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# *DO ADRENERGIC ALPHA-ANTAGONISTS REALLY INCREASE THE RISK OF POOR CARDIOVASCULAR OUTCOMES?*

## *A SYSTEMATIC REVIEW AND META-ANALYSIS*

REVISÃO SISTEMÁTICA COM META-ANÁLISE

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## Scientific Divulgation

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# Do Adrenergic Alpha-Antagonists Really Increase the Risk of Poor Cardiovascular Outcomes? A systematic review and meta-analysis

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## Abstract

**Background:** Due to concerns regarding neurohormonal activation and fluid retention, adrenergic alpha-1 receptor antagonists (A1Bs) are generally avoided in the setting of heart disease, namely symptomatic heart failure (HF) with reduced ejection fraction (HFrEF). However, this contraindication is mainly supported by ancient studies, having recently been challenged by newer ones.

**Purpose:** To perform a comprehensive meta-analysis aimed at ascertaining the extent to which A1Bs might influence cardiovascular (CV) outcomes.

**Methods:** We systematically searched MEDLINE, Cochrane Central Register of Controlled Trials and Web of Science for both prospective and retrospective studies, published up until November 29th 2020, addressing the impact of A1Bs on clinical outcomes, namely acute heart failure (AHF), acute coronary syndrome (ACS), CV and all-cause mortality, and on CV surrogate measures, specifically left ventricular ejection fraction (LVEF) and exercise tolerance, by means of exercise duration (in seconds). Both randomized controlled trials (RCTs) and studies including only HF patients were further investigated separately. Study-specific odds ratios (ORs) and mean differences (MDs) were pooled using traditional meta-analytic techniques, under a random-effects model. A record was registered in PROSPERO database with the code number CRD42020181804.

**Results:** 15 RCTs, 3 non-randomized prospective and 2 retrospective studies, encompassing 32851, 19287 and 71600 patients, respectively, were deemed eligible. 62256 patients were allocated to A1B, on the basis of multiple clinical indications: chronic HF (14 studies, with 72558 patients, including 7 studies, with 850 patients, comprising only HFrEF), arterial hypertension (4 studies, with 44184 patients) and low urinary tract symptoms (2 studies, with 6996 patients). There were 25998 AHF events, 1325 ACS episodes, 955 CV deaths and 33567 all-cause deaths. When considering only RCTs, A1Bs were, indeed, found to increase AHF risk (OR 1.78 [1.46, 2.16] 95% CI, $p<0.00001$, $i^2$ 2%), although displaying no significant effect on ACS, CV, and all-cause mortality rates (OR 1.02 [0.91, 1.15] 95% CI, $i^2$ 0%; OR 0.95 [0.47, 1.91] 95% CI, $i^2$ 17%; OR 1.1 [0.84, 1.43] 95% CI, $i^2$ 17%, respectively). In addition, when only HF patients were evaluated, A1Bs revealed themselves neutral towards AHF, ACS, CV, and all-cause mortality events (OR 1.13 [0.66, 1.92] 95% CI, $i^2$ 0%; OR 0.49 [0.1, 2.47] 95% CI, $i^2$ 0%; OR 0.7 [0.21, 2.31] 95% CI, $i^2$ 21%; OR 1.09 [0.53, 2.23] 95% CI, $i^2$ 17%, respectively). As for HFrEF patients, A1Bs were found to exert a similarly inconsequential

effect on AHF risk (OR 1.01 [0.5-2.05] 95% CI, $i^2$ 6%). Likewise, LVEF was not significantly influenced by A1Bs (MD 1.66 [-2.18, 5.50] 95% CI, $i^2$ 58%) and, most strikingly, exercise tolerance was even higher in those under this drug class (MD 139.16 [65.52, 212.8] 95% CI, $p<0.001$, $i^2$ 26%).

**Conclusion:** A1Bs do seem to increase AHF odds, even though this effect appears to be driven by those at lower risk, thus contradicting current guidelines. These drugs' impact on other major CV outcomes might be trivial.

**Keywords**

Adrenergic alpha-antagonists; heart failure; mortality; acute coronary syndrome.

## Abbreviations

HF Heart Failure

ESC European of Society of Cardiology

AHF Acute Heart Failure

CHF Chronic Heart Failure

A1Bs Adrenergic alpha-1 Receptor Antagonists

AHT Arterial Hypertension

LUTS Lower Urinary Tract Symptoms

HFrEF Heart Failure with Reduced Ejection Fraction

CV Cardiovascular

PRISMA Preferred Reporting Items for Systematic Reviews and Meta-Analyses

RCTs Randomized Controlled Trials

ACS Acute Coronary Syndrome

LVEF Left Ventricular Ejection Fraction

ED Exercise Duration

OCAS Oral Controlled Absorption System

MR Modified Release Formulation

NOS Newcastle-Ottawa Scale

ROBINS-I The Risk of Bias in Non-Randomized Studies – of Intervention Tool

RoB Risk of Bias Tool

robvis Risk-of-bias VISualization

MD Mean Difference

SDs standard deviations

NYHA New York Heart Association

OR Odds Ratio

CIs Confidence Intervals

HFmrEF Heart Failure with Mid-Range Ejection Fraction

RR Relative Risk

HR Hazard Ratio

## Introduction

Heart failure (HF) affects 64.34 million people worldwide.[1] European Society of Cardiology (ESC) 2016 guidelines define HF as “a clinical syndrome characterized by typical symptoms (e.g. breathlessness, ankle swelling and fatigue) that may be accompanied by signs (e.g. elevated jugular venous pressure, pulmonary crackles and peripheral oedema) caused by a structural and/or functional cardiac abnormality, resulting in a reduced cardiac output and/or elevated intracardiac pressures at rest or during stress”.[2] Its clinical presentations may be classified as either acute or chronic. Acute HF (AHF) is the most common cause of hospital admission and in-hospital mortality varies between 4% and 7%,[3] manifesting as a decompensation of previous chronic HF (CHF) or due to an abrupt development of the syndrome *de novo*.[2]

Adrenergic alpha-1 receptor antagonists (A1Bs) are a pharmacologic class that may be used in patients with resistant arterial hypertension (AHT),[4] since they induce arterial vasodilation and thus decrease systemic vascular resistance. Resistant AHT may be defined as the inability to reach the arterial pressure goal despite the use of three antihypertensive drug classes, being one a diuretic, and is an important phenomenon, since its prevalence varies between 12 and 15%.[5] A1Bs also inhibit sympathetic tone, particularly in prostate and at bladder outlet, establishing themselves as the first-line treatment in patients with lower urinary tract symptoms (LUTS).[6] These represent a set of clinical manifestations that affect 50% of men with at least fifty years and 80% with seventy years or more,[7] and benign prostatic hyperplasia serves as its most frequent underlying condition. Examples of drugs within this class are prazosin, doxazosin, terazosin, tamsulosin, alfuzosin, silodosin, indoramin, trimazosin, bunazosin, urapidil and naftopidil.

Since the discontinuation of the doxazosin arm in the ALLHAT[8] trial, due to an increase in the risk of congestive HF, when compared against the one seen in the chlorthalidone group, questions were raised about the safety of A1Bs. In HF, there is typically an activation of the sympathetic nervous system,[9] which could, in fact, represent a basis for the use of these drugs in this condition. However, studies[8,10,11] consistently revealed a greater risk of HF decompensation in patients treated with A1Bs, probably due to neurohormonal activation and fluid retention. Due to these concerns, they are currently contraindicated as antihypertensive drugs in patients with HF with reduced ejection fraction (HFrEF) (class of recommendation III and level of evidence A), by the latest ESC specific guidelines.[2] Nevertheless, in 2018, a new large retrospective cohort study[12] found that treatment of patients with CHF with A1Bs was associated with a reduction in HF readmission and all-cause mortality rates. All in all, the impact of A1Bs in the natural history of HF is still insufficiently known.

Our goal is to systematically review and meta-analyse published literature on the comparison between A1Bs and other classes of drugs and/or placebo, analysing the risk of major cardiovascular (CV) outcomes associated with the former therapeutic class, with a particular emphasis on AHF events.

## Methods

### Protocol and registration

This systematic review with meta-analysis was developed according to the criteria of Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA). A record has been submitted to the PROSPERO database and registered (CRD42020181804) and is available at https://www.crd.york.ac.uk/prospero/display_record.php?ID=CRD42020181804.

### Literature search

Based on PRISMA statement we systematically searched MEDLINE through PubMed, Cochrane Central Register of Controlled Trials and Web of Science Core Collection on November 29th 2020, for observational and interventional studies appraising the effect of A1Bs on major CV outcomes, namely on AHF. The search was limited by article type at PubMed ("Clinical Study", "Clinical Trial", "Clinical Trial Protocol", "Clinical Trial, Phase I", "Clinical Trial, Phase II", "Clinical Trial, Phase III", "Clinical Trial, Phase IV", "Comparative Study", "Controlled Clinical Trial", "Journal Article", "Letter", "Multicenter Study", "Observational Study", "Pragmatic Clinical Trial" and "Randomized Controlled Trial") and Web of Science Core Collection ("Article", "Proceedings Paper", "Letter" and "Early Access"); by species ("Humans") at PubMed and by language (English, Spanish, Portuguese) whenever possible. MeSH terms were used at PubMed. No date publication restrictions were implemented. Appendix I represents the search equation and strategy used in this study. Different publications with the same patients' sample were considered as a single study.

### Eligibility criteria

The following criteria were established to identify studies suitable to be included in our study: (1) randomized controlled trials (RCTs), prospective non-randomized studies (both observational and interventional) or retrospective studies comparing A1Bs with any other drug(s) and/or placebo; (2) studies encompassing patients with an indication for A1B treatment, with a particular focus in those with CHF, AHT and LUTS; (3) studies reporting AHF events (which was given primacy), but also mortality, acute coronary syndrome (ACS) events, mean left ventricular ejection fraction (LVEF) change and exercise tolerance - mainly by exercise duration (ED) measurement - modification. Studies with beta-blockers with A1Bs

properties, like carvedilol or labetalol, used as experimental or control arms, and studies with less than a four-week follow-up were excluded.

**Primary and secondary outcomes**

Primary outcome consists of AHF events, whereas secondary outcomes include all-cause mortality, CV-specific mortality, ACS events, exercise tolerance change - by means of ED - and LVEF modification.

**Data collection and management**

Two authors (DM and JPS) systematically screened titles and abstracts from the studies obtained from the literature search with the aim of identifying publications that fulfil the previously indicated eligibility criteria. The full text of the studies which apparently met eligibility criteria was independently examined by DM and JPS in order to confirm their eligibility status. Any disagreement between the two review team members were resolved by discussion and whenever necessary with the opinion of the third author (RT). Data extraction focused on baseline demographic and clinical variables, interventions employed, and the previously outlined primary and secondary outcomes. Studies with sequential publications were accessed to ensure no duplication of results and gathering of most up-to-date information.

Chapple and co-workers[13] showed distinct data for three types of tamsulosin formulations: oral controlled absorption system (OCAS) 0.4 mg, OCAS 0.8 mg and modified release formulation (MR) 0.4 mg. To increase statistical power, we combine dichotomous data of these three formulation types, since they all represent the A1B group. Roehrborn and co-authors[14] reported on patients under tamsulosin in monotherapy, dutasteride in monotherapy and an association of both drugs. In this case, we combined dichotomous data of monotherapy of tamsulosin and the association, for the same reason. Cohn and colleagues[15] made a comparison between prazosin, the association of hydralazine and isosorbide dinitrate, and placebo, therefore we added the dichotomous data of hydralazine/isosorbide dinitrate and placebo, because they both account for the non-A1B group. In a study by Faconti *et al.* (2018),[16] some baseline characteristics from doxazosin and spironolactone groups were presented as per active or placebo juice intake, so, whenever possible, we added these dichotomous data to form our own pool of both A1B and non-A1B groups.

We defined an AHF event as any decompensation of previously known HF or *de novo* AHF and death by HF; all-cause mortality as a death event by any reason; CV mortality as any

death caused by ACS, stroke, HF, arrhythmia, “other CV” causes or “sudden” reasons; ACS event as both fatal and non-fatal myocardial infarction and unstable angina.

**Risk of bias assessment**

DM and JPS independently evaluated the risk of bias of the studies included in this review. These authors used the Newcastle-Ottawa Scale (NOS)[17] for observational studies and accessed selection, comparability and outcome domains. In non-randomized clinical trials, the risk of bias was evaluated using a simplified version of “The risk of bias in non-randomized studies – of intervention” tool (ROBINS-I)[18] addressing the following domains: confounding bias, selection bias, information bias by means of recall and detection bias, and reporting bias through “yes”, “probably yes”, “probably no”, “no” and “no information” judgements. The risk of bias of RCTs was gauged using the Cochrane Collaboration’s “Risk of bias” tool (RoB)[19] using the following verdicts: “low risk”, “high risk” or “unclear risk”, for random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other biases. The quality assessment for each study is represented at the NOS summary (Fig. 1A), ROBINS-I simplified summary (Fig. 1B) and RoB summary (Fig. 1C), the last one created with Risk-of-bias VISualization (robvis)[20].

In observational studies, and as for the selection domain, there is a possibility of bias since all studies lack representativeness of the general population. Moreover, in one study,[21] ascertainment of exposure was made by self-report. Comparability domain appears not to be a problem since the majority of the results were adjusted for a multitude of variables (particularly age, sex and systolic blood pressure). Regarding the outcome domain, bias is thought to be present in one study,[21] because outcome assessment was evaluated by patients’ self-report.

In the non-randomized clinical trial,[22] confounding bias may be present because the non-A1B group (metoprolol) showed worse hemodynamic indexes at baseline. In addition, there seems to be selection bias since four patients in the active group (metoprolol + doxazosin) received only half the drug dose, due to intolerance. There was also detection bias since the study was unblinded.

Most of the RCTs showed an unclear risk of selection bias since their authors often do not explain how allocation concealment and random sequence generation were processed. When evaluating performance bias, most studies revealed themselves to be at low risk, since almost all had a double-blind design and pills used were identical in both groups. However, three studies served as exceptions: two articles[23,24] due to a single-blind design and one

study[25] because of lack of blinding altogether. In the latter, blood pressure was even self-monitored by patients. On the other hand, double blinding also mitigated detection bias in the majority of studies.

Four studies[10,23,26,27] were analysed through a per-protocol approach and five studies[11,14,15,28,29] suffered from a significant percentage of withdrawals, some of which were even possibly related with our outcomes of interest, thus revealing a high risk of attrition bias; another study[30] managed to report dropouts, though did not clarify the cause, so it was given an unclear risk in this domain. Reporting bias was also a problem since some RCTs failed to report quantitative data judged as relevant [namely p-values, other statistics that would permit estimation of mean difference (MD), standard deviations (SDs) or other potential outcomes of interest, like change in weight and New York Heart Association (NYHA) class], preventing them to be included in the meta-analysis. A high risk of bias was also verified in the cross-over clinical trial,[11] due to not reporting results at the time of cross-over. In the “other biases” domain, two studies[10,31] were judged as displaying high risk since a premature termination was reported.

**A**

| | Selection | Comparability | Outcome |
|---|---|---|---|
| Bryson 2004 | ** | ** | ** |
| Chapman 2008 | *** | ** | *** |
| Matsui 2008 | *** | ** | *** |
| Dhaliwal 2009 | *** | ** | *** |
| Spoladore 2009 | *** | ** | *** |
| Jackevicius 2018 | *** | ** | *** |
| Faconti 2019 | *** | ** | *** |

**B**

| | Confounding | Selection | Information | | Reporting | Overall |
|---|---|---|---|---|---|---|
| | | | Recall | Detection | | |
| Kukin 1996 | Yes | Yes | No | Yes | No | Yes |

**C**

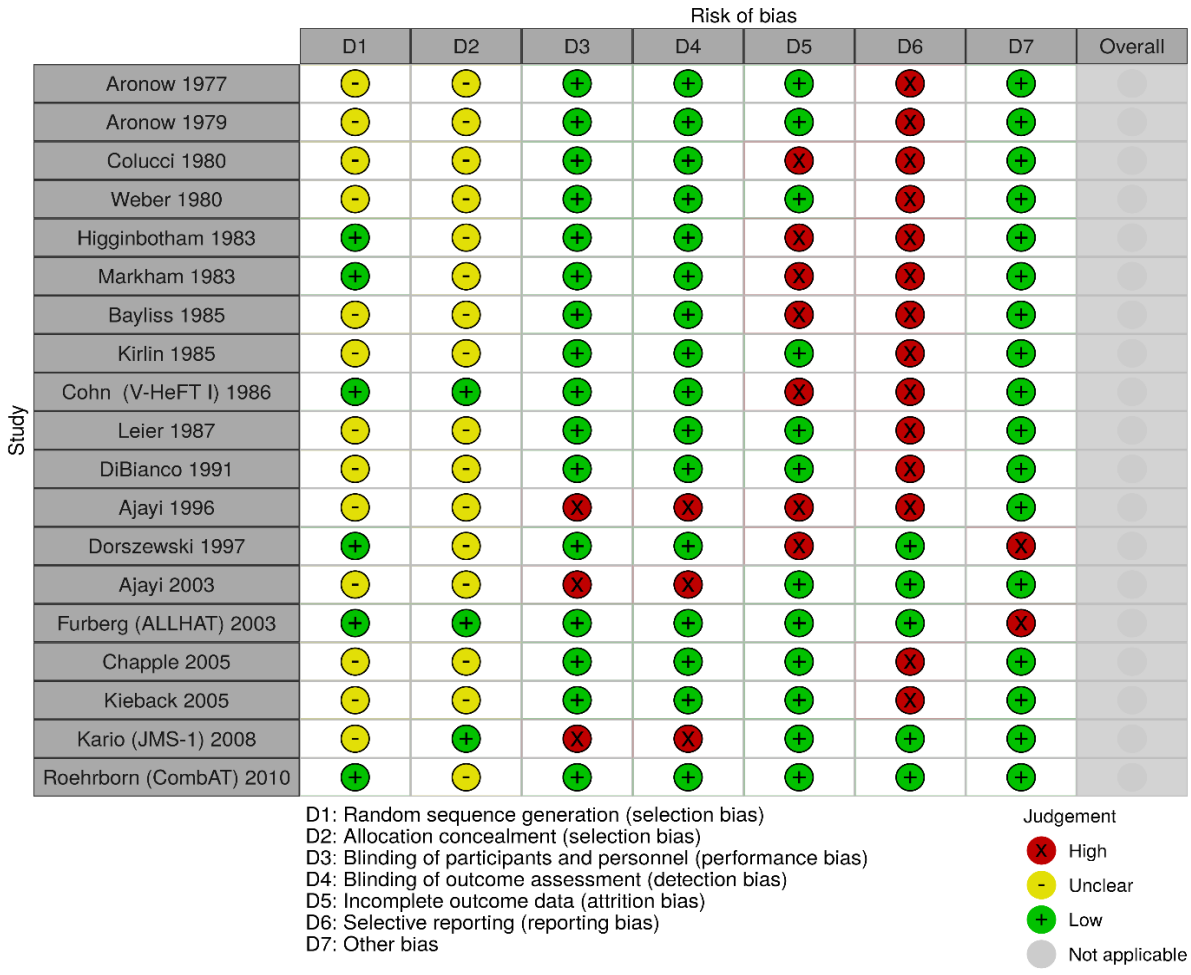


*Figure* 1 – Risk of bias summary:

A – Newcastle-Ottawa Scale; B – Simplified version of "The risk of bias in non-randomized studies – of intervention" tool; C – Cochrane Collaboration's "Risk of bias" tool.

## Statistical analysis

We pooled dichotomous data using odds ratio (OR) and continuous data using MD to describe effect sizes, further analysing them under a random-effects and a Mantel-Haenszel model, as long as a minimum of three studies were deemed suitable. Significance was postulated if 95% confidence interval (CI) does not contain the number 1 for dichotomous variables and the number 0 for continuous variables. Study heterogeneity was accessed by the $i^2$ statistic (considered excessive if it overtakes 50%) and by funnel plots.

It should be stated that most studies reported the continuous variables of interest only at baseline and at end of study[15,26,28,32–34], thus allowing MD calculation but without associating them with the respective SDs. This frequently precluded their incorporation in the quantitative synthesis, despite SDs being manually calculated whenever possible.

The statistical analysis was performed using Cochrane Review Manager 5.4.1.

# Results

## Search results

Literature review resulted in 1030 articles and the JMS-1[25] RCT, from which the sub-study Matsui *et al.* (2008)[35] derived its sample, was added after manual research. After dismissing 259 duplicate results, 689 articles were excluded through title and abstract screening and study type (RCTs, non-randomized prospective and retrospective studies comparing A1Bs with other(s) drug(s) and/or placebo). The eligibility of the remaining 83 studies was confirmed by full-text analysis, leading to further exclusion of 56 records: 15 were trial sub-analyses [12 from ALLHAT[31], 1 from V-HeFT[15] and 2 from Bayliss *et al.* (1985)[11]; ALLHAT[31], V-HeFT-I[15], Leier *et al*. (1987)[36] and Aronow *et al.* (1977)[37] were themselves picked between two possible articles with the exact same population, for each RCT; in 16 papers it was not possible to access the full-text; 7 were just conference meeting abstracts; in 1 study both the active and control groups were under A1B therapy; and 13 articles did not report relevant or comparable outcomes. 27 studies were finally assessed as fulfilling the criteria to be included in the qualitive synthesis. Furthermore, from these, 1 record[11] corresponded to a cross-over trial that did not report outcomes at the exact cross-over period; 1 article[21] presented assigned sample dimension in relative terms (percentage); in 2 studies[30,38], quantitative data reported were not stratified by assigned group allocation; in 1 study[34], SDs of the MDs of LVEF and ED, between baseline and end of study, could not be obtained; 1 study[16] described LVEF change from baseline through least square means; and 1 study[24] focused primarily on NYHA change from baseline, a variable not looked upon in other articles, thus making it impossible to employ these 7 articles in the meta-analysis. Therefore, 20 records were engaged in the quantitative review. From these, 15 were RCTs and encompassed 32851 patients, 3 were non-randomized prospective studies including 19287 patients and 2 were retrospective studies featuring 71600 patients. 62256 patients were treated with A1Bs, which were introduce for multiple clinical indications. In 14 studies (11 RCTs, 1 prospective non-randomized and 2 retrospective studies) a total of 72558 patients exhibited CHF. From these 14 articles, 7 (6 RCTs and 1 prospective non-randomized) focused only on HFrEF, accounting for 850 patients. In addition, 4 other studies (2 RCTs and 2 prospective non-randomized), which included 44184 patients, AHT was the main clinical indication for A1B initiation. In this regard, it should be noted that Matsui study[35] patients represent a sample from Kario study[25] population, hence the inclusion of only the latter. The remaining 2 studies (2 RCTs) were conducted in 6996 patients with LUTS (Fig. 2). Characteristics of the included studies are summarized in Table 1.

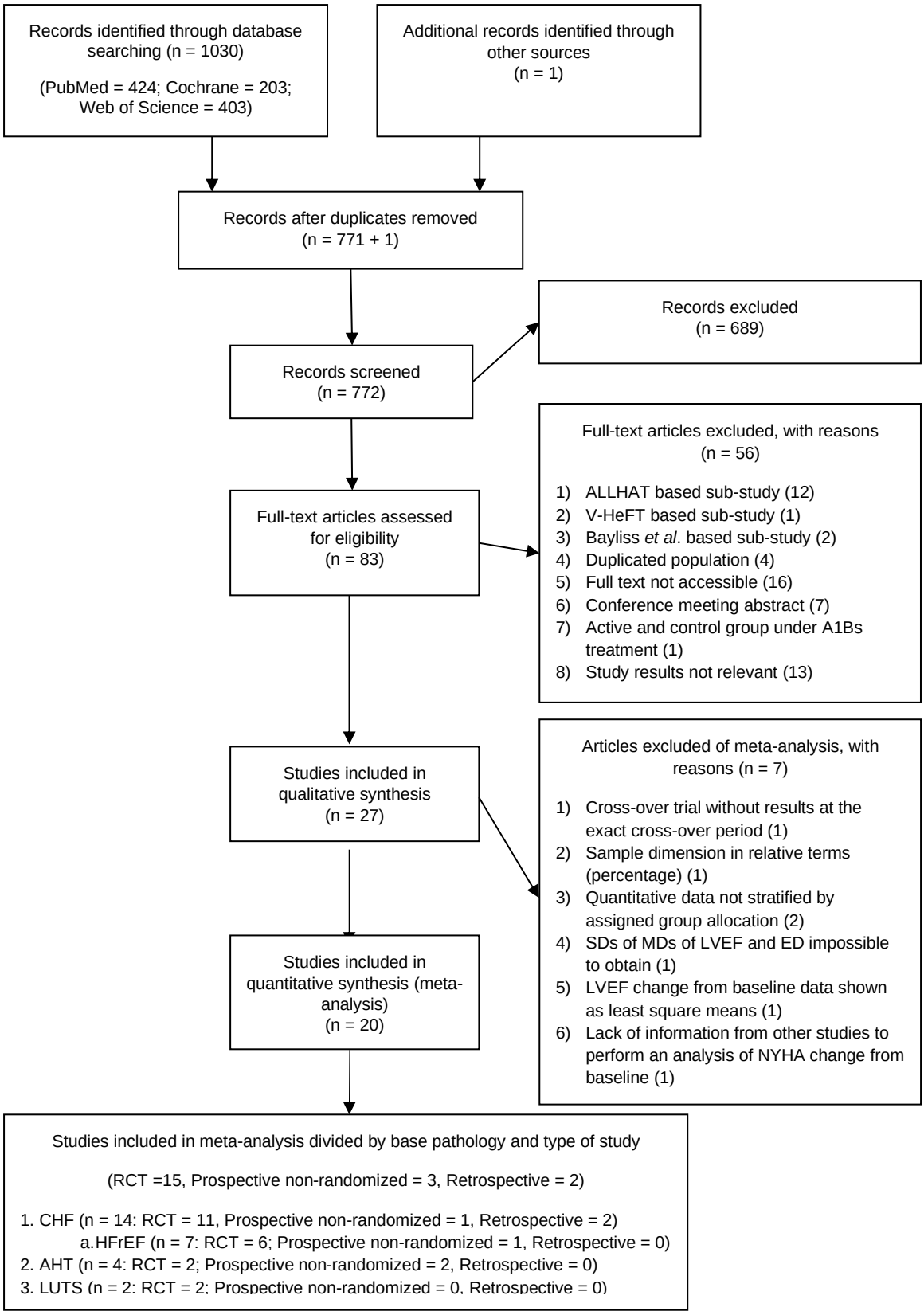


*Figure* 2 – PRISMA 2009 flow diagram of literature search.

A1B adrenergic alpha-1 receptor antagonist; SDs standard deviations; MDs mean differences; LVEF left ventricular ejection fraction; ED exercise duration; CHF chronic heart failure; HFrEF heart failure with reduced ejection fraction; AHT arterial hypertension; LUTS lower urinary tract symptoms.

| Study | Design | Base pathology | A1B group | Non-A1B group | Number of patients | | Age (years ± SD) | | Sex (males) | | Follow-up (months) |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | A1B | Non-A1B | A1B | Non-A1B | A1B | Non-A1B | |
| **Studies included in meta-analysis** | | | | | | | | | | | |
| **Jackevicius, C[12] 2018** | Retrospective cohort | CHF | A1B-treated | A1B-untreated | 35713 | 35713 | 74.6 ± 10.1 | 74.7 ± 10.3 | 35651 | 35660 | 24 (outcomes reported) |
| **Roehrborn, C[14] 2010 (CombAT)** | RCT | LUTS | Tamsulosin mon + Tamsulosin and Dutasteride | Dutasteride mon | 3221 | 1623 | (a) | 66.0 ± 6.99 | 1611 | 1623 | 48 |
| **Spoladore, R[32] 2009** | Retrospective cohort | CHF | Doxazosin | Non-doxazosin | 52 | 122 | 69.3 ± 10.1 | 67.1 ± 9.1 | 33 | 91 | 50 Dox / 41 Non-Dox |
| **Chapman, N[39] 2008** | RCT sub-analysis | AHT | Doxazosin | Non-doxazosin | 11768 | 7489 | 62.7 ± 8.5 | 62.2 ± 8.5 | 9254 | 5488 | Median 66 |
| **Kario, K[25] 2008 (JMS-1)** | RCT | AHT | Doxazosin | Non-doxazosin | 308 | 303 | 70.2 ± 9.2 | 70.1 ± 10.0 | [45.1%] | [43.6%] | 6 |
| **Matsui, Y[35] 2008** | RCT sub-analysis | AHT | Doxazosin | Non-doxazosin | 112 | 111 | 70.1 ± 10.4 | 70.4 ± 11.2 | [46.4%] | [45.0%] | 6 |
| **Chapple, C[13] 2005** | RCT | LUTS | Tamsulosin 0,4 OCAS + Tamsulosin 0.8 OCAS + Tamsulosin 0.4 MR | Placebo | 1795 | 357 | (b) | | 1795 | 357 | 2.76 |
| **Furberg, C[31] 2003 (ALLHAT)** | RCT | AHT | Doxazosin | Chlortalidone | 9061 | 15255 | 66.8 ± 7.7 | 66.9 ± 7.7 | 4858 | 8084 | 48 |
| **Dorszewski, A[10] 1997** | RCT | CHF | Urapidil | Placebo | 18 (c) | 18 (c) | 55.7 ± 2.4 | 55.3 ± 3.3 | 17 | 16 | 2.76 |
| **Ajayi, A[23] 1996** | RCT | CHF | Prazosin and Enalapril | Placebo and Enalapril | 24 (d) | | (d) | | (d) | | 0.92 |
| **Kukin, M[22] 1996** | Non-randomized Controlled Trial | CHF | Doxazosin and Metoprolol | Metoprolol mon. | 16 (e) | 14 (e) | From 29 to 76 Mean 50 | | 25 | | 3 |
| **DiBianco, R[33] 1991** | RCT | CHF | Doxazosin | Placebo | 36 | 37 | Mean 59.7 | Mean 60.0 | 33 | 32 | 3 |
| **Leier, C[36] 1987** | RCT | CHF | Indoramin | Placebo | 11 | 10 | 55 ± 10 | 59 ± 6 | 6 | 6 | 2 |
| **Cohn, J[15] 1986 (V-HeFT I)** | RCT | CHF | Prazosin | Hydralazine and Isosorbide Dinitrate + Placebo | 183 | 459 | Mean 58.3 | (f) | 183 | 459 | Up to 68.4 |
| **Higginbotham, M[27] 1983** | RCT | CHF | Prazosin | Placebo | 11 (g) | 11 (g) | From 25 to 68 | | 11 | 11 | 6 |
| **Markham, R[26] 1983** | RCT | CHF | Prazosin | Placebo | 13 (h) | 12 (h) | (h) | | 8 | 6 | 6 |
| **Colucci, W[28] 1980** | RCT | CHF | Prazosin | Placebo | 10 | 12 | 59 ± 9.5 | 58 ± 10.4 | 7 | 10 | 2 |
| **Weber, K[29] 1980** | RCT | CHF | Trimazosin | Placebo | 10 (i) | 13 (i) | (i) | | (i) | | 1.38 |
| **Aronow, W[40] 1979** | RCT | CHF | Prazosin | Placebo | 12 | 12 | From 26 to 67 | | 12 | 12 | 1.38 |
| **Aronow, WS[37] 1977** | RCT | CHF | Trimazosin | Placebo | 8 | 8 | From 41 to 66 | | 8 | 8 | 1.38 |

| Studies only included in qualitative analysis | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| **Faconti, L[16] 2019** | RCT sub-analysis | Patients with or at risk of DMII | Doxazosin | Spironolactone | 43 | 44 | (j) | | 32 | 28 | 6 |
| **Dhaliwal, A[38] 2009** | Prospective cohort | CHF | A1B-treated | A1B-untreated | 98 | 290 | 73 ± 8 | 67 ± 11 | [100%] | [99%] | Up to 37.42 |
| **Kieback, A[30] 2005** | RCT | CHF | Doxazosin 4 + Doxazosin 8 | Placebo | 15 | 15 | (k) | 63.6 ± 7.7 | 11 | 11 | 2.76 |
| **Bryson, C[21] 2004** | Prospective cohort | Elderly individuals | A1B-treated | A1B-untreated | (l) | | (l) | | (l) | | Up to 137.96 |
| **Ajayi, A[24] 2003** | RCT | CHF | Prazosin and Enalapril | Atenolol and Enalapril + Enalapril mon. | 8 | 20 | From 50 to 56 | | 3 | 11 | 0.92 |
| **Bayliss, J[11] 1985** | Randomized cross-over trial | CHF | Prazosin | Captopril | 19 (m) | | From 48 to 74 Mean 62 | | 18 | | 2 (cross-over at 1 month) |
| **Kirlin, P[34] 1985** | RCT | CHF | Trimazosin | Placebo | 9 | 8 | 49 ± 9 | 51 ± 11 | Not reported | | 6 |

(a) The tamsulosin mon group age was 66.2 ± 7.00 years. The tamsulosin and doxazosin association group age was 66.0 ± 7.05 years.

(b) The tamsulosin 0.4 mg OCAS group age was 64.7 ± 8.3 years (360 patients). The tamsulosin 0.8 mg OCAS group age was 64.6 ± 8.1 years (722 patients). The tamsulosin 0.4 mg MR group age was 64.7 ± 8.3 years (709 patients). The placebo group age was 64.9 ± 7.9 years (356 patients). This information was related to the ones who received at least one dose of medication and reported post-baseline safety information.

(c) 36 patients were randomized, although only in the 29 patients (13 in the urapidil group and 16 in the placebo group) who completed the study was reported LVEF data.

(d) 24 patients were randomized, although only in the 17 patients [10 (7 men) in the prazosin + enalapril group and 7 (5 men) in the placebo + enalapril group] who completed the study was reported age (49 ± 15 years and 53 ± 9 years, respectively) and ED data.

(e) 30 patients entered the study, although only in the 26 patients (15 in the doxazosin + metoprolol group and 11 in the metoprolol mon group) who completed the long-term study was reported LVEF data.

(f) The hydralazine and isosorbide dinitrate group mean age was 58.3 years (186 patients). The placebo group mean age was 58.5 years (273 patients).

(g) 22 patients were randomized, although only in 18 patients (9 in prazosin group and 9 in placebo group) was reported ED data.

(h) 25 patients were randomized, although only 23 patients comprised the subject of this report. Within the latter, the prazosin group (11 patients) age was 50 ± 14 years, and the placebo group (12 patients) age was 53 ± 13 years.

(i) The study population encompassed 27 patients [10 men; mean age 58 years (41 to 79 years)], although only 23 patients were randomized.

(j) Within the doxazosin group, 27 patients received a placebo juice (age 54.9 ± 13.8 years) and 16 patients an active juice (age 58.4 ± 14.7 years). Within the spironolactone group, 20 patients received a placebo juice (age 58.2 ± 9.9 years) and 24 patients an active juice (age 57.1 ± 13.2 years).

(k) The doxazosin 4 mg/d group (6 patients) age was 57.7 ± 11.2 years. The doxazosin 8 mg/d group (9 patients) age was 67.0 ± 7.8 years.

(l) 1195 men (22% in the A1B group, age 71.5 ± 4.7 years; 78% in the non-A1B group, age 72.9 ± 5.4 years) and 1910 women (8% in the A1B group, age 71.8 ± 4.9 years; 92% in the non-A1B group, age 72.7 ± 5.6 years) were enrolled in the cohort of hypertensive patients. 930 men (5% in the A1B group, age 72.8 ± 5.0 years; 95% in non-A1B group, age 72.8 ± 5.7 years) were enrolled in the cohort of normotensive patients.

(m) 19 patients were randomized, although only 16 patients completed the study

Table 1 – Baseline characteristics of included studies.

RCT randomized controlled trial; CHF chronic heart failure; LUTS lower urinary tract symptoms; AHT arterial hypertension; DMII diabetes mellitus type II; A1B adrenergic alpha-1 receptor antagonist; mon monotherapy; OCAS oral controlled absorption system; MR modified release formulation; SD standard deviation; Dox doxazosin; LVEF left ventricular ejection fraction; ED exercise duration.

**AHF events**

We found sixteen studies comparing A1Bs with other medications and/or placebo and reporting on AHF events, which reached 25998 cases in total. Analysis of the thirteen RCTs included showed a significantly higher odds of AHF among the A1B group (pooled OR 1.78 [1.46, 2.16] 95% CI, p<0.00001, $i^2$ 2%, Fig. 3A). On the other hand, a sub-analysis featuring the nine RCTs which included only CHF patients did not show a statistically significant difference between groups in this outcome (pooled OR 1.13 [0.66, 1.92] 95% CI, p=0.66, $i^2$ 0%, Fig. 3B). Furthermore, when considering only patients with LVEF below normal [both HFrEF and HF with mid-range ejection fraction (HFmrEF), that is, a LVEF lower than 50%], the joint analysis of six RCTs also failed to reveal a statistically significant difference between study groups, as far as AHF events are concerned (pooled OR 1.01 [0.50, 2.05] 95% CI, p=0.97, $i^2$ 6%, Fig. 3C).

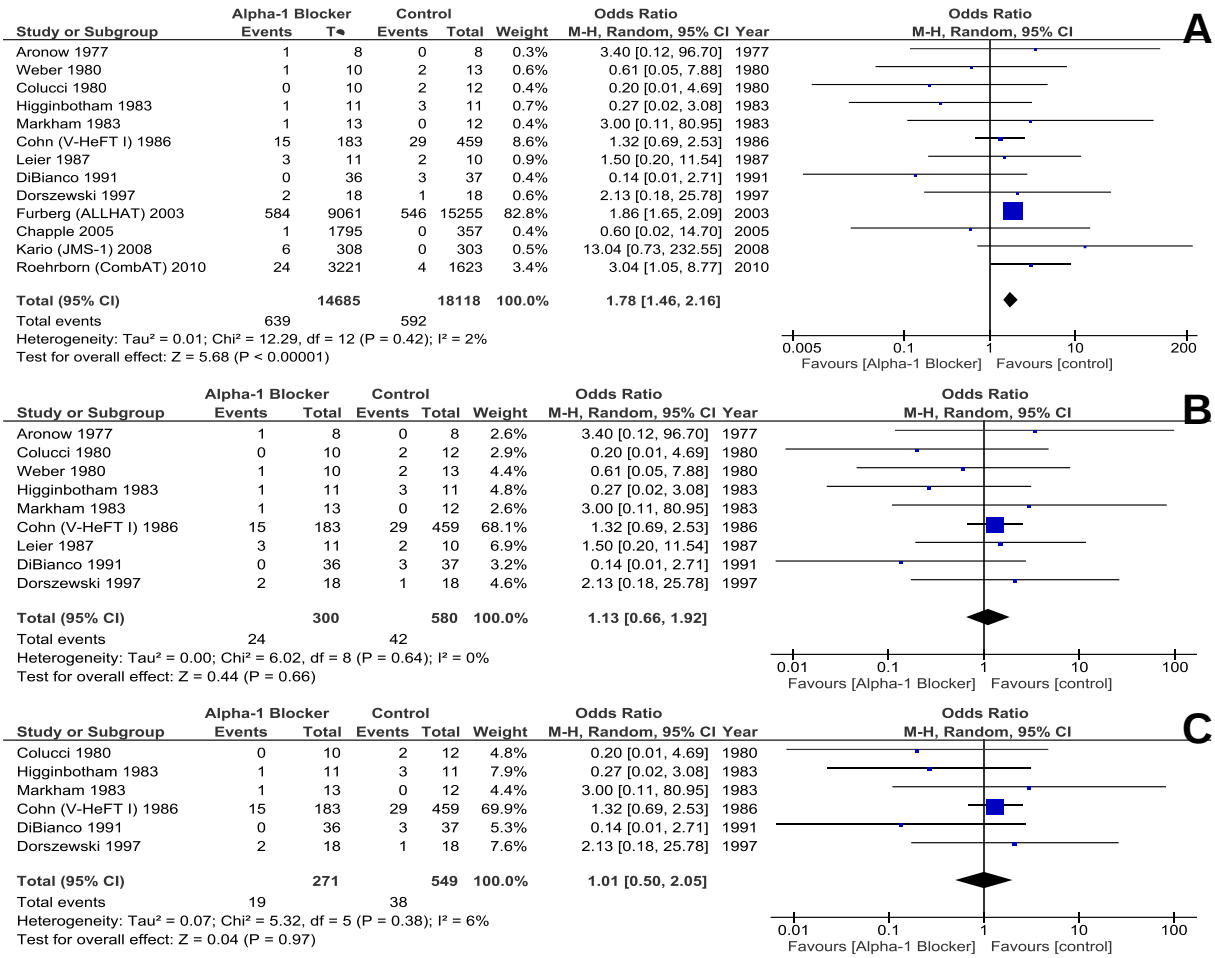


*Figure* 3 – AHF events – RCTs:

A – Unselected patients; B - CHF patients; C - HFrEF patients.

AHF acute heart failure; RCTs randomized controlled trials;

CHF chronic heart failure; HFrEF heart failure with reduced ejection fraction.

**All-cause and CV mortality**

There were thirteen studies reporting on the number of deaths in each group during follow-up. Ten articles were RCTs and our joint analysis of these did not unveil a statistically significant difference regarding all-cause mortality between the A1B and the non-A1B groups (pooled OR 1.10 [0.84, 1.43] 95% CI, p=0.48, $i^2$ 17%, Fig.4A). Moreover, when sub-analysing eight RCTs featuring only CHF patients, a similar trend was observed (pooled OR 1.09 [0.53, 2.23] 95% CI, p=0.81, $i^2$ 17%, Fig. 4B).

Moreover, we identified ten studies that discriminate which patients died from CV causes in each group, eight of them being RCTs. In these, A1B and non-A1B groups also did not behave differently as far as CV mortality is concerned (pooled OR 0.95 [0.47, 1.91] 95% CI, p=0.88, $i^2$ 17%, Fig. 4C). In addition, a sub-analysis encompassing the seven RCTs especially directed towards CHF patients was also not able to identify statistically significant differences regarding this outcome (pooled OR 0.70 [0.21, 2.31] 95% CI, p=0.56, $i^2$ 21%, Fig. 4D).

Of note, in Markham,[26] Higginbotham[27] and Kukin[22] trials, sudden death cases were reported without undoubtedly establishing if they were due to CV or non-CV aetiology. In this position, we felt justified to include these events in our CV mortality outcome. Additionally, Ajayi *et al.* (1996)[23] reported one sudden death event, though not specifying in which study arm it occurred, thus resulting in its exclusion from this analysis. However, by adding this event, there was a total of 33567 all-cause deaths, of which 955 were CV in nature.

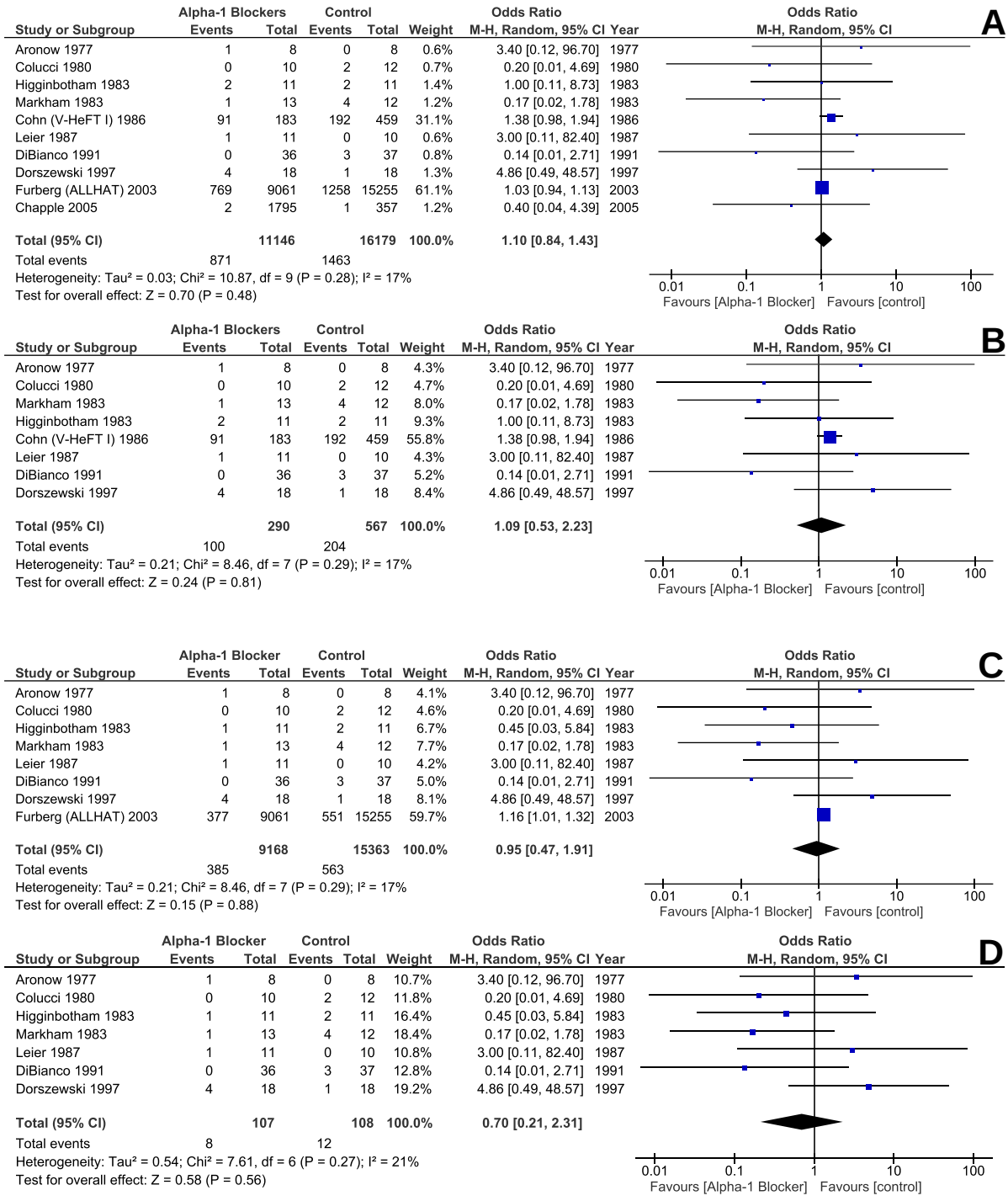


*Figure* 4 – Mortality – RCTs:

**All-cause mortality**: A – Unselected patients; B – CHF patients;

**CV mortality**: C – Unselected patients; D – CHF patients.

RCTs randomized controlled trials; CHF chronic heart failure; CV cardiovascular.

## ACS events

Seven studies, all of them RCTs, reported 1325 events of ACS. Their conjoint analysis did not reveal a statistically significant difference between groups in this outcome (pooled OR 1.02 [0.91, 1.15] 95%, p=0.71, $i^2$ 0%, Fig. 5A). Furthermore, a sub-analysis of four articles including only CHF patients also did not report a meaningful variation in ACS events between the A1B and the non-A1B arms (pooled OR 0.49 [0.10, 2.47] 95% CI, p=0.39, $i^2$ 0%, Fig. 5B).

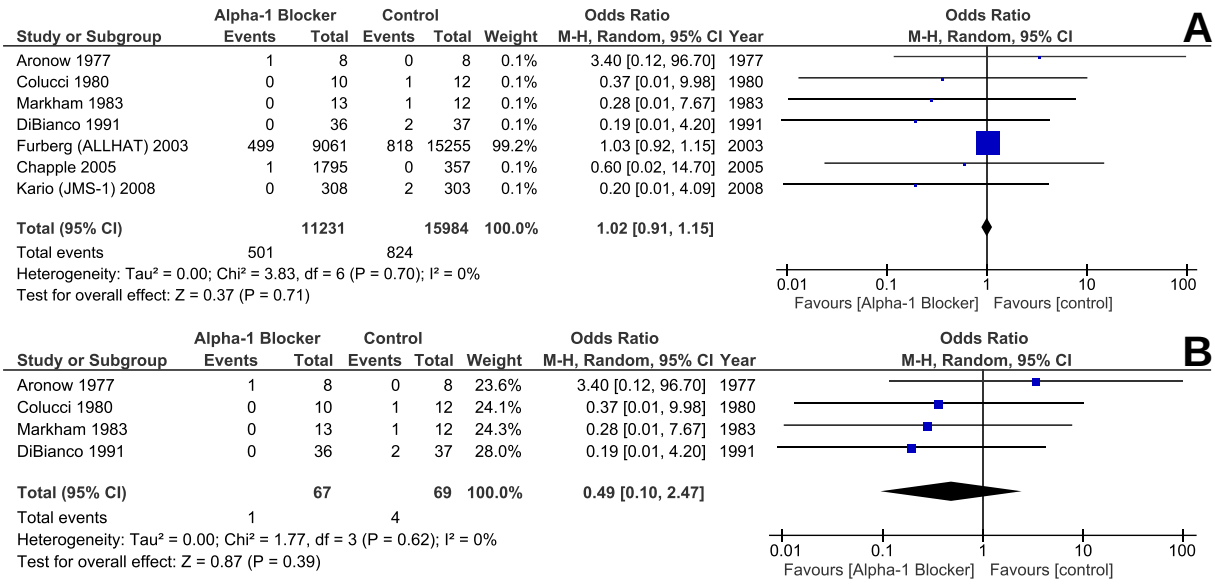


*Figure* 5 – ACS events – RCTs:

A – Unselected patients; B - CHF patients;

ACS acute coronary syndrome; RCTs randomized controlled trials; CHF chronic heart failure.

We chose to present, in the main paper, the analyses and the sub-analyses of the dichotomic variables assessed (AHF, ACS, CV and all-cause mortality) considering only RCTs, since we identified an elevated interstudy heterogeneity while jointly regarding RCTs, prospective non-randomized and retrospective studies, particularly for the AHF ($i^2$ 88%) and all-cause mortality ($i^2$ 59%) outcomes. The forest plots encompassing all study designs are presented as appendices (appendix II and III).

## LVEF change from baseline

We found four studies allowing for the input of mean LVEF change from baseline in A1B and non-A1B groups, as well as their respective SDs, either by information directly reported or through calculation. Their conjoint analysis showed no between-group statistically significant difference in this outcome (pooled MD 1.66 [-2.18, 5.50] 95%, p=0.40, $i^2$ 58%, Fig. 6).

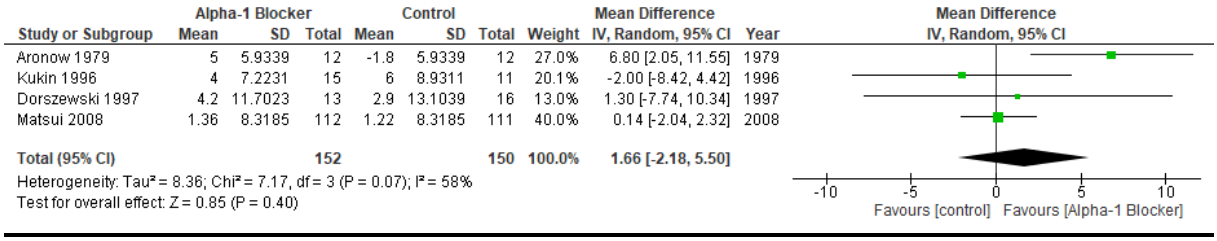


*Figure* 6 – LVEF change from baseline – All study designs:

Unselected patients.

LVEF left ventricular ejection fraction.

## ED change from baseline

Four studies presented data from which it was possible to obtain the difference between end of follow-up and baseline mean ED in both A1B and non-A1B groups, as well as their corresponding SDs, either directly or indirectly. There was a statistically significant increase in exercise tolerance, by means of ED, in seconds, in the A1B group when compared with other(s) drug(s) and/or placebo (pooled MD 139.16 [65.52, 212.80] 95% CI, p=0.0002, $i^2$ 26%, Fig. 7).

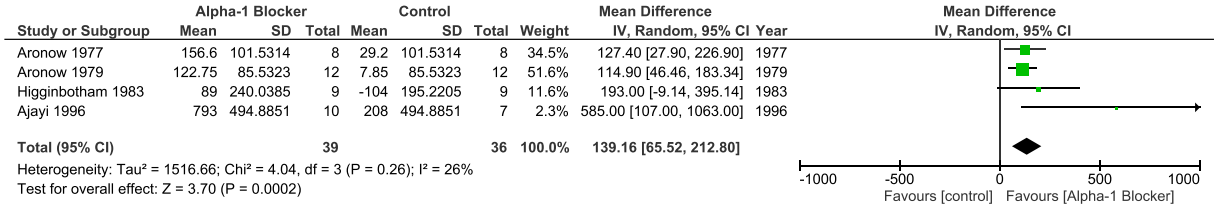


*Figure* 7 – ED change from baseline – All study designs:

Unselected patients.

ED exercise duration.

Funnel plots of all analyses are presented as appendices (appendix IV to VIII).

## Discussion and Limitations

Based on our findings, A1B-treated patients, when compared with non-A1B-treated ones: (i) exhibited a greater AHF risk in an unselected setting; (ii) showed similar odds of AHF in a background of CHF; (iii) had a similar AHF event rate when the HFrEF context is considered (iv) displayed an equivalent all-cause mortality in an unselected setting; (v) showed a comparable all-cause mortality rate in a background of CHF; (vi) had similar CV mortality in an unselected scenario; (vii) exhibited equivalent CV mortality in a CHF setting; (viii) showed a comparable ACS risk in an unselected setup; (ix) displayed a similar ACS event rate if only CHF patients are to be considered; (x) saw no significant change in LVEF; (xi) experienced an increase in ED, surprisingly.

To the best of our knowledge, this is the first systematic review with meta-analysis that focused on AHF odds in patients treated with A1B as opposed to patients treated with other drug(s) and/or placebo.

### AHF

Our findings, namely the ones addressing an unselected patient population in whom A1Bs were prescribed – which even featured scenarios in which A1Bs are currently contraindicated[2] - state that these agents result in a 78% greater odds of AHF, which corroborates the results noted in the ALLHAT study [31] [relative risk (RR) 1.80 [1.61, 2.02] 95% CI, congestive HF fatal, hospitalized and treated]. In fact, this trial yielded a rather disproportional weight in the corresponding forest plot. Furthermore, Kieback *et al.* (2005)[30] suggested that doxazosin might exert deleterious effect after twelve weeks of treatment, since by that period only the placebo group demonstrated a sustained benefit on hemodynamic measures. Likewise, in Bayliss *et al.* (1985),[11] eight patients deteriorated, five improved and three remained unchanged while under prazosin treatment, whereas none deteriorated, fifteen improved and one remained unchanged while under captopril, after one month of treatment with each drug, suggesting a clinical benefit of the inhibition of the renin-angiotensin-aldosterone system but not of the alpha-adrenergic system, despite both of them being majorly overactivated in CHF.[9] Moreover, while studying the patient cohort of the Cardiovascular Health Study, Bryson *et al.* (2004)[21] also lend support to an increase in AHF risk in hypertensive patients treated with A1B monotherapy, as compared with patients treated with thiazide monotherapy [hazard ratio (HR) 1.90 [1.03, 3.50] 95% CI, adjusted by age], even though adjustment for systolic blood pressure reverted statistical significance (HR 1.31 [0.67, 2.56] 95% CI). In addition, this study[21] also suggested that hypertensive patients treated with

two or more drugs to reduce blood pressure, one of which being an A1B, did not display an additional risk of AHF when compared with a multi-antihypertensive regimen with no A1B agent. Besides, in normotensive men - presumably treated with A1Bs for LUTS – a similar trend seems to apply. On a same note, Dhaliwal *et al.* (2009)[38] indicated that A1Bs, employed primarily for LUTS, were not linked with a significant rise in AHF events through HF rehospitalizations (HR 1.20 [0.85, 1.70] 95% CI, adjusted by age, LVEF, previous HF hospitalization, NYHA class, history of renal insufficiency, ventricular ectopy, admission systolic and diastolic blood pressure and admission heart rate). However, when considering only the patients left without beta-blocker background therapy - a class of drugs with a known favourable prognostic impact in HFrEF -,[2,41–45] a higher AHF event rate (HR 1.94 [1.14, 3.32] 95% CI) was identified in the A1B-treated arm. Spoladore and co-workers[32] reported no association whatsoever between doxazosin and HF hospitalization, even when adjusting to a wide panel of possible confounding variables. In turn, Chapman *et al.* (2008)[39] also stated that doxazosin does not contribute to an excess in HF events, both during administration and after drug discontinuation [rate ratio 1.17 [0.92, 1.49] 95% CI, p=0.20, in person-years], when compared with non-doxazosin users. Even more surprising findings were reported by Jackevicius *et al.* (2018),[12] since, in their study, besides the fact that unselected patients treated with A1Bs and with no beta-blocker background therapy showed no increase in HF rehospitalization (HR 0.95 [0.90, 1.00] 95% CI), in the propensity score matched cohort, A1Bs were even associated with a reduction in this outcome (HR 0.95 [0.92, 0.97] 95% CI). Even though apparently at odds with the ALLHAT[31] study, a reinterpretation of the latter might skew the discordance. In fact, Chen *et al.* (2015),[46] in a meta-analysis, defended that the seemingly higher risk of AHF in the doxazosin arm of the ALLHAT[8,31] trial was not primarily caused by a deleterious effect of the drug, but rather by a cardioprotective effect arising from chlortalidone. In fact, a letter[47] to the editor claimed that, since chlorthalidone promotes diuresis and sodium excretion, that may contribute positively for the treatment of HF symptoms (namely those associated with congestion) or, at very least, for its masking[48], which might have led to reduced therapy intensity or even HF admissions. Moreover, Kjeldsen,[49] in another letter to the editor, suggested that doxazosin was titrated more slowly than chlorthalidone, ending up achieving a rather suboptimal dose, a finding which is in line with the report that most of the AHF events in the doxazosin group occurred in the first year of follow-up. In this regard, it is interesting to note that, in the ALLHAT trial, blood pressure was 3 mmHg higher in the doxazosin arm, which could have single-handedly justified the difference in AHF risk between both groups.[47] This theory was, however, apparently refuted by a sub-analysis of the trial,[50] in which data derived from the 2000 ALLHAT report[8] was used, which came to demonstrate that adjusting for baseline and follow-up systolic and diastolic blood pressure produced no significant modification in the between-group AHF odds (RR 2.00 [1.76, 2.28] CI 95%). In addition, yet

another letter[51] postulated that the decision to prematurely discontinue the doxazosin arm in the ALLHAT trial was well-founded, since despite decreasing blood pressure, doxazosin offers reduced benefits in terms of general and major CV outcomes when compared to chlorthalidone. Apparently reconciling the afford mentioned arguments, and while regarding the CHF setting only – that is, excluding the ALLHAT[31] study from the analysis, for instance - our findings revealed a neutral effect of A1Bs towards decompensation risk.

All in all, it should be noted that ESC currently contraindicates A1Bs in the specific HFrEF setup.[2] Therefore, we managed to investigate these patients as well: an analysis expressly directed towards articles in which all patients presented LVEF lower than 50% (HFrEF and HFmrEF) revealed a non-statistically significant modification in AHF odds. This result seems to suggest that the greater AHF risk in an unselected population taking A1Bs was, in fact, driven by those at lower risk, namely the ones with LUTS or AHT. This is, of course, in sharp contrast with the ESC recommendation. This way, new studies are needed to ultimately clarify the impact of A1Bs in the natural history of HF.

**All-cause and CV mortality**

Our results regarding the impact of A1B treatment on all-cause mortality reinforced the ALLHAT[31] findings, which pointed towards a neutral effect (RR 1.03 [0.94, 1.13] 95% CI). On the other hand, as far as CV mortality is concerned, the two studies appear to disagree with one another, since the latter revealed a small but significant increase in this outcome (RR 1.15 [1.01, 1.32] 95% CI) and the former showed no relevant difference. A clear contrast might also be detected between our own study and the one from Jackevicius *et al.* (2018),[12] since, in the latter, A1Bs proved themselves to be able to reduce death by all causes, not only in a propensity score matched-cohort (HR 0.93 [0.91, 0.94] 95% CI), but also in an unselected A1B-treated population sample without beta-blocker background therapy (HR 0.93 [0.90, 0.96] 95% CI). In line with our results, Dhaliwal *et al.* (2009)[38] found that A1Bs did not contribute to a significant increase in all-cause mortality (HR 1.10 [0.78, 1.56] 95% CI, adjusted by age, LVEF, previous HF hospitalization, NYHA class, history of renal insufficiency, ventricular ectopy, admission systolic and diastolic blood pressure and admission heart rate), which held true when only a beta-blocker untreated subgroup was considered (HR 1.12 [0.67, 1.89] 95% CI). In addition, Spoladore *et al.* (2009)[32] also reported a neutral effect of doxazosin therapy on all-cause mortality (HR 0.39 [0.03, 5.76] 95% CI, p=0.50, when adjusting for age, sex, NYHA at baseline, heart rate at baseline and beta-blocker use). Finally, Bryson and co-workers[21] studied a cohort of hypertensive patients in whom a non-statistically significant CV

mortality effect attributed to the A1B class was also demonstrated (HR 0.92 [0.32, 2.69] 95% CI, adjusted by age).

All in all, this apparently insignificant ability of A1Bs to modify all-cause death might concur to diminish our own finding of an increase in AHF odds in an unselected population, since this syndrome is well-known for its elevated in-hospital fatality rate.[3]

**ACS**

As for the ACS event rate, our findings corroborated those of the ALLHAT[31] study, in which a similar risk was found between the A1B-treated and the non-A1B-treated patients (RR 1.03 [0.92, 1.15] 95% CI). Moreover, Bryson *et al.* (2004),[21] when evaluating their cohort of hypertensive patients, also supported these results, suggesting no influence of A1Bs on the natural history of coronary artery disease, namely in myocardial infarction risk (HR 0.81 [0.28, 2.31] 95% CI, adjusted by age).

The striking concordance among studies concurs to postulate that A1B pharmacological class is unable to influence the atherosclerotic process, either by plaque progression or erosion/rupture.

**LVEF**

A major limitation detected when evaluating LVEF change from baseline was that only four of the ten studies in which MDs were directly or indirectly reported were able to be incorporated in our specific forest plot. Nevertheless, all the unemployed studies provided data rich enough to merit discussion. Firstly, a study by DiBianco *et al*. (1991)[33] revealed a numerically higher increase in LVEF in the doxazosin-treated group, when compared with the placebo-treated group, despite failing statistically significance. In addition, in the V-HeFT I[15] study, which compared LVEF changes from baseline between the prazosin and the placebo-treated arms, a non-significant increment was also revealed. Furthermore, Markham *et al.* (1983)[26] RCT also did not disclose a meaningful difference in left ventricular global systolic function between prazosin and placebo. However, all these results seemed to be contradicted by the findings of Colucci,[28] in whose study a significant increase in LVEF in the groups taking prazosin was revealed ($p<0.01$), as opposed to the ones randomly assigned to a placebo intervention, in whom LVEF remained approximately constant. Likewise, Kirlin *et al.* (1986),[15] using trimazosin in a randomized fashion, also reported a meaningful rise in left ventricular systolic function in the active group while no significant difference in this regard was detected in the placebo arm. In parallel, in an observational study, Spoladore *et al.* (2009)[32] pointed to

a higher end-of-study LVEF in the group of patients managed with A1B, even though a similar finding was already present at baseline. Beyond these six studies, two additional ones managed to compare LVEF dynamics between the A1B and the placebo arms, despite doing so without MD measurement. The most recent of these is a sub-analysis of the VaSera[52] RCT, published by Faconti *et al.* (2019),[16] which exhibited a neutral effect of doxazosin, when compared to spironolactone, on LVEF modification, through a statistical model that presented data as least square mean change (least square mean 0.21 [-0.88, 1.29] 95% CI). The other paper is a RCT by Higginbotham and co-workers,[27] in which LVEF change from baseline was evaluated at one, three and six months, ultimately revealing a meaningful increase in the prazosin-treated patients in the first two measurements (p-values =0.011 and =0.010, respectively; p-values were considered significant if <0.0167), although not in the last one. The placebo arm showed an unchanged LVEF during follow-up.

It should be noted that, in some of the studies, statistical analyses were primarily directed towards longitudinal intra-group LVEF changes from baseline, that is, not directly comparing between-group MDs. That was the case in Higginbotham,[27] Colucci[28] and Kirlin[34] papers. Furthermore, another potential setback in LVEF evaluation is the high likelihood of missing data bias, since some of the articles left unconsidered for this specific forest plot - by lack of indispensable quantitative data reported - apparently revealed results that stand in sharp contrast with ours. In addition, our analysis showed an elevated inter-study heterogeneity ($i^2$ 58%), which was not possible to overcome by just employing RCTs, since only two of these studies[10,40] were found among the literature. Due to these limitations, conclusions drawn based on our findings must be taken into account with caution.

**Exercise Tolerance**

Just as in the latter endpoint, MDs of ED change from baseline were able to be obtained in seven articles, even though only four of them reported data complete enough for forest plot inclusion. Moreover, in this case as well, not all seven studies appear to bring forth a concordant finding. Nevertheless, our analysis revealed a somewhat unexpected increase in exercise tolerance in the A1B-treated group, when compared with the non-A1B arm. This increment in ED was estimated as 139.16 seconds, in mean. As for the unconsidered studies, Markham and co-authors[26] did not disclose a statistically significant difference in final ED between the prazosin and the placebo groups. Similarly, in a paper by Kirlin,[34] a meaningful positive effect of trimazosin on ED, as compared with placebo, was also not confirmed. Furthermore, DiBianco and coleagues[33] also failed to uncover a significant difference between ED change from baseline between patients under either doxazosin or placebo.

The non-significant findings reported by the aforementioned unconsidered studies were able to be reproduced elsewhere. For instance, even more striking findings were established in Bayliss *et al.* (1985)[11] study, in which the prazosin-treated group exhibited a non-meaningful increase in ED (MD 42s [-342, 420] 95% CI), whereas the captopril-treated patients experienced a significant improvement in exercise time (MD 372s [180, 570] 95% CI, p=0.0012). Moreover, Leier *et al.* (1987)[36] results were also rather unforeseen: on one hand, they showed a non-meaningful influence of indoramin on ED and, on the other, a small but significant increase in ED in the placebo group was detected. On the contrary, a Colucci *et al.* (1980)[28] paper postulated a substantial improvement in ED in the prazosin-treated patients ($p<0.003$) and a neutral effect on the same variable by placebo. Likewise, Weber *et al.* (1980)[29] revealed a sustained increase in ED in the group assigned to trimazosin, an effect which was not reproduced in the placebo arm.

Beyond maximum ED change from baseline, exercise tolerance was also assessed, in some studies, through a six-minute walk test. Within these, a Dorszewski and co-workers'[10] paper revealed a neutral effect of urapidil, when compared with placebo. Diversely, Kukin *et al.* (1996)[22] showed that both the association of doxazosin and metoprolol and metoprolol monotherapy resulted in a significant increase in the covered distance. Furthermore, Ajayi *et al. (*2003)[24] postulated a substantial distance increment with various therapeutic regimens, namely an association of prazosin and enalapril, an association of atenolol and enalapril and enalapril monotherapy ($F=5.36$, $p<0.001$), even though with no statistically significant differences between them.

As described previously, particularly for the LVEF endpoint, in some studies,[10,11,22,28,29,34,36] statistical analyses targeted only longitudinal time or distance variations within the same group, thus differing from our selected approach, which featured between-group MDs. Lastly, since some of the studies not considered for our quantitative analysis displayed different findings from the ones we obtained through direct evaluation of ED MDs, our conclusions might, once again, be hindered by missing data bias, thus assumptions based on them should not be made lightly.

Since ED might represent an indirect measure of quality of life, it seems conceivable for A1B therapy to contribute to its improvement, even though potentially increasing AHF risk. This hypothesis should, however, be the object of future studies.

## Future perspectives

Our primary outcome analysis, while encompassing an unselected setup, endorsed the ALLHAT[8,31] trial findings. However, the different results obtained while considering only CHF and HFrEF patient subgroups, coupled with an apparent neutral effect of A1Bs in all-cause and CV mortality, seem to justify the need for a new large outcome-driven RCT. Ideally, this should follow a placebo-controlled design. However, if this comparator is impossible to obtain or judged inappropriate, a control substance with no cardioprotective effect (for instance no thiazide-like diuretics)[46] should be applied so as not to overshadow the real effect of the active drug. This research would be of major interest, since the two clinical entities - LUTS and AHT - from which the apparent increase in AHF risk might stem from are highly prevalent.[5,7] Besides, A1Bs are widely regarded as a first-line therapeutic approach in male patients suffering from the former,[6] while the main clinical complication of the latter is precisely AHF[53].

In addition, since ED might represent an indirect measure of quality of life, it seems conceivable for A1B therapy to contribute to its improvement, even though potentially increasing AHF risk. This hypothesis should, however, be the object of future studies, this time directed towards softer endpoints.

## Limitations

First, as depicted in our supplementary appendix, our search equation encompassed only studies that were designed as to consider HF as either a clinical indication or an outcome, given the fact that an acute event of this syndrome represented our primary endpoint. However, this approach might have led to the omission of studies potentially reporting outcomes as all-cause and CV mortality, ACS, and LVEF and ED dynamics, hailed as secondary endpoints in our article.

Furthermore, in accordance with what was already anticipated by us, the inclusion of prospective non-randomized and retrospective studies in our forest plots resulted in an elevated interstudy heterogeneity, thus justifying our decision to relegate these analyses to the supplementary appendix. For instance, while encompassing all study designs, our primary endpoint (AHF) was finally met with an $i^2$ of 88%. Moreover, following the same methodology, the evaluation of such a strong and unbiased outcome as all-cause mortality reached an $i^2$ of 59%. In turn, continuous variables were also found not to be safe from this issue, as, for example, the LVEF analysis revealed an $i^2$ as high as 58%. This assumed predilection for RCT inclusion led us to somewhat undermine the Jackevicius *et al.* (2018)[12] article, the large retrospective cohort whose results raised the main question of this systematic review and

meta-analysis. Additionally, a relative paucity of RCTs addressing CV outcomes or even surrogate measures specifically in patients with LUTS and AHT (two for each disease)[13,14,25,31] prevented us from analysing these subgroups this way, as three studies were deemed necessary to produce a specific forest plot. In turn, a sub-analysis featuring only AHT patients encompassing RCTs as well as non-randomized prospective and retrospectives studies is included in the appendix, despite exhibiting an elevated interstudy heterogeneity ($i^2$ 93%).

Moreover, as previously stated, it was somewhat hard to pool SDs of MDs of LVEF and ED, which might have led to missing data bias. In fact, this issue also stopped us from going as further as to extend the span of our attention to other outcomes, such as NYHA class and weight dynamics, since, once again, less than three articles would be able to be featured in each variable potential forest plot.

In addition, whenever the ALLHAT[31] study was employed in our analyses, its relative weight was somewhat dominant, being even superior to the influence exerted by all the other RCTs combined.

Lastly, the definition of HF has revealed itself arguably dynamic. So, in our article, in which a large time gap between the publication date of the first and the last study meeting eligibility criteria exists, an AHF adjudicated as an event of interest in one trial may not be considered so in another one.[15,31]

## Conclusion

A1Bs do seem to increase the likelihood of an AHF event, although not at the expense of patients with established CHF. In fact, even the high-risk HFrEF subgroup appear safe from this pharmacological class effect. On the other hand, those at lower risk (e.g., patients with LUTS and AHT) were found to single-handedly drive the increase in AHF odds. The impact of A1Bs on other CV outcomes emerged as neutral, except for exercise tolerance, in which a surprising increment was detected. A new clinical trial comparing A1B-treated patients with placebo controls, appears necessary to finally settle these ambiguities.

## Impact on daily practise

Our results are at odds with 2016 ESC HF guidelines, which contraindicated A1Bs as antihypertensives in patients with HFrEF,[2] and thus may prove insightful for future recommendations.

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No funding was required for this study.

## Conflict of interest

The review team states that there are no conflicts of interest potentially leading to a biased analysis in this article.

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## References


1. GBD 2017 Disease and Injury Incidence and Prevalence Collaborators. Global, regional, and national incidence, prevalence, and years lived with disability for 354 diseases and injuries for 195 countries and territories, 1990–2017: a systematic analysis for the Global Burden of Disease Study 2017. Lancet. 2018;392(10159):1789–858.

2. Ponikowski P, Voors A, Anker S, Bueno H, Cleland J, Coats A, et al. 2016 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure: The Task Force for the diagnosis and treatment of acute and chronic heart failure of the European Society of Cardiology (ESC). Eur Heart J. 2016;37(27):2129–200.

3. Farmakis D, Parissis J, Lekakis J, Filippatos G. Acute heart failure: Epidemiology, risk factors, and prevention. Rev Esp Cardiol (Engl Ed). 2015;68(3):245–8.

4. Williams B, Mancia G, Spiering W, Rosei E, Azizi M, Burnier M, et al. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology (ESC) and the European Society of Hypertension (ESH). Eur Heart J. 2018;39(33):3021–104.

5. Carey R, Calhoun D, Bakris G, Brook R, Daugherty S, Dennison-Himmelfarb C, et al. Resistant Hypertension: Detection, Evaluation, and Management: A Scientific Statement From the American Heart Association. Hypertension. 2018;72(5):e53–90.

6. Gravas S, Cornu J, Gacci M, Gratzke C, Herrmann T, Mamoulakis C, et al. EAU Guidelines on Management of Non Neurogenic Male Lower Urinary Tract Symptoms (LUTS), incl. Benign Prostatic Obstruction (BPO) [Internet]. 2020 [cited 2021 Jan 11]. Available from: https://uroweb.org/guideline/treatment-of-non-neurogenic-male-luts/

7. Egan K. The Epidemiology of Benign Prostatic Hyperplasia Associated with Lower Urinary Tract Symptoms: Prevalence and Incident Rates. Urol Clin North Am. 2016;43(3):289–97.

8. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Major Cardiovascular Events in Hypertensive Patients Randomized to Doxazosin vs Chlorthalidone The Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). JAMA. 2000;283(15):1967–75.

9. Cohn J, Levine T, Francis G, Goldsmith S. Neurohumoral control mechanisms in congestive heart failure. Am Heart J. 1981;102(3 Pt 2):509–14.

10. Dorszewski A, Göhmann E, Dorszewski B, Werner G, Kreuzer H, Figulla H. Vasodilation by urapidil in the treatment of chronic congestive heart failure in addition to

angiotensin-converting enzyme inhibitors is not beneficial: results of a placebo-controlled, double-blind study. J Card Fail. 1997;3(2):91–6.

11. Bayliss J, Norell M, Canepa-Anson R, Reid C, Poole-Wilson P, Sutton G. Clinical importance of the renin-angiotensin system in chronic heart failure: double blind comparison of captopril and prazosin. Br Med J (Clin Res Ed). 1985;290(6485):1861–5.

12. Jackevicius C, Ghaznavi Z, Lu L, Warner A. Safety of Alpha-Adrenergic Receptor Antagonists in Heart Failure. JACC Heart Fail. 2018;6(11):917–25.

13. Chapple C, Al-Shukri S, Gattegno B, Holmes S, Martínez-Sagarra J, Scarpa R, et al. Tamsulosin Oral Controlled Absorption System (OCAS) in Patients with Lower Urinary Tract Symptoms Suggestive of Benign Prostatic Hyperplasia (LUTS/BPH): Efficacy and Tolerability in a Placebo and Active Comparator Controlled Phase 3a Study. Eur Urol Suppl. 2005;4(2):33–44.

14. Roehrborn C, Siami P, Barkin J, Damião R, Major-Walker K, Nandy I, et al. The effects of combination therapy with dutasteride and tamsulosin on clinical outcomes in men with symptomatic benign prostatic hyperplasia: 4 year results from the CombAT study. Eur Urol. 2010;57(1):123–31.

15. Cohn J, Archibald D, Ziesche S, Franciosa J, Harston W, Tristani F, et al. Effect of vasodilator therapy on mortality in chronic congestive heart failure. Results of a Veterans Administration Cooperative Study. N Engl J Med. 1986;314(24):1547–52.

16. Faconti L, Mills C, Govoni V, Gu H, Morant S, Jiang B, et al. Cardiac effects of 6 months' dietary nitrate and spironolactone in patients with hypertension and with/at risk of type 2 diabetes, in the factorial design, double-blind, randomised-controlled, VASERA TRIAL. Br J Clin Pharmacol. 2019;85(1):169–80.

17. GA Wells, Shea B, O'Connell D, Peterson J, Welch V, Losos M, et al. The Newcastle-Ottawa Scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses [Internet]. The Ottawa Hospital Research Institute. 2000 [cited 2021 Jan 11]. Available from: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp

18. Sterne J, Hernán M, Reeves B, Savović J, Berkman N, Viswanathan M, et al. ROBINS-I: a tool for assessing risk of bias in non-randomised studies of interventions. BMJ. 2016;355:i4919.

19. Review Manager (RevMan) [Computer program]. Version 5.4. The Cochrane Collaboration; 2020.

20. McGuinness LA, Higgins JPT. Risk-of-bias VISualization (robvis): An R package and Shiny web app for visualizing risk-of-bias assessments [Internet]. Research Synthesis Methods. John Wiley & Sons, Ltd; 2020 [cited 2021 Jan 11]. Available from: https://doi.org/10.1002/jrsm.1411

21. Bryson C, Smith N, Kuller L, Chaves P, Manolio T, Lewis W, et al. Risk of congestive heart failure in an elderly population treated with peripheral alpha-1 antagonists. J Am Geriatr Soc. 2004;52(10):1648–54.

22. Kukin M, Kalman J, Mannino M, Freudenberger R, Buchholz C, Ocampo O. Combined alpha-beta blockade (doxazosin plus metoprolol) compared with beta blockade alone in chronic congestive heart failure. Am J Cardiol. 1996;77(7):486–91.

23. Ajayi A, Sofowora G, Balogun M. Concurrent alpha 1 adrenergic blockade and angiotensin converting enzyme inhibition in the treatment of congestive heart failure. Int J Cardiol. 1996;57(2):173–6.

24. Ajayi A, Sofowora G, Adigun A, Asiyanbola B. Adjunctive sympathoplegic therapy to ACE inhibition in Blacks with congestive heart failure: a comparison of alpha-1 with beta-1 blockade on exercise tolerance and cardiac sympathovagal reflex activity. Ethn Dis. 2003;13(1):71–9.

25. Kario K, Matsui Y, Shibasaki S, Eguchi K, Ishikawa J, Hoshide S, et al. An alpha-adrenergic blocker titrated by self-measured blood pressure recordings lowered blood pressure and microalbuminuria in patients with morning hypertension: the Japan Morning Surge-1 Study. J Hypertens. 2008;26(6):1257–65.

26. Markham R, Corbett J, Gilmore A, Pettinger W, Firth B. Efficacy of prazosin in the management of chronic congestive heart failure: a 6-month randomized, double-blind, placebo-controlled study. Am J Cardiol. 1983;51(8):1346–52.

27. Higginbotham M, Morris K, Bramlet D, Coleman R, Cobb F. Long-term ambulatory therapy with prazosin versus placebo for chronic heart failure: relation between clinical response and left ventricular function at rest and during exercise. Am J Cardiol. 1983;52(7):782–8.

28. Colucci W, Wynne J, Holman B, Braunwald E. Long-term therapy of heart failure with prazosin: a randomized double blind trial. Am J Cardiol. 1980;45(2):337–44.

29. Weber K, Kinasewitz G, West J, Janicki J, Reichek N, Fishman A. Long-term vasodilator therapy with trimazosin in chronic cardiac failure. N Engl J Med. 1980;303(5):242–50.

30. Kieback A, Rödiger O, Jaenecke H, Grohmann A, Wernecke K-D, Baumann G, et al. Hemodynamic effects of alpha1-adrenoceptor antagonist, doxazosin, in patients with chronic congestive heart failure. J Cardiovasc Pharmacol. 2005;46(4):399–404.

31. The ALLHAT Officers and Coordinators for the ALLHAT Collaborative Research Group. Diuretic versus alpha-blocker as first-step antihypertensive therapy: final results from the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT). Hypertension. 2003;42(3):239–46.

32. Spoladore R, Roccaforte R, Fragasso G, Gardini C, Palloshi A, Cuko A, et al. Safety and efficacy of doxazosin as an “add-on” antihypertensive therapy in mild to moderate heart failure patients. Acta Cardiol. 2009;64(4):485–91.

33. DiBianco R, Parker J, Chakko S, Tanser P, Emmanuel G, Singh J, et al. Doxazosin for the treatment of chronic congestive heart failure: results of a randomized double-blind and placebo-controlled study. Am Heart J. 1991;121(1 Pt 2):372–80.

34. Kirlin P, Das S, Pitt B. Chronic alpha-adrenoceptor blockade with trimazosin in congestive heart failure. Int J Cardiol. 1985;8(1):89–92.

35. Matsui Y, Eguchi K, Shibasaki S, Ishikawa J, Hoshide S, Pickering T, et al. Effect of doxazosin on the left ventricular structure and function in morning hypertensive patients: the Japan Morning Surge 1 study. J Hypertens. 2008;26(7):1463–71.

36. Leier C, Binkley P, Randolph P, Unverferth D. Long-term indoramin therapy in congestive heart failure: a double-blind, randomized, parallel placebo-controlled trial. J Am Coll Cardiol. 1987;9(2):426–32.

37. Aronow W, Greenfield R, Alimadadian H, Danahy D. Effect of the vasodilator trimazosin versus placebo on exercise performance in chronic left ventricular failure. Am J Cardiol. 1977;40(5):789–93.

38. Dhaliwal A, Habib G, Deswal A, Verduzco M, Souchek J, Ramasubbu K, et al. Impact of alpha 1-adrenergic antagonist use for benign prostatic hypertrophy on outcomes in patients with heart failure. Am J Cardiol. 2009;104(2):270–5.

39. Chapman N, Chang C, Dahlöf B, Sever P, Wedel H, Poulter N, et al. Effect of doxazosin gastrointestinal therapeutic system as third-line antihypertensive therapy on blood pressure and lipids in the Anglo-Scandinavian Cardiac Outcomes Trial. Circulation. 2008;118(1):42–8.

40. Aronow W, Lurie M, Turbow M, Whittaker K, van Camp S, Hughes D. Effect of prazosin vs placebo on chronic left ventricular heart failure. Circulation. 1979;59(2):344–50.

41. Hjalmarson A, Goldstein S, Fagerberg B, Wedel H, Waagstein F, Kjekshus J, et al. Effects of controlled-release metoprolol on total mortality, hospitalizations, and well-being in patients with heart failure: the Metoprolol CR/XL Randomized Intervention Trial in congestive heart failure (MERIT-HF). JAMA. 2000;283(10):1295–302.

42. Packer M, Coats A, Fowler M, Katus H, Krum H, Mohacsi P, et al. Effect of carvedilol on survival in severe chronic heart failure. N Engl J Med. 2001;344(22):1651–8.

43. MERIT-HF Study Group. Effect of metoprolol CR/XL in chronic heart failure: Metoprolol CR/XL Randomised Intervention Trial in Congestive Heart Failure (MERIT-HF). Lancet. 1999;353(9169):2001–7.

44. CIBIS-II Investigators and Committees. The Cardiac Insufficiency Bisoprolol Study II (CIBIS-II): a randomised trial. Lancet. 1999;353(9146):9–13.

45. Flather M, Shibata M, Coats A, van Veldhuisen D, Parkhomenko A, Borbola J, et al. Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure (SENIORS). Eur Heart J. 2005;26(3):215–25.

46. Chen P, Chaugai S, Zhao F, Wang D. Cardioprotective Effect of Thiazide-Like Diuretics: A Meta-Analysis. Am J Hypertens. 2015;28(12):1453–63.

47. Poulter N, Williams B. Doxazosin for the management of hypertension: implications of the findings of the ALLHAT trial. Am J Hypertens. 2001;14(11 Pt 1):1170–2.

48. SHEP Cooperative Research Group. Prevention of stroke by antihypertensive drug treatment in older persons with isolated systolic hypertension. Final results of the Systolic Hypertension in the Elderly Program (SHEP). JAMA. 1991;265(24):3255–64.

49. Kjeldsen S. Warning for antihypertensive drug? Lancet. 2001;358(9288):1181–2.

50. Davis B, Cutler J, Furberg C, Wright J, Farber M, Felicetta J, et al. Relationship of antihypertensive treatment regimens and change in blood pressure to risk for heart failure in hypertensive patients randomly assigned to doxazosin or chlorthalidone: further analyses from the Antihypertensive and Lipid-Lowering treatment t. Ann Intern Med. 2002;137(5 Pt 1):313–20.

51. Messerli FH. Implications of discontinuation of doxazosin arm of ALLHAT. Lancet. 2000;355(9207):863–4.

52. Mills C, Govoni V, Faconti L, Casagrande M-L, Morant S, Crickmore H, et al. A randomised, factorial trial to reduce arterial stiffness independently of blood pressure: Proof of concept? The VaSera trial testing dietary nitrate and spironolactone. Br J Clin Pharmacol. 2020;86(5):891–902.

53. Kazzam E, Ghurbana B, Obineche E, Nicholls M. Hypertension-still an important cause of heart failure? J Hum Hypertens. 2005;19(4):267–75.

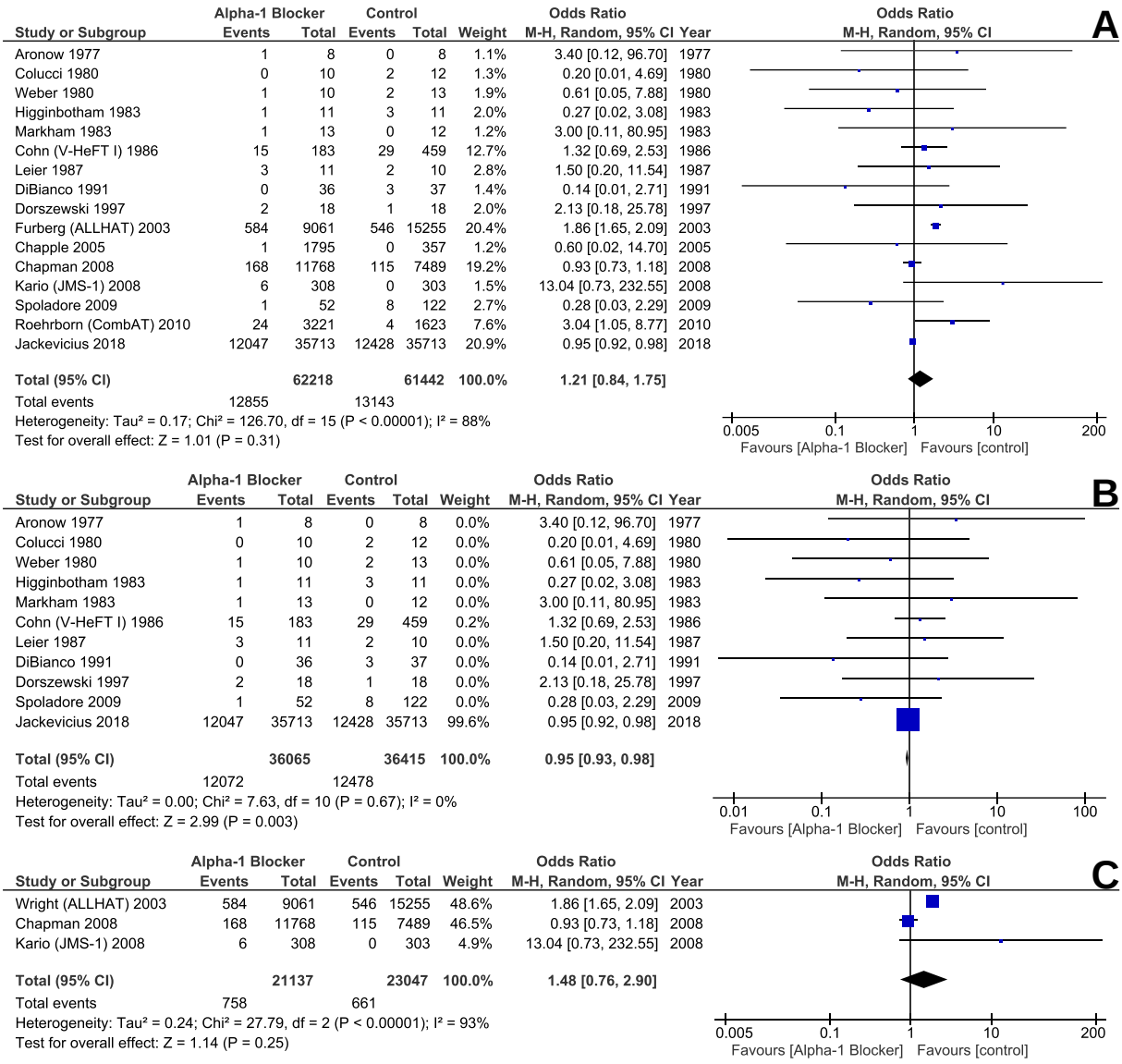
# Appendices

| **PubMed Search** | | **Date: 29/11/2020** |
|---|---|---|
| **#1** | Search: **("Adrenergic alpha-Antagonists"[Mesh] OR "Adrenergic alpha Receptor Antagonists" OR "alpha-Adrenergic Receptor Blockaders" OR "alpha Adrenoceptor Blockade" OR "Adrenergic alpha-Blockers" OR "alpha-Adrenergic Blocking Agents" OR "alpha-Adrenoceptor Blocking Agents" OR "Doxazosin"[Mesh] OR "Tamsulosin"[Mesh] OR "Terazosin" OR "Alfuzosin" OR "Silodosin" OR "Prazosin"[Mesh] OR "Indoramin"[Mesh] OR "Urapidil" OR "Naftopidil" OR "Trimazosin" OR "Bunazosin") AND ("Heart Failure"[Mesh] OR "Cardiac Failure" OR "Myocardial Failure" OR "Heart Decompensation" OR "Cardiac Decompensation" OR "Myocardial Decompensation" OR "Heart Insufficiency" OR "Cardiac Insufficiency" OR "Myocardial Insufficiency")** Filters: **Clinical Study, Clinical Trial, Clinical Trial Protocol, Clinical Trial, Phase I, Clinical Trial, Phase II, Clinical Trial, Phase III, Clinical Trial, Phase IV, Comparative Study, Controlled Clinical Trial, Journal Article, Letter, Multicenter Study, Observational Study, Pragmatic Clinical Trial, Randomized Controlled Trial, Humans, English, Portuguese, Spanish, MEDLINE** Sort by: **Publication Date** | **424** |

| **Cochrane Central Register of Controlled Trials Search** | | **Date: 29/11/2020** |
|---|---|---|
| **#1** | **("Adrenergic alpha-Antagonists" OR "Adrenergic alpha Receptor Antagonists" OR "alpha-Adrenergic Receptor Blockaders" OR "alpha Adrenoceptor Blockade" OR "Adrenergic alpha-Blockers" OR "alpha-Adrenergic Blocking Agents" OR "alpha-Adrenoceptor Blocking Agents" OR "Doxazosin" OR "Tamsulosin" OR "Terazosin" OR "Alfuzosin" OR "Silodosin" OR "Prazosin" OR "Indoramin" OR "Urapidil" OR "Naftopidil" OR "Trimazosin" OR "Bunazosin") AND ("Heart Failure" OR "Cardiac Failure" OR "Myocardial Failure" OR "Heart Decompensation" OR "Cardiac Decompensation" OR "Myocardial Decompensation" OR "Heart Insufficiency" OR "Cardiac Insufficiency" OR "Myocardial Insufficiency") in All Text** | **203** |

| **Web of Science Core Collection Search** | | **Date: 29/11/2020** |
|---|---|---|
| **#1** | **ALL FIELDS:** (("Adrenergic alpha-Antagonists" OR "Adrenergic alpha Receptor Antagonists" OR "alpha-Adrenergic Receptor Blockaders" OR "alpha Adrenoceptor Blockade" OR "Adrenergic alpha-Blockers" OR "alpha-Adrenergic Blocking Agents" OR "alpha-Adrenoceptor Blocking Agents" OR "Doxazosin" OR "Tamsulosin" OR "Terazosin" OR "Alfuzosin" OR "Silodosin" OR "Prazosin" OR "Indoramin" OR "Urapidil" OR "Naftopidil" OR "Trimazosin" OR "Bunazosin") AND ("Heart Failure" OR "Cardiac Failure" OR "Myocardial Failure" OR "Heart Decompensation" OR "Cardiac Decompensation" OR "Myocardial Decompensation" OR "Heart Insufficiency" OR "Cardiac Insufficiency" OR "Myocardial Insufficiency")) **Refined by: LANGUAGES:** ( ENGLISH OR SPANISH ) AND **DOCUMENT TYPES:** ( ARTICLE OR PROCEEDINGS PAPER OR LETTER OR EARLY ACCESS ) **Timespan:** All years. **Indexes:** SCI-EXPANDED, SSCI, A&HCI, CPCI-S, CPCI-SSH, BKCI-S, BKCI-SSH, ESCI, CCR-EXPANDED, IC. | **403** |

Appendix I – Search Equation.

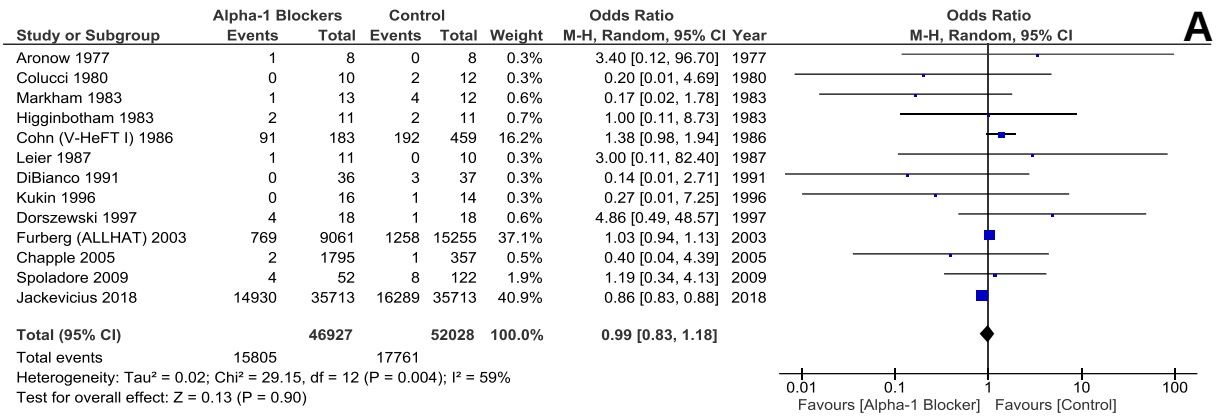


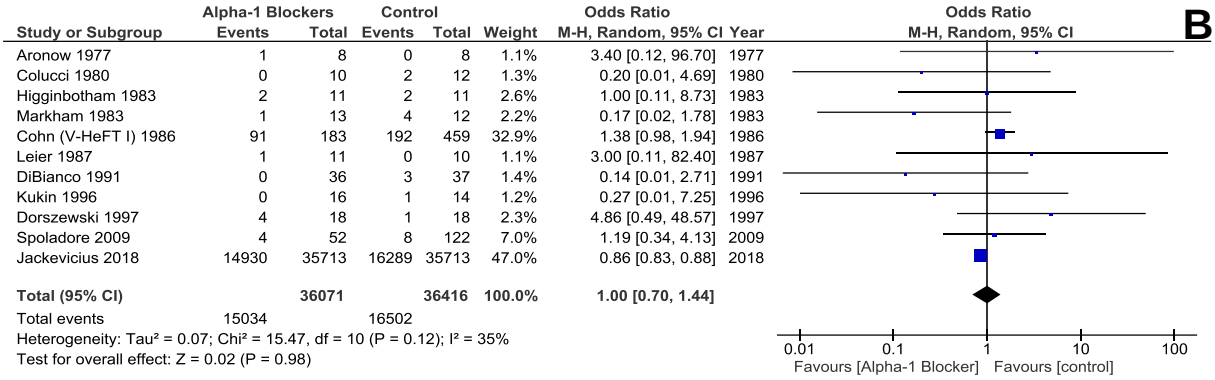

Appendix II – AHF events – All study designs:

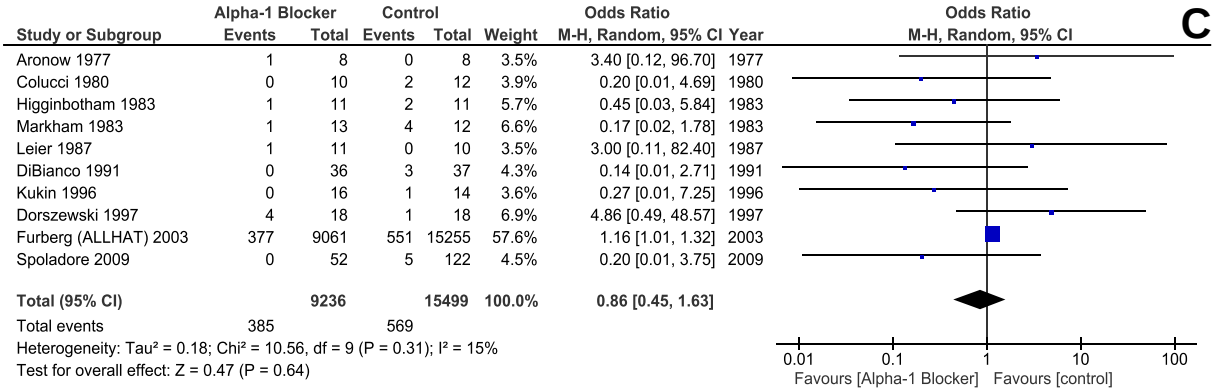
A – Unselected patients; B – CHF patients; C - AHT patients.

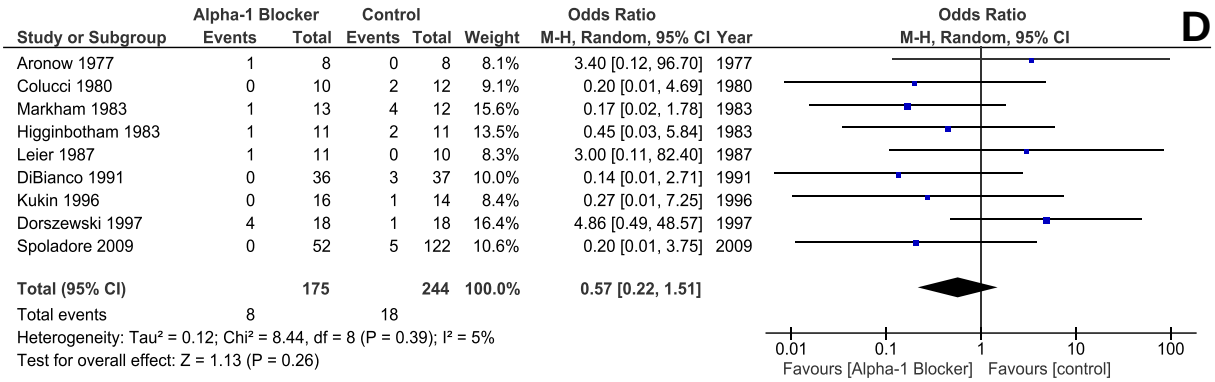
AHF acute heart failure; CHF chronic heart failure; AHT arterial hypertension.

Note: In the retrospective cohort by Spoladore and co-workers[32] there were two deaths attributed to and nine readmissions explained by AHF, even though it was not clearly stated that the two deceased patients were, in fact, included in the rehospitalized subgroup. We assumed, for analysis purposes, that these two patients were, indeed, among those nine readmitted to hospital.



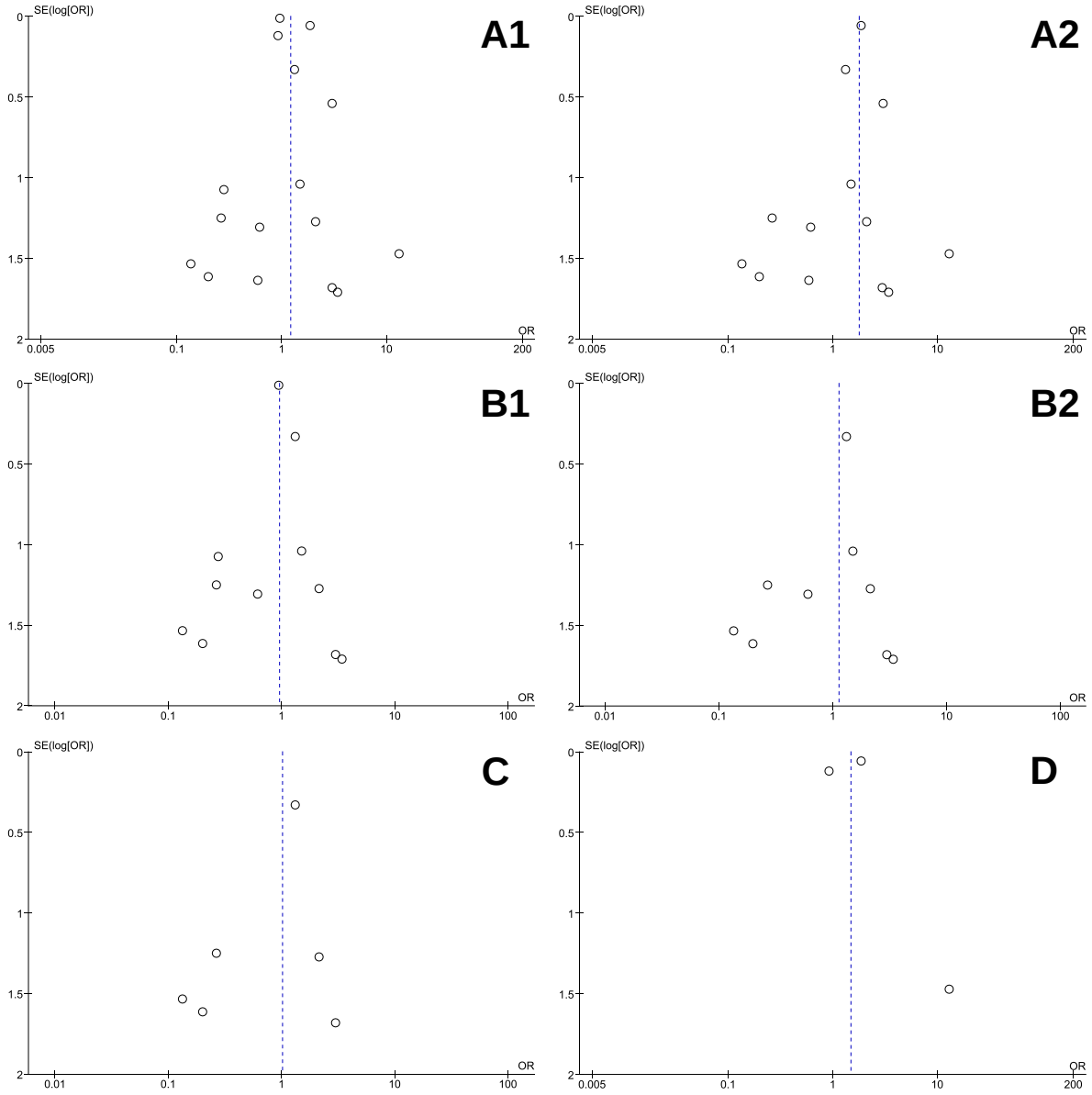




Appendix III – Mortality – All study designs:

**All-cause mortality**: A – Unselected patients; B – CHF patients;

**CV mortality**: C – Unselected patients; D – CHF patients.

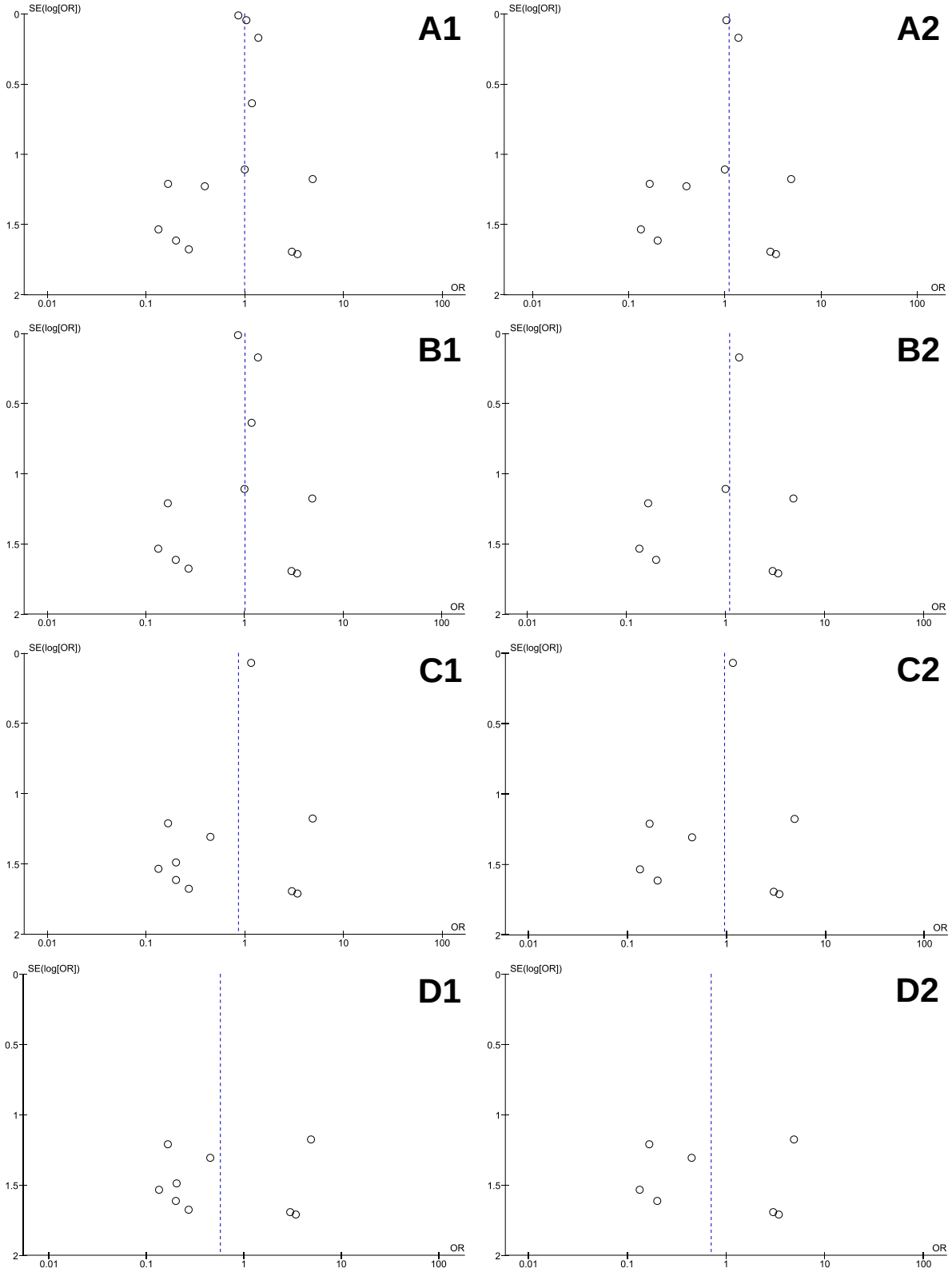
CHF chronic heart failure; CV cardiovascular.




*Appendix* IV – AHF events – Funnel plot:

Unselected patients (A): A1- All study designs, A2- RCTs; CHF patients (B): B1- All study designs, B2- RCTs; HFrEF patients (C) – RCTs; AHT patients (D) - All study designs.

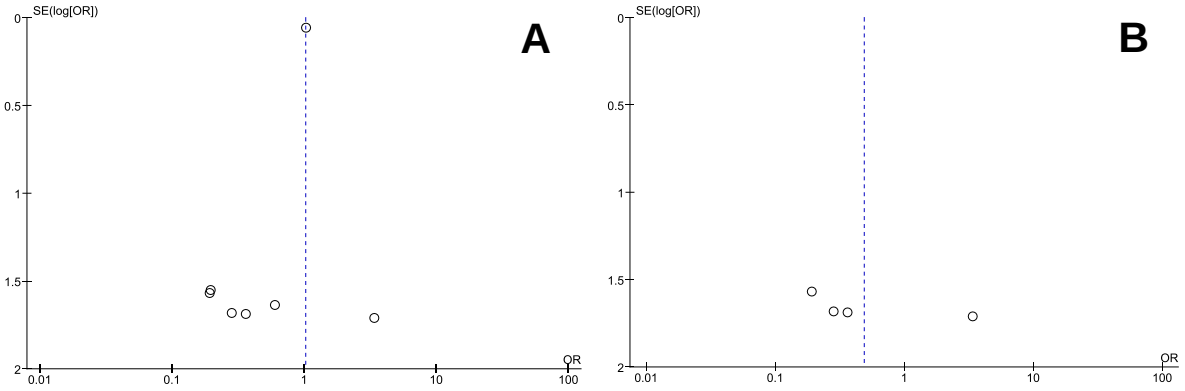
AHF acute heart failure; RCTs randomized controlled trials; CHF chronic heart failure; HFrEF heart failure with reduced ejection fraction; AHT arterial hypertension.




*Appendix* V – Mortality – Funnel plot:

**All-cause mortality** – Unselected patients (A): A1 - All study designs, A2 - RCTs; CHF patients (B): B1 - All study designs, B2 – RCTs; **CV mortality** – Unselected patients (C): C1 - All study designs; C2 – RCTs; CHF patients (D): D1 – All study designs, D2 – RCTs.

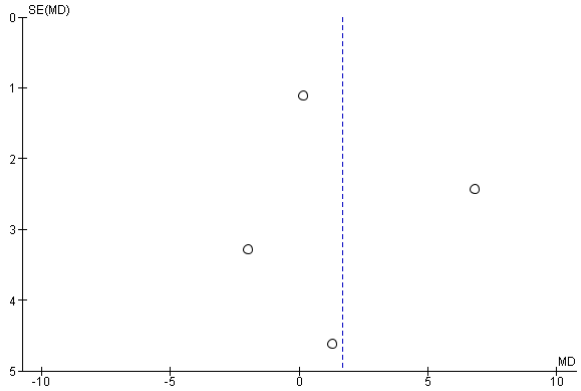
RCTs randomized controlled trials; CHF chronic heart failure; CV cardiovascular.




*Appendix* VI – ACS events – Funnel plot:

Unselected patients (A) - RCTs; CHF patients (B) – RCTs.

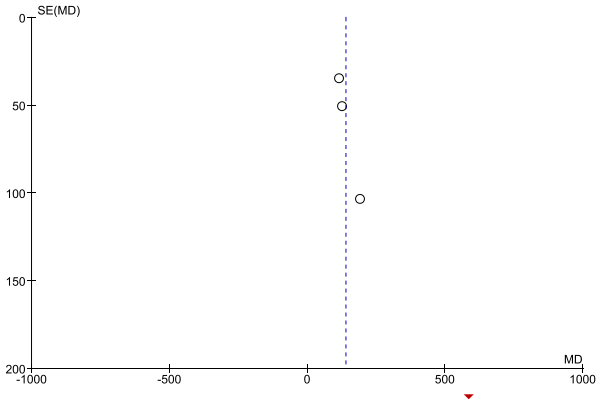
ACS acute coronary syndrome; RCTs randomized controlled trials; CHF chronic heart failure.




*Appendix* VII - LVEF change from baseline – Funnel plot:

Unselected patients - All study designs.

LVEF left ventricular ejection fraction.




*Appendix* VIII - ED change from baseline – Funnel plot:

Unselected patients - All study designs.

ED exercise duration.