Personalized Treatment of Heart Failure with Reduced Ejection Fraction: Ivabradine, Nitrate/Hydralazine, and Digoxin – A Systematic Review and Meta-Analysis

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Introduction

In the last 30 years, treatment of chronic heart failure with reduced ejection fraction (HFrEF) has evolved considerably, and a significant reduction was achieved in mortality over time and hospitalization rates for chronic heart failure (CHF).[1]

Neurohormonal blockade has become key in the treatment of CHF, but with the discovery of new therapies such as sodium-glucose cotransporter-2 inhibitors (SGLT2i), neprilysin inhibitors, resynchronization therapies, and new procedures, the number of treatment options in addition to standard therapy has increased considerably. However, it is known that the start of medications that reduce outcomes in CHF has historically been recommended following the order of publication of efficacy trials. Considering the many treatment options available today, a clinical question arises: is it possible to personalize additional treatments according to the patient's clinical characteristics? This meta-analysis aims to look for populations of interest where ivabradine, hydralazine and nitrate, and digoxin could have incremental beneficial effects.

Methods

This work aimed to identify, evaluate, and systematically summarize the available evidence of randomized clinical trials on ivabradine, hydralazine/isosorbide dinitrate, and digoxin in adult patients with chronic HFrEF compared with placebo or optimized medication therapy regarding outcomes of total mortality, cardiovascular mortality, and hospitalization for heart failure as determined by the Core Outcomes Measures in Effectiveness Trials; we searched for populations of interest where these drugs seemed to have better effectiveness.

Inclusion criteria

- Adults over 18 years old;
- Patients with HFrEF of any etiology;
- Randomized clinical trials;
- Subanalyses of randomized clinical trials;
- Date of publication: from 2012 on, due to the publication of studies on the effectivity of ivabradine;
- The original trials do not need to comply with the year of publication criterion.

Exclusion criteria

- Patients with heart failure and preserved ejection fraction, acute or decompensated heart failure;
- Pediatric population (< 18 years old);
- Observational studies, case reports, or pre-published protocols;
- Date of publication: prior to 2012, for post-hoc studies.

Search and sources of information

Our search was performed using the PubMed (Medline) and Virtual Health Library (BVS) databases using MeSH and DeCS descriptors for each drug of interest; the inclusion of studies in this review underwent peer analysis. Preference was given to research domains.

The search terms used in this review were:

- Ivabradine – using ("Heart Failure"[Mesh]) AND "Ivabradine"[Mesh] in English and "insuficiência cardíaca" AND ivabradina in Portuguese.
- Hydralazine and nitrate – using ("isosorbide-hydralazine combination" [Mesh] AND "Heart Failure"[Mesh] in English and "insuficiência cardíaca" AND hidralazina AND isossorbida in Portuguese.
- Digoxin – using ("Digoxin"[Mesh]) AND "Heart Failure"[Mesh] in English and "insuficiência cardíaca" AND digoxina in Portuguese.

Studies published in English and Portuguese were included in our research and a search for duplicates was initially performed for removing studies on both databases. In addition, data will be reported separately for each drug of interest. The original publication of each drug was added to the review for comparing relative risks; our search was performed using the Boolean operators "OR" and "AND."

Data collection

Data were collected by selecting studies that approached subgroups of interest in order to identify populations where the treatment could have a different performance than that displayed in the initial publication. The information of interest collected from each publication was reported and stored as tables.

Keywords

Heart Failure; Hydralazine; Nitrates; Digoxin.

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Risk of bias in each study

A limitation of systematic reviews lies in the risk of bias of the selected studies; in this meta-analysis, all studies were analyzed with the Cochrane risk of bias tool. The criteria used in this review were: analysis of selection bias, blinding, performance, detection bias, incomplete data, and reporting bias.

Data summarization and synthesis

In this meta-analysis, we used the Cochrane Handbook for Systematic Reviews of Interventions as guideline. For dichotomous outcomes, the results were expressed as odds ratios (ORs) with 95% confidence intervals (CIs). For continuous outcomes, data were grouped and described as weighted mean differences and 95% CIs. The heterogeneity of trial results was assessed through a standard chi-squared test with a significance of $p < 0.10$ and I^2 statistic with significance set at 50%. We used a Mantel-Haenszel random-effects model in our statistical analysis due to the large clinical and populational variability of the studies. Publication bias was assessed through a funnel plot. All analyses used Review Manager version 5.0 (Revman, Cochrane, Oxford, United Kingdom). p values < 0.05 were considered statistically significant. For evaluating the effect of the methodological character of studies on our results, the weight of these characteristics' components in our meta-analysis was evaluated through a sensitivity analysis.

Results

Qualitative analysis

Studies selected for assessing populations of interest were predominantly found in the search for ivabradine treatment; for this drug, all selected studies were post-hoc analyses of the original SHIFT study.

We found 207 studies in this search, which were added to 37 studies retrieved from the BVS database. We removed 131 duplicate studies. After analyzing the titles, 99 studies were selected for screening; of these, 70 were excluded after going through the inclusion and exclusion criteria. Our of the 29 remaining studies, 9 were classified after complete reading and were included in the quantitative and qualitative analyses, as shown in Figure 1.

We found 31 studies when searching for digoxin. After analyzing the titles, 16 studies were selected for screening; of these, 6 were excluded after going through the inclusion and exclusion criteria. Our of the 10 remaining studies, 3 were classified after complete reading and were included in the quantitative and qualitative analyses.

We found 16 studies when searching for the combination of hydralazine and nitrate. After analyzing the titles, 12 studies were selected for screening; of these, 9 were excluded after going through the inclusion and exclusion criteria. Our of the 3 remaining studies, 2 were classified after complete reading and were included in the quantitative analysis.

Characteristics of studies

Tables 1 and 2 summarize the characteristics of the included studies. The evaluated criteria were: sample size, percentage of male patients, inclusion criteria of each study, percentage of beta-blocker use, percentage of angiotensin-converting enzyme inhibitor (ACEI) use, percentage of diuretic use, and percentage of mineralocorticoid receptor antagonist use.

Risk of bias

All studies included in this meta-analysis were post-hoc analyses of the original SHIFT, DIG, and A-HEFT studies. The risk of selection bias was considered high in all studies, since these are trials of populations of interest; blinding bias was also considered high in all studies.

Synthesis of results

Ivabradine results

We found 9 randomized clinical trials for the composite outcome of death or hospitalization for heart failure (HF), and subpopulations of interest were: populations with Chagas disease, left bundle branch block (LBBB), advanced CHF, chronic obstructive pulmonary disease (COPD), heart rate (HR) over 77 beats per minute (bpm), who used less than 50% of the maximum beta-blocker dose, patients with diabetes, and those using carvedilol or not.

In total, the number of events for the composite outcome of death or hospitalization for HF was 2423 for the ivabradine group and 3346 for the control group; ivabradine significantly reduced the composite outcome with an OR of 0.77 ($Z = 8.32$ $p < 0.0001$ and 95% CI 0.72–0.82) and calculated heterogeneity of $I^2 = 0\%$. (Figure 2)

The number of events considering the cardiovascular death outcome was 1288 for the ivabradine group and 1727 for the control group; ivabradine significantly reduced this outcome with an OR of 0.83 ($Z = 2.91$ $p = 0.004$ and 95% CI 0.73–0.94) and calculated heterogeneity of $I^2 = 53\%$. (Figure 3)

Considering the hospitalization for CHF outcome, the number of events in the ivabradine group was 1621, in comparison with 2380 in the control group. There was a significant difference between groups, with an OR = 0.72 ($Z = 8.99$, $p = <0.00001$ and 95% CI 0.67–0.78) and calculated heterogeneity of $I^2 = 0\%$. (Figure 4)

Digoxin results

For the composite outcome of death or hospitalization for HF, we found 3 randomized clinical trials, and the study of advanced HF was added twice due to information related to patients with New York Heart Association (NYHA) class III and IV HF and ejection fraction < 25%.

In total, the number of events for the composite outcome of death or hospitalization for HF was 1495 for the digoxin group and 1748 for the control group; digoxin significantly reduced the composite outcome with an OR of 0.76 ($Z = 2.41$ $p < 0.02$ and 95% CI 0.61–0.95) and calculated heterogeneity of $I^2 = 81\%$. (Figure 5)

For the cardiovascular death outcome, the number of events was 2029 in the digoxin group and 1998 in the control group, with no significant difference between groups OR =

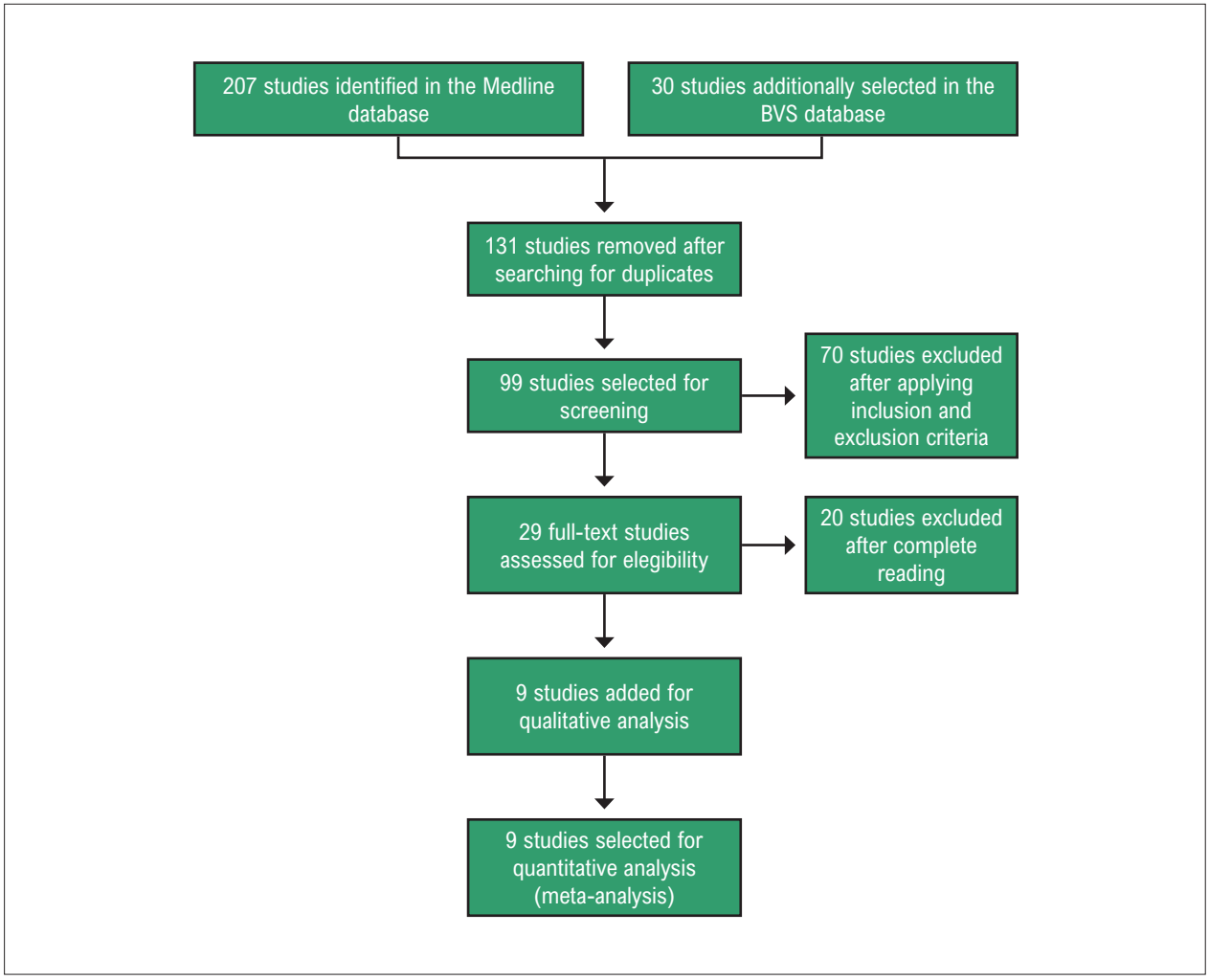

Figure 1 – *PRISMA flow diagram for the selection of studies on ivabradine.*

1.02 (Z = 0.57 p = 0.57 and 95% CI 0.95–1.10) and calculated heterogeneity of I^2 = 0%. The original study (DIG Trial) was included in this analysis. (Figure 6)

For the hospitalization for CHF outcome, the number of events in the digoxin group was 1936, in comparison with 2547 in the control group. There was a significant difference between groups, with an OR = 0.67 (Z = 7.47, p < 0.00001 and 95% CI 0.60–0.74) and calculated heterogeneity of I^2 = 47%. The original study (DIG Trial) was included in this analysis. (Figure 7)

Hydralazine/nitrate results

We found 2 populations of interest for the study of the outcomes of this drug combination: patients with atrial fibrillation and patients aged 65 years or older. The weight of these studies was small in comparison with the original A-HEFT study included in the analysis, thus our results may have been influenced by the greater number of patients in the original study.

The total number of events for the composite outcome of death or hospitalization for HF was 235 for the hydralazine/nitrate group and 324 for the control group; the combination of hydralazine and nitrate significantly reduced the composite outcome with an OR of 0.62 (Z = 4.49 p < 0.0001 and 95% CI 0.50–0.76) and calculated heterogeneity of I^2 = 0%. (Figure 8)

For the cardiovascular death outcome, the number of events was 47 in the hydralazine/nitrate group and 84 in the control group; the combination of hydralazine and nitrate significantly reduced the composite outcome with an OR of 0.54 (Z = 3.22 p < 0.001 and 95% CI 0.37–0.79) and calculated heterogeneity of I^2 = 0%. (Figure 9)

For the hospitalization for CHF outcome, the number of events in the hydralazine/nitrate group was 148, as opposed to 218 in the control group, with a significant difference between groups: OR = 0.62 (Z = 4.0, p = < 0.0001 and 95% CI 0.49–0.78) and calculated heterogeneity I^2 = 47%. The original study (A-HEFT Trial) was included in this analysis. (Figure 10)

Discussion and limitations

We performed a meta-analysis of post-hoc studies of randomized trials, searching for subpopulations of interest

Table 1 – Characteristics of the selected studies

Trial (reference)	Sample size (n)	Mean age	Male (%)	Inclusion criteria
Bouabdallaoui et al.[2]	1657	59.5 ± 11	66	HFrEF < 35%, NYHA II–IV, with HR > 77 bpm, sinus rhythm despite maximum tolerated beta-blocker dose.
Bocchi et al.[3]	20	62 ± 11	65	HFrEF < 35%, NYHA II–IV, with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose. Patients with Chagas disease.
Komajda et al.[4]	1979	62 ± 9.8	75	HFrEF < 35%, NYHA II–IV, with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose. Patients with diabetes.
Bocchi et al.[5]	1318	59.3 ± 11	77	HFrEF < 35%, NYHA II–IV, with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose. Patients using carvedilol.
Borer et al.[6]	712	60 ± 12.2	77	NYHA IV HFrEF or EF < 20% with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose.
Tavazzi L et al.[7]	730	65.2 ± 9.5	81	HFrEF < 35%, NYHA II–IV, with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose. Patients with COPD.
Reil et al.[8]	912	62 ± 10.6	69	HFrEF < 35%, NYHA II–IV, with HR > 70 bpm, sinus rhythm despite maximum tolerated beta-blocker dose. Patients with LBBB.
Swedberg K et al.[9]	1624	60 ± 11.5	77.2	HFrEF < 35%, NYHA II–IV, with HR < 70 bpm, sinus rhythm beta-blocker dose.
Mihai Gheorghiade et al.[10]	1118	65 ± 11	81	Patients with EF < 25% and HF diagnosis.
Mihai Gheorghiade et al.[11]	1127	63 ± 11	73	Patients with EF < 45% with a diagnosis of NYHA III and IV HF.
Azimil Abdul-Rahim et al.[12]	1195	64 ± 10.6	71.1	Patients with EF < 45% were enrolled in an auxiliary study performed in parallel with the main trial.
Azimil Abdul-Rahim et al.[13]	1933	64.2	73.6	Patients with diabetes, EF ≤ 45%, and sinus rhythm. HF diagnosis was based on current or past clinical symptoms (activity limitation, fatigue and dyspnea or orthopnea), signs (edema, elevated jugular venous pressure, stertor, or gallop rhythm), or radiological evidence of pulmonary congestion.
Mitchell JE et al.[14]	183	61 ± 12	68	NYHA class III or IV for at least 3 months – subpopulation with AF. Evidence of left ventricular dysfunction in the 6 months prior to randomization and EF < 35% or rest EF < 45% with LVEDD < 2.9 cm/m^2 of body surface area or > 6.5 cm at echocardiography.
Taylor AL et al.[15]	157	72 ± 5.7	52	NYHA III or IV for at least 3 months – subpopulation aged 65 years and older. Evidence of left ventricular dysfunction in the 6 months prior to randomization and EF < 35% or rest EF < 45% with LVEDD < 2.9 cm/m^2 of body surface area or > 6.5 cm at echocardiography.
Taylor AL et al.[16]	1050	56 ± 12.7	55.8	Afro-descendants with NYHA class III or IV HF for at least 3 months – evidence of left ventricular dysfunction in the 6 months prior to randomization and EF < 35% or rest EF < 45% with LVEDD < 2.9 cm/m^2 of body surface area or > 6.5 cm at echocardiography.

HFrEF: heart failure with reduced ejection fraction; NYHA: New York Heart Association; HR: heart rate; EF: ejection fraction; AF: atrial fibrillation; COPD: chronic obstructive pulmonary disease; LBBB: left bundle branch block; LVEDD: left ventricular end-diastolic diameter.

Table 2 – Characteristics of the selected studies

Trial (reference)	Beta-blocker use (%)	ACEI use (%)	Diuretic use (%)	Spironolactone use (%)
Bouabdallaoui, Nadia et al.[2]	86.1	89.7	---	63.1
Bocchi et al.[3]	90	56	94	83
Komadja et al.[4]	90	91	86	---
Bocchi et al.[5]	100	77	88	70
Borer et al.[6]	87	78	90	---
Tavazzi L et al.[7]	68	80	91	---
Reil et al.[8]	89.9	77	90.6	---
Swedberg K et al.[9]	100	78.6	82.1	62.1
Mihai Gheorghiade et al.[10]	---	95	88	---
Mihai Gheorghiade et al.[11]	---	95	84	---
Azimil Abdul-Rahim et al.[12]	---	90.5	70.4	7.6
Azimil Abdul-Rahim et al.[13]	---	94.9	84.7	7.8
Mitchell JE et al.[14]	83	89	94	38
Taylor AL et al.[15]	76.4	63.7	89.2	37.6
Taylor AL et al.[16]	74.1	69.4	88	40.2

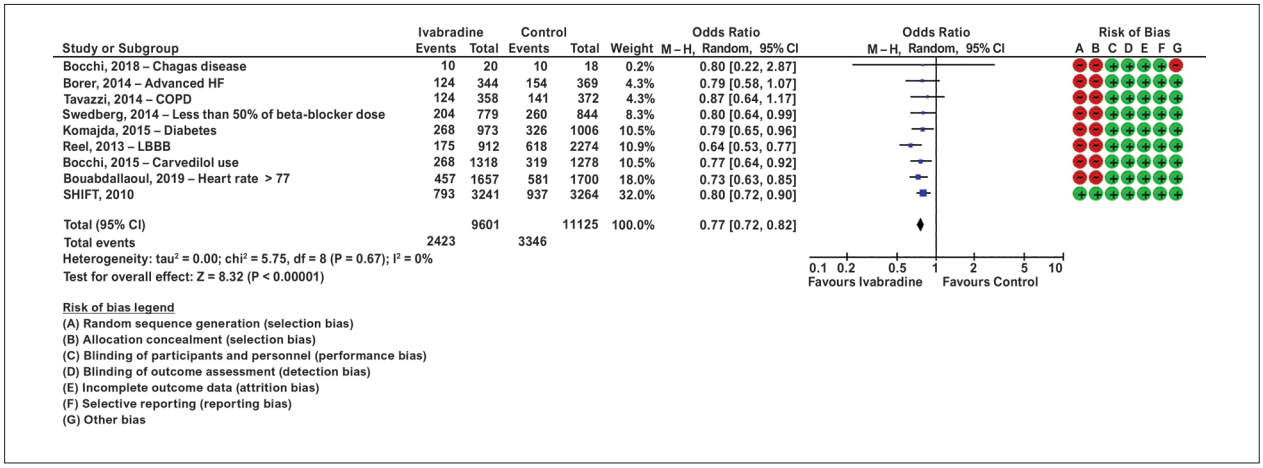

Figure 2 – *Forest plot for the composite outcome of death and hospitalization regarding ivabradine and analysis of study bias. M-H: Mantel-Haenszel.*

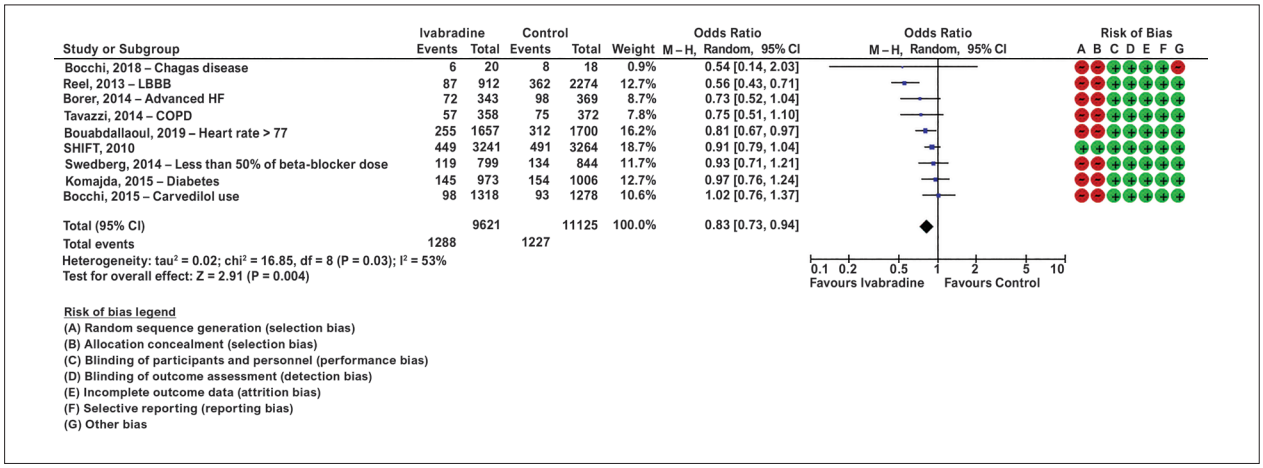

Figure 3 – *Forest plot for the cardiovascular death outcome regarding ivabradine and analysis of study bias. M-H: Mantel-Haenszel.*

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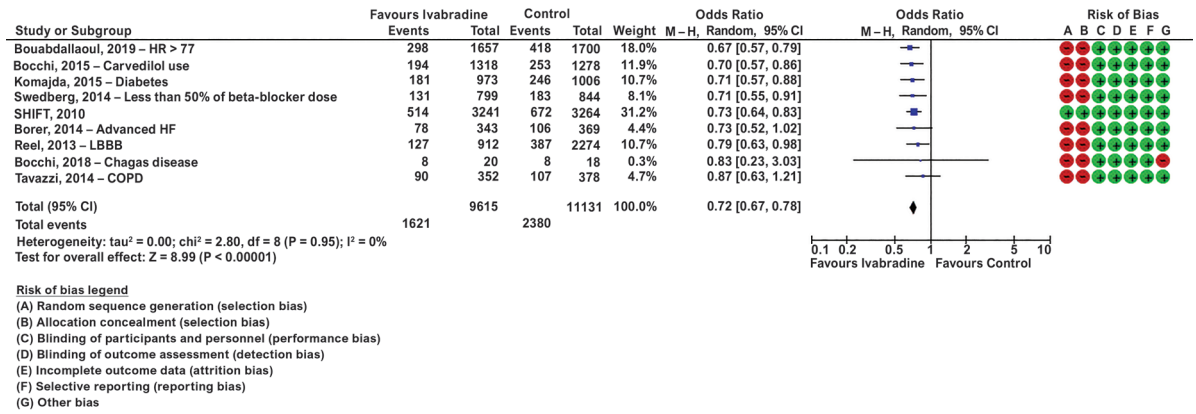

Figure 4 – *Forest plot for the composite outcome of hospitalization for CHF regarding ivabradine and analysis of study bias. M-H: Mantel-Haenszel.*

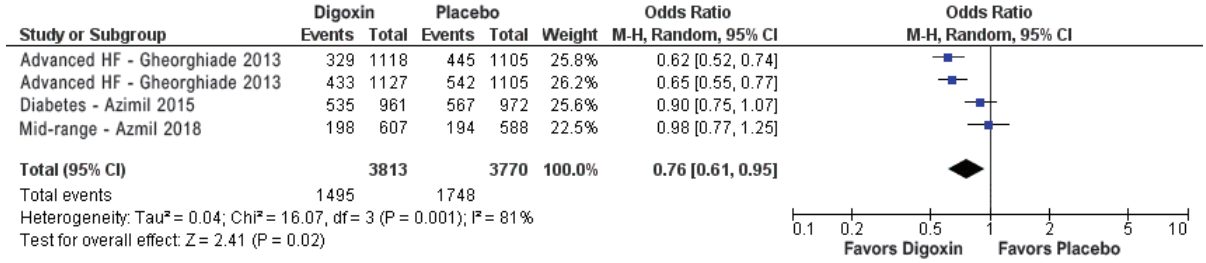

Figure 5 – *Forest plot for the composite outcome regarding digoxin. M-H: Mantel-Haenszel.*

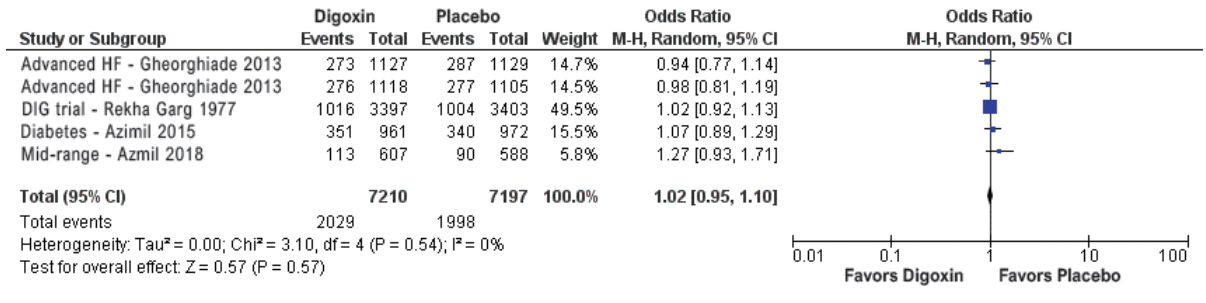

Figure 6 – *Forest plot for the cardiovascular death outcome regarding digoxin. M-H: Mantel-Haenszel.*

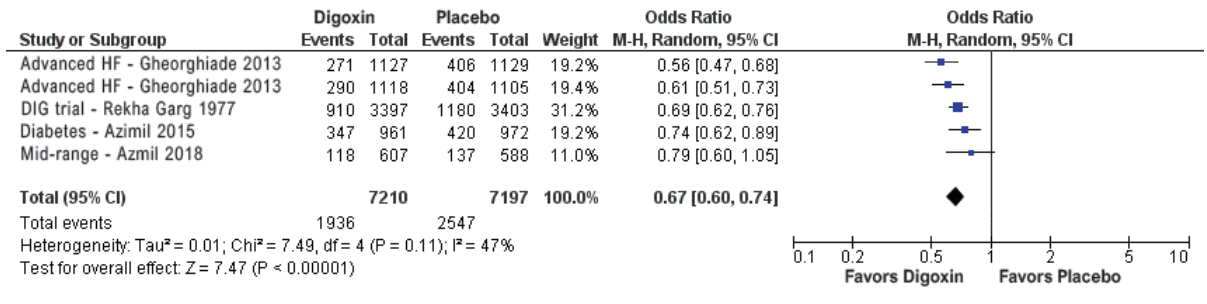

Figure 7 – *Forest plot for the outcome of hospitalization for HF regarding digoxin. M-H: Mantel-Haenszel.*

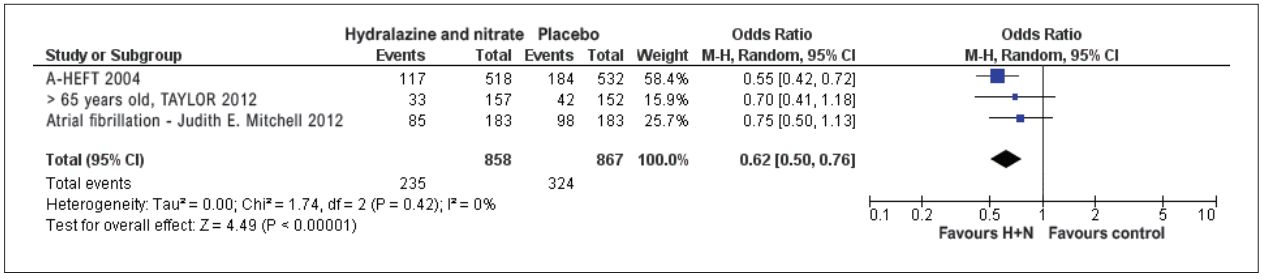

Figure 8 – *Forest plot for the composite outcome regarding the combination of hydralazine and nitrate. M-H: Mantel-Haenszel.*

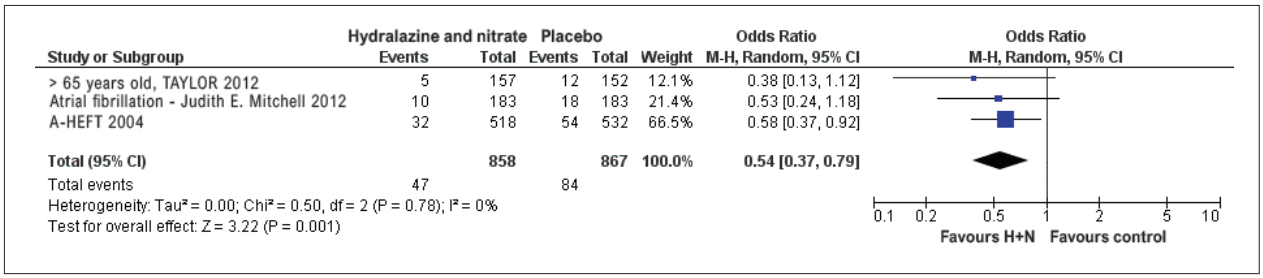

Figure 9 – *Forest plot for the cardiovascular death outcome regarding the combination of hydralazine and nitrate. M-H: Mantel-Haenszel.*

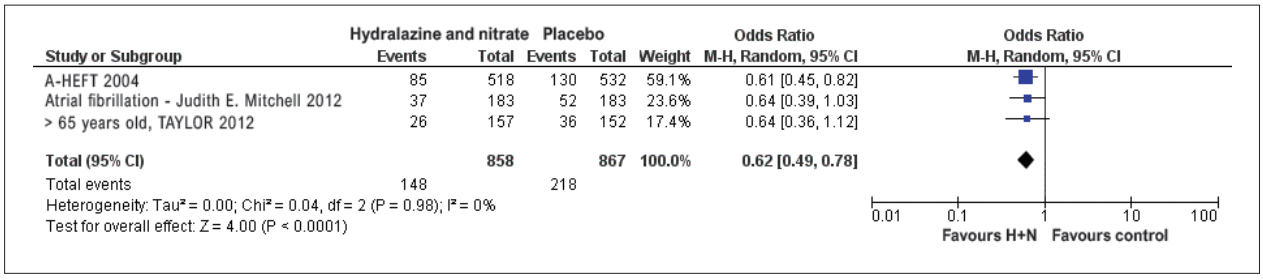

Figure 10 – *Forest plot for the outcome of hospitalization for HF regarding the combination of hydralazine and nitrate. M-H: Mantel-Haenszel.*

where the drugs ivabradine, hydralazine/nitrate, and digoxin could have better performances than in the general population of the initial SHIFT (ivabradine), A-HEFT (hydralazine and nitrate), and DIG (digoxin) trials. This was an attempt to find an improved manner of personalizing the current treatment of chronic HFrEF.

For the composite outcome of death or hospitalization for CHF, ivabradine had a similar effect measure in most subgroups. On the other hand, the performance of this drug was superior in patients with diabetes, those who did not tolerate more than 50% of the maximum beta-blocker dose, patients with LBBB, patients who did not use carvedilol, or those with HR over 77 bpm than in the general population. This showed a potential benefit of the medication related to the control of HR, which is an important marker of risk of death in patients with HFrEF. It is important to note that, for the cardiovascular death outcome, we found a heterogeneity > 50% among studies.

A consistent reduction was observed in the hospitalization for HF outcome in patients who used digoxin; in the population with advanced HF (patients with NYHA class III and IV HF and ejection fraction < 25%), the performance of this drug was superior than in the original study. However, when considering cardiovascular mortality, our analysis could not find a subpopulation where this medication showed benefits or a superior performance when compared to the DIG trial. The possible benefit in hospitalization found with the use of digitalis compounds in patients with advanced HF may stem from multiple mechanisms; one possible explanation is the positive inotropic mechanism of glycosides, in addition to the control of HR. On the other hand, it is important to highlight that the benefit of this treatment may have been dampened by possible side effects related to medication toxicity; safety outcomes were not assessed in this study.

For the combination of hydralazine and nitrate, beneficial effects had large CIs in both identified populations, leading to speculations regarding a possible effect of chance on our findings. However, in the afro-descendant population included in the A-HEFT trial (used for comparison), this drug combination was able to reduce the composite outcome of death and hospitalization in a consistent manner when compared to the control group, favoring this recommendation as stated by previous guidelines.

Conclusion

The aim of this meta-analysis was not to substitute the classical indications of drugs as already stated by guidelines, but instead to find subpopulations of interest; to the best of our knowledge, this search strategy is innovative.

Considering the composite outcome, the performance of ivabradine was superior in patients with diabetes, those who did not tolerate more than 50% of the maximum beta-blocker dose, patients with LBBB, those who did not use carvedilol, or those with HR over 77 bpm than in the general population. For the hospitalization outcome, the performance of digoxin was superior in the population with advanced HF (NYHA class III and IV and ejection fraction < 25%) than in the original study. Finally, for the combination of hydralazine and nitrate and composite outcome, the studied populations showed similar beneficial effects to the original study.

Author Contributions

Conception and design of the research, Writing of the manuscript and Critical revision of the manuscript for intellectual content: Lima IGCV, Bocchi EA; Acquisition of data, Analysis and interpretation of the data and Statistical analysis: Lima IGCV.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

Sources of Funding

There were no external funding sources for this study.

Study Association

This study is not associated with any thesis or dissertation work.

Ethics approval and consent to participate

This article does not contain any studies with human participants or animals performed by any of the authors.

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