomes were temporal trends of oral cardiovascular therapies and their influence on primary outcomes.

Among the 45143 studies screened, 285 were included, representing 15 million AHFs. In the past decades, though mortality and readmission remain high, there was a decline in 30-day all-cause death (OR for a 10-year increment: 0.74 (0.61–0.91); p=0.004) that persisted at one year (OR 0.86 (0.77– 0.96); p=0.007), while 30-day and one-year all-cause readmission rate remained roughly unchanged. Trends of primary outcomes were linear and did not differ among continents. Decline in one-year all-cause death rate correlated with high proportions of oral or beta-blockers, especially when combined with oral renin-angiotensin-aldosterone system inhibitors, but not with diuretics while trends in readmission remained unchanged with these therapies.

Conclusions: Though AHF outcomes remain poor, the present study revealed global favorable trends of survival after AHF episodes probably associated with greater use of oral neurohormonal antagonists. The present study urges to implement the combination of oral renin-angiotensin-aldosterone system inhibitors and beta-blockers in patients at risk of AHF.

Keywords: Acute heart Failure; meta-analysis; systematic review; outcomes

Introduction

Acute heart failure (AHF) mostly refers to the occurrence and rapid worsening of symptoms and signs of lung and/or systemic congestion. It is a very frequent disease with roughly one million emergency department visit and hospitalization in the United States[1]. It is also a life-threatening medical condition associated with a high risk of in-hospital and post-discharge death and, in survivors, with a high risk of severely altered quality of life with a striking rate of non-elective readmission[2,3]. Furthermore, no novel agent showed benefits on any of AHF outcomes[4]. Hence, in the context of lack of recommended AHF medication and of heterogenous recommendations on AHF management, it is important to assess whether death and readmission rates following AHF episodes were altered over the past decades. It is recognized that poor management of hypertension or coronary artery disease, both often associated with preserved left ventricle contraction defined by ejection fraction (EF), and/or HF with reduced EF may lead to AHF. Yet, to prevent the occurrence of AHF episodes, neurohormonal inhibition by oral renin-angiotensin-aldosterone inhibitors (RAASi) is recommended in case of hypertension or coronary artery disease and by the combination of oral RAASi and beta-blockers (BBs) in case of HF with reduced EF[5–7]. Long-lasting oral diuretics are also frequently added to those neurohormonal antagonists. However, whether those long-lasting medications may also affect death and/or readmission when the AHF episode occurs remains elusive.

To answer those concerns, we performed a global meta-analysis extracted from a systematic review of AHF studies. Using meta-regressions, we assessed temporal trends of AHF-related outcome at 30 days and one year, compared those outcomes among continents and evaluated influences of oral cardiovascular medications.

Materials and Methods

Protocol registration.

The project was initiated in 2018 and the protocol was registered on PROSPERO (CRD42018099885) July 9, 2018.

Information sources.

A comprehensive and systematic literature search on MEDLINE and Embase was performed for the period ranging from January 1, 1980 through December 31, 2017.

Search.

The search strategy has been performed between June 23rd, 2019 and June 26th, 2019. The following MeSH terms were applied in Pubmed website: (("Heart Failure/epidemiology"[MeSH Terms] OR "Heart Failure/mortality"[MAJR] OR "Heart Failure/physiopathology"[MAJR] OR "Heart Failure/drug therapy"[MAJR] OR "Heart Failure/therapy"[MAJR] OR "Heart Failure/complications"[MAJR] OR "Heart Failure/blood"[MAJR] OR "Heart Failure/diagnosis"[MAJR]) AND has abstract[text] AND ("1980/01/01"[PDat]: "2017/12/31"[PDat]) AND Humans[Mesh] AND English[lang]).

In the Embase database, the following terms were applied: ('acute heart failure'/exp OR 'adhf (acute decompensated heart failure)' OR 'acute cardiac failure' OR 'acute coronary failure' OR 'acute coronary insufficiency' OR 'acute decompensated heart failure' OR 'acute destabilised heart failure' OR 'acute destabilized heart failure' OR 'acute heart failure' OR 'acute heart insufficiency' OR 'acutely decompensated heart failure' OR 'acutely destabilised heart failure' OR 'acutely destabilized heart failure' OR 'heart failure, acute') AND [embase]/lim AND [1980-2017]/py AND [english]/lim AND [abstracts]/lim AND ([article]/lim OR [article in press]/lim OR [data papers]/lim OR [letter]/lim OR [review]/lim OR [short survey]/lim).

Study selection.

Inclusion criteria were clinical studies, in English language, with a sample size ≥ 100 patients, including patients admitted to the hospital with a primary diagnosis of AHF and in which 30-day or one-year all-cause death and/or readmission rates were reported as primary or secondary outcomes. Exclusion criteria were studies in which AHF was not the main topic or which included only or mainly acute ischemic myocardial infarction or cardiogenic shock patients or with no above cited outcomes. Studies were also excluded if they consisted in subgroup analysis from an already published study. Reasons for exclusion were recorded at full text review stage.

Data collection process.

Data collection was achieved by eight trained reviewers. There were all physicians: intensivists or cardiologists. All reviewers (KT, EmG, AB, PH, NEB, HP-S, GC) were trained by the same investigator (AK) and a dedicated framework was systematically provided with definitions, inclusion and exclusion criteria. Conflicts, data accuracy, were resolved throughout the whole process by consensus with an instant electronic messaging shared between all reviewers.

The first step which began July 1st of 2019 and ended October 10th of 2019 was to identify papers that should be reviewed on title or abstract. The second step which began October 11th of 2019 and ended December 22nd of 2019 was to analyze papers that should be fully reviewed. Studies reporting outcomes with individual period of times were reported, when possible, separately in successive rows in the dataset. The third step which began January 14th of 2020 and ended January 21st of 2020 was to eliminate duplicated registries by crosschecking, registry names, inclusion period, localization and authors. Finally, the database was double-checked from January 22nd of 2020 to February 17th of 2020 for all data presented.

Outcome data. Primary outcomes were the temporal trends between 1980 and 2017 for 30-day and/or one-year all-cause death and/or non-elective hospital readmission rates. Secondary outcomes were the temporal trends of oral cardiovascular medications proportions at admission and their influence on 30-day and/or one-year all-cause death and readmission rates. Whole population proportions for each main outcome were directly collected from each study or, if the whole population proportion was not provided, calculated from subgroups in each study.

Demographic data. From each study were collected: medical history rates (history of: HF, hypertension, diabetes mellitus, coronary artery disease, chronic obstructive pulmonary disease, atrial fibrillation), proportion of oral cardiovascular medications at admission (RAASi that include angiotensin converting enzyme inhibitors and/ or angiotensin II receptor blockers but not angiotensin receptor neprilysin inhibitor, BBs, diuretics and digoxin) and clinically relevant variables accounting for the severity of AHF at admission: sex, age, heart rate (HR), systolic blood pressure (SBP), EF.

Year of recruitment. Year of recruitment was calculated as the median year between start and end year of recruitment, when both were available, or the value of the only available variable when both were not available. For the few studies with no start or end of recruitment, the year of recruitment was imputed by estimating the mean of time between year of recruitment and the year of publication. Then, this mean time was subtracted to the publication year.

Specific management for continuous variables. For continuous variables (age, HR, SBP, EF), the weighted average was estimated according to the following method: 1) The overall mean was collected every time it was available; 2) When the overall mean was not available, an overall weighted mean was calculated from subgroups described in the study; 3) When there was no overall mean and no mean per subgroup, medians were considered as surrogate of means and processed as described above.

Study type moderators. Additionally, informations on the following moderators were collected, if available: study from the MEDICARE cohort, survey vs. trial, monocentric vs. multicentric, death outcomes assessed from admission vs. from discharge.

Assessment of study quality.

Eight investigators assessed quality of studies as either having a low, unclear, or high risk of bias. As similar data from trial and survey studies were extracted, we developed, from an existing tool (Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies from NIH, https://www.nhlbi.nih.gov/health-topics/study-quality-assessment-tools), a global specific risk of bias tool which could be applied for all study types of this meta-analysis. This classification has been internally developed and validated by consensus. This classification included nine domains 1) representativeness of the study population, 2) inclusion and exclusion criteria clearly stated, 3) clinical and biological assessment of cohort at baseline, 4) assessment of the four outcomes, 5) individual follow-up, 6) loss of follow-up reported, 7) correct statistical method, 8) results believable and 9) funding reported.

Statistical analysis.

Description of patient characteristics included in AHF studies. We described the temporal trends in reported clinical characteristics in two ways.

First way, we divided our study period in four categories (1981-2000; 2001-2005; 2006-2010 and 2011-2015) chosen to balance sample size and to correspond to the American Heart Association/American College of Cardiology guidelines publication on diagnosis and treatment of HF in 2005[8]. For variables expressed as proportions (sex-ratio, medical history variables and treatments at admission), weighted logistic regressions were performed to estimate averaged proportions at each time period. The log of study size was used as weight in the model to account for between-study differences in population size. For continuous variables (age, HR, SBP, EF), only mean or median values for each study were available (see

above). Thus, proportions of studies above cutoff values were calculated for each study period.

Second way, continuous temporal trends were represented using year of recruitment as a continuous predictor. For variables expressed as proportions the same models as above were used, while for continuous variables, weighted linear regressions were used (with the same weighting as above).

Data transformation for main outcomes. Proportions of 30-day and/or one-year all-cause death and/or non-elective hospital readmission often have a skewed distribution which can violate the normality assumption of the residuals. Logit transformations were used to normalize the residuals when needed. Double arcsine transformations of proportions were also tested but results and residuals were very similar, so logit transformations were only used throughout.

Meta-analytical analyses. Random-effects meta-analyses and mixed-effects meta-regressions with restricted maximum likelihood estimation and inverse-variance weights were conducted to estimate overall, moderator effect sizes and confidence interval (CI), respectively. In meta-regressions, the significance of moderators was tested using likelihood-ratio tests comparing a model with the moderator to a model without using maximum likelihood estimation.

The overall effect size was calculated for each outcome (30-day and one-year proportions of all-cause death and readmission). Thereafter, the temporal trend between 1980 and 2017 was defined for each outcome using meta-regressions and whether the trends differed among continents (only Asia, Europe and North America were included in the analyses considering that there was insufficient number of studies for other continents).

Then, it was investigated whether 30-day and one-year all-cause death and readmission rates were influenced by the proportions of these oral cardiovascular medications at admission, while accounting for the effect of year of recruitment. Combined effect of RAASi

and BBs on 30-day and one-year proportions of all-cause death were also analysed. For these analyses, a four-class variable was created describing the combination of high and low (*i.e.* above and below the median, respectively) percentages of RAASi and BBs.

Effect sizes on the logit scale were either back-transformed on the raw proportion scale, mostly for figures, or expressed as odds-ratios.

Heterogeneity and sensitivity analyses

Random-effects intercept-only meta-analyses were used to calculate the heterogeneity statistic I^2, which represents the percentage of variability in the effect sizes that is not due to sampling error.

Temporal trend models for primary outcomes were checked for normality of the residuals and influential points, which were identified using a combination of 7 leave-one-out diagnostics (e.g. Cook's distance, externally standardized residuals) calculated for each study with the *influence* function of the *metafor* package[9]. Because AHF definitions, coding (in US database for instance) and management have changed over time, the non-linearity of the overall temporal trend was tested by comparing an interaction model with restricted cubic spline for year of recruitment to a model without.

Given that strong methodological differences among studies were anticipated, effects of above cited moderators were tested on 30-day and one-year proportions of all-cause death using models with an interaction between each moderator and year of recruitment. The same moderators were also tested on 30-day and one-year all-cause proportions of readmission except the moderator "admission vs. discharge" which was applicable only to death outcomes.

In addition, it was investigated whether results differed according to clinically relevant variables accounting for the severity of AHF at admission as described above. For each of these continuous variables, studies were allocated to one of two groups (below or above the median value) to enable comparisons between more homogeneous groups. We tested the

effect of those variables on the temporal trends of 30-day and one-year proportions of all-cause death and readmission. For each outcome and severity criteria, a model with the interaction between the group variable and year of recruitment was compared to a model without it. All analyses were conducted using the *metafor* package in R 3.6.1[9,10].

Results

Study selection.

The initial search strategy identified 45144 studies from which 1248 were fully reviewed. Two hundred eighty-five studies including 243 surveys and 42 trials reported at least one of the pre-specified outcomes, namely 30-day and/or one-year death or readmission. Reasons for non-inclusion were described in the flow chart (Figure S1**)**.

The number of AHF in this meta-analysis was 15 387 782 from 70 countries from four continents. North and Latin American countries (Canada, USA, Mexico) participated in 35% of the studies and European countries (representing 50 countries) in 36% of the studies (**Graphical abstract).** Characteristics of each cohort included in the present study were described in detail in the **Table S1**. Of note, selected studies were published from 1998 to 2017 and patients recruited from 1981 to 2015.

Characteristics of patients included in AHF studies.

Figure 1 shows high prevalence of history of cardiovascular disorders that increased over time. For instance, histories of heart failure, hypertension and atrial fibrillation increased over time from 36% to 60%, 25% to 78% and 22 to 41% respectively. Other characteristics are presented in **Table S2 and Figure S2**.

Primary outcomes: AHF-related all-cause death and readmission rates

Total 30-day (n=148 AHF studies) and one-year (n=204 AHF studies) all-cause death rates were high: 7 % (6 – 8) and 24 % (23 - 26), respectively (I^2=99% for both outcomes). When looking at temporal trends, **Figure 2A** and **2B** show that there was a decline in 30-day all-cause death (OR for a 10-year increment: 0.74 (0.61–0.91); p=0.004) that persisted at one year (OR 0.86 (0.77– 0.96); p=0.007) after AHF episodes over past four decades.

Concerning non-elective readmission, total 30-day (n=108 AHF studies) and one-year (n=61 AHF studies) all-cause readmission rates were high: 18% (16 - 19) and 46 % (41 - 51)

respectively (I^2=99% for both outcomes). **Figure 2C** and **2D** show that 30-day all-cause readmission rate worsened (OR for a 10-year increment: 1.19 (1.01 - 1.41), p = 0.041), while one-year all-cause readmission rate remained unchanged (0.76 (0.53 – 1.1), p = 0.143) after AHF episodes over past four decades.

One-year readmission decreased in Europe over the past four decades (0.4 (0.2 - 0.78), p = 0.0075). Importantly, temporal trends in AHF-related death and readmission in the past four decades did not differ among studied continents, namely Asia, Europe and North America. **(Figure 3** and **Table S3)**.

Association between studied oral cardiovascular medications at admission and AHF-related outcomes

While trends of reported proportions of BBs markedly increased (OR for a 10-year increment: 2 (1.51 – 2.66), p<0.001, **Figure 4, Panel A**), proportions of RAASi and diuretics remained unchanged (**Figures 4, Panel B** and **Panel C**) and proportion of digoxin declined (OR 0.38 (0.25 – 0.57), p<0.001, **Figure 4, Panel D**) over past decades in AHF studies.

Figure 5 further shows that decline in AHF-related one-year all-cause death rate was correlated with high proportions of BBs (OR 0.9 (0.84-0.96), p < 0.001), but not with any other classes of oral cardiovascular medications. Decline in 30-day death was also correlated with high proportions of BBs (OR 0.9 (0.81-0.99), p = 0.033), and also with high proportions of RAASi (OR 0,8 (0,7 – 0,91), p = 0,001) but not with diuretics or digoxin (**Table S4**). Most importantly, **Graphical abstract** shows that AHF studies reporting the combination of high proportion of RAASi and of high proportion of BBs were associated with the lowest odds of one-year all-cause death. Roughly similar results were found for 30-day death (**Table S5**)

By contrast, no associations were found between proportions of oral cardiovascular medications at admission and 30-day or one-year all-cause readmission rates (**Table S6**).

Sensitivity and subgroup analyses, and quality assessment.

Concerning the impact of influential studies, the temporal decline in 30-day and one-year all-cause death rates remained significant after removing influential studies (n=7, 0.74 (0.6-0.92), p = 0.008 and n=6, 0.89 (0.79-0.99), p = 0.04, respectively), while 30-day all-cause readmission rate became unchanged (n=3, 1.14 (0.95-1.38), p = 0.17) and the decline of one-year readmission rate became significant (n=1, 0.70 (0.51 – 0.96); p = 0.03). Furthermore, trends of all primary outcomes, except 30-day death, were linear over the four decades (**Figure S3**). Sensitivity analyses on prespecified subgroups, namely, MEDICARE or not, on outcome from admission or discharge, on mono or multicentric design, on trials or surveys, all roughly confirmed our main results (**Figure S4**). In addition, usual parameters describing clinical characteristics at admission - age, gender, SBP and most importantly EF (below or equal *versus* greater than 40%) did not influence temporal trends of 30-day and one-year all-cause death rates (**Table S7** and **Table S8**) nor 30-day and one-year all-cause readmission rates (**Table S9 and Table S10**).

Regarding assessment of study quality, **Figure S5** shows most of the items reported have a low risk of bias. Reviewers considered that the risk of bias was low in 67 % of studies for the representativeness of the study population, 66% of studies for clearness of inclusion/exclusion criteria, 67% of studies for clinic-biological assessment at baseline. Individual follow-up and report of loss-of follow-up were described with a low risk of bias in respectively 58 and 50% of the studies. Results were considered reliable with a low risk of bias in 81% of studies. The item “assessment of the four outcomes in the same study” was considered at high risk because only 14 studies assessed the four outcomes simultaneously. Of note, in 31 % of the studies, funding was not reported.

Discussion

Our robust meta-analysis revealed that even if short-term and long-term AHF mortality remained elevated, trends in AHF survival were continuously favorable in the past four decades, especially in Asia, Europe and North America. Those favorable trends in AHF survival were associated with better neurohormonal inhibition over years but not with high use of diuretics. These findings help to give an effective therapeutic strategy in AHF, using the combination of RAASi and BBs, the most available classes of cardiovascular drugs, to improve outcome in one of the most deadly disease in medicine. By contrast, high rates of short- and long-term readmissions were unchanged over the past four decades.

Many therapies have been tested in AHF population without success, and as a result AHF care was mostly based on experts opinion [11,12]. Our study revealed that, despite the lack of novel therapies, short-term AHF survival improved by a quarter for each of the past decades. Interestingly, favorable trends in AHF survival persisted one year after AHF episode. Favorable trends in short- and long-term AHF survival remained true in all studied continents and in most subgroups. In addition, the trends in roughly all primary outcomes were linear over the past four decades, in all patients and by studied continents, suggesting that changes in coding, definition of AHF or management did not influence results of the present study. Very few studies analyzed temporal changes in AHF death and our favorable trends in AHF survival contrasts with the study of de Peuter *at al.* performed in the Netherlands that showed no change in one-year death after AHF, while another recent study showed a temporal decrease in one-year death[13,14]. Our favorable trend in one-year AHF survival was in line with Chen J *et al.* that analyzed MEDICARE patients from 1998 to 2008 and partially with Chang PP *et al.* showing unchanged 28-day and one-year AHF death in white men but decrease in one-year death in black men[15,16]. Mechanisms of continuous improvement in both short- and long-term AHF survival in past decades remains elusive.

Even if a causal connection remains to be proven, our study revealed however a positive association between AHF survival rates and the degree of neurohormonal inhibition at admission. However, improvement in short-term mortality over time may also, at least partly, be explained by a better comprehensive in-hospital management of AHF over decades. Oral antagonists of neurohormonal system that include RAASi and BBs are the blackbone of medical treatment of HF patients with reduced EF for whom it reduces long-term mortality and delay AHF episodes[17]. Our observation of positive correlations between oral RAASi and BBs, ideally combined, but not diuretics, and AHF survival, in a meta-analysis including several millions of AHF patients with the greater part with preserved EF, is novel. In our study, the beneficial association between, at admission, RAASi and BBs (especially when combined) and long-term survival in AHF (regardless to the degree of EF) is likely related to a better control of the deleterious neurohormonal stimulation that is usually associated with AHF[18]. Beneficial association of neurohormonal inhibition with long-term survival seen in our study is in line with studies showing that cardiovascular medications are often unchanged during the year following AHF episodes[19]. In our study, improved inhibition of neurohormonal system in the past decades seemed mostly driven by BBs, up to 70% in recent years, than RAASi that remained stagnant at 50%. This is in line with recent studies showing that less than 25% of stable HF patients with reduced EF received all classes of recommended HF drugs and less than 1% had optimal doses in the United States and that half of patients treated for hypertension continued to have uncontrolled blood pressure in Europe[20]. Finally, despite numerous trials, no short-term intravenous treatments tested has positively impacted long-term clinical outcomes[21]. Our study adds no novel information in the early management of an AHF episode except that patients admitted with RAAS and BB will have better chance of survival. More importantly, our data strongly suggest that patients at risk of AHF, namely with HFrEF and/or other cardiovascular diseases, should be heavily treated to prevent future

AHF episodes. Yet, focusing on strategies to prevent and/or decrease residual fluid overload and to introduce as early as possible chronic goal directed cardiovascular medications is currently tested to improve outcome after an AHF episode[22].

Thus, our study strongly urges for global improvement in evidence-based therapies of the major causes of AHF, namely hypertension, coronary artery disease and HF, favoring the inhibition of neurohormonal system by the combination of RAASi and BBs, and not only diuretics, to improve AHF survival. This is being explored in the STRONG-HF study[22]. Novel classes of HF drugs, including angiotensin receptor neprilysin inhibitor or sodium glucose cotransporter- 2 inhibitor showed few benefits in AHF and need to be further explored on short- and long-term outcome in future AHF studies[23,24].

Despite favorable trends in survival after AHF episodes, our study showed that rate of non-elective readmission remains strikingly high, roughly unchanged and not related to any studied therapy. Whether the rate of readmission following an AHF episode was altered over years remained unclear. Concerning short-term all-cause readmission, Samsky *et al.* showed, in Canada and United States, a decline from 2005 to 2015[25]. Conversely, in a larger period of observation (1980-2017), our study shows an increase in short-term readmission though influenced by MEDICARE studies. Our study further showed that long-term readmission was roughly stable, over time, except for Europe continent, and that oral cardiovascular medical therapies did not alter these outcomes. Most probably underpowered, the trend difference between Europe and the two other continents for long-term readmission will have to be confirmed. These results should be cautiously interpreted knowing that all-cause readmission is far less studied compared to all-cause death and none of the recorded study had tested oral cardiovascular medical therapy with readmission as primary endpoint.

Several limitations of this study should be acknowledged. First, to perform this study, we adapted the usual methodology for meta-analysis[26]. Primary outcomes were all-cause 30-day

and one-year death and non-elective readmission independently of the study design *i.e.* monocentric versus multicentric or trial versus survey. The second limitation is that we studied all-cause rather than cardiovascular outcomes following AHF episodes. All-cause death event was more often reported in early studies and, rates of all-cause and cardiovascular often HF-related death are usually superimposable in HF studies[27]. However, differences may exist in cardiovascular and all-cause readmission in HF studies and future studies should assess trends in AHF all-cause and cardiovascular readmission. The third limitation is that only two time-points were selected 30 days and one year and AHF studies with other endpoints (mostly three and six months) were not selected. This is related to the higher number of studies with those selected endpoints and because they classically represent short- and long-term outcome in HF studies. The fourth limitation is that AHF studies very often do not record doses of oral cardiovascular medications. Despite this, our study revealed that combining RAASi and BBs, regardless of the doses, was associated with improved AHF survival. The fifth limitation is that patients might have been included in two studies or more despite our efforts to limit duplication. However, studies were performed in different countries and in the United States where many studies were performed, removing MEDICARE studies confirmed the favorable trends in AHF survival. The sixth limitation is that the impact on outcomes of recently introduced oral chronic cardiovascular medications, for instance, mineralocorticoid receptor antagonists, or association of valsartan and neprilysin inhibitor has not been assessed. The seventh limitation is that we could not fully exclude a change in definition of AHF and criteria for hospital admission over-time. The final limitation is that the present study mainly involved industrially countries, emphasizing the paucity of studies conducted on African and South American population.

In summary, our study revealed global favorable trends of AHF survival probably related to greater use of neurohormonal inhibition, but not to the use of diuretics, in the past decades.

Our study further confirmed that, despite those favorable trends, AHF remains a deadly disease with high readmission rate. Altogether, our study urges to discover new AHF therapies and most importantly to favor the combination of RAASi and BBs in the global effort to better implement evidence-based therapies in cardiovascular diseases, to improve AHF survival.

One-sentence Summary.

Over the last four decades, after an AHF episode, short and long-term survivals improve markedly but all-cause short and long-term readmissions remain unacceptably high.

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Authors' contributions. AK, AM, EtG: study concept and design. AK, KT, EmG, AB, NE-B, GC, HP-S, PH: Literature search and data acquisition. AK, EtG, TM: Statistical analysis. AK, AM: Interpretation of the data. AK, AM: Drafting of the manuscript. Critical revision of the manuscript: all declared authors. All authors read and approved the final manuscript.

Availability of supporting data. Literature screening data, raw and clean datasets and R code for data cleaning and analyses are all available on the Open Science Framework : https://osf.io/cxv5k/?view_only=770ba512f61a4153aec88e35b40300f8 (This is a provisional private link only for the reviewing process that will be updated to an open link in case the paper would be accepted).

AM take responsibility for the integrity of the data and the accuracy of the data analysis.

Ethics committee approval. Not required

Conflict of interest statements. Antoine Kimmoun. AK received speaker's honoraria from Baxter, Aguettant and Aspen. Alexandre Mebazaa. AM reports personal fees from Orion, grants and personal fees from Roche, personal fees from Servier, personal fees from Otsuka, personal fees from Philips, grants and personal fees from Adrenomed, personal fees from Neuro Tronik, grants and personal fees from 4TEEN4, personal fees from Sanofi. Etienne Gayat. EG received research grant from Sphingotec, radiometer and Philips and consultancy fees from Baxter and Edwards Lifescience.

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Figure legends

Graphical Abstract: Methodology, screening and main results. For main results, upper panel 1: global and by continents ORs per decade for one-year all-cause mortality. Lower panel 2: Combined effect of RAASi and BBs at admission on one-year all-cause death. For these analyses, a four-class variable describing the combination of high and low (i.e. above and below the median, respectively) percentages of prescription of RAASi and BBs was created. Odds-ratios and 95% CI are represented.

Figure 1: Temporal trends for reported demographic characteristics and cardiovascular medical history at admission. Proportions at the beginning and at the end of the study period were calculated as back-transformed adjusted means from the model.

Figure 2: Temporal trends for 30-day and one-year all-cause death and readmission rates in AHF studies. Point sizes are relative to the number of included patients. Plain and dashed blue lines are meta-regression model predictions and 95% CI, respectively. Odds-ratio are calculated for a 10-year increment. Proportions at the beginning and at the end of the study period were calculated as back-transformed adjusted means from the model.

Figure 3: Temporal trends for 30-day and one-year all-cause death and readmission rates in AHF studies according to continents namely Europe, Asia and North America. Point sizes are relative to the number of included patients. Plain and dashed blue lines are meta-regression model predictions and 95% CI, respectively. Odds-ratio are calculated for a 10-year increment.

Figure 4: Temporal trends on reported rates of oral cardiovascular medications at admission. Point sizes are relative to the number of included patients. Plain and dashed blue lines are weighted logistic regression model predictions and 95% CI, respectively. Odds-ratio are calculated for a 10-year increment. Proportions at the beginning and at the end of the study period were calculated as back-transformed adjusted means from the model.

Figure 5: Effects of oral cardiovascular medications rates prescribed at admission on one-year all-cause death. Point sizes are relative to the number of included patients. Plain and dashed blue lines are meta-regression model predictions and 95% CI, respectively. For those analyses we also added the year of recruitment as a moderator, model predictions are shown for a median year of 2003. Odds-ratio are calculated for a 10 % increment.

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Graphical abstract

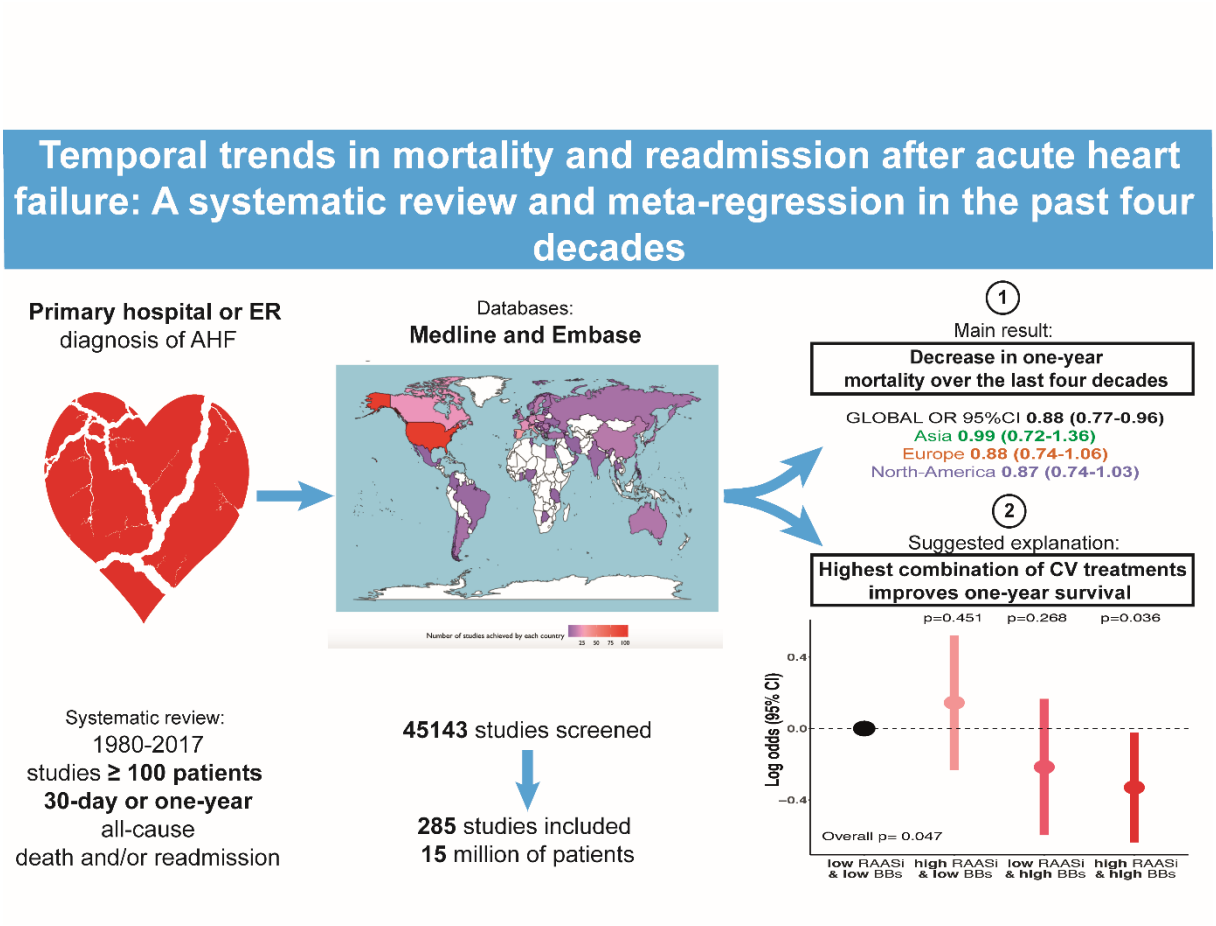


Figure 1

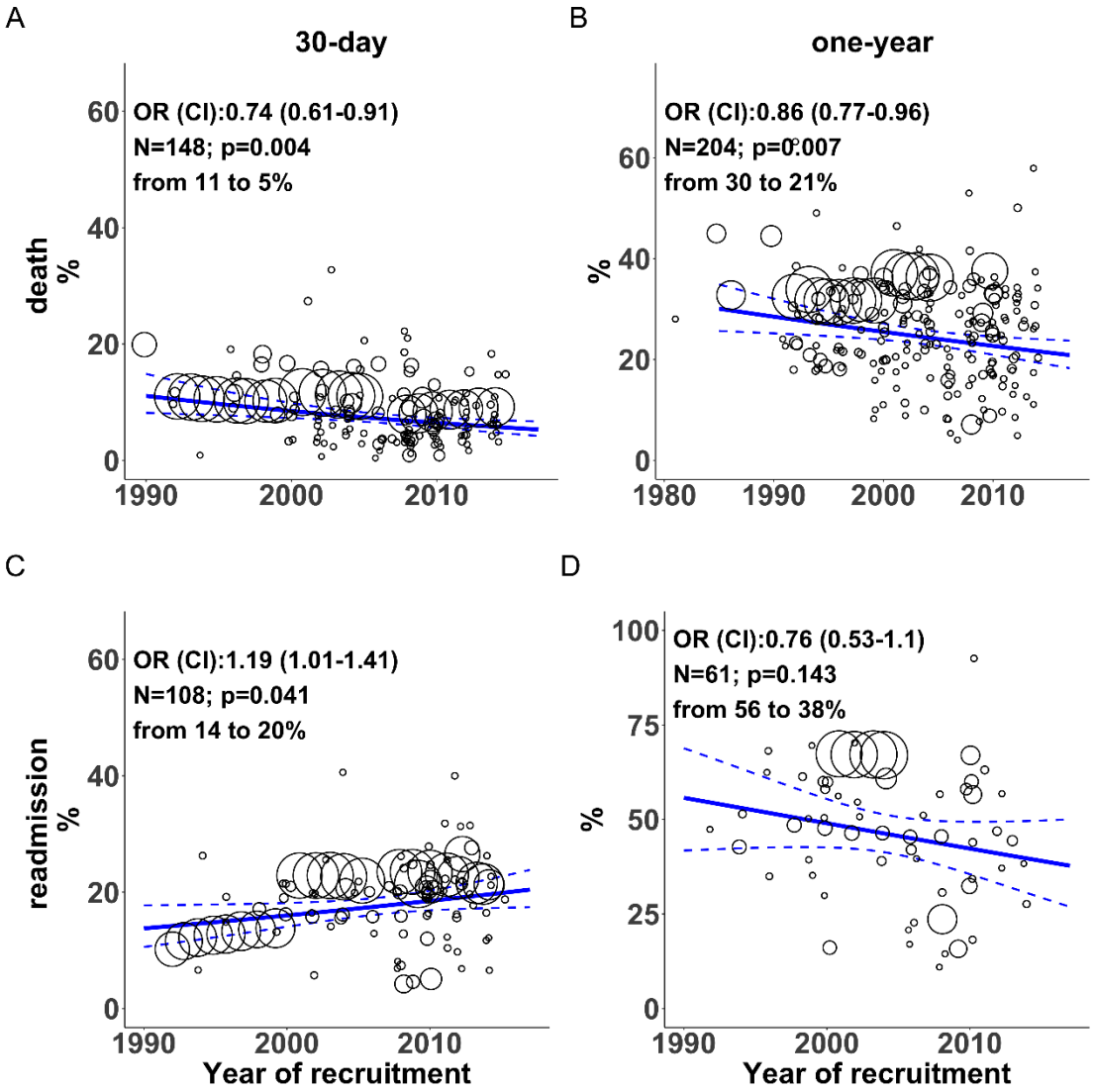

A
30-day
OR (CI):0.74 (0.61-0.91)
N=148; p=0.004
from 11 to 5%
death %
B
one-year
OR (CI):0.86 (0.77-0.96)
N=204; p=0.007
from 30 to 21%
%
C
OR (CI):1.19 (1.01-1.41)
N=108; p=0.041
from 14 to 20%
readmission %
Year of recruitment
D
OR (CI):0.76 (0.53-1.1)
N=61; p=0.143
from 56 to 38%
%
Year of recruitment

Figure 2

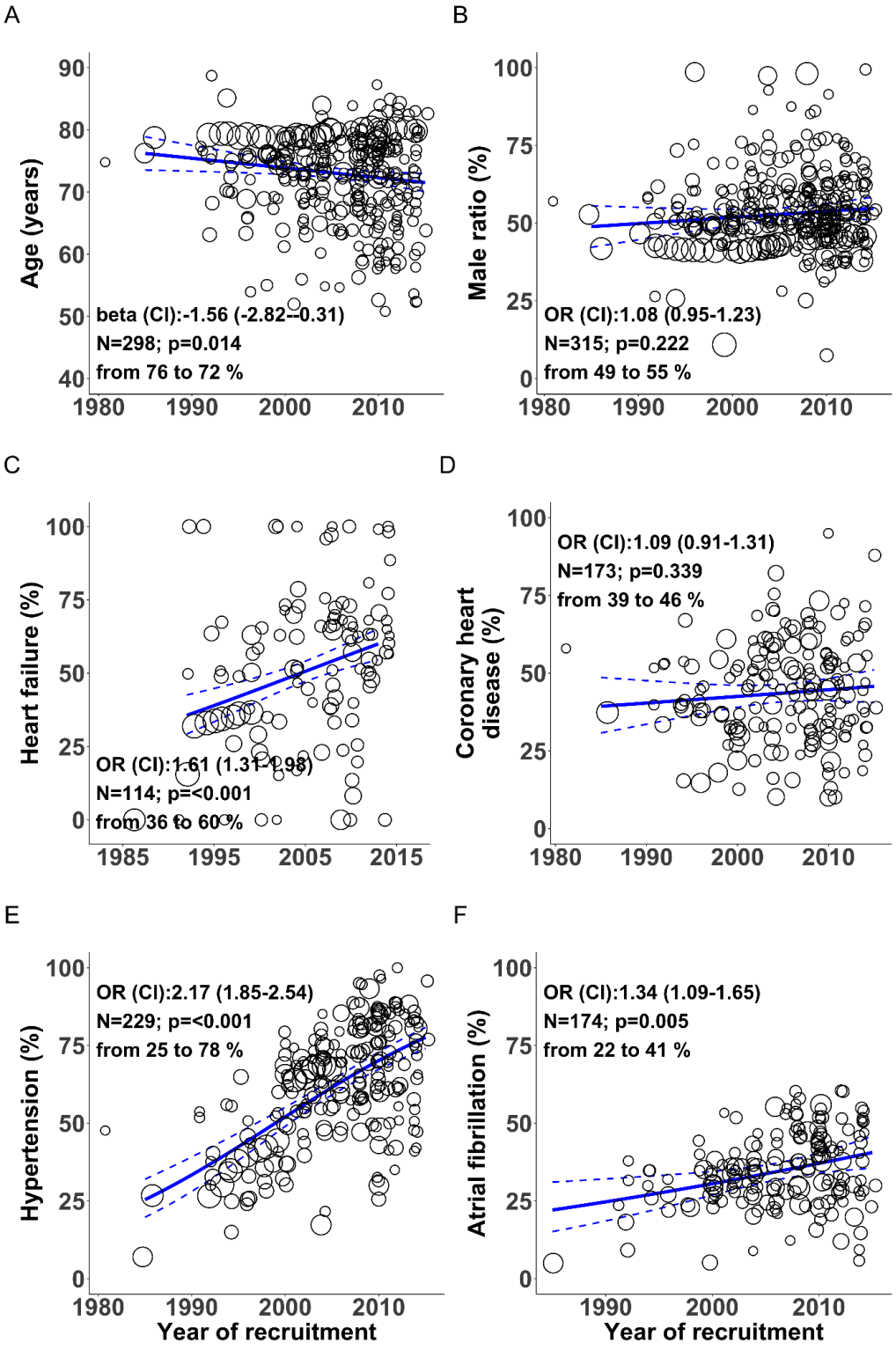
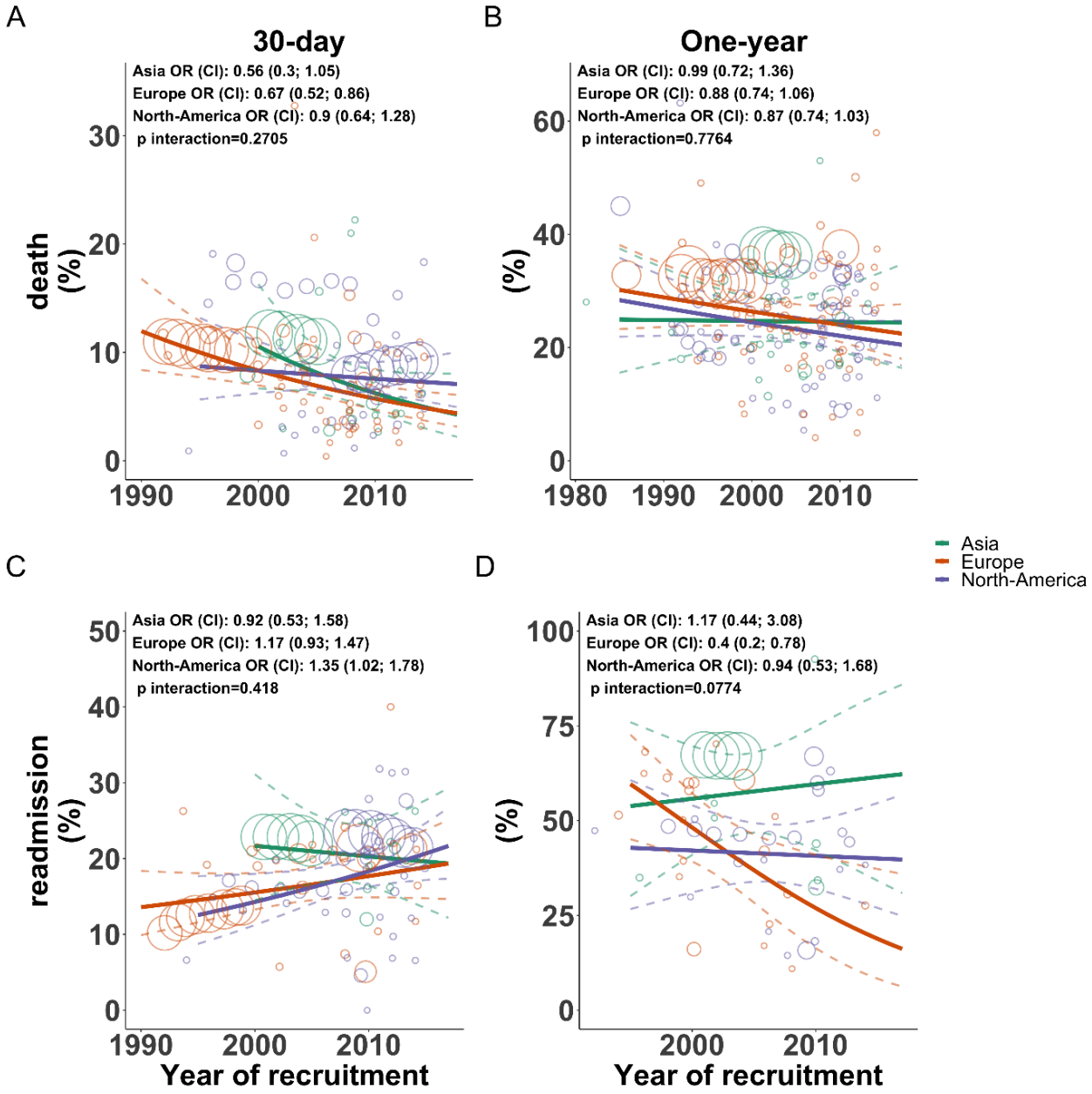
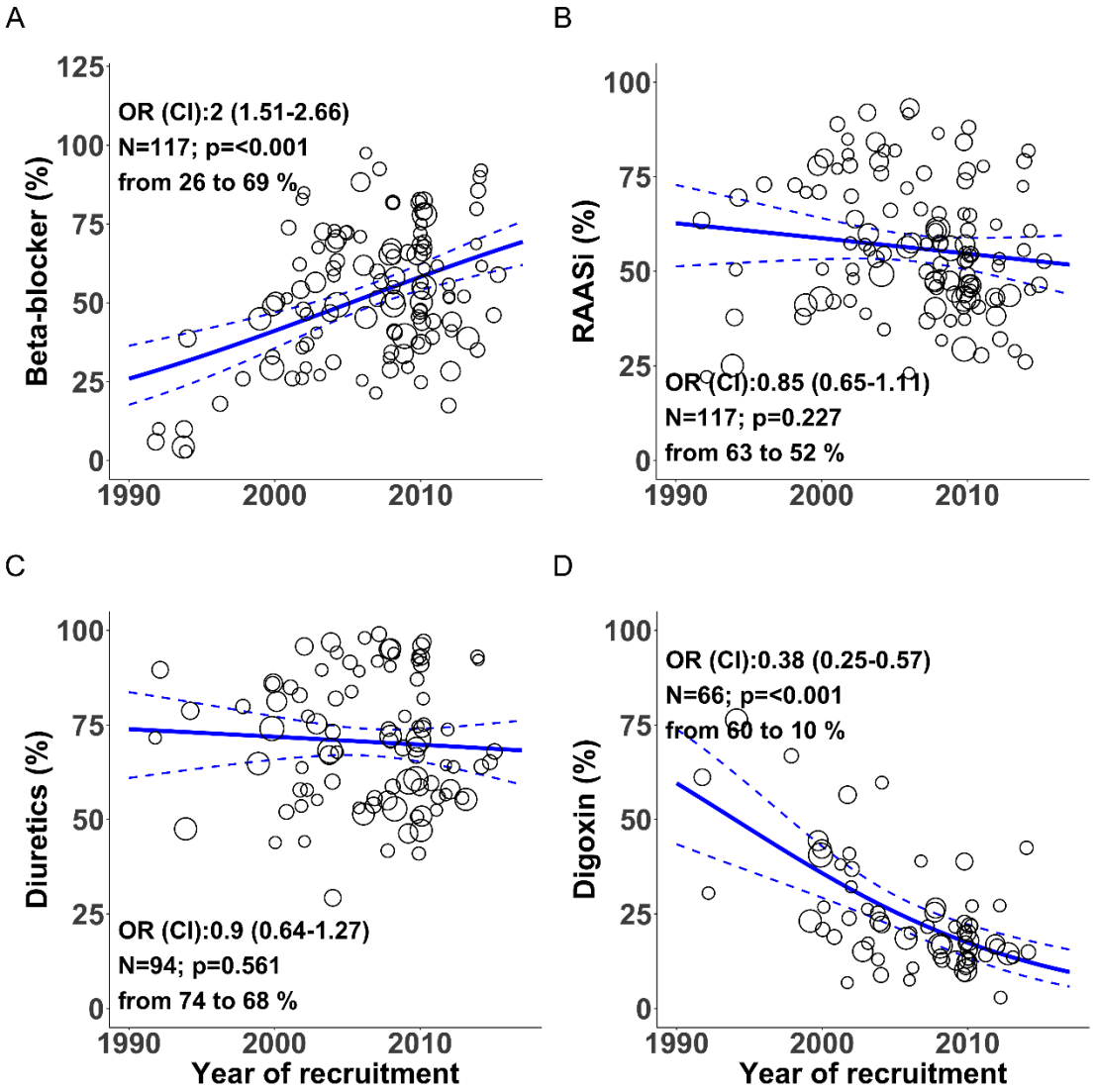

A
Age (years)
beta (CI):-1.56 (-2.82--0.31)
N=298; p=0.014
from 76 to 72 %
B
Male ratio (%)
OR (CI):1.08 (0.95-1.23)
N=315; p=0.222
from 49 to 55 %
C
Heart failure (%)
OR (CI):1.61 (1.31-1.98)
N=114; p=<0.001
from 36 to 60 %
D
Coronary heart disease (%)
OR (CI):1.09 (0.91-1.31)
N=173; p=0.339
from 39 to 46 %
E
Hypertension (%)
OR (CI):2.17 (1.85-2.54)
N=229; p=<0.001
from 25 to 78 %
Year of recruitment
F
Atrial fibrillation (%)
OR (CI):1.34 (1.09-1.65)
N=174; p=0.005
from 22 to 41 %
Year of recruitment

Figure 3


A
30-day
Asia OR (CI): 0.56 (0.3; 1.05)
Europe OR (CI): 0.67 (0.52; 0.86)
North-America OR (CI): 0.9 (0.64; 1.28)
p interaction=0.2705
death (%)
B
One-year
Asia OR (CI): 0.99 (0.72; 1.36)
Europe OR (CI): 0.88 (0.74; 1.06)
North-America OR (CI): 0.87 (0.74; 1.03)
p interaction=0.7764
(%)
C
Asia OR (CI): 0.92 (0.53; 1.58)
Europe OR (CI): 1.17 (0.93; 1.47)
North-America OR (CI): 1.35 (1.02; 1.78)
p interaction=0.418
readmission (%)
Year of recruitment
D
Asia OR (CI): 1.17 (0.44; 3.08)
Europe OR (CI): 0.4 (0.2; 0.78)
North-America OR (CI): 0.94 (0.53; 1.68)
p interaction=0.0774
(%)
Year of recruitment
Asia
Europe
North-America

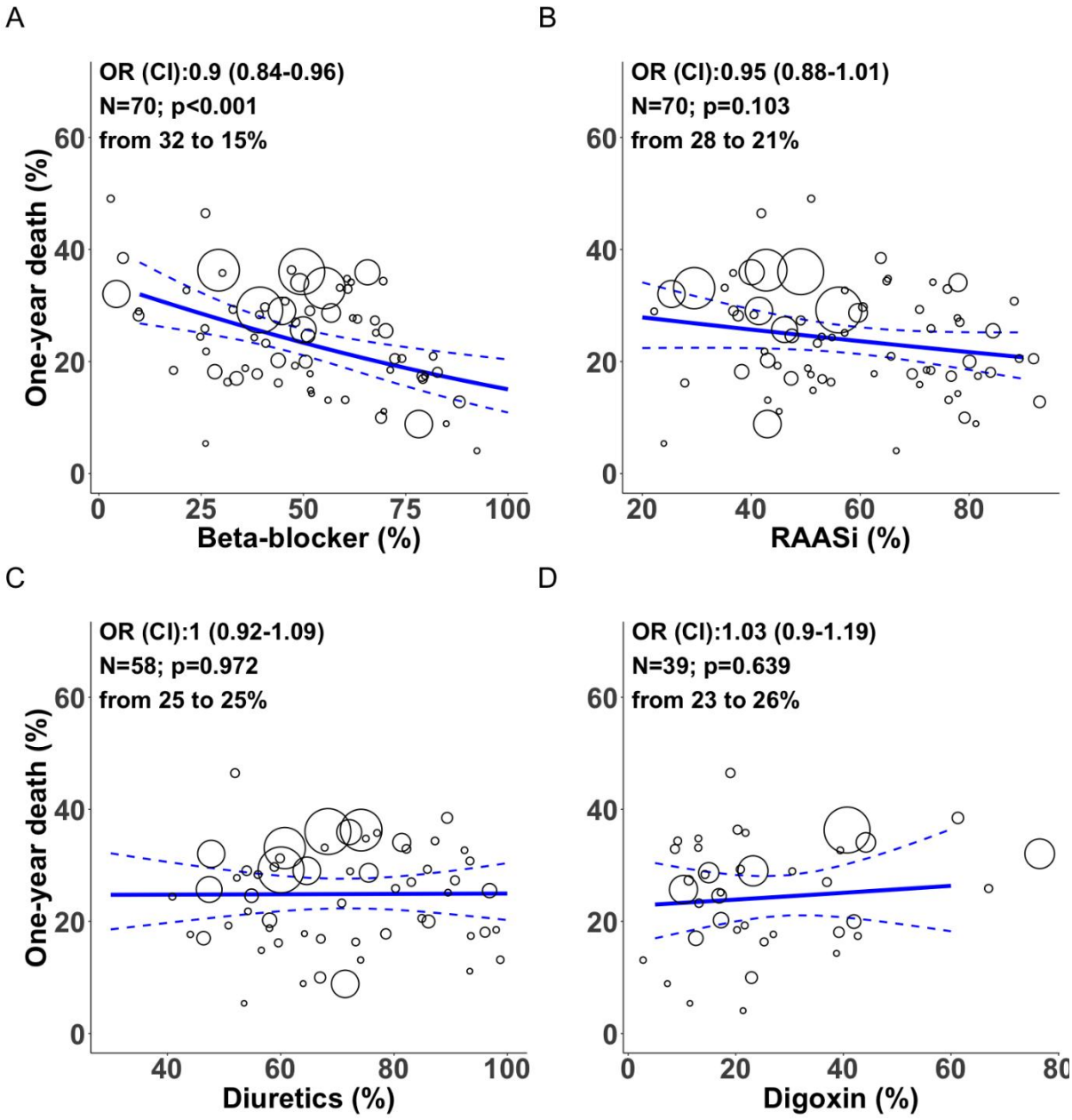
1 Figure 4


A
Beta-blocker (%)
OR (CI):2 (1.51-2.66)
N=117; p=<0.001
from 26 to 69 %
B
RAASi (%)
OR (CI):0.85 (0.65-1.11)
N=117; p=0.227
from 63 to 52 %
C
Diuretics (%)
OR (CI):0.9 (0.64-1.27)
N=94; p=0.561
from 74 to 68 %
D
Digoxin (%)
OR (CI):0.38 (0.25-0.57)
N=66; p=<0.001
from 60 to 10 %
Year of recruitment
Year of recruitment

2

3

1 Figure 5


A
OR (CI):0.9 (0.84-0.96)
N=70; p<0.001
from 32 to 15%
One-year death (%)
Beta-blocker (%)
B
OR (CI):0.95 (0.88-1.01)
N=70; p=0.103
from 28 to 21%
RAASi (%)
C
OR (CI):1 (0.92-1.09)
N=58; p=0.972
from 25 to 25%
Diuretics (%)
D
OR (CI):1.03 (0.9-1.19)
N=39; p=0.639
from 23 to 26%
Digoxin (%)

2

3