Year : 2018

Optimization of stratégies of sudden cardiac death prévention in heart failure patients

Al-Gobari Muaamar

Al-Gobari Muaamar, 2018, Optimization of stratégies of sudden cardiac death prévention in heart failure patients

Originally published at : Thesis, University of Lausanne

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Document URN : urn:nbn:ch:serval-BIB_7C77538B4F647

UNIL | Université de Lausanne
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et de médecine

Centre Hospitalier Universitaire Vaudois (CHUV)
Institut Universitaire de Médecine Sociale et Préventive

Optimization of strategies of sudden cardiac death prevention in heart failure patients

Thèse de doctorat ès sciences de la vie (PhD)

Présentée à la

Faculté de biologie et de médecine
de l'Université de Lausanne

par

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Lausanne 2018

UNIL | Université de Lausanne
Faculté de biologie et de médecine

Ecole Doctorale
Doctorat ès sciences de la vie

Imprimatur

Vu le rapport présenté par le jury d'examen, composé de

Président·e	Monsieur	Prof. Charles	**Benaim**
Directeur·trice de thèse	Monsieur	Prof. Bernard	**Burnand**
Co-directeur·trice	Monsieur	Prof. François	**Gueyffier**
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le Conseil de Faculté autorise l'impression de la thèse de

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intitulée

Optimization of strategies of sudden cardiac death prevention in heart failure patients

Lausanne, le 19 juillet 2018

pour le Doyen
de la Faculté de biologie et de médecine

Prof. Charles Benaim

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DEDICATION

To my wife (Afrah), parents and all family members for their patience, encouragement, and support.

ACKOWLEDGMENTS

I would like to express my deepest gratitude to my doctoral thesis director, **Prof. Bernard Burnand**, for his not only supervision/mentorship (even in weekends), projects administration, or financial assistance, but also for his availability in busy days, ethical values, and sense of responsibility. A million of thanks goes to my Master thesis director and doctoral thesis co-director, **Prof. François Gueyffier**, who opened the door for me to start my postgraduate studies, who scientifically contributed to every aspect of my academic achievements, not to mention his encouragement, mentorship, and thoughtful and novel ideas. I take this occasion to thank the thesis committee members, namely, **Prof. Charles Benaim** (President), **Prof. Roger Hullin** (expert), **and Prof. Pablo Perel** (expert), who gave me a useful feedback and instructions in my mid-thesis exam and for the time they offered throughout the thesis period. I cannot forget to thank **Dr. Abdullah Al-Osaimi** who inspired me and paved my way for epidemiology (the story of John Snow with Cholera infection determinants in London) and public health issues during my 4th year as a pharmacy student. I am also grateful to **Dr. Patrick Taffé**, with whom I discussed many scientific issues and statistical methods and modeling within my or his own projects and for his occasional feedbacks during my PhD projects. My sincerest thanks go to my colleagues and friends, namely, **Dr. Emilie Zuercher, Dr. Emilie Bovet, Ms. Tania Carron, Ms. Chantal Arditi, Ms. Carla Vaucher**, **Ms. Julia Miéville,** for their exchanges, occasional help, and suitable working environment. My gratitude is deserved to **Dr. Marie-Annick Le Pogam,** who get me familiar with PhD studentship, Swiss School of public health (SSPH+) regulations, and academic requirements, in addition to being a very encouraging and most friendly person I met in my working place. With my gratitude for discussions and friendships, I mention the following colleagues: **Mr. Aziz Chaouch**, **Dr. Nadia Danon-Hersch, Prof. Marc Dusheiko,** and for scientific contributions and authorships to, **Prof. Nathalie Thilly**, **Dr. Hai-Ha Le, Mr. Mor Fall, and Prof. Sinaa Al-Aqeel.** I thankfully acknowledge the Swiss Government Excellence scholarship program (n° 2014.0193) and DUMSC (UES) for their financial support. I would like to extend my gratitude to **Dr. Erik von Elm (**for being part of Cochrane Switzerland and for his advices and help during my PhD or future career plans), to **Prof. Pascal Bovet** (for e-mail exchanges, feedbacks and discussion), to **Prof. Gabriel Rada** (for author correspondences replies), to **Dr. Michael Amiguet** (for a statistical help in my first year), to **Mr. Thomas Brauchli, Ms. Chantal Petoud Dei Rossi and Ms. Cécile Jaques** (for their help in library issues and requests; books, journals, literature search…etc.), to my teaching professors and doctors, and, of course, to our secretary office and administration, **Ms. Nathalie Rouge, Ms. Janine Carroscosa, Ms. Lucienne Boujon**, and **Ms. Katja Weigl**, to name a few. Finally, I would like to thank all persons whom I may have forgotten to namely mention and to all those who contributed in any way to this work.

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LIST OF ABBREVIATIONS

AADs: anti-arrhythmic drugs

AAs: anti-aldosterone agents

ACE-i: angiotensin-converting enzyme inhibitors

AMSTAR: a Measurement Tool for the Assessment of Multiple Systematic Reviews

ARB: angiotensin receptor blocker

BB: beta-blocker

CRT: cardiac resynchronization therapy

DUMSC: Département universitaire de médecine et santé communautaires

ESC: the European society of cardiology

GRADE: Grading of Recommendations Assessment, Development and Evaluation

HF: heart failure

HFmrEF: heart failure with mildly reduced ejection fraction

HFpEF: heart failure with preserved ejection fraction

HFrEF: heart failure with reduced ejection fraction

ICD: implantable cardioverter defibrillator

PROSPERO: international prospective register of systematic reviews

PUFA: omega-3 polyunsaturated fatty acids

RCT: randomized controlled trials

SCD: sudden cardiac death

UES: unité d’évaluation de soins (Healthcare evaluation unit)

ABSTRACT

Heart failure (HF) causes high mortality and morbidity of whom at least 50% die suddenly, termed sudden cardiac death (SCD). HF is an independent risk factor of SCD and its incidence are comparable to the total incidence of common cancers (i.e., lung, prostate, breast, colon). Current preventive strategies are suboptimal and there is a growing need to optimize treatment to further improve the actual poor survival. In fact, HF patients are usually put under a polydrug regimen (e.g., beta-blockers (BB), angiotensin-converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARBs), aldosterone antagonists, diuretics, hydralazine/isorbide di-nitrate, ivabradine, digoxin, amiodarone and anti-arrhythmic agents (AADs), omega-3 polyunsaturated fatty acids (PUFA)…etc.) in addition to non-drug devices (e.g., cardiac resynchronization therapy (CRT) and implantable cardioverter defibrillators (ICD)). Importantly, it is known that *not* all HF evidence-based drugs reduce SCDs or all-cause mortality. Therefore, we reviewed the current evidence on SCD prevention for commonly prescribed drug interventions; and our findings showed three evidence categories:

- **effective interventions** as BB, anti-aldosterone agents or mineralocorticoid-receptor antagonists, and combined ARB/neprilysin inhibitors.
- **ineffective interventions** as ACE-i, ARBs, and statins.
- **uncertain evidence** (conflicting or inconclusive evidence) as amiodarone & AADs, PUFA or fish oil supplementation.

We used a variety of evidence-based medicine methodology: systematic reviews and meta-analysis, overviews, survival analysis, statistical models such as Cox proportional hazards model, Kaplan-Meier survival curves, propensity score analysis and instrumental variables approaches. Through adopting effective drugs, our work allowed paving the way toward an optimization of SCD prevention strategies in HF that would finally lead to a better survival and quality of life and a potential reduction of public health expenditure.

Keywords: sudden cardiac death, heart failure, evidence-based medicine, drugs, prevention

RÉSUMÉ

L'insuffisance cardiaque (IC) entraîne une morbidité et une mortalité élevées dont au moins 50% de décès surviennent subitement, appelée mort subite cardiaque (MSC). L'IC est un facteur de risque indépendant de MSC ; son incidence est comparable à l'incidence totale de cancers courants (c'est-à-dire poumon, prostate, sein, côlon). Les stratégies préventives actuelles sont sous optimales ; il est ainsi de plus en plus nécessaire d'optimiser le traitement pour améliorer la mauvaise survie actuelle. En effet, les patients souffrants d'IC sont généralement soumis à un traitement polyconsommateur (par exemple, bêtabloquants (BB), inhibiteurs de l'enzyme de conversion de l'angiotensine (IEC), antagonistes des récepteurs de l'angiotensine (ARA), antialdostérone (AA), diurétiques, hydralazine/ dinitrate d'isorbide, ivabradine, digoxine, amiodarone et autres antiarythmique, acides gras poly-insaturés oméga-3 (AGPI), etc.) en plus des dispositifs non médicamenteux (par exemple la thérapie de resynchronisation cardiaque et les défibrillateurs implantables). Il est important de savoir que les médicaments prescrits chez l'IC ne sont pas tous efficaces contre la mort subite ou la mortalité totale. Par conséquent, nous avons examiné les preuves actuelles sur la prévention de MSC par les interventions médicamenteuses couramment prescrites; nos résultats ont montré trois catégories de preuves :

- **interventions efficaces** comme BB, AA, et inhibiteurs combinés ARB/ néprilysine.
- **interventions inefficaces** comme l'IEC, les ARA et les statines.
- **preuves incertaines** (preuves contradictoires ou non concluantes) comme l'amiodarone et autres antiarythmique, les AGPI ou les suppléments en huile de poisson.

Nous avons utilisé diverses méthodologies de médecine factuelle : revues systématiques et méta-analyses, analyse de survie, modèles statistiques tels que le modèle de Cox, les courbes de survie de Kaplan-Meier, l'analyse par score de propension et la méthode de variables instrumentales. Grâce à l'adoption de médicaments efficaces, nos travaux pourraient permettre d'optimiser les stratégies de prévention des MSC chez les patients atteints d'IC, ce qui mènerait finalement à une meilleure survie et qualité de vie, et à une réduction potentielle des dépenses de santé.

Mots-clés: mort subite cardiaque, insuffisance cardiaque, médecine factuelle, médicaments, prévention

1. GENERAL INTRODUCTION

Heart failure (HF) contributes to a high a public health burden [1]. HF causes a high morbidity and substantial mortality [2]. In addition, HF is a very costly disease [3]. The incidence of HF is reported to be as high as the incidence of the four common cancers combined (i.e., lung, prostate, breast and colon) [4]. HF patients are frequently hospitalized, have reduced quality of life and highly prevalent pain, have often comorbidities, and consume healthcare constantly [5-7]. Consequently, the prognosis of HF is extremely bad and reported to be comparable to cancer with a 5-year survival rate of about 60% [8]. Moreover, it has been extensively reported that at least 50% of HF mortality is attributed to sudden cardiac death (SCD). SCD is defined as a death that occurs within 1 or 2 hours from the onset of symptoms [9] not associated with the severity of HF prognosis; indeed SCD may occur in HF patients who are clinically stable. Despite advances in therapy and management, there is still an unfilled gap and unmet needs in HF related to SCD prevention or all-cause mortality in general. A justified thought - that comes to mind - focuses on evidence-based HF therapies. In practice, the so-called evidence-based drugs and non-drug interventions are underused as observed in the Euro Heart Survey [10] (e.g., beta-blockers were prescribed only 37% and 49% for HF population and HFrEF, respectively) and - in some cases- wrongly indicated in HF patients in contrary to current guidelines [11]. In fact, clinical decisions and current practice should be based on the best available evidence and guided by the most updated guidelines. That is why it is important to distinguish effective interventions from ineffective ones. Therefore, an evaluation of the effectiveness of drug and non-drug interventions on SCD prevention is warranted (**Figure 1**), which would play a key role on the final target to optimize HF therapy to further improve the quality of life of patients and their survival.

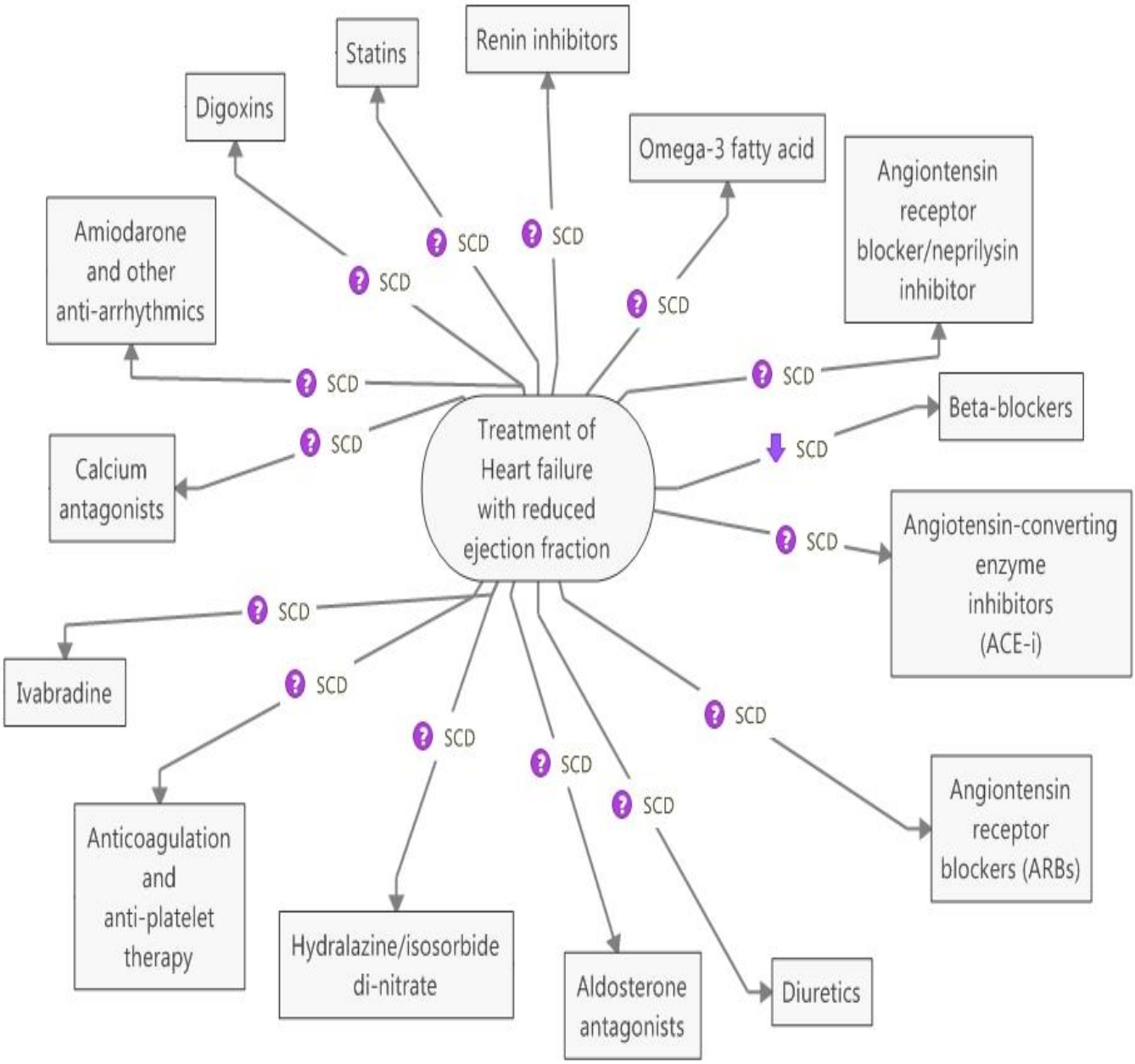


Figure 1: Effectiveness of drug interventions in heart failure with reduced ejection fraction (HFrEF).
SCD: sudden cardiac death. ?: uncertain effectiveness. ⬇: reduce or decrease

1.1.1. Definitions of heart failure and sudden cardiac death

The definition of heart failure (HF) in the current European Society of Cardiology (ESC) guideline [11] is that:

> HF is 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.

The American College of Cardiology and American Heart Association HF have introduced a staging system. (Stage A) and (Stage B) are asymptomatic patients with clinical risk factors for HF without or with an evidence of cardiac structural and functional abnormalities, respectively. Patients with current or previous symptoms of HF are defined as (Stage C) while (Stage D) patients are those with refractory symptoms despite optimal medical therapy or specialized cardiac support [12]. Moreover, the patient's true functional capacity is estimated by the New York Heart Association (NYHA) functional class (see **Table 1**) [13]

Table 1: The New York Heart Association functional classification (NYHA)

Class	New York Heart Association functional classification
I	Patients have no limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea (shortnesss of breath) or anginal pain.
II	Patients have slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea or anginal pain.
III	Patients have a marked limitation of physical activity. They are comfortable at rest. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or anginal pain.
IV	Patients are unable to carry on any physical activity without discomfort. Symptoms of HF may be present even at rest. If any physical activity is undertaken, discomfort increases.

Mortality in HF are mainly due to two types of causes:

1. progressive HF (pump failure)
2. unexpected death termed sudden cardiac death (SCD).

The former occurs more likely in IV-stage HF while the latter occurs in II-III stage HF whose life expectancy is relatively longer.

The definition of SCD varies from one source to another. SCD has been defined as “natural death due to cardiac causes, heralded by abrupt loss of consciousness within one hour of the onset of acute symptoms; pre-existing heart disease may have been known to be present, but the time and mode of death are unexpected” [14]. The time interval between sudden death occurrence and the onset of symptoms lies preferably within 1 hour instead of “6 or 24 hours” period [15]. This definition variation has an impact not only on the prevalence and incidence of SCD but also on the evaluation of medical interventions that estimate survival. Of note, sudden death occurring in infancy is a different issue and is neither presented, nor studied here.

1.1.2. Epidemiology and risk factors

The prevalence of heart or circulation problems in fourteen European countries is reported around 9.2% overall [16]. For instance, 7.6 % in France, 7.0 % in Switzerland, 12.8% in Germany, 10% in Austria. However, heart failure (HF) prevalence varies

depending on the definition of the denominator, whether it is a certain population, region or community [17, 18]. Meanwhile, the prevalence of HF in the US is estimated as 1.9% [19] and an estimated annual incidence of SCD in the US (total population approx. 300,000,000), would range between 180,000 – 250,000 cases per year [20]. Risk factors of SCD were reported to be similar to cardiovascular diseases. However, the most studied and proven predictor of SCD in HF patients is left ventricular ejection fraction (LVEF) [21]. Indeed, individuals with depressed ejection fraction and better functional class have the highest SCD risk [21, 22]. Nevertheless, SCD accounted for up to 40% of cardiovascular-related deaths in HF patients with preserved ejection fraction (HFpEF) [23]. HF is, therefore, a risk factor of SCD and of out-of-hospital cardiac arrest [24].

1.1.3. Treatment of heart failure & current strategies

Heart failure (HF) patients are currently managed and treated regardless of their risk to present an SCD outcome. This is true because SCD is a mode of death that is difficult to identify and so challenging. On the contrary, if we hypothesize that risk score models to predict SCD have been externally validated with good discriminatory power, we would need an optimal preventive strategy. The evaluation of drug effectiveness of clinical outcomes - such as SCD or total mortality – would eventually contribute to optimize treatment for HF patients with reduced ejection fraction (HFrEF). The European Society of Cardiology (ESC) guideline [11] categorizes pharmacological treatment of HFrEF according the level of recommendation and stages of HF (**table 2**).

Table 2: Therapeutic strategies in heart failure patients

Recommendation for HFrEF	Drug/non-drug Intervention
All symptomatic patients	Beta-blockers
	Angiotensin-converting enzyme inhibitors
	Mineralocorticoid/aldosterone receptor antagonists
Selected symptomatic patients	Diuretics
	Angiotensin receptor neprilysin inhibitors
	I_f –channel inhibitor (e.g., ivabradine)
	Angiotensin receptor blockers
	Hydralazine/isosorbide dinitrate
Less certain benefits in symptomatic patients	Digoxin and other digitalis glycosides
	n-3 polyunsaturated fatty acids
Not recommended (Unproven benefit) in symptomatic patients	Statins (3-Hydroxy-3-methylglutaryl-coenzyme A reductase inhibitors)
	Oral anticoagulants and anti-platelet therapy
	Renin inhibitors
Not recommended (believed to cause harm) in symptomatic patients	Calcium-channel blockers
Non-surgical device treatment	Implantable cardioverter defibrillators
	Cardiac resynchronization therapy
	Other implantable electrical devices

Adapted from ref. [11].

We hypothesize that a good preventative strategy of SCD involves identifying and predicting high-risk patients and the availability of effective interventions.

It is noteworthy that HF patients are currently categorized according to left ventricular ejection fraction (LVEF) into: HF with reduced ejection fraction (HFrEF, <40%), HF with mid-range ejection fraction (HFmrEF, 40–50%) and HF with preserved ejection fraction (HFpEF, >50%) [11]. Of note, our work evaluated drug interventions on HFrEF as most randomized clinical trials (RCTs) excluded the other two types of HF. It is also important to mention that we did not evaluate non-drug devices in HF, which we acknowledge later as a limitation.

2. OUTLINE OF THE THESIS

In this work, we reviewed and updated the evidence for beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACE-i), angiontensin receptor blockers (ARBs), combined angiotensin receptor blockers (ARB)/neprilysin inhibitors, aldosterone antagonists, omega-3 fatty acids, statins, amiodarone and anti-arrhythmic drugs. We used standard reporting methods and a variety of evidence-based medicine methodology: systematic reviews and meta-analysis (cf. **chapter 1&4** and **appendix I&V**), overviews (cf. **chapter 2** and **appendix III**), survival analysis, statistical models such Cox proportional hazards model, Kaplan-Meier survival curves, propensity score analysis and instrumental variables approaches (cf. **chapter 3** and **appendix IV**). Separating this work into four chapters, we provided a summary of findings for each chapter. Thereafter, we wrote an overall discussion and highlighted the limitations, clinical implications and perspectives for future work.

CHAPTER 1

Statins in Heart Failure with Reduced Ejection Fraction

1.1. Article title and statement of permission

"No benefits of statins for sudden cardiac death prevention in patients with heart failure and reduced ejection fraction: A meta-analysis of randomized controlled trials"

Al-Gobari M, Le HH, Fall M, Gueyffier F, Burnand B. PLoS One. 2017 Feb 6;12(2):e0171168. doi: 10.1371/journal.pone.0171168. eCollection 2017.

Enclosed in **appendix I**, the above-cited manuscript has been published as an open access article in a peer-reviewed journal. Use of this manuscript is distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited (**Copyright:** © 2017 Al-Gobari et al.).

1.2. Contribution of authors and co-authors

As stated in the original work [25], conceptualization: **MA**. Data curation: **MA** HHL MF. Formal analysis: **MA** BB FG. Investigation: **MA** HHL MF. Methodology: **MA** BB FG. Project administration: BB. Software: **MA**. Supervision: **MA** BB FG. Writing – original draft: **MA**. Writing – review & editing: **MA** BB FG HHL MF.

1.3. Introduction and objectives

Patients with heart failure (HF) often take multi-drug therapy, including 3-methylglutaryl coenzyme A (HMG-Co A) reductase inhibitor or simply statins, over which efficacy is debated in the literature [26-28]. In fact, randomized clinical trials and observational studies showed mixed results related to clinical outcomes such as all-cause mortality, sudden cardiac death (SCD), and hospitalization for worsening HF [26-30]. The European society of cardiology (ESC) guidelines do not recommend statins use in patients with merely a diagnosis of HF [11], but the current practice is often not in line with such recommendations [31]. This might be related to discordant and multiple available evidence or simply due to the complexity of clinical benefits in primary prevention, as often coronary artery syndrome and myocardial infarction or other comorbidities are coexisting with HF. Such situation generated biases, serious limitations and/or indirectness of evidence. Therefore, it is noteworthy that such potential biases in the current literature related to statin benefits in HF merit to be

explored and explained in detail. Hence, our objective was to systematically evaluate and update the current evidence.

2.1. Methods of chapter 1

Apart from refining the research question, we started to design a search strategy to retrieve related evidence published in the literature. Searched databases were Medline, Embase, Cochrane central library and www.clinicaltrials.gov and hand searched references of included studies. After that, we abstracted data in pre-defined forms after selection of relevant studies. Then, we analyzed the data according to the following steps:

- build statistical models (fixed-effects and random-effects models) according to Mantel-Haenzel methods
- determine the effect size for the pooled data: risk ratio (RR) and used odds ratios (OR) in sensitivity analyses.
- calculate the absolute effect or the absolute risk reduction (ARR) for measured outcomes (all-cause mortality, SCD, and hospitalization for worsening HF).
- create a prediction interval whenever a random-effects model is used; a prediction interval is an interval that estimate a treatment effect of a new or future trial within which we are confident it lies. By definition, it helps to predict the effects - of adding new data from a future trial- upon our current effect size estimation.
- sample size computation
- meta-regression and heterogeneity measurement as well as subgroup and sensitivity analysis
- risk of bias assessment and quality of studies
- GRADE assessment of the quality of the evidence per outcome. Five key elements: risk of any bias, inconsistency, indirectness, imprecision or publication bias.

3.1. Main findings of chapter 1 (cf. Appendix I)

Summary

The pooled studies resulted into no added benefits for HF patients with reduced ejection fraction concerning SCD prevention or all-cause mortality. A slight significant decrease in the occurrence of hospitalizations due to HF was, however, observed. A further investigation to the trend the lower lipoprotein cholesterol (LDL-c), the lower mortality showed insignificant output (**figure 1.1**).

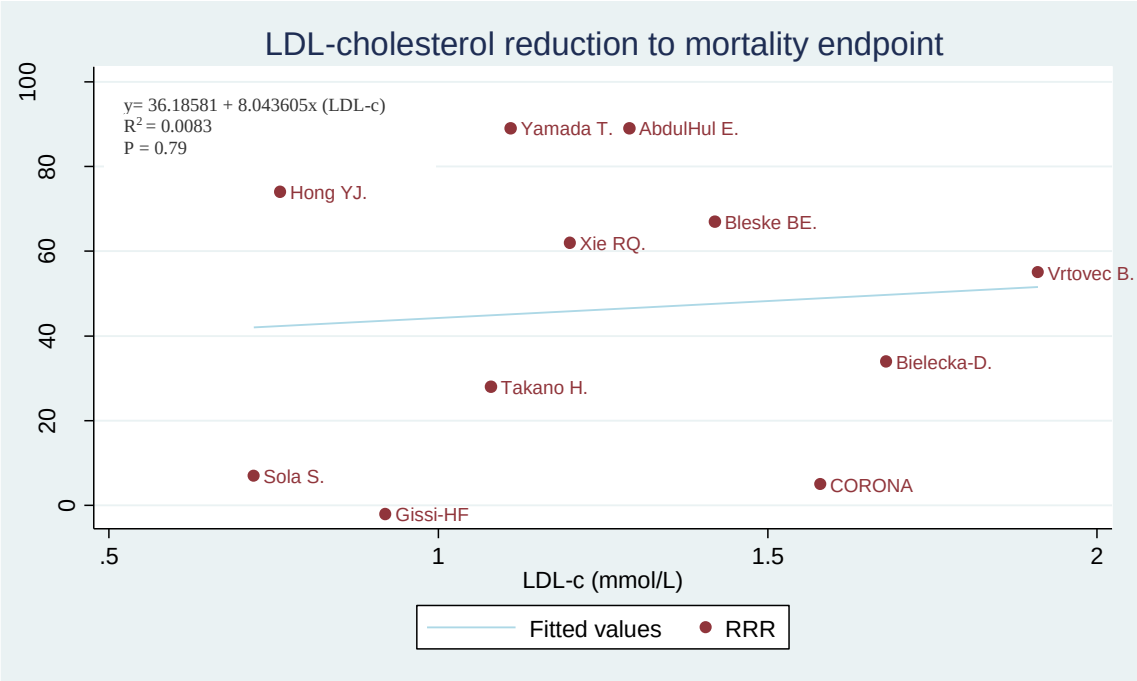


Figure 1.1: LDL-c: low-density lipoprotein cholesterol; RRR: relative risk reduction. (cf. table 1 in **Appendix I**).

Conclusion

This article provides a clear message to the existed debate and to the discordant or inconsistent results and multiple systematic reviews. Statins do not show significant benefits on SCD or all-cause mortality prevention. The study offered a plausible explanation by observed publication bias and small-study effects in the current literature.

CHAPTER 2

Overview of Effectiveness of Drug Interventions

2.1. Article title and statement of permission

"Effectiveness of drug interventions to prevent sudden cardiac death in patients with heart failure and reduced ejection fraction: an overview of systematic reviews"

Al-Gobari M, Alaqeel S, Gueyffier F, Burnand B. http://dx.doi.org/10.1136/bmjopen-2017-021108

2.2. Contribution of authors and co-authors

As stated in the original work (**appendix III**), design and conception: **MA**, FG, BB. (**MA** is the guarantor). Project administration: BB. Writing original draft: **MA**. Critical analysis: **MA**, SA, FG, BB. Data curation: **MA**, SA. Statistical analysis: **MA**. Proofread and approved the final draft: **MA**, SA, FG, and BB.

2.3. Introduction and objectives

One important target of heart failure (HF) therapy is to alleviate symptoms, improve the quality of life and reduce the mortality of the disease. It is noteworthy that 50% of HF patients die within 5 years of initial diagnosis and at least half of them die suddenly, termed "sudden cardiac death" (SCD). Since HF with reduced ejection fraction patients adopt a multi-regimen therapy (**Figure 2.1**) and the necessity, not only from economic viewpoint but also clinically, to determine whether a particular drug intervention is effective or not in all-cause mortality and SCD prevention, we aimed to summarize and update the current evidence in the literature. We categorized the evidence into effective, ineffective, and unclear evidence of effectiveness.

2.2. Methods of Chapter 2

We developed an a priori protocol (cf. **Appendix II**) for this study and registered it on the international prospective register of systematic reviews (PROSPERO). The protocol included a search strategy, data sources, inclusion and exclusion criteria, and data abstraction forms. We looked on the literature on methods of quality assessment of included reviews and selected AMSTAR measurement tool. To assess the quality of evidence in included reviews, we used the GRADE (Grading of Recommendations, Assessment, Development and Evaluation) approach. GRADE categorizes the quality of evidence into four levels: high, moderate, low and very low.

- After data collection, we statistically analyzed it and provided a narrative synthesis of the evidence.
- We also meta-analyzed one intervention (i.e. angiotensin receptor blockers (ARBs)) in order to update the existed evidence using random-effects and fixed-effects models with Mantel-Haenszel methods [32]. Odds ratios (OR) or relative risk (RR) was used as a summary statistic with confidence intervals(CIs) and a significance level at two-sided alpha < 0.5.
- Other than scrutinizing the heterogeneity and inconsistencies between retrieved reviews, we categorized the resulted synthesis into:
  1- effective interventions;
  2- ineffective interventions;
  3- uncertain evidence (conflicting or inconclusive evidence).

3.2. Main findings of chapter 2 (cf. Appendix III)

Summary

The published protocol [33] was followed and all outcomes were reported, namely SCD and all-cause mortality. Measuring quality by AMSTAR and GRADE, the study resulted into three categories of evidence (see **Table 2.1**)

Table 2.1: Result of drug evaluation on SCD prevention for HFrEF patients

Evidence for SCD outcome	**Drugs**	**RR/OR**
Effective interventions	- beta-blockers (BB) - anti-aldosterone (AAs) - combined ARB/neprilysin inhibitor	- 0,69 - 0,81 - 0,81
Ineffective interventions	- angiotensin-converting enzyme inhibitors (ACE-i) - angiotensin receptor blockers (ARBs) - statins	-
Uncertain evidence	- amiodarone & anti-arrhythmic drugs (AADs) - omega-3 polyunsaturated fatty acids (PUFA) - fish oil supplementation	-

SCD: sudden cardiac death; RR: risk ratio; OR: odds ratio

We reported the risk ratio (RR) or odds ratio (OR) of the effective interventions (i.e., BBs, AAs, combined ARB/neprilysin inhibitor). It is possible to compute the association of the three drug interventions by multiplying the effect size, assuming that there is no interaction. The resulted effect size estimation suggested an SCD reduction of almost 50%.

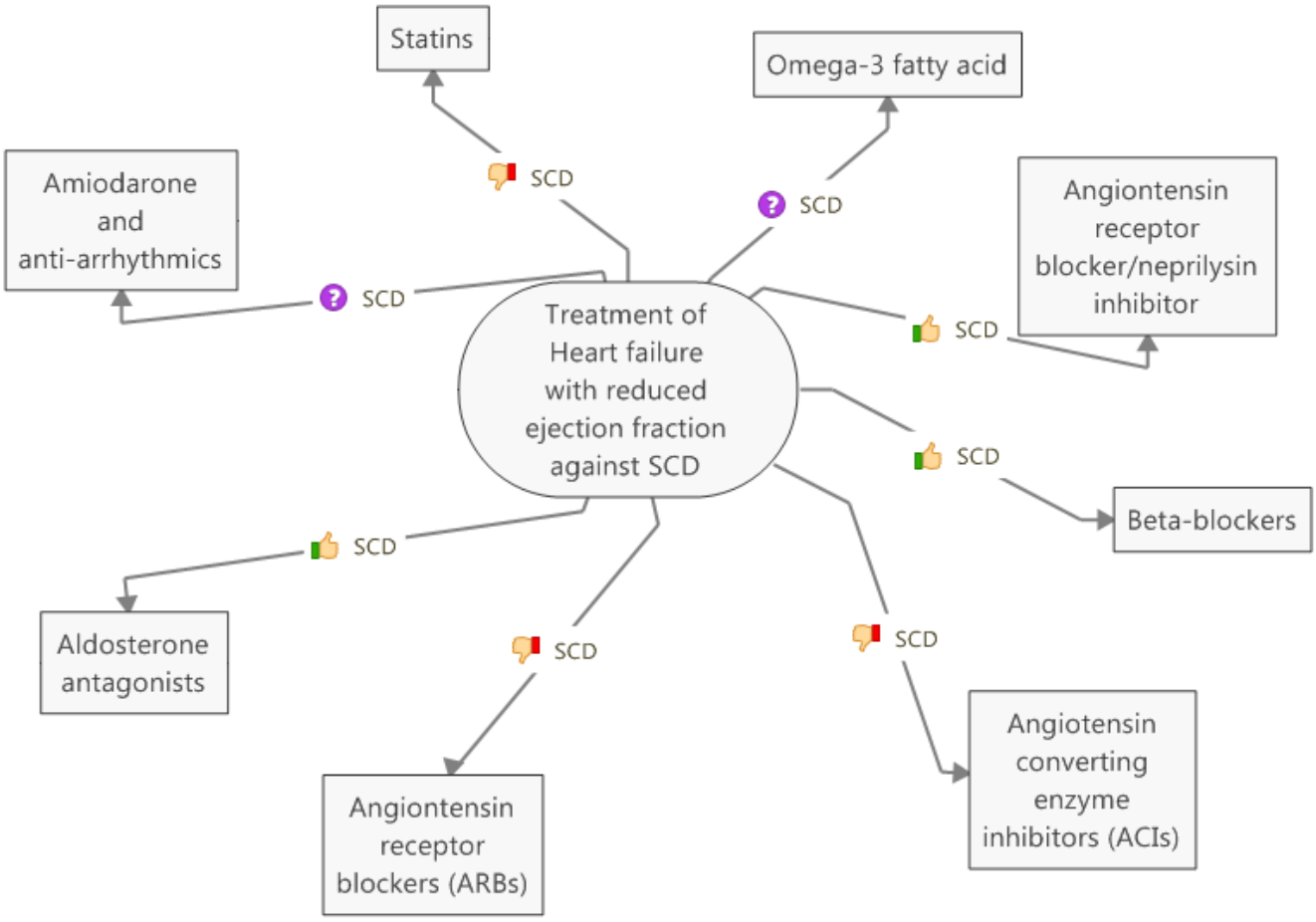


Figure 2.1: Drug and non-drug interventions in heart failure with reduced ejection fraction (HFrEF). SCD: sudden cardiac death. Thumb up= reduce SCD. Thumb down: failed to significantly reduce SCD. Question mark (?): uncertain evidence.

Conclusion

This overview contributes to enhance the understanding of the current evidence of effectiveness of the strategies used to prevent SCD and all-cause mortality in HF patients with reduced ejection fraction. It helps to adopt an optimal strategy in patients with high risk of SCD.

CHAPTER 3

Statins in real-world Clinical Cohort (EPICAL2)

3.1. Article title and statement of permission

"Effects of statins to reduce all-cause mortality in heart failure patients: findings from the EPICAL2 cohort study"

Al-Gobari M, Agrinier N, Burnand B. Thilly N.

Enclosed in **appendix IV, t**he above-cited manuscript has been drafted or prepared for submission to a peer-reviewed journal.

3.2. Contribution of authors and co-authors

Drafted the manuscript: **MA**. Original data possession: NT. Data Analysis: **MA**.
Supervision: NA BB NT. Writing- review & editing: **MA** NA BB NT

3.3. Introduction and objective

Heart failure (HF) patients have poor survival despite current advances in therapy and management. Statins showed contradictory results in observational data and randomized clinical trials (RCTs) [29, 30, 34, 35]. Unlike RCTs, observational studies are prone to selection and allocation bias. Advanced statistical techniques, such as propensity score analysis and instrumental variables methods, have been developed to reduce bias and mimic some aspects of experimental studies [36, 37]. Using these statistical techniques, we aimed to evaluate the effects of statins on all-cause mortality prevention in HF. In our analysis, we used data from an observational study of 2,254 subjects hospitalized for acute heart failure and recruited between October 2011 and October 2012 from 20 hospitals located in the Lorraine region of northeast France.

2.2. Methods of Chapter 3

2.3.1 Participants

This clinical cohort (EPICAL2, NCT 02880358) has included 2,254 patients. We excluded patients who were lost to follow-up, were dead before discharge or discharged with unknown treatment status for statins. After exclusion, the study cohort finally consisted of 2,032 patients, 919 (45 %) of whom received statins (treated group) versus 1,113 (55 %) not treated with statins as a (control group)

2.3.3.1. Propensity score analysis

We calculated the propensity scores (i.e., the probability of being treated with statins) using multivariable logistic regression, without including the outcome (all-cause mortality) and performed balance assessment tests to compare the distribution of covariates between treated and control patients [38]. We used one-to-many matching with replacement as it produced better balance between treated and control groups than one-to-one matching without replacement. Then we estimated treatment effects and their standard errors using propensity score matching methods within a caliper distance of 0.2 [39, 40].

2.3.3.2. Instrumental variable analysis

Propensity scores balance for measured covariates but not necessarily for unmeasured covariates [40]. However, instrumental variables approach takes into account unmeasured variables that are associated with the treatment but not directly with the outcome. We used “the prevalence or the percentage of statin prescription” in participating health centers as an instrumental variable. Using a two-stage least square method, we regressed the instrumental variable, the prevalence of statin treatment in the participating hospitals (dichotomized as above or below the median of 47%), on other covariates previously used for the propensity score analysis. Thereafter, we tested the endogeneity (Durbin (score) and Wu-Hausman) and weakness of our instrument.

2.3.3.3. Kaplan-Meier survival curves and Cox proportional-hazards model

We used a log-rank test to determine the equality of survivor functions, used a stratified log-rank test (on propensity scores), and stratified Wilcoxon (Breslow) test to compare survival curves. To illustrate the increased rate of having an event, we regressed all-cause mortality (the outcome) on independent variables - previously adjusted for in Kaplan-Meier survivor curves- in a multivariable Cox proportional-hazard model with Breslow methods for ties. We verified the proportional-hazards assumption by a global test for all covariates included in the model and based on Schoenfeld residuals for all covariates individually.

3.2. Main findings of chapter 3 (cf. Appendix III)

3.3.2. Propensity score matching

The overlap of the propensity scores between treated and control groups appeared subjectively satisfying (**Figure 3.2**).

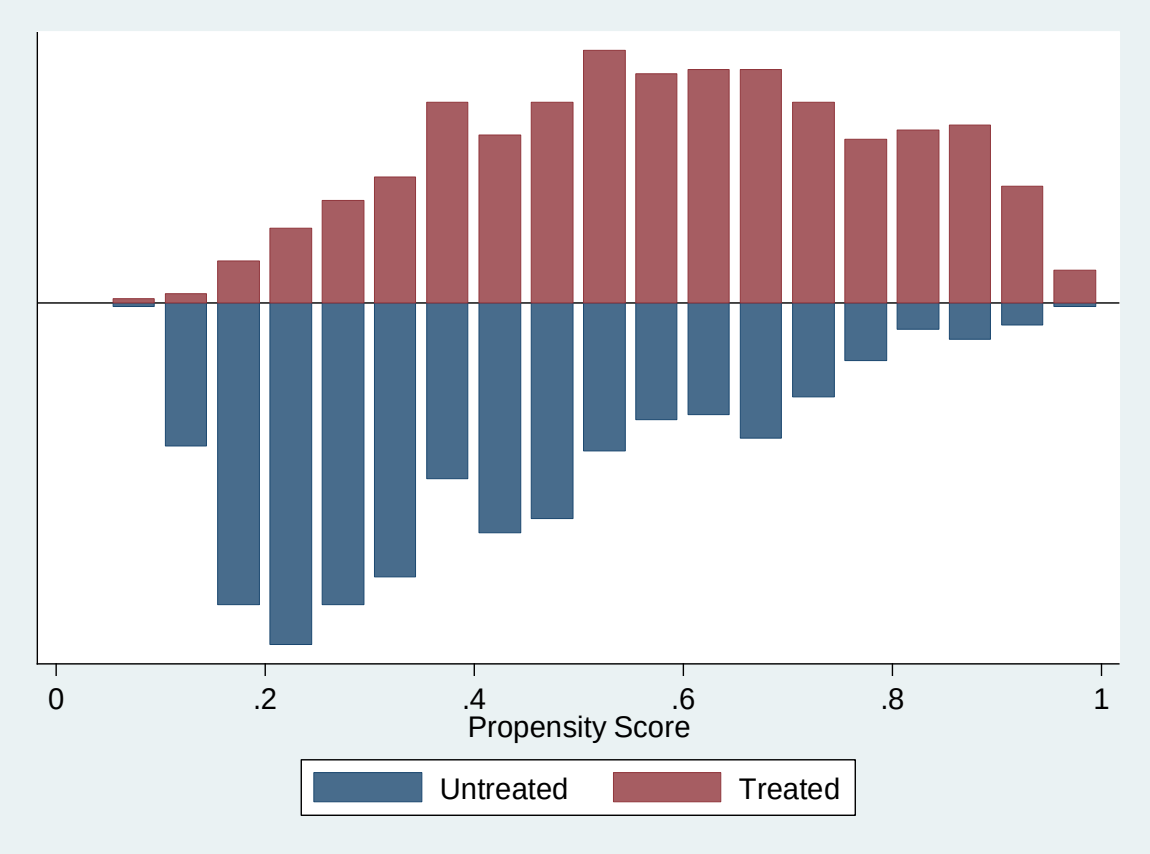


Figure 3.2: Distribution and degree of overlap of the propensity score between statin-treated and control groups in the included HF patients.

The estimated satin-treatment effects (the average treatment effects on the treated, ATT) for all-cause mortality in HF resulted into negative result [Coefficient: - 0.055, AI robust standard errors: 0.032, Z: -1.73; 95% CI: (-0.11 to 0.007), p-value: 0.083].

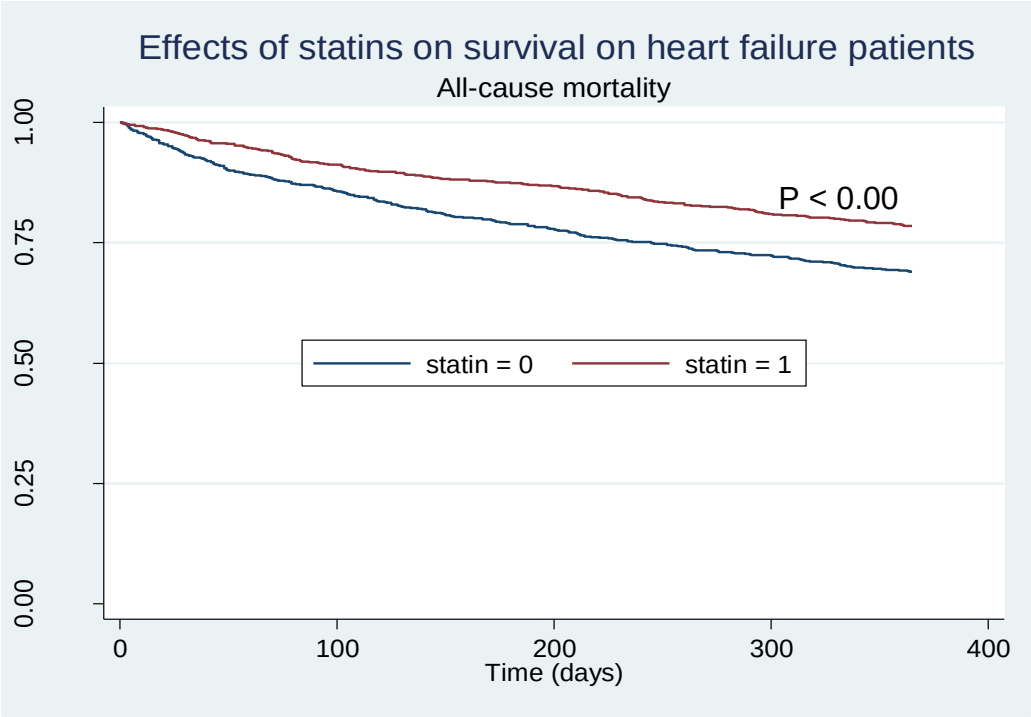
3.3.3. Instrumental variable analysis

The hypotheses related to the correlation of our instrument with the treatment and indirectly with the outcome (all-cause mortality) via the treatment were satisfied. In addition, the test of endogeneity (Durbin (score) and Wu-Hausman) failed to reject our null hypothesis that the variables are exogenous (p-value = 0.3). The treatment estimation, using the two-stage least squares regression, did not show a significant

decrease of death in the statin group versus the control group [Coefficient: -0.43, standard errors: 0.46, Z: -0.95; 95% CI: (-1.34 to 0.46), p-value: 0.34].

3.3.4. Kaplan-Meier curves and cox-proportional hazards model

The number of deaths in our sample was 539 (26.53%). Of those, 195 (21.22%) occurred in the treated group versus 344 (30.91%) in the control group. Unadjusted Kaplan-Meier survivor curves **(Figure 3.3)** and log-rank test showed significant result (P-value < 0.0000). However, the adjusted Kaplan-Meier survivor curves and the stratified log-rank test failed to show a significant result (P-value: 0.317) (**Figure 3.4)**. We adjusted using the same covariates as in the propensity score analysis.



At risk (events):

0	1107	(158)	948	(88)	858	(60)	797
1	915	(80)	832	(40)	790	(53)	732

Figure 3.3: 1-year survival in statin and control groups (Unadjusted Kaplan-Meier survivor curve)

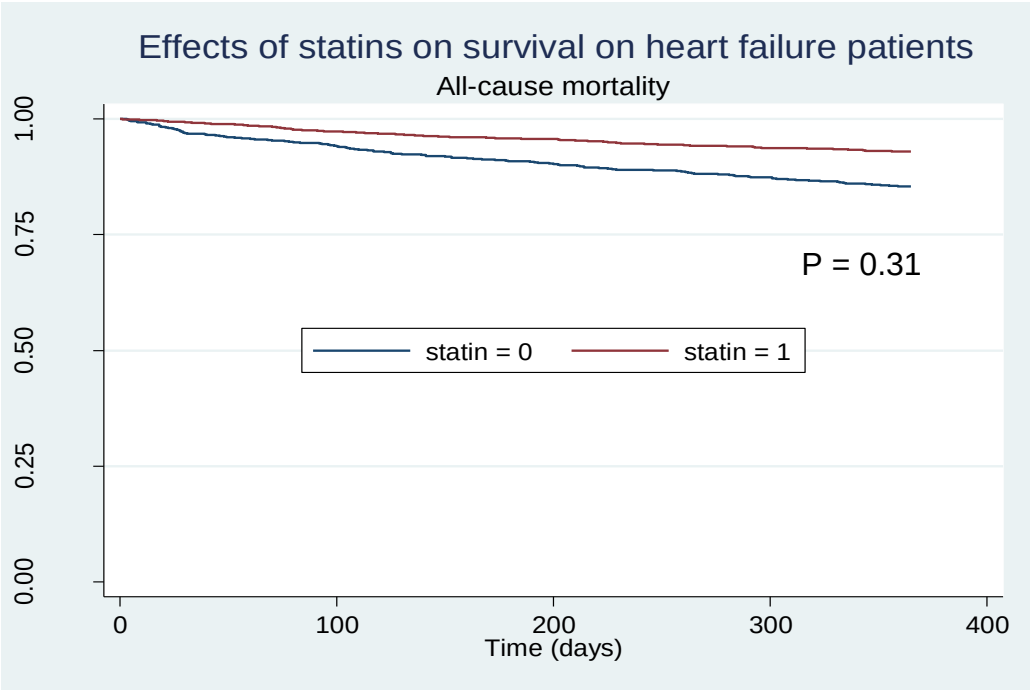


Figure 3.4: 1-year survival in statin and control groups
(Adjusted Kaplan-Meier survivor curves)

Conclusion

Statins were not associated with a decrease in all-cause mortality in statin-treated group in heart failure patients after one-year hospital discharge compared to those not treated with statins.

CHAPTER 4

Other Scientific Contributions

4.1. Article title and statement of permission

"Impact of Aldosterone Antagonists on Sudden Cardiac Death Prevention in Heart Failure and Post-Myocardial Infarction Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials"

Le HH, El-Khatib C, Mombled M, Guitarian F, **Al-Gobari M**, Fall M, Janiaud P, Marchant I, Cucherat M, Bejan-Angoulvant T, Gueyffier F. PLoS One. 2016 Feb 18;11(2):e0145958. doi: 10.1371/journal.pone.0145958. eCollection 2016

Enclosed in **appendix V**, the above-cited manuscript has been published as an open access article in a peer-reviewed journal. Use of this manuscript is distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited (**Copyright:** © 2016 Hai-Ha LE et al.).

4.1.1. Contribution of authors and co-authors

As stated in the original work [41], conceived and designed the experiments: HHL F. Guitarian TBA F. Gueyffier. Performed the experiments: HHL MMF. Guitarian CE MC TBA F. Gueyffier. Analyzed the data: HHL F. Guitarian CE MM MC F. Gueyffier. Wrote the paper: HHL CE F. Guitarian MM **MA** MF MC TBA F. Gueyffier. Literature and data extraction: HHL MMF. Guitarian CE TBA F. Gueyffier. Proofreading: HHL **MA** MM CE MF F. Guitarian PJ IM MC TBA F. Gueyffier. Editing: HHL.

4.1.2. Summary

In a subgroup analysis, anti-aldosterone antagonists reduced SCD in heart failure (HF) patients ([Risk Ratio (RR) 0.79; 95% Confidence interval (CI), 0.68 to 0.91, P = 0.002]. However, a particular attention and risk/benefits evaluation should be ensured because of adverse effects such as hyperkalemia, degradation of renal function, and gynecomastia.

4.2. Article title and statement of permission

"A sudden death risk score specifically for hypertension: based on 25 648 individual patient data from six randomized controlled trials"

Le HH, Subtil F, Cerou M, Marchant I, **Al-Gobari M**, Fall M, Mimouni Y, Kassaï B, Lindholm L, Thijis L, Gueyffier F. Journal of hypertension. 2017;35:2178-84

Enclosed in **appendix VI as author version**, the above-cited manuscript has been published in a peer-reviewed journal. Use of this manuscript is governed by the publisher ().

4.2.1. Contribution of authors and co-authors

As stated in the original work [42], F.G. proposed the idea of the study. F.S., L.T. made substantial contributions to study conception and design. H.H.L. and M.C. performed the analyses. H.H.L. wrote the article. F.S., M.C., **M.A**., I.M., L.L., L.T., and F.G. have been involved in revising the manuscript critically for important intellectual content.

4.2.2. Summary

We have developed a risk score model to predict SCD in hypertensive patients with or without cardiovascular disease. To calculate a five-year risk of SCD, seven risk factors are needed (i.e. age, sex, systolic blood pressure, serum total cholesterol, cigarette smoking, diabetes, and history of myocardial infarction). This tool might help identify those at high risk of SCD in hypertensive patients and hence optimize the therapeutic strategy accordingly.

4.3. Article title and statement of permission

"Beta-blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials"

Al-Gobari M, El Khatib C, Pillon F, Gueyffier F. BMC Cardiovascular Disorders 2013, 13:52

Enclosed in **appendix VI**, the above-cited manuscript has been published as an open access by a peer-reviewed journal. Use of this manuscript is distributed under the terms of the Creative Commons Attribution License, which permits unrestricted use, distribution, and reproduction in any medium, provided the original author and source are credited (**Copyright:** © 2013 Al-Gobari et al.).

4.3.1. Contribution of authors and co-authors

As stated in the original work [43], **MA** and FG participated in the conception and design of the study. **MA**, FP and CK extracted the data. **MA** drafted the study. **MA**, FP and FG had critically analyzed and interpreted the data. All authors read and approved the final manuscript.

4.3.2. Summary

Beta-blockers (BB) reduce SCD and all-cause mortality in heart failure (HF) patients [OR 0.69; 95% CI, 0.62-0.77, P<0.00001], and [OR 0.67; 95% CI, 0.59-0.76, P<0.00001], respectively. BBs should be given to all eligible patients for mortality benefits.

5. GENERAL SUMMARY AND DISCUSSION

5.1. Synthesis

Overall, heart failure (HF) patients use a combination of drugs and non-drug interventions to alleviate symptoms and impede the mortality and morbidity of the disease. Currently, there is no an established strategy to deal with patients at high risk of SCD. In such patients, a particular attention should be considered and a careful selection of available therapeutic options is needed. We appraised the effectiveness of evidence-based HF drugs and updated the evidence of the most commonly prescribed ones. Namely, we reviewed beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARBs), combined angiotensin receptor blockers (ARB)/neprilysin inhibitors, aldosterone antagonists, omega-3 fatty acids, statins, amiodarone and anti-arrhythmic drugs.

In **chapter 1**, our findings showed that statins add no more benefits in solely HF patients. Thus, our systematic review supports the current ESC guideline [11]. It concurs with the two large-scale RCTs in HF [29, 30] and thus represents a convincing evidence to recent controversial results [27, 28].

In **chapter 2**, ARBs, a recommended HF drugs, failed to significantly reduce SCD and all-cause mortality. ACE-i tended to reduce all-cause mortality but not SCD. Only one trial [44] suggested beneficial effects of ACE-i on SCD prevention in non-MI HF patients [45] but failed in the pooled data. This is perhaps due to small study effects. Oppositely, BBs reduced SCD significantly. Hence, BBs remain the mainstay of therapeutic strategies in HF. Similarly, both aldosterone antagonists and combined ARB/neprilysin inhibitors significantly reduced SCD events, whereas omega-3 fatty acids or fish oil supplementation as well as amiodarone and anti-arrhythmic drugs had uncertain evidence of effectiveness.

In **chapter 3**, we evaluated the effectiveness of statins in a real-world setting to prevent all-cause mortality. The data came from a French cohort of hospitalized acute HF patients (n= 2254). Advanced statistical methods were used, namely, propensity score analysis and instrumental variable approach that help to mimic controlled experiments such as RCTs. In our study, statins remained ineffective in HF patients in consistency with large RCTs, which confirmed our previous findings in the updated meta-analysis (cf. **chapter 1**).

In **chapter 4**, aldosterone antagonists showed to reduce SCD in HF subgroup analysis. However, there were more adverse events (e.g., hyperkalemia, degradation of renal function, and gynecomastia) in the treated group compared to the control group.

Of note, it has been reported that antihypertensive treatment failed to reduce SCD [46]. In **chapter 4**, we also developed a risk score model to predict SCD in hypertensive patients.

Acknowledging the high potentially avoidable HF mortality, there is an urgent need to improve clinical outcomes, to optimize therapy, to identify compliance issues and to adopt evidence-based clinical decisions. Nevertheless, current strategies and management plans in HF do not fully address the needs of patients with high risk of SCD.

Importantly, a commonly known intervention in HF to prevent SCD is an implantable cardioverter defibrillator (ICD) implantation. However, studies showed that only a small proportion of patients are potential candidates for an ICD [11, 47]. In addition, despite reducing SCD, ICD therapy does not preclude the progression of HF [48], which might be explained by an increase in deaths from pump failure [49]. ICDs implantation comes with high financial costs and periprocedural and long-term risks [50-52]. In fact, the 2016 ESC guideline recommends ICD implantation only after an optimal medical therapy has failed to increase the left ventricular ejection fraction (LVEF) to > 35%. That is why it is of importance to optimize therapy beforehand. Nevertheless, we acknowledge that our work did not fully review ICDs or other non-drug devices such as cardiac resynchronization therapy (CRT), which we consider important for future research

The patients' characteristics in our study (cf. **chapter 3**) also revealed that the use of life-saving drugs is still suboptimal. One can raise the question of the representativeness of the EPICAL 2 cohort but we found that it was comparable to findings from other countries [53, 54].

By advocating the most effective interventions, this might not only result in a much less number of deaths and a better quality of life but also in a reduction of public health expenditure.

It is noteworthy that before introducing those interventions in the intent to reduce SCD events, it is important that a patient's risk is properly stratified and predicted and that warning signs are timely detected [55]. To this end, a number of prediction risk models were developed [22, 56]. However, their external validity and clinical applicability may not be well established. In the athletic community, most SCDs occur without prodromal warning symptoms [55] but obligatory screening decreased events rate up to 90% in Italy, for instance [57]. It is important to emphasize that the public access to automated external defibrillators (i.e. in libraries, museums, sport clubs, concert/theater, government buildings, and hotels) has substantially improved survival rate of victims of SCDs [55, 58].

5.2. Limitations and Strengths

We acknowledge several limitations in our work. First, we evaluated (cf. **chapter 1-4**) only drug interventions in HF excluding non-drug interventions or devices. In addition, our work did not cover all drug interventions but the most widely prescribed ones. Although devices such as implantable cardioverter defibrillators are considered an important intervention in SCD prevention strategies, they are recommended only after optimal medical therapy failed to increase LVEF >35%.

Second, we were not able to update the evidence at primary-study level for some interventions like angiotensin-converting enzyme blockers (ACE-i).

Third, we used grouped published data and did not have individual patient data that would allow us to stratify patients according to their ischaemic and non-ischaemic status, for instance.

Fourth, we adjusted for selected variables - in the propensity score analysis - to which we believe that both treatment assignment and the outcome are related (cf. **chapter 3**). Even if the assumption of treatment assignment ingorability is satisfied, because of adjustment on selected observable covariates, a selection bias still potentially exists [59].

Fifth, the variables (left ventricular ejection fraction (LVEF), body mass index (BMI), hospital stay duration, and hemoglobin level), used in the propensity score model, had missing values and the way to deal with this missingness involved another methods [60, 61] to be considered in further research.

Finally, most of aforementioned limitations and others have been mentioned in the original related published work (cf. **Appendix I – V**). It is noteworthy that before conducting our overview (cf. **chapter 2**), we wrote a protocol to help avoiding biases such as reporting bias (cf. **Appendix III**). According to our knowledge, our work is a valuable contribution to an original high-demand research that used a standard methodology in agreement with current guidelines, the Equator's (http://www.equator-network.org/) recommendations and the GRADE approach, as well.

5.3. Clinical implications and perspectives

Our work paved the way toward optimization of therapeutic strategies in patients at high risk of SCD. A suggested design for a good therapeutic strategy in SCD prevention might be to **i**dentify, **t**reat, **m**onitor and **e**valuate (ITME) high-risk individuals in HF population. This implies that we should correctly stratify and predict those at risk and then select the most effective therapeutic regimen, taking into account net clinical benefits, patient preference and quality of life and in light of our findings. Those patients should also be closely monitored as HF prognosis is extremely bad, particularly in individuals with existing comorbidities. Thereafter, we would need to evaluate whatever adopted strategy in a regular basis.

In line with limitations of our work, it would be interesting to investigate the overall evidence altogether (i.e., drug and non-drug interventions). A suggested methodology would be to use network meta-analyses. This might highlight which intervention is the most effective and which intervention is perhaps preferred to another. Other approaches are under development that involve the use of GRADE to evaluate complex interventions.

It is noteworthy that our study evaluated pharmacological interventions on HFrEF patients and our result may not extend to other patients groups (i.e., HFmrEF or HFpEF). This highlights the importance of launching new clinical trials and research on those patients [62] because they are also concerned with the incidence of SCD outcome as HFrEF patients.

6. CONCLUSION

In our work, we reviewed most drug interventions in heart failure (HF) patients in the context of a potentially alternative strategy to optimize medical therapy for SCD prevention in HF patients. Using published data from randomized trials of HF with reduced ejection fraction and a cohort of hospitalized acute HF patients (one-year follow-up), statins added no benefits in SCD prevention or all-cause mortality. Moreover, angiotensin receptor blockers (ARB) and angiotensin-converting enzyme inhibitors (ACE-i) failed to significantly reduce SCD events. The latter reduced all-cause mortality. By contrast, beta-blockers (BB), combined ARB/neprilysin inhibitors and anti-aldosterones decrease SCD and all-cause mortality events. The possibility to distinguish whether a particular HF drug prevents SCD (or not) might contribute toward an optimal strategy in patients with high risk of SCD. If only the most effective interventions were adopted, we would expect not only a much less number of deaths and a better quality of life but also a reduction of public health expenditure.

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APPENDIX I “No benefits of statins for sudden cardiac death prevention in patients with heart failure and reduced ejection fraction: A meta-analysis of randomized control trials”

PLOS ONE

RESEARCH ARTICLE

No benefits of statins for sudden cardiac death prevention in patients with heart failure and reduced ejection fraction: A meta-analysis of randomized controlled trials

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OPEN ACCESS

Citation: Al-Gobari M, Le H-H, Fall M, Gueyffier F, Burnand B (2017) No benefits of statins for sudden cardiac death prevention in patients with heart failure and reduced ejection fraction: A meta-analysis of randomized controlled trials. PLoS ONE 12(2): e0171168. doi:10.1371/journal.pone.0171168

Editor: Pasquale Abete, Universita degli Studi di Napoli Federico II, ITALY

Received: October 21, 2016

Accepted: January 16, 2017

Published: February 6, 2017

Data Availability Statement: All relevant data are within the paper and its Supporting Information files.

Funding: MA, the corresponding author, received a financial grant (2014.0193) from The Federal Department of Economic Affairs, Education and Research (EAER), Switzerland. HHL received a financial grant from University Claude Bernard Lyon 1 (scholarship of French Ministry of Higher Education & Research) for a three-year PhD

Abstract

Background and objectives

Statins showed mixed results in heart failure (HF) patients. The benefits in major HF outcomes, including all-cause mortality and sudden cardiac death (SCD), have always been discordant across systematic reviews and meta-analyses. We intended to systematically identify and appraise the available evidence that evaluated the effectiveness of statins in clinical outcomes for HF patients.

Design

Systematic review and meta-analysis

Data sources

We searched, until April 28, 2016: Medline, Embase, ISI Web of Science and EBM reviews (Cochrane DSR, ACP journal club, DARE, CCTR, CMR, HTA, and NHSEED), checked clinicaltrials.gov for ongoing trials and manually searched references of included studies.

Eligibility criteria for selecting studies

We identified 24 randomized clinical trials that evaluated the efficacy of statins for HF patients. All randomized clinical trials were assessed for risk of bias and pooled together in a meta-analysis. Pre-specified outcomes were sudden cardiac death, all-cause mortality, and hospitalization for worsening heart failure.

Results

Statins did not reduce sudden cardiac death (SCD) events in HF patients [relative risk (RR) 0.92, 95% confidence interval (CI) 0.70 to 1.21], all-cause mortality [RR 0.88, 95% CI 0.75

contract (10/2014-09/2017) at the UMR 5558 CNRS. All funding is independent from the study design, data interpretation, writing or the decision to submit the article for publication.

Competing Interests: All authors have declared that no competing interests exist.

Abbreviations: AMI, Acute Myocardial Infarction; CHF, Chronic Heart Failure; DC, Dilated Cardiomyopathy; DCM, Dilated Cardiomyopathy; GRADE, Grading of Recommendation Assessment, Development and Evaluation; HF, Heart Failure; HFpEF, Heart Failure with preserved Ejection Fraction; HWHF, Hospitalization for Worsening Heart Failure; IDCM, Idiopathic Dilated Cardiomyopathy; LVEF, Left Ventricular Ejection Fraction; NA, Not Available; NICM, Non-Ischaemic Cardiomyopathy; NR, Not Reported; NYHA, New York Heart Association; PCI, Percutaneous Coronary Intervention; RCTs, Randomized Clinical Trials; SCD, Sudden Cardiac Death; WHO, World Health Organization; ACCF, American College of Cardiology Foundation; AHA, American Heart Association.

to 1.02] but significantly reduced hospitalization for worsening heart failure (HWHF) although modestly [RR 0.79, 95% CI 0.66 to 0.94]. Nevertheless, estimated predictive intervals were insignificant in SCD, all-cause mortality and HWHF [RR, 0.54 to 1.63, 0.64 to 1.19, and 0.54 to 1.15], respectively. An important finding was the possible presence of publication bias, small-study effects and heterogeneity of the trials conducted in HF patients.

Conclusions

Statins do not reduce sudden cardiac death, all-cause mortality, but may slightly decrease hospitalization for worsening heart failure in HF patients. The evaluation of the risk of biases suggested moderate quality of the published results. Until new evidence is available, this study supports the 2013 ACCF/AHA guidelines to not systematically prescribe statins in "only" HF patients, which should help avoid unnecessary polypharmacy.

Introduction

Heart failure (HF) patients are likely to take more than one drug and tend toward polypharmacy. Guideline-directed medical therapy includes angiotensin converting enzyme inhibitors, beta-blockers, aldosterone antagonists as well as implantable cardioverter defibrillators, which all have reported a reduction in mortality and morbidity in heart failure patients [1–4]. Though, such benefits are still insufficient to the current management need as almost half of HF patients die within 5 years after initial diagnosis and half of the mortality is attributed to sudden cardiac death (SCD) [5,6]. More potential benefits are hypothesized with statin treatment but current ACCF/AHA guidelines do not recommend statins for only HF diagnosis [7]. However, 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co A) reductase inhibitors or simply statins are still widely prescribed for HF patients [8].

Several studies [9–11] evaluated the effects of statin on sudden cardiac death prevention but with a variety of population characteristics which made the result difficult to apply for HF patients. Oppositely, two large randomized clinical trials (RCTs) [12,13] in heart failure reported no reduction of all-cause mortality and SCD events by statins. Moreover, studies often evaluated surrogate endpoints or biomarkers other than important clinical endpoints such as mortality and that might have exaggerated the expected benefits of statins[14].

A systematic review [15], published in 2006, stressed on the importance of this research question and pointed out the conflicting and unclear evidence. CORONA [13] and GISSI-HF [12] (unpublished at that time) was expected to resolve the issue. In the contrary, both studies, after publication, raised controversial statements and debates. The morbidity and mortality rate among HF patients is considerably high and an emphasis on effective prevention strategies would lead to a significant reduction of such events. Similarly, HF patients have a reduced longevity thus the need for providing clinicians and health care actors an optimal evidence-based strategy is of vital importance.

Nevertheless, current trials, systematic reviews and meta-analyses [16–24] for statins have shown mixed results for major HF outcomes. Positive studies were not immune to bias, serious limitations or indirectness. Therefore, we intended to evaluate and update the quality of evidence of statins efficacy to reduce SCD, mortality or hospitalization for worsening heart failure (HWHF) by means of a systematic review and a meta-analysis with a careful consideration of potential biases in published studies.

Methods

Study search strategy

We searched Medline (1946 to April 28, 2016), Embase (1974 to April 28, 2016), EBM reviews (Cochrane DSR, ACP journal club, DARE, CCTR, CMR, HTA, and NHSEED) (to April 28, 2016), and ISI web of science ("All years" to April 28, 2016) via an Ovid online interface and identified systematic reviews and meta-analyses via a search strategy accessible on S1 File. In a first step, we used a filter [25,26] to search for systematic reviews and meta-analyses and initially excluded individual clinical trials for the purpose of our study. In a second step, we searched for primary studies and included randomized clinical trials evaluating statins in heart failure patients. In Medline and Embase, we combined medical subject heading terms (MeSH and EMTREE respectively), text words as well as a truncation when appropriate. The method included a combination of a disease (i.e., heart failure), an intervention (i.e., statins) as well as the aforementioned filter. Also, we added an outcome (i.e., sudden cardiac death and/or mortality) to limit the research output. No language restrictions were applied and a bimonthly alert was set up for an automatic update during the study. We also checked the references of included studies for potential additional studies, searched clinicaltrials.gov and tried to contact authors for additional or missing data. Fig 1 shows the search strategy results according to the PRISMA guidelines (see also S2 File).

Selection criteria and data abstraction

We included randomized clinical trials (RCTs) that evaluated statins efficacy in heart failure patients and contained at least one outcome of interest. No exclusion was based on treatment duration or follow-up period, language or *intention-to-treat* analysis. Risk of bias was determined by the Cochrane risk bias assessment tool [27]. Two reviewers (MA&HHL) independently collected data and were checked by a third reviewer (MF) while discrepancies were resolved via discussion and consensus. Abstracted data included eligibility criteria, baseline characteristics, study design (including treatment and control arms), follow-up duration, and

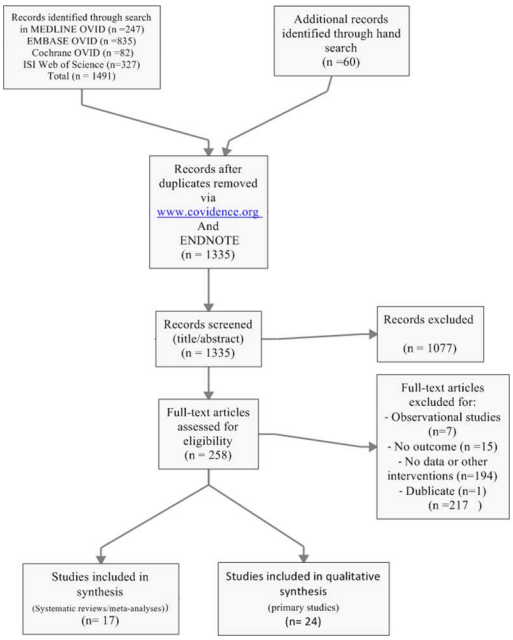

Fig 1. Flow chart for search result.

doi:10.1371/journal.pone.0171168.g001

outcomes. Pre-specified outcomes of interest included sudden cardiac death (SCD), all-cause mortality and hospitalization for worsening heart failure (HWHF) and were analyzed according to an *intention-to-treat* principle when possible.

Statistical analysis

We pooled the data in a meta-analysis, using random-effects and fixed-effects model with Mantel-Haenszel methods that are preferable to inverse variance methods in case of few events [27]. Sensitivity and subgroup analyses were done to verify the extent to which different hypotheses might change our confidence in the result. The effect size was relative risk or risk ratio (RR), confidence intervals (CIs) of 95% was given when applicable and a significance level was determined at two-sided alpha less than 5%. We reported both fixed-effect and random-effects models for the meta-analysis and used risk ratios (RR) as the summary effect estimate that may give better interpretation as the outcome is hospitalization or death events, termed bad outcome. We calculated the absolute effect or the absolute risk reduction (ARR) for SCD, all-cause mortality and HWHF with an assumed control risk (ACR) of 0.11, 0.27 and 0.38 respectively. To check the validity of choosing the summary statistic, odds ratio (OR) was used instead of RR in a sensitivity analysis. The 95% prediction interval, an interval that estimate a treatment effect of a new or future trial within which we are confident it lies, was given when a random-effects model is used. Also, we rated the quality of the evidence using a summary of findings table from the GRADE approach [28]. We computed the sample size required to reach a statistical significance according to the observed differences between the groups of statin and placebo or control for all outcomes [α = 5% and power (1- β) = 0.80] and intended to stratify the studies according to follow-up and sample size in subgroup and sensitivity analyses. Heterogeneity was measured by I-squared (I^2, variation in RR/OR attributable to heterogeneity) and Tau-squared (Tau^2, estimate of between-study variance). We noticed that the follow-up period differed largely from one study to another from one month [29,30] to more than 30 months [12,13,31]. Therefore, studies were grouped according to follow-up as a potential determinant of any heterogeneity among studies. Data was analyzed with STATA version 14.1 (StataCorp LP, Texas), RevMan (version 5.3) and GradePro (version 3.6.1).

Results

Study selection

Electronic databases and manual searches resulted in 1335 studies after removal of duplicates. After screening of titles and abstracts and examination of selected full-texts, we ended up with 17 systematic reviews/meta-analyses [9,11,18–24,32–39] and 24 randomized controlled trials (RCTs) [12,13,40–51] [29,31,52] [30,53–58] (Fig 1).

Study and baseline patient characteristics

As shown in Tables 1 and 2, we identified 24 RCTs of statins in heart failure (HF) patients for inclusion in this meta-analysis, which enrolled a total of 11,463 patients. The mean and the median of follow-up duration were 11.5 and 6 months respectively. The studies included in majority male participants (ratio ranged from 54% to 100%) with an average age of 60 years. The mean age of the three biggest studies (CORONA [13], GISSI-HF [12] and Takano H. et al. (PEARL) [31]) was 68 years. All studies included HF patients with New York Heart Association classification (NYHA) ranging from I-IV and at least 9 studies included stable HF patients. Seven studies included non-ischaemic HF patients, 4 studies exclusively ischaemic, 12 included both types and one unknown. All patients in included studies had an ejection fraction less than

Table 1. Randomized trials of statins in heart failure patients.

Trial [Reference]	Publication Year	Number of patients (statin/comparator)	Name of drug	Comparator	Mean baseline Lipids	Primary Endpoint	Dosage (mg/day)	Follow-up (months)
AbdulHul E. et al. [40]	2012	56(28/28)	Atorvastatin	No statin	LDL-c = 2.73 mmol/L	Biomarkers, BNP	40	6
Bielecka-D. et al. [41]	2009	68(41/27)	Atorvastatin	No statin	LDL-c = 3.15 mmol/L	Factors affect HWHF/mortality	10–40	6
Bleske BE. et al. [42]	2006	18(9/9)*	Atorvastatin	Placebo	LDL-c = 2.84 mmol/L	Surrogate markers in NICM	80	3
CORONA [13]	2007	5011(2514/2497)	Rosuvastatin	Placebo	LDL-c = 3.55 mmol/L	HWHF/SCD/mortality	10	32.8
Erbs S.et al. [43]	2011	42(22/20)	Rosuvastatin	Placebo	LDL-c $\geq$ 3.78 mmol/L	Pleiotropic effects	40	24
Gissi-HF Investigators [12]	2008	4574(2285/2289)	Rosuvastatin	Placebo	NR	HWHF/SCD/mortality	10	46.8
Hammad A. et al. [44]	2005	23(13/10)	Atorvastatin	Placebo	TC $\approx$ 3.5 mmol/L	Autonomic nervous system	40	3
Hong et al.[58]	2005	202(106/96)	Simvastatin	No statin	LDL-c $\approx$ 3.62 mmol/L	PCI rate, restenosis, mortality	40	12
Horwich TB. et al. [45]	2011	26(14/12)	Atorvastatin	Placebo	LDL-c $\approx$ 2.79 mmol/L	Sympathetic nervous system	10	3
Krum et al. [46]	2007	86(40/45)	Rosuvastatin	Placebo	NR	Ventricular remodeling	10–40	6
Laufs U. et al.[47]	2004	15(8/7)	Cerivastatin	Placebo	LDL-c $\approx$ 3.46 mmol/L	Pleiotropic effects	0.4	5
Liu M. et al. [48]	2009	64(32/32)	Atorvastatin	Placebo	LDL-c $\approx$ 3.03mmol/L	Inflammation	10	3
Mozaffarian D.et al. [49]	2005	22(12/10)	Atorvastain	Placebo	LDL-c = 3.33 mmol/L	Inflammation	10	2
Node K. et al. [50]	2003	51(23/25)	Simvastatin	Placebo	LDL-c $\approx$ 3.85 mmol/L	Cardiac function	5–10	3.5
Sola S. et al. [51]	2006	108(46/43)	Atorvastatin	Placebo	LDL-c $\approx$ 3.12 mmol/L	Inflammation	20	12
Strey CH. et al. [52]	2006	23(11/12)*	Atorvastatin	Placebo	LDL-c $\approx$ 3.56 mmol/L	Endothelial function	40	1.5
Takano H. et al.[31]	2013	577(288/286)	Pitavastatin	No statin	LDL-c $\approx$ 3.24 mmol/L	Mortality /HWHF/ stroke	2	35.5
Tousoulis D.et al. [29]	2005	38(19/19)	Atorvastatin	No statin	TC $\approx$ 4.83 mmol/L	Inflammation	10	1
Tousoulis D.et al. [30]	2004	38(14/12)	Atorvastatin	No statin	TC $\approx$ 5.04 mmol/L	Inflammation	10	1
Vrtovec B. et al. [53]	2005	80(40/40)	Atorvastatin	No statin	TC $\approx$ 5.07 mmol/L	HRV/ QTV/ QTc	10	3
Vrtovec B. et al. [54]	2008	110(55/55)	Atorvastatin	No statin	LDL-c = 2.45 mmol/L	SCD	10	12
Wojnicz R. et al. [55]	2006	74(36/38)	Atorvastatin	No statin	LDL-c $\approx$ 4.18 mmol/L	Inflammation	40	6
Xie RQ. et al.[56]	2008	119(78/41)	Atorvastatin	Statin/no statin	LDL-c $\approx$ 3.64 mmol/L	Cardiac function	10–20	12
Yamada T. et al. [57]	2007	38(19/19)	Atorvastatin	No statin	LDL-c $\approx$ 3.02 mmol/L	Cardiac function	10	31

BNP: B-type natriuretic peptide; HRV: heart rate variability; QTV: QT variability; QTc: QTc interval; HWHF: Hospitalization for worsening heart failure; LDL-c: lowdensity lipoprotein cholesterol; NICM: Non-Ischaemic Cardiomyopathy; PCI: percutaneous coronary intervention; SCD: sudden cardiac death; TC: total cholesterol; NR: not reported; $\approx$: approximately.

* Estimated values

doi:10.1371/journal.pone.0171168.t001

45% and no one included HF with a preserved ejection fraction (HFpEF). Baseline mean lipid levels were relatively similar from one study to another with mean low-density lipoprotein

Table 2. Patient characteristics in randomized trials of statins in heart failure patients.

Trial [Reference]	Mean age (Years)	Male (%)	Inclusion criteria	Population (Ischaemic or non-ischaemic, %)	Mean LVEF (%)	NYHA
AbdulHul E. et al.[40]	72	68	Mild-moderate HF, LVEF $\leq$ 45%	Ischaemic, 64	35	II-III
Bielecka-D. et al.[41]	57	85	Stable HF with DC	NR	29	I-III
Bleske BE. et al.[42]	56	60	CHF due to NICM, LVEF<40%	Non-ischaemic	25	I-III
CORONA [13]	73	76	Ischaemic HF, age $\geq$ 60, LVEF < 40%	Ischaemic,100	31	II-IV
Erbs S.et al. [43]	62	76	CHF—Ischaemic HF or DC	Ischaemic,28	30	II-III
Gissi-HF Investigators [12]	68	77	CHF, No LVEF restriction	Ischaemic,40	33	II-IV
Hammad A. et al. [44]	67	86	Stable systolic HF	Ischaemic, 57	31	II-III
Hong et al.[58]	61	72	Patients underwent PCI for AMI	Ischaemic, 100	31	II-IV
Horwich TB. et al. [45]	48	62	Symptomatic HF, LVEF $\leq$ 35%	Non-ischaemic	26	I-III
Krum et al. [46]	62	80	NYHA II-IV, LVEF $\leq$ 35% or $\leq$ 40%	Ischaemic,12	29	II-IV
Laufs U. et al.[47]	51	NR	CHF with NICM	Non-ischaemic	42	II-III
Liu M. et al. [48]	67	94	NYHA II-III, CHF with IDCM	Ischaemic/ Non-ischaemic	20	II-IV
Mozaffarian D.et al. [49]	51	86	Ambulatory HF, LVEF < 40%	Ischaemic, 9	31	II-III
Node K. et al. [50]	54	69	HF with IDCM	Non-ischaemic	33	II-III
Sola S. et al. [51]	54	63	Stable non-ischaemic HF	Non-ischaemic	33	II-IV
Strey CH. et al. [52]	61	70	Symptomatic HF, LVEF < 40%	Non-ischaemic	30	II-III
Takano H. et al.[31]	63	81	CHF, LVEF $\leq$ 45%	Ischaemic, 27	34	II-III
Tousoulis D.et al.[29]	69	100	Ischaemic HF, LVEF $\leq$ 35%	Ischaemic	25	III-IV
Tousoulis D.et al.[30]	58	NR	Stable HF. LVEF $\leq$ 35%	Ischaemic, 65.7	25	II-IV
Vrtovec B. et al. [53]	67	54	Stable HF, LVEF < 30%	Ischaemic, 62	25	III
Vrtovec B. et al. [54]	62	61	Stable HF, LVEF < 30%	Ischaemic, 59	25	III
Wojnicz R. et al. [55]	38	81	Stable HF with DC	Non-Ischaemic	28	II-III
Xie RQ. et al.[56]	NR	NR	Ischaemic HF, LVEF<45%	Ischaemic,100	38	II-IV
Yamada T. et al.[57]	64	79	Stable HF, NYHA I-III	Ischaemic, 53	34	I-III

AMI: acute myocardial infarction; CHF: Chronic Heart Failure; DC: dilated cardiomyopathy; DCM: dilated cardiomyopathy; HF: heart failure; IDCM: idiopathic dilated cardiomyopathy; LVEF: Left Ventricular Ejection Fraction; NICM: Non-Ischaemic Cardiomyopathy; NR: not reported; NYHA: New York Heart Association; PCI: percutaneous coronary intervention.

doi:10.1371/journal.pone.0171168.t002

cholesterol (LDL-c) of 3.3 for 19 studies and mean total cholesterol (TC) of 5.19 for 3 studies and unknown for 2 studies. Only 5 studies[13] [12] [31] [58] [54] had a mortality endpoint while others evaluated surrogate endpoints and biomarkers. Statins were compared to placebo in 13 studies and to no statin in 10 studies; one study compared two different doses of statins to a no statin group[56].

Risk of bias and quality of studies

We assessed studies' risk of bias by means of the Cochrane bias tool[27]. We noticed that the *intention-to-treat* principle was not followed in all trials, among which 10 had either high or unclear risk (Fig 2(B)). Most of the included trials had unclear risk towards blinding of investigators or outcome assessors. Overall, the studies fluctuated from high to moderate/low level of quality. Fig 2 (A) shows the summary of bias risk assessment in percentages and for each included trial. We also rated each outcome (SCD, All-cause mortality and hospitalization for worsening heart failure (HWHF)) according to the GRADE approach (Fig 3). Studies were evaluated per outcome for any bias, inconsistency, indirectness, imprecision or publication bias. The latter was

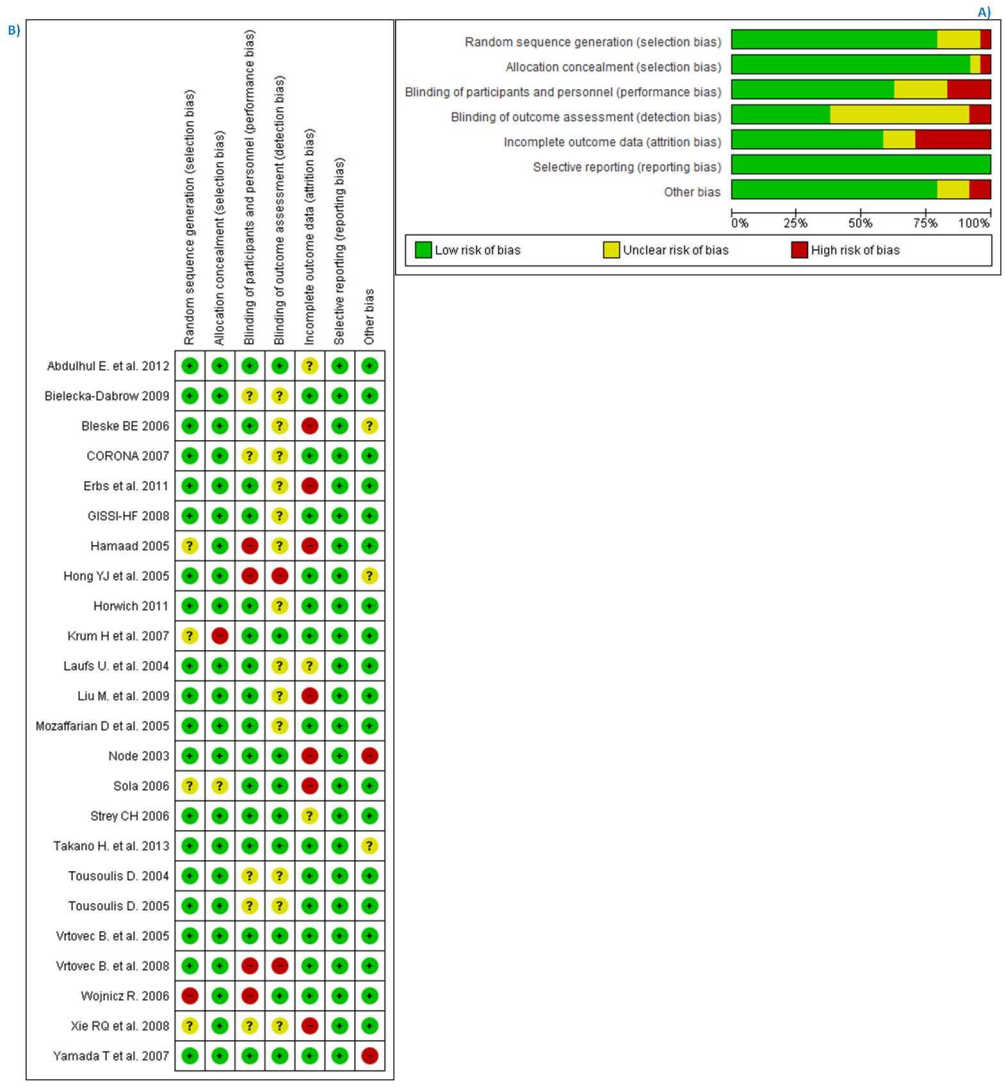

Fig 2. Risk of bias for included studies. A) Risk of bias graph for statin trials in heart failure patients: review authors' judgments about each risk of bias item presented as percentages across all included studies. B) Risk of bias summary for statins in heart failure patients: review authors' judgments about each risk of bias item for each included study.

doi:10.1371/journal.pone.0171168.g002

a concern for all outcomes and this resulted in moderate evidence. Due to missing data or absence of events, only 8 studies for SCD, 13 studies for all-cause mortality and 12 studies for HWHF were analyzed.

Efficacy of statins and synthesis of results

We pooled the studies to evaluate effects of statins on the reduction of sudden cardiac death (SCD), all-cause mortality, and hospitalization due to worsening heart failure (HWHF). The forest plots in Fig 4 shows insignificant reduction in SCD [Risk Ratio (RR) 0.92; 95% CI, 0.70 to 1.21, P = 0.554] and all-cause mortality [RR 0.88; 95% CI, 0.75 to 1.02, P = 0.092] and a statistically significant difference in HWHF [RR 0.79; 95% CI, 0.66 to 0.84, P = 0.008]. Random-effects and fixed-effect models were used to quantify the summary statistic by RR. The effect

Statins for prevention of clinical outcomes in heart failure patients

Patient or population: patients with heart failure
Settings:
Intervention: Statins

Outcomes	Illustrative comparative risks* (95% CI) Assumed risk* Control	Corresponding risk Statins	Relative effect (95% CI)	No of Participants (No of studies)	Quality of the evidence (GRADE)	Comments
Sudden cardiac death	108 per 1000	100 per 1000 (76 to 131)	RR 0.92 (0.7 to 1.21)	10077 (8 studies)	⊕⊕⊕⊖ moderate[1]	
All-cause mortality	273 per 1000	240 per 1000 (205 to 278)	RR 0.88 (0.75 to 1.02)	11024 (13 studies)	⊕⊕⊕⊖ moderate[1]	
Hospitalization for worsening heart failure	380 per 1000	300 per 1000 (251 to 357)	RR 0.79 (0.66 to 0.94)	10761 (12 studies)	⊕⊕⊕⊖ moderate[1]	

*The basis for the **assumed risk** (e.g. the median control group risk across studies) is provided in footnotes. The **corresponding risk** (and its 95% confidence interval) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

CI: Confidence interval; **RR:** Risk ratio;

GRADE Working Group grades of evidence
High quality: Further research is very unlikely to change our confidence in the estimate of effect.
Moderate quality: Further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.
Low quality: Further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate.
Very low quality: We are very uncertain about the estimate.

* The basis of the assumed risk is the average risk of control group patients.

[1] Publication bias is likely as the funnel plot seems asymmetric.

Fig 3. GRADE summary of findings table.

doi:10.1371/journal.pone.0171168.g003

size of fixed-effects models was quite similar to CORONA [13] which weighted 59.9%, 50.8%, and 63.7% for the respective outcomes of the study population.

In Grade output (Fig 3), the SCD rate was 10.7% (n = 540/5057) in those treated with statins compared with 10.8% (n = 544/5020) in those treated with placebo/control with an absolute effect of 9 fewer per 1000 (from 33 fewer to 23 more). All-cause mortality rate was 25.9% (n = 1436/5549) in those treated with statins compared with 27.3% (n = 1494/5475) in those treated with placebo/control with an absolute effect of 33 fewer per 1000 (from 68 fewer to 5 more). Also, hospitalization rate was 33.33% (n = 1804/5412) in those treated with statins compared with 38% (n = 2033/5349) in those treated with an absolute effect of 80 fewer per 1000 (from 23 fewer to 129 fewer) (see also S1 Table). The estimated sample size needed to detect a statistically significant difference, given the effect size found, were 599506, 15394 and 1642 respectively for SCD, all-cause mortality and HWHF [59]. Moreover, the estimated predictive intervals (PIs) were statistically insignificant [0.52 to 1.63, 0.54 to 1.15, and 0.64 to 1.19] in SCD, all-cause mortality and HWHF, respectively, as shown in Fig 4.

The retrieved published systematic reviews and meta-analyses were evaluated against potential biases and are compared with the results of our systematic review in the discussion section.

Meta-regression and heterogeneity of combined studies

For SCD, all-cause mortality and HWHF, heterogeneity estimators were, respectively: I^2 = (42.8%, 37.9%, and 58%) and Tau^2 = (0.0353, 0.0135, and 0.0215). We intended to explain the heterogeneity by a meta-regression analysis for cholesterol levels changes for each outcome but this was not statistically feasible because of zero events in the intervention or control group in some trials [log (OR) or log (RR) became undefined]. Also, at least because the number of studies left for any outcome assessment decreased and the risk of type error may have probably increased.

However, we tried to explain the heterogeneity observed for assessed outcomes by stratification according to follow-up duration. As shown in Fig 5, studies were classified into three categories: 6 months or less, more than 6 months and less than 12, and more than 12 months. Negative result was maintained in this analysis except for studies of less than 12 months of follow-up which was likely due to small-study effects, revealed by insignificant reduction for studies more than 12 months which represented between 85–92% of the studied population.

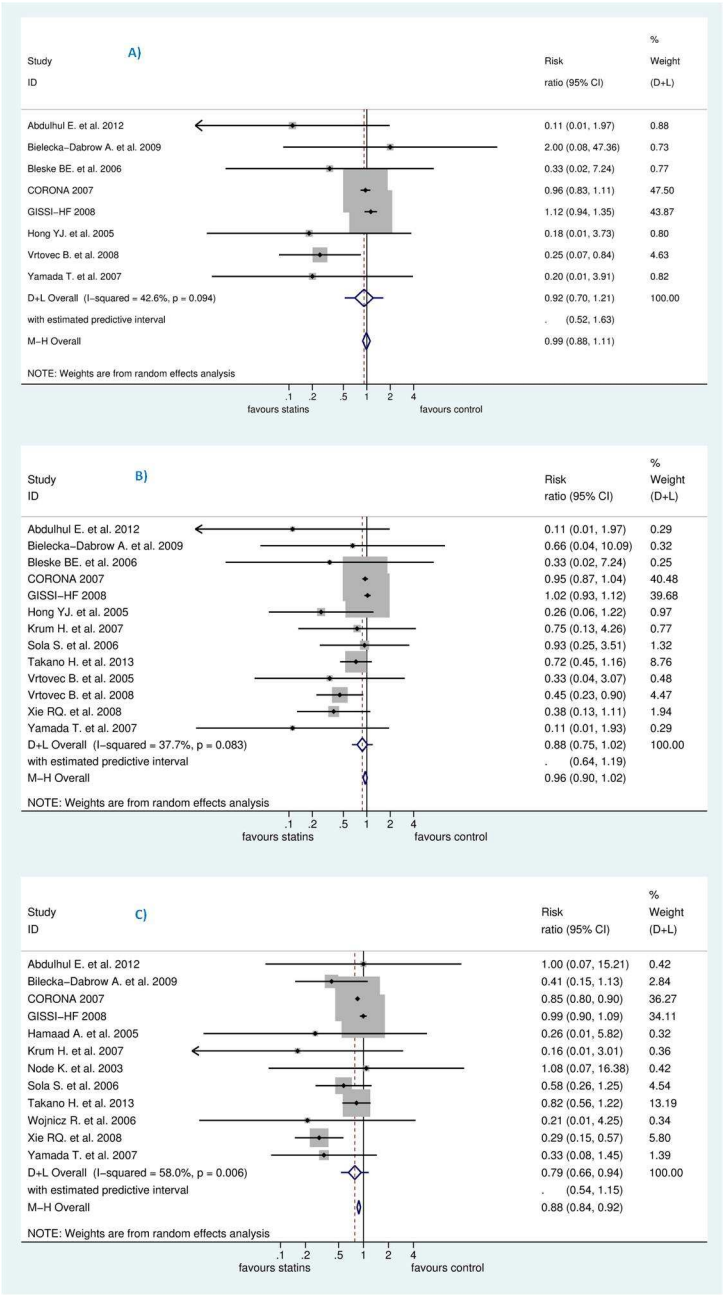

Fig 4. Efficacy of statins compared with control in heart failure for the prevention of (A) sudden cardiac death (SCD) **(B)** all-cause mortality, and **(C)** hospitalization for worsening heart failure (HWHF).

doi:10.1371/journal.pone.0171168.g004

Sensitivity and subgroup analyses

Both CORONA [13] and GISSI-HF [12] comprised at least 70% of the study population irrespective of the outcome or the model used. Therefore, we conducted a sensitivity analysis to assess the impact of these trials on the results by excluding them from the random-effect estimate. This resulted into significant difference: RR for SCD [0.27 (95% CI, 0.11 to 0.66), P = 0.004], RR for all-cause mortality [0.55 (95% CI, 0.40 to 0.77), P = 0.0001], and RR for HWHF [0.54 (95% CI, 0.39 to 0.76), P = 0.0001] (see Fig 6).

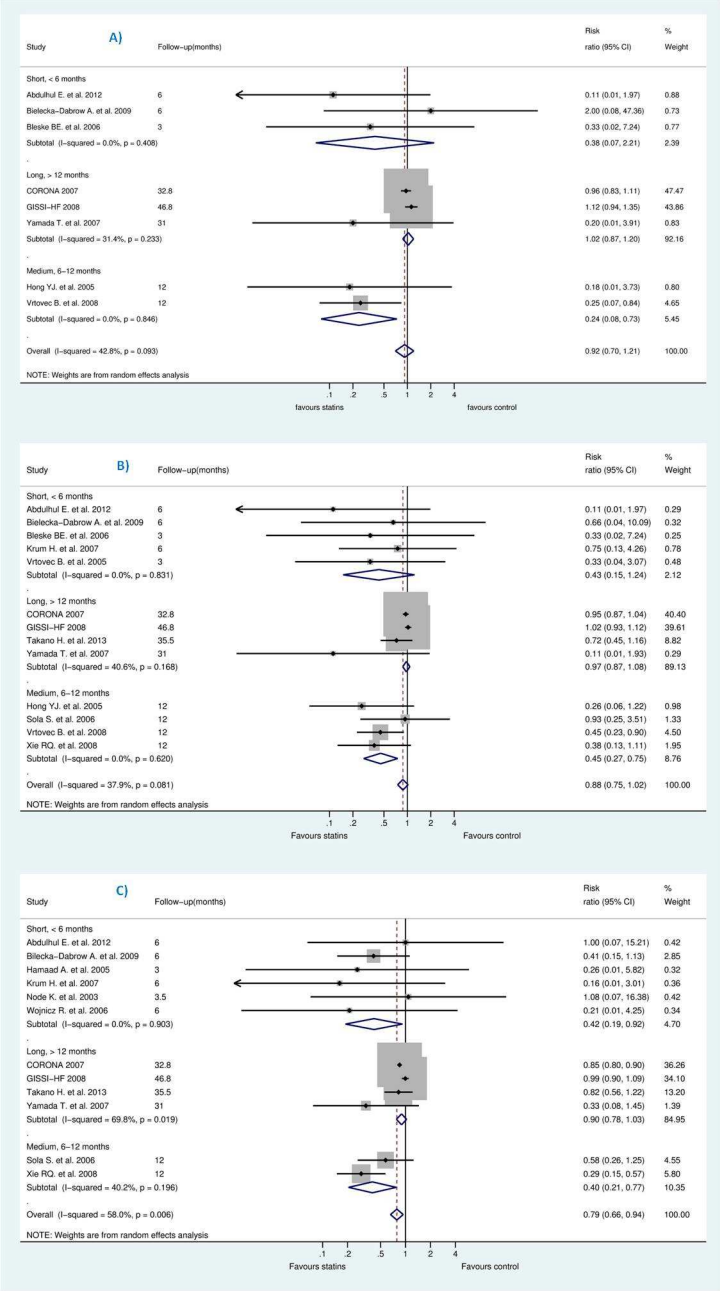

Fig 5. Efficacy of statins compared with control in heart failure stratified by follow-up duration for the prevention of (A) sudden cardiac death (SCD) **(B)** all-cause mortality, and **(C)** hospitalization for worsening heart failure (HWHF).

doi:10.1371/journal.pone.0171168.g005

On the other hand, after deleting less powered studies, i.e., those with less than 100 patients in each group, this resulted into insignificant increase in SCD [RR 1.03 (95% CI, 0.88 to 1.20), P = 0.725], RR for all-cause mortality [0.98 (95% CI, 0.90 to 1.06), P = 0.566], and RR for HWHF [0.90 (95% CI, 0.79 to 1.04), P = 0.149]. The remaining studies were (CORONA [13], GISSI-HF [12] for SCD plus Takano H. et al. (PEARL) [31] for all-cause mortality and HWHF outcomes) (see Figs 7 and 8).

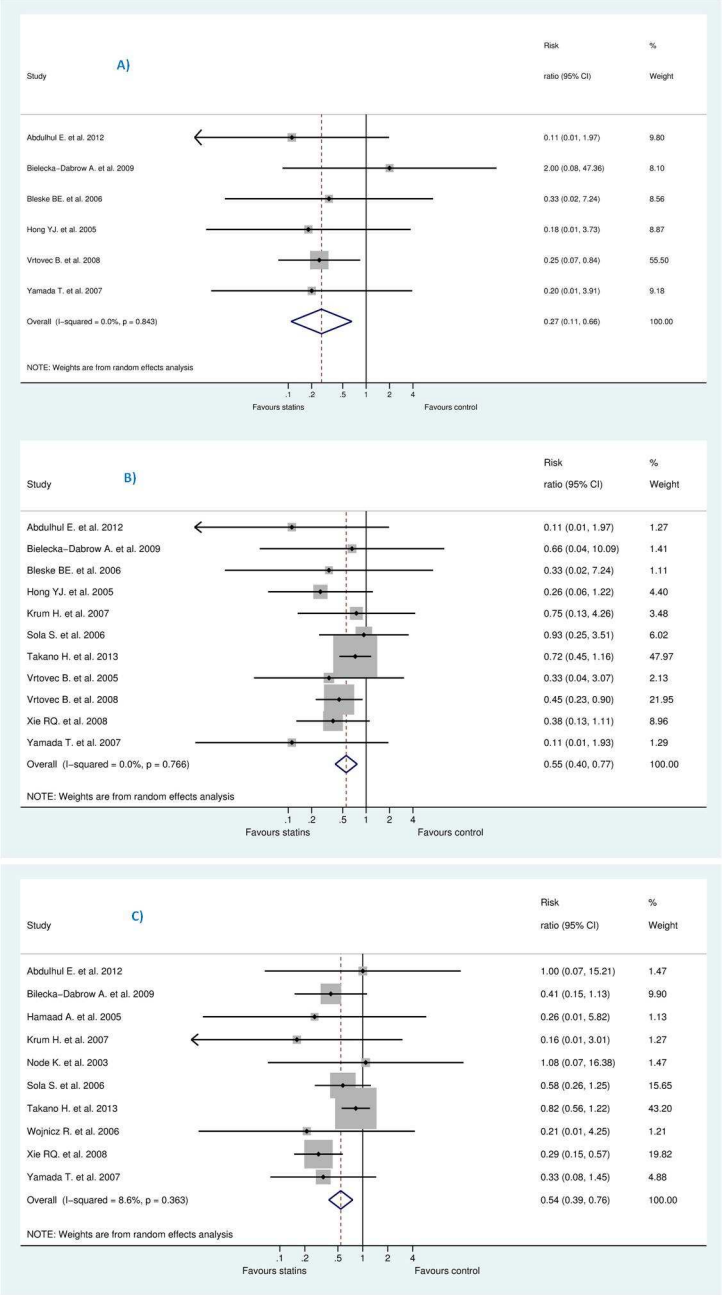

Fig 6. Sensitivity analysis without corona and GISSI-HF.

doi:10.1371/journal.pone.0171168.g006

To test our choice of the summary statistic, we shifted to OR instead of RR, the result changed slightly: OR for SCD [0.89 (95% CI, 0.65–1.23), P = 0.49], OR for all-cause mortality [0.81 (95% CI, 0.65–1.00), P = 0.05] and OR for HWHF [0.66 (95% CI, 0.50 to 0.87), P = 0.008]. Also, we stratified studies according to being ischaemic, non-ischaemic or both (see Fig 9). This resulted into statistically insignificant difference for all outcomes: SCD, all-cause mortality and HWHF. The effect size for ischaemic group, non-ischaemic and ischaemic/non-ischaemic were, respectively: SCD [RR 0.42 (95% CI, 0.12–1.47), 0.33 (95% CI, 0.02–7.24), and 0.85 (95%

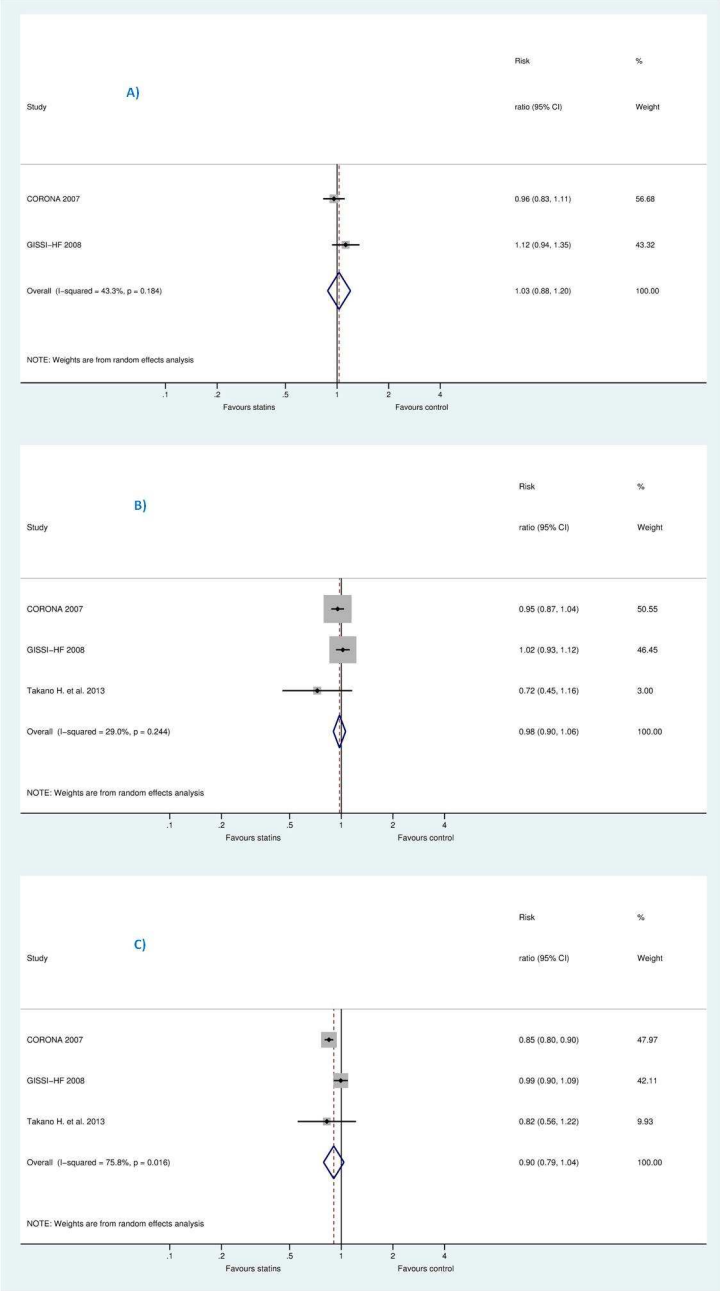

Fig 7. Sensitivity analysis without less powered studies.

doi:10.1371/journal.pone.0171168.g007

CI, 0.36–1.99), overall P = 0.49]; all-cause mortality [RR 0.68 (95% CI, 0.44–1.05), 0.80 (95% CI, 0.24–2.68), and 0.57 (95% CI, 0.24–1.34), overall P = 0.087]; HWHF [RR 0.97 (95% CI, 0.86–1.09), 0.53 (95% CI, 0.19–1.49), and 0.57 (95% CI, 0.28–1.17), overall P = 0.015]. We noticed that only five studies had our outcome of interest as a primary endpoint. When studies were stratified according to their respective endpoints, this resulted into significant differences and a considerable heterogeneity among studies with mortality and/or hospitalization endpoints (Fig 10).

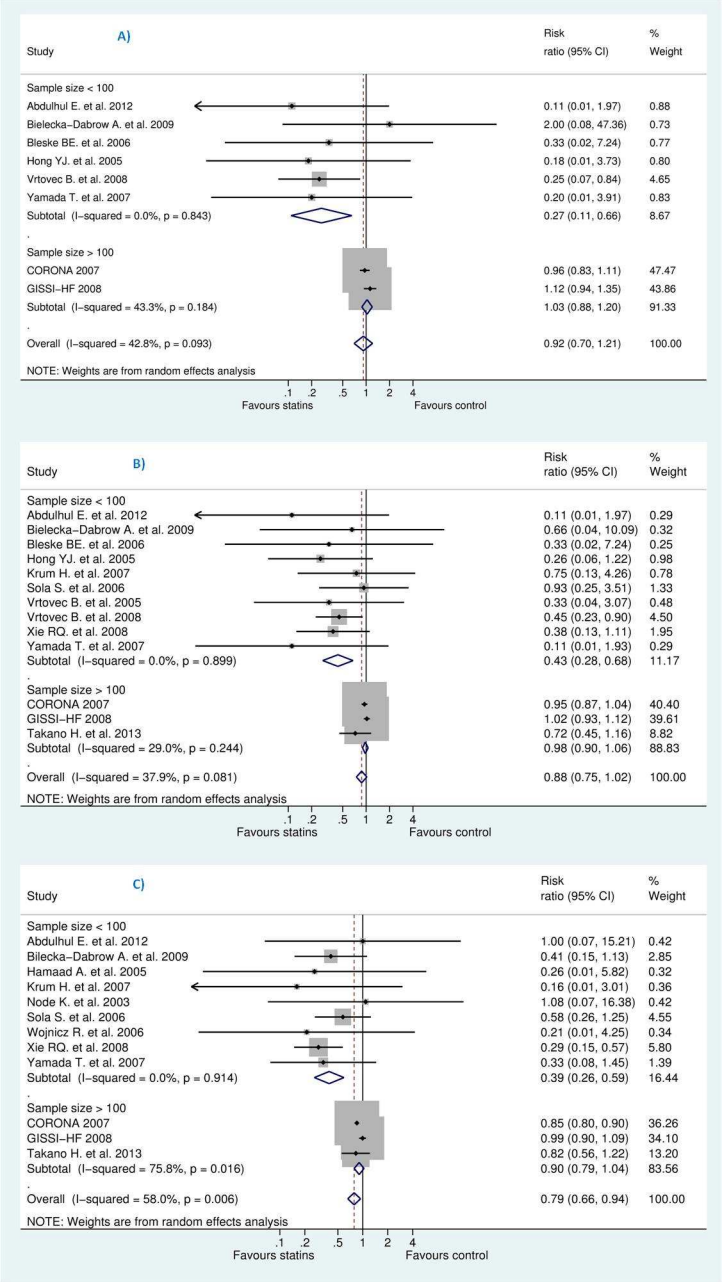

Fig 8. Efficacy of statins compared with control in heart failure stratified by sample size (more than 100 or less than 100) for the prevention of (A) sudden cardiac death (SCD) **(B)** all-cause mortality, and **(C)** hospitalization for worsening heart failure (HWHF).

doi:10.1371/journal.pone.0171168.g008

Publication bias

According to the funnel plots, we estimated that publication bias was likely for the three outcomes (SCD, all-cause mortality, and HWHF); asymmetry appeared bigger for all-cause mortality (Fig 11). Funnel plot analyses were reinforced [60] for all-cause mortality and HWHF (for which the number of trials was above 10) by Egger and Harbord tests which showed significant small-study effects for all-cause mortality (P = 0.001) but insignificant result for

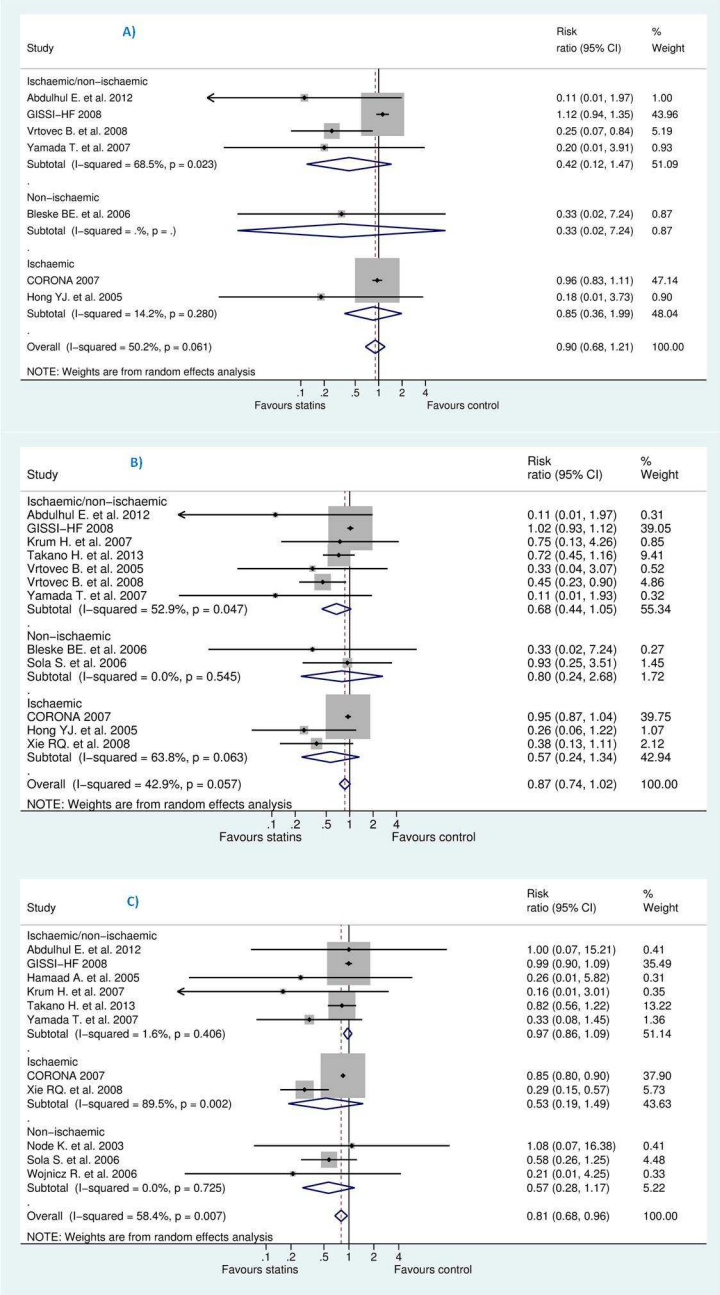

Fig 9. Efficacy of statins compared with control in heart failure stratified by population type (ischaemic or non-ischaemic) for the prevention of (A) sudden cardiac death (SCD) **(B)** all-cause mortality, and **(C)** hospitalization for worsening heart failure (HWHF).

doi:10.1371/journal.pone.0171168.g009

HWHF (P = 0.088 and P = 0.062). Overall, publication bias was taken into account in the GRADE evaluation and the synthesis of the study results.

Discussion

Our systematic review and meta-analysis showed no clinical benefits of adding statins to the treatment of HF patients with reduced left ventricular ejection fraction. Statins are ineffective

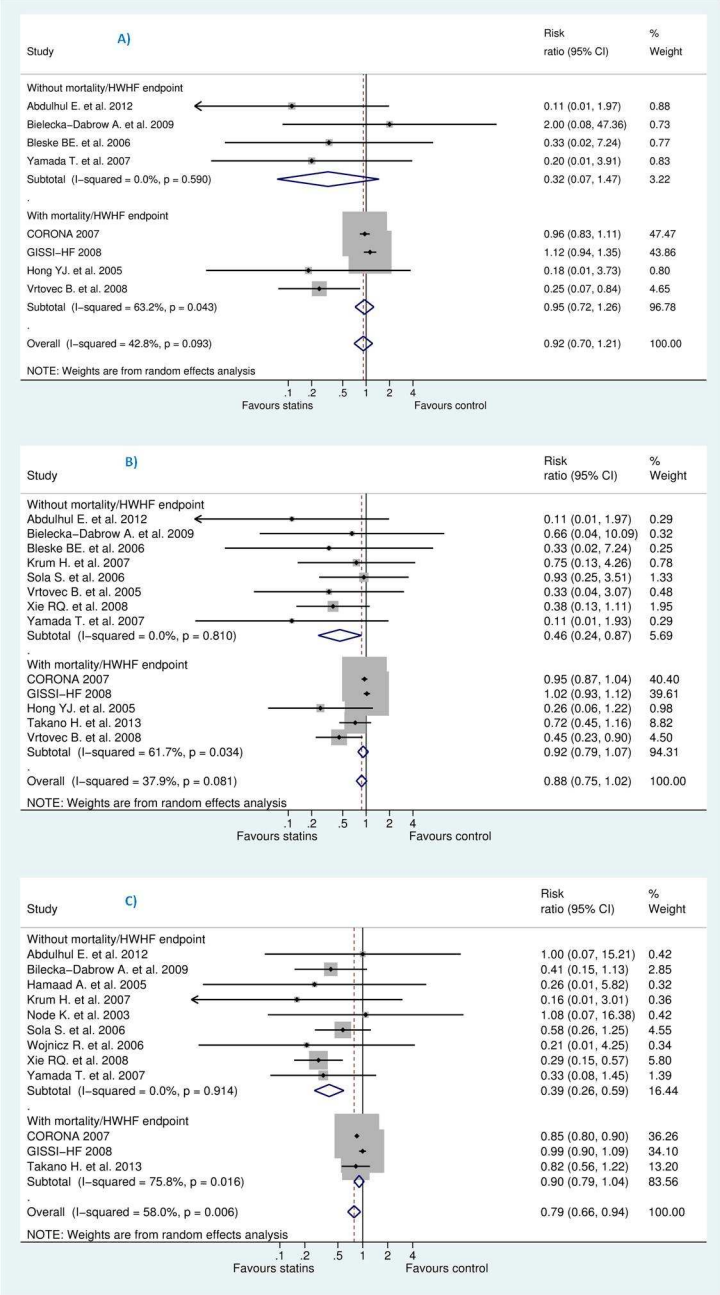

Fig 10. Efficacy of statins compared with control in heart failure stratified by endpoint (those with against without mortality and/or HWHF) for the prevention of (A) sudden cardiac death (SCD) **(B)** all-cause mortality, and **(C)** hospitalization for worsening heart failure (HWHF). [Random-effects model].

doi:10.1371/journal.pone.0171168.g010

for the prevention of sudden cardiac death (SCD), all-cause mortality but may slightly decrease hospitalization for worsening heart failure (HWHF). However, the apparent reduction of HWHF might result from small-study effects. Actually the studies with a longer follow-up (more than one year), represented almost 85% of the population in this analysis, showed insignificant reduction. The little reduction in the number of hospitalization is not supported by the estimated predictive intervals [0.64 to 1.19] derived from random effects models.

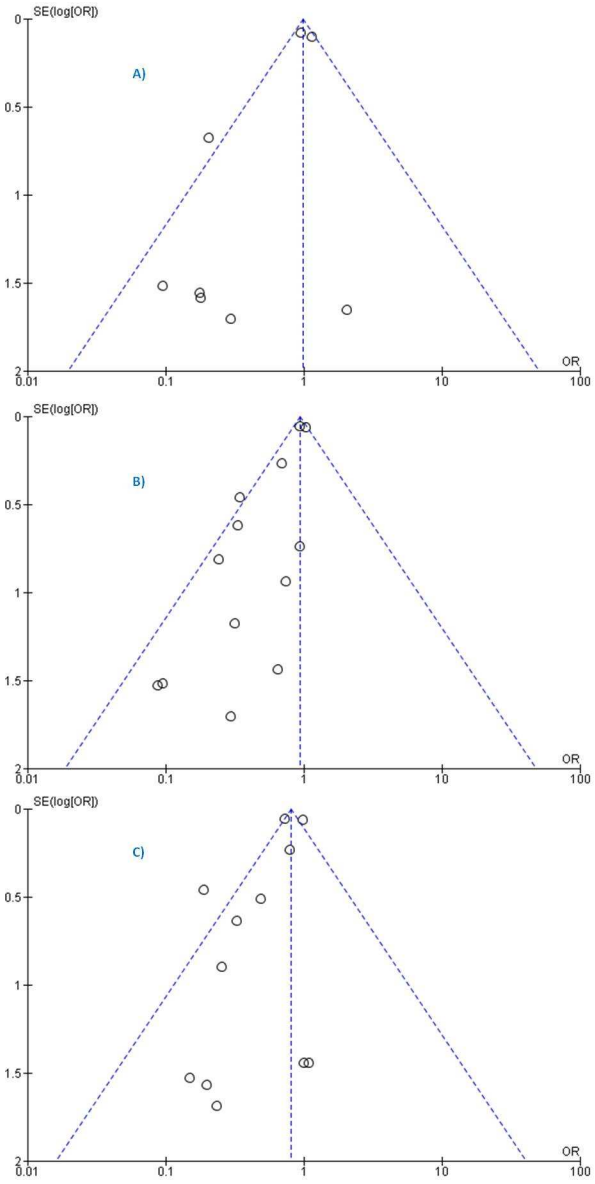

Fig 11. Funnel plots of SE (log odds ratio) by odds ratio to evaluate publication bias for the effect of treatment for prevention of (A) sudden cardiac death (SCD) **(B)** all-cause mortality, and **(C)** hospitalization for worsening heart failure (HWHF). (Fixed-effects model).

doi:10.1371/journal.pone.0171168.g011

Several previously published meta-analyses [9,11,18,38] evaluated the effects of statins in SCD prevention and reported a decrease but all studies were limited by indirectness as they included different populations, i.e. patient with coronary heart disease (CHD), recent and history of myocardial infarction (MI), or diabetes, and even primary-and-secondary prevention statin trials [18].

Another meta-analysis [24] claimed that statins reduce all-cause mortality in chronic heart failure. The study had a biased result as authors lumped together randomized clinical trials (RCTs) with non-causal observational studies [61] with a high heterogeneity ($I^2 = 90\%$).

Our sensitivity and subgroup analyses suggested a potential publication bias, as indicated by the unbalanced presence of small studies which showed beneficial effects and heterogeneity

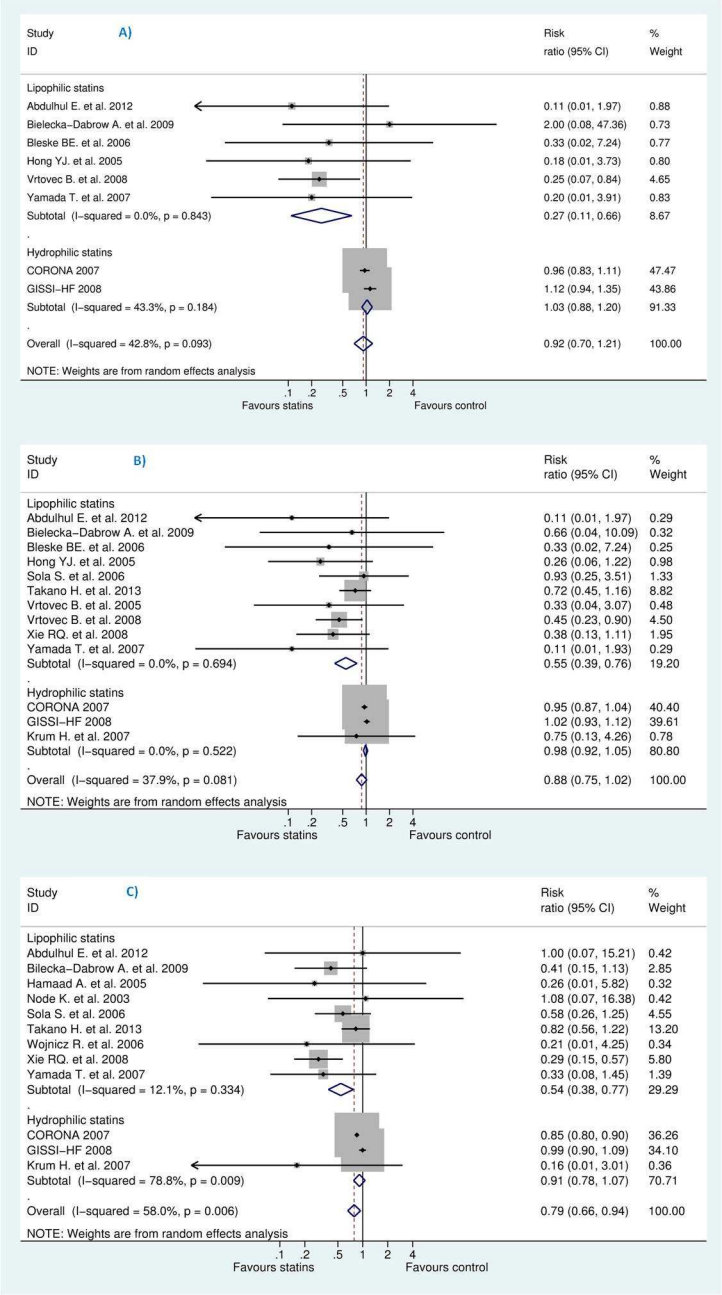

Fig 12. Efficacy of statins compared with control in heart failure stratified by statin type (lipophilic versus hydrophilic) for the prevention of (A) sudden cardiac death (SCD) **(B)** all-cause mortality, and **(C)** hospitalization for worsening heart failure (HWHF).

doi:10.1371/journal.pone.0171168.g012

among included studies. The two large clinical trials CORONA [13] and GISSI-HF [12] showed no benefit of statins and thus different results than the small studies. Many argued that CORONA [13] and GISSI-HF [12] used a hydrophilic statin (rosuvastatin) that may have a different effectiveness than the predominantly lipophilic statins (atorvastatin, simvastatin, lovastatin, fluvastatin, cerivastatin and pitavastatin)—pravastatin and rosuvastatin are relatively hydrophilic[62].

Based on statin type, two meta-analyses [17,21] included lipophilic statins and stated that they decreased all-cause mortality, cardiovascular death and HWHF. Both studies included only 13 RCTs, compared to 24 in this analysis, and the latter mistakenly reported death events in Hammad A. et al. [44] and Node K. et al [50] whereas the authors of those small trials stated that no death occurred during the study period. This limitation created more small-scale trials that exaggerated the benefits of lipophilic statins In addition, those meta-analyses included *Takano H. et al.* [31], representing at least 48% of the population in the analysis, which used a lipophilic statin (pitavastatin) and reported no overall significant decrease in all-cause death or HWHF.

Moreover, a meta-analysis [63] pooled 10 trials (out of the 24 in our analysis) and showed no benefits for overall non stratified population and concluded for trend toward benefits for atorvastatin at subgroup analysis. However, given the influence of small, poor quality RCTs on the overall pooled results and only 5% of the studied population for atorvastatin, the authors' conclusion seemed overstated [64]. Such result was quite similar to a study [22] which excluded both CORONA [13] and GISSI-HF [12] for no apparent reason.

Although one cannot exclude that different statins would have different effects on HF outcomes, the hypothesis of differences among statins does not seem to be biologically plausible [16]. According to our sensitivity analysis, the inclusion or exclusion of CORONA [13] and GISSI-HF [12] impacted the result and changed it significantly. Also, since both studies represented 80% of the population in the analysis, we believe that only large RCTs with head-to-head comparison would give us reliable evidence (see Fig 12). Of note, two studies [36,39] directly compared atorvastatin (lipophilic statin) to rosuvastatin (hydrophilic statin) but for surrogate endpoints like C-reactive protein and hence did not evaluate any clinical outcomes with a similar output to *Lei Zhang et al.* [35,37].

On the other hand, a meta-analysis [33] evaluated statins' effect in mortality prevention in heart failure with preserved ejection fraction (HFpEF) but included only cohorts and other observational studies. Our study, restricted to RCTs, did not include these patients. Similarly, a study [34] reported statin benefits in non-ischaemic cardiomyopathy and included two observational studies and ad-hoc analysis of 4 RCTs of which 2 were beta-blockers' trials and so are not immune to bias. Although our analysis included 7 non-ischaemic HF trials, we could not pool them all together because of the limited data on mortality events.

A recent systematic review [19] concluded that statins did not decrease mortality, and might lead to little or no decrease in HWHF which is consistent with our findings. Likewise, a meta-analysis [20], included 13 trials, among the 24 trials in our analysis, concluded that statins might have no beneficial effects on all-cause death, cardiovascular death or pump failure and rehospitalization for heart failure in the overall (non-stratified) CHF populations. The authors stratified CHF patients according to age but since individual data were not used, the possible benefits for younger patients (< 65 years) might be unreliable as this could also be related to the stage and severity of CHF.

Of note, we think that the inability to prove the benefits of statins may be outweighed by a negative impact of cholesterol lowering in chronic heart failure (CHF) patients, as some evidence suggests that low levels of total cholesterol are associated with worse outcomes and a marked increase in mortality in CHF.[22,65–67]. Also any harm for statins in HF might also be masked, given the potential publication bias.

Overall, our updated review supports the current guidelines and do not recommend statins in patients with diagnosis of heart failure as this will avoid unnecessary prescriptions, overuse of care, and might help reluctant or hesitating physicians to make an evidence-based decision based on updated knowledge.

Limitations and strength of this study

One principle of a meta-analysis is that included studies should be as much as similar to each other as possible. However, it is almost impossible to find identical studies with the same patient characteristics. This limitation is common and particularly in heart failure (HF) patients who usually have various characteristics and co-morbidities.

Our study revealed a potential for publication bias as shown from funnel plots for clinical outcomes. Although, this might be a serious limitation, we tried to take it into account in the study synthesis. As a consequence, this limitation had also downgraded the quality of the evidence from high to moderate within GRADE approach.

Our study had no access to individual data and unpublished studies and no data received by correspondence, though we have contacted studies' corresponding authors.

For SCD outcome, for instance, due to the limited number of studies in ischaemic and non-ischaemic groups and potential heterogeneity, we could not investigate if statins have the same effects on ischaemic and non-ischaemic heart failure.

For blinding of investigators or outcome assessors in included trials, most studies had unclear risk but we believe this might have little impact due to weak subjectivity at least for all-cause mortality outcome in double blind trials.

The studies, in our analysis, had not recruited HF patients with preserved ejection fraction (HFpEF) and so this result might not be applicable to them.

Our study could contribute to the understanding of the existing discordant evidence in the evaluation of statins efficacy in clinical outcomes in heart failure with reduced ejection fraction which is revealed by heterogeneity, publication bias and small-study effects within clinical trials.

To our knowledge, this is the first analysis that evaluates the efficacy of statins for SCD prevention in HF patients; it helps bridge the gap of controversy towards statin benefits in important clinical outcomes rather than surrogate endpoints.

Ongoing studies and perspectives

An ongoing study [https://clinicaltrials.gov/ct2/show/NCT01554592] is expected to resolve the issue of statin withdrawal in CHF patients. Future RCTs are still needed to: (i) compare lipophilic statins with hydrophilic statins. (ii) verify any class effect for statins and (iii) if any subpopulation of heart failure might benefit from statins in order to improve survival and reduce morbidity.

Conclusion

Limited by a potential publication bias, and heterogeneity between studies, our systematic review and meta-analysis showed that statins do not decrease SCD or all-cause mortality. The benefits of statins regarding a possible decrease in hospitalization for worsening heart failure was not supported by estimated predictive intervals which means the expected treatment effects for a new brand trial. Physicians should follow the current guidelines of ACCF/AHA and not systematically prescribe statins for heart failure patients with left ventricular ejection fraction less than 45%. Ongoing and future trials should shed more light if any subpopulation might benefit from a particular statin.

Summary for current knowledge

Heart failure has a high morbidity and mortality rate despite significant advances in therapy, diagnosis and management.

There is some evidence that low total cholesterol is associated with worse outcomes in (advanced) chronic heart failure, contrary to the general population.

Statin effects in sudden cardiac death prevention in heart failure is unknown and current discordant studies for other clinical outcomes like all-cause mortality are unresolved.

Summary for this study outcome

This study delivers a clear message of no benefits of statins in HF patients in response to an existing controversy.

Publication bias and small-study effects offer a possible explanation to the observed discrepancies between trials, and between previous and our meta-analyses.

Within available data and potential publication bias, statins are ineffective in sudden cardiac death prevention and all-cause mortality reduction and may or may not slightly reduce hospitalization for worsening heart failure.

Supporting information

S1 File. search strategy equations and result.
(PDF)

S2 File. PRISMA Checklist for statins in heart failure.
(DOCX)

S1 Table. Number of events in statin group versus control group for each outcome.
(DOCX)

Acknowledgments

We thank Mr. Thomas Brauchli and Mrs. Cécile Jaques for the help in the search strategy in this paper.

Author contributions

Conceptualization: MA.

Data curation: MA HHL MF.

Formal analysis: MA BB FG.

Investigation: MA HHL MF.

Methodology: MA BB FG.

Project administration: BB.

Software: MA.

Supervision: MA BB FG.

Writing – original draft: MA.

Writing – review & editing: MA BB FG HHL MF.

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APPENDIX II “Protocol: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017067442”

Effectiveness of drug interventions to prevent sudden cardiac death in patients with heart failure and reduced ejection fraction: an overview of systematic reviews

Muaamar Al-Gobari, Sinaa Al-Aqeel, François Gueyffier, Bernard Burnand

Citation

Muaamar Al-Gobari, Sinaa Al-Aqeel, François Gueyffier, Bernard Burnand. Effectiveness of drug interventions to prevent sudden cardiac death in patients with heart failure and reduced ejection fraction: an overview of systematic reviews. PROSPERO 2017 CRD42017067442 Available from: http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017067442

Review question

Which guideline-directed drug therapy shows efficacy or inefficacy for sudden cardiac death prevention in heart failure patients with reduced ejection fraction?
Whether beta-blockers (BBs), angiotensin converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARBs), anti-aldosterone antagonists or mineralocorticoid-receptor antagonists, amiodarone, antiarrhythmics, LCZ696, statins and fish oil supplementation are effective or not in sudden cardiac death and all-cause mortality reduction?

Searches

MEDLINE (up to May 23, 2017), Embase (up to May 23, 2017), and Cochrane Central Register of Controlled Trials (CENTRAL) (up to May 23 2017) will be searched, with free full access in Switzerland.
The search strategy will include a filter, a mixture of medical subject heading terms [MeSH and EMTREE in MEDLINE and Embase, respectively], text words, as well as truncation, where possible, without any language, publication or date restrictions.
Manual searches will be conducted for more potential studies. Automatic bi-monthly update alerts will be created. Contact corresponding authors will be made for any relevant unreported data.

Types of study to be included

Overviews (if they exist), systematic reviews and meta-analyses and landmark clinical trials (if no systematic review exists for a particular intervention).

Condition or domain being studied

Heart failure with reduced ejection fraction (HFrEF); evaluation of drug therapy for sudden cardiac death (SCD) and all-cause mortality prevention.

Participants/population

Inclusion: Patients with heart failure (HF), being treated with any of the drugs listed above/below and an outcome of interest (SCD and/or all-cause mortality) is evaluated.
Exclusion: Non-drug or device therapy in the targeted HF population, and where patients < 18 years old were excluded from the analyses.

Intervention(s), exposure(s)

Any drug therapy for heart failure, includes: Beta-blockers (BBs), angiotensin converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARBs), anti-aldosterone antagonists or mineralocorticoid-receptor antagonists, amiodarone, antiarrhythmics, LCZ696, statins and fish oil supplementation, under which they were evaluated for efficacy to prevent SCD and/or all-cause mortality, in heart failure with reduced ejection fraction. SCD is defined as an unexpected death that occurs after 1h or 2h from the onset of symptoms. If the specific definition is different, in the included studies, it will be reported in the final manuscript.

Comparator(s)/control

Subjects receiving a placebo or a usual care treatment, other than the intervention of interest, will serve as a comparator.

Primary outcome(s)
Sudden cardiac death.

Secondary outcome(s)
All-cause mortality.

Data extraction (selection and coding)
After screening titles/abstracts and full-text papers, the final selection, which meet the inclusion criteria, will be used, to independently extract relevant data, by at least two reviewers. Discrepancies will be resolved through a discussion involving a third reviewer, where necessary. Extracted data will include: Study authors, study design, drug used, control/comparator, type of population or setting, baseline characteristics, demographics, and AMSTAR Score. Relevant missing or unreported data will be requested from corresponding authors or study investigators, where applicable.

Risk of bias (quality) assessment
The quality of included studies will be assessed using AMSTAR (Cochrane tool to assess systematic reviews). Two reviewers will independently score the studies according to a pre-defined sheet. It will include an a priori design, double study selection and data extraction, search strategy, quality assessment and how the quality informs the review conclusions, publication bias and conflict of interest declaration (https://amstar.ca/Amstar_Checklist.php). Where applicable, GRADE will be used to assess consistency, indirectness, imprecision and publication bias of the included studies.

Strategy for data synthesis
We will provide a narrative synthesis of the findings from the included studies and explain if any multiple reviews exist. The results will not be combined in one synthesis for all interventions, but rather individually synthesised by (each) intervention against the outcome of interest. Heterogeneity and inconsistency between reviews will be assessed and an appraisal for potentially discordant reviews and their respective quality will be presented. We will report and state our conclusion for each intervention against the outcomes in the targeted population of heart failure in a way that will ensure a full response to the research question.

Analysis of subgroups or subsets
We plan to do a subgroup analysis for each intervention according to the etiology of heart failure: ischaemic versus non-ischaemic. This will only be possible if the data exist.

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Anticipated or actual start date
23 May 2017

Anticipated completion date
29 December 2017

Funding sources/sponsors
The funding of this study is integrated into the work of our research group. The Funds are obtained from affiliated institutions for the respective authors.

Conflicts of interest
None known

Language
English

Country
Saudi Arabia, France, Switzerland

Stage of review
Review_Completed_not_published

Subject index terms status
Subject indexing assigned by CRD

Subject index terms
Death, Sudden, Cardiac; Heart Failure; Humans; Ventricular Function, Left

Date of registration in PROSPERO
15 June 2017

Date of publication of this version
12 January 2018

Details of any existing review of the same topic by the same authors

Stage of review at time of this submission

Stage	Started	Completed
Preliminary searches	Yes	Yes
Piloting of the study selection process	Yes	Yes
Formal screening of search results against eligibility criteria	Yes	Yes
Data extraction	Yes	Yes
Risk of bias (quality) assessment	Yes	Yes
Data analysis	Yes	Yes

Versions
15 June 2017
12 January 2018

APPENDIX III “Effectiveness of drug interventions to prevent sudden cardiac death in patients with heart failure and reduced ejection fraction: an overview of systematic reviews”

BMJ Open

Effectiveness of drug interventions to prevent sudden cardiac death in patients with heart failure and reduced ejection fraction: an overview of systematic reviews

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To cite: Al-Gobari M, Al-Aqeel S, Gueyffier F, *et al*. Effectiveness of drug interventions to prevent sudden cardiac death in patients with heart failure and reduced ejection fraction: an overview of systematic reviews. *BMJ Open* 2018;**8**:e021108. doi:10.1136/bmjopen-2017-021108

► Prepublication history and additional material for this paper are available online. To view these files, please visit the journal online (http://dx.doi.org/10.1136/bmjopen-2017-021108).

Received 11 December 2017
Revised 12 June 2018
Accepted 26 June 2018

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ABSTRACT

Objectives To summarise and synthesise the current evidence regarding the effectiveness of drug interventions to prevent sudden cardiac death (SCD) and all-cause mortality in patients with heart failure with reduced ejection fraction (HFrEF).

Design Overview of systematic reviews.

Data sources MEDLINE, Embase, ISI Web of Science and Cochrane Library from inception to May 2017; manual search of references of included studies for potentially relevant reviews.

Eligibility criteria for study selection We reviewed the effectiveness of drug interventions for SCD and all-cause mortality prevention in patients with HFrEF. We included overviews, systematic reviews and meta-analyses of randomised controlled trials of beta-blockers, angiotensin-converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARBs), antialdosterones or mineralocorticoid-receptor antagonists, amiodarone, other antiarrhythmic drugs, combined ARB/neprilysin inhibitors, statins and fish oil supplementation.

Review methods Two independent reviewers extracted data and assessed the methodological quality of the reviews and the quality of evidence for the primary studies for each drug intervention, using Assessing the Methodological Quality of Systematic Reviews (AMSTAR) and Grading of Recommendations, Assessment, Development and Evaluation(GRADE), respectively.

Results We identified 41 reviews. Beta-blockers, antialdosterones and combined ARB/neprilysin inhibitors appeared effective to prevent SCD and all-cause mortality. ACE-i significantly reduced all-cause mortality but not SCD events. ARBs and statins were ineffective where antiarrhythmic drugs and omega-3 fatty acids had unclear evidence of effectiveness for prevention of SCD and all-cause mortality.

Conclusions This comprehensive overview of systematic reviews confirms that beta-blockers, antialdosterone agents and combined ARB/neprilysin inhibitors are effective on SCD prevention but not ACE-i or ARBs. In patients with high risk of SCD, an alternative therapeutic strategy should be explored in future research.

Systematic review registration PROSPERO 2017: CRD42017067442.

Strengths and limitations of this study

- A major strength of our study is that it summarises and synthesises the effectiveness of most evidence-based drug interventions in heart failure patients with reduced ejection fraction for sudden cardiac death (SCD) prevention and classified drug interventions according to the current evidence of their effectiveness.
- Our study used data from published studies and no data from unpublished studies.
- Our study reviews most heart failure drugs on the prevention of SCD and all-cause mortality but limited in scope for not including some drugs such as digoxin, ivabradine and non-drug interventions/devices such as implantable cardioverter defibrillators.

INTRODUCTION

Heart failure (HF) morbidity and mortality constitute an important burden for patients and for the healthcare systems in both developed and developing countries.[1] Patients with HF are frequently hospitalised and have a high mortality risk because of a poor prognosis or an unexpected death, termed sudden cardiac death (SCD). In people diagnosed with HF, SCD occurs at 6–9 times the rate of the general population. Almost 20% and 80% of patients die within one year and eight years of initial diagnosis, respectively.[1 2] Risk factors of SCD were reported to be similar to cardiovascular diseases. However, the most studied and proven predictor of SCD in patients with HF is left ventricular ejection fraction.[3] Potential drug interventions in patients with heart failure with reduced ejection fraction (HFrEF) include beta-blockers (BBs), angiotensin-converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARBs), antialdosterones or mineralocorticoid receptor antagonists, amiodarone, other

antiarrhythmic agents, combined ARB/neprilysin inhibitors, statins and fish oil supplementation.[4] Some of these interventions aimed at improving survival and reducing total mortality and SCD in HF. For instance, a newly licensed drug (sacubitril/valsartan) in PARADIGM-HF trial (Prospective Comparison of angiotensin neprilysin inhibitor (ARNI) with ACE-i to Determine Impact on Global Morbidity and Mortality in Heart Failure) showed around 20% SCD reduction compared with enalapril.[5]

Nevertheless, optimal strategies for SCD prevention in HF are warranted if we take into account the high portion of mortality that still occurs in this population. Had a practitioner identified a patient with high risk of SCD, it would be important to know which drug is effective or not in SCD prevention other than non-drug interventions such as implantable cardioverter defibrillators (ICDs). However, the large amount of information and the multiple and sometimes discordant systematic reviews on drug interventions could be misleading.[6]

Therefore, it is vital to identify the pharmacological agents that confer the greatest benefit in SCD risk reduction particularly in high-risk patients and if any optimisation of therapeutic strategies to those patients is possible accordingly. Thus, we decided to conduct an overview of systematic reviews to summarise and synthesise the available evidence about the effectiveness of drug interventions in the prevention of SCD in HFrEF and categorised the evidence into effective, ineffective and unclear evidence of effectiveness.

METHODS

We developed an a priori protocol for this review according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (online supplementary file S1) and registered it in the PROSPERO International prospective register of systematic reviews (CRD42017067442).

Data sources and search strategy

Using the Ovid online interface, we searched MEDLINE (up to 24 May 2017), Embase (up to 23 May 2017), ISI Web of Science and the Cochrane Library (up to 24 May 2017). We identified overviews, systematic reviews and meta-analyses of randomised clinical trials by means of a search strategy (available on online supplementary file S2). The search strategy was composed of a filter,[7 8] a mixture of Medical Subject Heading terms (MeSH and EMTREE in MEDLINE and Embase, respectively), text words as well as a truncation when possible without any language or publication date restriction. We did not search conference proceedings nor the grey literature. Reference lists of the included reviews were manually checked for any additional eligible studies. We contacted corresponding reviews' and primary studies' authors to seek for relevant unreported data. If judged necessary, we intended to update the included reviews by searching primary studies published after the systematic review publication date. Apart from authors' expertise in the field, we decided to update if the most up-to-date review of a drug intervention was published more than 5 years ago and/or new clinical trials are not integrated into the evidence.

Selection criteria and data abstraction

Studies were eligible if they were overviews, systematic reviews and meta-analyses of randomised clinical trials that evaluated the effectiveness of drug interventions in patients with HFrEF. Reviews were included if they examined the effectiveness of the following drugs: BBs, ACE-i, ARBs, antialdosterones or mineralocorticoid receptor antagonists, amiodarone, antiarrhythmics, combined ARB/neprilysin inhibitors, statins and fish oil supplementation. The selected reviews should have contained at least one of the aforementioned HF therapy and had evaluated SCD and/or all-cause mortality prevention as outcomes. We used Endnote and Rayyan[9] to remove duplicates during the selection based on titles and abstracts, and full-text screening.

The abstracted data included eligibility criteria, population type, ejection fraction, study design (including intervention and comparator arms), follow-up duration and authors' evaluation of outcomes. Two reviewers (MA and SA) independently abstracted data. We resolved discrepancies by consensus or by adding a third reviewer's judgement when necessary.

Quality assessment of the included reviews

Methodological quality of the included reviews

Two authors (MA and SA) independently used the AMSTAR (Assessing the Methodological Quality of Systematic Reviews) measurement tool to assess systematic reviews included in our overview. The AMSTAR checklist comprises 11 questions (online supplementary S3 table) and each question accounted for one score point.[10] The answer of 'yes' gave a score of 1 and zero otherwise. This increasingly adopted tool was used at the data collection step as stipulated in the overview protocol.[11] If the authors of included reviews failed to publish their protocol, we deducted a score of one. In addition, we scored 'yes' if the authors mentioned that two reviewers were involved in the study screening, selection or data extraction.

Quality of evidence in the included reviews

Two authors (MA and SA) independently used the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach[12] to assess the quality of evidence of each intervention. GRADE is a widely accepted tool that allows the assessment of five key elements: risk of bias, inconsistency, indirectness, imprecision and publication bias. GRADE categorises the quality of evidence into four levels: high, moderate, low and very low. In the presence of a high risk of bias, the quality of the evidence is downgraded from high to moderate and so on. We also reported the GRADE assessments reported by the authors of the included reviews, or assessed them

otherwise. Moreover, we did not reassess the risk of bias at primary study level if authors of included reviews had sufficiently assessed their quality. In the case of the updated review of ARBs, however, we assessed the quality of newly added randomised clinical trials and integrated it into the evidence synthesis.

Statistical analysis and data synthesis

We provided a narrative synthesis of the findings of the included reviews and if multiple reviews existed for the same intervention. However, in the case of ARBs, we updated the evidence and meta-analysed the data using random effects and fixed effects model with Mantel-Haenszel methods[13] and reported random effects model to account for heterogeneity. Meanwhile, we evaluated each intervention against our outcomes of interest and synthesised the evidence taking into account heterogeneity and inconsistencies between reviews. As a rule of thumb, I^2 (I-square) values of 25%, 50% and 75% correspond to low, moderate and high levels of heterogeneity, respectively.[14]

For the purpose of our overview, we categorised the evidence of the included interventions into three categories: (1) effective interventions; (2) ineffective interventions; and (3) uncertain evidence (conflicting or inconclusive evidence). We used odds ratios (OR) and relative effect or risk ratio (RR) as a summary statistic from the most recent or largest published systematic reviews, and confidence intervals (CIs) of 95% with a significance level determined at two-sided alpha less than 5%.

Patient and public involvement

Our study did not involve direct contact with patients or the public.

RESULTS

Search result

According to our predefined eligibility criteria, our search strategy in electronic databases and manual searches resulted in 41 studies.[6 15–54] Figure 1 shows the search strategy results. At full-text level, we excluded studies that did not assess our outcome of interest (n=129), were narrative reviews (n=4), did

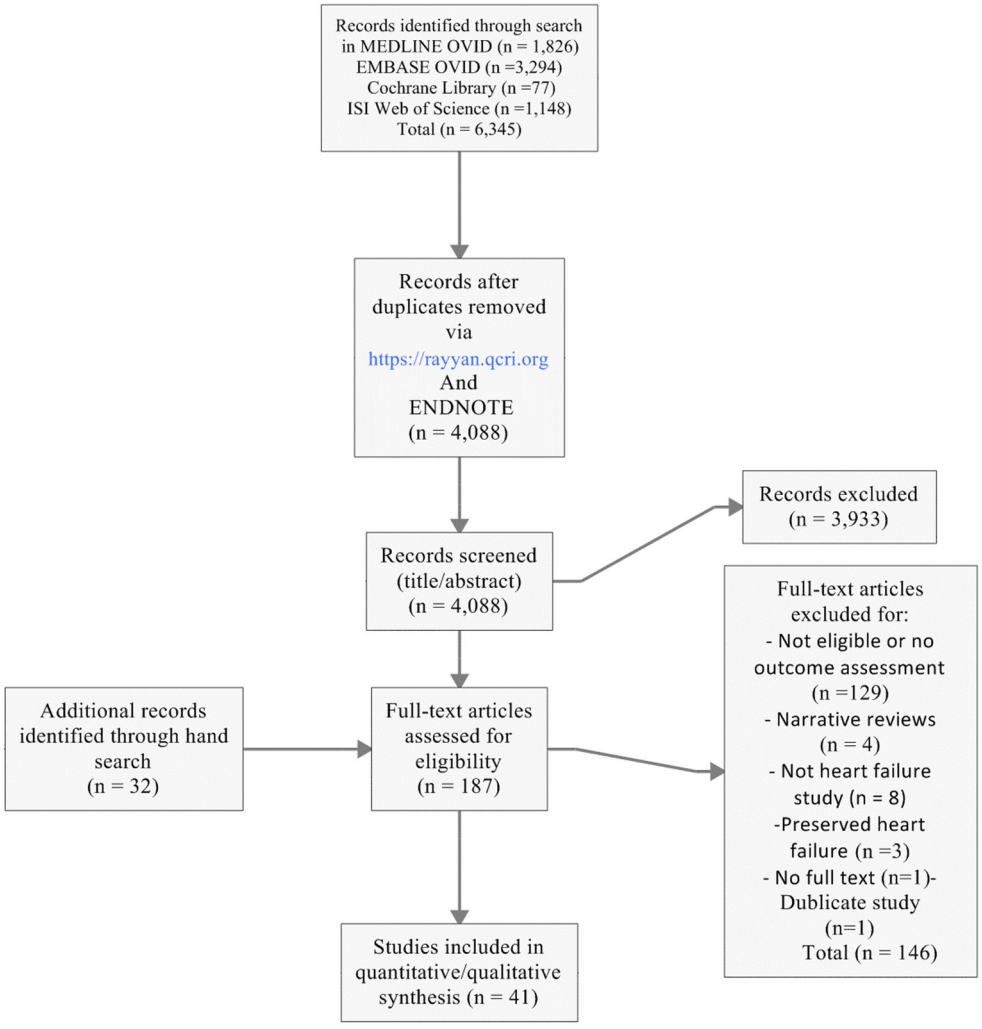

Figure 1 Flow chart for search result.

not include HF patients (n=8), included preserved patients with HF (n=3), were duplicate or had no full text (n=2).

Characteristics of the included reviews

As shown in table 1, the population of the included reviews consisted of HF patients with an ejection fraction ≤45% in most studies and a corresponding New York Heart Association classification ranging from I to IV. The effectiveness of each drug intervention has been assessed in at least one review. All reviews were systematic, except two reviews for antiarrhythmic drugs (AADs). At the time of their publication, 15 out of 41 reviews (37%) had corresponding authors based in the USA, 7 (17%) in Canada, 6 (15%) in China, 3 in Chile, 2 in France, 2 in the UK and the 6 remaining in other countries.

The disclosure and reporting of financial resources or funding varied from one study to another. Twenty-one reviews (51%) did not report the source of funding. Ten reviews (24%) reported financial supports that included governments, academic institutions and device industry. Six reviews declared financial resources as none or no external funds. Three reviews reported industry sponsorship for at least one author. One review[53] stated that one author obtained funds for the review without clarifying the source (online supplementary S4 table). We also reported findings summary of each review as stated by their respective authors (table 1).

Risk of bias and quality of reviews

As shown in table 1, the AMSTAR scores for quality assessment of the included reviews widely ranged from 2 to 10 (out of 11). All reviews had one score less because of non-listing of excluded primary studies except Cochrane reviews,[27 41] which scored 10 because of non-inclusion of grey literature in the search strategy in one review and missing information for funding resources of included primary studies in another, cited respectively (online supplementary S3 table). We did not assess the AMSTAR score for six studies, of which two[46 47] were narrative reviews, two[25 44] were individual participant or patient data meta-analyses and the other two[26 32] were overviews of reviews.

The risk of bias of the included primary studies within reviews remained as judged by the original reviews' authors with the exception of the newly added randomised trials in the update of the ARBs review that we assessed (GRADE) (table 2). The quality of evidence for BBs and antialdosterone agents obtained a high quality on the GRADE scale, while ACE-i, amiodarone and statins obtained a moderate quality. However, combined ARB/neprilysin inhibitors had a moderate and high quality for SCD and all-cause mortality outcomes, respectively, whereas ARBs had a low quality of evidence (table 2).

Up-to-dateness of included reviews

Most retrieved evidence was published within the last 10 years (2008 and on), and seven (out of nine) drug interventions with updated systematic reviews were within the last 5 years (2012 and on). Moreover, we updated the pooled results for ARBs, which resulted in slightly different results compared with the original Cochrane review.[27]

Effectiveness of interventions

We report below the summaries of our evaluation on the effectiveness of the drug interventions considered that we have categorised into effective, ineffective and uncertain effectiveness (inconclusive or conflicting evidence).

EFFECTIVE INTERVENTIONS

Beta-blockers

Meta-analyses and systematic reviews of randomised controlled trials[15–20] provided overwhelming evidence that BBs decrease the risk of SCD and all-cause mortality in patients with HFrEF. The quality of the evidence was rated high with a relative effect of 0.69 for SCD (OR, 95% CI (0.62 to 0.77)) and of 0.67 for all-cause mortality (OR, 95% CI (0.59 to 0.76)) (table 2).

Antialdosterone agents

Published studies about mineralocorticoid receptor antagonists (antimineralocorticoids) or (so-called) antialdosterones appeared effective in SCD and all-cause mortality prevention.[21 22 54] However, in a recent systematic review,[21] adverse effects (hyperkalaemia, degradation of renal function and gynaecomastia) were significantly higher in the antialdosterone-treated group compared with placebo. The quality of the evidence was rated high with relative effect for SCD (RR 0.81, 95% CI (0.67 to 0.98)) and all-cause mortality (RR 0.81, 95% CI (0.74 to 0.88)) (table 2).

ARB/neprilysin inhibitor

One meta-analysis[23] estimated the effects of combined neprilysin renin-aldosterone system inhibition and reported a reduction in SCD and all-cause mortality. The finding was principally derived from one RCT (PARADIGM-HF)[5] that showed about 16% reduction of all-cause mortality in favour of sacubitril/valsartan (LCZ696 previously) compared with enalapril (an ACE-i). This mortality reduction was attributed to a decline on both SCD (20%) and pump failure deaths.[55] Table 2 shows the relative effect for SCD (RR 0.81, 95% CI (0.69 to 0.95)) and all-cause mortality (RR 0.86, 95% CI (0.79 to 0.94)). The moderate quality of the evidence for SCD outcome was due to the estimation from one single clinical trial and the absence of data from other included studies. All-cause mortality was, however, rated as high with a possibility of downgrading

Table 1 Summary of characteristics of included studies of HF (ordered by intervention)

Author (year), country	Review type	Intervention/comparator	Population type; ejection fraction (%); NYHA	Study design n; participants n	Mean follow-up/ range (months)	Authors' findings summary	AMSTAR score
Al-Gobari *et al* (2013), France[16]*	Systematic review and meta-analysis.	Beta-blockers/placebo; 'usual care'.	HF; <45% except one study <62%; I–IV.	RCTs n=30; n=24 779.	Mean: 11.51.	Beta-blockers significantly reduced SCD, cardiovascular death and all-cause mortality.	6
Chatterjee *et al* (2013), USA[15]	Systematic review and meta-analysis.	Beta-blockers/placebo; beta-blocker; 'usual care'.	HF; <45%; II–IV.	RCTs n=21; n=23 122.	Median: 12.	The study confirmed mortality benefits of BBs compared with placebo or usual care in HF with reduced ejection fraction.	8
Brophy *et al* (2001), Canada[17]	Meta-analysis.	Beta-blockers/placebo; 'usual care'.	CHF; <45%; I–IV.	RCTs n=22; n=10 135.	Range: 3–23.	This study reported a reduction in mortality and morbidity in CHF.	4
Lee *et al* (2001), USA[18]	Systematic review and meta-analysis.	Beta-blockers/placebo.	HF; <30%; II–III.	RCTs n=6; n=9335.	Range : 12–23.	The authors recommended use of beta-blockers in HF with reduced ejection fraction and NYHA II–III.	4
Bonet *et al* (2000), USA[19]	Meta-analysis.	Beta-blockers/placebo; 'usual care'.	HF; <45%; NA.	RCTs n=21; n=5849.	Median: 6.	Beta-blockers reduce total mortality by reducing pump failure and SCD events. Vasodilating beta-blockers have perhaps greater effects on overall mortality than non-vasodilating agents.	4
Heidenreich *et al* (1997), USA[20]	Meta-analysis.	Beta-blockers/placebo; 'usual care'.	HF; <30%; I–IV	RCTs n=17; n=3039.	Range: 3–24.	Beta-blockers significantly reduced all-cause mortality but showed a trend towards better reduction in non-SCD compared with SCD.	5
Le *et al* (2016), France[21]*	Systematic review and meta-analysis.	Anti-aldosterone/placebo; 'usual care'.	HF, post-MI; <40%–>50%; I–IV.	RCTs n=25; n=19 333.	Range: 3–39.6.	In HF, antialdosterones or mineralocorticoid receptor blockers reduced SCD (subgroup analysis: 5 RCTs), all-cause mortality (subgroup analysis: 10 RCTs) and cardiovascular, all-cause and cardiovascular hospitalisation. Adverse effects (hyperkalaemia, degradation of renal function and gynaecomastia) were, however, significantly higher in the treated group compared with placebo.	7
Bapoje *et al* (2013), USA[54]	Systematic review and meta-analysis.	Antialdosterone/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=8; n=11 875.	Range: 3–24.	Mineralocorticoid receptor antagonists (or aldosterone antagonists) reduced the risk of SCD in patients with left ventricular dysfunction.	8
Wei *et al* (2010), China[22]	Meta-analysis.	Antialdosterone/placebo; 'usual care'.	HF; <45%; NA.	RCTs n=6 (two are not double blind); n=00 000.	Range: 2–24.	Two [67 68] of the six included studies showed a significant reduction of SCD in the group of spironolactone versus placebo and the group of eplerenone versus placebo cited respectively.	5
Solomon *et al* (2016), USA[23]*	Meta-analysis.	Sacubitril; valsartan/ACE-i.	HF; <30%; II–IV.	RCTs n=3; n=14 742.	Range: 6–27.	The authors concluded that combined neprilysin/RAS inhibition reduced all-cause mortality in HFrEF.	7
Flather *et al* (2000), Canada[25]	Systematic review.	ACE-i/placebo.	CHF; post-MI <45%; NA.	RCTs n=5; n=12 763.	Range: 15–42.	This meta-analysis showed a lower risk of death in ACE-i treated group compared with placebo.	NA
Garg *et al* (1995), Canada[24]*	Systematic review and meta-analysis.	ACE-i/placebo.	CHF; <45%; I–IV.	RCTs n=32; n=7105.	Range: 3–42.	Overall, this study reported a significant reduction of total mortality (attributed mainly to less progressive HF deaths) and hospitalisation for worsening HF.	2

Continued

Table 1 Continued

Author (year), country	Review type	Intervention/comparator	Population type; ejection fraction (%); NYHA	Study design n; participants n	Mean follow-up/ range (months)	Authors' findings summary	AMSTAR score
Rain and Rada (2015), Chile[26]	Systematic review.	ARB/ACE-i.	HF; <45%–<35%; II–IV.	RCTS=8; n=5201.	NA	The authors concluded that ARBs are probably as effective in mortality reduction as ACE-i with probably less withdrawal rate due to adverse effects.	NA
Heran *et al* (2012), Canada[27*]	Systematic review and meta-analysis (Cochrane).	ARB (or ARB+ACEi)/ placebo; ACE-i.	HF; ≤40% ; II–IV.	RCTS n=24; n=25051.	Range: 1–49.5.	Compared with placebo or in addition to ACE-i, ARBs did not reduce all-cause mortality.	10
Shibata *et al* (2008), Canada[28]	Systematic review and meta-analysis	ARB/placebo; ACE-i.	HF; <40%; I–IV.	RCTs n=7; n=27495.	Range: 11–41.	Compared with ACE-i or used in combination, ARBs provided no beneficial effects on mortality. A 17% reduction in hospitalisations was observed.	4
Lee *et al* (2004), USA[29]	Meta-analysis.	ARB/placebo; ACE-i.	CHF, AMI; ≤45%; II–IV.	RCTs n=24; n=38080.	Range: 1–41.	Compared with ACE-i, ARBs do not differ in efficacy for reducing all-cause mortality in CHF and AMI patients.	7
Dimopoulos *et al* (2004), UK[30]	Meta-analysis.	ARB/placebo; ACE-i.	CHF; <40%; II–IV.	RCTs n=4; n=7666.	Mean: 31.	ARBs can be used to prevent events in ACE-i-treated HF patients who are not suitable for beta-blockers.	3
Jong *et al* (2002), Canada[31]	Systematic review and meta-analysis.	ARB (or ARB+ACEi)/ placebo ; ACE-i.	HF; ≤35%–≤45%; II–IV.	RCTs n=17; n=12469.	Range: 1–23.	The authors could not conclude any superiority of ARBs versus controls, stating this might be due to the use of ACE-i as a comparator or background treatment in the majority of included trials.	8
Rain and Rada (2017), Chile[32]	Systematic review.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=25; n=NR.	NA	The authors summarised that statins do not decrease mortality in chronic HF and might lead to a small reduction in hospital admissions for HF.	NA
Al-Gobari *et al* (2017), Switzerland[6*]	Systematic review and meta-analysis.	Statins/placebo; 'usual care'.	HF, ischaemic/non-ischaemic; NA; I–IV NA.	RCTs n=24; n=11463.	Range: 1–46.8.	Statins do not significantly reduced SCD and all-cause mortality. They may or may not reduce hospitalisations due to worsening HF.	7
Bonsu *et al* (2015), Malaysia[33]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=13; n=10966.	Range: 3–46.8.	Lipophilic statins showed significant decrease in all-cause mortality, cardiovascular mortality and hospitalisation for worsening HF.	8
Wang *et al* (2014), China[34]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; NA; NA.	RCTs n=6 (9: observational studies); n=10016.	Range: 12–46.8.	The authors concluded that statins reduce SCD and all-cause mortality in HF.	5
Liu *et al* (2014). China[35]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=13; n=1532.	Range: 3–35.5.	The authors reported significant decrease in all-cause mortality but recommended cautious interpretation and further research.	7
Rahimi *et al* (2012), UK[40]	Meta-analysis.	Statins/placebo; 'usual care'.	HF, MI, primary prevention, diabetes, ACS, CHD; NA; NA.	RCTs n=37; n=155020.		Statins have a modest effect on SCD but no substantial protective effect on ventricular arrhythmic events.	6
Zhang *et al* (2011), China[36]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=13; n=10447.	Range: 2–46.8.	This meta-analysis concluded of no difference between treatment groups but benefits may occur in some specific populations and with a specific statin.	7

Continued

Table 1 Continued

Author (year), country	Review type	Intervention/comparator	Population type; ejection fraction (%); NYHA	Study design n; participants n	Mean follow-up/ range (months)	Authors' findings summary	AMSTAR score
Xu *et al* (2010), China[37]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=7; n=540.	Range: 3–31.	The authors suggested that atorvastatin treatment is effective and reduce all-cause mortality and hospitalisation for worsening HF.	6
Lipinski (2009), USA[38]	Meta-analysis.	Statins/placebo; 'usual care'.	HF; <45%; I–IV.	RCTs n=10; n=10 192.	Range: 3–47.	The authors stated that statins are safe and improve LVEF and decrease hospitalisation for worsening HF.	7
Levantesi *et al* (2007), Italy[39]	Meta-analysis.	Statins/placebo; 'usual care'.	Secondary prevention; NA; NA.	RCTs n=10; n=22 275.	Range: 6–73.2.	Statins were associated with a significant risk reduction for SCD (in secondary prevention settings).	3
Claro *et al* (2015), Chile[41*]	Systematic review and meta-analysis (Cochrane).	Amiodarone/placebo; 'usual care'.	Subanalysis: HF; NA; NA.	RCTs n=11; n=5006.	NA	In HF subpopulation, amiodarone showed a statistically significant reduction for SCD but not for all-cause mortality. Authors judged the quality of the evidence for the whole population (primary prevention) as low to moderate and for secondary prevention population as very low.	10
Santangeli *et al* (2012), USA[42]	Systematic review.	Amiodarone/placebo.	Cardiovascular disease; NA; NA.	NA	NA	Amiodarone has less favourable net clinical benefits for prophylaxis of SCD because of adverse effects.	5
Piccini *et al* (2009), USA[43]	Meta-analysis.	Amiodarone/placebo; 'usual care'.	HF, AMI; <45%; II–IV.	RCTs n=15; n=8522.	Range: 2–12.	In HF subpopulation, amiodarone showed a statistically significant reduction for SCD but not all-cause mortality.	7
ATMA Investigators (1997)[44]	Meta-analysis.	Amiodarone/placebo; 'usual care'.	Post-MI and CHF; 31%; NA.	NA	Range: 4.8–25.8.	Amiodarone reduced arrhythmic/sudden death in high-risk patients with recent MI or CHF. All-cause mortality decreased by 13%.	NA
Sim *et al* (1997), USA[45]	Meta-analysis	Amiodarone/placebo; 'usual care'.	Subgroup: HF;<45%; NA.	RCTs n=5; n=4125.	Range: 6–45.6.	Amiodarone reduced all-cause mortality in high SCD risk groups.	5
Das *et al* (2010), USA[46]	Narrative review.	Antiarrhythmics/placebo; 'usual care'.	Subgroup: HF; NA; NA.	NA	NA	Class I antiarrhythmic drugs (AADs) increased all-cause mortality and SCD in post-MI patients. Amiodarone (class III AADs) decreased or have neutral effect on SCD. Caution is warranted to outweigh risks of proarrhythmia and other adverse effects.	NA
Hilleman *et al* (2001), USA[47]	Narrative review.	Antiarrhythmics/placebo; 'usual care'.	HF; <45%; NA.	RCTs n=6; n=10 440.	Range: 6.5–45.	Beta-blockers (bisoprolol, carvedilol and metoprolol) reduced total mortality and SCD in HF. Class I antiarryhthmics increased mortality and SCD in a post hoc analysis of SPAF-I study. Amiodarone had mixed results, and dofetilide did not reduce mortality or SCD.	NA
Rizos *et al* (2012), Greece[48]	systematic review and meta-analysis.	Omega 3 Fatty acids/ placebo; 'usual care'.	Cardiovascular diseases; NA; NA.	RCTs n=20; n=68 680.	NA	Omega-3 polyunsaturated fatty acids supplementation were not associated with a lower risk of all-cause mortality or SCD.	8
Kotwal *et al* (2012), Australia[49]	Systematic review and meta-analysis.	Omega 3 Fatty acids/ placebo; 'usual care'.	Cardiovascular diseases, HF admissions; NA; NA.	RCTs n=20; n=62 851.	Range: 6–72.	The authors concluded that there is no clear effect on total mortality and sudden death outcomes.	7

Continued

Table 1 Continued

Author (year), country	Review type	Intervention/comparator	Population type; ejection fraction (%); NYHA	Study design n; participants n	Mean follow-up/ range (months)	Authors' findings summary	AMSTAR score
Kwak *et al* (2012), Korea[50]	Meta-analysis.	Omega 3 fatty acids/ placebo; 'usual care'.	Secondary prevention of cardiovascular disease; NA; NA.	RCTs n=14; n=20 485.	NA	This meta-analysis concluded of insufficient evidence.	8
Chen *et al* (2011), China[51]	Meta-analysis.	Omega 3 fatty acids/ placebo; 'usual care'.	Cardiovascular disease; NA; NA.	RCTs n=10; n=33 429.	NA	Omega-3 fatty acids did not appear to reduce SCD under guideline-adjusted treatment for CVD secondary prevention.	7
Marik *et al* (2009), USA[52]	Systematic review.	Omega t3 dietary supplements/placebo; olive oil; corn oil, sunflower oil; 'usual care'.	Cardiovascular disease; NA; NA.	RCTs n=11; n=39 044.	Range: 12–55.2.	Dietary supplementation with omega-3 fatty acids reduced SCD and all-cause mortality.	4
Wang *et al* (2006), USA[53]	Systematic review.	n-3 Fatty acids/placebo/ olive oil; corn oil, sunflower oil; 'usual care'.	Primary and secondary prevention; NA; NA.	RCTs n=12; n=32 981.	Range: 12–48.	The authors concluded of a significant reduction in all-cause mortality and SCD with n-3 fatty acids from fish or fish oil supplements but not α-linolenic acid.	6

ACE-i, angiotensin-converting enzyme ACE inhibitors; ACS, acute coronary syndrome; AMI, acute myocardial infarction; AMSTAR, assessing the methodological quality of systematic reviews ; ARBs, angiotensin receptor blockers ; BBs, beta-blockers; HF, heart failure; CHD, coronary heart disease; CHF, Chronic heart failure; LVEF, left ventricular ejection fraction; MI, myocardial infarction; NR, not reported; NYHA, New York Heart Association classification ; RAS, renin-angiotensin system; RCTs, randomized clinical trials; SCD, sudden cardiac death; SPAF-I, stroke prevention atrial fibrillation study

in case of a detectable publication bias or unestablished class effect.

INEFFECTIVE INTERVENTIONS

ACE inhibitors

Although two systematic reviews,[24 25] with an AMSTAR score of 2/11 and 3/11, respectively, reported a decline in total mortality and less progressive HF deaths, SCD events did not significantly decrease (OR 0.91, 95% CI (0.73 to 1.12)). The quality of the evidence was rated as moderate because of the unclear or high risk of bias in included primary studies (table 2).

Angiotensin receptor blockers

As shown in figures 2 and 3, we updated a Cochrane review[27] by including more eligible primary studies such as SUPPORT trial.[56] Comparing ARBs with controls resulted in a slightly different effect size estimation. Eventually, we did not combine the different control groups to account for heterogeneity. In stratified analyses, ARBs compared with placebo remained ineffective for all-cause mortality (RR 0.79, 95% CI (0.55 to 1.13)). Similarly, ARBs, compared with ACE-i or in combination versus ACE-i alone, were not superior in all-cause mortality reduction (RR 0.87, 95% CI (0.56 to 1.36); RR 0.99, 95% CI (0.90 to 1.09), respectively) (figure 2). The quality of the evidence is rated as low because of risk of bias, imprecision and inconsistency ($I^2 \approx 78$, p=0.010 for SCD outcome) (table 2). Data were limited for studies reporting SCD, in particular those comparing ARBs versus placebo, or versus ACE-i (figure 2). In addition, the funnel plot for all-cause mortality outcome showed no evidence of publication bias (figure 4). No estimation of publication bias and no funnel plot was drawn for SCD as only five studies reported this outcome.

Statins

Published systematic reviews and meta-analyses about statins in HF were inconsistent[6 32–40] with a recent tendency towards inefficacy in total mortality and SCD prevention. The quality of the evidence was rated as moderate because of a likelihood of publication bias revealed on the most up-to-date systematic review[6] (table 2).

UNCLEAR EVIDENCE OF EFFECTIVENESS

The evidence of effectiveness of the drug interventions reported below was considered uncertain due either to conflicting or inconclusive evidence.

Amiodarone and AADs

Recently published systematic reviews[41 43] for amiodarone showed a significant reduction for SCD but not for all-cause mortality with less favourable net clinical benefits.[42] Other older reviews[44 45] of minor quality (AMSTAR of 3/11 and 5/11 cited respectively) reported a decline of both SCD and all-cause mortality.

Table 2 Summary of findings and GRADE evaluation for sudden cardiac death (SCD) and all-cause mortality prevention

Drug interventions for SCD and all-cause mortality prevention in heart failure patients

Outcome	Intervention/comparison	Assumed risk with comparator	Corresponding risk with intervention	Relative effect (95% CI)	Number of participants (no. of studies)	Quality of the evidence (GRADE)	Comments
SCD							
	Beta-blockers/placebo	77 per 1000	54 per 1000 (49–60)	OR 0.69 (0.62 to 0.77)	24 779 (26 RCTs)	⊕⊕⊕⊕ High*	I^2=0% (p=0.57)
	Antialdosterone inhibitor/ placebo; 'usual care'	61 per 1000	49 per 1000 (41–60)	RR 0.81 (0.67 to 0.98)	8301 (5 RCTs)	⊕⊕⊕⊕ High*	I^2=8% (p=0.36)
	ARB; neprilysin inhibitor/ACE-i	74 per 1000	60 per 1000 (51–70)	RR 0.81 (0.69 to 0.95)	8399 (1 RCsT)	⊕⊕⊕⊖ Moderate†	
	ACE-i/placebo	59 per 1000	54 per 1000 (43–65)	OR 0.91 (0.73 to 1.11)	6988 (30 RCTs)	⊕⊕⊕⊖ Moderate‡	I^2=0% (p=0.94)
	ARB (or ARB+ACE i)/Placebo; ACE-i	See comment	See comment	Not estimable	13 884 (5 RCTs)	⊕⊕⊖⊖ Low‡§	I^2=78% (p=0.010). Overall, we did not pool the studies because of heterogeneity
	Statins/placebo; 'usual care'	108 per 1000	100 per 1000 (76–131) (99 per 1000 (72–131))	RR 0.92 (0.7 to 1.21) (OR 0.90 (0.64 to 1.24))	10 077 (8 RCTs)	⊕⊕⊕⊖ Moderate¶	I^2=42.6% (p=0.094)
	Amiodarone/placebo; 'usual care'	118 per 1000	93 per 1000 (79–110)	RR 0.79 (0.67 to 0.93)	5006 (11 RCTs)	⊕⊕⊖⊖ Low¶‡	
	Omega 3 fatty acids/placebo; 'usual care'	93 per 1000	88 per 1000 (77–102)	RR 0.94 (0.82 to 1.09)	6975 (1 RCT)	⊕⊕⊕⊖ Moderate†	
All-cause mortality							
	Beta-blockers/placebo	178 per 1000	127 per 1000 (113–141)	OR 0.67 (0.59 to 0.76)	24 779 (26 RCTs)	⊕⊕⊕⊕ High*	I^2=40 % (p = 0.02)
	Antialdosterone inhibitor / placebo; ' usual care'	200 per 1000	162 per 1000 (148–176)	RR 0.81 (0.74 to 0.88)	9019 (10 RCTs)	⊕⊕⊕⊕ High	I^2= 0% (p= 0.56)
	ARB; neprilysin inhibitor /ACE -i	183 per 1000	158 per 1000 (145–172)	RR 0.86 (0.79 to 0.94)	14 742 (3 RCTs)	⊕⊕⊕⊕ High	I^2= 0% (p = 0.42)
	ACE-i/placebo	219 per 1000	178 per 1000 (158–198)	OR 0.77 (0.67 to 0.88)	7105 (32 RCTs)	⊕⊕⊕⊖ Moderate	I^2=0% (p= 0.95)
	ARB (or ARB+ACE -i)/ placebo; ACE-i.	183 per 1000	177 per 1000 (161–197)	RR 0.97 (0.88 to 1.08)	19 510 (27 RCTs)	⊕⊕⊖⊖ Low‡**	I^2= 24% (p = 0.14)
	Statins/placebo; 'usual care'	273 per 1000	240 per 1000 (205–278) (233 per 1000 (199–273))	RR 0.88 (0.75 to 1.02) OR 0.81 (0.66 to 1)	11 024 (13 RCTs)	⊕⊕⊕⊖ Moderate¶	I^2= 37.7% (p =0.083)
	Amiodarone/placebo; 'usual care'	264 per 1000	237 per 1000 (211–266)	RR 0.90 (0.80 to 1.01)	5006 (11 RCTs)	⊕⊕⊖⊖ Low¶‡	
	Omega 3 fatty acids/ placebo; 'usual care'	291 per 1000	274 per 1000 (253–294)	RR 0.94 (0.87 to 1.01)	6975 (1 RCT)	⊕⊕⊕⊖ Moderate	

*Although graded high, this might be downgraded into moderate if we strictly consider the risk of bias of primary studies other than an overall estimation.
†Estimation comes from one single clinical trial. No data obtained from other relevant studies for this outcome.
‡The studies reported to generally have a moderate to high risk of bias due to allocation concealment and blinding reporting.
¶Likelihood of publication bias presence with an asymmetric funnel plot.
§Inconsistent results ranged from no effect to insignificant increase of events ($I^2 \approx$ 71%).
**Most studies have small sample and wide CIs including no effect with appreciable harm or benefit.
ACE-i, ACE inhibitors; ARBs, angiotensin receptor blockers; GRADE, Grading of Recommendations, Assessment, Development and Evaluation; I^2, between-study variance due to heterogeneity; RR, risk ratio.

The quality of evidence for amiodarone was rated as low because of the unclear or high risk of bias and potential publication bias in primary studies (table 2). No systematic review for AADs of other classes or drugs (other than amiodarone) were retrieved. Nevertheless, two narrative reviews[46 47] reported that class I antiarrhythmics increased SCD and all-cause mortality. These narrative reviews called for caution regarding the mixed results of amiodarone and its adverse effects.

Omega-3 polyunsaturated fatty acids (PUFAs) and fish oil supplementation

No systematic review was exclusively conducted in patients with HF for this intervention. One primary study,[57] known as GISSI-Prevenzione HF, recruited patients with chronic HF and reported a lower mortality events in the n-3 PUFAs group compared with the placebo group. The authors reported an adjusted HR of 0.91 (95.5% CI 0.833 to 0.998), p=0.041). However,

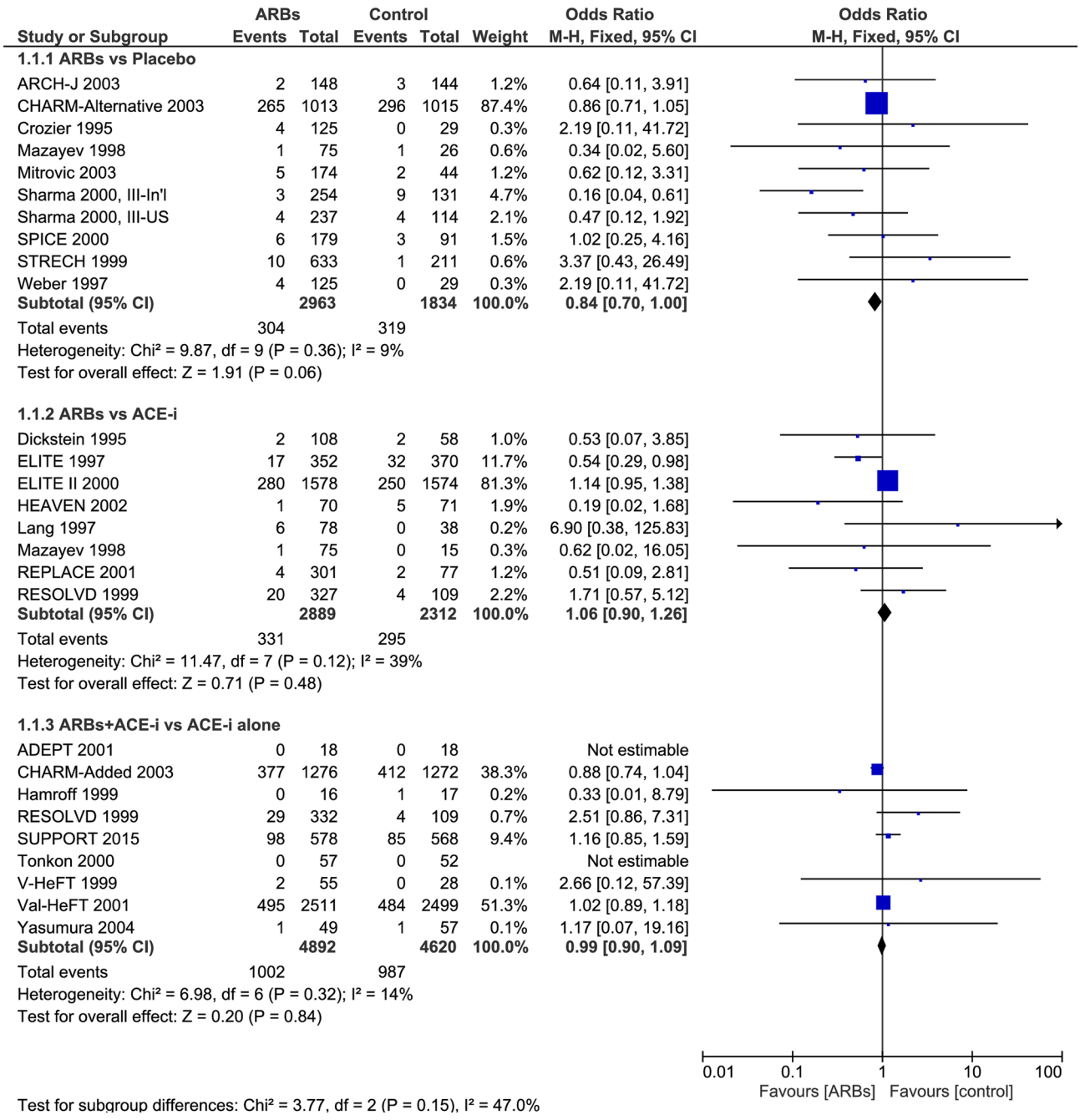

Figure 2 Efficacy of angiotensin receptor blockers (ARBs) compared with placebo, angiotensin-converting enzyme inhibitor (ACE-i) or combined in heart failure with reduced ejection fraction (HFrEF) for the prevention of all-cause mortality.

relative risk in our analysis remained statistically insignificant (RR 0.94, 95% CI (0.87 to 1.01), p=0.10) and (RR 0.94, 95% CI (0.81 to 1.09), p=0.42) for all-cause mortality and SCD, respectively. Our assessment of the quality of the evidence involving GISSI-Prevenzione HF was moderate because of an absence of data of any other relevant studies (table 2). In addition, some recent systematic reviews[48–51] included patients regardless of their cardiovascular disease and concluded of no clear effect, insufficient evidence or no reduction on SCD and all-cause mortality outcomes. Meanwhile, some older studies[52 53] reported that omega-3 fatty acids and fish oil supplements (other than α-linolenic acid[53]) reduced SCD and all-cause mortality.

DISCUSSION

Our assessment of the effectiveness of drug interventions to prevent SCD in patients with HFrEF indicated that BBs, antialdosterone agents, as well as combined ARB/neprilysin inhibitors were effective.

Previously reported meta-analyses and systematic reviews of RCTs[15–20] indicated that BBs are effective in the prevention of SCD and all-cause mortality in HFrEF.

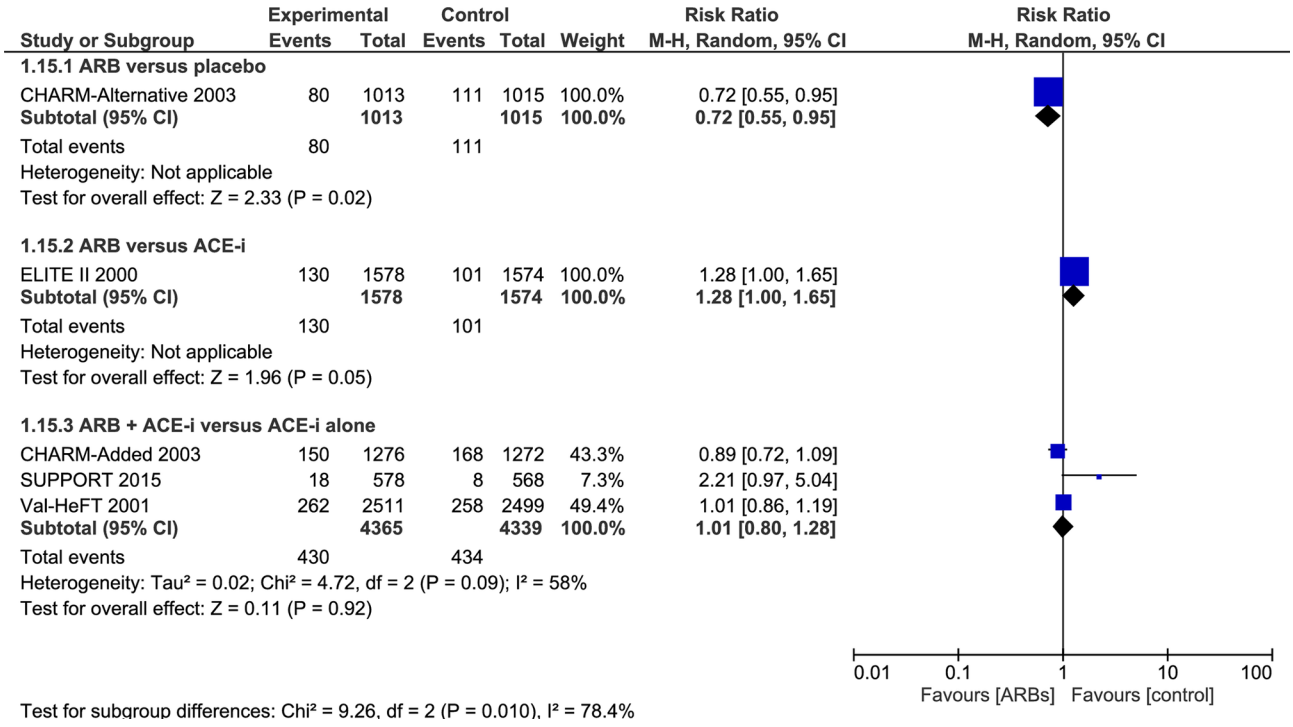

Figure 3 Efficacy of angiotensin receptor blockers (ARBs) compared with placebo, angiotensin-converting enzyme inhibitor (ACE-i) or combined in heart failure with reduced ejection fraction (HFrEF) for the prevention of sudden cardiac death (SCD).

However, although they were increasingly used as a usual 'routine' care in the compared arms of the more recently published clinical trials,[58] BBs stayed underused for long time and may still be.[59] Mineralocorticoid receptor antagonists or antialdosterone drugs have been reported effective in HFrEF by reducing SCD and all-cause mortality.[21 22 54 60] Our summary of the findings and the consistency of the results support this claim

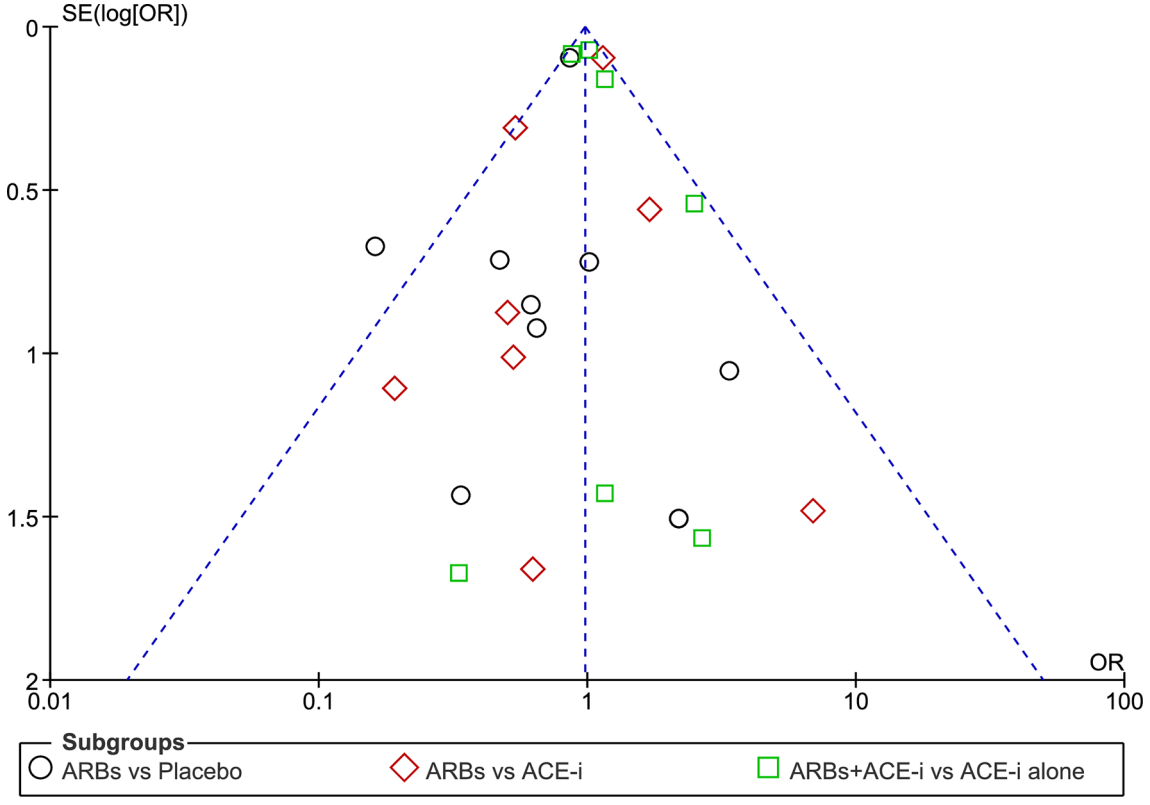

Figure 4 Funnel plot of SE (log OR) by OR to evaluate publication bias for the efficacy of angiotensin receptor blockers (ARBs) compared with control in heart failure and reduced ejection fraction (HFrEF) for the prevention of all-cause mortality.

with a high quality of evidence. Only one retrieved meta-analysis[23] supported the effectiveness of combined ARB/neprilysin inhibitor. The authors acknowledged the limitation of their meta-analysis, which was not based on a systematic review, but merely pooling three well-known trials published in high impact journals (ie, IMPRESS,[61] OVERTURE[62] and PARADIGM-HF).[5] The quality of the evidence is, however, moderate for SCD and high for all-cause mortality, although our inability to assess any presence of a class effect or a potential publication bias.

We found that ACE-i showed a total mortality reduction in clinical trials and systematic reviews of patients with HF.[24 25] However, our overview showed that ACE-i, surprisingly, did not significantly decrease SCD with a moderate quality of evidence.

In addition, we found that neither ARBs nor statins reduced SCD and/or all-cause mortality. Our findings for ARBs were in agreement with Jong and colleagues,[31] Shibata *et al*[28] and Dimopoulos *et al*,[30] but in contradiction to Lee *et al*[29] and Rain and Rada's conclusions.[26] Our up-to-date meta-analysis for ARBs included only five primary studies, but large-scale trials, that reported SCD events. Eventually, we did not pool all the different comparators together but separately estimated the effect size for each group to account for the heterogeneity. Moreover, the addition of current trials such as SUPPORT[56] improved the statistical power of detecting an effect if existed and the summary statistic remained statistically insignificant (figure 2). Of note, Jong and colleagues[31] attributed this inefficacy of ARBs in HF to the background treatment with ACE-i.

Within the current evidence, ARBs should not be seen as interchangeable with ACE-i, which also showed a neutral effect on SCD, without a proper reason. Therefore, in a high-risk SCD patient, another therapeutic strategy should be sought, and an ARB/neprilysin inhibitor might be an alternative in patients similar to those of the PARADIGM-HF trial.[5]

The addition of statins to the therapy regimen of patients with HF had no survival benefits. Actually, a recent systematic review and meta-analysis indicated that statins did not reduce SCD nor all-cause mortality.[6] Our current study reached the same conclusion with similar quality of evidence.

Our overview showed unclear evidence of effectiveness of omega-3 PUFAs, fish oil supplementation and AADs. The latter intervention had an evidence originated from only narrative reviews, as we did not identify any systematic reviews. Also, only one n-3 PUFA clinical trial[57] was conducted in patients with HF and reported a statistically significant mortality reduction; this result was not supported by other trials and recent systematic reviews,[48–51] a finding that justified our conclusion of unclear evidence. Moreover, no other data or systematic reviews conducted in HF were retrieved by our electronic and manual searches.

AADs are classified into four categories[46]: sodium channel blocking drugs (class I), BBs (class II), potassium channel blockers (class III) and calcium channel blockers (class IV). We found inconclusive evidence of effectiveness of all categories, with the exception of BBs. The evidence of effectiveness of class I, III and IV is inconclusive, neutral or even detrimental to patients as for class I AADs.[46 47] Amiodarones, which present class I, II, III and IV effects, reported mixed results with potential SCD prevention with adverse effects[43] and potentially, but rare,[63] life-threatening proarrhythmias.[46]

Our overview has some limitations. First, we limited the scope of our study to drug treatment, thus excluding devices like ICDs. We believe that non-drug devices should be tackled in future research. European Society of Cardiology (ESC) Guideline (2016)[64] and others (eg, www.uptodate.com) recommend the use of ICDs for only ≤35% of patients with HF and only after optimisation of drug therapy. In fact, SCDs occur in both reduced and preserved HF. Our overview might help to optimise therapy as a first step before introducing ICDs, which applies to a limited HF subpopulation, regardless of costs. Second, we may have failed to include other drug interventions used in HFrEF. Such drug candidates include digoxin, I_f-channel blockers (ivabradine), hydralazine/isosorbide dinitrate, nitroglycerin and phosphodiesterase 3 or 5 inhibitors. However, our overview included most commonly prescribed and evidence-based pharmacological therapy in HF as prespecified in our published protocol.[11] Third, we did not use specific drug names in our literature search strategy, in order to avoid omitting a therapy that evaluated SCD and/or all-cause mortality prevention in patients with HF. Fourth, we based our analyses on existing systematic reviews and meta-analyses, and we updated only one meta-analysis. Consequently, we were unable to update the evidence for ACE-i. Furthermore, as indicated by the AMSTAR score, the methodological quality of some of the existing reviews was suboptimal. Fifth, we did not assess the safety of the evaluated drug interventions, nor the contraindications for their prescription, drug–drug interactions, as well as treatment adherence. Indeed, we considered that these important aspects were out of the scope of our analysis. Sixth, we were unable to do a sensitivity analysis, initially suggested in our protocol, for ischaemic versus non-ischaemic HF due to limited data availability. Finally, a potential source of bias relates to authors of this overview being the authors of three of the included reviews.[16 21 65] However, the adopted methodology is in line with systematic reviews guidelines and ensured a double check of data and methodological evaluation by at least two reviewers and a published protocol.[11]

It is noteworthy that high-quality evidence does not necessarily imply strong recommendations, and strong recommendations can arise from low-quality evidence.[66] Therefore, when one intervention is graded high, it is not our intention to say that it is highly recommended, as we did not assess the level of recommendation in our study. In fact, a level of recommendation depends on the strength of evidence and (among others) on values and preferences of

patients, net benefits and cost-effectiveness of a particular intervention.

Implications for practice

Our study summarises and synthesises the effectiveness of most evidence-based drug interventions in patients with HFrEF for SCD prevention. It classified drug interventions according to the current evidence of their effectiveness. This categorisation could help health professionals and patients making evidence-based decisions based on updated knowledge, particularly whenever a high-risk SCD patient is identified. Currently, there is no an established strategy to deal with patients at high risk of SCD. In such patients, a particular attention should be considered, and a careful selection of available therapeutic options is needed. Furthermore, there might be a shift towards an alternative therapeutic strategy based on SCD prevention-effective drugs in light of our findings.

CONCLUSION

Our overview indicates that only three drug interventions (BBs, antialdosterones, combined ARB/neprilysin inhibitors) significantly reduce SCD and improve overall survival among individuals with HF and reduced ejection fraction. However, there is no evidence of effectiveness of ARBs to reduce neither all-cause mortality nor SCD (with a low quality of evidence), and ACE-i do not significantly reduce SCD events. When the goal of drug therapy is to reduce SCD, especially in high-risk patients, our synthesis supports the use of the most effective regimen.

Acknowledgements We would like to thank Dr Emilie Zuercher for her technical assistance.

Contributors Design and conception: MA, FG and BB. MA is the guarantor. Project administration: BB. Writing original draft: MA. Critical analysis: all authors. Data curation: MA and SA. Statistical analysis: MA. Proofread and approved the final draft: all authors.

Funding MA, the corresponding author, received a financial grant (2014.0193) from The Federal Department of Economic Affairs, Education and Research (EAER), Switzerland, also from Département universitaire de médecine et santé communautaires (DUMSC), Lausanne university hospital (CHUV), Switzerland.

Disclaimer The former funders had no role in study design or conception, study analysis, writing or preparation of the manuscript.

Competing interests We declare that some authors of this overview are also authors of some of the included reviews. However, at least two reviewers systematically checked and validated the extracted data including study qualities. We declare that no other competing interests exist.

Patient consent Not required.

Provenance and peer review Not commissioned; externally peer reviewed.

Data sharing statement All data are available in the manuscript and its supported files. Any more information can be requested from the corresponding author.

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APPENDIX IV “Effects of statins to reduce all-cause mortality in heart failure patients: findings from the EPICAL2 cohort study”

“Effects of statins to reduce all-cause mortality in heart failure patients: findings from the EPICAL2 cohort study”

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Abstract

Introduction

The addition of statins to standard care in heart failure (HF) patients remains controversial in clinical practice. Large-scale clinical trials failed to show mortality benefits but uncertainty persists in real-world settings.

Objective

We evaluated whether the prescription of statins at hospital discharge is associated with a reduction in all-cause mortality up to one year of follow-up in HF patients.

Methods

Analysis of EPICAL2 patients who were admitted to 21 hospitals located in northeast France for acute HF between October 2011 and October 2012 and who received statins at discharge compared to patients who did not. We used a propensity score matching and instrumental variable analyses to estimate the treatment effects of statins, and a multivariable Cox proportional hazards model to examine survival with statin use, adjusting for patient demographics, HF characteristics, medical history, comorbidities, drug treatment and other known potential confounders. We plotted Kaplan-Meier survivor curves and used log-rank test to determine the equality of survivor functions.

Results

We included 2032 patients in this investigation: 919 (45%) in the statin-treated group and 1,113 (55%) in the control group. The estimated average statin-treatment effects for all-cause mortality in HF failed to demonstrate a significant effect on mortality [Z: -1.73; 95% CI: (-0.11 to 0.007), p-value: 0.083] and [Z: -0.95; 95% CI: (-1.34 to 0.46), p-value: 0.34] for propensity score matching and instrumental variable analyses, respectively. Moreover, the Cox proportional-hazard model showed that statins prescription was not significantly associated with the rate of death [Hazard ratio: 0.85, (95% CI 0.66 to 1.11), p-value: 0.26], adjusted for all confounders.

Conclusion

In patients with heart failure (HF), the prescription of statins was not associated with better survival after one year of follow-up in the EPICAL2 cohort. We cannot exclude that a subpopulation of HF patients may have some benefits compared to the whole HF population or that there might be a lack of power to show such effect.

Keywords

Heart failure; statins; propensity score, observational study, cohort, effectiveness, all-cause mortality

KEY POINTS

There is moderate evidence from large-scale clinical trials and meta-analyses that statins failed to reduce mortality in heart failure (HF) patients, including ischemic cardiomyopathy.

Scarce real-world data exist in the literature to encourage or discourage the use of statins in clinical practice.

The EPICAL2 observational cohort study failed to show mortality benefits for statins use post-discharge in line with large-scale clinical trials but we do not exclude potential benefits in a particular HF subpopulation.

1. Introduction

Despite progress and current advances in heart failure (HF) therapies, 50% of patients die within five-years of initial diagnosis [1]. Therefore, there is a growing need to prevent all-cause mortality and to optimize therapeutic strategies. 3-hydroxy-3-methylglutaryl coenzyme A (HMG-Co A) reductase inhibitors or simply statins, in addition to drugs recommended in HF (angiotensin converting enzyme inhibitors, β blockers, mineralocorticoid inhibitors), have been hypothesized to further reduce mortality compared to usual care. However, HF patients were systematically excluded from most clinical trials with statins, leaving us with limited data and moderate evidence [2]. Unlike large-scale clinical trials [3, 4], some observational studies reported that statins were effective in all-cause mortality reduction [5, 6] raising discrepancies and debates. Therefore, it appeared important to find out if a further analysis of a well-conducted observational study could add a new evidence to the current literature. In our analysis, we used data from the *Epidemiologie et Pronostic de l'Insuffisance Cardiaque Aiguë en Lorraine* (EPICAL2) cohort study of 2,254 hospitalized acute HF patients, recruited between October 2011 and October 2012 from 21 hospitals located in the Lorraine region of northeast France to examine if the prescription of statins at hospital discharge for an HF-related hospitalization was associated with better 1-year survival.

2. Methods

2.1 Participants

The methods of recruitment and patient characteristics were already published elsewhere [7, 8]. In brief, this cohort (EPICAL2, NCT 02880358) included 2,254 patients who were hospitalized in the Lorraine region of northeast France (2,350,000 inhabitants, according to the 2012 census) for acute HF between October 2011 and October 2012, and followed during one year after hospital discharge. In the present analysis, we excluded patients who died before discharge from the index hospitalization, who had unknown prescription status for statins or those who were lost to follow-up or had an unknown vital status after one year of follow-up from the index hospitalization (**Figure 1**).

The EPICAL2 cohort study was conducted according to the principles of the Declaration of Helsinki and approved by national ethics committees (*Comité Consultatif sur le Traitement de l'Information en Matière de Recherche, Comission Nationale de l'Informatique et des Libertés*). All eligible patients were informed about the study protocol and were free to refuse to be included in the cohort.

2.2. Variables selection

Independent variables used for the present analysis were those known to influence mortality and those that might be related to initiating or maintaining statin treatment. These variables were age, gender, hypertension, body mass index (BMI), left ventricular ejection fraction, NYHA class III or IV, increased BNP or NT pro-BNP, hemoglobin level, alcohol abuse, smoking status, previous history of HF, hospital stay duration, angina, history of stroke/ transient ischemic attack (TIA), arrhythmias, dyslipidemia, history of acute coronary syndrome, chronic obstructive pulmonary disease (COPD)/Asthma, diabetes, chronic kidney disease, malignant hemopathies or any cancer, current treatment with beta-blockers, angiotensin-converting enzyme inhibitors, and spironolactone. We included the prescription of beta-blockers, angiotensin-converting enzyme inhibitors, and spironolactone among selected variables because they are known to be associated with a better prognosis [7, 9]. We defined the variable "increased BNP or NT-proBNP (pg/mL)" based on the literature [8, 10] at the time of EPICAL2 recruitment phase: BNP >400 pg/ml or NT-proBNP >450 pg/ml in patients <50 years, NT-proBNP >900 pg/ml in patients 50-75 years, NT-proBNP >1800 pg/ml in patients >75 years.

2.3. Statistical analysis

For bivariate analyses, we used Pearson chi-square for dichotomous categorical variables and two-sample unpaired t-test for continuous variables. We assumed that the data were normally distributed and used the Shapiro-Wilk and the Shapiro-Francia test statistics to verify normality in addition to plotting histograms. We reported the baseline characteristics between compared groups. In our study, patients with missing data were

deleted from the analyses. We considered a two-sided alpha value of <5% as statistically significant. We analyzed data with STATA version 14.2 (StataCorp LP, Texas).

2.3.1. Propensity score analysis

Propensity score has been defined as the conditional probability of assignment to a particular treatment (here statins) given a vector of observed covariates [11]. Propensity scores allow reducing bias and increasing precision of treatment effects estimation [12, 13]. We calculated the propensity scores (i.e., the probability of being treated with statins) using multivariable logistic regression, without including the outcome (all-cause mortality) and performed balance assessment tests to compare the distribution of covariates between treated and control patients [14]. We used one-to-many matching with replacement as it produced better balance between treated and control groups than one-to-one matching without replacement. Then we estimated treatment effects and their standard errors using propensity score matching methods within a caliper distance of 0.2 [15, 16]. On the propensity score step calculation, we included variables associated with both the outcome and the treatment assignment.The selected independent variables were age, gender, hypertension, BMI, left ventricular ejection fraction (LVEF), NYHA class III or IV, increased BNP or NT pro-BNP, hemoglobin level, alcohol abuse, smoking status, hospital stay duration, angina, history of stroke/TIA, arrhythmias, dyslipidemia, history of acute coronary syndrome, COPD/asthma, diabetes, chronic kidney disease, malignant hemopathies or any cancer, atrial fibrillation and prescription of beta-blockers, angiotensin-converting enzyme inhibitors and spironolactone. We included all aforementioned variables in our models except the variable “History of heart failure” because of collinearity. We tested beforehand the overlap of the propensity score between the treated and control groups. Thereafter, we checked the balance of the mean of the propensity score throughout the blocks where 8 blocks was created in the propensity scores calculation. We intended to re-specify the selected covariates (by categorizing or dichotomizing, for instance) if imbalance appeared. To avoid imbalance between groups, we deleted the “atrial fibrillation” variable from propensity score calculation as it caused an unsatisfied balance. This is perhaps attributed to the potentially perfect prediction by the variable “arrhythmia”. Nonetheless, we re-entered this

variable in the propensity score model in sensitivity analyses. For the same reason of achieving balance of covariates, we categorized the variable “age” into three classes (≤65, 66-80, >80) and dichotomized the variable “hospital stay duration (days)” to less or more than 9 days”. Before estimating treatment effects, we further assessed the balance or the distribution of covariates across treated and control groups by measuring the standardized differences between compared groups. We measured the average effect of the treatment on the patients who received the treatment (i.e., the average treatment effects on the treated group (ATT)). In addition to ATT estimation, we reported the respective standard errors, coefficients, confidence intervals and p-values.

2.3.2. Instrumental variable analysis

Propensity scores balance for measured covariates but not necessarily for unmeasured covariates [16]. Conversely, the instrumental variables approach takes into account unmeasured variables that are associated with the treatment but not directly with the outcome. As an instrumental variable, we used the prevalence of statin prescription at discharge in our cohort in participating hospitals, denoted F. The endogenous explanatory variable was the statin treatment, denoted X. The outcome was all-cause mortality, denoted Y. We, therefore, tested the following hypothesis:

- F is correlated with X, conditional on other covariates
- F has no direct effect on Y but only via X.

Using a two-stage least squares method, we regressed the instrumental variable, the prevalence of statin treatment in the participating hospitals (dichotomized as above or below the median of 47%), on other covariates previously used for the propensity score analysis. We verified the null hypotheses that our instrument is weak and/or that the variables are exogenous (test of endogeneity).

2.3.3. Kaplan-Meier survival curves and Cox proportional-hazards model

For survival analyses, we declared our data to be time to event. Our event of interest was all-cause mortality while the time of follow-up was set up at 1 year and censored

afterwards. We plotted Kaplan-Meier survivor curves by statin treatment once unadjusted and adjusted on the other time for the same covariates used in the propensity score analysis.

We used a log-rank test to determine the equality of survivor functions, used a stratified log-rank test (on propensity scores), and the stratified Wilcoxon (Breslow) test to compare survival curves. To illustrate the increased rate of having an event, we regressed all-cause mortality (the outcome) on independent variables - previously adjusted for in Kaplan-Meier survivor curves - in a multivariable Cox proportional-hazard model with Breslow methods for ties. We verified the proportional-hazards assumption by a global test for all covariates included in the model and based on Schoenfeld residuals for all covariates individually.

3. Results

3.1. Participants, socio-demographic, medical history, and clinical characteristics

As shown in **Figure 1**, we analyzed 2,032 subjects out of 2,254 included in the cohort. Those treated with statins (Treated group (45%)) were compared to those not treated with statins (Control group (55%)). The number of deaths in our sample was 539. Of those, 195 (21%) occurred in the treated group versus 344 (31%) in the control group.

Table 1 shows comparisons of demographic, clinical and therapeutic characteristics between the group treated with statins and the control group. Statin-group patients were younger, more often male, and smokers; they had less severe heart failure (HF), but more often angina or history of acute coronary syndrome, dyslipidemia, or diabetes. However, they had less often arrhythmia or atrial fibrillation related events. In addition, statin-group patients were more often treated with beta-blockers, angiotensin-converting enzyme inhibitors, and were more exposed to statins before hospitalization, but less often treated with spironolactone. The test of normality for the selected variables, including the Shapiro-Wilk and Shapiro-Francia statistics, confirmed our hypothesis of normality assumption.

3.2. Propensity score matching

Once the propensity scores calculated, we assessed the overlap of the propensity scores between the treated and control groups that appeared subjectively satisfying (**Figure 2**). After that, we matched the treated group to the control group and estimated the average treatment effects on the treated (ATT). The matched sample had 1,197 patients (60%), excluding 835 observations with missing values in the following covariates: LVEF, BMI, hospital stay duration, and hemoglobin level. We described the characteristics of unmatched compared to matched patients in **Table 2**.

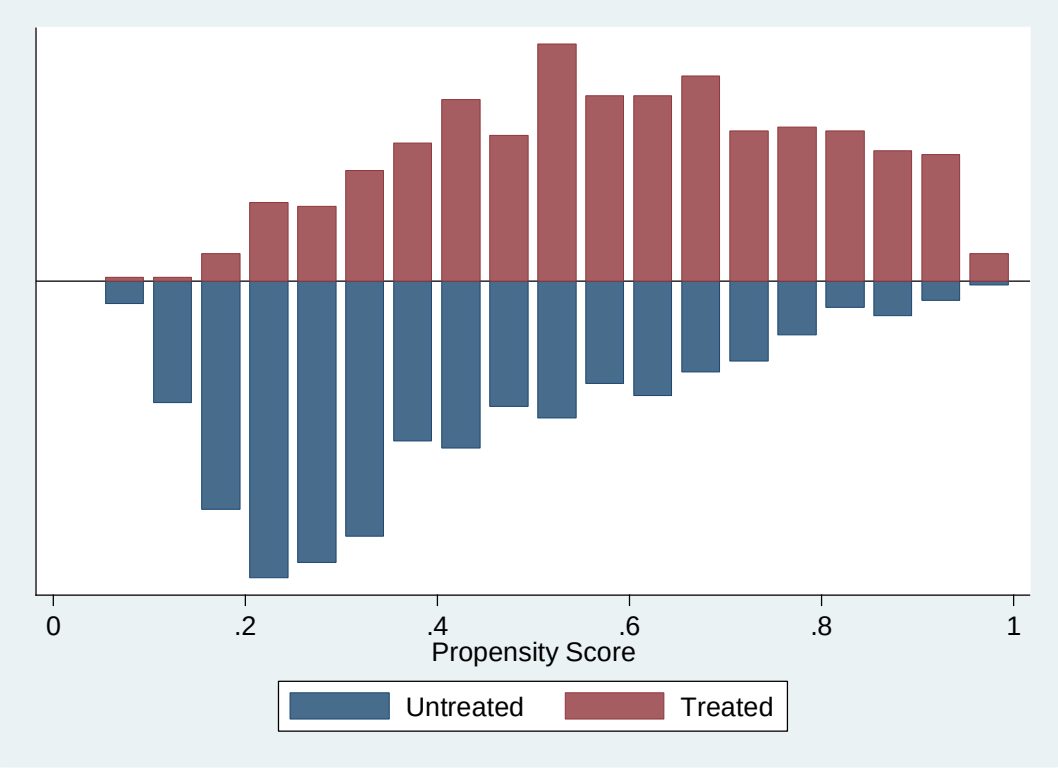

Figure 2: Distribution and degree of overlap of the propensity score between statin-treated and control groups in the included HF patients.

After propensity score matching, t-tests showed that the distribution of covariates were balanced between treated and control groups, except for the variable hypertension that showed imbalance in one block. In addition, the lack of differences between the statin and control groups was confirmed by the standardized differences (18.2% for unmatched sample versus 5.3% for matched sample)**.** In the matching step, the number of matches per observation that had the best distribution of covariates among compared groups was three (max. four) and the caliper used was 0.2 times the standard deviation of the logit of the propensity scores. As a result, the estimated satin-treatment effects (the average treatment effects on the treated, ATT) for all-cause mortality in HF showed no evidence of significant reduction [Coefficient: - 0.055, AI robust standard errors: 0.032, Z: -1.73; 95% CI: (-0.11 to 0.007), p-value: 0.083]. The re-entry of the variable “atrial fibrillation” into the propensity score model caused unsatisfied balance in one block but the estimated ATT were still insignificant: [Coefficient: -0.056, AI robust standard errors: 0.029 Z: -1.89; 95% CI: (-0.11 to 0.002), p-value: 0.058]

3.3. Instrumental variable analysis

Our instrumental variable, designated as the prevalence of statin prescription (denoted F) in participating hospitals, was associated with the treatment (denoted X) conditional on other covariates (P-value: 0.019). In addition, F showed no direct association with the outcome, all-cause mortality (denoted Y). The test of endogeneity (Durbin (score) and Wu-Hausman) failed to reject our null hypothesis that the variables are exogenous (p-value = 0.3). With the two-stage least squares treatment estimation, the instrumental variable regression did not show a significant decrease of death in the statin group versus the control group [Coefficient: -0.43, standard errors: 0.46, Z: -0.95; 95% CI: (-1.34 to 0.46), p-value: 0.34].

3.4. Kaplan-Meier curves and cox-proportional hazards model

As mentioned before, the number of deaths in our study was 539. Of those, 195 (%) occurred in the treated group versus 344 (%) in the control group. Unadjusted Kaplan-

Meier survivor curves **(Figure 3)** and the log-rank test showed significant result (p-value < 0.001). However, the adjusted Kaplan-Meier survivor curves and the stratified log-rank test failed to show a significant difference between the statin and control groups (p-value: 0.317) (**Figure 4)**. We had similar results when we used a stratified log-rank test on propensity scores (P-value: 1.00). Moreover, the multivariable Cox proportional-hazard model showed that statins use was not significantly associated with the rate of death [Hazard ratio (HR): 0.85, (95% CI 0.66 to 1.11), p-value: 0.26] and [(HR): 0.86, (95% CI 0.66 to 1.13), p-value: 0.3] when adjusted for the aforementioned independent variables or the propensity scores respectively. The test of proportional-hazard assumption was globally satisfied (p-value: 0.21) but it appeared that the variable “hospital stay duration” was not, when checked individually. Consequently, we re-ran the Cox model without this variable but the output stayed almost similar for statins treatment (p-value: 0.20) and the global test of proportional-hazard assumption was satisfied again (p-value: 0.69).

4. Discussion

Statins are not solely recommended in HF but are still widely prescribed in current practice [17] and, in contrast, observational studies had often reported mortality benefits [6, 18]. Our analysis from the cohort EPICAL2 failed to show an impact of statins on all-cause mortality in HF. These results are in accordance with those found in previous clinical trials and a meta-analysis of randomized clinical trials [2-4]. Patients who received statins were younger, more often men, obese, and had comorbidities (diabetes, kidney disease) but less severe HF, less often arrhythmia or atrial fibrillation, more often treated with beta-blockers and angiotensin converting enzyme inhibitors, and previously more exposed to statins.

Our study used propensity score matching to estimate treatment effects. This method is believed to reduce inherent biases like allocation or selection bias. We verified covariate balance by measuring standardized differences before and after matching. A balance of covariates is satisfied if it resulted into a standardized difference of <21.2% [19-21]. We estimated the ATT (i.e. an estimation on the average) because it is an interesting

summary of individual causal effects [22]. An Instrumental variable is often difficult to identify and it has to be strongly related to the treatment and indirectly to the outcome. An instrument is potentially bad if it is correlated with omitted variables or the error term [23]. Our instrument “prevalence of statin prescription by participating hospital” appeared potentially strong, and we were able to estimate the treatment by statins using a two-stage least square regression. The similar results from instrumental variable approach and propensity score analyses might be of interest [24].

We acknowledge several limitations. First, we adjusted for selected variables that we believe are related to both the treatment assignment and the outcome. Even if the assumption of treatment assignment ignorability is satisfied, because of selection of observable covariates, a selection bias still potentially exists [25]. Second, we ignored the fact that we could have included in our models only those variables with significant p-values but this might have been a source of bias of not including a relevant variable that might affect the outcome. Third, statin treatment is considered among the cholesterol lowering drugs, our analysis did not include any cholesterol level measurement at baseline nor at follow-up. Fourth, the variables (LVEF, BMI, hospital stay duration, and hemoglobin level), used in the propensity score model, had missing values and the way to deal with this missingness involved other methods [26, 27] to be considered in further research and this might lead to a lack of power in our results. Fifth, Kaplan-Meier curves did not have censored patients other than those who survived beyond one-year follow-up (potential performance bias). Those who left the study before the end or lost to follow-up at some time during the study 1-year follow-up were deleted at pre-analysis level (**Figure 1**) instead of being censored. This is due to our primary analysis method that involved propensity score analyses. Moreover, only all-cause mortality was recorded, not the more specific HF related mortality. Sixth, our study did not follow patient’s drug prescriptions by a family physician, for instance, after hospital discharge, nor the observance and real intake of statins. Finally, our study provides evidence consistent with large-scale randomized clinical trials and recent systematic reviews and current ESC guidelines [2-4, 28], though it should be interpreted with caution in light of the aforementioned limitations.

In conclusion, statins prescription was not associated with a decrease in all-cause mortality in the statin-treated group in heart failure patients after one-year hospital discharge compared to those not treated with statins. Within limitations, our study adds an evidence to the current literature because our results are based on real-world data.

Acknowledgements

We would like to thank all the participant of EPICAL2 (Epidemiologie et Pronostic de l'Insuffisance Cardiaque Aiguë en Lorraine) clinical cohort study. Special thanks are due to Marc Soudant for data management and to Patrick Taffé, statistician, for his counseling.

Contributions (draft only)

Conception and design: MA, BB, and NT. Writing the Initial draft of the manuscript: MA. Contribution to writing and editing: MA, NA, BB, and NT. Critical analysis: MA, NA, BB, and NT. Statistical analyses: MA. Proofread and read the manuscript: MA, NA, NT, and BB.

Competing interests

We declare no conflicts of interest.

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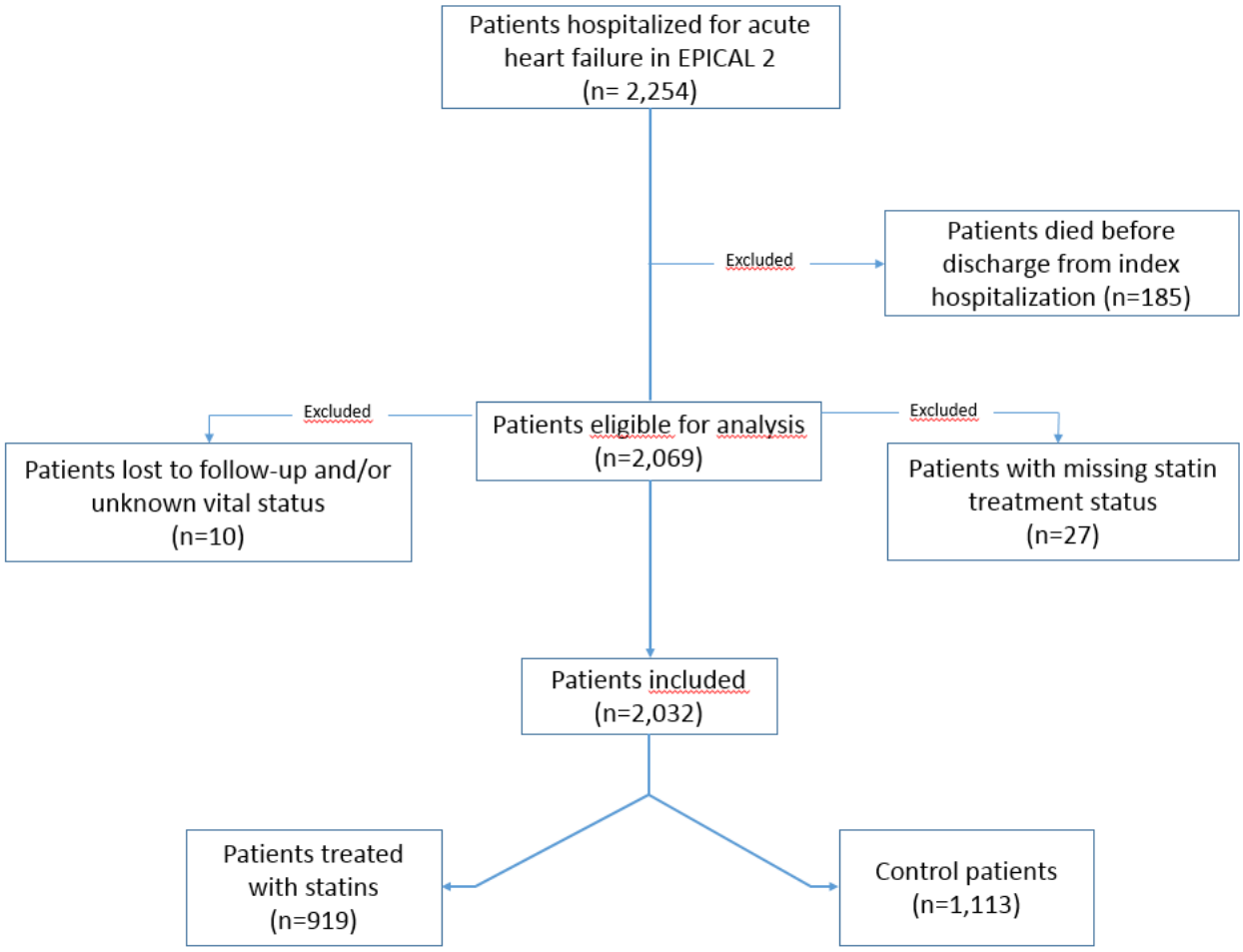


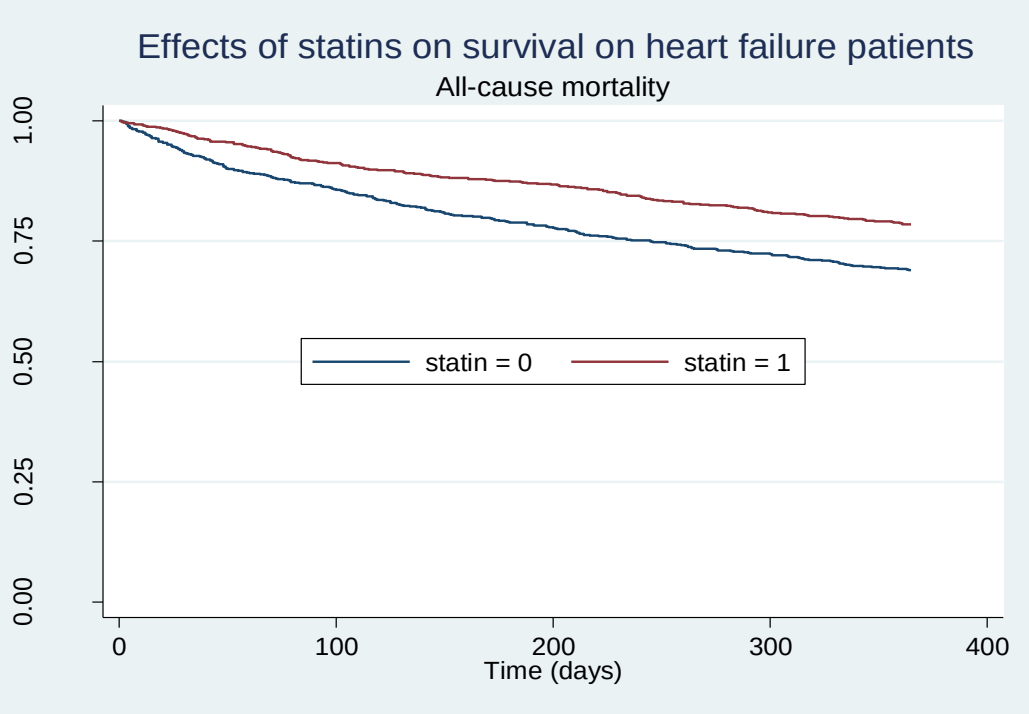
Figure 1. Flow chart for heart failure patients from EPICAL2 to evaluate statin effectiveness on all-cause mortality.

Table 1: Characteristics of included heart failure patients according to treatment with statins

Selected variables	Statins (N=919) - n(%)	No statins (N= 1,113) - n(%)	P-value	Standardized differences for unmatched sample (%)	Standardized differences for matched sample
Demographic characteristics					
Mean (SD) age (years) ≤ 65 ≥ 66 - ≤ 80 > 80	74.92 (11.06) 186 (20.24%) 400 (43.53%) 333 (36.24%)	79.15 (SD 11.57) 155 (13.93%) 329 (29.56%) 629 (56.51)	<0.001	-30.8	1.8
Female	383 (41.68%)	536 (58.85%)	<0.001	-35.9	-0.5
Clinical characteristics					
Hypertension	716 (77.91%)	841 (75.56%)	0.213	2.3	-3.1
Mean (SD) BMI (kg/m^2) <25 (underweight or normal) ≥25 - <30 (overweight) ≥30 (Obese)	28.91 (6.4) 207 (27.20%) 255 (33.51%) 299 (39.29%)	28.17 (6.7) 310 (35.59%) 264 (30.31%) 297 (34.10%)	%)0.0247	16.9	-3.0
LVEF (%) < 40 ≥ 40	 317 (43.66%) 409 (56.34%)	 311 (39.82%) 470 (60.18%)	0.039	11.7	-8.5
NYHA class III or IV (%) (severe HF)	734 (79.96%)	927 (83.59%)	0.034	-17.6	-3.9
Increased BNP or NT pro-BNP (pg/mL)*	580 (63.11%)	680 (61.10%)	0.351	2.4	7.1
Hemoglobin < 10 g/dL	 97 (10.90%)	 121 (11.27%)	 0.796	-6.7	-2.7
Medical history					
Alcohol abuse	80 (8.71%)	113 (10.15%)	0.268	-3.7	4.7
Smoking	396 (43.09%)	340 (30.55%)	<0.001	29.3	2.9
Previous history of HF	507 (55.17%)	641 (57.59%)	0.273	*	
Mean (SD) hospital stay duration (days)	11.89 (10.83)	12.31(10.86)	0.3830	-3.6	5.0
Previous angina	139 (15.13%)	95 (8.54%)	<0.001	16.2	-2.7
Previous stroke/TIA	131 (14.25%)	129 (11.59%)	0.074	5.0	3.3
Previous or precipitating arrhythmias	450 (48.97%)	700 (62.89%)	<0.001	-34.2	-0.3
Dyslipidemia	533 (58%)	299 (26.86%)	<0.001	61.2	-5.9
HF etiology					
Acute coronary syndrome (ACS) (%)	204 (22.20%)	61 (5.48%)	<0.001	50.3	8.3
Comorbidities					

COPD/asthma	216 (23.50%)	241(21.65%)	0.320	6.5	5.0
Diabetes	378 (41.13%)	355 (31.90%)	<0.001	18.3	-6.0
Chronic renal failure	210 (22.85%)	268 (24.08%)	0.516	-9.3	-0.4
Leukemia or any cancer	145 (15.78%)	188 (16.89%)	0.500	-7.0	-2.0
Atrial fibrillation	266 (28.94%)	515 (46.27%)	<0.001		
Treatments					
Beta-blocker (%)	552 (60.07%)	531 (47.71%)	<0.001	19.0	3.9
ACE-i (%)	563 (61.26%)	535 (48.07%)	<0.001		
ARB (%)	151 (16.43%)	204 (8.33%)	0.262		
Spironolactone (%)	86 (9.36%)	145 (13.03%)	0.009		
Amiodarone (%)	225 (24.48%)	267 (23.99%)	0.796		
Previous exposure to statins	675 (77.68%)	83 (8.01%)	<0.001		

BNP >400 pg/ml or NT-proBNP>450 pg/ml in patients < 50 years, NT-proBNP > 900 pg/ml in patients (50-75 years), NT-proBNP > 1800 pg/ml in patients >75 years [7, 9]
SD: standard deviation; TIA: transient ischaemic attack; COPD: chronic obstructive pulmonary disease; LVEF: left ventricular ejection fraction; HF: heart failure.
*deleted in models for collinearity



At risk (events):

0	1107	(158)	948	(88)	858	(60)	797
1	915	(80)	832	(40)	790	(53)	732

Figure 3.3: 1-year survival in statin and control groups (Unadjusted Kaplan-Meier survivor curve)

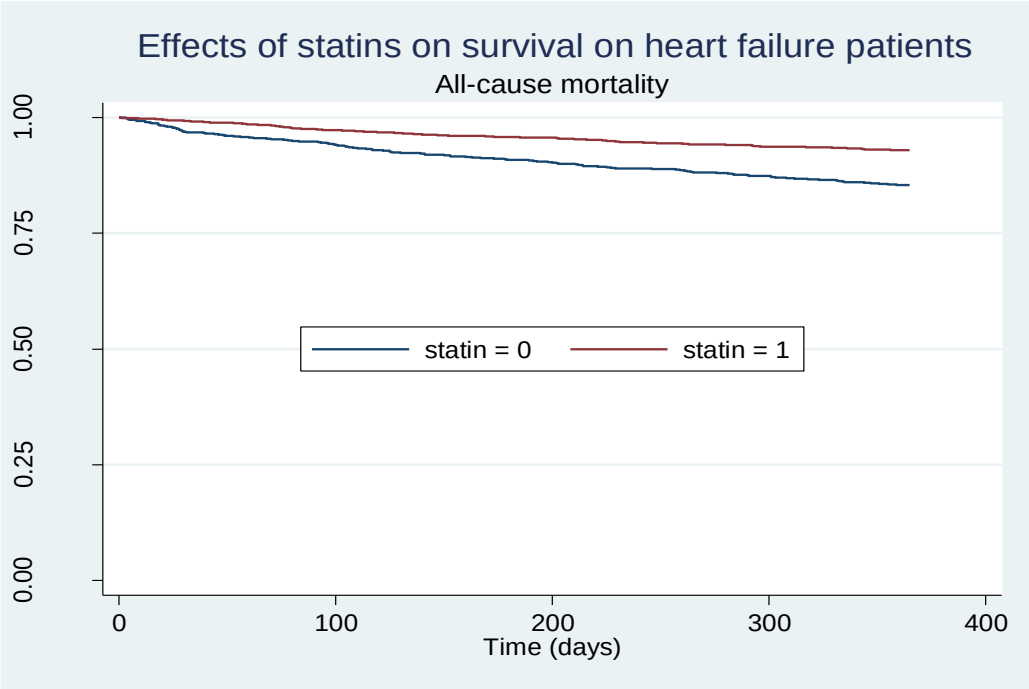


Figure 3.4: 1-year survival in statin and control groups (Adjusted Kaplan-Meier survivor curves)

APPENDIX V “Impact of Aldosterone Antagonists on Sudden Cardiac Death Prevention in Heart Failure and Post-Myocardial Infarction Patients: A Systematic Review and Meta-Analysis of Randomized Control Trials”

PLOS | ONE

RESEARCH ARTICLE

Impact of Aldosterone Antagonists on Sudden Cardiac Death Prevention in Heart Failure and Post-Myocardial Infarction Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials

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Citation: Le H-H, El-Khatib C, Mombled M, Guitarian F, Al-Gobari M, Fall M, et al. (2016) Impact of Aldosterone Antagonists on Sudden Cardiac Death Prevention in Heart Failure and Post-Myocardial Infarction Patients: A Systematic Review and Meta-Analysis of Randomized Controlled Trials. PLoS ONE 11(2): e0145958. doi:10.1371/journal.pone.0145958

Editor: C. Mary Schooling, Hunter College, UNITED STATES

Received: February 2, 2015

Accepted: December 10, 2015

Published: February 18, 2016

Data Availability Statement: All relevant data are within the paper.

Funding: The work has been done as a part of master internships of the three co-authors (HHL, CEK and MM). HHL is currently receiving a salary from Claude Bernard Lyon 1 University (scholarship of French Ministry of Higher Education & Research) for her three-year PhD at the UMR 5558 CNRS. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

Abstract

Background and Objectives

Sudden cardiac death (SCD) is a severe burden of modern medicine. Aldosterone antagonist is publicized as effective in reducing mortality in patients with heart failure (HF) or post myocardial infarction (MI). Our study aimed to assess the efficacy of AAs on mortality including SCD, hospitalization admission and several common adverse effects.

Methods

We searched Embase, PubMed, Web of Science, Cochrane library and clinicaltrial.gov for randomized controlled trials (RCTs) assigning AAs in patients with HF or post MI through May 2015. The comparator included standard medication or placebo, or both. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Event rates were compared using a random effects model. Prospective RCTs of AAs with durations of at least 8 weeks were selected if they included at least one of the following outcomes: SCD, all-cause/cardiovascular mortality, all-cause/cardiovascular hospitalization and common side effects (hyperkalemia, renal function degradation and gynecomastia).

Competing Interests: The authors have declared that no competing interests exist.

Abbreviations: AA, Aldosterone Antagonist; (A)MI, (Acute) Myocardial Infarction; ACEI, Angiotensin-Converting Enzyme Inhibitor; ARB, Angiotensin Receptor Blocker; DRI, Direct Renin Inhibitor; HF, Heart Failure; (LV)EF, (Left Ventricular) Ejection Fraction; LVSD, Left Ventricular Systolic Dysfunction; NYHA, New York Heath Association; RAAS, Renin-Angiotensin Aldosterone hormone System; RCT, Randomized Controlled Trial; SCD, Sudden Cardiac Death.

Results

Data from 19,333 patients enrolled in 25 trials were included. In patients with HF, this treatment significantly reduced the risk of SCD by 19% (RR 0.81; 95% CI, 0.67–0.98; p = 0.03); all-cause mortality by 19% (RR 0.81; 95% CI, 0.74–0.88, p<0.00001) and cardiovascular death by 21% (RR 0.79; 95% CI, 0.70–0.89, p<0.00001). In patients with post-MI, the matching reduced risks were 20% (RR 0.80; 95% CI, 0.66–0.98; p = 0.03), 15% (RR 0.85; 95% CI, 0.76–0.95, p = 0.003) and 17% (RR 0.83; 95% CI, 0.74–0.94, p = 0.003), respectively. Concerning both subgroups, the relative risks respectively decreased by 19% (RR 0.81; 95% CI, 0.71–0.92; p = 0.002) for SCD, 18% (RR 0.82; 95% CI, 0.77–0.88, p < 0.0001) for all-cause mortality and 20% (RR 0.80; 95% CI, 0.74–0.87, p < 0.0001) for cardiovascular mortality in patients treated with AAs. As well, hospitalizations were significantly reduced, while common adverse effects were significantly increased.

Conclusion

Aldosterone antagonists appear to be effective in reducing SCD and other mortality events, compared with placebo or standard medication in patients with HF and/or after a MI.

Introduction

Sudden cardiac death (SCD) is defined as unexpected natural death from a cardiac cause within a short time period, generally within one hour from the onset of symptoms, in a person without any prior condition that would appear fatal [1][2]. Patients with previous myocardial infarctions (MI) or cardiac arrest or congestive heart failure (HF) were much more likely to have inducible arrhythmias, considered as a common cause of SCD [3].

The renin-angiotensin aldosterone hormone system's (RAAS) main function is to maintain the homeostasis of arterial pressure and of extracellular fluids [4]. Dysregulation of this system leads to cardiovascular (CV) disorders including left ventricular remodeling, vasoconstriction/hypertension, and ventricular hypertrophy which may eventually result in SCD [5]. The hormonal cascade is initially induced by a decrease in blood volume which enhances renin secretion into the blood stream, resulting in the production of angiotensin II that is responsible for blood pressure increase via blood vessel constriction and the stimulation of the aldosterone hormone production. Aldosterone in its turn promotes the reabsorption of sodium and water, also leading to an increase in blood pressure [4].

Aldosterone antagonist (AA) inhibits sodium reabsorption and slightly increases water excretion [6]. This group of drugs, including spironolactone, eplerenone, and canrenone among others, is often used in managing chronic and congestive HF [7][8]. Officially, AA treatment is recommended in clinical practice at a low-dose in all patients with a left ventricular ejection fraction (LVEF) $<$ 35% and severe symptomatic HF, i.e. currently New York Heath Association (NYHA) functional class III or IV, in absence of hyperkalemia and significant renal dysfunction, unless contraindicated or not tolerated. It is also recommended in patients suffering acute myocardial infarction (AMI) with LVEF $\leq$ 40% and developing HF symptoms or having a history of diabetes mellitus, unless contraindicated [9][10].

The benefits of AA in reducing the negative effects of aldosterone hence decreasing death and hospitalization in HF or AMI patients have been demonstrated in four major trials, including RALES (Randomized Aldactone Evaluation Study) [11], EMPHASIS-HF (Eplerenone in

Mild Patients Hospitalization and Survival Study in Heart Failure) [12], EPHESUS (Eplerenone Post-AMI Heart Failure Efficacy and Survival Study) [13] and most currently TOPCAT (Treatment of Preserved Cardiac Function Heart Failure with an Aldosterone Antagonist) [14].

Our study aimed to assess the efficacy of AA on SCD, hospitalization admission and several common adverse events in patients with HF or post MI.

Methods

Inclusion and exclusion criteria

We included randomized controlled trials (RCTs) comparing spironolactone or eplerenone or canrenoate potassium to placebo or standard treatment. Studies were included if they recruited patients with left ventricular dysfunction HF (NYHA class I to IV) and/or post AMI with Killip scores between I and IV and indicated at least one assessment criteria. Our meta-analysis classified these patients into two corresponding sub-categories: HF and post-MI. The included studies had to report at least one of the following outcomes: SCD, all-cause/CV mortality, all-cause/CV hospitalization and common side effects (hyperkalemia, renal function degradation and gynecomastia).

We excluded studies with a follow-up period < 8 weeks. Trials with inestimable treatment effect (no event in both arms for all criteria) and small sample size (<40 patients/arm) were excluded. The lack of double-blind and/or intention-to-treat analysis of AA efficacy was not an exclusion criterion but was re-examined by sensibility test afterwards.

Search strategy

The research was conducted systematically from Embase, Medline (Pubmed), Cochrane Library, Web of science and clinicaltrials.gov from 1966 to 31/05/2015 (details of search strategy in S1 App). We searched for studies involving human subjects, clinical trials, RCTs and/or meta-analyses and/or systematic reviews. No language restriction was applied. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15] were followed (S2 App).

Study screening and analyzing through titles and abstracts was performed independently by several investigators in different periods (HHL, MM, CK, TA, FG), according to the pre-specified selection criteria. Data were extracted independently and compared afterwards. The latest screening and data extraction (through May 2015) were conducted independently by two investigators (HHL & MM) with kappa statistics (S3 App). Cochrane bias criteria [16] were used to evaluate the overall quality of the articles. An included trial was considered as of high quality if all its risks of bias were low. Disagreements were discussed and decisions were made through consensus. A third party (FG) was involved when necessary. The following information was extracted from the studies: the first author or study name, year of publication, baseline patient characteristics, intervention and related outcomes. Besides database searching, reference lists of all included studies, meta-analyses and reviews were manually searched for further potential trials and/or information validation.

Outcomes assessment

The primary endpoints were SCD, total mortality and CV mortality at the end of the follow-up duration. Secondary outcomes were hospitalization (from all causes and CV causes) and adverse reaction events (hyperkalemia, renal function degradation and gynecomastia) by AAs.

Statistical analysis

Kappa statistic was calculated for agreement ratio between two latest reviewers (HHL & MM) (S3 App). We extracted aggregate data, number of events and number of patients in each subgroup from included studies, using fixed-effect and random-effect models to pool the data. Results were reported as relative risk (RR) at 95% confidence intervals (CI) using the Mantel and Haenszel method for the fixed-effect model [17] or the DerSimonian and Laird method for the random-effect model [18]. When similar outcomes were obtained by both methods, we only reported the random-effect results to cover possible heterogeneity as several pharmacologic drugs and different patients were included.

Heterogeneity across studies was estimated using I^2 test [18]. I^2 values of 25%, 50%, and 75% correspond to low, moderate, and high levels of heterogeneity [19]. Meta-analysis results were considered only if the I^2 value was below 75%. Potential existence of publication bias was assessed in both subgroups at each criterion of outcome by funnel plots and verified by the Egger tests [20] using odds ratio (OR) since firm guidance for RR is not yet available [21]. Sensitivity analysis was carried out for each outcome measure to evaluate the contribution of each study to the pooled estimate by excluding important trials/ lack of blinding trials/ lack of intention-to-treat analysis trials at one time and recalculating the combined RR for the remaining studies. Statistical testing was two-tailed, with statistical significance declared at 5%. All analyses were performed using RevMan (version 5.3) and R (version 3.2.2) softwares.

Results

Search results

Our search through Embase, Medline (Pubmed), Cochrane Library, Web of science, clinicaltrials.gov and other sources (www.clinicaltrialsregister.eu & www.trialdetails.com) returned a total of 3653 studies. After elimination of duplicates, 3143 studies were retained for evaluation. Through screening of titles and abstracts, 2644 and 320 irrelevant studies were respectively excluded, respectively. Following full manuscript review of the remaining 80 studies, 54 additional ones were excluded: full-text not available (n = 10) (correspondences to authors were made but we have not received positive responses), study period <8 weeks (n = 8), review, editorial commentary or study design (n = 8), sub-study (n = 3), not RCT (n = 5), and outcomes of interest not available (n = 21). Finally, 25 studies satisfying all selection criteria were included in this meta-analysis (Fig 1). The kappa statistic indicated a subtidal agreement good at 0.75 (IC 95% CI, 0.49–1.02; p = 0.0005) (S3 App).

The quality of evidence of included studies was relatively high: 100% of low risk for selection, attrition and reporting biases, 70% of low risk for performance bias and >85% of low risk for detection bias (S1 Fig).

Study characteristics

In total, 25 RCTs [11],[13–14],[22–32],[33–43] were selected in this meta-analysis, which enrolled a total of 19333 patients (9750 for AA arm and 9583 for control/placebo arm). The mean follow-up duration was 12.42 months (1.04 year). All trials were placebo controlled except three trials [22][23][24] which applied routine treatment. Nine trials [25][26][27][28][13][29][30][31][24] assessed the effect of AAs in post-AMI patients with left ventricular dysfunction; while the other trials recruited HF patients. Duration of follow-up varied from 3 to 44 months. Spironolactone was the most commonly used AAs (15 studies), followed by eplerenone (7 studies) and canrenone (3 studies) (Table 1). The risk of bias of included trials was presented in S1 Table and S1 Fig.

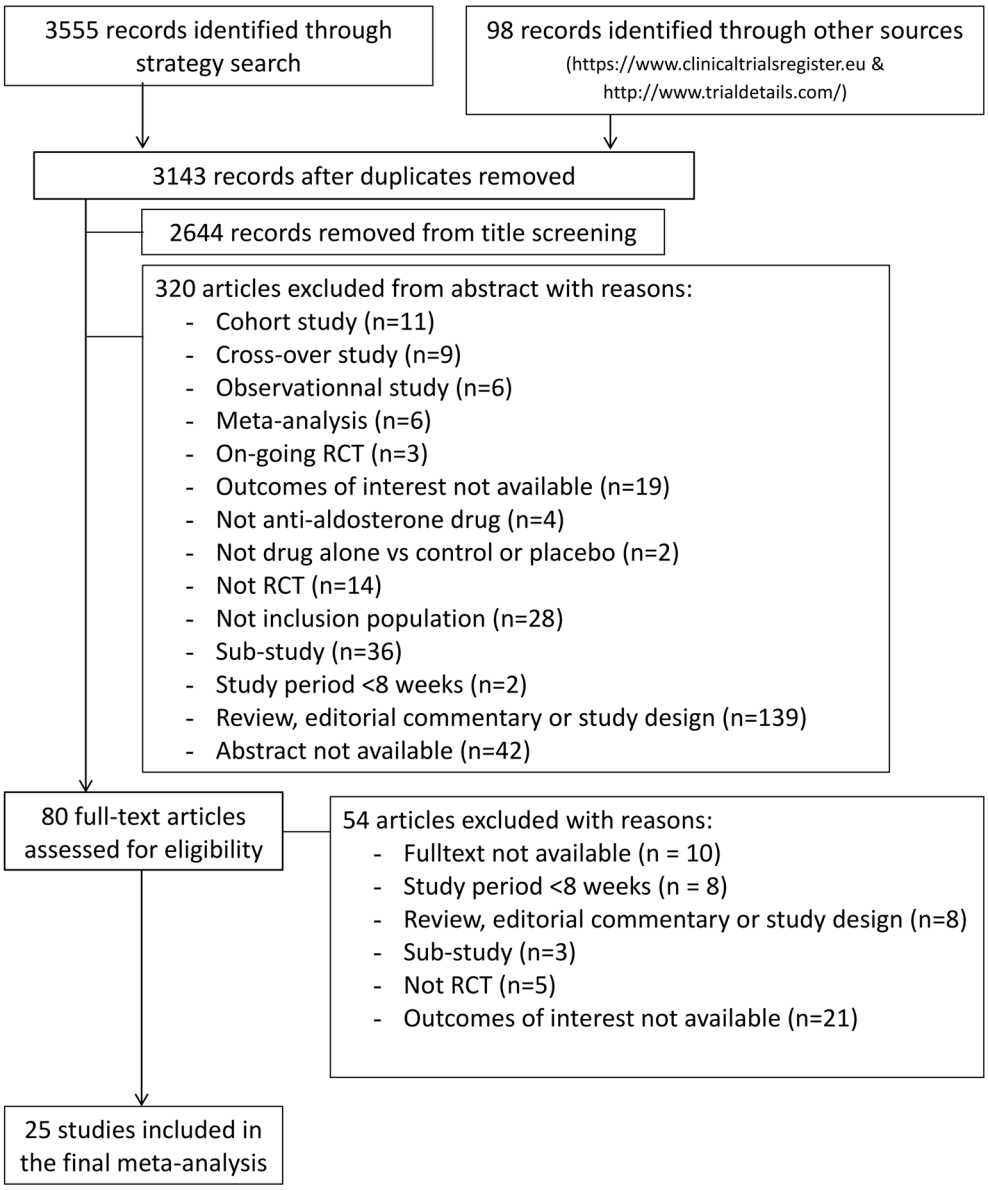


Fig 1. Study flowchart for the selection process of the final included trials.

doi:10.1371/journal.pone.0145958.g001

Baseline patient characteristics

Most trials included elderly people with mean age ranged from 50–80 years (Table 1). Most of studies consisted dominantly male participants, except two trials [26][23] where more women were recruited and the trial of Edelmann *et al.* [32] which had a relatively equal sex ratio. All trials were restricted to patients without renal dysfunction (kalemia <5.5 mmol/l and creatinine < 2.5 mg/dL) (Table 2).

Primary outcomes

Sudden cardiac death. In the 25 included articles, six accounting for 8301 subjects (4132 used AAs and 4169 received placebo/control) reported SCD events in patients with HF. In the

Table 1. Main characteristics of included studies.

Studies, (abbreviation name), year of publication	*Patients; duration (follow-up); countries*	*Comparison*	*Study design, intention to treat analysis (ITTA)*	*Number of randomized patients (excluded during follow-up)*	*Mean age (SD)*	*Male sex (%)*	*Ischemic etiology (%)*	*Ejection fraction (%)*
Boccanelli et al. 2009 (AREA-in-HF) [35]	HF; 12 months; Italy	Canrenone 25 mg (titrated to 50 mg/ day) vs. Placebo	DB; without ITTA	231(43)/ 236(42)	62.3(9.5)/ 62.7(9.5)	82/85	51.1/ 52.1	39.9(8.6)/ 39.7(8.6)
Chan et al. 2007 [56]	HF; 12 months; China	Spironolactone 25 mg/day + candesartan vs. Placebo + candesartan	DB; with ITTA	23(0)/25(0)	61.4(12.3)/ 65(0.6)	87/80	47.8/ 64.0	26(2)/28(2)
Cicoira et al. 2002 [22]	HF; 12 months; Italy	Spironolactone 25 mg (titrated to 50 mg/day) vs. Routine treatment	Open label, without ITTA	54(7)/52(6)	62.5(7.9)/ 61.7(9.8)	85/88	65/63	33(7)/34(7)
Deswal et al. 2011 (RAAM-PEF) [36]	HF; 6 months; USA	Eplerenone 25 mg (titrated to 50 mg/ day) vs. Placebo	DB; without ITTA	23(2)*/23(0)*	72.2(9.8)*/ 68.7(9.1)*	95*/ 91*	NR/NR	62.1(5)*/ 62.5(7.5)*
Di Pasquale et al. 2005 [25]	MI; 6 months; Italy	Canrenoate IV 1 mg/h then 25 mg PO/day + Captopril vs. Placebo + Captopril	DB; without ITTA	341(33)/ 346(30)	62.6(6)/ 62.8 (5)	71/71	100/100	NR/NR
Edelmann et al. 2013 (Aldo-DHF) [32]	HFPEF; 12 months; Germany &Austria	Spironolactone 25 mg/day vs. Placebo	DB; with ITTA	213(0)/209(0)	67(8)/67(8)	48/47	NR/NR	67(8)/68(7)
Gao et al. 2007 [57]	HF; 6 months; China	Spironolactone 20 mg/day vs. Placebo	DB, with ITTA	58(0)/58(0)	55(13)/54(12)	64/66	50/52	42(11)/43 (10)
Kayrak et al. 2010 [26]	AMI; 6 months; Turkey	Spironolactone 25 mg/day vs. Routine treatment	Open label, without ITTA	71(16)/71(16)	55.3(10)*/ 57.2(11)*	18*/ 26*	100/100	50.5(8.3)*/ 49.5(8)*
Mak et al. 2009 [23]	DHF; 12 months; Ireland	Eplerenone 25 mg (titrated to 50 mg/ day) vs. Routine treatment	Open label, without ITTA	24(1)/20(3)	80(7.7)/ 79 (7.9)	38/55	NR/NR	63(9.0)/64 (9.6)
Modena et al. 2001 [27]	MI; 12 months; Italy	Potassium canrenoate 50 mg/ day vs. Placebo	NR, with ITTA	24(0)/22(0)	59(10)/62(13)	71/77	100/100	47(6)/46(5)
Montalescot et al. 2014 (REMINDER) [28]	MI; 10.5 months; International (11 countries)	Eplerenone 25 mg (titrated to 50 mg/ day) vs. Placebo	DB; with ITTA	506(82)/506(79)	58.5(10.8)/ 57.8(11.0)	83/80	100/100	NR/NR
Pitt et al. 2014 (TOPCAT) [14]	HF; 3.3 years; International (6 countries)	Spironolactone (15 to 45 mg/day) vs. Placebo	DB; with ITTA	1722(0)/ 1723(0)	68.7(median) range 61.0–76.4/ 68.7 (median) range 60.7–75.5	NR/ NR	NR/NR	56(median) range 51–61/ 56 (median) range 51–62
Pitt et al. 2003 (EPHESUS) [13]	LVD after MI; 16 months (range 0–33); International (37 countries)	Eplerenone 25 mg (titrated to 50 mg/ day) vs. Placebo	DB; with ITTA	3319(0)/ 3313(0)	64(11)/64(12)	72/70	100/100	33(6)/33(6)

(*Continued*)

Table 1. (*Continued*)

Studies, (abbreviation name), year of publication	*Patients; duration (follow-up); countries*	*Comparison*	*Study design, intention to treat analysis (ITTA)*	*Number of randomized patients (excluded during follow-up)*	*Mean age (SD)*	*Male sex (%)*	*Ischemic etiology (%)*	*Ejection fraction (%)*
Pitt et al. 1999 (RALES) [11]	HF; 24 months; International (15 countries)	Spironolactone 25 mg (titrated to 50 mg/day) vs. Placebo	DB; with ITTA	822(0)/841(0)	65(12)/65(12)	73/73	55/54	25.6(6.7)/ 25.2(6.8)
Taheri et al. 2012 [37]	CHF; 6 months; Iran	Spironolactone 25 mg/day vs. Placebo	DB; without ITTA	9(2)/9(3)	50.7(17.4)/ 57.2(13.1)	55/55	NR or 0/ NR or 0	26.6(8.3)/ 31.1(10.5)
Taheri et al. 2009 [38]	HF; 6 months; Iran	Spironolactone 25 mg/day vs. Placebo	DB; without ITTA	8(3)/8(2)	59.5(6.5)/ 56.8(9.3)	63/75	NR or 0/ NR or 0	31.3(8.7)/ 33.8(9.2)
The RALES Investigators [58]	HF; 3 months; International	Spironolactone 12.5, 25, 50, 75 mg/day (4 groups) vs. Placebo	DB; with ITTA	174(0)/40(0)	63/61(12)	79/83	NR/NR	NR/NR
Udelson et al. 2010 [39]	HF; 9 months; USA (multicenter)	Eplerenone 25 mg (titrated to 50 mg/ day) vs. Placebo	DB; without ITTA	117(13)/109(20)	63.3(12.2)/ 62.0(12.9)	84/84	60/61	26.2(0.6)/ 27.0(0.6)
Uzunhasan et al. 2009 [29]	AMI; 6 months; Turkey	Spironolactone 50 mg/day vs. Placebo	DB; with ITTA	41(0)/41(0)	52(10)/52(10)	79/71	NR/NR	47/44
Vatankulu et al. 2013 [30]	AMI; 6 months; Turkey	Spironolactone 12.5 & 25 mg/day (2 groups) vs. Routine treatment	Open label; with ITTA	104(0)/56(0)	56/57(11)	84/80	100/100	NR/NR
Vizzardi et al. 2013 [34]	CHF; 44 ± 16 months; Italy	Spironolactone 25 mg (titrated to 100 mg/day) vs. Placebo	SB; without ITTA	65(5)/65(1)	61(14.7)/ 65 (17.4)	NR/ NR	NR/NR	34.5(6.8)/ 37.7(11)
Vizzardi et al. 2010 [59]	HF; 6 months; Italy	Spironolactone 25 mg (titrated to 100 mg/day) vs. Placebo	SB; with ITTA	79(0)/79(0)	61(13)/58(13)	84/82	NR/NR	35.2(0.7)/ 35.4(1.0)
Weir et al. 2009 [31]	MI; 5.5 months; UK	Eplerenone 25 mg (titrated to 50 mg/ day) vs. Placebo	DB; without ITTA	50(4)/50(3)	61.0 12.0)*/ 56.8(12.0)*	74*/ 80*	100/100	35.2(3.9)*/ 32.3(4.8)*
Wu et al. 2013 [24]	AMI; 12 months; China	Spironolactone 20 mg/day vs. Routine treatment	Open label; without ITTA	308(46)/308(42)	59.8(11.7)*/ 59.9(10.3)*	74*/ 72*	100/100	NR/NR
Zannad et al. 2011 (EMPHASIS-HF) [33]	HF; 21 months; International	Eplerenone 25 mg (titrated to 50 mg/ day) vs. Placebo	DB; with ITTA	1364(0)/ 1373(0)	68.7(7.7)/ 68.6(7.6)	77/78	70/68	26.2(4.6)/ 26.1(4.7)

The results are shown according to the mean (SD), except for additional explanation in exceptional cases. BD: double blind; ITTA: intention to treat analysis; HF: Heart failure; DHF: Diastolic heart failure; CHF: congestive heart failure; HFPRE: Heart failure with preserved ejection fraction; MI: Myocardial infarction; LVD: Left Ventricular Dysfunction; IV: Intra-venous; DB: Double blind; SB: Single blind; NR: not reported; AREA-in-HF: Aldosterone Receptor Antagonists improve outcome in severe Heart Failure; RAAM-PEF: Randomized Aldosterone Antagonism in Heart Failure with Preserved Ejection Fraction; Aldo-DHF: Aldosterone Receptor Blockade in Diastolic Heart Failure; TOPCAT: Treatment of Preserved Cardiac Function Heart Failure With an Aldosterone Antagonist; EPHESUS: Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival Study; RALES: Randomized Aldactone Evaluation Study; EMPHASIS-HF: Eplerenone in Mild Patients Hospitalization and Survival Study in Heart Failure.

(*) For only the patients included in final analyses.

doi:10.1371/journal.pone.0145958.t001

follow-up duration, the SCD rate in HF patients was 4.89% (n = 202/4132) in those treated with AAs, compared with 6.09% (n = 254/4169) in those treated with placebo/control. In post-MI patients, SCD was reported only in the EPHESUS trial [13] at the rates of 4.88% (n = 162/3319) and of 6.07% (n = 201/3313) in groups receiving AAs and placebo, respectively.

Table 2. Main criteria for patients' eligibility in the included studies.

Studies	NYHA class	Killip class	Creatinine (mg/dL or other units)	Serum potassium (mmol/L)	Ejection fraction (%)
Boccanelli et al. 2009 (AREA-in-HF) [35]	II	NR	≤2.5	≤5.0	≤45
Chan et al. 2007 [56]	II to III	NR	≤200 μmol/l	≤5.0	<40
Cicoira et al. 2002 [22]	NR	NR	≤150 μmol/l	≤5.0	≤45
Deswal et al. 2011(RAAM-PEF) [36]	II to III	NR	≤2.5	≤5.0	≥50
Di Pasquale et al. 2005 [25]	NR	I to II	<2.0	<5.0	NR
Edelmann et al. 2013 [32]	II to III	NR	NR	<5.1	≥50
Gao et al. 2007 [57]	II to IV	NR	<2.5	<5.5	<45
Kayrak et al. 2010 [26]	NR	I to II	≤2.0	≤5.0	≥40
Mak et al. 2009 [23]	IV	NR	≤200 μmol/l	NR	≥45
Modena et al. 2001 [27]	NR	I to III	≤2.5	NR	NR
Montalescot et al. 2014 (REMINDER) [28]	NR	NR	≤2.5	NR	≤40
Pitt et al. 2014 (TOPCAT) [14]	I to IV	NR	<2.5	≤5.0	≥45
Pitt et al. 2003 (EPHESUS) [13]	I to IV	NR	≤2.5	≤5.0	≤40
Pitt et al. 1999(RALES) [11]	III to IV	NR	≤2.5	≤5.0	≤35
Taheri et al. 2012 [37]	III to IV	NR	NR	<5.5	≤45
Taheri et al. 2009 [38]	III to IV	NR	NR	≤5.5	≤45
The RALES Investigators [58]	III to IV	NR	≤2.0	<5.5	≤35
Udelson et al. 2010 [39]	II to III	NR	NR	≤5.5	≤35
Uzunhasan 2009 [29]	NR	I to II	<2.5	≤5.0	NR
Vatankulu et al. 2013 [30]	NR	I to II	≤2.0	<5.5	≥40
Vizzardi et al. 2013 [34]	I to II	NR	NR	≤5.0	<40
Vizzardi et al. 2010 [59]	I to II	NR	≤2.5	≤5.0	≤40
Weir et al. 2009 [31]	NR	I to II	≤2.5	≤5.0	<40
Wu et al. 2013 [24]	NR	I to III	≤2.5	≤5.0	NR
Zannad et al. 2011 (EMPHASIS-HF) [33]	II	NR	NR	≤5.0	≤35

NYHA: New York Heath Association; ND: Not Defined; NR: Not Reported; 221 μmol/l ~ 2.5 mg/dL.

doi:10.1371/journal.pone.0145958.t002

There was a significant reduction of SCD rate with AAs in patients with HF (19% SCD reduction; RR 0.81; 95% CI, 0.67–0.98; p = 0.03) or with post-MI left ventricular dysfunction (20% SCD reduction; RR 0.80; 95% CI, 0.66–0.98; p = 0.03). In total, the SCD rate was 4.88% (n = 364/7451) in those treated with AAs compared with 6.08% (n = 455/7482) in those treated with placebo/control (19% SCD reduction; RR 0.81, 95% CI, 0.71–0.92; p = 0.002) without any evidence of statistical heterogeneity (I^2 = 0%) (Fig 2A).

All-cause mortality. All-cause mortality rate in patients with HF were 16.21% (n = 729/4496) in those treated with AAs and 19.96% (n = 903/4523) in those assigned to placebo/control (RR 0.81, 95% CI, 0.74–0.88, p<0.00001) through the follow-up duration. The corresponding numbers in the sub-group of MI were 11.64% (n = 519/4460) and 13.71% (n = 611/4457), respectively, with 15% reduction (RR 0.85; 95% CI, 0.76–0.95, p = 0.003). Altogether, there were 1248/8956 (13.93%) and 1514/8980 (16.86%) deaths from all causes, respectively, observed in treatment and placebo arms with a general reduction rate of 18% (RR 0.82; 95% CI, 0.77–0.88, p<0.00001). Heterogeneity was not found in each sub-group (consisting 10 and 8 trials, respectively) and in the whole population (all I^2 = 0%) (Fig 2B).

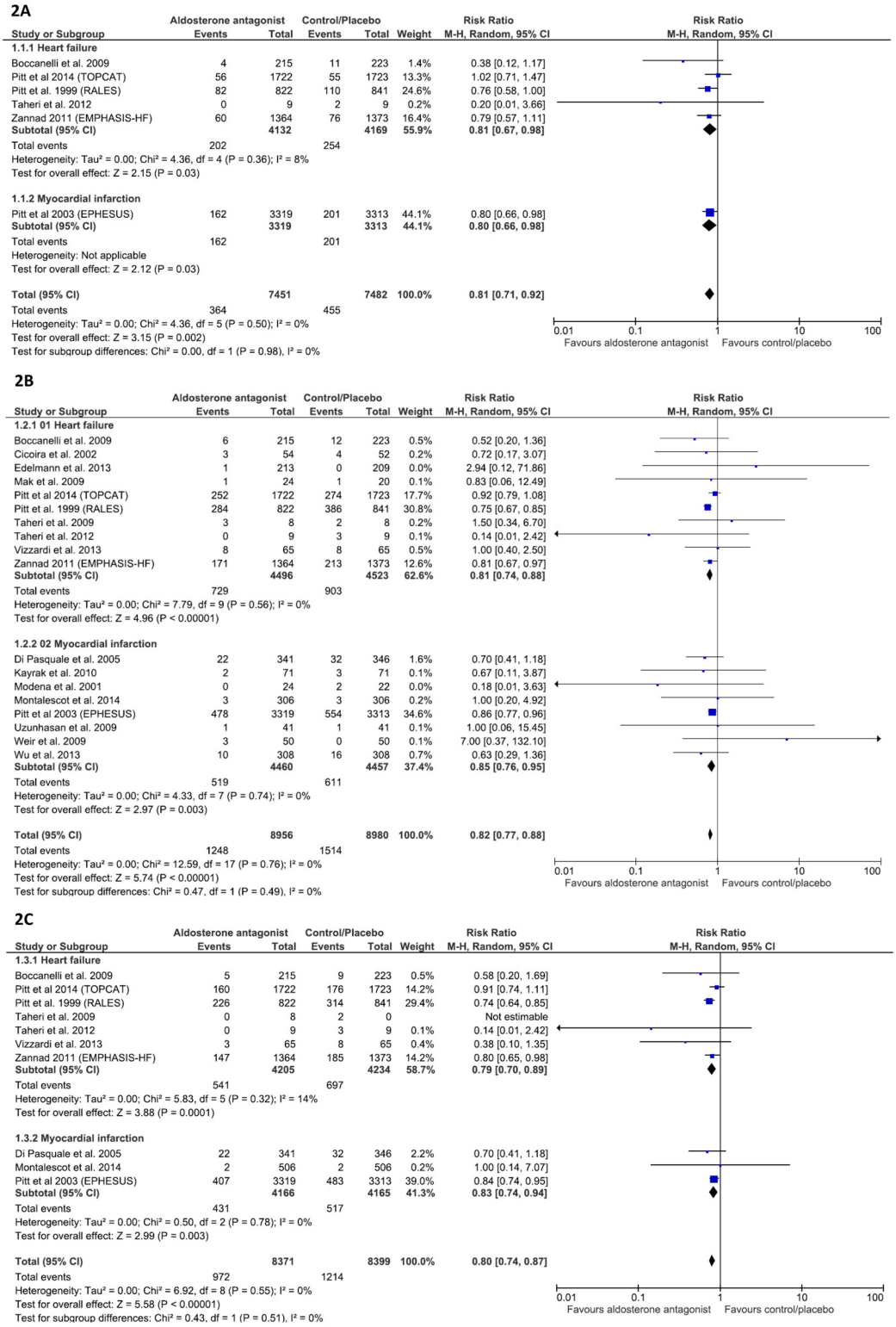


Fig 2. Efficacy of aldosterone antagonist compared with control for the prevention of (A) Sudden death, (B) All-cause mortality, and (C) Cardiovascular death in patients with heart failure or myocardial infarction.

doi:10.1371/journal.pone.0145958.g002

Cardiovascular mortality. In the follow-up duration, CV mortality rate was 17.03% (n = 541/4205) in those treated with AAs and 22.54% (n = 697/4234) in those received placebo in the HF subgroup, resulting in a reduction rate of 21% (RR 0.79; 95% CI, 0.70–0.89, p<0.00001). In the MI subgroup, the efficacy of AAs was demonstrated by a reduction of 17% (RR 0.83; 95% CI, 0.74–0.94, p = 0.003) of CV mortality in treated patients compared with those receiving placebo (431/4166 vs 517/4165 deaths, respectively). AAs contributed a general reduction of 20% for the two categories of patients (RR 0.80; 95% CI, 0.74–0.87, p<0.00001) (Fig 2C).

Generally, there were likely no heterogeneity found in SCD, all-cause mortality and CV mortality (all I^2 = 0%), regarding both categories of patients.

Secondary outcomes

All-cause hospitalization. Relative risk reductions in all-cause hospitalization rate by AAs compared with placebo/control were 9% in HF patients (RR 0.91; 95% CI, 0.86–0.96; p = 0.0008) and 37% in post-MI patients (RR 0.63; 95% CI, 0.19–2.05; p = 0.44). In overall analysis, the results showed a significant decrease of 7% of all–cause hospitalization in patients receiving AAs compared with those taking placebo/control (RR 0.93; 95% CI, 0.88–0.98; p = 0.008) (Fig 3A). However, heterogeneity was likely considerable (I^2 = 17%, 29% and 35% respectively).

Cardiovascular hospitalization. In patients with HF, a significant relative risk reduction of 21% for CV hospitalization was observed in those assigned to AAs, compared with placebo/control (RR 0.79; 95% CI, 0.68–0.91; p = 0.002). In patients with MI, the corresponding value was 20% but not significant (RR 0.80; 95% CI, 0.47–1.35; p = 0.44). An analysis for both subgroups showed a relative risk reduction of 18% (RR 0.82, 95% CI, 0.72–0.92; p = 0.001) (Fig 3B). However, heterogeneity detected was moderate (I^2 = 49%, 31% and 51% respectively).

Adverse reactions

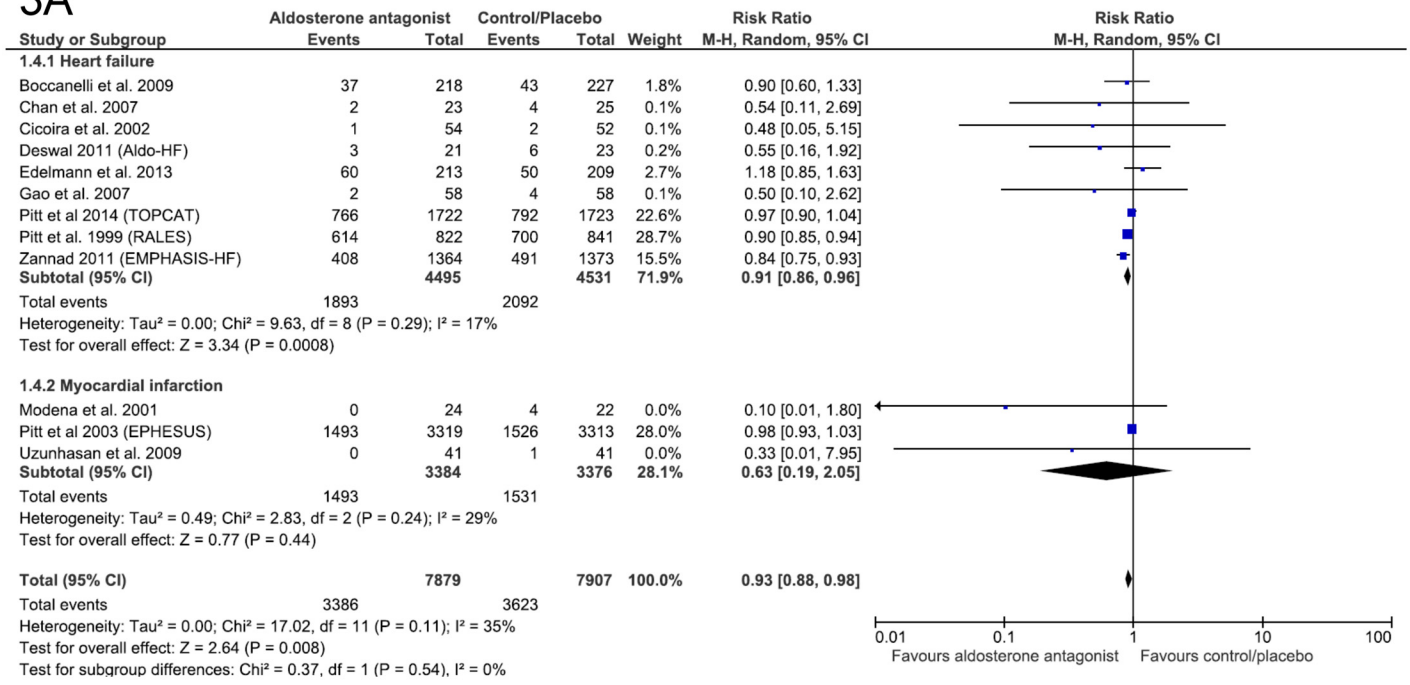
Hyperkalemia, worsening renal function and gynecomastia were the main observed side effects of AAs in the 25 included studies, as compared to placebo or control. In general, the incidence of all considered adverse events significantly doubled in patients treated with AAs, compared to those receiving placebo or reference therapy. Corresponding RRs were 1.88 (Cl 95%, 1.68–2.12, p<0.00001) for hyperkalemia; 1.45 (CI 95%,1.08–1.93, p = 0.01) for degradation of renal function; 3.88 (CI 95%, 1.69–8.91, p = 0.001) for gynecomastia and 1.99 (95% CI, 1.64–2.41; p<0.00001) for all considered side-effects in general, with remarkably various heterogeneities found among the subgroups (0%, 23%, 70% and 46% respectively) (Fig 4). Exceptions appeared for the two big RALES and EMPHASIS-HF trials [11][33], where interestingly enough, patients in the placebo groups had slightly higher rate of gynecomastia (RALES and EMPHASIS-HF) and of renal function degradation (EMPHASIS-HF).

Publication bias

Visual analysis of funnel plots suggested the possibility of publication biases in SCD, CV mortality, total/CV hospitalization analyses, with some asymmetries (Figs 5A, 5C and 6A, 6B); this bias was unlikely in two cases: total mortality (Fig 5B) and side effects (Fig 7).

Statistically, potential existence of publication bias was tested by Egger approach, using OR instead of RR for the reason explained in the Method session. For clinical outcome with low incidence (SCD, total/CV mortality, side effects), these two indicators were similar. For example, the SCD prevention effect of AAs estimated by RR was 0.81 (95% CI, 0.71–0.92, p = 0.002) and by OR was 0.80 (95% CI, 0.69–0.92, p = 0.002), both using random effect model. However,

3A



3B

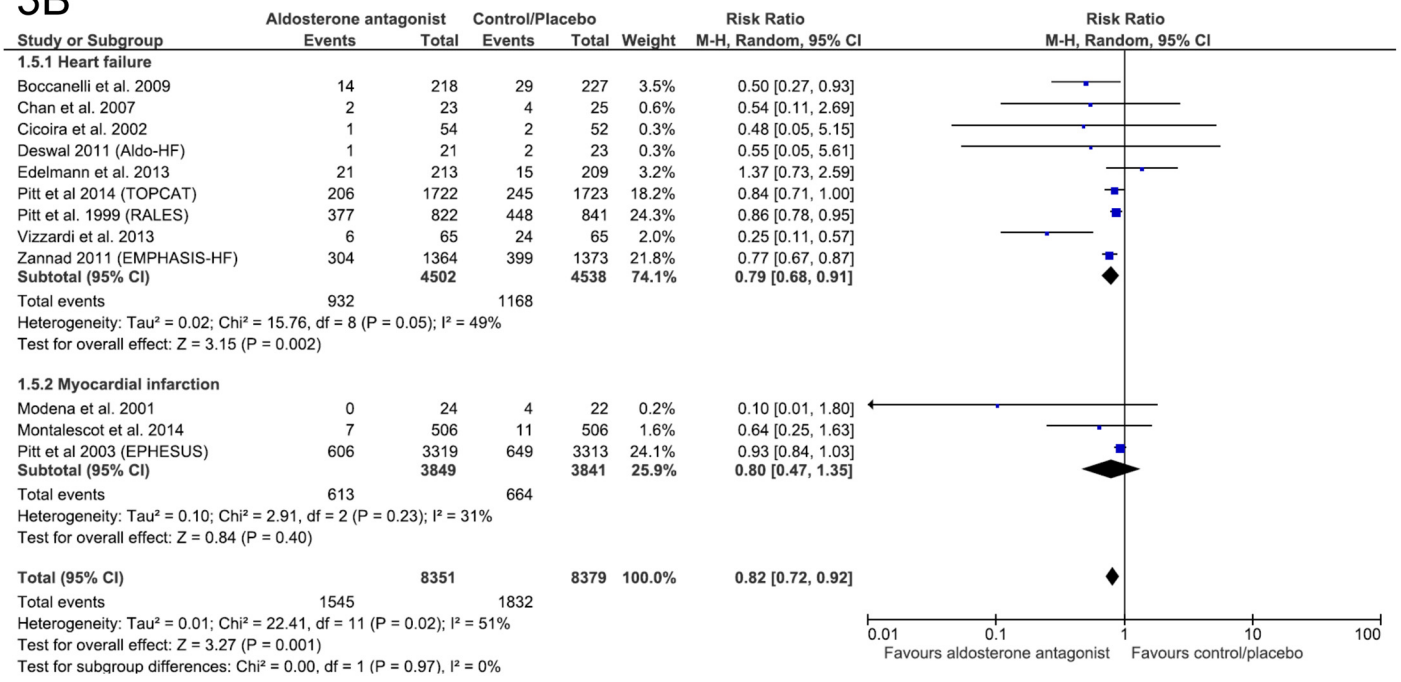


Fig 3. Efficacy of aldosterone antagonist compared to control for the prevention of (A) All-cause hospitalization and (B) Cardiovascular hospitalization in patients with heart failure or myocardial infarction.

doi:10.1371/journal.pone.0145958.g003

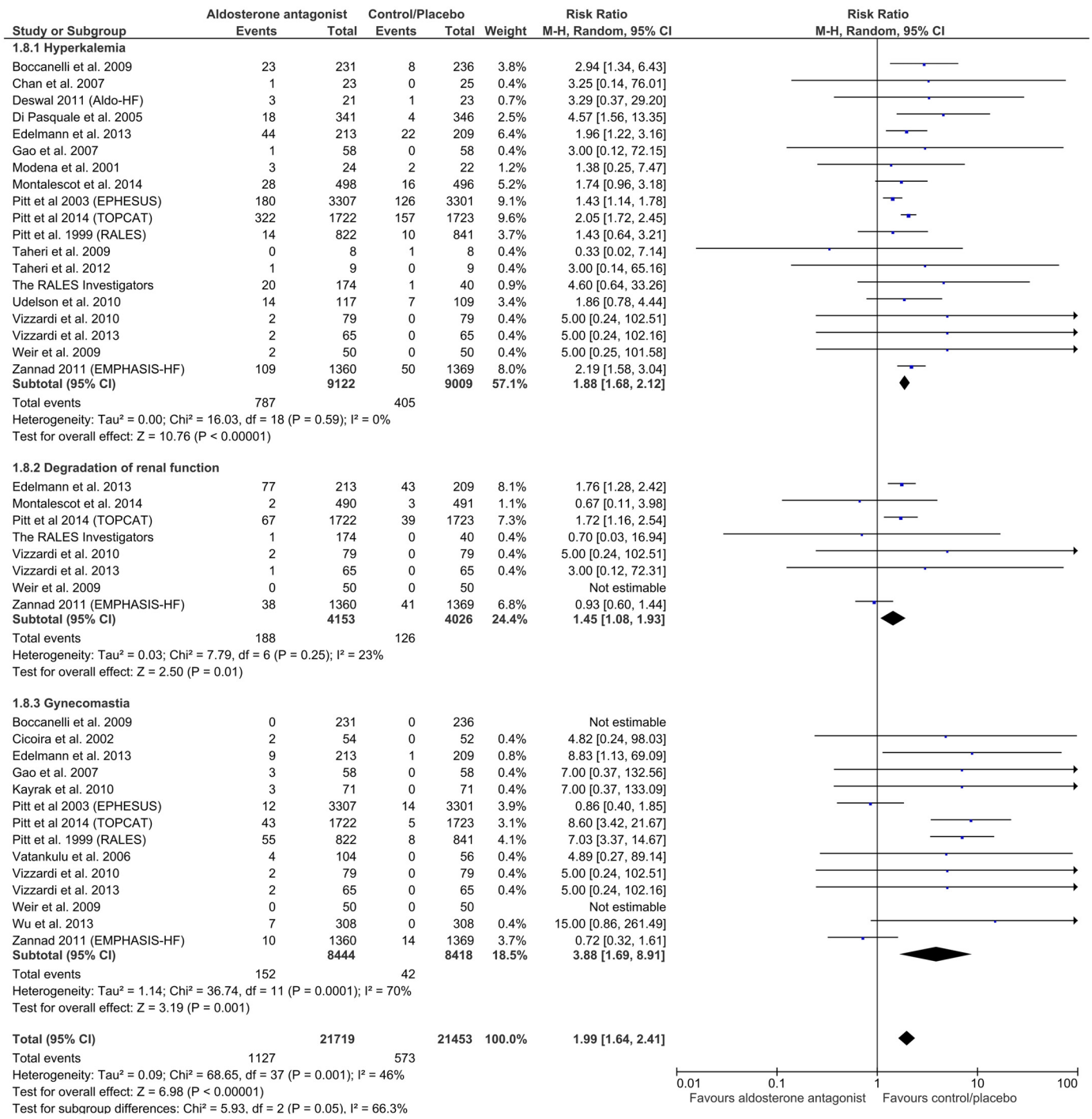


Fig 4. Incidences of adverse effects (hyperkalemia, degradation of renal function and gynecomastia) under aldosterone antagonist treatment, compared with control/placebo group, in patients with heart failure or myocardial infarction.

doi:10.1371/journal.pone.0145958.g004

the higher the incidence was, the more different these estimators were. For example, for total hospitalization criteria which had the highest incidence (over 40%), intervention effect measured by RR was 0.93 (95% CI, 0.88–0.98, p = 0.008) but by OR was 0.84 (95% CI, 0.72–0.97, p = 0.018), both using random effect model.

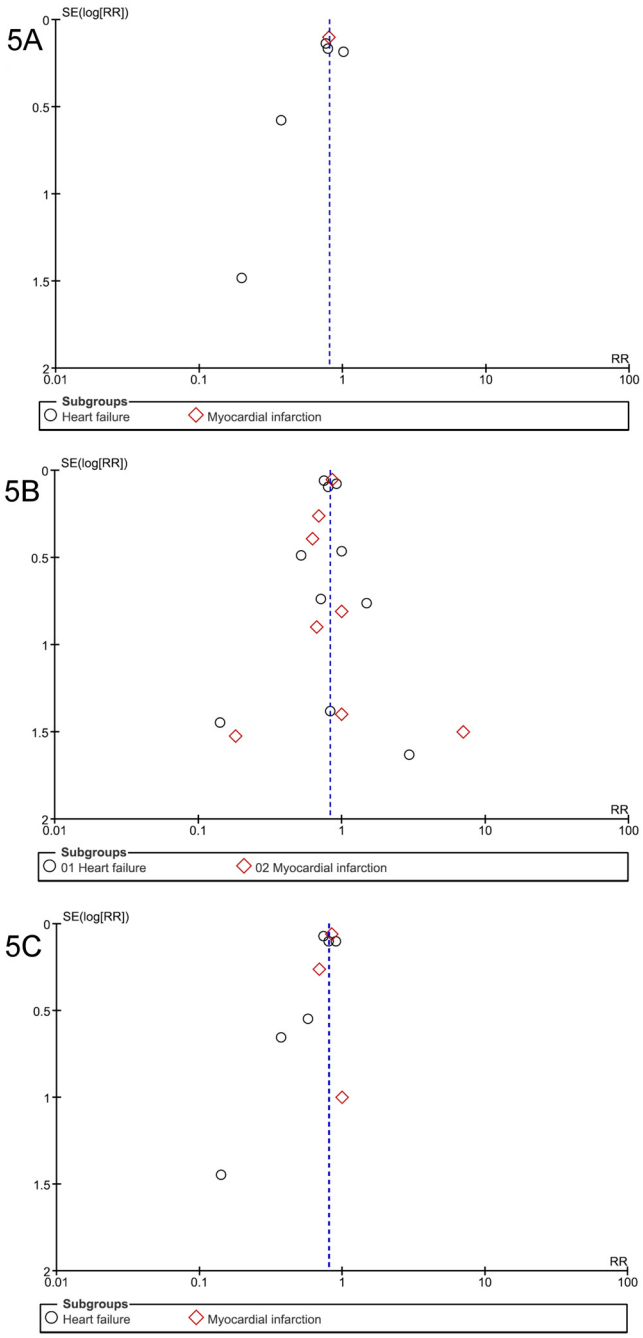


Fig 5. Funnel plot of standard error (log odds ratio) by odds ratio to evaluate publication bias for effect of aldosterone antagonist treatment in preventing (A) Sudden death, (B) All-cause mortality, and (C) Cardiovascular mortality in patients with heart failure or myocardial infarction.

doi:10.1371/journal.pone.0145958.g005

Most clinical outcomes in this meta-analysis included at least 10 trials, thus satisfied the recommendations on testing for funnel plot asymmetry, except the primary outcome (SCD). The p-values of Egger tests were 0.21 for SCD, 0.79 for total mortality, 0.17 for CV mortality, 0.13 for total hospitalization, 0.08 for CV hospitalization, 0.23 for hyperkalemia, 0.94 for renal function degradation and 0.29 for gynecomastia, none supporting evidence for publication bias. Of

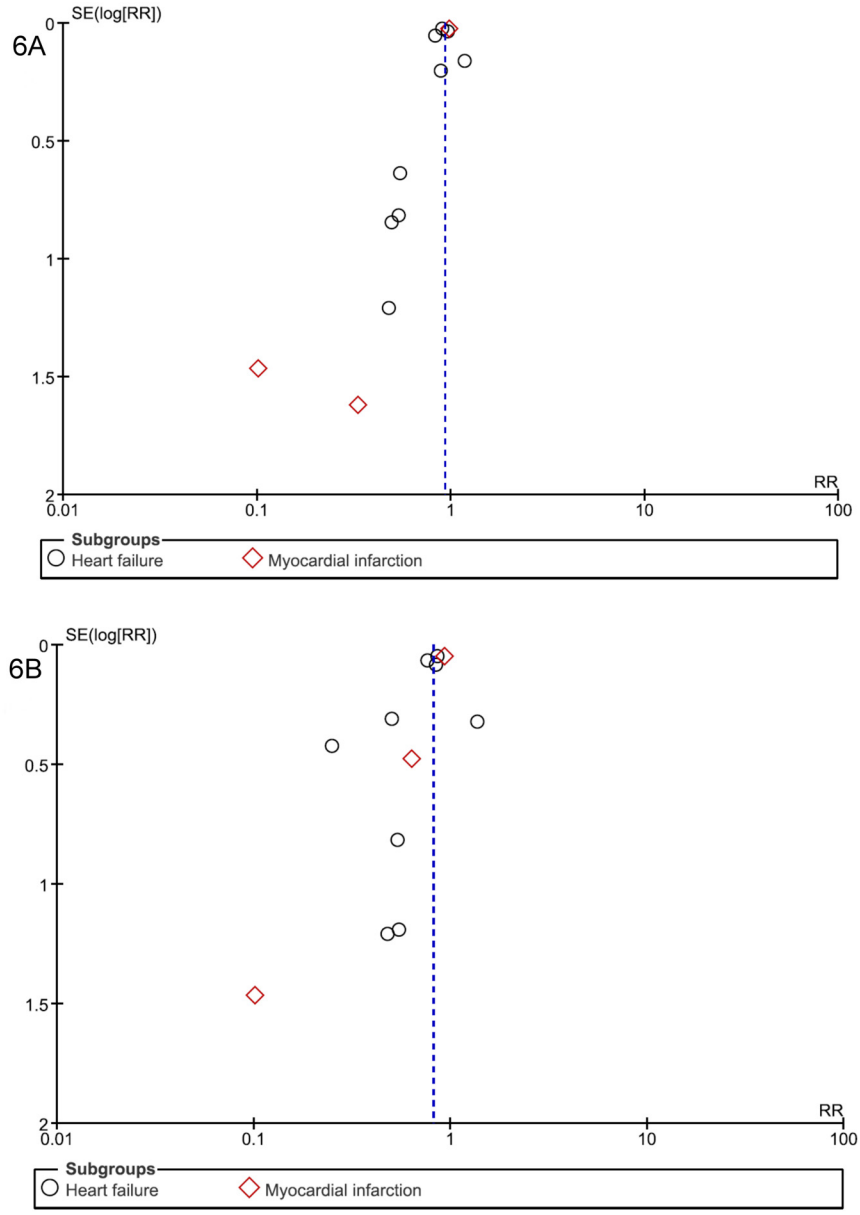


Fig 6. Funnel plot of standard error (log odds ratio) by odds ratio to evaluate publication bias for effect of aldosterone antagonist treatment in preventing (A) All-cause hospitalization and (B) Cardiovascular hospitalization in patients with heart failure or myocardial infarction.

doi:10.1371/journal.pone.0145958.g006

note, regarding both funnel plots & Egger tests, publication biases were not formally assessable for SCD outcome due to the few number of trials included (n = 6).

Sensitivity analysis

Sensitivity analyses were tested for the biggest trial in each subgroup (among the greatest ones REMINDER [28], TOPCAT [14], EPHESUS [13], RALES [11], EMPHASIS-HF [33]) which had the greatest weight percentages, for eight open label/single blind/not reported design trials if applicable (Cicoira *et al.* [22], Kayrak *et al.* [26], Mak *et al.* [23], Modena *et al.* [27],

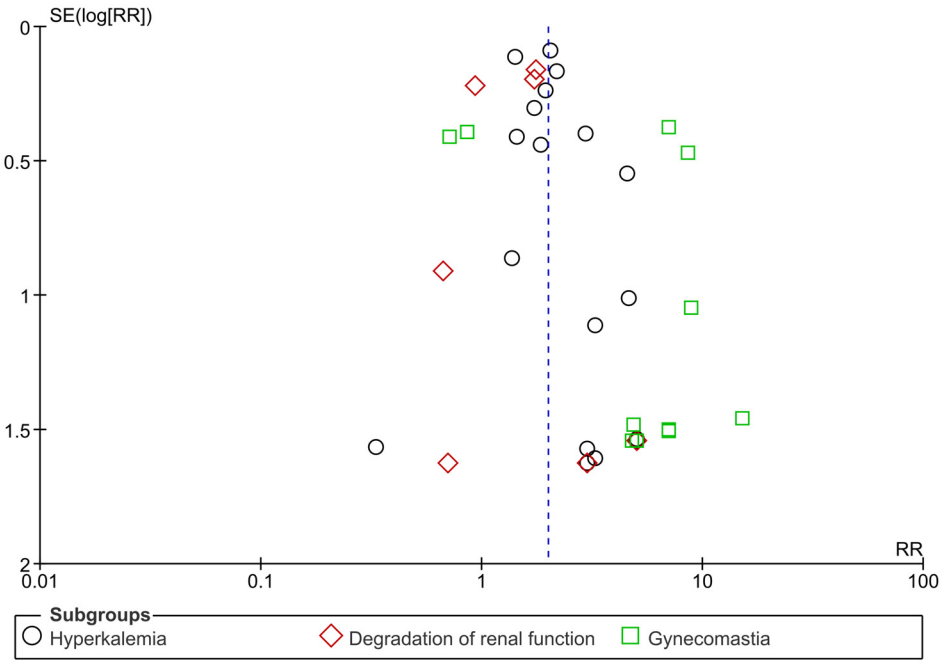


Fig 7. Funnel plot of standard error (log odds ratio) by odds ratio to evaluate publication bias for effect of aldosterone antagonist treatment in inducing common side effects (hyperkalemia, degradation of renal function, gynecomastia) in comparison with placebo/control, in patients with heart failure or myocardial infarction.

doi:10.1371/journal.pone.0145958.g007

Vatankulu *et al.* [30], Vizzardi *et al.* 2013 [34], Vizzardi *et al.* 2010 40], Wu *et al.* [24]) and for 11 trials which had no intention to treat analysis (ITTA) if applicable (Boccanelli *et al.* [35], Cicoira *et al.* [22], Deswal *et al.* [36], Di Pasquale *et al.* [25], Kayrak *et al.* [26], Mak *et al.* [23], Taheri *et al.* 2012 [37], Taheri *et al.* 2009 [38], Udelson *et al.* [39], Vizzardi *et al.* 2013 [24], Weir *et al.* [31]) (Table 1). As well, we conducted these analyses only for primary outcome, i.e the preventive effect of AAs on mortality (SCD, total and CV death) in patients with HF or post-MI.

Among all included trials in considering both subgroups, EPHESUS trial [13] contributed the largest weight with relative overall weights of 44.1% for SCD, 34.6% for all-cause mortality and 39.0% for CV mortality analyses. However, when performing a sensitivity test by excluding this trial, no significant differences of RRs were detected for three cases: from (0.81, 95% CI 0.71–0.92, p = 0.002) to (0.81, 95% CI 0.67–0.98, p = 0.03), from (0.82, 95% CI 0.77–0.88, p<0.00001) to (0.80, 95% CI 0.74–0.87, p<0.00001) and from (0.80, 95% CI 0.74–0.87, p<0.00001) to (0.78, 95% CI 0.71–0.86, p<0.00001), respectively.

For patients with HF, the RALES trial [11] had the largest relative weights of 24.6%, 30.8% and 29.4% for these three criteria, respectively. Excluding this trial resulted in no significant difference of estimate effect for SCD analysis: RR (0.81; 95% CI, 0.67–0.98; p = 0.03) changed to (0.82, 95% CI, 0.59–1.14) but the effective estimator turned out non-significant (p = 0.24). The RRs for all-cause and CV mortality changed moderately from (0.81, 95% CI, 0.74–0.88, p <0.00001) to (0.87, 95% CI, 0.77–0.98, p = 0.02) and from (0.79, 95% CI, 0.70–0.89, p = 0.0001) to (0.83, 95% CI, 0.71–0.97, p = 0.02) respectively, with the results remained significant.

In these patients, removing two trials which had no intention-to-treat analysis (ITTA) (Boccanelli *et al.* [35], Taheri *et al.* 2012 [37]) gave no remarkable influence on the AAs' effect in

preventing SCD: RR changed from (0.81; 95% CI, 0.67–0.98; p = 0.03) to (0.83; 95% CI, 0.69–0.99; p = 0.04). The same attempt for three trials (Boccanelli *et al.* [35], Taheri *et al.* 2012 [37], Taheri *et al.* 2009 [38]) resulted in slight changes: RR changed from (0.81, 95% CI, 0.74–0.88, p<0.00001) to (0.81, 95% CI, 0.75–0.88, p <0.00001) and from (0.79, 95% CI, 0.70–0.89, p = 0.0001) to (0.79, 95% CI, 0.70–0.90, p = 0.0004) in case of total/CV mortality, respectively.

Open or single blind trials in HF subgroup were also excluded for sensitivity analyses (applicable for total and CV mortality analyses). Removing the three trials Cicoira *et al.* [22], Mak *et al.* [23], Vizzardi *et al.* 2013 [34] for total mortality and removing the trial of Vizzardi *et al.* 2013 [34] for CV mortality resulted in slight changes: RR changed from (0.81, 95% CI, 0.74–0.88, p<0.00001) to (0.81, 95% CI, 0.73–0.91, p = 0.0004) and from (0.79, 95% CI, 0.70–0.89, p = 0.0001) to (0.83, 95% CI, 0.74–0.94, p = 0.003), respectively.

In those with MI, the EPHESUS trial [13] was the only for SCD prevention analysis. This trial occupied the greatest relative overall weights of 34.6% and 39.0% in case of total and CV mortality, respectively. Removing this trial returned significant changes of RRs from (0.85, 95% CI, 0.76–0.95, p = 0.003) to (0.71, 95% CI 0.48–1.05, p = 0.09) and from (0.83, 95% CI, 0.74–0.94, p = 0.003) to (0.71, 95% CI 0.43–1.18, p = 0.19), respectively.

For total mortality analysis, there was only one trial without ITTA (Weir *et al.* [31]) presented in the MI subgroup and removing this trial had likely no impact on RR: from (0.85, 95% CI, 0.76–0.95, p = 0.003) to (0.85, 95% CI, 0.76–0.94, p = 0.003). Similarly, when three open design trials (Kayrak *et al.* [26], Modena *et al.* [27], Wu *et al.* [24]) were removed, only slight influences on the final effect were observed: RR changed from (0.85, 95% CI, 0.76–0.95, p = 0.003) to (0.83, 95% CI 0.77–0.88, p = 0.006). No trial without ITTA or with single-blind/open design involved MI patients was included for CV mortality analysis.

For SCD, all the included trials concerned HF patients with reduced LVEF, except TOPCAT trial [14] which recruited HF patients with preserved LVEF. Removing this trial resulted in slight change for treatment effect: RR from (0.81, 95% CI, 0.71–0.92, p = 0.002) to (0.78, 95% CI 0.67–0.90, p = 0.0006 and the heterogeneity remained likely absent (both I^2 = 0%).

Discussion

In our meta-analysis, we evaluated the efficacy of AAs in reducing mortality (SCD, overall/CV death) and hospitalization rate, as well as their toxicity via the common side effects in 19,333 patients with HF or post-MI from 25 trials. Our findings demonstrated the effectiveness of AAs in preventing SCD, all-cause mortality and CV mortality, yet a double rate of three studied adverse effects in these patients.

The cardio-protective effect of AAs is quite well proven in literature for CV protection [40]. Some of the proposed mechanisms of action in HF of AAs include (i) inhibition of myocardial and vascular remodeling, (ii) blood pressure reduction, (iii) decreased collagen deposition, (iv) decreased myocardial stiffness, (v) prevention of hypokalemia and arrhythmia, (vi) modulation of nitric oxide synthesis, and (vii) immunomodulation [41]. For instance, the meta-analysis of Li *et al.* [42] demonstrated beneficial effects of AAs on the reversal of cardiac remodeling and improvement of left ventricular function. Another quantified AAs' positive effect on ejection fraction (EF) and functional capacity improvement in different HF functional classes [43].

The RALES trial [11], published in 1999 was the first big study concerning AAs' effect that recommended this treatment which significantly decreased mortality rate (SCD, all cause and CV death) as well as CV hospitalization rate in patients with severe chronic HF (NYHA III to IV). Next, in 2003, the EPHESUS trial [13] re-confirmed the role of AAs for the same outcomes in patients with AMI complicated by left ventricular dysfunction. This therapy was thus limited to patients with severe HF or those with HF following MI until the publication of EMPHASIS-

HF trial [12] in 2011, which reported additional beneficial evidence for AAs use in mild-to-moderate HF (NYHA II), regarding the same clinical criteria. However, the current TOPCAT trial [14] finished in 2014 showed only a significant lower incidence of cardiac hospitalization in those treated by spironolactone vs. placebo, but not for total deaths and all-cause hospitalization, in patients with HF and preserved EF. Sensitivity analysis with this trial suggested that the treatment effect of AAs was likely similar in HF patients with reduced or preserved EF for SCD prevention.

The work of Ezekowitz *et al.* [44] evaluated the effect of aldosterone blockade on left ventricular dysfunction in HF and post-MI participants and reported a significant reduction in overall mortality of 20% (RR 0.80, 95% CI, 0.74–0.87, $p<0.00001$). That of Hu *et al.* [45], which showed a 21% (RR 0.79, 95% CI 0.66–0.95, $p = 0.65$) decrease for overall mortality and a 38% (RR 0.62, 95%, CI 0.52–0.74, $p = 0.54$) decrease for cardiac re-hospitalization by the use of AAs in patients with mild to moderate chronic HF (NYHA I to II). Another current meta-analysis of Bapoje *et al.* [46] that included 8 RCTs, concluded a 23% reduction (OR 0.77; 95% CI, 0.66–0.89; $p = 0.001$) of SCD in patients with a left ventricular systolic dysfunction of $\leq 45\%$, treated with AAs. On the contrary, the most recent meta-analysis of Chen *et al.* [47] in 2015 did not observe any all-cause mortality benefit, yet a reduced CV hospitalization rate (RR 0.83; 95% CI; 0.70 to 0.98), in patients with either HF or MI and preserved EF by AA treatment. Our meta-analysis, included MI/ HF patients with both preserved and primarily reduced EF, approved the positive effect of AAs in preventing all considered outcomes: SCD (RR 0.81; 95% CI, 0.71–0.92; $p = 0.002$), all-cause mortality (RR 0.82; 95% CI, 0.77–0.88, $p < 0.0001$), CV mortality (RR 0.80; 95% CI, 0.74–0.87, $p<0.0001$), all–cause hospitalization (RR 0.93; 95% CI, 0.88–0.98; $p = 0.008$) and CV hospitalization (RR 0.82, 95% CI, 0.72–0.92; $p = 0.001$) in patients with HF or post MI.

In terms of security, our work demonstrated a doubled rate of common adverse reactions (hyperkalemia, worsening renal function and gynecomastia) in those receiving AAs vs. control or placebo (RR 1.99, 95% CI, 1.64–2.41; $p<0.00001$). These findings agreed with the results of currently conducted analyses by Clark *et al.* [48] for renal function insufficiency, or by Rossignol *et al.* [49] for hyperkalemia and renal function degradation.

In 2013, a systematic study [50] of conventional HF therapies, including angiotensin-converting enzyme inhibitor (ACEI), angiotensin receptor blocker (ARB), direct renin inhibitor (DRI), and AA compared their effects (on prevention of total death, CV death, non-fatal MI, HF hospitalization and composite of CV death or HF hospitalization) and their safety (on hyperkalemia, hypotension, renal failure). By risk-benefit ratio comparison, this review favored the administration of AA over ARB or DRI, despite its 110% generated increase in hyperkalemia. Likewise, higher proportion of developed hyperkalemia and higher rate of hospitalization for hyperkalemia by AAs in HF patients were recorded in RALES trial, especially in combined use of AAs with either ACEIs or ARBs [51]. Moreover, the benefit of AAs on morbi-mortality prevention seems to overweigh its side-effects, i.e. the reduction in mortality associated with the use of AA was significantly greater than its use complications. Our work estimated numbers of 83, 27 and 18 HF patients need to be treated with AAs to prevent one SCD, one all-cause death and one CV death in one year, respectively. For patients with MI, the corresponding numbers needed to treat (NNT) were 84, 48 and 48, respectively. Considering both patient groups, the estimated NNTs were 83, 34 and 35, respectively. As well, the number needed to harm i.e the number of patients treated on average to have one who suffers at least one of the three common side effects studied, was 77.

Noticeably, focusing on SCD prevention, while AAs help to reduce CV risk factors thus prevent CV accidents including SCD, paradoxically, their side effects of hyperkalemia may induce this accident from cardiac arrhythmia [52]. By this point, a study [53] proved that AAs were

independently associated with increased rates of total mortality (hazard ratio HR 1.4; 95% CI 1.1–1.8; P = 0.005), of CV mortality (HR 1.4; 95% CI 1.1–1.9; P = 0.009) and a doubled incidence of SCD (HR 2.0; 95% CI 1.3, 3.0; P = 0.001) in patients with atrial fibrillation and HF. This implied a careful examination of risk/benefit ratio for each individual patient before the prescription of this treatment.

Based on our comprehensive and meticulous search strategy, we believe that we have identified all existing studies that met our inclusion criteria, hence yielding robust results. However, certain limitations should be considered when interpreting these outcomes. For instance, publication bias was not reliably assessed (though seemly negative) for the most important outcome (SCD) when less than 10 studies were included for pooled analyses by funnel plot (Fig 5A) or Egger test.

In summary, to gain the maximum benefit from AAs and reduce possible complications, it is legitimate to individualize and closely monitor their use. For examples, risk-benefit balance should be carefully considered before using AAs in patients with severe renal insufficiency. Also, other factors such as time of treatment initiation [54] and cost difference between AA agents [55] should be taken into account to optimize this therapy.

Conclusion

Our meta-analysis demonstrates that AA treatment may provide beneficial effects on the prevention of SCD, as well as all-cause and CV mortality, for selected patients with HF with altered left ventricular function or after a MI. Nevertheless, careful consideration before prescribing should be given simultaneously to the therapeutic benefit and the overall safety profile of this medication.

Supporting Information

S1 App. Search strategies in details for the meta-analysis.
(DOCX)

S2 App. PRISMA checklist for the meta-analysis.
(DOC)

S3 App. Kappa statistic for data extraction between two independent reviewers of the meta-analysis.
(DOCX)

S1 Fig. Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.
(EPS)

S1 Table. Quality assessment of eligible trials comparing aldosterone antagonists with placebo or control.
(DOCX)

Acknowledgments

We would like to thank Garry Taverny for his bibliographic assistance.

Author Contributions

Conceived and designed the experiments: HHL F. Guitarian TBA F. Gueyffier. Performed the experiments: HHL MM F. Guitarian CE MC TBA F. Gueyffier. Analyzed the data: HHL F.

Guitarian CE MM MC F. Gueyffier. Wrote the paper: HHL CE F. Guitarian MM MA MF MC TBA F. Gueyffier. Literature and data extraction: HHL MM F. Guitarian CE TBA F. Gueyffier. Proofreading: HHL MA MM CE MF F. Guitarian PJ IM MC TBA F. Gueyffier. Editing: HHL.

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APPENDIX VI “A sudden death risk score specifically for hypertension: based on 25 648 individual patient data from six randomized controlled trials”

CE: Swati; JH-D-17-00152; Total nos of Pages: 7;

JH-D-17-00152

Review

A sudden death risk score specifically for hypertension: based on 25 648 individual patient data from six randomized controlled trials

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Objective: To construct a sudden death risk score specifically for hypertension (HYSUD) patients with or without cardiovascular history.

Methods: Data were collected from six randomized controlled trials of antihypertensive treatments with 8044 women and 17 604 men differing in age ranges and blood pressure eligibility criteria. In total, 345 sudden deaths (1.35%) occurred during a mean follow-up of 5.16 years. Risk factors of sudden death were examined using a multivariable Cox proportional hazards model adjusted on trials. The model was transformed to an integer system, with points added for each factor according to its association with sudden death risk.

Results: Antihypertensive treatment was not associated with a reduction of the sudden death risk and had no interaction with other factors, allowing model development on both treatment and placebo groups. A risk score of sudden death in 5 years was built with seven significant risk factors: age, sex, SBP, serum total cholesterol, cigarette smoking, diabetes, and history of myocardial infarction. In terms of discrimination performance, HYSUD model was adequate with areas under the receiver operating characteristic curve of 77.74% (confidence interval 95%, 77.86–81.35) for the derivation set, of 77.46% (77.70–80.83) for the validation set, and of 79.17% (79.48–82.40) for the whole population.

Conclusion: Our work provides a simple risk-scoring system for sudden death prediction in hypertension, using individual data from six randomized controlled trials of antihypertensive treatments. HYSUD score could help assessing a hypertensive individual's risk of sudden death and optimizing preventive therapeutic strategies for these patients.

Keywords: cardiovascular diseases, cardiovascular risk factor, diabetes, hypertension, risk score, sudden death

Abbreviations: ARIC, Atherosclerosis Risk in Communities; AUROC, area under the receiver operating characteristic curve; CAST, Cardiac Arrhythmia Suppression Trial; CHADS2-VASC, updated score for atrial fibrillation stroke risk; CHS, Cardiovascular Health Study; CI, confidence interval; Duke SCD, Duke Sudden Cardiac Death Risk Score for Patients With Angiographic(>75% Narrowing) Coronary Artery Disease; EWPHE, European Working Party on Hypertension in the Elderly; MRFIT, Multiple Risk Factor Intervention Trial; RCT, randomized controlled trial; ROC, receiver operating characteristic; SCORE, Systemic Coronary Risk Estimation; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients; SYSTEUR, Systolic Hypertension in Europe

INTRODUCTION

Sudden death, a major cardiovascular event which occurs only within 1 h (or 24 h according to other definition) after the first onset of symptoms [1,2], is responsible for approximately 360 000 deaths (half of all cardiovascular deaths) annually in the United States [3]. In France, the annual incidence of sudden death was estimated as 50–70/100 000, thus about 40 000 deaths/year, occur mainly in men (69%), with a mean age of 65 years and at home (75%) [4]. Such event is important to be prevented but unfortunately remains underestimated in public health [5]. Hypertension is considered as a worldwide epidemiology, a well known risk factor for several diseases, and the leading cause for morbidity and mortality, including sudden

Journal of Hypertension 2017, 35:000–000

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Received 31 January 2017 **Revised** 17 May 2017 **Accepted** 30 May 2017

DOI:10.1097/HJH.0000000000001451

death, accounting for 7.0% (95% confidence interval (CI) 6.2–7.7) of global disability-adjusted life years and 9.4 (CI 8.6–10.1) million deaths in 2010 [6].

To better protect patients with hypertension regarding sudden death occurrence, a risk score is needed to stratify their risks and to adapt therapy. Up to now, two sudden death risk predictors were developed. One is Duke Sudden Cardiac Death Risk Score for Patients With Angiographic(>75% Narrowing) Coronary Artery Disease (Duke SCD) [7], designed specifically for patients with high coronary risk thus concerns secondary prevention patients. The second one was recently built from two prospective cohorts and for the general population in the United States [3].

We aimed to build here a quantitative and discriminative 5-year sudden death risk predictor from six randomized controlled trials (RCTs) of 25 648 patients with raised blood pressure (BP), treated or not by antihypertensive agents.

METHODS

Participants

The INdividual Data ANalysis of Antihypertensive intervention trials (INDANA) database includes most of major RCTs of antihypertensive drugs vs. placebo or control during the period of 1985–1995, which characteristics detailed elsewhere [8]. We assessed here data from six trials of this database having unbiased information regarding sudden death with 25 648 participants [9–14]. Causes of death were adjudicated in each trial by experts' committee.

Statistical analysis

We used the Cox proportional hazards regression (semiparametric time-to-event) model to establish our sudden death risk score for hypertension. The population was divided randomly into two subpopulations: derivation and validation sets (ratio 2 : 1) to ensure their similar baseline characteristics. Covariable selection was done in two steps. First, we conducted univariable analyses with 29 covariables to evaluate their associations with the sudden death outcome, adjusted on trials (by adding the covariable trial). Second, multivariable analyses were operated, where all covariables were offered simultaneously, but separately for SBP and DBP on one hand, mean BP and pulse BP on the other hand. Similarly, we did not assess serum creatinine in the multivariable testing, considering that glomerular filtration rate did reflect more accurately renal function. We used concurrently 'backward' and 'forward elimination' (stepwise screening) strategies, always adjusted on trials until obtaining the final model (where all the covariables were significant). All these uni and multivariable analyses were done using data of the derivation set.

Tests on time dependence or the linearity of the effect of continuous covariables on log hazard scale were performed using martingale residuals plots, and in comparing the model assuming a linear effect to a model assuming a quadratic effect. We also investigated possible biological interactions among them, particularly interactions with trial and antihypertensive treatment covariables. As well, we explored the impact of the trial covariable on sudden death risk, alone (univariable analysis) or adjusted on other risk factors (multivariable analysis).

The discrimination performance of the final predictive model was assessed by the areas under the receiver operating characteristic curve (AUROC) of the derivation set, the validation set, the whole population, and of each separated trial, with 95% CI [15]. For model calibration and external validation, we used the (k−1) approach: the final 7-risk factor model was rebuilt on five trials and tested on the remaining for six times.

We converted this final model predictor into an integer score using the method of Sullivan *et al.* [16]. Briefly, the score was directly related to an individual's probability of sudden death within 5 years. The zero score (risk of reference) was assigned for an adult at the lowest/most optimal risk represented in the application population. Having grouped each factor into convenient intervals, such as every 10 mmHg for SBP, an individual's score increases by an integer amount for each risk factor level above the reference risk category. Each integer amount is a rounding of the exact figure obtained from the proportional hazards model, thus the risk score is a simple addition of whole points.

All statistical tests were two-sided with a type I error of 0.05. All the analyses were performed with 'survival', 'riskset receiver operating characteristic (ROC)', and 'timeROC' packages on R software, version 3.2.5.

RESULTS

Among 25 648 participants from six RCTs, 345 sudden death occurred during a mean of 5.16 years of follow-up [9–14] (Appendix 1, http://links.lww.com/HJH/A803). ~~All the trials were double blind, except Coope *et al.* [9] which was an open-label trial. The biggest one is Multiple Risk Factor Intervention Trial (MRFIT) [10],~~ which recruited 12 866 patients and the smallest one was European Working Party on Hypertension in the Elderly (EWPHE) [11] with 840 participants. Characteristics of the derivation and validation sets are shown in the Table 1.

In univariable analyses, the following parameters were linked significantly with the incidence of sudden death: age, male sex, SBP and pulse BP, smoking status, serum creatinine, glomerular filtration rate, history of myocardial infarction (MI), history of angina pectoris, and baseline diabetes but not antihypertensive treatment (Table 2).

No significant interaction was detected between studied covariables, or between any covariable with antihypertensive treatment and trial ones. As antihypertensive treatment seemed to have no effect on reducing the risk of sudden death in univariable analysis (Table 2) and had no interaction with other covariables, we developed the final model on both treatment and placebo groups in the derivation set.

Using multivariable method, we identified seven significant risk factors of sudden death including age, sex (male), smoking status, serum cholesterol, SBP, baseline of type 2 diabetes, and history of MI, among which serum cholesterol was not statistically significant in univariable analyses (Table 2).

Impact of the trial covariable was tested, indicating a significantly lower sudden death risk (nearly one-third) in

TABLE 1. Baseline characteristics of derivation and validation sets

Covariables	Derivation set	Validation set
Number of patients	17 094	8554
Number of sudden death events (%)	329 (1.6)	170 (1.7)
Trials (*n*, weight % vs. the whole set)		
Coope	589 (3.4)	295 (3.4)
EWPHE	559 (3.3)	281 (3.3)
MRFIT	8577 (50.2)	4289 (50.1)
SHEP	3156 (18.5)	1580 (18.5)
STOP	1084 (6.3)	543 (6.3)
SYSTEUR	3129 (18.3)	1566 (18.3)
Sudden death incidence (*n*, %)		
Coope	14 (2.4)	4 (1.4)
EWPHE	9 (1.6)	4 (1.4)
MRFIT	98 (1.1)	55 (1.3)
SHEP	53 (1.7)	38 (2.4)
STOP	11 (1.0)	5 (0.9)
SYSTEUR	35 (1.1)	19 (1.2)
Treated (%)	50.0	50.0
Male (%)	68.3	69.3
Mean (SD) age (years)	58.9 (14.0)	58.9 (14.1)
Smoker (%)	35.0	35.2
Mean (SD) height (cm)	169.6 (10.3)	169.6 (10.3)
Mean (SD) weight (kg)	79.1 (14.8)	79.0 (14.5)
Mean (SD) BMI (kg/m^2)	27.4 (4.1)	27.4 (4.0)
Mean (SD) SBP (mmHg)	156.4 (25.9)	156.3 (26.0)
Mean (SD) DBP (mmHg)	88.4 (11.3)	88.5 (11.3)
Mean (SD) arterial/mean BP (mmHg)	111.1 (12.4)	111.1 (12.4)
Mean (SD) pulse BP (mmHg)	67.9 (26.4)	67.8 (26.4)
Mean (SD) serum creatinine (μmol/l)	95.1 (17.6)	95.0 (17.4)
Mean (SD) fasting blood glucose (mmol/l)	5.5 (1.2)	5.5 (1.2)
Mean (SD) serum total cholesterol (mmol/l)	6.4 (1.1)	6.4 (1.1)
Mean (SD) serum uric acid (μmol/l)	376.5 (88.7)	376.4 (88.5)
Mean glomerular filtration rate (ml/min)	84.9 (29.0)	84.8 (28.9)
Proteinuria (%)	4.4	4.5
Mean (SD) serum potassium (mmol/l)	4.4 (0.5)	4.4 (0.5)
Mean (SD) heart rate (beats/min)	76.0 (11.7)	76.0 (11.8)
History of angina pectoris (%)	1.6	1.4
History of atrial fibrillation (%)	0.15	0.09
History of leg intermittent claudication (%)	0.4	0.4
Positive dilated fundus examination (%)	27.6	27.3
Baseline of diabetes (%)	5.9	6.1
History of myocardial infarction (%)	4.6	5.0
History of stroke (%)	1.3	1.1
History of antihypertensive treatment (%)	23.5	23.5
History of high BP (%)	72.7	73.4

Baseline characteristics of the 25 648 randomized participants, according to the derivation/validation sets. Values are numbers (percentages) of patients unless stated otherwise.
BP, blood pressure; EWPHE, European Working Party on Hypertension in the Elderly; MRFIT, Multiple Risk Factor Intervention Trial; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients; SYSTEUR, Systolic Hypertension in Europe.

MRFIT trial [10], compared with that of Coope *et al*. [9] trial in univariable analysis. However, this significance disappeared in multivariable analysis (the final model), suggesting the difference of sudden death incidence was explained by the adjustment (Appendix 2, http://links.lww.com/HJH/A803).

The discrimination performance of the final model was quantified by AUROC for the derivation set, validation set, and for each individual trial (Table 3). Overall, our model's performance was good with AUROC at 78, 77, and 79% for the derivation set, validation set, and the whole population, respectively. However, separate assessment for each trial varied considerably from 60% for Systolic Hypertension in the Elderly Program (SHEP) trial [12] to 75% for EWPHE trial [11].

The final model is then converted to an integer score [16]. We took a woman, nonsmoker, aged 37, nondiabetic, total serum cholesterol at 3.5 mmol/l, SBP at 115 mmHg, and without history of MI as the reference profile. The scoring system is presented in the Appendix 3, http://links.lww.com/HJH/A803, allowing to assess the effect of each risk factor on the overall risk of sudden death (the total point). In our sudden death risk score specifically for hypertension (HYSUD) score, one increased year in age was corresponding with one point plus for sudden death risk. In terms of sudden-risk attribution, male sex and history of MI contributed in the same way by 10 points added, followed by smoking (nine points) and baseline diabetes (seven points). For any individual, points scored for each risk factor were cumulated together to estimate their total risk scores.

The model calibration was assessed in comparing the incidence of sudden death predicted vs. observed for each trial in each tertile of predicted risk. Model seemed to work best for EWPHE [11] and Systolic Hypertension in Europe (SYSTEUR) [13] trials for all categories, for Swedish Trial in Old Patients (STOP) [14] except an overestimate in high-risk category; noticeably underestimate for Coope *et al*. [9] and SHEP [12] trials; and largely overestimate for MRFIT [10] trial (Appendix 4, http://links.lww.com/HJH/A803).

Appendix 5, http://links.lww.com/HJH/A803 presents the similarity in predicted 5-year sudden death risks by the scoring system, compared with those obtained by the final Cox proportional hazards model equation. The former was converted from the latter.

Appendix 6, http://links.lww.com/HJH/A803 shows the exponential relation between the risk score and the probability of dying from sudden death in 5 years for men and women of the whole population. Figure 1 presents the distribution of 5-year sudden death risk according to scenarios of sex and age, illustrating higher risks for men comparing with women at the same age categories. Of note, in our database, women accounted for nearly one-third of the population and were older than men (range age 60–98, mean age 72 vs. 35–95, and 53 years old).

DISCUSSION

Our study brings a simple and user-friendly predictor for sudden death risk, specifically for patients of hypertension. HYSUD risk score included seven risk factors: age, male sex, history of MI, smoking status, high BP, high blood cholesterol, and baseline diabetes, ordered by their significant impacts. These factors were well known for cardiovascular events in general [17] and for sudden death in particular [18]. Similarly, according to a recent meta-analysis of 330 376 patients from 47 lipid-modifying trials [19], baseline diabetes is a significant predictor of cardiovascular outcomes including sudden death. The score was built on the point system for an easy assessment of a hypertensive individual's risk of sudden death in 5 years.

Up to now, two sudden death risk predictors were developed: one is Duke SCD [7], designed specifically for secondary coronary prevention and recently, another one

TABLE 2. Univariable analyses and multivariable analysis (final model) for sudden death prediction

	Univariable analyses		Multivariable analysis (final model)	
Covariables	**Hazard ratio (95% CI)**	***P* value**	**Hazard ratio (95% CI)**	***P* value**
Age (by 5-year increase)	1.33 (1.20–1.48)	<0.001	1.37 (1.23–1.53)	<0.001
Male sex	1.83 (1.47–2.19)	<0.001	2.06 (1.40–3.03)	<0.001
SBP (by 10-mmHg increase)	1.15 (1.05–1.26)	0.002	1.14 (1.04–1.25)	0.006
Pulse BP (by 10-mmHg increase)	1.17 (1.06–1.29)	0.002		
Smoking status	1.55 (1.24–1.87)	0.007	1.81 (1.31–2.51)	<0.001
Serum creatinine (by 10-μmol/l increase)	1.10 (1.02–1.19)	0.01		
Glomerular filtration rate (by 10-ml/min increase)	0.92 (0.85–0.99)	0.02		
History of myocardial infarction	1.74 (1.23–2.25)	0.03	1.71 (1.02–2.85)	0.041
History of angina pectoris	2.51 (1.07–5.90)	0.04		
Baseline diabetes	1.61 (1.13–2.09)	0.05	1.65 (1.02–2.67)	0.040
Mean BP (by 10-mmHg increase)	1.14 (0.99–1.32)	0.08		
Weight (10 kg)	0.93 (1.03–0.84)	0.16		
Heart rate (by 10-beats/min increase)	1.09 (0.96–1.24)	0.17		
BMI (by kg/m^2 increase)	0.98 (0.94–1.01)	0.18		
Serum total cholesterol (by 1-mmol/l increase)	1.08 (0.95–1.20)	0.24	1.17 (1.04–1.33)	0.011
Treatment	0.89 (0.62–1.15)	0.34		
Height (by 10-cm increase)	0.94 (0.80–1.11)	0.49		
Serum potassium (by 1-mmol/l increase)	1.13 (0.78–1.48)	0.49		
History of stroke	0.72 (−0.68–2.12)	0.65		
DBP (by 10-mmHg increase)	1.03 (0.89–1.19)	0.72		

All the univariable analyses were adjusted on trials. Univariable analyses of nine risk factors with frequently lacking data, including fasting blood glucose, serum uric acid, proteinuria, positive dilated fundus examination, history of high BP, history of antihypertensive treatment, history of atrial fibrillation, and history of leg intermittent claudication, gave nonsignificant associations and are not presented in this table. Multivariable analysis was adjusted on trials and treatments. All the analyses were performed on 17 094 individual patient data of the derivation set.
BP, blood pressure; CI, confidence interval.

for the general population [3]. The work of Deo *et al*. [3] was derived from 17 884 individual data free of baseline cardiovascular diseases (some patients had hypertension) from two cohorts in the United States (Atherosclerosis Risk in Communities and Cardiovascular Health Study). Our score included 25 648 patients with hypertension with or without other cardiovascular diseases or histories (diabetes, previous stroke/MI/angina, and so on) from six RCTs and of a wider geographic zone (Europe and the United States). The score of Deo *et al*. [3] contained more significant risk factors than ours (12 vs. 7). However, our HYSUD was transformed into an easy and friendly pointing system, as proposed by the work of Pocock *et al*. [20] for cardiovascular death prediction. A table comparing these two scores is displayed in Appendix 7, http://links.lww.com/HJH/A803.

TABLE 3. Performance and validation of a sudden death risk score specifically for hypertension risk score using areas under the receiver operating characteristic curve

Subset/trial	Number of patients	AUROC (95% CI)
Derivation set	17 094	77.74 (77.86–81.35)
Validation set	8554	77.46 (77.70–80.83)
Coope	884	60.99 (48.55–73.43)
EWPHE	840	75.40 (59.26–91.53)
MRFIT	12 866	65.91 (60.76–71.07)
SHEP	4736	60.12 (53.24–66.99)
STOP	1627	74.07 (60.70–87.45)
SYSTEUR	4695	61.68 (51.72–71.65)
Whole population	25 648	79.17 (79.48–82.40)

AUROC, area under the receiver operating characteristic curve; CI, confidence interval; EWPHE, European Working Party on Hypertension in the Elderly; MRFIT, Multiple Risk Factor Intervention Trial; SHEP, Systolic Hypertension in the Elderly Program; STOP, Swedish Trial in Old Patients; SYSTEUR, Systolic Hypertension in Europe.

The internal validation of HYSUD risk score indicated a good routine performance for this prognostic prediction type, with AUROC reaching almost 80%. However, model performances differed largely among trials, as was noted in a recent meta-analysis exploring the applicability of the updated score for atrial fibrillation stroke risk score predicting stroke risk in atrial fibrillation patients [21]. These differences could be partially explained by trial heterogeneity regarding: different sudden death definitions: an unexpected death occurring in a time interval of 1 h in SHEP [12] and STOP [14], prolonged to 24 h in MRFIT [10] and SYSTEUR [13], and not given in other trials (details in Appendix 1, http://links.lww.com/HJH/A803); different eligibility criteria for age, BP, etc.; different baseline cardiovascular disease severities that could result in various event rates of cardiovascular death including sudden death [22]; different antihypertensive treatments, geographic zones, periods, follow-up durations; and so on. Nonetheless, pooling data from several studies as we did increases the power of analyses, and allows exploring heterogeneity of information between trials. We also explored the heterogeneity of the links between individual characteristics and sudden death occurrence between trials, as well as its interactions with other covariables on sudden death risk: none was significant. In addition, apparent poor model calibration may come from low incidence of sudden death in our database (only 1.35% during trials' follow-up durations).

Our HYSUD score was built from a database collected in the period of 1970–1990, similarly to classical scores such as Framingham [17] or Systemic Coronary Risk Estimation [23] and hence, should be calibrated before application for nowadays patients, to limit possible bias coming from change in covariable hazards ratio over time or other

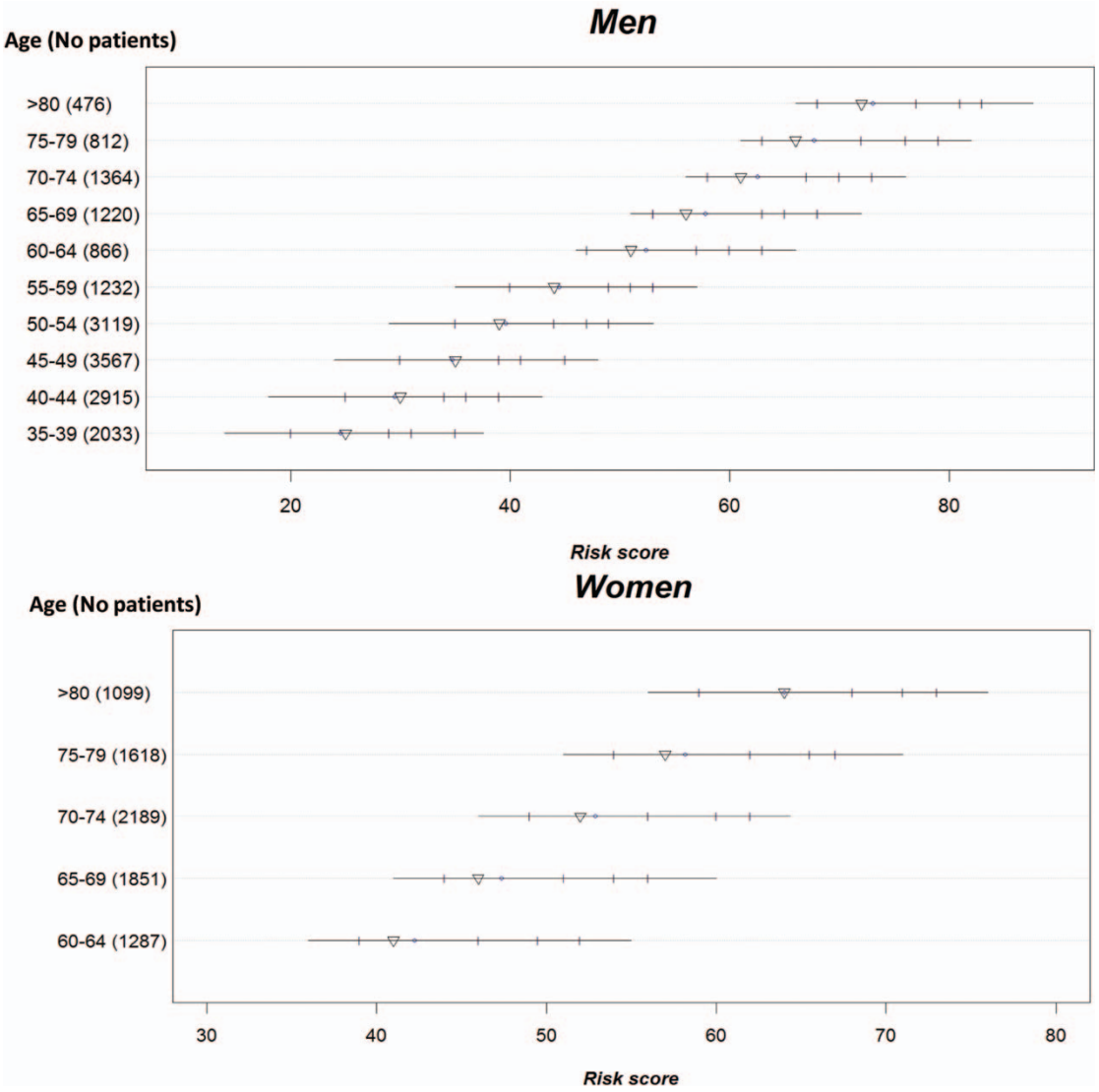

FIGURE 1 Distribution of risk scores by sex and age groups.

reasons. Concerning this point, the risk score of Deo *et al.* [3] which used more updated data (1985–2016, details in appendix 7, http://links.lww.com/HJH/A803) and Duke SCD score [7] which is built from 37 258 patients undergoing coronary angiography in the period of 1 January 1985 to 31 May 2005, could give more accurate estimates.

Another limitation is that our tool was developed in the RCT setting, where individuals have clinical characteristics that are usually different of observational populations and routine practice clinical settings. For example, individuals in the RCT used generally had SBP higher than 160 mmHg and with a lower proportion of men, except MRFIT trial [10]. This latter one [10] recruited only middle-aged men (35–58 years old) and provided approximately half of the studied population (12 866/total of 25 648), one additional reason for caution in potential extrapolation to other individuals. Last but not least, trial-based outcomes are more accurate but they are also limited by a shorter duration of follow-up.

All these elements call for external validations and calibrations of HYSUD score in nowadays hypertensive patients with various cardiovascular risk levels in different countries, before being locally applied. This type of work has been performed for other classical scores by several studies [24,25], strongly suggesting to adapt model predictors for each specific population. Anyway, our HYSUD score could help clinicians estimating individual risk and stratifying patients with regard to their sudden death risks.

As SBP, hypercholesterolemia, and baseline diabetes were significant risk factors, this suggests logically that the use of BP/lipid and glucose-lowering drugs may reduce sudden death risk in these study participants. Paradoxically,

our study, collecting data from six RCTs of antihypertensive drugs, observed no treatment effect on sudden death risk, in agreement with a meta-analysis of 39 908 patients with hypertension [26]. Furthermore, as history of MI was a significant indicator of sudden death risk, the use of antiarrhythmic drugs could appear logical to prevent this event. However, the Cardiac Arrhythmia Suppression Trial (CAST) [27] clearly demonstrated that these drugs significantly increased sudden death and total mortality incidence. These examples illustrate how such risk score must not be used to justify preventive drug prescription, which has to rely on clinical trials' results only. Of note, till now, the prevention of sudden death by pharmacological measures appears effective by β-blockers [28] and antialdosterones [29] for patients with heart failure but again, not by antihypertensive agents for hypertension [26]. Another meta-analysis only showed a modest sudden death risk reduction (one in 10) by statin in populations at risk [30].

Our HYSUD score was built on 17 094 individual data (derivation set) and validated on the remainder 8554 ones (validation set) as well as on each separated trial and on the whole population. This approach integrated the internal and external validations, and illustrated its transportability.

To summarize, sudden death is a major cardiovascular event but remains unfortunately underestimated in public health. This event is associated with considerable loss in terms of health and economy. Our work provides a good-performance, user-friendly predictor to assess 5-year individual sudden death risk in hypertension. This HYSUD risk score could help to stratify patients and thus optimize preventive therapeutic strategies in this population. Local validation process appears important to check that the score was appropriately calibrated.

ACKNOWLEDGEMENTS

François Pillon has done the first draft analyses. H.H.L. would like to thank Professor Hervé Maisonneuve for his advice and his training on scientific writing. We thank the investigators who provided the individual trial data used in our analyses: John Coope (Coope), Eleanor Schron (SHEP), L. L. (STOP), Robert Fagard (EWPHE), Jeffrey Cutler (MRFIT), and Jan Staessen (EWPHE and SYSTEUR).

The whole article was submitted at BMJ but not accepted (January 2017).

Part of the work has been presented as oral/poster communications in the following congresses:

H.H.L., F.S., M.C., M.A., M.F., E. Hénin, P. Janiaud, A. Berrima, M. Girard, S. Erpeldinger, B.K., P. Chevalier, F.G. The first risk score for sudden death prediction in primary prevention patients. Oral presentation at the 35th SFHTA Conference, Paris December 2015 (French Society of Hypertension). Ann Cardiol Angeiol (Paris). December 2015;64 Suppl 1:S5. doi: 10.1016/S0003−3928(16)30005−1.

H.H.L., F.S., M.C., M.A., M.F., I.M., B.K., P. Chevalier, F.G. The first risk scoring system for sudden death prediction in primary prevention patients. Poster presentation at the 26th European Meeting on Hypertension and Cardiovascular Prevention, Paris June 2016 (European Society of Hypertension).

H.H.L., M.F., and M.A. are currently receiving scholarships of the French Ministry of Higher Education and Research, The Academic Agency of La Francophonie (West Africa Regional Office), and The Federal Department of Economic Affairs, Education, and Research (EAER) Switzerland, respectively. The funders had no role in study design, data collection and analysis, decision to publish, or preparation of the manuscript.

F.G. proposed the idea of the study. F.S., L.T. made substantial contributions to study conception and design. H.H.L. and M.C. performed the analyses. H.H.L. wrote the article. F.S., M.C., M.A., I.M., L.L., L.T., and F.G. have been involved in revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

Conflicts of interest

There are no conflicts of interest.

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Reviewers' Summary Evaluations

Reviewer 1

Among strengths, good performance of the tool, and the potential educational use of this score (sudden death is quite an impressive outcome, even for older people). Among limitations are the dependence on age and use of data from the 1980s.

APPENDIX VII “β-Blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials”

BMC Cardiovascular Disorders

RESEARCH ARTICLE Open Access

Beta-blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials

Muaamar Al-Gobari[1*], Chadia El Khatib[1], François Pillon[2] and François Gueyffier[1,2]

Abstract

Background: In many studies, beta-blockers have been shown to decrease sudden cardiac death (SCD) in heart failure patients; other studies reported mixed results. Recently, several large randomized control trials of beta blockers have been carried out. It became necessary to conduct a systematic review to provide an up-to-date synthesis of available data.

Methods: We conducted a meta-analysis of all randomized controlled trials examining the use of beta-blockers vs. placebo/control for the prevention of SCD in heart failure patients. We identified 30 trials, which randomized 24,779 patients to beta-blocker or placebo/control. Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines were followed. Eligible studies had to be randomized controlled trials and provide information on the incidence of sudden cardiac death in heart failure patients. Additional inclusion criteria included: treatment for >30 days and follow-up ≥ 3 months. Studies of patients <18 years, randomization to beta-blocker vs. an angiotensin converting enzyme (without placebo) and/or beta-blocker in both arms were excluded from the analysis. Pre-specified outcomes of interest included SCD, cardiovascular death (CVD), and all-cause mortality and were analyzed according to intention-to-treat.

Results: We found that beta-blockers are effective in the prevention of SCD [OR 0.69; 95% CI, 0.62–0.77, P < 0.00001], cardiovascular death (CVD) [OR 0.71; 95% CI, 0.64–0.79, P < 0.00001], and all-cause mortality [OR 0.67; 95% CI, 0.59–0.76, P < 0.00001]. Based on the study analysis, 43 patients must be treated with a beta-blocker to prevent one SCD, 26 patients to prevent one CVD and 21 patients to prevent all-cause mortality in one year.

Conclusion: Beta-blockers reduce the risk of sudden cardiac death (SCD) by 31%, cardiovascular death (CVD) by 29% and all-cause mortality by 33%. These results confirm the mortality benefits of these drugs and they should be recommended to all patients similar to those included in the trials.

Keywords: Beta, Blocker, Sudden cardiac death, Heart failure, Meta, Analysis

Background

Sudden cardiac death is defined as a non-violent death that cannot be explained, occurring less than 24 hours from the onset of symptoms [1]. Sudden cardiac death accounts for 300 000 to 400 000 deaths annually in the United States, depending on the definition used [2,3]. When restricted to death <2 hours from the onset of symptoms, 12% of all natural deaths were classified as sudden in one study, and 88% of those were due to cardiac disease [2,3]. Sudden cardiac death is the most common and often the first manifestation of coronary heart disease and is responsible for ≈50% of the mortality from cardiovascular disease in the United States and other developed countries [4]. The risk of sudden cardiac death (SCD) is most pronounced among patients with heart failure, in whom the 1 year absolute risk of SCD is between 4 and 13% [5]. It is worth mentioning that BEST [6], a randomized trial of the beta-blocker bucindolol in patients with advanced chronic heart failure, reported that it did not reduce sudden cardiac death and/or all-cause

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mortality. However, BEST included demographically diverse groups and severe heart failure patients [7]. In this study, we intended to quantify the effect of beta-blockers in the risk reduction of sudden cardiac death in patients with heart failure by using pooled analysis techniques. Recently, several large randomized control trials of beta-blockers have been carried out. Therefore, a systematic review is required to provide an up-to-date synthesis of available data.

Methods

Study search

We searched the Cochrane Central Register of Controlled Trials (Central) in the Cochrane Library (Version 2012) and MEDLINE (1966 to March 2012). The bibliographies of identified studies were checked. The Medline query was limited to studies involving human subjects, randomized controlled trials and/or meta-analyses. No language restrictions were applied.

Selection criteria and data abstraction

A systematic review of the literature with meta-analysis was needed to identify all clinical trials evaluating beta-blockers for heart failure and reporting all-cause mortality. Eligible studies had to be placebo-controlled trials and provide information on the incidence of sudden cardiac death. Additional inclusion criteria included: treatment for >30 days and follow-up ≥3 months. Studies of patients <18 years, randomization to beta-blocker vs. an angiotensin converting enzyme (without placebo), and/or beta-blockers in both arms were excluded from the analysis.

Abstracted data included eligibility criteria, baseline characteristics, study design (including treatment and control arms), follow-up, and outcomes. Pre-specified outcomes of interest included SCD, cardiovascular death (CVD), and all-cause mortality. Outcomes were analyzed according to intention-to-treat. Study quality was formally evaluated using the Jadad score [8] for the quality assessment of randomized controlled trials. For the purpose of this analysis, studies which had a score of 3/5 or more were considered high quality. The study selection process (according to the PRISMA guidelines) is shown in Figure 1.

Statistical analysis

The patient was chosen as the individual unit of analysis (as opposed to person years). The effects of beta-blockers on SCD, CVD, and all-cause mortality were determined using fixed-effect and random-effect modeling.

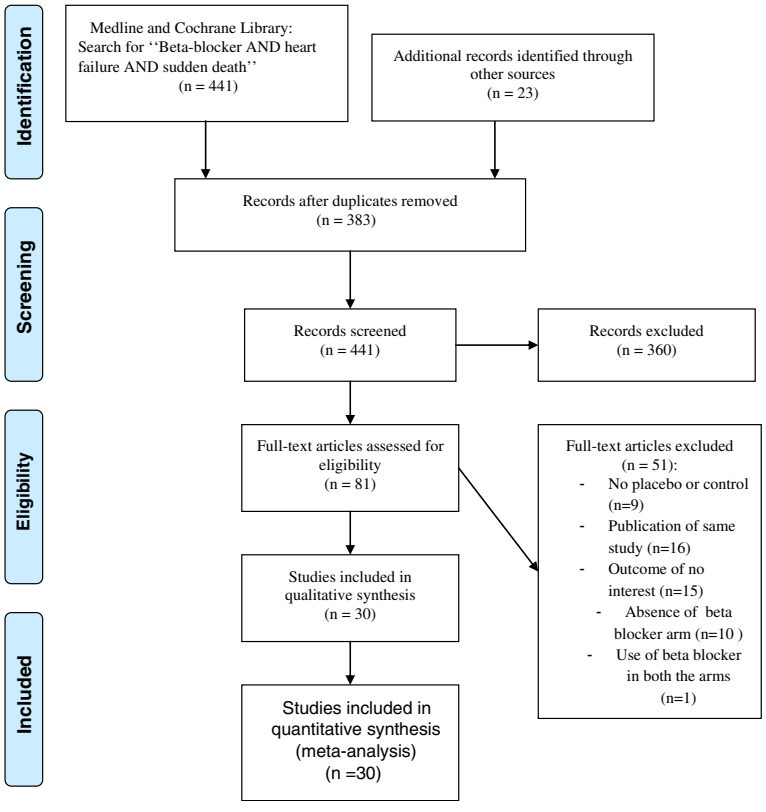

Figure 1 PRISMA flow diagram for the meta-analysis. Study selection process according to Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.

Fixed-effect modeling was performed using the Mantel and Haenszel method. Random-effect modeling was conducted using the DerSimonian and Laird method [9]. The results were similar with both methods, so we only reported the random-effect results. Treatment effect was measured using odds ratios (ORs) with 95% confidence intervals (CIs).

Heterogeneity across the studies was estimated using I-square test [9]. I-square values of 25%, 50%, and 75% correspond to low, moderate, and high levels of heterogeneity [10]. Meta-analysis results were reported only if the I-square value was under 75%. Sensitivity analyses were performed for each outcome measure to assess the contribution of each study to the pooled estimate by excluding individual trials one at a time and recalculating the combined OR for the remaining studies. Statistical testing was two-tailed, and statistical significance was declared with $\alpha = 0.05$. All analyses were conducted using RevMan software (Version 5.1).

Results

Search results

After searching Medline and the Cochrane Library, we identified 441 abstracts which were reviewed for inclusion and exclusion criteria (Figure 1). Out of these, 361 were excluded for the following reasons: non-randomized study (including observational studies, pharmacokinetic and pharmacodynamic studies, substudies, editorials, etc.;

Table 1 Randomized trials of beta blockers for the prevention of sudden cardiac death

Trial (Reference)	Year	Number of patients	Name of drug	Comparator	Daily maintenance dose (mg)	Follow-up (months)	Jadad scoring
Anderson et al.[12]	1985	50	Metoprolol	Control	61	19	3
ANZ[16]	1997	415	Carvedilol	Placebo	12.5	19	4
BEST[6]	2001	2708	Bucindolol	Placebo	152	24	5
BHAT[39]	1986	3837	Propranolol	Placebo	180/240	25	5
Bristow et al.[17]	1994	139	Bucindolol	Placebo	12.5/50/200	3	5
Bristow et al.[18]	1996	345	Carvedilol	Placebo	12.5/25/50	6	5
Capricorn[19]	2001	1959	Carvedilol	Placebo	50	15.6	5
CIBIS II[21]	1999	2647	Bisoprolol	Placebo	10	15	5
CIBIS[20]	1994	641	Bisoprolol	Placebo	5	23	5
CILICARD[33]	2000	124	Celiprolol	Placebo	100	12	5
Colucci et al.[22]	1996	366	Carvedilol	Placebo	100	15	5
COPERNICUS[8]	2002	2289	Carvedilol	Placebo	50	10.4	5
De Milliano et al.[34]	2002	59	Metoprolol	Placebo	150	6	5
ELANDD[35]	2011	116	Nebivelol	Placebo	5/10	6	5
Engleimeir et al.[23]	1985	25	Metoprolol	Placebo	92	12	4
Fisher et al.[24]	1994	50	Metoprolol	Placebo	87	6	5
Hansteen V. et al.[25]	1982	560	Propranolol	Placebo	160	12	5
Krum et al.[26]	1995	49	Carvedilol	Placebo	50	4	5
MDC[27]	1993	383	Metoprolol	Placebo	108/115	18	3
MERIT-HF[28]	1999	3991	Metoprolol	Placebo	159/170	12	5
Metra et al.[29]	1994	40	Carvedilol	Placebo	50	4	4
Olsen et al.[30]	1995	60	Carvedilol	Placebo	81	4	5
Packer et al.[31]	1996	1094	Carvedilol	Placebo	60	6	5
Pollock et al.[32]	1990	19	Bucindolol	Placebo	200	3	4
RESOLVD[36]	2000	426	Metoprolol	Placebo	156	6	5
SENIORS[14]	2005	2128	Nebivelol	Placebo	7.7	21	5
Sturm[37]	2000	100	Atenolol	Placebo	89	24	5
UHLIR et al.[38a]	1997	91	Nebivelol	Placebo	2.5/5	3.5	5
Wisenbaugh et al.[15]	1993	24	Nebivelol	placebo	5	3	5
Woodley et al.[13]	1991	50	Bucindolol	Placebo	175	3	5

ANZ: Australian/New Zealand Heart Failure Research Collaborative Group; BEST: *Beta-blocker Bucindolol* in *patients* with *advanced chronic heart failure*; CAPRICORN: Effect of carvedilol on outcome after myocardial infarction inpatients; COPRINCUS: Effect of Carvedilol on the Morbidity of Patients with Severe chronic Heart Failure; MDC: Metoprolol in Dilated Cardiomyopathy Trial study; Merit-HF: Metoprolol CR/XL Randomized Intervention Trial in Congestive Heart Failure; SENIORS: Randomized trial to determine the effect of nebivolol on mortality and cardiovascular hospital admission in elderly patients with heart failure.

n=349), absence of placebo or inactive control arm (n=11), and inclusion of subjects < 18 years (n=1).

The full manuscripts of the remaining 81 studies were retrieved for detailed review. Following full manuscript review, an additional 51 studies were excluded: no placebo or control (n= 9), duplicate report or substudy (n= 16), absence of a beta-blocker arm (n=10), outcome of no interest (n=15) and use of beta-blockers in both arms (n= 1).

Trial characteristics and study quality

As shown in Table 1, we identified 30 randomized controlled trials of beta-blocker for inclusion in this meta-analysis, which enrolled a total of 24,779 patients [6,11-39]. The mean follow-up duration was 11.51 months (0.96 year) and all trials are placebo controlled except the trial of Anderson et al. [11] which used standard therapy. Using the Jadad score [8], all studies were estimated with score of 3–5 and qualified as high quality. All trials were analyzed according to the intention-to treat paradigm.

Baseline patient characteristics

Baseline patient characteristics (Table 2) were remarkably similar in age and gender in all trials except for Woodley et al. [12] which included younger patients and the SENIORS [13] which included elderly patients. Therefore, the mean age ranged from 28–76 and all trials enrolled mostly men except for Wisenbaugh et al. [14] and ELANDD [35] which enrolled 50% and 65% women respectively. Copernicus [22] and RESOLVD [36] were not evaluated for cardiovascular death

Table 2 Patient characteristics in randomized trials of beta blockers for the prevention of sudden cardiac death

Trial (Reference)	Mean age (Years)	Male (%)	Inclusion criteria	Population (Ischaemic or non-ischaemic)	Mean EF (%)	NYHA
Anderson et al.	50	66	IDC	Non-ischaemic	29	II-IV
ANZ[13]	67	80	chronic heart failure	Ischaemic	29	II-III
BEST[6]	60	78	NYHA III-IV, EF ≤ 35%	Both	23	III-IV
BHAT[39]	55	NR	MI, HF	NR	NR	NR
Bristow et al.[14]	55	61	IDC and ISCD	Both	24	I-IV
Bristow et al.[15]	60	76	Mild, moderate, chronic heart failure	Both	23	II-IV
CAPRICORN[16]	63	74	Acute MI, EF ≤ 40%	Ischaemic	32	NR
CELICARD[33]	57	89.5	NYHA II- IV, LVEF<40%	Both	26	II-III
CIBIS II[18]	61	80	NYHA III or IV, EF ≤ 35%	Both	28	III-IV
CIBIS[17]	60	83	IDC, NYHA III-IV, ≤ 40%	Both	25	III-IV
Colucci et al.[19]	54	85	Mildly symptomatic heart failure	Both	23	II-III
COPERNICUS[20]	63.3	79.5	HF and EF ≤ 25%	67% ischaemic	20	NR
De Milliano et al.[34]	65	60	HF,, LVEF<35%,	Both	25	II-III
ELANDD[35]	66	35	HF, age>40 years, LVEF>45%	Non-ischaemic	62	II-III
Engleimeir et al.[21]	50	64	IDC	Both	17	II-III
Fisher et al[22]	63	96	HF and CAD	NR	23	II-IV
Hansteen V. et al.[23]	58	84.5	Acute MI	NR	NR	NR
Krum et al.[24]	55	78	Advanced heart failure	Both	16	II-IV
MDC[25]	49	73	DCM and EF<40%	Non-ischaemic	22	I-III
MERIT-HF[26]	64	77	NYHA II-IV,EF ≤ 40%	Both	28	II-IV
Metra et al.[27]	51	90	NYHA II-III, IDC	Non-ischaemic	20	II-III
Olsen et al.[28]	52	94	NYHA II-III, IDC/CAD	Both	20	II-IV
Packer et al.[29]	58	77	Chronic heart failure	Both	23	II-IV
Pollock et al.[30]	54	79	CHF	Both	21	II-IV
RESOLVD[36]	62	82	CHF(NYHA II- IV), LVEF<35%	Both	28.5	I-IV
SENIORS[11]	76	63	HF,EF ≤ 35%	NR	35	I-IV
Sturm et al.[37]	62	88	Age(18-75), LVEF≤25%	Both	17	II-IV
UHLIR et al.[38]	56	89	Age(18-75), NYHA II- III, LVEF<40%	Ischaemic	NR	II-III
Wisenbaugh et al.[12]	50	50	NYHA II-III, IDC/ISCD	Both	24	II-III
Woodley et al.[10]	52	72	NYHA II- III, IDC/CAD	Both	22	II-III

CAD Coronary artery disease, *CHF* congestive heart failure, *DCM* dilated cardiomyopathy, *ISCD* ischemic dilated cardiomyopathy, *EF* ejection fraction, *HF* Heart failure, *IDC* ischemic dilated cardiomyopathy, *MDC* Metoprolol in Dilated Cardiomyopathy, *MI* myocardial infarction, *NR* not reported, *NYHA* 'Classification of' New York Heart Association.

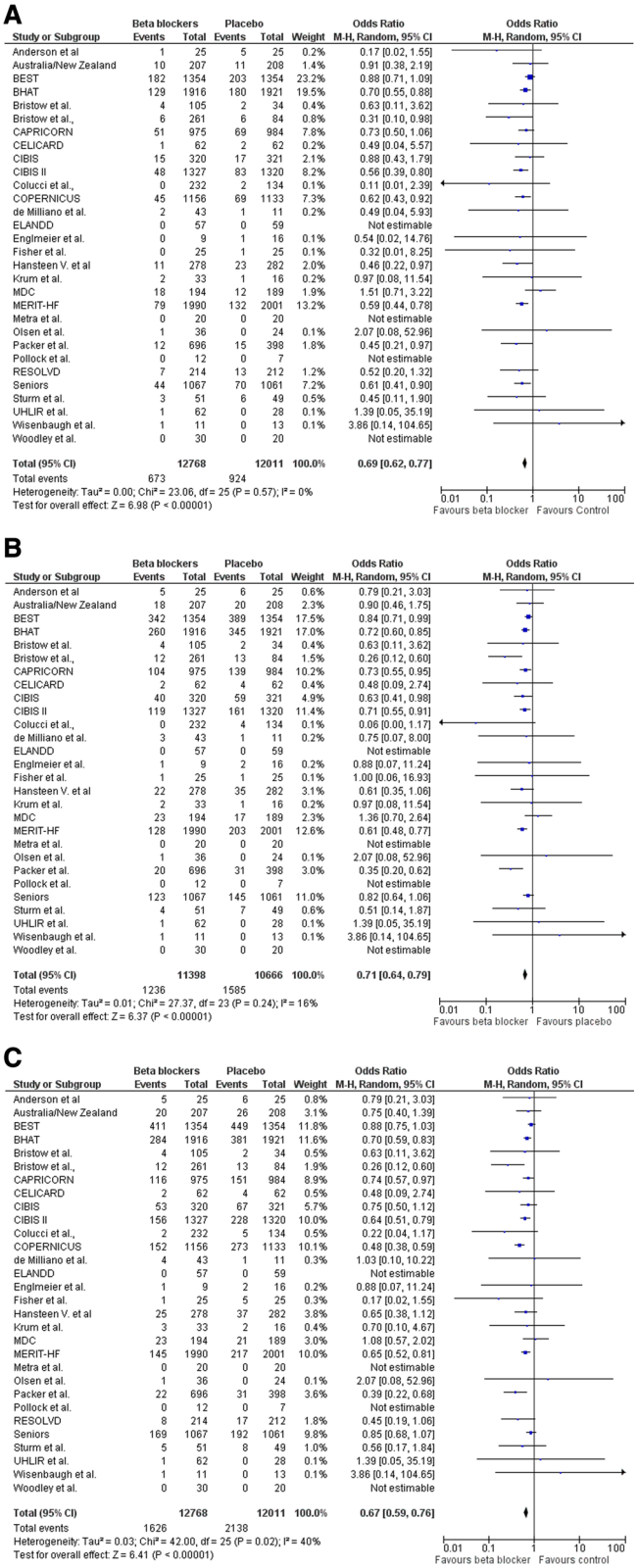

Figure 2 Efficacy of beta blockers compared with control for the (A) Prevention of sudden death. (B) Cardiovascular death, and **(C)** all-cause mortality in patients with heart failure.

outcome due to missing data. Four trials were restricted to patients with non-ischaemic cardiomyopathy, three to ischaemic patients, three not reported, and the remainder enrolled patients with ischaemic and non-ischaemic cardiomyopathy. Mean left ventricular ejection fraction ranged from 16-62%.

Efficacy of beta-blockers

A total of 3,764 deaths occurred in the 24,779 patients included in this analysis, including 1,597 SCDs. The SCD rate was 5.27% (n= 673/12768) in those treated with beta-blockers compared with 7.69% (n = 924/12011) in those treated with placebo/control [OR 0.69; 95% CI, 0.62–0.77, P < 0.00001] as shown in Figure 2(A). Cardiovascular mortality rate was 10.84% (n = 1236 /11398) in those treated with beta-blockers and 14.86% (n =1585/10666) in those assigned to placebo/control [OR 0.71; 95% CI, 0.64–0.79, P < 0.00001] see Figure 2(B). All-cause mortality rate was 12.82% (n = 1626 /12678) in those treated with beta-blockers and 17.80% (n =2138/12011) in those assigned to placebo/control [OR 0.67; 95% CI, 0.59–0.76, P < 0.00001] as shown in Figure 2(C).

Based on these data, 43 patients need to be treated (NNT) with beta-blockers to prevent one SCD, 26 patients to prevent one CVD, and 21 patients to prevent all-cause mortality in one year. The forest plot comparison of beta-blockers vs. placebo for SCD and all-cause mortality is shown in Figure 3 and Figure 4 respectively. The I-square test of heterogeneity was relatively low in SCD, CVD, and all-cause mortality with I^2 =0%, 20%, and 43% respectively.

Sensitivity analysis

The BEST trial had the largest relative overall weight of 23.2%, 17.5%, and 11.8% in SCD, CVD and all-cause mortality respectively. Therefore, we conducted a sensitivity analysis to assess the impact of this trial on the results. When excluding the BEST trial from the random-effect estimates, there was no significant difference: OR for SCD [0.64 (95% CI 0.57 -0 .72), p = 0.00001], OR for CVD [0.69 (95% CI 0.62 -0 .77), p = 0.00001] and OR for all-cause mortality [0.65 (95% CI 0.58 -0 .73), p = 0.00001]. I^2 = 0%, 7%, and 25% respectively. The Capricorn [18] and Hansteen et al. [25] and BHAT [39] studies included patients with acute myocardial infarction. But when they were excluded from the analysis, no significant difference was found: OR for SCD [0.69 (95% CI 0.61 -0 .78), p = 0.00001], OR for CVD [0.70 (95% CI 0.60 -0 .82), p = 0.00001] and OR for all-cause mortality [0.65 (95% CI 0.55 -0 .77), p = 0.00001]. I^2 = 0%, 26%, and 47% respectively. Also, the trial of ELANDD [35] had included patients with LVEF>45%. The sensitivity analysis showed no significant difference: OR for SCD [0.69 (95% CI 0.62 - 0 .77), p = 0.00001], OR for CVD [0.71 (95% CI 0.67–0.79), p = 0.00001] and OR for all-cause mortality [0.67 (95% CI 0.59 - 0 .76), p = 0.00001]. I^2 = 0%, 20%, and 43% respectively.

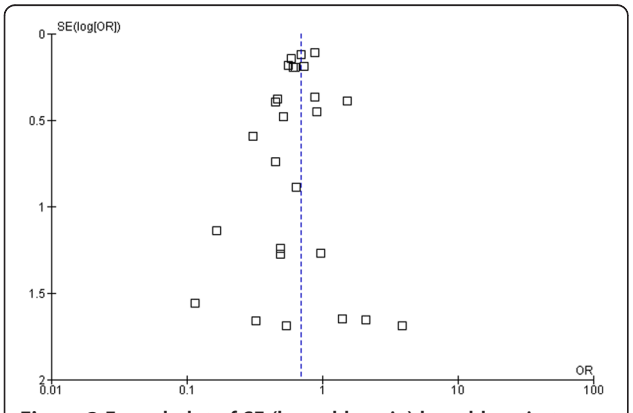

Figure 3 Funnel plot of SE (log odds ratio) by odds ratio to evaluate publication bias for effect of treatment in sudden cardiac death (SCD).

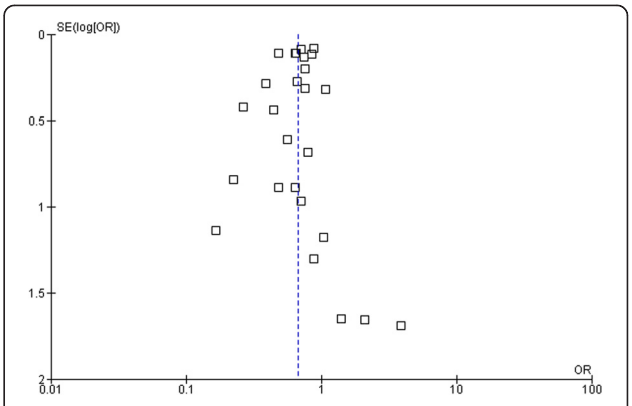

Figure 4 Funnel plot of SE (log odds ratio) by odds ratio to evaluate publication bias for effect of treatment for all-cause mortality.

Publication bias

To assess a potential existence of publication bias in the effect of beta-blockers in sudden cardiac death and all-cause mortality, a funnel plot as shown in Figure 3 and Figure 4 indicates large symmetry and therefore a publication bias is likely excluded.

Discussion

There exist several meta-analyses which evaluated the mortality benefits of beta-blockers among chronic heart failure patients [40-44]. One of the eldest is the study of Heidenreich et al. [40] that reported significant reduction in all-cause mortality but had not concluded for sudden cardiac death. This is apparently due to lack of power and sudden death missing data in the studied clinical trials. Also, the meta-analysis of McAllister et al.

[41] showed 24% risk reduction of mortality related to the magnitude of heart rate reduction but not to dosing of beta-blockers. A recent meta-analysis by Chatterjee et al. [42] included 21 trials using beta-blockers in patients with heart failure and reduced ejection fraction showing a 31% reduction in overall mortality with no difference among the different agents used. However, this study, like many others, had not evaluated the overall reduction of beta-blockers in the prevention of sudden cardiac death. Another study, Fauchier et al. [44], found similar beneficial effects of beta-blockers in ischemic and non-ischemic cardiomyopathy. Though, the number of clinical trials that classified such patients accounts for <22% in our meta-analysis. Similarly, study of Bonet et al. [43] reported no difference in mortality benefits among ischemic and non-ischemic heart disease and proposed greater benefit of vasodilating beta-blockers compared with the non-vasodilating agents particularly in patients with non-ischemic cardiomyopathy and attributed mortality benefits to significant reduction of pump failure and sudden death. Briefly, previous studies whether had not evaluated overall reduction of beta-blockers in the prevention of sudden cardiac death or need to be updated such as the studies of Bonet et al. [43] and Heidenreich et al. [40] as several recent and large randomized clinical trials have been carried out.

In this meta-analysis of 24,779 randomized patients, we found that beta-blockers are effective in the prevention of SCD with [OR 0.69; 95% CI, 0.62–0.77, P < 0.00001], CVD [OR 0.71; 95% CI, 0.64–0.79, P < 0.00001], and all-cause mortality [OR 0.67; 95% CI, 0.59–0.76, P < 0.00001]. Ventricular arrhythmias (including non-sustained ventricular tachycardia) have been documented in up to 85% of patients with severe congestive heart failure [45]. As anti-arrhythmic agents, beta-blockers have been shown to reduce morbidity and mortality in patients with chronic heart failure in randomized controlled trials, and consistently reduce the risk of SCD by 40–55% [20,28]. However, our meta-analysis showed a 32% reduction of SCD risk. As indicated earlier, the 1-year absolute risk of SCD in heart failure patients is 4-13% [5]. In our study, the 1-year absolute risk of SCD in the beta-blocker group and placebo/control group is 5.5% and 8.10% respectively. Mortality rates increase the higher the New York Heart Association (NYHA) class, but the proportion of patients dying suddenly (rather than from progressive pump failure) is highest among those with less severe heart failure (NYHA class II or III) [28]. The evaluation of clinical benefits for patients at different stages of heart failure by subgroup analysis merits further investigation. Our study included two clinical trials with acute myocardial infarction patients. When they were excluded from the meta-analysis, no significant differences were found in a sensitivity analysis of the remaining trials. Our study provides a high level of evidence given the large number of randomized patients included.

Clinical implications

American College of Cardiology (ACC), American Heart Association (AHA), and European Society of Cardiology (ESC) guidelines recommend the use of beta-blockers to reduce sudden death and especially in patients with heart failure [46,47]. Our results support such recommendations with a high level of argument.

Conclusion

Out of all antiarrhythmic agents, only beta-blockers have been shown to be effective at reducing the risk of SCD. Beta-blockers reduce the risk of SCD by 31%, CVD by 29%, and all-cause mortality by 33% and therefore, this meta-analysis study confirms beta-blockers' clinical benefits and should be recommended to all patients similar to those included in the trials.

Abbreviations

ANZ: Australia/New Zealand Heart Failure Study; BEST: Beta-blocker evaluation survival trial; CAPRICORN: Carvedilol post-infarct survival control in LV dysfunction study; CIBIS I: Cardiac insufficiency bisoprolol study; CIBIS-II: Cardiac insufficiency bisoprolol study II; COPERNICUS: Carvedilol prospective randomized cumulative survival study; HF: Heart failure; LV: Left ventricular; MDC: Metoprolol in idiopathic dilated cardiomyopathy study; MDC: Metoprolol in dilated cardiomyopathy trial study; MERIT-HF: Metoprolol CR/XL randomized intervention trial in congestive heart failure; MI: Myocardial infarction; NYHA: New York Heart Association; RCTs: Randomized controlled trials; SENIORS: Study of the effects of nebivolol intervention on outcomes and rehospitalisation in seniors with heart failure study.

Competing interests

No conflict of interest is declared.

Authors' contributions

MA and FG participated in the conception and design of the study. MA, FP and CK extracted the data. MA drafted the study. MA, FP and FG had critically analyzed and interpreted the data. All authors read and approved the final manuscript.

Acknowledgement

We would like to thank Mr. Kent Neal for technical assistance and proofreading the manuscript.

Funding

MA received a research grant from the scholarship program of YEMEN LNG COMPANY LTD, Sana'a; Yemen. This study was supported by a student grant from UMR 5558, Biometry and Evolutionary Biology Laboratory, Lyon, France.

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Received: 18 February 2013 Accepted: 10 July 2013
Published: 13 July 2013

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doi:10.1186/1471-2261-13-52
Cite this article as: Al-Gobari *et al.*: Beta-blockers for the prevention of sudden cardiac death in heart failure patients: a meta-analysis of randomized controlled trials. *BMC Cardiovascular Disorders* 2013 **13**:52.