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

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5 **Word count:** 4117

6 **Abbreviations:**

7 AHF, acute heart failure

8 HF, heart failure

9 MeSH, medical subject headings

10 SBP, systolic blood pressure

11 HR, heart rate

12 EF, ejection fraction

13 RAASi, renin-angiotensin-aldosterone inhibitors

14 BB, Beta-Blocker

15 OR, odds ratio

16 CI, confidence interval

17

18

1 **Abstract**

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

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

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

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

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

1 **Introduction**

2 Acute heart failure (AHF) mostly refers to the occurrence and rapid worsening of symptoms
3 and signs of lung and/or systemic congestion. It is a very frequent disease with roughly one
4 million emergency department visit and hospitalization in the United States¹. It is also a life-
5 threatening medical condition associated with a high risk of in-hospital and post-discharge
6 death and, in survivors, with a high risk of severely altered quality of life with a striking rate
7 of non-elective readmission^{2,3}. Furthermore, no novel agent showed benefits on any of AHF
8 outcomes⁴. Hence, in the context of lack of recommended AHF medication and of
9 heterogenous recommendations on AHF management, it is important to assess whether death
10 and readmission rates following AHF episodes were altered over the past decades. It is
11 recognized that poor management of hypertension or coronary artery disease, both often
12 associated with preserved left ventricle contraction defined by ejection fraction (EF), and/or
13 HF with reduced EF may lead to AHF. Yet, to prevent the occurrence of AHF episodes,
14 neurohormonal inhibition by oral renin-angiotensin-aldosterone inhibitors (RAASi) is
15 recommended in case of hypertension or coronary artery disease and by the combination of
16 oral RAASi and beta-blockers (BBs) in case of HF with reduced EF⁵⁻⁷. Long-lasting oral
17 diuretics are also frequently added to those neurohormonal antagonists. However, whether
18 those long-lasting medications may also affect death and/or readmission when the AHF
19 episode occurs remains elusive.

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

24

1 **Materials and Methods**

2 **Protocol registration.**

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

5 **Information sources.**

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

8 **Search.**

9 The search strategy has been performed between June 23rd, 2019 and June 26th, 2019. The
10 following MeSH terms were applied in Pubmed website: (("Heart
11 Failure/epidemiology"[MeSH Terms] OR "Heart Failure/mortality"[MAJR] OR "Heart
12 Failure/physiopathology"[MAJR] OR "Heart Failure/drug therapy"[MAJR] OR "Heart
13 Failure/therapy"[MAJR] OR "Heart Failure/complications"[MAJR] OR "Heart
14 Failure/blood"[MAJR] OR "Heart Failure/diagnosis"[MAJR]) AND has abstract[text] AND
15 ("1980/01/01"[PDat]: "2017/12/31"[PDat]) AND Humans[Mesh] AND English[lang]).

16 In the Embase database, the following terms were applied: ('acute heart failure'/exp OR 'adhf
17 (acute decompensated heart failure)' OR 'acute cardiac failure' OR 'acute coronary failure' OR
18 'acute coronary insufficiency' OR 'acute decompensated heart failure' OR 'acute destabilised
19 heart failure' OR 'acute destabilized heart failure' OR 'acute heart failure' OR 'acute heart
20 insufficiency' OR 'acutely decompensated heart failure' OR 'acutely destabilised heart failure'
21 OR 'acutely destabilized heart failure' OR 'heart failure, acute') AND [embase]/lim AND
22 [1980-2017]/py AND [english]/lim AND [abstracts]/lim AND ([article]/lim OR [article in
23 press]/lim OR [data papers]/lim OR [letter]/lim OR [review]/lim OR [short survey]/lim).

24 **Study selection.**

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

9 **Data collection process.**

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

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

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

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

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

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

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

4 **Assessment of study quality.**

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

15 **Statistical analysis.**

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

18 First way, we divided our study period in four categories (1981-2000; 2001-2005; 2006-2010
19 and 2011-2015) chosen to balance sample size and to correspond to the American Heart
20 Association/American College of Cardiology guidelines publication on diagnosis and
21 treatment of HF in 2005⁸. For variables expressed as proportions (sex-ratio, medical history
22 variables and treatments at admission), weighted logistic regressions were performed to
23 estimate averaged proportions at each time period. The log of study size was used as weight
24 in the model to account for between-study differences in population size. For continuous
25 variables (age, HR, SBP, EF), only mean or median values for each study were available (see

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

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

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

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

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

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

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

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

6 *Heterogeneity and sensitivity analyses*

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

10 Temporal trend models for primary outcomes were checked for normality of the residuals and
11 influential points, which were identified using a combination of 7 leave-one-out diagnostics
12 (e.g. Cook's distance, externally standardized residuals) calculated for each study with the
13 *influence* function of the *metafor* package⁹. Because AHF definitions, coding (in US database
14 for instance) and management have changed over time, the non-linearity of the overall
15 temporal trend was tested by comparing an interaction model with restricted cubic spline for
16 year of recruitment to a model without.

17 Given that strong methodological differences among studies were anticipated, effects of
18 above cited moderators were tested on 30-day and one-year proportions of all-cause death
19 using models with an interaction between each moderator and year of recruitment. The same
20 moderators were also tested on 30-day and one-year all-cause proportions of readmission
21 except the moderator "admission vs. discharge" which was applicable only to death outcomes.
22 In addition, it was investigated whether results differed according to clinically relevant
23 variables accounting for the severity of AHF at admission as described above. For each of
24 these continuous variables, studies were allocated to one of two groups (below or above the
25 median value) to enable comparisons between more homogeneous groups. We tested the

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

1 **Results**

2 **Study selection.**

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

7 The number of AHF in this meta-analysis was 15 387 782 from 70 countries from four
8 continents. North and Latin American countries (Canada, USA, Mexico) participated in 35%
9 of the studies and European countries (representing 50 countries) in 36% of the studies
10 **(Graphical abstract)**. Characteristics of each cohort included in the present study were
11 described in detail in the **Table S1**. Of note, selected studies were published from 1998 to
12 2017 and patients recruited from 1981 to 2015.

13 **Characteristics of patients included in AHF studies.**

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

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

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

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

1 respectively ($I^2=99\%$ for both outcomes). **Figure 2C** and **2D** show that 30-day all-cause
2 readmission rate worsened (OR for a 10-year increment: 1.19 (1.01 - 1.41), $p = 0.041$), while
3 one-year all-cause readmission rate remained unchanged (0.76 (0.53 – 1.1), $p = 0.143$) after
4 AHF episodes over past four decades.
5 One-year readmission decreased in Europe over the past four decades (0.4 (0.2 - 0.78), $p =$
6 0.0075). Importantly, temporal trends in AHF-related death and readmission in the past four
7 decades did not differ among studied continents, namely Asia, Europe and North America.
8 **(Figure 3 and Table S3).**

9 **Association between studied oral cardiovascular medications at admission and AHF-** 10 **related outcomes**

11 While trends of reported proportions of BBs markedly increased (OR for a 10-year increment:
12 2 (1.51 – 2.66), $p<0.001$, **Figure 4, Panel A**), proportions of RAASi and diuretics remained
13 unchanged (**Figures 4, Panel B and Panel C**) and proportion of digoxin declined (OR 0.38
14 (0.25 – 0.57), $p<0.001$, **Figure 4, Panel D**) over past decades in AHF studies.

15 **Figure 5** further shows that decline in AHF-related one-year all-cause death rate was
16 correlated with high proportions of BBs (OR 0.9 (0.84-0.96), $p < 0.001$), but not with any
17 other classes of oral cardiovascular medications. Decline in 30-day death was also correlated
18 with high proportions of BBs (OR 0.9 (0.81-0.99), $p = 0.033$), and also with high proportions
19 of RAASi (OR 0,8 (0,7 – 0,91), $p = 0,001$) but not with diuretics or digoxin (**Table S4**). Most
20 importantly, **Graphical abstract** shows that AHF studies reporting the combination of high
21 proportion of RAASi and of high proportion of BBs were associated with the lowest odds of
22 one-year all-cause death. Roughly similar results were found for 30-day death (**Table S5**)
23 By contrast, no associations were found between proportions of oral cardiovascular
24 medications at admission and 30-day or one-year all-cause readmission rates (**Table S6**).

25 **Sensitivity and subgroup analyses, and quality assessment.**

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

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

23

1 **Discussion**

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

10 Many therapies have been tested in AHF population without success, and as a result AHF care
11 was mostly based on experts opinion^{11,12}. Our study revealed that, despite the lack of novel
12 therapies, short-term AHF survival improved by a quarter for each of the past decades.
13 Interestingly, favorable trends in AHF survival persisted one year after AHF episode.
14 Favorable trends in short- and long-term AHF survival remained true in all studied continents
15 and in most subgroups. In addition, the trends in roughly all primary outcomes were linear
16 over the past four decades, in all patients and by studied continents, suggesting that changes
17 in coding, definition of AHF or management did not influence results of the present study.

18 Very few studies analyzed temporal changes in AHF death and our favorable trends in AHF
19 survival contrasts with the study of de Peuter *et al.* performed in the Netherlands that showed
20 no change in one-year death after AHF, while another recent study showed a temporal
21 decrease in one-year death^{13,14}. Our favorable trend in one-year AHF survival was in line with
22 Chen J *et al.* that analyzed MEDICARE patients from 1998 to 2008 and partially with Chang
23 PP *et al.* showing unchanged 28-day and one-year AHF death in white men but decrease in
24 one-year death in black men^{15,16}. Mechanisms of continuous improvement in both short- and
25 long-term AHF survival in past decades remains elusive.

1 Even if a causal connection remains to be proven, our study revealed however a positive
2 association between AHF survival rates and the degree of neurohormonal inhibition at
3 admission. However, improvement in short-term mortality over time may also, at least partly,
4 be explained by a better comprehensive in-hospital management of AHF over decades. Oral
5 antagonists of neurohormonal system that include RAASi and BBs are the backbone of
6 medical treatment of HF patients with reduced EF for whom it reduces long-term mortality
7 and delay AHF episodes¹⁷. Our observation of positive correlations between oral RAASi and
8 BBs, ideally combined, but not diuretics, and AHF survival, in a meta-analysis including
9 several millions of AHF patients with the greater part with preserved EF, is novel. In our
10 study, the beneficial association between, at admission, RAASi and BBs (especially when
11 combined) and long-term survival in AHF (regardless to the degree of EF) is likely related to
12 a better control of the deleterious neurohormonal stimulation that is usually associated with
13 AHF¹⁸. Beneficial association of neurohormonal inhibition with long-term survival seen in
14 our study is in line with studies showing that cardiovascular medications are often unchanged
15 during the year following AHF episodes¹⁹. In our study, improved inhibition of
16 neurohormonal system in the past decades seemed mostly driven by BBs, up to 70% in recent
17 years, than RAASi that remained stagnant at 50%. This is in line with recent studies showing
18 that less than 25% of stable HF patients with reduced EF received all classes of recommended
19 HF drugs and less than 1% had optimal doses in the United States and that half of patients
20 treated for hypertension continued to have uncontrolled blood pressure in Europe²⁰. Finally,
21 despite numerous trials, no short-term intravenous treatments tested has positively impacted
22 long-term clinical outcomes²¹. Our study adds no novel information in the early management
23 of an AHF episode except that patients admitted with RAAS and BB will have better chance
24 of survival. More importantly, our data strongly suggest that patients at risk of AHF, namely
25 with HFrEF and/or other cardiovascular diseases, should be heavily treated to prevent future

1 AHF episodes. Yet, focusing on strategies to prevent and/or decrease residual fluid overload
2 and to introduce as early as possible chronic goal directed cardiovascular medications is
3 currently tested to improve outcome after an AHF episode²².

4 Thus, our study strongly urges for global improvement in evidence-based therapies of the
5 major causes of AHF, namely hypertension, coronary artery disease and HF, favoring the
6 inhibition of neurohormonal system by the combination of RAASi and BBs, and not only
7 diuretics, to improve AHF survival. This is being explored in the STRONG-HF study²².

8 Novel classes of HF drugs, including angiotensin receptor neprilysin inhibitor or sodium
9 glucose cotransporter- 2 inhibitor showed few benefits in AHF and need to be further
10 explored on short- and long-term outcome in future AHF studies^{23,24}.

11 Despite favorable trends in survival after AHF episodes, our study showed that rate of non-
12 elective readmission remains strikingly high, roughly unchanged and not related to any
13 studied therapy. Whether the rate of readmission following an AHF episode was altered over
14 years remained unclear. Concerning short-term all-cause readmission, Samsky *et al.* showed,
15 in Canada and United States, a decline from 2005 to 2015²⁵. Conversely, in a larger period of
16 observation (1980-2017), our study shows an increase in short-term readmission though
17 influenced by MEDICARE studies. Our study further showed that long-term readmission was
18 roughly stable, over time, except for Europe continent, and that oral cardiovascular medical
19 therapies did not alter these outcomes. Most probably underpowered, the trend difference
20 between Europe and the two other continents for long-term readmission will have to be
21 confirmed. These results should be cautiously interpreted knowing that all-cause readmission
22 is far less studied compared to all-cause death and none of the recorded study had tested oral
23 cardiovascular medical therapy with readmission as primary endpoint.

24 Several limitations of this study should be acknowledged. First, to perform this study, we
25 adapted the usual methodology for meta-analysis²⁶. Primary outcomes were all-cause 30-day

1 and one-year death and non-elective readmission independently of the study design *i.e.*
2 monocentric versus multicentric or trial versus survey. The second limitation is that we
3 studied all-cause rather than cardiovascular outcomes following AHF episodes. All-cause
4 death event was more often reported in early studies and, rates of all-cause and cardiovascular
5 often HF-related death are usually superimposable in HF studies²⁷. However, differences may
6 exist in cardiovascular and all-cause readmission in HF studies and future studies should
7 assess trends in AHF all-cause and cardiovascular readmission. The third limitation is that
8 only two time-points were selected 30 days and one year and AHF studies with other
9 endpoints (mostly three and six months) were not selected. This is related to the higher
10 number of studies with those selected endpoints and because they classically represent short-
11 and long-term outcome in HF studies. The fourth limitation is that AHF studies very often do
12 not record doses of oral cardiovascular medications. Despite this, our study revealed that
13 combining RAASi and BBs, regardless of the doses, was associated with improved AHF
14 survival. The fifth limitation is that patients might have been included in two studies or more
15 despite our efforts to limit duplication. However, studies were performed in different
16 countries and in the United States where many studies were performed, removing
17 MEDICARE studies confirmed the favorable trends in AHF survival. The sixth limitation is
18 that the impact on outcomes of recently introduced oral chronic cardiovascular medications,
19 for instance, mineralocorticoid receptor antagonists, or association of valsartan and neprilysin
20 inhibitor has not been assessed. The seventh limitation is that we could not fully exclude a
21 change in definition of AHF and criteria for hospital admission over-time. The final
22 limitation is that the present study mainly involved industrially countries, emphasizing the
23 paucity of studies conducted on African and South American population.

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

1 Our study further confirmed that, despite those favorable trends, AHF remains a deadly
2 disease with high readmission rate. Altogether, our study urges to discover new AHF
3 therapies and most importantly to favor the combination of RAASi and BBs in the global
4 effort to better implement evidence-based therapies in cardiovascular diseases, to improve
5 AHF survival.
6

1 **One-sentence Summary.**

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

4 **Funding source.**

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

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

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

17 *Ethics committee approval.* Not required

18 *Conflict of interest statements.* Antoine Kimmoun. AK received speaker's honoraria from
19 Baxter, Aguetant and Aspen. Alexandre Mebazaa. AM reports personal fees from Orion,
20 grants and personal fees from Roche, personal fees from Servier, personal fees from Otsuka,
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24 fees from Baxter and Edwards Lifescience.

25

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2

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1 **Figure legends**

2 **Graphical Abstract:** Methodology, screening and main results. For main results, upper panel
3 1: global and by continents ORs per decade for one-year all-cause mortality. Lower panel 2:
4 Combined effect of RAASi and BBs at admission on one-year all-cause death. For these
5 analyses, a four-class variable describing the combination of high and low (i.e. above and
6 below the median, respectively) percentages of prescription of RAASi and BBs was
7 created. Odds-ratios and 95% CI are represented.

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

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

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

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

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

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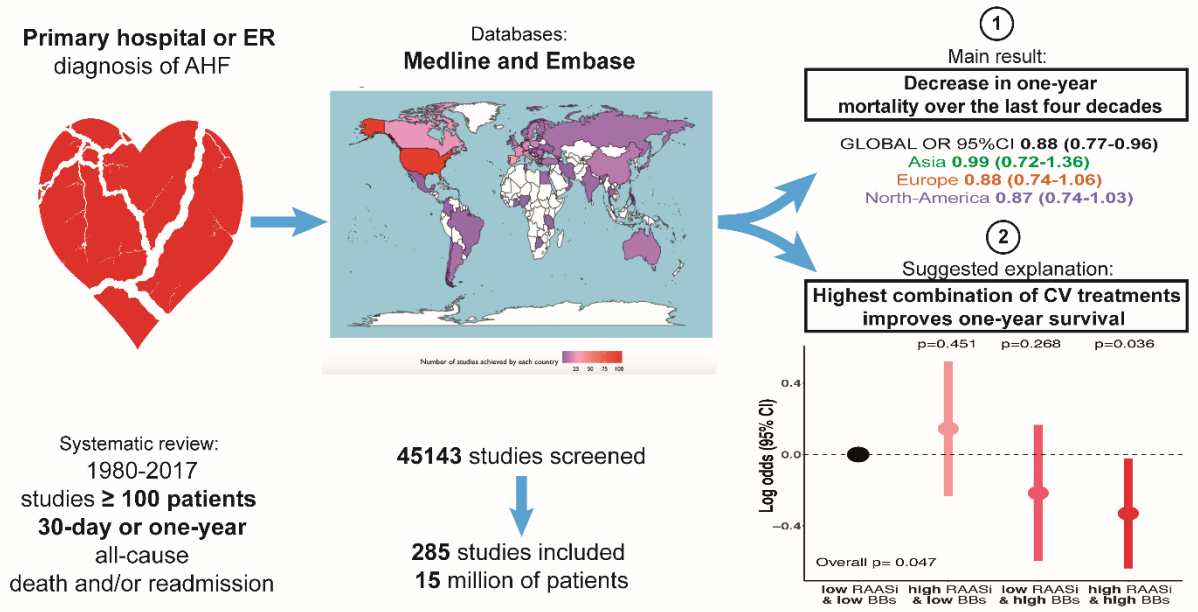
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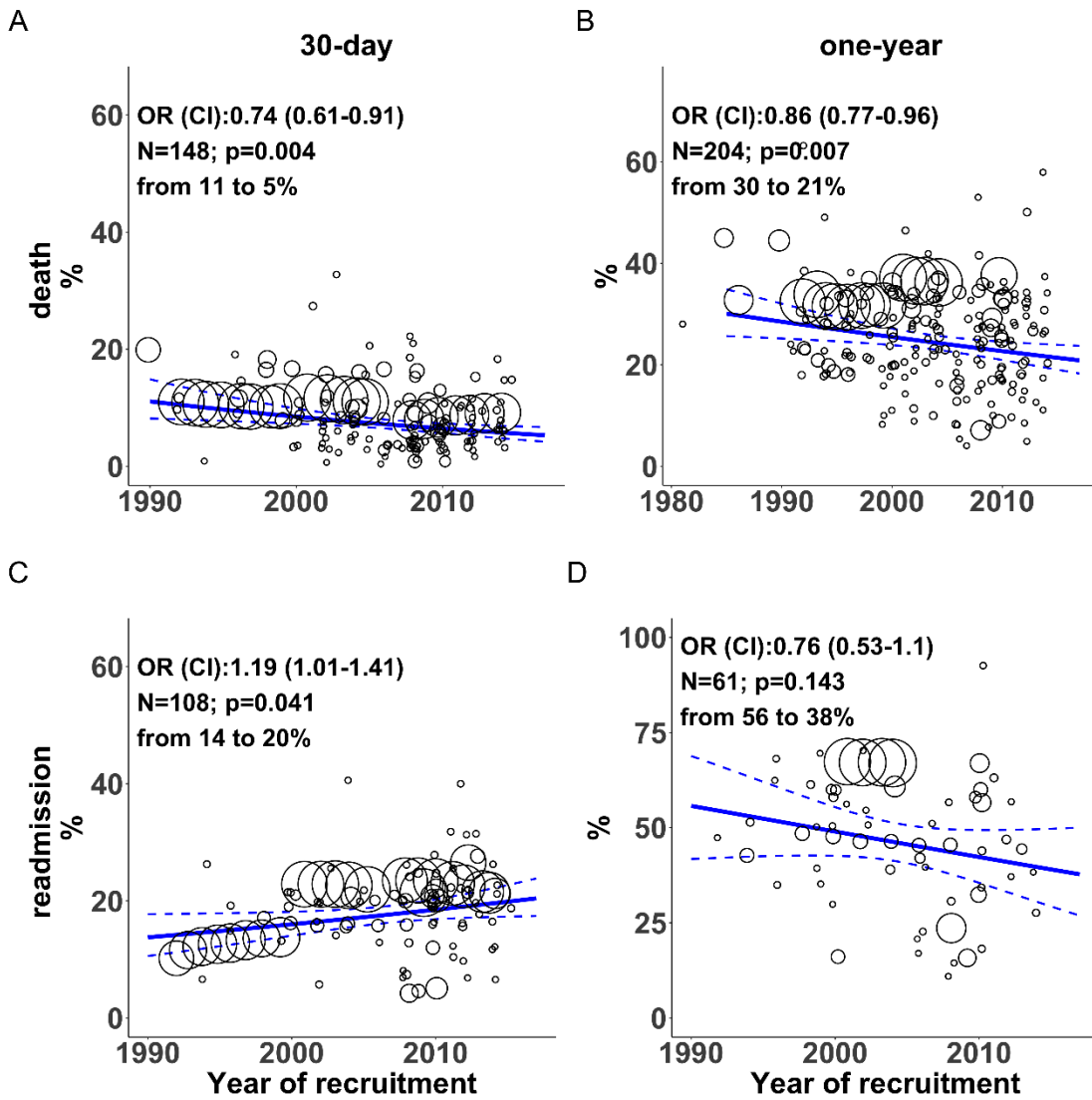
1 Graphical abstract

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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1 **Figure 1**

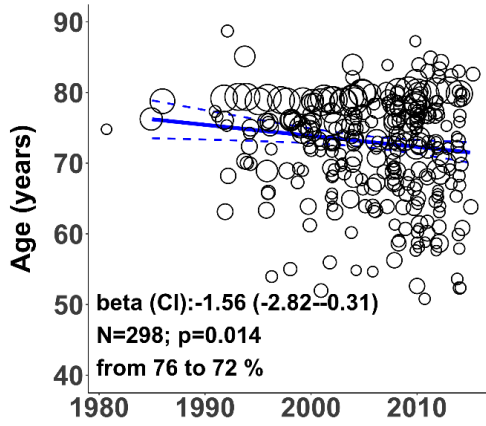


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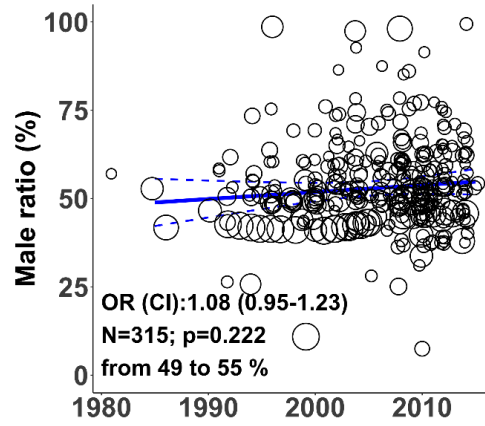
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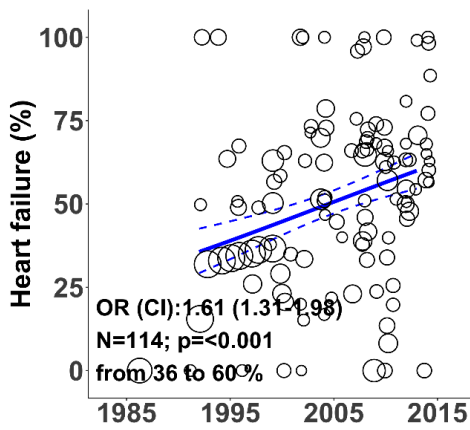
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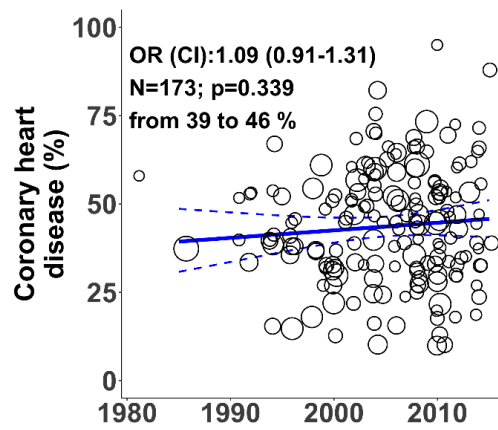
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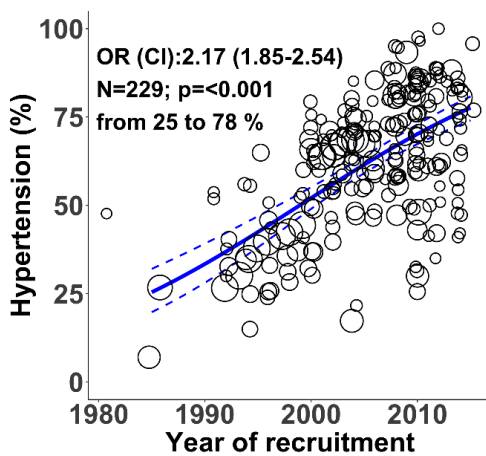
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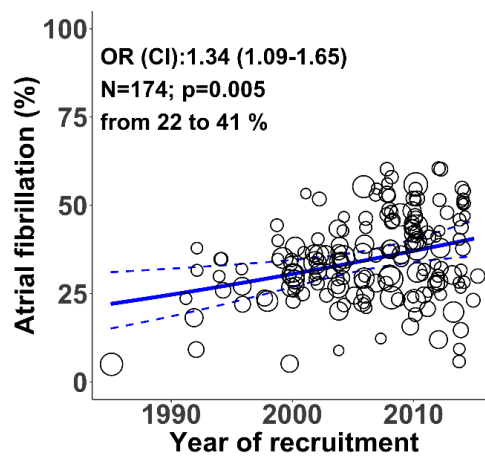
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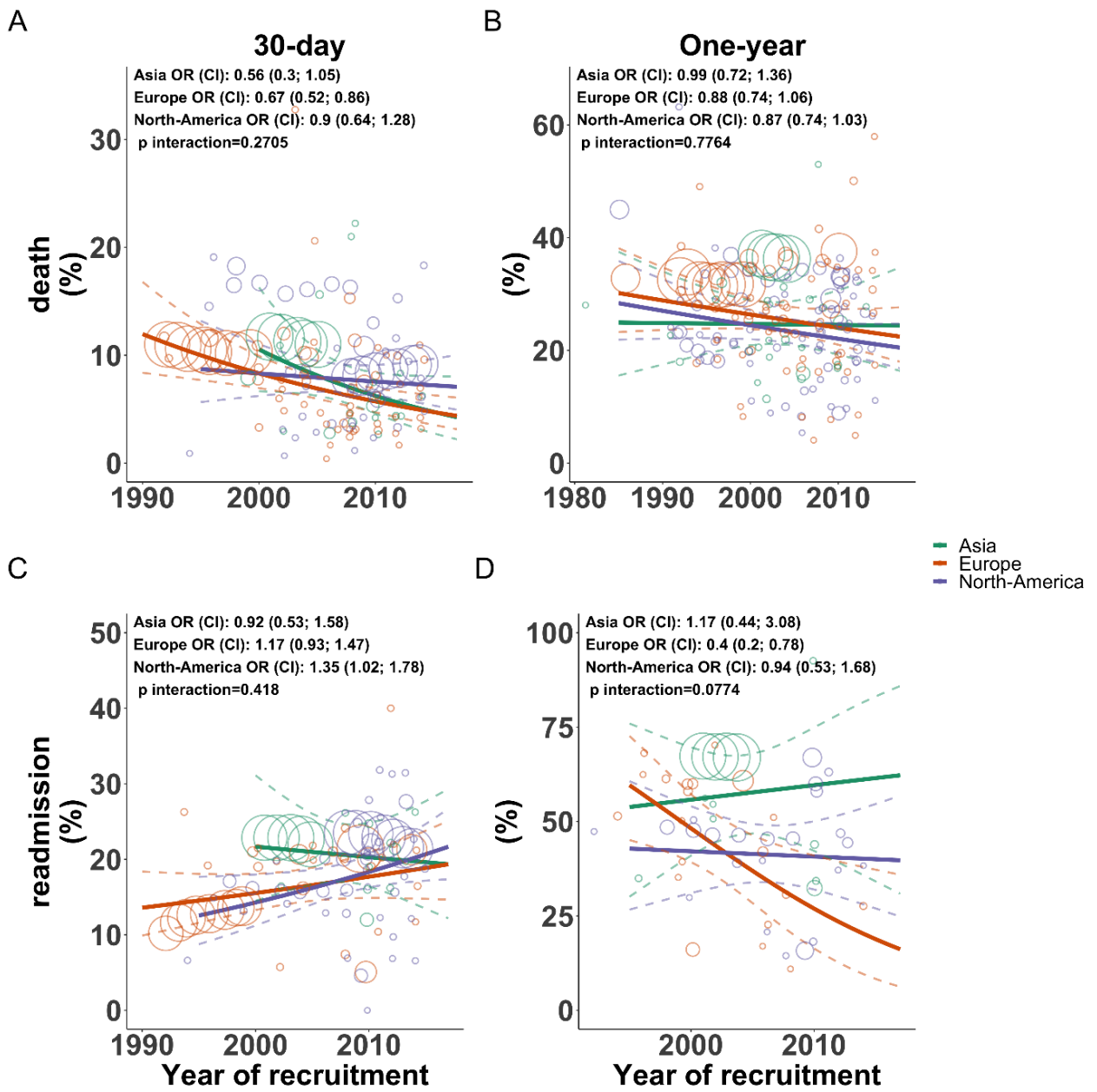


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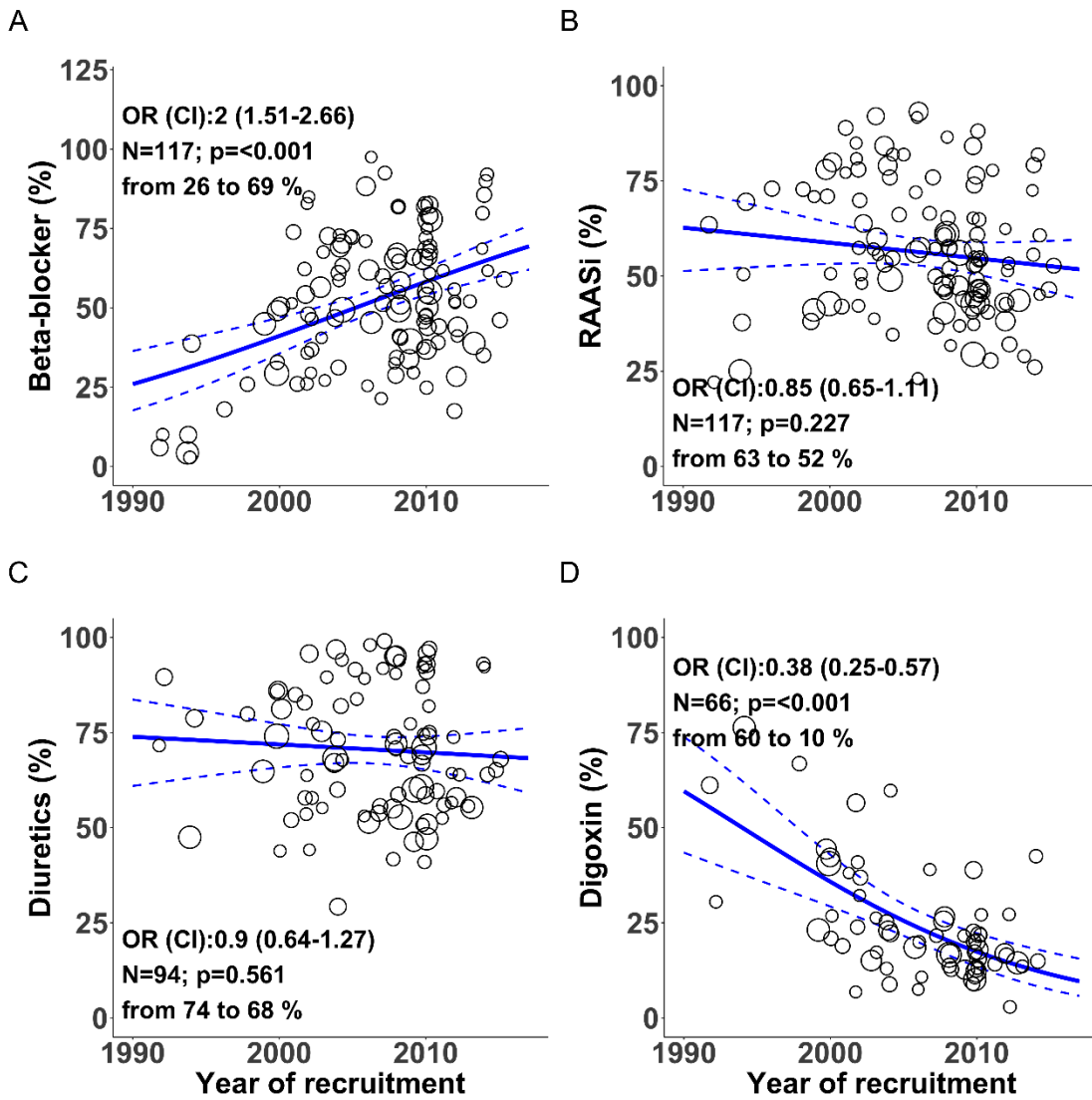
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1 **Figure 3**



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1 Figure 4

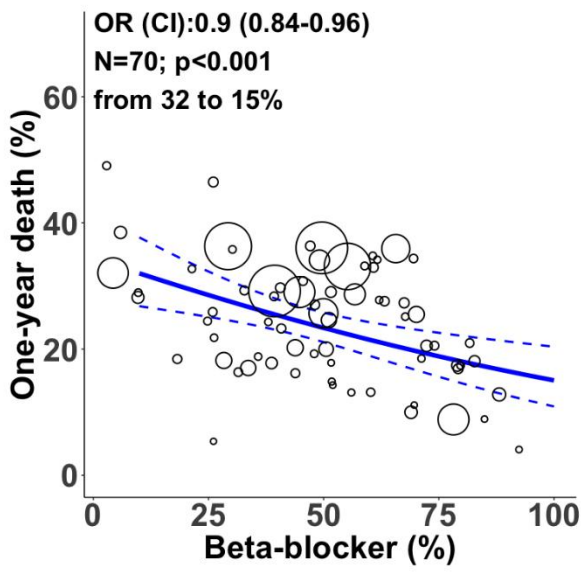


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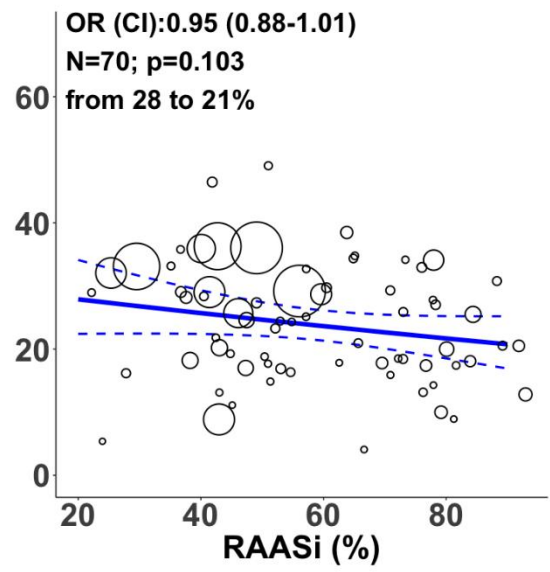
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1 Figure 5

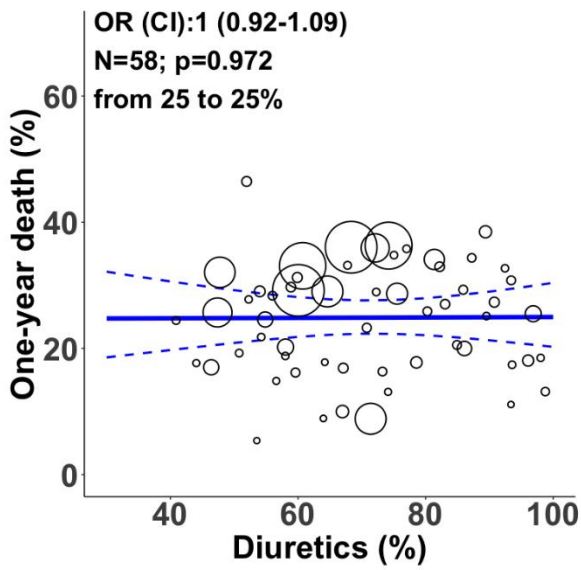
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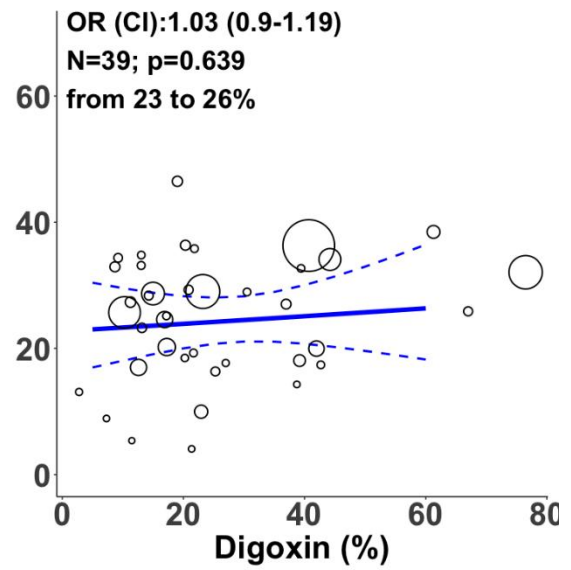
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