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Optimization of sudden cardiac death prevention in type 2 diabetes in France: a public health simulation study on a realistic virtual population

Hai-Ha Le

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Optimisation de la prévention de la mort subite chez les diabétiques de type 2 en France par simulation des scénarios médicamenteux sur une population virtuelle réaliste

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À toi, pour ton amour, ta grande amitié et ton accompagnement...

À mon pays natal...

À mon pays d'accueil...

Je ne pourrai jamais assez citer tout ce que vous avez fait pour moi !

Sans vous, ni moi, ni cette thèse ne pourraient exister !

UN GRAND MERCI À VOUS TOUS!

Ma thèse en 180s (sujet vulgarisé)

Pour une meilleure prévention de la mort subite dans le diabète de type 2

Pour le concours « Ma thèse en 180s », organisé par l'Université Lyon-St Etienne, le 28/04/2016

Cette prestation a gagné le 2ème prix du Jury.

Molière est sur scène, il joue « Le malade imaginaire ».

Il tousse, tousse encore et grimace. Quelle virtuosité ! La pièce est un grand succès. On l'emmène, et il décède trois quarts d'heure après. Quelle qu'en soit la cause, c'était par définition, une mort subite. C'est à dire, une mort survenant dans l'heure suivant les premiers symptômes. (Mais en fait, Molière n'est jamais mort : parce qu'aujourd'hui, je continue d'apprendre la langue de Molière.)

Et je vais vous parler d'une maladie, qui n'est pas du tout imaginaire, qui touche une personne sur 10, et qui entraîne de graves complications : le diabète de type 2. Quatre diabétiques sur cinq meurent de causes cardiovasculaires et au premier rang, on retrouve la mort subite.

C'est là que ma thèse intervient : il s'agit d'optimiser les traitements actuels afin de mieux prévenir la mort subite, en trois étapes : identifier les patients, trouver les bons médicaments, et évaluer leurs effets sur cette population diabétique.

D'abord, qui est diabétique ici?

Ah, voici un gentilhomme, de 50 ans, d'un 1 mètre 80 pour 100 kilos. Vous me dites que vous fumez chaque jour un seul paquet, buvez encore une seule bouteille par jour, et que vous avez eu un AVC ! Selon notre modèle, statistiquement, vous avez 50% de chance d'avoir une mort subite dans les 5 ans !

Vous avez tous compris : la première étape s'agit de construire un score prédictif de mort subite qui permettra, non pas de vous faire peur, mais de bien adapter les traitements à chaque profil déterminé.

Mais alors, quel médicament va-t-on utiliser ?

Deuxième étape, nous allons examiner tous les médicaments prescrits dans le diabète de type 2, et réaliser une synthèse de leurs résultats. Le but est de voir, si ces médicaments sont plus efficaces que délétères, pas trop chers, et si l'on peut les combiner, afin de proposer les meilleures stratégies.

Troisième étape, **comment peut-on évaluer l'impact de ces stratégies sur la santé publique ?**

Pour cela, il faudrait mener des essais cliniques sur un panel de patients. C'est long, coûteux, et ça génère même des questions de bioéthique.

Alors, notre équipe a innové: nous avons généré une population virtuelle réaliste de patients. Sur cette population, nous allons estimer les risques, tester différents traitements et observer leurs efficacités respectives. Nous pourrions ensuite envisager d'appliquer aux patients réels les meilleurs traitements possibles.

En fin, comme disait Molière : « La mort est un remède à trouver quand on veut ; et l'on doit s'en servir le plus tard que l'on peut. »

N'oubliez pas les meilleurs remèdes naturels restent: vos sourires et votre joie de vivre. MERCI !

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ABBREVIATIONS

ACEI: Angiotensin Converting Enzyme Inhibitor

ADA: Anti-Diabetic Agent

AHA: Anti-Hypertensive Agent

(A)MI: (Acute) Myocardial Infarction

APA: Anti-Platelet Agent

ARA/B: Angiotensin Receptor Antagonist/Blocker

AUROC: Area Under the Receiver Operating Characteristic Curve

BMI: Body Mass Index

BP: Blood Pressure, SBP: Systolic BP, DBP: Diastolic BP

CAD: Coronary Artery Disease

CCB: Calcium Channel Blocker

CI: Confidence Interval

CKD: Chronic Kidney Disease

CHD: Coronary Heart Disease

(C)HF: (Congestive) Heart Failure

CV: Cardiovascular

CV(D): Cardiovascular (Disease)

ECG: electrocardiogram

(e)GFR: (estimated) Glomerular Filtration Rate

HbA1c: glycated hemoglobin

HDL-C: High-Density Lipoprotein Cholesterol

HR: Heart Rate

LDL-C: Low-Density Lipoprotein Cholesterol

LLA: Lipid Lowering Agents

LV: Left Ventricle/Left Ventricular

LVH: Left Ventricular Hypertrophy

IHD: Ischemic Heart Disease

MACE: Major Adverse Cardiac Event

NEP: Number of Events Prevented

NNT: Number Needed To Treat

RAS: Renin-Angiotensin System

RCT: Randomized Controlled Trial

ROC: Received Operating Characteristics

RR: Relative Risk

RVP: Realistic Virtual Population

SCD: Sudden Cardiac Death

SGLT2: Sodium-Glucose Co-Transporter 2

T2D(M): Type 2 Diabetes (Mellitus)

NAMES OF TRIALS & DATABASES

4D: Deutsche Diabetes Dialyse Studie

ASPEN: Atorvastatin Study for Prevention of Coronary Heart Disease Endpoints in Non-Insulin-Dependent Diabetes Mellitus

ACCORD: Action to Control Cardiovascular Risk in Diabetes

ADVANCE: Action in Diabetes and Vascular disease: PreterAx and Diamicron MR Controlled Evaluation

ALTITUDE Aliskiren Trial in Type 2 Diabetes Using Cardiovascular and Renal Disease Endpoints

CANVAS: CANagliflozin cardioVascular Assessment Study

CARDS: Collaborative Atorvastatin Diabetes Study

CTT: Cholesterol Treatment Trialists' Collaboration

Dapa-CKD: Dapagliflozin on Renal Outcomes and Cardiovascular Mortality in Patients with Chronic Kidney Disease

DECLARE-TIMI 58: Dapagliflozin Effect on CardiovascuLAR Events

DIABHYCAR: Type 2 DIABetes, Hypertension, CARdiovascular Events and Ramipril

EMPAREG-OUTCOME: Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

ETDRS: Early Treatment Diabetic Retinopathy Study

EWPHE: European Working Party on High blood pressure in the Elderly

FIELD: Fenofibrate Intervention and Event Lowering in Diabetes

HOME: Hyperinsulinaemia, the Outcome of Its Metabolic Effects

HOPE: Heart Outcomes Prevention Evaluation

HPS: Heart Protection Study

INDANA: INdividual Data ANalysis of Antihypertensive intervention trials

JPAD: Japanese Primary Prevention of Atherosclerosis with Aspirin for Diabetes

LIFE: Losartan Intervention For Endpoint reduction in hypertension

MRFIT: Multiple Risk Factor Intervention Trial

ROADMAP: The Randomized Olmesartan and Diabetes Microalbuminuria Prevention

SCORE: Systematic Coronary Risk Estimation

SHEP: Systolic Hypertension in the Elderly Program

SPRINT: Systolic Blood Pressure Intervention Trial

STOP: Swedish Trial in Old Patients

SYSTEUR/Syst-Eur: Systolic Hypertension in Europe

UGDP: University Group Diabetes Program

UKPDS: United Kingdom Prospective Diabetes Study

VADT: Veterans Affairs Diabetes Trial

VA CSDM: Veterans Affairs Cooperative Study on glycemic control and complications in type 2 diabetes

WOSCOPS: West of Scotland Coronary Prevention Study

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THESIS ESSENTIALS

Towards a better prevention of sudden cardiac death in type 2 diabetes

What is already known about the topic?

- ✚ Patients with type 2 diabetes (T2D) present a 2 to 4 times higher risk of cardiovascular (CV) mortality, including sudden cardiac death (SCD);
- ✚ Four groups of drugs are effective in preventing CV complications in T2D: antidiabetic (modestly...), antihypertensive, antiplatelet and lipid lowering agents (ADA, AHA, APA, and LLA);
- ✚ In personalized medicine, risk stratification is recommended to better adapt the treatment.

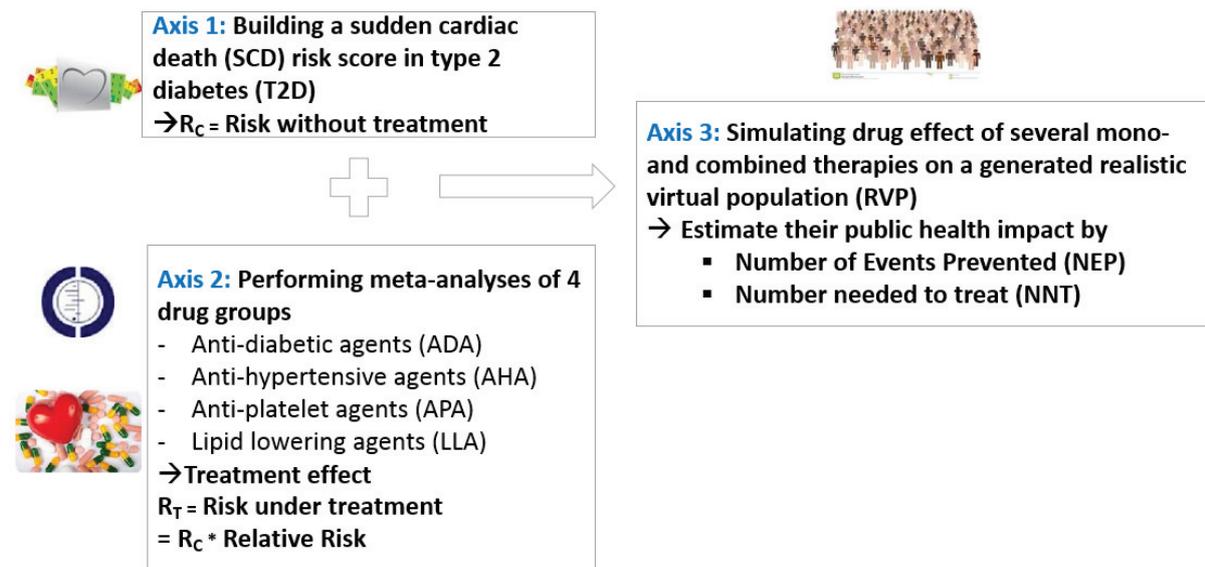
What is still unknown about the topic?

- ✚ No score to predict SCD risk in T2D is available;
- ✚ The effects of these drugs (ADA, AHA, APA, LLA) on SCD in T2D are not well documented;
- ✚ No clinical decision-making tool at population (public health impact) and individual levels is available.

This work has:

- ✚ Built a SCD risk score in T2D
 - Confirmed that diabetes is an independent risk factor of SCD;
 - Identified seven risk factors of SCD: diabetes, male sex, age, smoking, systolic blood pressure, serum cholesterol and history of myocardial infarction;
 - Detected the interaction between gender and diabetes: diabetic men & women present a similar risk of SCD or, in other words, diabetes harms more women than men.
- ✚ Studied the effects of drugs (ADA, AHA, APA, LLA) on SCD in T2D
 - Confirmed that AHAs in general have no benefit in reducing the risk of SCD in T2D, as suggested by our team in another meta-analysis in patients with hypertension;
 - Observed that ACE-inhibitors, aspirin and empagliflozin may potentially be the most beneficial drugs, but their effects are not statistically significant;
 - Suggested that the new ADA class gliflozin may be a promising candidate, if results from other trials (CANVAS, CANVAS, Dapa-CKD, DECLARE-TIMI 58) confirm that of EMPAREG-OUTCOME;
 - Faced a lack of data on SCD outcome (only reported indistinctly within composite ones) and/or data on diabetic subgroup. This calls for the necessity of building an open sharing data system of clinical trials, as exemplified by the SPRINT trial investigators.
- ✚ Developed an *in-silico* tool to optimize treatment for individuals and in public health
 - Used a French realistic virtual population of diabetic people generated from the most representative real data;
 - Compared mono and tri-therapy strategies (ACE-inhibitors, aspirin and empagliflozin), assuming there is no drug interaction, as suggested by another work of our team;
 - Proposed a solution to take into account treatment effect uncertainty (confidence interval of each risk ratio);
 - Illustrated how our *in-silico* simulations could help making clinical decision for individuals and in public health;
 - Illustrated the potential of using poly-pills in diabetic people.

RELATED PUBLICATIONS



Axis 1

- **HH Le, F Subtil, M Cerou, I Marchant, M Al-Gobari, M Fall, Y Mimouni, B Kassai, L Lindholm, L Thijs, F Gueyffier.** *HYSUD: A Sudden death risk score in Hypertension. Based on 25,648 individual patient data from six randomized controlled trials.* *J Hypertens.* 2017 Jun 24. doi: 10.1097/HJH.0000000000001451
- I Marchant, T Bejan-Angoulvant, **HH Le, F Gueyffier.** *Improving risk prediction performance for a better guidelines application.* *J Hypertens.* 2014 Jun;32(6):1192-3. (Editorial Comment)
- **HH Le, F Subtil, M Cérou, L Thijs, F Gueyffier.** *Does diabetes really harm more women than men? Observations from 30560 patient individual data.* *Oral communication, ESH Milan 2017 (Accommodation Grant)*
- **HH Le, F Subtil, M Cérou, M Al-Gobari, M Fall, E Hénin, P Janiaud, A Berrima, M Girard, S Erpeldinger, B Kassai, P Chevalier, F Gueyffier.** P-136. *Do sudden death & fatal myocardial infarction have the same risk factors in primary prevention?* *Ann Cardiol Angeiol.* doi: 10.1016/S0003-3928(16)30180-9, *Poster SFHTA 2015 (Accommodation Grant)*
- **HH Le, H Ottomani, G Sitruck, F Subtil, F Gueyffier.** *HYChEF: A risk score to predict Congestive Heart Failure Incidence in Hypertension. Based on 11 942 patient individual data.* *Posters, International Congress of Heart Failure Paris 2017 & ESC Barcelone 2017*
- **HH Le, F Subtil, M Cérou, L Thijs, F Gueyffier.** Renal function predicts sudden cardiac death risk in type 2 diabetes. Analysis from 6600 individual patient data (to be submitted)
- **HH Le, F Subtil, M Cérou, L Thijs, F Gueyffier.** Renal function predicts stroke risk in hypertension. Analysis from 30 560 individual patient data (to be submitted)

Axis 2

- **HH Le, A Berrima, M Girard, S Erpeldinger, F Gueyffier.** *Pharmacological prevention of sudden cardiac death in type 2 diabetes: lack of data. A systematic review and meta-analyses from 26 RCTs.* *Oral communication SFHTA 2017 (Accommodation Grant)*
- **HH Le, C El-Khatib, M Mombled, F Guitarian, M Al-Gobari, M Fall, P Janiaud, I Marchant, M Cucherat, T Bejan-Angoulvant, F Gueyffier.** *Impact of aldosterone antagonist on the sudden cardiac death in heart failure and myocardial infarction: a systematic review and meta-analysis of randomized-control trials.* *PLoS ONE* 11(2): e0145958. doi:10.1371/journal.pone.0145958
- M Al-Gobari, **HH Le, M Fall, F Gueyffier, B Burnand.** *Statins for sudden cardiac death prevention in heart failure patients: an analysis of systematic reviews and a meta-analysis.* *PLoS ONE* 12(2):e0171168- February 2017. DOI: 10.1371/journal.pone.0171168.
- G Grenet, **HH Le, F Gueyffier, M Cucherat.** *Does the decrease of blood pressure explain the decrease of cardiovascular risk for patients with type 2 diabetes?* *Poster, SFD Lille 2017*

Axis 3

- **HH Le**, I Marchant, JP Boissel, P Nony, B Kassai, C Cornu, **F Gueyffier**. *Synergetic prevention of sudden death by ACEI, statin and gliflozin in type 2 diabetes: a simulation study*. Oral communication DIA Philadelphia 2016 (Travel Grant)
- **HH Le**, I Marchant, JP Boissel, P Nony, B Kassai, C Cornu, **F Gueyffier**. *From meta-analysis to practical decision using realistic virtual population simulation: an illustration on sudden death prevention in type 2 diabetes (the OPTI-RVP approach)*. Poster, Cochrane Colloquium, Vienna 2015
- **HH Le**, I Marchant, JP Boissel, P Nony, B Kassai, C Cornu, **F Gueyffier**. *Pharmacological prevention of sudden cardiac death in type 2 diabetes: a public health simulation study*. Oral communication, SFHTA Paris 2014 (Accommodation Grant)
- M Fall, **HH Le**, I Marchant, **F Gueyffier**. *Public health impact of cardiovascular treatments in primary prevention: a simulation study on a virtual realistic population*. Oral communication, ESH Milan 2017 (Accommodation Grant)
- **HH Le**, I Marchant, JP Boissel, P Nony, B Kassai, C Cornu, **F Gueyffier**. *Virtual realistic population: a new tool to illustrate the impact of both drug combination & risk – based patient selection strategies*. Oral communication, SFPT Caën 2015
- M Fall, **HH Le**, M Al-Gobari, G Grenet, AM Dieye, **F Gueyffier**. *Do drugs interact together in cardiovascular prevention? A meta-analysis of powerful or factorial randomized controlled trials*. Under revision of Journal of Hypertension, posters at DIA Philadelphia 2016 & ESH Paris 2016 and oral communication at 27th World Congress of the International Union of Angiology and 15th Congress of the French Society of Vascular Medicine, Lyon 2016. Poster Alberto Ferrari Prize, ESH Paris 2016
- **HH Le**, G Grenet, I Marchant, M Cucherat, JP Boissel, **F Gueyffier**. *Credibility of surrogate criteria in predicting stroke incidence by gliflozin in type 2 diabetes: a simulation study*. Oral communication, Journée scientifique 'Décrypthèse' à l'école doctorale E2M2, One of the Best Communication Prizes, Lyon 2017

Generality

- **HH Le**, M Fall, M Al-Gobari, G Taverny, **F Gueyffier**. *Drug Prevention of Sudden Death in Adults*. Poster SFPT Rouen 2017
- **F Gueyffier**, M Fall, **HH Le**. *Targets for cardiovascular prevention: good use or misuse of drugs?* Poster SFPT Rouen 2017

Other works

- **HH Le**, F Subtil, M Cérou, M Fall, I Marchant, **F Gueyffier**. *Effect of antihypertensive treatment at different baseline blood pressure levels*. Poster ESH Milan 2017
- **HH Le**, I Marchant, F Subtil, JP Boissel, F Gueyffier. *Validation of Framingham and SCORE in 30 560 patients with hypertension*. Oral communication. ESH Milan 2017
- **HH Le**, F Subtil, M Cerou, M Fall, I Marchant, B Kassai, **F Gueyffier**. *Are heart failure incidence and baseline diabetes similarly associated with sudden death risk?* Poster. SFIC Lyon, 2016
- K Ali, **HH Le**, P Nony, N Eymard, **F Gueyffier**. *Effect of combining methionine depletion and chemotherapy as an anti-cancer therapeutic pathway: A meta-analysis of randomized controlled clinical trials* (to be submitted)

These publications allowed the document applied for the [Oréal-UNESCO For Women and Science scholarship to be classified in the top 100](#) (faire partie des 100 talents 2017 L'Oréal-UNESCO Pour les Femmes et la Science)

DIA: Drug Information Association; E2M2: Evolution Ecosystèmes Microbiologie Modélisation; ESC: European Society of Cardiology; ESH: European Society of Hypertension; SFD: Société Francophone du Diabète; SFIC: Société Française de l'Insuffisance Cardiaque; SFHTA: Société française d'Hypertension Artérielle; SFPT: Société Française de Pharmacologie et de Thérapeutique

SHORT ABSTRACT IN ENGLISH

Optimization of sudden cardiac death prevention in type 2 diabetes in France: a public health simulation study on a realistic virtual population

Type 2 diabetes (T2D) has increasingly become a common metabolic condition, associated with numerous micro and macro-vascular complications. Diabetic patients are about two-times more at risk of sudden cardiac death (SCD), compared to non-diabetic ones. Pharmacological intervention (anti-platelet, anti-hypertensive, lipid lowering, and to a lesser extent, anti-diabetic agents) appear to be the most efficient and economic candidates to prevent this event on a long term basis, yet their effects on SCD risk are not well known. We aimed to optimize their use and estimate their impact on public health via analysis, synthesis and modeling studies.

This work engaged three phases: First, constructing a risk score to predict SCD risk in T2D from the INDANA database. Secondly, performing the meta-analyses/systematic reviews of different therapeutic strategies in order to estimate their effects on SCD risk. Finally, simulating therapeutic strategies on a generated realistic virtual population (RVP) of French subjects with T2D by estimating the occurrence of SCD with and without treatment, and thus their absolute benefits, through the Number of Events Prevented (NEP) due to treatment, and the Number of patients Needed to be Treated to prevent one SCD (NNT).

We built a 7-risk factor to predict a 5-year risk of SCD in patients with hypertension (+/-diabetes), and collected the best evidence on the effects of these drugs. Integrating and simulating altogether on a generated RVP of French diabetic subjects suggested that, for every 57 individuals of the 10% highest predicted SCD risk, the co-prescription of angiotensin converting enzyme inhibitor-aspirin-empagliflozin could prevent one SCD in 5 years. For the whole population, the corresponding number was 135. In perspective, this approach could help better transposing clinical trial results into practice and facilitating clinical decision at both public health and individual levels.

Keywords: Sudden cardiac death, type 2 diabetes, public health impact, simulation, meta-analysis, risk score, realistic virtual population.

COURT RÉSUMÉ EN FRANCAIS

Optimisation de la prévention de la mort subite chez les diabétiques de type 2 en France par simulation des scénarios médicamenteux sur une population virtuelle réaliste

Le diabète de type 2 (DT2) est devenu une maladie métabolique chronique de plus en plus fréquente, associée à de nombreuses complications micro et macro-vasculaires. Les patients diabétiques ont environ deux fois plus de risque de mort subite d'origine cardiaque (MSC) que les patients sains. L'intervention pharmacologique (anti-plaquettaires, anti-hypertenseurs, anti-diabétiques et hypolépimants) nous semble être l'option la plus efficace, accessible et économique pour prévenir cet événement à long terme. Cependant, les effets de ces médicaments sur la MSC ne sont pas bien connus. Notre objectif est d'estimer leur impact sur la santé publique et d'optimiser leur utilisation chez les DT2, grâce à des études d'analyse, de synthèse et de modélisation.

Ce travail inclut trois étapes: premièrement, d'établir un score de risque permettant de prédire le risque de MSC en cas de DT2 en utilisant les bases de données INDANA. Deuxièmement, d'effectuer des méta-analyses/revues systématiques de différentes stratégies thérapeutiques afin d'estimer leurs effets sur le risque de MSC. Enfin, de simuler différentes stratégies sur une population virtuelle réaliste (PVR) de français diabétiques et d'intégrer les résultats obtenus sur la plate-forme pour estimer le risque de MSC avec et sans traitement. Cette simulation permet d'estimer les bénéfices absolus de ces stratégies, en prenant en compte le nombre d'événements prévus (Number of Events Prevented, NEP) et le nombre de patients à traiter pour prévenir une MSC (Number Needed to Treat, NNT).

Nous avons élaboré un score incluant 7 facteurs de risque de MSC chez les patients atteints d'hypertension artérielle (+/- diabète) et collecté les meilleures estimations sur l'effet des médicaments. Notre simulation sur la PVR générée a suggéré que chez 10% des patients ayant le risque de MSC prédit le plus haut, la co-prescription d'inhibiteurs de l'enzyme de conversion, d'aspirine et d'empagliflozine permettait de prévenir une MSC chez 57 individus traités sur 5 ans. Pour toute la PVR, le chiffre correspondant était 135. Nous en concluons que cette approche pourrait permettre de mieux transposer les résultats des essais cliniques à la pratique et de faciliter la décision clinique aux niveaux populationnel et individuel.

Mots-clés: mort subite (d'origine) cardiaque, diabète de type 2, impact sur la santé publique, simulation, méta-analyse, score de risque, population virtuelle réaliste

SUBSTANTIAL ABSTRACT IN ENGLISH

Optimization of sudden cardiac death prevention in type 2 diabetes in France: a public health simulation study on a realistic virtual population

BACKGROUND

Type 2 diabetes (T2D), accounting for 90–95% of all diabetes mellitus cases, results from a combination of the inability of muscle cells to respond to insulin properly (insulin resistance) and the inadequate compensatory insulin secretion. This metabolic chronic condition, with numerous macro/micro-vascular complications, is associated with an increased risk of cardiovascular (CV) diseases and higher all-cause mortality rates, including sudden cardiac death (SCD). A recent risk score by Deo *et al.* for general population has identified T2D as an independent risk factor of SCD.

CV mortality is one of the leading causes of death in the world. Approximately 50% of these deaths are SCDs, which account for more than three out of four cases of myocardial infarctions complicated with ventricular fibrillation. Indeed, SCD, defined as a death occurring within an hour after the onset of the first symptoms, remains a frequent cause of early mortality, estimated at around 40 000 cases per year in France, half of them before 60 years of age. The number of hospitalizations due to acute myocardial infarction each year in France is about 50 000, with an intra-hospital mortality of about 9%. In epidemiology, and especially in clinical trials of CV preventive drugs, SCD was often considered as a major coronary accident, in the same category of fatal and non-fatal infarctions.

The resulting confusion raises a problem in terms of prevention strategy: the health care system has considerably developed the early management of acute myocardial infarction, with coronary angioplasty validated as the most effective treatment. However, most of SCDs occur before any possibility of implementing an angioplasty. In addition, the use of defibrillators at public sites is not completely effective, limited by cost, access and skills.

The remaining solution to prevent SCD in the long term, in T2D and other populations at risk, is the use of CV protective medication such as anti-diabetic, anti-hypertensive, lipid lowering drugs, and antiplatelet agents (ADA, AHA, LLA, APA), with a legitimate hope. These drugs appear effective to reduce the risk of myocardial infarction in clinical trials, with 30% of SCDs, 46% of non-fatal, and 24% of fatal myocardial infarctions. Unfortunately, in opposition to this legitimate expectation, several studies showed that AHAs and oral ADAs do not reduce the risk of SCD and CV / total mortality, while reducing the risk of fatal infarction for AHAs and of non-fatal infarction for both drug groups.

OBJECTIVE

Based on the available data in the literature and on the INDANA (INdividual Data ANALysis of Antihypertensive intervention trials) database (http://lbbe-dmz.univ-lyon1.fr/spip_indana/), this study aimed to assess the efficacy of pharmacological treatments and optimize their uses for better preventing SCD in type 2 diabetic patients.

This objective requires several investigational phases:

- (i) to develop a refined scoring scheme for calculating the risk of SCD events among type 2 diabetic subjects;
- (ii) to perform systematic reviews and meta-analyses that evaluate the effectiveness of cardiovascular (CV) preventive therapies in preventing SCD in T2D;
- (iii) finally, to integrate the results obtained into a realistic virtual population (RVP) generated from real French cohorts to simulate the treatment effect.

METHODS

- (i) A predictor to estimate SCD risk in patients with hypertension +/- diabetes (called HYSUD) was derived using *time-to-event* Cox proportional hazards model, with data of 17 604 men and 8044 women, age range 35-98 years, from six randomized controlled trials (RCTs) of INDANA database.
- (ii) Clinical trials, systematic reviews, and meta-analyses were searched through PubMed, Science Direct, Web of Science, Cochrane library database, clinicaltrials.gov, trialresultscenter.org and google scholar until 30/06/2017, and considered eligible if related to the prevention of SCD in T2D by one of the four drug groups (ADA, AHA, LLA, APA).
- (iii) We used a RVP generated from the LPD and ENTRED database of French diabetic people to evaluate the effect of several mono- and combined therapies according to patient particularities (age, gender, CV risk) in order to figure out the optimal strategies.

RESULTS

(i) HYSUD predictor identified seven risk factors of SCD in hypertensive +/- diabetic patients: age, sex (male), serum cholesterol, systolic BP, smoking status, history of myocardial infarction and T2D status. The area under the receiver-operating characteristics (AUROC) curve, obtained on an independent validation sample, was 0.77 (confidence interval CI 95%, 0.74-0.81). We confirmed a result that is not considered enough in medical practice & guidelines: T2D is a risk factor which is more powerful in women.

(ii) In the limit of current biomedical evidence, pharmacological intervention seems to have no benefit in preventing SCD in those with T2D. In detail, we have found the following results (until 30/06/2017):

- For AHAs (angiotensin-converting-enzyme inhibitor (ACE) inhibitors, beta-blockers, aldosterone antagonists, calcium channel blockers, *etc.*), no effect for SCD prevention in patients with T2D was found: relative risk RR 1.00 (0.84-1.18, p =0.96). Our specific meta-analysis on the effect of ACE inhibitors, pooling results of two trials (HOPE & DIABHYCAR), did not find out a significant reduction of the SCD risk: RR 0.86 (0.54-1.24, p =0.41).
- For LLAs, our meta-analysis gathering four trials (4D, ASPEN, CARDS, WOSCOP) suggested no beneficial effect of statins in preventing SCD in T2D: RR 0.96 (0.75-1.24).
- For APAs, only two trials reported the effect of aspirin in preventing SCD in T2D: ETDRS and JPAD. Their pooled results suggested a probable favorable effect, but not significant: RR = 0.72 (0.51-1.02, p = 0.06, I² = 0%) and not conclusive, which may be due to the different characteristics/reaction of the studied populations towards aspirin (one trial conducted in Europe and other in Japan).
- Intensive blood pressure control did not significantly reduce the risk of SCD: RR 0.86 (0.57-1.29, p =0.46). Combining this with AHA gave RR =0.97 (0.83-1.14, p =0.75).
- Our meta-analysis of eight trials (HOME, UGDP A UGDP B, UKPDS 33, UKPDS 34, VADT, ACCORD, VA CSDM), comparing intensive to standard glycemic controls, detected no significant effect on SCD: RR 1.14 (0.74-1.76, p =0.54).
- In general, intensive (blood pressure and/or glucose) control seemed to bring no benefit to prevent SCD in T2D: RR 1.05 (0.78-1.41, p =0.77).
- Until now, empagliflozin seemed to be the only ADA which could reduce the risk of SCD by 31% in T2D, but not significantly: RR = 0.69 (0.46-1.05, p=0.08, data from supplementary appendix of EMPAREG-OUTCOME trial).
- Pooled effect of all treatments gave a poor result: RR 0.94 (0.83-1.07, p =0.35).

(iii) Using the HYSUD predictor on a French diabetic RVP of 175 968 subjects (generated from a 8 995-patient sample), we estimated a median 5-year SCD risk of 1.1%. Taking 31%, 28% and 14% of risk reductions by empagliflozin, aspirin and ACE inhibitor respectively, and supposing there was no interaction between these drugs, the relative risk of the tri-therapy was $RR = 0.69 * 0.72 * 0.86 = 0.43$. A simulation of the public health impact on this platform estimated the numbers needed to treat (NNT) at 135 people for the whole population and at 57 among individuals of the 10% highest predicted SCD risk, if treated simultaneously by this tri-therapy for five years. We obtained these results based on Bayesian considerations regarding the uncertainty in the estimation of treatment effect, leading us to consider confidence intervals as credibility intervals.

CONCLUSION

This study has identified seven risk factors of SCD in patients with hypertension (with/without T2D), confirming the similarity with those of myocardial infarction or with CV classical scorers (Framingham, SCORE, risk score for CV death by Pocock *et al.* 2001). The benefits of the four drug groups (ADA, AHA, LLA, APA) were assessed through the available literature: no specific/conclusive data was found for diabetic patients. Our search called for more evidence on drug effect in preventing SCD in these subjects and an open data sharing system of clinical trials. Simulations were performed in a French diabetic RVP by applying results obtained from the risk score and related meta-analyses/clinical trials, suggesting that the strategy based on the three best potential drugs, i.e ACE inhibitor-statin-empagliflozin co-prescription could prevent one SCD in 5 years among every 124 patients at possible risk of SCD. No interaction between these three drugs was found in our previous work. We proposed here an innovative approach to estimate the impact of various drug strategies on a RVP: The platform we setup allows a straightforward evaluation of current pharmacologic treatments, and would further be used for the optimization of therapeutic strategies to prevent other CV accidents in populations at risk.

In general, we suggested the OPTI-RVP (OPTimize therapeutic strategies on a Realistic Virtual Population) approach to simulate public health impact (PHI), step by step:

1. O (Outcome): Choose outcome(s) of interest
2. P (Population): Define the population on which optimizing PHI
3. T (Treatment): Choose treatments of interest
4. I (Integration): Generate the targeted RVP and integrate available information obtained from OPT (three items above) to simulate PHI.

This OPTI-RVP is a multi-component approach which allows accurate fitting to the characteristics of the particular population of interest. In perspective, we could: i. Re-use RVP for other objectives, such as validation of risk scores; ii. Enrich the RVP platform by external data/information sources; and iii. Integrate various constraints of optimization, eg. cost-effectiveness, cost-utility, side effects, etc... Our OPTI-RVP approach that gathers the effect models (through meta-analyses and risk scores) and RVP simulation, provides a powerful clinical tool. This could help valuing each evidence-based component, better transposing clinical trial results into practice, facilitating clinical decision at both public health and individual levels, on both medical and economic aspects.

Keywords: Sudden cardiac death, type 2 diabetes, public health impact, simulation, meta-analysis, risk score, realistic virtual population.

RESUME SUBSTANTIEL EN FRANÇAIS

Optimisation de la prévention de la mort subite chez les diabétiques de type 2 en France par simulation des scénarios médicamenteux sur une population virtuelle réaliste

CONTEXTE

Le diabète de type 2 (DT2), qui représente 90 à 95% des cas de diabète, résulte d'une incapacité combinée de la cellule musculaire à répondre correctement à l'insuline (résistance à l'insuline) et d'une sécrétion d'insuline compensatoire inadéquate. Cette condition métabolique chronique s'accompagne de nombreuses complications macro et micro-vasculaires est associée à un risque élevé de maladies cardiovasculaires (CV) et de mortalité toutes causes confondues, y compris la mort subite d'origine cardiaque (MSC). Un score de risque récent de Deo *et al.*, établi dans la population générale, a identifié le DT2 comme étant un facteur de risque indépendant de la MSC.

La mortalité CV est l'une des premières causes de décès dans le monde. Environ 50% de ces décès sont des MSC, qui correspondent pour plus de trois cas sur quatre à un infarctus du myocarde compliqué de fibrillation ventriculaire. En effet, la mort subite, définie par un décès survenant dans l'heure suivant des premiers symptômes, reste une cause de mortalité précoce fréquente, estimée à près de 40 000 cas par an en France, dont la moitié avant 60 ans. Chaque année en France, le nombre d'infarctus aigus donnant lieu à une hospitalisation est de l'ordre de 50 000, avec une mortalité intra-hospitalière de 9%. En épidémiologie, et surtout dans le cadre des essais cliniques sur la prévention médicamenteuse des accidents CV, la MSC est comptabilisée au sein des accidents coronariens majeurs, au même titre que les infarctus fatals et non fatals.

Cet amalgame logique pose un paradoxe dans la stratégie préventive : en effet, le système de soins s'est considérablement développé en termes de prise en charge précoce de l'infarctus en phase aiguë, et l'angioplastie avec désobstruction artérielle est considérée comme étant la mesure la plus efficace. Le problème est que la plupart des MSC surviennent avant toute possibilité de mise en œuvre d'une angioplastie, ne sont donc pas affectées par l'amélioration de la prise en charge des infarctus du myocarde. En outre, la mise en place de défibrillateurs dans les lieux publics est une mesure peu efficace et limitée par les coûts, l'accès et les compétences du public.

Les seuls moyens pour prévenir la MSC à long terme chez les DT2, et autres populations à haut risque, sont des médicaments préventifs comme les antihypertenseurs, les hypocholestérolémiants, les antidiabétiques et les antiplaquettaires, qui offrent un espoir légitime. Il a été démontré que ces médicaments sont capables de réduire le risque d'infarctus du myocarde dans les essais cliniques,

représenté pour 30% par des MSC, 46% par des infarctus non fatals, et 24% par des infarctus fatals. Néanmoins, contrastant avec cet espoir, plusieurs travaux ont montré que les antihypertenseurs et les antidiabétiques oraux ne réduisent pas le risque de MSC et de mortalité CV/totale, alors que ces deux médicaments réduisent le risque d'infarctus non fatal, et fatal pour les antihypertenseurs.

A ce stade de la réflexion, il nous paraît légitime de dresser un tableau plus précis de l'effet des médicaments dans la prévention de la MSC, et de vérifier si leur utilisation peut être optimisée. Il nous semble également important d'attirer l'attention de la communauté scientifique et des autorités publiques sur cette préoccupation majeure et méconnue posée par la MSC et sur le défaut de sa prise en charge.

OBJECTIF

Fondée sur les données factuelles disponibles dans la littérature et la base de données INDANA (http://lbbe-dmz.univ-lyon1.fr/spip_indana/), notre travail visait à évaluer l'efficacité des traitements pharmacologiques et à optimiser leur administration dans la prévention de la MSC chez les patients atteints de DT2. Cet objectif comportait plusieurs phases d'investigation:

- (i) élaborer un score de risque pour calculer le risque de MSC chez les sujets diabétiques de type 2;
- (ii) effectuer des méta-analyses évaluant l'efficacité des thérapies préventives CV afin de prévenir cet accident dans le DT2;
- (iii) et enfin, intégrer les résultats obtenus dans une population virtuelle réaliste (PVR) générée à partir des cohortes françaises réelles les plus représentatives.

MÉTHODES

(I) Un prédicteur estimant le risque de MSC chez les patients atteints d'hypertension artérielle +/- diabète (appelé HYSUD) a été établi en utilisant le modèle de risque proportionnel de Cox '*time-to-event*' avec des données de 17 604 hommes et 8044 femmes, âgés de 35 à 98 ans, recrutés et suivis dans 6 essais randomisés contrôlés (ECR) intégrés dans la base de données INDANA (Analyse des données individuelles des essais d'intervention des antihypertenseurs).

(II) Les essais cliniques, les revues systématiques et les méta-analyses concernés ont été recherchés dans PubMed, Science Direct, Web of Science, Cochrane library, clinicaltrials.gov, trialresultscenter.org et google scholar jusqu'au 30/06/2017, et considérés éligibles si liés à la prévention de MSC dans le DT2 par l'un des quatre groupes de médicaments (antihypertenseurs, hypolipidémiques, antiplaquettaires et anti-diabétiques).

(III) Une PVR avait été générée en utilisant les bases de données LPD et ENTRED de patients diabétiques français selon la méthode mise au point par le Pr. Ivanny Marchant. Nous avons examiné l'effet de

plusieurs monothérapies et thérapies combinées sur ces patients virtuels en fonction de leurs particularités (âge, sexe, risque CV) afin d'exposer les stratégies optimales.

RÉSULTATS

(i) Le prédicteur HYSUD inclut sept facteurs de risque de MSC chez les patients hypertendus +/- diabétiques: âge, sexe (hommes), taux de cholestérol total, pression artérielle systolique, tabagisme, antécédents d'infarctus du myocarde et diabète. L'aire sous la courbe ROC (Receiver Operating Characteristic) obtenue sur un échantillon de validation indépendant était de 0,77 (intervalle de confiance IC 95%, 0,74-0,81). Nous avons aussi confirmé un résultat qui n'est pas suffisamment pris en compte dans la pratique médicale et les recommandations ; le DT2 est un facteur de risque plus puissant chez les femmes.

(ii) Dans la limite des données biomédicales actuelles, l'intervention pharmacologique semble n'avoir pas ou peu de bénéfice dans la prévention de la MSC chez les personnes atteintes de DT2. En détail, jusqu'au 30/06/2017, nous avons trouvé :

- Pour les agents anti-hypertenseurs de tous les groupes (inhibiteurs de l'enzyme de conversion IEC, bêta-bloquants, antagonistes de l'aldostérone, bloqueurs des canaux calciques, *etc.*), aucun effet n'a été observé pour la prévention de la MSC chez les patients DT2: RR 1,00 (0,84-1,18, $p = 0,96$). Notre méta-analyse, mise à jour sur l'effet des IEC depuis les résultats de deux essais (HOPE et DIABHYCAR), a marqué une réduction du risque de 14%, mais non significative: RR 0,86 (0,59-1,24).
- De la même manière, pour les agents hypolipémiants, notre méta-analyse réunissant quatre essais (4D, ASPEN, CARDS, WOSCOP) n'a suggéré aucun effet bénéfique des statines dans la prévention de la MSC chez les DT2: RR 0,96 (0,75-1,24).
- Pour les agents antiplaquettaires, selon nos recherches, seulement deux essais ont rapporté l'effet de l'aspirine dans la prévention de la MSC dans le DT2: ETDRS et JPAD. Leurs résultats combinés ont suggéré un effet probablement favorable mais non significatif: risque relatif RR = 0,72 (0,51-1,02 ; $p = 0,06$; $I^2 = 0\%$) et non concluant, ce qui peut être dû aux différentes caractéristiques / réponses des populations étudiées (un essai mené en Europe et l'autre au Japon) à l'aspirine.
- L'abaissement intensif de la pression artérielle n'a pas réduit le risque de MSC de manière significative: RR 0,86 (0,57-1,29, $p = 0,46$). Combiner cela avec les agents antihypertenseurs aboutit à un RR 0,97 (0,83-1,14 ; $p = 0,75$).
- Notre méta-analyse réunissant huit essais (HOME, UGDP A UGDP B, UKPDS 33, UKPDS 34, VADT, ACCORD, VA CSDM) comparant le contrôle glycémique intensif versus standard, n'a également détecté aucun effet positif significatif sur la MSC : RR 1,14 (0,74-1,76, $p = 0,54$).
- En général, le contrôle intensif (de la pression artérielle / de la glycémie) semble ne générer aucun avantage pour prévenir la MSC dans le DT2: RR 1,05 (0,78-1,41 ; $p = 0,77$).

- À ce jour, l'empagliflozine semble être le seul agent antidiabétique ayant été associé à une réduction de 31% du risque de MSC dans le DT2, mais là encore non significative : RR = 0,69 (0,46-1,05 ; p = 0,08, données de l'annexe complémentaire de l'essai EMPAREG-OUTCOME).
- L'effet combiné de tous les traitements a donné un résultat non conclusif: RR 0,94 (0,83-1,07 ; p = 0,35).

(iii) Une PVR diabétique française de 175 968 patients a été générée à partir d'un échantillon de 8 995 patients, ce qui donnait une médiane de risque de MSC de 1.1% sur 5 ans, en utilisant le prédicteur HYSUD. En prenant respectivement des réductions de risque de MSC de 31%, 28% et 14% par l'empagliflozine, l'aspirine et les IEC, et en supposant qu'aucune interaction n'existe entre ces médicaments, le risque relatif de la tri-thérapie était $RR = 0,69 * 0,72 * 0,86 = 0,43$. Une simulation de l'impact de la santé publique sur cette plate-forme a estimé le nombre de personnes nécessaires à traiter (NNT, Number Needed to Treat) à 135 personnes pour l'ensemble de la population et à 57 parmi les 10% des individus avec le risque de MSC le plus élevé, si traités simultanément par cette tri-thérapie pendant 5 ans. L'obtention de ces résultats a fait appel à un raisonnement Bayésien pour tenir compte de l'incertitude autour de l'estimation de l'effet des traitements, considérant les intervalles de confiance comme des intervalles de crédibilité.

CONCLUSION

Notre travail a identifié sept facteurs de risque de MSC chez les patients atteints d'hypertension (avec / sans DT2), confirmant la similitude avec ceux de l'infarctus du myocarde ou d'autres scores de risque CV classiques (Framingham, SCORE, score de risque pour la mortalité CV de Pocock *et al.* 2001). L'effet des quatre groupes de médicaments CV préventifs chez les patients diabétiques a été recherché dans la littérature : aucune donnée significative/concluante n'a été trouvée. Notre recherche a mis en évidence un manque de preuves sur l'intervention pharmacologique dans la prévention de la MSC dans le DT2 et la nécessité de construire une base de données ouverte et partagée des essais cliniques. Des simulations ont été effectuées sur une PVR diabétique française en appliquant les résultats moyens obtenus (à partir du score de risque HYSUD et des méta-analyses/essais cliniques concernés), reposant sur des résultats non significatifs et combinés selon une logique bayésienne. Cette approche a suggéré que la plus grande stratégie de la co-prescription d'IEC-aspirine-empagliflozine pourrait prévenir une MSC tous les 5 ans parmi les 135 patients à risque de MSC. L'hypothèse d'absence d'interaction entre ces médicaments a été vérifiée par notre équipe et nous avons démontré qu'aucune interaction importante ne pouvait être suspectée, et que de telles interactions pouvaient être éliminées pour plusieurs associations de traitements et sur plusieurs critères de jugement.

Nous proposons ici une approche innovante pour estimer l'impact de diverses stratégies médicamenteuses sur une PVR : la plate-forme que nous avons ainsi mise au point et testée permet

une illustration directe de l'impact des traitements pharmacologiques actuels et des différentes stratégies qui les utiliseraient. Cette plateforme pourrait être utilisée pour l'optimisation de stratégies thérapeutiques pour prévenir d'autres accidents CV dans d'autres populations à risque. En général, nous proposons l'approche OPTI-PVR (OPTIMiser les stratégies thérapeutiques sur une population virtuelle réaliste) pour simuler l'impact sur la santé publique (ISP) étape par étape:

1. O (Outcome): Choisir les outcomes/critères de jugement d'intérêt
2. P (Population): Définir la population sur laquelle optimiser l'ISP
3. T (Traitement): Choisir les traitements d'intérêt
4. I (Intégration): Générer la PVR ciblée et intégrer les informations obtenues à partir d'OPT (trois étapes ci-dessus) pour simuler l'ISP.

OPTI-PVR est une approche multi-composante qui permet d'adapter précisément les éléments des stratégies aux caractéristiques de la population d'intérêt. En perspective, nous pourrions:

- i. Réutiliser la PVR pour d'autres objectifs, tels que la validation des scores de risque;
- ii. Enrichir l'approche par autres sources externes de données / informations;
- iii. Intégrer diverses contraintes d'optimisation, p.ex. coût-efficacité, effets secondaires, *etc.*

Notre approche OPTI-PVR regroupe les modèles d'effets (valorisant les résultats des méta-analyses et les scores de risque) et la simulation appliquée à une PVR. Elle fournit un outil avec un fort potentiel d'application clinique. Cet outil pourrait aider à mieux utiliser chaque médicament dont l'estimation d'efficacité serait fondée sur des données probantes, à mieux transposer les résultats des essais cliniques à la pratique en facilitant les décisions cliniques, à la fois sur la santé publique et au niveau individuel, tant sur le plan médical que sur le plan économique.

Mots-clés: mort subite (d'origine) cardiaque, diabète de type 2, impact sur la santé publique, simulation, méta-analyse, score de risque, population virtuelle réaliste

INTRODUCTION

Sudden cardiac death (SCD) is described as an unexpected death from a cardiac cause within a short time period, generally ≤ 1 hour or ≤ 24 hours from the onset of symptoms, in a person without any prior condition that would appear fatal (1). In epidemiology, especially in clinical trials of cardiovascular (CV) preventive drugs, SCD is often recorded as a major coronary event, as well as fatal and non-fatal myocardial infarctions (MI) (2). This amalgam logically raises critical questions in terms of SCD prevention strategy: actually, the health care system has grown considerably for the early therapy of acute MI (AMI), in which primary angioplasty of coronary arteries or cardiac implantable electronic devices transplantation were validated as the most effective treatments (3,4). Unfortunately, this improvement of AMI management has no possible preventive impact on SCD rate, since this major accident occurs before any access to this support. Indeed, at least 90% to 95% of patients experiencing sudden cardiac arrest cases in the community-setting end in death before receiving medical assistance (5,6). In addition, implanting cardioverter defibrillator is limited by cost, technology access, and the lack of stratification tools outside specific populations (7–9). Moreover, introducing defibrillators in all public places showed to be not completely effective and economically favorable (10).

The remaining strategy against SCD is therefore preventive measures, with a legitimate hope for CV protective medications, such as antihypertensive, lipid-lowering, anti-diabetic and antiplatelet agents (AHA, LLA, ADA, APA). The scientific basis is that these drugs appear to reduce the risk of MI in clinical trials; while MI outcome comprises 30% of SCD, 46% of non-fatal MI, and 24% of fatal MI (11).

Type 2 diabetes (T2D), accounting for 90–95% of all diabetes mellitus cases, results from a combination of the inability of muscle cells to respond to insulin properly (insulin resistance) and the inadequate compensatory insulin secretion (12). This metabolic chronic condition, with numerous macro/micro-vascular complications, is associated with an increased risk of CV diseases and higher all-cause mortality rates, including SCD (13–17). A recent risk score of Deo *et al.* for general population has identified T2D as an independent risk factor of SCD (18).

Prevention of SCD for patients with T2D is thus a major problem in public health, yet only partially addressed in the literature. In these patients, co-prescription of AHA, LLA, ADA, APA have showed the benefit to reduce the morbid-mortality rate (19–21); yet controversies for their risk-benefit balance and their optimal use remain. Likewise, to date, no score predicting SCD risk specifically for type 2 diabetic patients was established. Such a score may help to better target interventions towards highest risk individuals, following the effect model law (22) and as suggested by several papers (6).

For all these reasons, it is necessary to draw more accurate pictures on SCD risk, on preventive treatment effects and whether their use could be optimized in T2D, with assistance of a realistic virtual population (RVP) simulation. The objective of our study is to estimate the public health impact (PHI) of

different therapeutic strategies (monotherapy or combined therapy) for SCD prevention in T2D, based on available data in the medical literature and RVP modeling.

To realize this purpose, the planned scheme of our work was:

- First, to build a risk score to predict SCD risk in type 2 diabetic patients.
- Secondly, to conduct/review treatment effect of four groups of drugs (AHA, LLA, ADA, APA) in patients with T2D, through relevant meta-analyses and systematic reviews.
- Thirdly, to perform simulations on a French RVP with T2D. Constructed risk score was applied in this RVP to simulate the occurrence of SCD in type 2 diabetic patients without treatment. Results from the second step were used to simulate SCD occurrence in patients with different treatments, in order to estimate the absolute benefit expected through the Number Needed to Treat (NNT) or Number of Events Prevented (NEP).

STATE-OF-THE-ART

Sudden cardiac death

Epidemiology

SCD is responsible for 300 000 to 400 000 deaths annually in the United States, depending on the definition used: 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 a cardiac disease (1). This type of death is also the most common one and often the first manifestation of coronary heart disease (CHD), accounting for about 50% of CV mortality in the United States and other developed countries (5). In France, this major problem is considered as the cause of approximately 40 000 deaths per year, half of them before 60 years of age (23,24).

Etiology

Most of SCDs were thought to involve ventricular tachycardia degenerating to ventricular fibrillation, complicating ischemic event and subsequent asystole, although the percentage of ventricular tachyarrhythmias found as the first rhythm, at the time of collapse, appears to be decreasing. This event occurs primarily out-of-hospital with only a 2-3% survival rate (25). In 60% to 80% of cases, SCD occurs in the setting of coronary artery disease (CAD); non-ischemic cardiomyopathy and infiltrative, inflammatory, and acquired valvular diseases explained most of non-CAD SCD events (1).

A small percentage of SCDs occur in the setting of ion channel mutations responsible for inherited abnormalities, such as the long/short QT syndromes, Brugada syndrome, and catecholaminergic ventricular tachycardia, which could provide mechanistic insights. In addition, other genetic abnormalities, such as hypertrophic cardiomyopathy and congenital heart defects like anomalous coronary arteries, also contribute to cause SCD (1).

Risk factors

Due to its complex and dynamic nature, the early identification of risk factors of SCD remains a considerable challenge. Measurement of the left ventricular ejection fraction (LVEF) to evaluate severe LV systolic dysfunction is commonly presented for SCD risk stratification utilized in clinical practice (1). However, community-based studies clearly indicate that severely decreased LVEF is likely to manifest late in the natural history of SCD, and the minority of patients who suffer from SCD may not have severe LV dysfunction (26).

Other than LVEF, age, hypertension, male sex, African American race, smoking, systolic blood pressure (SBP), use of AHA, serum potassium, serum albumin, elevated serum cholesterol, high-density lipoprotein (HDL), estimated glomerular filtration rate (GFR), glucose intolerance, decreased vital

capacity, relative weight, QTc interval, intraventricular conduction block and diabetes were also detected as risk factors for SCD (18,27). Family history of MI was also described to be related to the risk of primary cardiac arrest (28). Moreover, the heart rate (HR) profile during exercises was another predictor of SCD (29). In addition, literature increasingly identifies potential novel risk markers and predictors of SCD, such as high-risk phenotypes and genetic variants (30–32). To better prevent SCD, risk stratification is necessary to classify patients earlier, according to their risk in the long term (2,33,34). In the short term, studies showed some biomarkers/warning symptoms which might help to avoid this accident earlier (35,36).

Prevention

Interestingly, the drugs having the most significant impact on total and SCD mortalities are those with no direct electrophysiological action on myocardial excitable tissue. This observation may provide insight into mechanisms that are responsible for ventricular tachyarrhythmias causing cardiac arrest (37). Ventricular fibrillation is thought to be the final common pathway of an electrically unstable heart, the most common in three main causes of SCD, while the two others are electromechanical dissociation, asystole, and heart block (1). In patients at high risk in general (not only in T2D), the only pharmacological advance have been achieved with drugs that influence the “upstream” regulatory events, such as statins, angiotensin converting enzyme (ACE) inhibitors, aspirin, beta-blockers (BBs), and aldosterone inhibitors, rather than with “traditional” ion channel–blocking antiarrhythmic agents (37). In fact, anti-arrhythmic drugs, whose use appears logical to prevent this accident, have been showed to increase SCD and total mortality incidence in the CAST trial (38), on the contrary.

Type 2 diabetes (mellitus)

Definition & classification

Diabetes is a chronic disease that occurs either when the pancreas does not produce enough insulin (type 1 diabetes) or when the body cannot effectively use the insulin produced (T2D), leading to an abnormally high level of blood glucose (12).

Epidemiology

In 2014, approximately 422 million people worldwide had diabetes, with about 90% of T2D (39), largely surmounting the prevalence estimated (366 million) by a review in 2004 for the year 2030 (40). In 2015, a large population-based JAMA review reported that half of American adults had diabetes or prediabetes (41). This global epidemic of DT2 is considered to be predominately due to population growth, aging, urbanization, and the state of obesity and physical inertia (42).

Diagnostics

The guideline of the American Diabetes Association recommends the use of any of the four following criteria for diagnosing diabetes: 1) glycated hemoglobin (A1C) value of 6.5% or higher, 2) fasting

plasma glucose ≥ 126 mg/dl (7.0 mmol/l), 3) 2-h plasma glucose ≥ 200 mg/dl (11.1 mmol/l) during an oral glucose tolerance test using 75 g of glucose, and/or 4) classic symptoms of hyperglycemia (e.g., polyuria, polydipsia, and unexplained weight loss) or hyperglycemic crisis with a random plasma glucose of 200 mg/dl (11.1 mmol/l) or higher. In the absence of unequivocal hyperglycemia, the first three criteria should be confirmed by repeat testing. Prediabetes is diagnosed with an A1C of 5.7–6.4%, fasting plasma glucose of 100–125 mg/dl (5.6–6.9 mmol/l; i.e., impaired fasting glucose [IFG]), or 2-h post-load glucose of 140–199 mg/dl (7.8–11.0 mmol/l; i.e., impaired glucose tolerance [IGT]) (43). The combination of results from several tests may bring higher accuracy. When using HbA1c of 6.5% or higher and FPG of 126 mg/dL or higher as the cut-points for diabetes, the results showed that there is a moderate agreement between the two tests for the diagnosis of diabetes. Diabetes classification was consistent for the majority of subjects, with 95.9% being classified as positive by both tests and 1.8% being classified as negative by both tests. Only 0.5% of subjects were classified as positive by one test and negative by the other (44).

The classification of patients with T2D by the means of the classical clinical and laboratory markers (HbA1c, glucose, lipids, body mass index-BMI and BP) is a symptoms-based categorization. Yet, to provide an insight into the underlying pathophysiological disorders, insulin resistance, beta-cell dysfunction, and adipogenesis are necessary for the selection of appropriate and successful therapeutic interventions, beyond simple glucose control (45).

Risk factors

Risk factors associated with T2D can be classified into two categories: modifiable and non-modifiable. The first category includes diets rich in saturated fats and simple carbohydrates, impaired glucose tolerance, metabolic syndrome, high BP ($\geq 140/90$ mm Hg), elevated plasma triglycerides (≥ 250 mg/dl), and low rates of physical activity (< 3 times a week); the second one consists of age (older than 45 years), family history of diabetes, ethnicity, and gestational diabetes (46). Genetic and environmental factors were also strongly implicated in the development of T2D (47). A multilingual, mobile-compatible Web-based tool has been established to estimate the 10-year risk of suffering from T2D by a Spanish team (48).

Complications

Diabetes significantly diminishes the quality of life, reduces life expectancy (49) and, more importantly, increases the risk of developing other life-threatening diseases and CV events (50). Epidemiological evidence indicates that T2D is an independent risk factor of premature mortality and morbidity, caused by its macrovascular complications (such as ischemic heart disease, stroke) and peripheral vascular diseases (like blindness, kidney and nerve disease and amputation) (20). The rate of CV death is approximately two times higher in diabetic as compared to non-diabetic subjects (51). CV death accounts for up to 80% of the excess mortality in patients with T2D; factors that underlie diabetic heart

diseases include multiple vessel CAD, long-standing hypertension, metabolic derangements such as hyperglycemia and dyslipidemia, microvascular disease, and autonomic neuropathy (52).

Screening & Prevention

An easily implementable first step to prevent diabetes should be to launch a primary prevention program comprising diabetes screening. By widely providing a simple questionnaire easily assessing available information such as family history, CV risk factors, age, and waist-to-hip circumference ratios, people at risk of developing T2D should be identified. Once identified, these individuals should undergo routine and inexpensive screening tests for diabetes such as measuring levels of plasma and urine glucose, fasting glucose levels and possibly undergo a glucose tolerance test, especially when T2D is strongly indicated (43). Importantly, T2D or its evolution can be prevented or impeded by implementing lifestyle changes. Modifications of lifestyle are highly recommended as they are cost-free, usually side effects free, and can be as (or even more) beneficial than some pharmacological approaches (53). Studies have figured out regular exercise as a beneficial strategy in the management of T2D (54).

Pharmacological treatments

To lower morbidity and mortality, improve the quality of life, and save costs for diabetic patients, the management of their risk factors and the use of multiple drugs were recommended (20,55). For instance, the use of ACE inhibitors and BBs to reduce BP and further reduce cardiac risk was emphasized (56). Remarkably, the ACE-inhibitor ramipril was associated with a highly significant CV risk reduction in the diabetic sub-group of the HOPE trial, irrespective of baseline BP level or hypertensive status (57). In summary, for patients with T2D, ACE inhibitors (or angiotensin II receptor blockers, ARBs, for those intolerant of ACE inhibitors) may slow progression to kidney failure and CV mortality and are preferred for managing coexisting diabetes and hypertension; thiazide diuretics at low dose minimize significant metabolic alterations clinically, may provide additional anti-hypertensive effects when combined with ACE inhibitors or ARBs; BBs help reduce CV events or symptoms and are useful in a multidrug regimen; dihydropyridine calcium channel blockers, CCBs, should be reserved for patients intolerant to preferred agents or those who need additional therapy to achieve target BP (58,59). A meta-analysis of our team suggested no effect of AHAs in preventing SCD in patients with hypertension (11).

A judicious utilization of statins and other LLAs, potentially acting in reducing low-density lipoprotein (LDL) and triglyceride levels and in elevating HDL levels (60), is also essential. Statins in particular were associated with lower rates of cardiac events in diabetic patients (56). If fibrates have for long been advocated in diabetes because of their specially intense effect on triglycerides, this reasoning was not confirmed in an indirect comparison with statins: ASPEN (61) and CARDS (62) with atorvastatin demonstrated indisputably better CV prevention than FIELD (63) with fenofibrate. Lastly, the ACCORD

trial did not show any significant benefit from the addition of fenofibrate to a statin treatment in diabetes (64). According to these results, statins remain the only class of LLAs to be used as first line drugs in T2D, even in patients without any abnormality of lipid profile (65). Two meta-analyses has shown that statins had a beneficial effect on reducing the risk of SCD, even lower compared with that of other fatal cardiac events; and the question whether statins significantly reduce the risk of ventricular tachyarrhythmia or not remained uncertain (66,67). Yet these studies not only concerned diabetes but also patients with MI, angina, CHD, primary prevention, vascular disease, hypertension, stroke and congestive/ischemic heart failure (HF). Of note, specifically in patients with HF, our group suggested that statins failed to reduce SCD, logically (68), whereas other drugs such as BBs (69) or aldosterone antagonists (70,71) substantially reduced this outcome.

In addition, the treatment of hyperglycemia has long been thought to reduce micro- and macrovascular complications in type 2 diabetic patients, based mainly on the UKPDS trial (19,72). However, most of anti-diabetic agents appear to have a neutral/non conclusive, even harmful effect on CV endpoints (73), except gliflozins (sodium-glucose co-transporter 2, SGLT2) from EMPAREG OUTCOME (74) and CANVAS (75) trials; and liraglutide (a glucagon-like peptide 1, GLP-1) from LEADER trial (76) which showed improved CV outcomes in high-risk patients. Anyway, the use of oral hypoglycemic agents should be considered seriously. An ongoing network meta-analysis evaluating effects of available ADAs, regarding vascular clinical outcomes, in patients with T2D (77) should bring more insight to better choose these drugs. It is notable that a meta-analysis of the trials assessing whether the intensification of T2D control was associated with changes in CV risk did not show significant benefit, except in reducing the risk of non-fatal MI (78) by 15% (RR of 85%).

In the prevention of CV diseases amongst diabetic patients, statins, ACE inhibitors, aspirin were proven to be efficient (19,79), yet their benefit on the SCD risk in T2D is not well documented and remains controversial.

Type 2 diabetes and sudden cardiac death

Attributable mechanisms

T2D was well reported as a risk factor for SCD (80) but, quite interestingly, not for fatal MI, in the Paris Prospective Study I (81). Potential factors contributing to the T2D-SCD relationship include silent myocardial ischemia, autonomic nervous system dysfunction, abnormal cardiac repolarization, hypoglycemia, a secondary hypercoagulable state linked to diabetes mellitus, diabetic cardiomyopathy, and impaired respiratory response to hypoxia and hypercapnia (80). T2D-related mortality, including SCD, may vary according to many other elements such as sex, age, ethnicity, family history, region development level, life style, concomitant diseases, *etc.* (82). Further investigation into

the pathophysiology of SCD in diabetes mellitus may help determine improved risk stratification tools and identify novel therapeutic targets (50).

Risk score of sudden cardiac death in type 2 diabetes

Currently, classical CV death predictors such as Framingham (83), SCORE (84) and DECODE (85) were noted as not reliable for T2D (86). In 2012, a 8-year risk score has recognized several demographic, socioeconomic, and biological risk factors of all-cause mortality in T2D: age, male sex, white race, lower income, smoking, insulin treatment, nephropathy, history of dyslipidemia, higher LDL cholesterol, angina, MI, other coronary diseases, coronary angioplasty bypass, congestive HF, aspirin, beta-blocker, diuretic use, and higher Charlson Index (87). However, no risk score predicting SCD in these subjects was established.

GENERAL METHODS

Building risk scores

Participants

Data was collected from 6 randomized controlled trials (RCTs) of INDANA (INdividual Data ANalysis of Antihypertensive intervention trials) database (88), including here Coope (89), EWPHE (90), MRFIT (91), SHEP (92), STOP (93) and SYSTEUR (94), and one RCT in diabetics DIABHYCAR (95). The total number of patients was 30 560, with age range of 35-98 years.

Potential risk factors & covariates

Different covariates were measured at the baseline of each individual. Some were continuous: age (years), systolic BP (SBP) (mm Hg), diastolic BP (DBP) (mm Hg), BMI (kg/m²), blood glucose (mmol/L), cholesterol level (mmol/L), creatinine (micromol/L), serum potassium (mmol/L) and HR (beats/minute). Other covariates were binary: sex, smoking status, presence of atrial fibrillation, history of HF, history of MI, history of stroke and baseline diabetes.

Statistical analysis

We divided the whole population into two sets: derivation (for model construction) and validation (for model validation) ones, with the ratio 2:1. *Time-to-event* Cox proportional hazards model was used to study the association of risk factors with SCD in univariate (each factor separately) and multivariate (several factors together) analyses, using "backward elimination" and/or "forward elimination", always adjusted by trial covariate and on the derivation set. We used the Martingale and Schoenfeld residual tests to examine the time linearity of continuous covariates and the proportional hypothesis in function of time, respectively. Interactions between trial covariate and others which could have biological links were also tested. Model performance was assessed through the area under the Received Operating Characteristics curve (AUROC). Final model was transformed to an integer system score to facilitate SCD risk estimating and clinical decision making.

Performing meta-analyses

Conception of the effect model

The effect model is a model by which the risk can be deduced from the experimental risk vs. the control group, to study the variation of the absolute benefit of a therapy. This allows individual prediction of the expected profit and thus a better definition of the therapeutic target population (96–98).

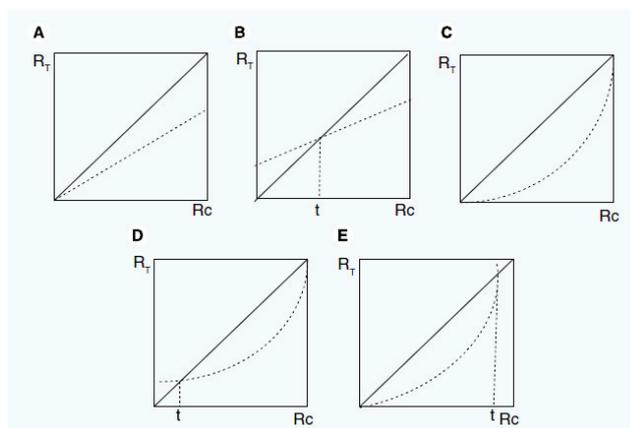


Figure 1. Possible effect models

The effect model is the relationship between R_T and R_C , it may be represented as $R_T = f(R_C, T, X)$. R_T and R_C are the frequencies of a defined event at time t , respectively under and without treatment. $R_T = R_C$ are represented by a bisector. Treatment is unfavorable if the curve is above and beneficial if the curve is below the line (extracted from (97)).

Data sources & trial selection

Clinical trials, systematic reviews and meta-analyses were searched through PubMed, ScienceDirect, Web of Science, Cochrane library database, clinicaltrials.gov, trialresultscenter.org, and Google Scholar, with no language restriction, until 30/06/2017, and considered eligible if related to the prevention of SCD in T2D by one of the four drug groups (AHA, ADA, LLA, APA). Key words used were: type 2 diabetes mellitus, sudden (cardiac) death, cardiovascular death, cardiovascular mortality, all-cause mortality, myocardial infarction, stroke, antiplatelet, platelet inhibitor, aspirin, clopidogrel, antihypertensive, blood pressure control, blood pressure lowering, statin, fibrate, lipolipidemic, anti hyperlipidemic, lipid lowering, cholesterol lowering, glucose control, glycemic control, anti-hyperglycemic, oral antidiabetic agent/drug. Furthermore, bibliographic lists of related reviews and meta-analyses were referred. We also wrote to authors of trials to obtain supplementary data of the diabetes subgroups if SCD outcome was available; or to obtain data on SCD outcome for trials recruiting 100% of patients with T2D. Eligibility criteria of included trials were i) RCT assessing the efficacy of therapies of interest versus control or placebo; ii) including patients with T2D; iii) reporting SCD outcome; iv) study duration longer than 12 months.

Data extraction & quality assessment

Data extraction and trial quality were assessed by two independent investigators (HL, MA/MF/AB/MG) using the Cochrane Score (99) and discussed to get consensus with a third party (FG) where difference occurred.

Statistical analysis

Relative risks (RR) at 95% confidence intervals (CIs) were calculated from the numbers of events/patients in each group, for every trial. Random effect model was preferred to be used than

fixed effect model to assess the effect of studied treatments versus standard treatment or placebo on the outcomes of interest (SCD). Statistical heterogeneity across trials was assessed with I^2 statistics. Statistical analyses were performed, not necessarily according to the intention-to-treat principle when possible. All p-values were two-sided ($p < 0.05$). The analyses were performed using the Revman software version 5. Recommendations "Preferred Reporting Items for Systematic Reviews and Meta-analysis (PRISMA)" were referred (100).

Simulation on the realistic virtual population

Notion of modeling and realistic virtual population

RVP is a population simulated from available knowledge (epidemiological and environmental data), to generate *in silico* a picture of the real population and its evolution with time. The virtual population can naturally become the support of explorations of different scenarios to use a drug or a therapeutic strategy, whether simple or complex, thus contributing to the evaluation of medicines and medical devices, from conception to prescription (marketing authorization, reimbursement, price setting and re-registrations) (101). Coupling effect models to virtual populations allows obtaining realistic results at the population level, testing diagnostic or therapeutic strategies, or estimating the consequences of transposing the results of clinical trials into real life and supporting public health decisions (101). This methodology has already been applied to estimate the public health impact (PHI) of different strategies in CV prevention (98,102,103).

The platform used to generate a realistic virtual population with mathematical algorithms has been developed in the environment of R software (with the package *tmvtnorm*-Truncated multivariate normal distribution) by Pr. Ivanny Marchant and applied for several publications (103,104).

Epidemiological data

To build the RVP, the individual characteristics required were the demographic information, the number of anti-diabetic drugs taken, the co-prescriptions of AHAs, statins and APAs, as well as other covariates used in the risk scores. Information used to generate the realistic virtual diabetic French population came from two epidemiological studies: ENTRED (105), the most current representative database for the French diabetic population, including type 1 and T2D; and the Longitudinal Patient Database (LPD) (106), a collection of prescriptions in T2D from a network of general practitioners. The combination of both data sources reinforced the ability of the final virtual population to appropriately represent the French population (107). LPD (106) was used to obtain the distribution of height, weight, HbA1c, smoking status, cholesterol total, LDL and HDL, serum creatinine and SBP, by age and gender groups, and by therapeutic sub-groups: without statin and AHAs, with statins only, with AHAs only, and with both. ENTRED (105) information used in this report concerns i. age distribution of the type 2

diabetic population, in men and women, which was used as a reference for validating the information from the LPD (106); and ii. relationship between age and duration of diabetes.

The size of the population (107) was based on: 1. The prevalence rate of diabetes treated in France, estimated at 3.8% in 2005, with an annual increase rate of 5.7% (105); 2. An estimate of the ratio type 2/type 1 diabetes from ENTRED study (105); 3. An estimate of the proportion represented by the ages 40 to 74 in the T2D population from ENTRED study (105); and 4. An estimate of the proportion of the T2D population treated by oral anti-diabetic drugs, from ECODIA2 (108).

General computation principles for public health impact estimation

Methods for predicting the public health impact using RVP include (107) (see Fig. 2 for illustration):

- Simulating a RVP reproducing the relevant characteristics of the population of interest, here a French type 2 diabetic population.
- Computing the risk of CV events of interest through validated published risk scores: here SCD using the HYSUD score (109).
- Computing the risk of the same CV events modified through treatment exposure via results of relevant meta-analyses and under the hypothesis that treatment effects found in these studies remain the same in the French population.
- The difference between the two predicted risks, with and without treatment of interest (through relative risk or odds ratio), represents the PHI, at the population level, expressed as NEP and NNT.

RESULTS

Building risk scores

A score to predict SCD risk in hypertensive +/- diabetic patients (HYSUD) was built, including seven risk factors: age, sex (male), total cholesterol level, systolic BP, smoking status, history of myocardial infarction and diabetes mellitus status. The AUROC obtained on an independent validation sample was of 0.77 (CI 95%, 0.74-0.81), indicating a fair performance. This work was published in the Journal of Hypertension (109) (see Published article 1).

Our multivariate analyses on the whole 30560 individual data have noticed an important interaction between diabetes and sex, suggesting comparable risks of SCD in diabetic women and men, i.e diabetes is a stronger risk factor for females than males. The work focusing on this diabetes-sex interaction on several outcomes such as SCD, total death, CV death, fatal myocardial infarction and stroke was accepted for an oral communication at the European Society of Hypertension Congress, Milan 2017 (Appendix 1) (110).

Performing meta-analyses

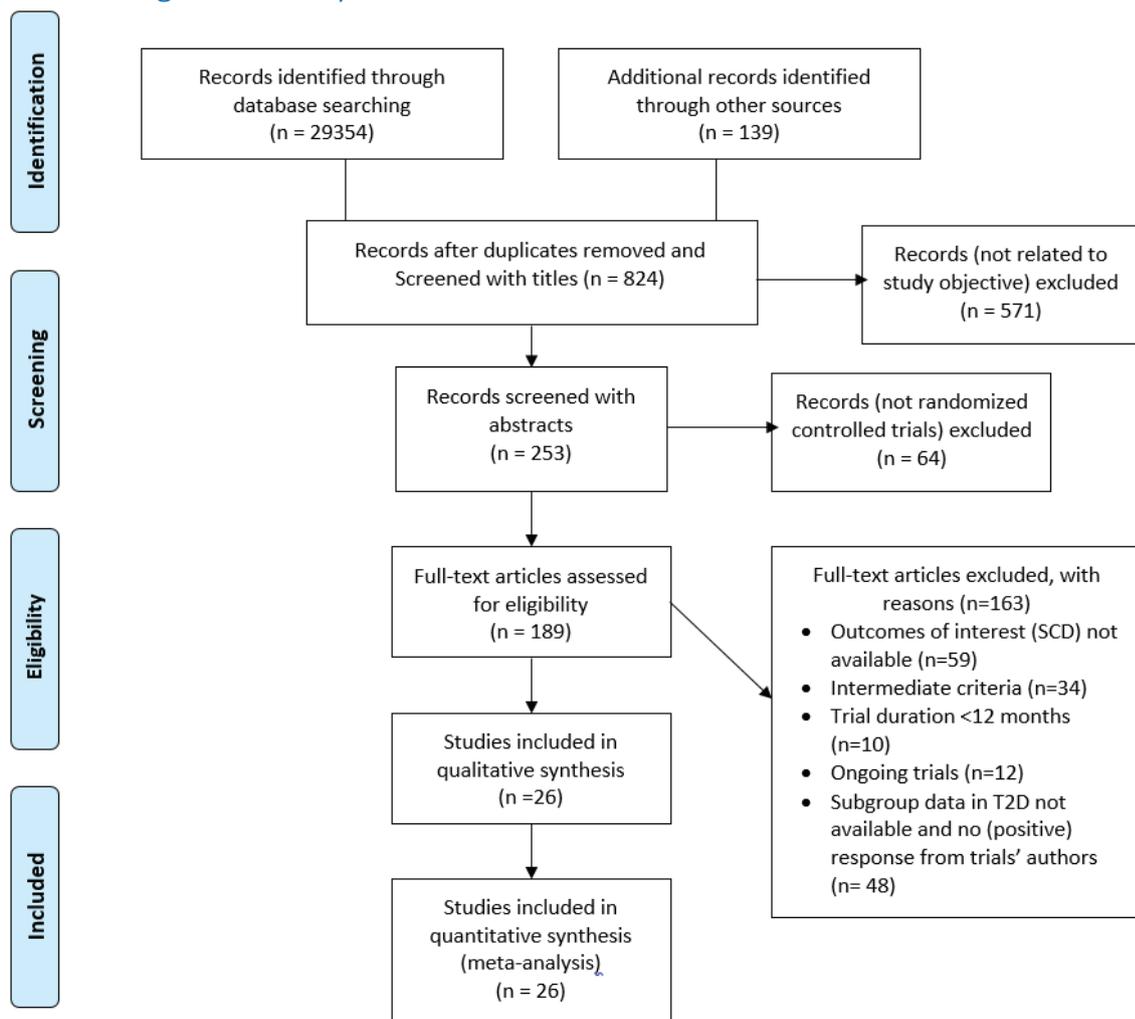


Figure 3. Search flow chart (search through 30/06/2017)

A conducted meta-analysis (until 01/01/2015) on four groups of drugs (AHA, APA, LLA, ADA) including 19 RCTs with 47 213 patients (in which SCD represented 49% of coronary deaths and 26% of major coronary events) did not allow any conclusion except the benefit of statins in reducing fatal myocardial infarction (RR=0.60; 0.39-0.94). This work was accepted for an oral communication at the French Society of Hypertension Congress, 2015 (Appendix 2) (111).

Our updated meta-analysis (until 30/06/2017), including 26 RCTs (baseline characteristics are in table 3/appendix 3) of relative high quality (Figure 7-8/Appendix 3) with 79 310 participants, gave the same conclusion (Table 1). Among these 26 RCTs, 14 were already included in the last meta-analysis. Forest plots are given with corresponding funnel plots, which could not exclude the possibility of publication bias (Figure 9-18/ Appendix 3).

In the same theme, another meta-analysis of our team, published in Plos One (Published article 2) (70), on SCD beneficial preventive effects of aldosterone antagonists was done, but for patients with heart failure and post-myocardial infarction.

Table 1. No significant evidence for sudden cardiac death pharmacologic prevention in type 2 diabetes: summary of all meta-analyses

	No of trials in the MA	No of patients (treatment /control)	Comparator	Effect on SCD	Effect model	I ² (%)
Empagliflozin	1 (EMPAREG-OUTCOME (74))	4687/2333	Placebo	RR 0.69 (0.46-1.05, p=0.08)	NA	NA
Aspirin	2 (ETDRS (112), JPAD (113))	3118/3132	Placebo	RR 0.72 (0.51-1.02, p=0.06)	Random	0
ACE Inhibitors	2 (HOPE (114), DIABHYCAR (95))	4251/4238	Placebo	RR 0.86 (0.54-1.24, p =0.41)	Random	52
Statins	4 (4D (115), ASPEN (61), CARDS (62), WOSCOPI (116))	3034/2991	Placebo	RR 0.96 (0.75-1.24, p =0.78)	Random	0
All anti-hypertensive agents	8 (ALTITUDE (117), DIABHYCAR (95), EWPHE (90), HOPE (114), MRFIT (91), ROADMAP (118), STOP-2 (119), SHEP (121))	11 107/10 901	Placebo/control	RR 1.00 (0.84-1.18, p =0.96)	Random	0
Intensive blood pressure control	3 (ADVANCE (120), SYSTEUR (94), UKPDS 38 (72))	6579/6201	Standard blood pressure control	RR 0.86 (0.57-1.29, p =0.46)	Random	0
Antihypertensive agents and Intensive blood pressure control	11 (ALTITUDE (117), DIABHYCAR (95), EWPHE (90), HOPE (114), MRFIT (91), ROADMAP (118), STOP-2 (119), ADVANCE (120), SHEP (121), SYSTEUR (94), UKPDS 38 (72))	17 686/17 102	Placebo/standard control	RR 0.97 (0.83-1.14, p =0.75)	Random	0
Intensive glycemetic control	8 (HOME (122), UGDP A (123), UGDP B (124), UKPDS 33 (72), UKPDS 34 (125), VADT (126), ACCORD (127), VA CSDM (128))	9696/8116	Standard glycemetic control	RR 1.14 (0.74-1.76, p =0.54)	Random	36
Intensive control	11 (HOME (122), UGDP A (123), UGDP B (124), UKPDS 33 (72), UKPDS 34 (125), VADT (126), ACCORD (127), VA CSDM (128), ADVANCE (120), SYSTEUR (94), UKPDS 38 (72))	16 275/14 317	Standard control	RR 1.05 (0.78-1.41, p =0.77)	Random	24
All treatments	26 RCTs	38 221/33 674	Placebo /control	RR 0.94 (0.83-1.07, p =0.35)	Random	15

Simulation on the realistic virtual population

Characteristics of the generated realistic virtual population

Based on the available database of French diabetic patients, a RVP of 175 968 subjects with HbA1c \geq 6.0% (aged 40-75) was generated from an 8 995-patient cohort. The size of the RVP and the characteristics regarding the main parameters were given, separately for men and women, by 10-year-age strata.

Table 2. Characteristics of individuals in the generated French realistic virtual population (A1c \geq 6.0%)

Characteristics	Women				Men			
	40-50	50-60	60-70	\geq 70	40-50	50-60	60-70	\geq 70
Age category (%)	(3)	(13)	(17)	(8)	(5)	(18)	(26)	(10)
Smoker (%)	10	8	6	3	14	16	13	8
Age (years)	46	55	64	72	46	55	64	72
Height (cm)	161	160	159	158	174	173	172	171
Weight (kg)	86	83	81	76	93	91	89	85
HbA1c (%)	7.7	7.3	7.2	7.2	7.5	7.3	7.2	7.1
TC (mmol/l)	1.9	1.9	1.9	1.9	1.9	1.9	1.8	1.8
LCL (mmol/l)	1.1	1.1	1.1	1.1	1.1	1.1	1.1	1.0
HDL (mmol/l)	0.5	0.5	0.5	0.5	0.4	0.5	0.5	0.5
Creatinin (mg/dl)	7.5	7.9	8.4	8.8	9.5	9.8	10.1	10.6
SBP (mmHg)	131	133	136	137	131	134	136	137
Duration (years)	9	8	11	15	7	8	11	14

TC: Total cholesterol

Predicted public health impact by empagliflozin/aspirin/ACE inhibitors

Where our meta-analyses could not conclude a certain effect of any treatment group (AHA, LLA, APA, ADA) on SCD risk in T2D, the three drugs ACE inhibitor, aspirin and empagliflozin seemed to be the most potentially beneficial, even their effects were not statistically significant.

The RVP was thus divided into 32 scenarios: 2 genders female/male * 4 treatment strategies (only aspirin, only ACE inhibitors, only empagliflozin and tri-therapy) * 4 groups of SCD risk thresholds (higher moiety, highest quartile, highest decile, and the whole population).

We used HYSUD model to estimate the baseline SCD risk R_0 . Individual risk under each treatment R_t ($R_t = R_0 * RR$) was generated using the random normal distribution function, in considering their mean relative risks and their confidence intervals extracted from the table 2. For each individual, the risk

under the tri-therapy would be: $R_T(\text{tri-therapy}) = R_T(\text{empagliflozin}) * R_T(\text{aspirin}) * R_T(\text{ACEIs})$. The confidence interval of the relative risk of the tri-therapy was estimated by the method of Altman (129).

Empagliflozin	RR 0.69 (0.46-1.05, p=0.08)
Aspirin	RR 0.72 (0.51-1.02, p=0.06)
ACEIs	RR 0.86 (0.54-1.24, p=0.41)
Tri-therapy	RR 0.43 (0.22-0.84, p=0.007)

Next, the impact on public health of each medication strategy was calculated through NEP and NNT in each sub-group. Our simulation indicated that the tri-therapy could prevent one SCD for each 135 treated individuals among the whole RVP and for 57 treated patients among the 10% with highest predicted risk (table 3).

Table 3. Predicted public health impact of exposure to empagliflozin/aspirin/ACE inhibitors or tri-therapy for preventing sudden cardiac death in a French realistic virtual population of type 2 diabetics

Treatment	Strata	50% higher risk		25% highest risk		10% highest risk			Total		
		F	M	F	M	F	M	Both sexes	F	M	Both sexes
No treatment	N.pat	32 527	55 457	15 496	28 496	4858	12 739	17 597	70 972	104 996	175 968
	Nc	598	1094	360	721	143	398	541	848	1433	2281
Empagliflozin	Nt	413	755	248	497	99	275	373	585	989	1574
	NEP	185	339	112	224	44	123	168	263	444	707
	NNT	175	164	139	127	110	103	105	270	236	249
Aspirin	Nt	431	788	259	519	103	287	390	611	1032	1642
	NEP	167	306	101	202	40	111	151	237	401	639
	NNT	194	181	154	141	121	114	116	299	262	276
ACE Inhibitors	Nt	514	941	310	620	123	342	465	729	1232	1962
	NEP	84	153	50	101	20	56	76	119	201	319
	NNT	389	362	307	282	243	229	232	598	523	551
Tri-therapy	Nt	255	467	154	308	61	170	231	362	612	975
	NEP	343	627	206	413	82	228	310	486	821	1306
	NNT	95	89	75	69	59	56	57	146	128	135

S1 = those with SCD risk \geq median; S2 = 25% of patients with highest SCD risk; S3 = 10% of patients with highest SCD; N= number of patients in (sub)-population; Nc = number of event (SCD) without treatment; Nt= number of event (SCD) with treatment; F= female; M= male; NEP: Number of SCD events prevented by treatment exposure; NNT: number needed to treat to prevent one SCD during the treatment exposure.

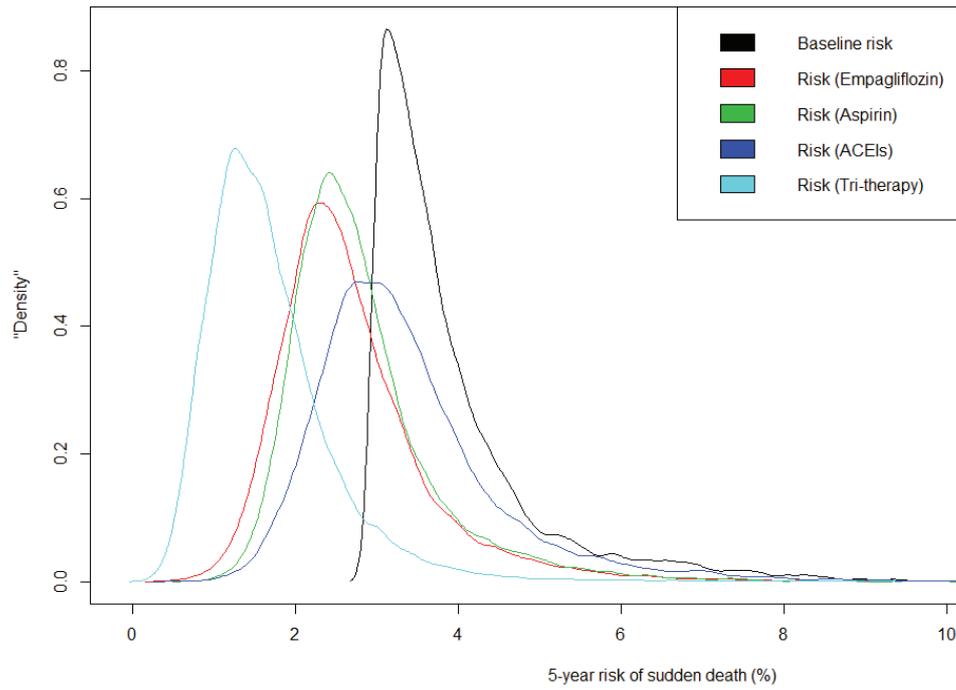


Figure 4. Reduction of 5-year sudden cardiac death risk by several monotherapies and combined therapies in 10% patients of highest predicted risk

Figure 4 illustrates the interest of decision making by the *in silico* simulation on how each monotherapy and the tri-therapy could shift the 5-year SCD risk in the 10% diabetic patients with highest predicted risk in the generated RVP. Similarly, figure 5 shows how each therapeutic strategy impacted on three individuals with different levels of predicted 5-year SCD risks.

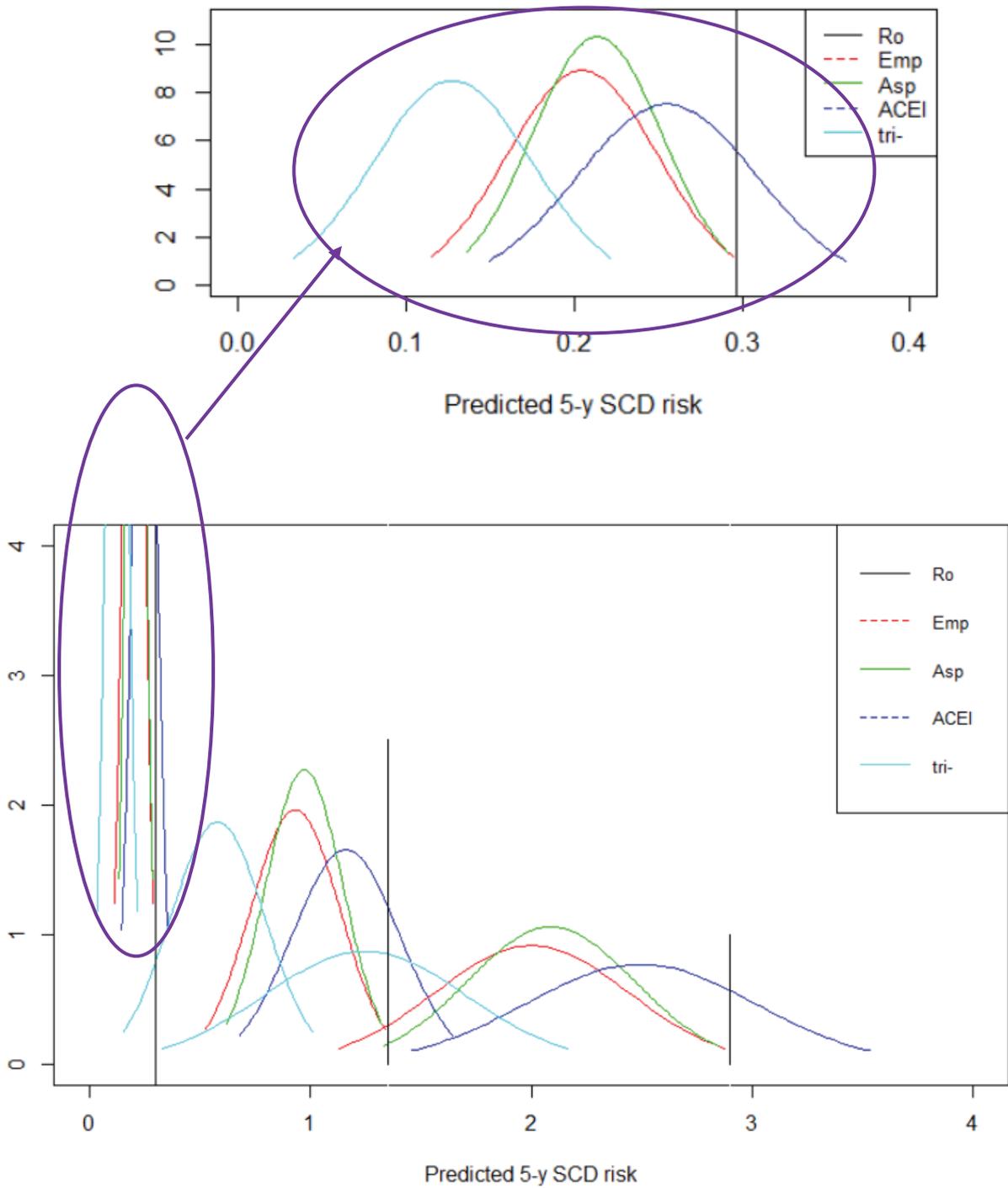


Figure 5. Effect of each monotherapy and of the tri-therapy on three virtual individuals of different 5-year sudden cardiac death risks (low, moderated and high, from the left to the right).

Ro: baseline SCD risk; Emp: SCD risk under empagliflozin; Asp: SCD risk under aspirin; ACEI: SCD risk under ACE Inhibitors; tri-: SCD risk under the tri-therapy. All the R_T (risks under treatment) include treatment effect uncertainty (confidence interval of relative risks).

DISCUSSION

Building risk scores

Significant covariates Our constructed risk score in multi-variate analysis identified that several risk factors of coronary diseases were also those of SCD: age, male sex, SBP (but not diastolic), smoking status and hyper serum cholesterol, diabetes and myocardial infarction history, in which age and sex are essential non-modifiable CV risks. However, in terms of smoking status, no information of quantitative or duration aspects were available.

Interaction No interaction between covariate ‘treatment’ with ‘SCD’ (also with ‘SBP’ or with any other significant covariates) was detected, meaning that the treatment (here mainly AHAs) had no effect in SCD prevention, in agreement with a previous meta-analysis (11). In addition, a sub-group analysis of the INDANA database (130) observed no heterogeneity in the results between diabetics and non-diabetics, suggesting that AHA effect were independent with other specific treatments taken by participants. The risk score hence could be applied for both treated and non-treated hypertensive/diabetic subjects. In parallel, interaction between diabetes and sex was noticed, suggesting comparable risks of SCD in diabetic women and men, which has been approved by previous studies (131). Concerning the CV risk due to gender, it is notable that many investigations have observed greater risks of CVD and CHD mortality associated with T2D in women (132–134).

Research implications An exploration of individual data seems to be necessary to evaluate whether patients at high risk of SCD have the same therapeutic benefits as patients with lower CV risk. External validation in other trial individual data is required to assess the value of this risk score; since even classical scores such as Framingham (83), SCORE (84) and DECODE (85) have presented uncertain results in some diabetic populations (86).

General limitations Risk scores allow predicting the risk of an accident as a function of individual characteristics; in our study, the risk of SCD. Risk score building is based on inter-individual relationships, typically from epidemiological cohorts. In therapeutic, it is common to consider that all the risk reductions obtained with a drug which lowers a risk factor is entirely and solely due to this lowering. This consideration confounds the epidemiological relationship between risk factors and risk, and its therapeutic counterpart. Confounding both relationships is common, but wrong, as illustrated by the differences of both relationships with blood pressure level (figure 6). This confusion would lead using risk score directly to infer the risk under treatment from the score computation updated with the value of the risk factor (BP for AHAs, total and HDL cholesterol for statins *etc.*). We carefully avoided such a mistake, considering risk score use only before treatment in our simulations: The risk level under treatment was systematically obtained from pre-treatment risk level multiplied by the relative risk attributable to treatment estimated from meta-analyses. The solution we proposed for

taking into account the treatment effect uncertainty was inspired from the Bayesian approach: we interpreted the confidence interval of relative risk as the credibility interval, knowing that Bayesian and classical frequentist approaches give similar results when prior is null.

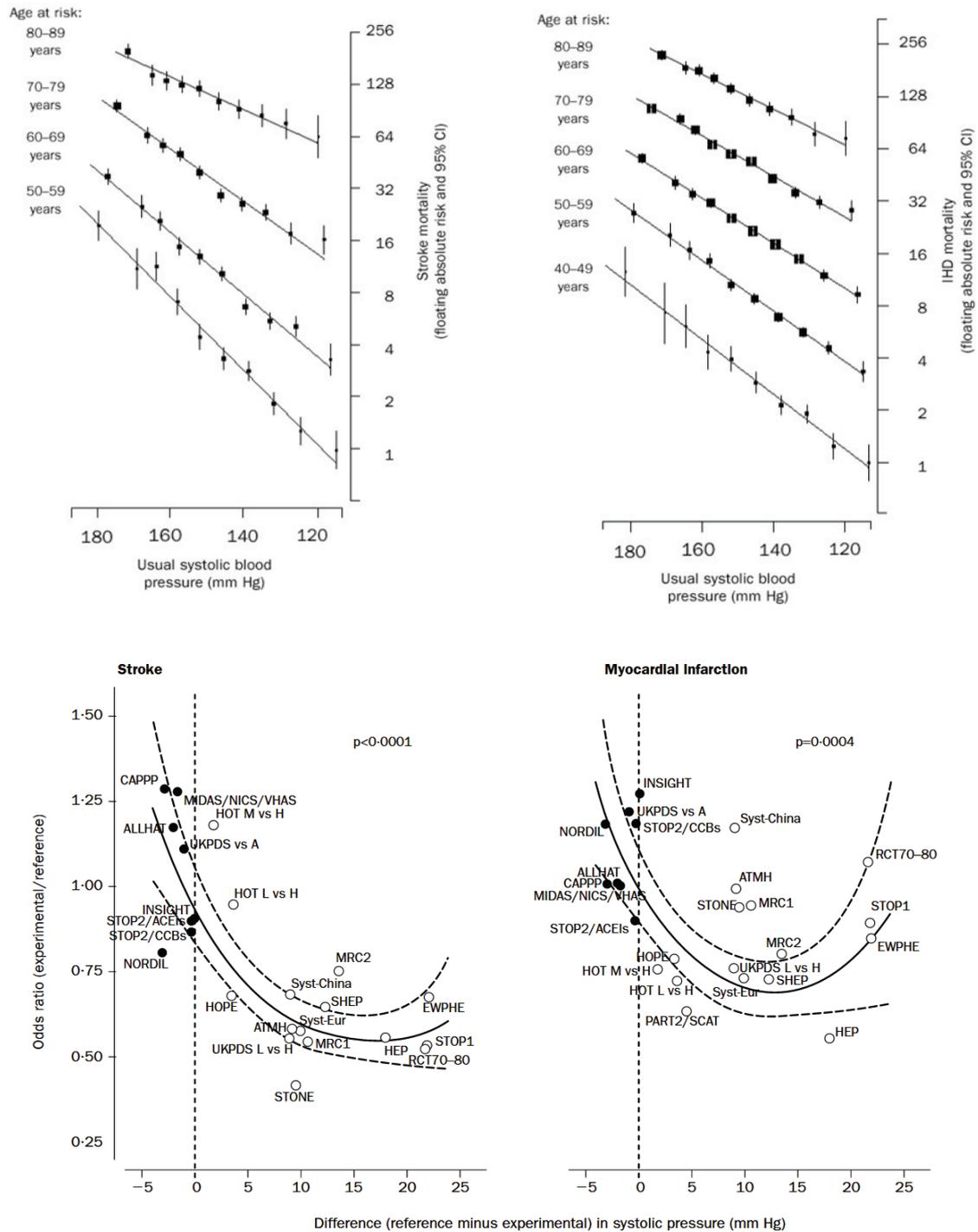


Figure 6. Illustration of the confusion between the epidemiological relationship between risk factors and risk, and its therapeutic counterpart. The upper figure (extracted from (135)) observed epidemiological associations between increased systolic blood pressure (SBP) and elevated risks of stroke mortality and ischemic heart disease mortality in all age groups; while the lower figure (extracted from (136)) showed that lowering SBP, at an extent, could increase the risks of stroke and myocardial infarction, on the contrary.

At the beginning, the objective of this work is to build a specific score evaluating SCD risk in patients with T2D. We finally applied HYSUD risk score, which was constructed in hypertensive patients with or without T2D, to carry out the simulation study on our diabetic RVP, due to two arguments. First, we have tried to extract only diabetic participants from the INDANA database and DIABHYCAR trial: on the obtained sample of 6600 individual data, multivariate analysis only detected two significant factors, which were age and renal function (glomerular filtration rate). Thus, application of such score for simulating drug effect on the PVR would be limited. Second, in the seven-risk-factor-HYSUD score, interactions between diabetes baseline or glucose level and SBP were not found, suggesting an eligible use of HYSUD in those with T2D, regardless of their blood pressure profile.

Performing meta-analyses

The benefits of the four drug groups (ADA, AHA, LLA, APA) were assessed through the available literature: no specific/conclusive data was found for diabetic patients.

- For AHAs (ACE inhibitors, BBs, aldosterone antagonists, CCBs *etc.*), no effect for SCD prevention in patients with T2D was found: relative risk RR 1.00 (0.84-1.18, $p=0.96$). Our specific meta-analysis on the effect of ACE inhibitors, pooling results of two trials (HOPE (114), DIABHYCAR (95)) did not find out a significant reduction of the SCD risk: RR 0.86 (0.54-1.24, $p=0.41$).
- For LLAs, our meta-analysis gathering four trials (4D (115), ASPEN (61), CARDS (62), WOSCOP (116)) suggested no beneficial effect of statins in preventing SCD in T2D: RR 0.96 (0.75-1.24).
- For APAs, only two trials reported the effect of aspirin in preventing SCD in T2D: ETDRS (112) and JPAD (113). Their pooled results suggested a probable favorable effect, but not significant: RR = 0.72 (0.51-1.02, $p = 0.06$, $I^2 = 0\%$), and not conclusive, which may be due to the different characteristics/reaction of the studied populations towards aspirin (one trial conducted in Europe and the other in Japan).
- Intensive blood pressure control from three trials (ADVANCE (120), SYSTEUR (94), UKPDS 38 (72)) did not reduce the risk of SCD significantly: RR 0.86 (0.57-1.29, $p=0.46$). Combining this with AHAs gave RR 0.97 (0.83-1.14, $p=0.75$).
- Our meta-analysis of eight trials (HOME (122), UGDP A (123), UGDP B (124), UKPDS 33 (72), UKPDS 34 (125), VADT (126), ACCORD (127), VA CSDM (128)), comparing intensive to standard glycemic controls, detected no significant effect on SCD as well: RR 1.14 (0.74-1.76, $p=0.54$).
- In general, intensive (blood pressure and/or glucose) control seemed to bring no benefit to prevent SCD in T2D: RR 1.05 (0.78-1.41, $p=0.77$).
- Until now, empagliflozin seemed to be the only ADA which could reduce the risk of SCD by 31% in T2D, but not significantly: RR = 0.69 (0.46-1.05, $p=0.08$, data from supplementary appendix of EMPAREG-OUTCOME trial (74)).

- Pooled effect of all treatments (26 trials of 79 310 participants) gave a poor result: RR 0.94 (0.83-1.07, $p=0.35$).

Our search called for more evidence on drug effect in preventing SCD in these subjects: this event should be considered as a separated outcome, as well, an open data sharing system of clinical trials is needed. On the other hand, while the effect of these therapies was not well elucidated on SCD in T2D, their use in these patients should be continued to prevent other CV events, such as MI, stroke, total/CV mortality, where scientific evidence has been firmly established.

Simulation on realistic virtual population

Result summary Using the HYSUD predictor on a French diabetic RVP of 175 968 subjects (generated from an 8 995-patient sample), we estimated a median 5-year SCD risk of 1.1%. Taking 31%, 28% and 14% of risk reductions by empagliflozin, aspirin and ACEI respectively, and supposing that no interaction existing between these drugs, the relative risk of the tri-therapy was $RR = 0.69 * 0.72 * 0.86 = 0.43$. A simulation of the public health impact on this platform estimated the number needed to treat (NNT) at 135 people for the whole population and at 57 among individuals of the 10% highest predicted SCD risk, if treated simultaneously by this tri-therapy for five years.

Strength The combination of ENTRED and LPD sources reinforced the ability that the RVP may appropriately represent the French diabetic population.

Computing the benefit from treatment exposure at individual level on a RVP gives realistic estimates of the treatment benefit, which could be significantly different from those obtained on summarized patient profiles. Further integration of results from subgroup meta-analyses (on treatment effect in function of age, sex, renal function) could give a more precise estimation.

In our simulation, we took into account not only the mean effect of each treatment but also their confidence intervals, i.e the possible effect variation in different individuals. Interestingly, the combination of credibility intervals (corresponding to non-significant confidence intervals of the three mono therapies) resulted in a credibility interval of the tri-therapy that corresponds to a highly significant confidence interval. This may raise the question of the relevance of the “p-value rule” in evaluating treatment effect.

Concomitant therapies We took the assumption that there was no interaction between the three drugs used in the simulation, which was validated by our previous study (137). In addition, the hypothesis that the risk reductions attributable to the decrease of glycemia and to that of BP are independent is still scientifically reasonable, from the analysis of RCTs. For example, in the HOPE and MICRO HOPE trials (57), the general relative risk reduction observed for MI and stroke were close for

the sub-group of diabetic participants, suggesting that beneficial effects of ramipril were independent from other treatments taken by these participants.

Treatment effect Treatment effects applied to the RVP were assumed to be sustained all over the simulation period: no treatment effect modifier was taken into account in the simulations, since none was known with sufficient reliability.

Poly-pill strategy The benefit of the combined therapy in our simulation is in agreement with the Steno-2 trial, which found the gain of an intensified multifactorial intervention (tight glucose regulation and the use of renin–angiotensin system blockers, aspirin, and LLAs) in preventing death from CV causes (hazard ratio, 0.43; 95% CI, 0.19 to 0.94; P=0.04) and CV events (hazard ratio, 0.41; 95% CI, 0.25 to 0.67; p<0.001) (138). The multifactorial management poly-pill approach for populations with frequent comorbidities such as T2D was recommended (139), which may improve adherence, cost-effectiveness balance and CV outcomes.

Cost-effectiveness analysis Estimating costs was not the objective of this present work. However, the availability of the number of events prevented by treatment (NEP), together with the number of patients-years of treatment in each scenario, could serve as an appropriate basis to initiate a cost effectiveness analysis, e.g. in integrating other direct costs such as laboratory measurements or prescribers consultations. In the future, rational economic evaluation of therapeutic interventions should be done by further manipulations on the platform to improve the professional practice.

Public health tool RVP was proposed as a gold standard to evaluate the impact of public health policies at the national level (103). This tool may help recognizing the gap between evidence and practice in managing CV risk factors (140), by comparing the effect obtained in reality and in theory for example; and providing a tool to predict optimal therapeutic strategies, in the prevention of SCD and other CV events.

CONCLUSION & PERSPECTIVES

SCD remains a major cause of CV death and the evaluation of treatment effect on this CV accident is seemingly inaccessible. We have developed and validated a reasonably good SCD risk prediction model through a large hypertensive/diabetic population from six high-quality RCTs. This risk score shows that age, male gender, smoking status, SBP, high cholesterol, baseline of diabetes and history of MI, which are the classical factors of coronary risks, are as well those of SCD. We found an important interaction between diabetes and sex, resulting in comparable risks of SCD, regardless of gender, i.e diabetes was a stronger risk factor in women than in men.

The findings from our meta-analysis raise a suspicion that current pharmacological therapies may not be efficient in preventing SCD in T2D. Developing a data open access system is necessary to elucidate the link between treatment effect and, not only SCD risk, but also other clinical endpoints (intermediate criteria, other sub-outcome of composite endpoints, *etc.*).

The present simulation on the generated French diabetic RVP have used the best available evidence, applied at the individual level with aspirin, empagliflozin and ACE inhibitors treatment effects.

In summary, our work underlines a legitimate need for advanced medical evidence on SCD prevention by pharmacological therapies in T2D. We called for the attention of the scientific community and public authorities to better deal with SCD, a major public health issue, with better treatment evidence.

In perspective, we proposed a clinical modeling tool, which could help better transposing clinical trial results into practice, facilitating clinical decision at both public health and individual levels, on both medical and economic aspects.

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APPENDICES

Appendix 1. Gender and diabetes interaction

Does diabetes really harm more women than men? Observations from 30560 patient individual data.

Oral communication, ESH Milan 2017

HH Le, F Subtil, M Cérou, L Thijs, F Gueyffier.

INTRODUCTION

Men are more likely than women to develop type 2 diabetes. However, women with diabetes are at higher risk of morbidity and mortality from diabetes complications.

OBJECTIVE

We aimed to explore here the interaction between gender and type 2 diabetes in terms of common cardiovascular outcomes from 30 560 individual patient data.

DESIGN AND METHOD

We used the proportional hazards regression Cox model to examine this interaction separately and in combination with other significant risk factors. Data was collected from seven randomized controlled trials including Coope, EWPHE, MRFIT, SHEP, STOP, SYSTEUR (INDANA database) and DIABHYCAR. Included patients were hypertensive, with or without type 2 diabetes and some cardiovascular histories, age range 35-98. Maximum duration of follow-up was 11.87 years (mean 4.97 years). Cardiovascular outcomes of interest were sudden death, total death, cardiovascular death, fatal myocardial infarction and stroke.

RESULTS

For all the outcomes, diabetes and male sex were independent risk factors. However, the interaction gender*diabetes seemed to make risks of sudden death, cardiovascular death, fatal myocardial infarction and stroke (adjusted in multi-analyses) similar in men and women. Differently speaking, diabetes was a stronger risk factor for women than for men (table 1).

CONCLUSIONS

In our database, the interaction between gender and type 2 diabetes was significant in terms of sudden death, total death, cardiovascular death, fatal myocardial infarction and stroke risks, with adjustment on treatments, trials, age, smoking status, systolic blood pressure, total cholesterol and history of myocardial infarction. Our observations were in accordance with the literature: for non-diabetic subjects, men represented 1.5 to 2.3 times higher risk for these studied endpoints; however, for diabetic ones, women seemed to be more affected.

Table 1. Risk of cardiovascular outcomes using adjusted models, vs. non-diabetic women (HR = 1)

	Sudden death		Total death		Cardiovascular death		Fatal myocardial infarction		Stroke	
	HR	p-value								
Non diabetic men	2.35 (1.69-3.25)	<0.001	1.60 (1.40-1.82)	<0.001	1.64 (1.37-1.97)	<0.001	2.59 (1.98-3.39)	<0.001	1.17 (0.96-1.43)	0.12
Diabetic men	2.97 (1.83-4.80)	0.003	2.08 (1.69-2.58)	<0.001	2.68 (2.02-3.57)	<0.001	3.10 (1.90-5.06)	<0.001	1.94 (1.44-2.61)	<0.001
Diabetic women	2.87 (1.78-4.61)	<0.001	1.88 (1.54-2.28)	<0.001	2.10 (1.61-2.74)	<0.001	2.80 (1.75-4.47)	<0.001	2.13 (1.62-2.79)	<0.001

HR: hazard ratio (95% confidence interval); Analyses adjusted by treatments, trials, age, smoking status, systolic blood pressure, total cholesterol and history of myocardial infarction. Analyses were performed on 30 560 individual patient data

CO-32: Could antihypertensive, hypoglycemic, hypolipidemic drugs and platelet aggregation inhibitors reduce sudden death risk in type 2 diabetes? A meta-analysis of randomized controlled trials.

Ann Cardiol Angeiol; 10.1016/S0003-3928(16)30032-4.

A Berrima, M Girard, **HH Le**, S Erpeldinger, **F Gueyffier**.

Oral communication SFHTA 2015

Background

Type 2 diabetes (T2D) is associated with an increased risk of sudden cardiac death (SCD). However, the role of cardiovascular preventive drugs on SCD is not well addressed in this population. In this work, we aimed to assess the effectiveness of antihypertensive agents, hypolipidemic agents, hypoglycemic agents and platelet aggregation inhibitors in preventing SCD in patients with T2D, without prior cardiovascular disease.

Methods

We researched articles from the following databases: Medline, Web of Science and Cochrane Library. We included randomized controlled trials, with at least 12-month follow-up and performed in T2D. Unpublished data were demanded to trials' investigators. Primary endpoint was SCD; secondary endpoints were fatal and non-fatal myocardial infarction.

Results

Nineteen trials (47 213 participants) were included in the main analyses. SCD represented 49% of deaths from coronary heart disease and 26% of major coronary events. Not any therapeutic class showed statistically significant difference on SCD risk in T2D against placebo or usual treatment. For fatal myocardial infarction, statins showed a benefit (RR=0.60; [CI 0.39 - 0.94]) versus placebo and intensive antihypertensive treatments versus conventional ones (RR=0.66; [CI 0.46 - 0.94]).

Conclusion

There is no evidence for any significant preventive effect of the four major cardiovascular therapeutic classes on SCD risk in patients with T2D. A specific reflection on this major coronary event is necessary to better understand and prevent it.

Appendix 3. Treatment effect on sudden cardiac death in type 2 diabetes (updated 2017 meta-analysis)

HH Le, A Berrima, M Girard, S Erpeldinger, F Gueyffier. Pharmacological prevention of sudden cardiac death in type 2 diabetes: lack of data. A systematic review and meta-analyses from 26 RCTs. Oral communication SFHTA 2017

Table 4. Characteristics of 26 included trials in the meta-analysis (search until 30/06/2017)

Author, year, trial name	Number of participants	Comparison	Design	Primary outcome	Mean duration of follow up (years)	Mean age (years)
Patel 2007, ADVANCE (120)	11 140 (5569 / 5571)	Perindopril (42 mg) and indapamide (1.25 mg) vs. placebo	DB	CV morbi-mortality	4.3	66
Group 2008, ACCORD (127)	10 251 (5128/5123)	Intensive vs. standard glycaemic control	Open	CV morbi-mortality	3.5	62
Investigators, 2000 HOPE (114)	9297 (4645 / 4652)	Ramipril 10 mg vs. placebo	DB	CV morbi-mortality	3.5	66
Parving 2012, ALTITUDE (117)	8606 (4274 / 4287)	Aliskiren (150mg ou 300mg/d) vs. placebo	DB	CV morbi-mortality	2.8	64
Zinman 2015, EMPAREG-OUTCOME (74)	7020 (4687/2333)	Empagliflozin 10/25mg vs. placebo	DB	CV morbi-mortality	2.6	63
Marre 2004, DIABHYCAR (95)	4912(2443/2469)	Ramipril 1.25mg vs. placebo	DB	CV morbi-mortality	3.9	65
Haller 2011, ROADMAP (118)	4447 (2232/ 2215)	Olmesartan at 40 mg vs. placebo	DB	CV morbi-mortality	3.2	58
UKPDS 33, 1998 (72)	3867 (2729 / 1138)	Sulphonylurea (chlorpropamide, glibenclamide, or glipizide) or with insulin vs. conventional policy	Open	CV morbi-mortality	10.7	54
Kassoff 1992, ETDRS 14 (112)	3711 (1856/1855)	Aspirin 325mg vs. placebo	DB	CV morbi-mortality	5.0	18-70
Colhoun 2004, CARDS (62)	2838 (1428/1410)	Atorvastatin 10mg vs. placebo	DB	CV morbi-mortality	3.9	62
Saito 2016, JPAD (113)	2539 (1262/1277)	Aspirin 81-100mg vs. placebo	Open	CV morbi-mortality	4.4	65
Knopp 2006, ASPEN (61)	2410 (1211/1199)	Atorvastatin 10mg vs. placebo	DB	CV morbi-mortality	4.0	61
Duckworth 2009, VADT (126)	1791 (892/899)	Intensive vs. standard glycaemic control	Open	CV morbi-mortality	5.6	60
Wanner 2004, 4D (115)	1255 (619/636)	Atorvastatin 20mg vs. placebo	DB	CV morbi-mortality	4.0	54
UKPDS 38, 1998 (72)	1148 (758/390)	Intensive (captopril or atenolol) +/- (furosemide, nifedipine, methylodopa, prazosine) vs. standard blood pressure control	Open	CV morbi-mortality	8.4	56
UKPDS 34 (125)	537 (268/269)	Metformin + sulphonylurea vs. sulphonylurea alone	Open	CV morbi-mortality	10.7	59
STOP-2 1999 (119). Diabetes subgroup	719 (466/253)	Enalapril 10 mg or lisinopril 10 mg daily vs. conventional treatment	Open	CV morbi-mortality	2.0	76
1999, SYSTEUR (94)	492 (252 / 240)	Nitrendipine 10 - 40 mg +/- enalapril 5-20 mg or hydrochlorothiazide 12.5- 25 mg vs. placebo	DB	CV morbi-mortality	2.0	70

SHEP 1996 (121) Diabetes subgroup	478 (237/241)	Low dose of chlorthalidone 12.5-25.0 mg with a step-up to atenolol 25.0-50.0 mg or reserpine 0.05-0.10 mg if needed vs. placebo	DB	CV morbi-mortality	5.0	70
1982, UGDP B (124)	414 (204/210)	Intensive insulin vs. standard insulin	Open	CV morbi-mortality	12.5	52
UGDP A 1976 (123)	409 (204/205)	Tolbutamide vs. placebo	Open	CV morbi-mortality	12.5	52
Kooy 2009, HOME (122)	390 (171/182)	Metformin vs. placebo (Insulin at baseline)	DB	CV morbi-mortality	4.3	61
MRFIT 1982 (91) Diabetes subgroup	346 (174/172)	Special intervention program consisting of stepped-care treatment for hypertension, counseling for cigarette smoking, and dietary advice for lowering blood cholesterol levels vs. no intervention	Open	CV morbi-mortality	6.0	46
Abraira 1995, VA CSDM (128)	153 (75/78)	Intensive glycemic control vs. Insulin standard	Open	CV morbi-mortality	2.3	60
Amery, 1985 EWPHE Diabetics subgroup (90)	72 (37/35)	Hydrochlorothiazide + triamterene vs. placebo	DB	CV morbi-mortality	4.3	72
Shepherd 1985, WOSCOP (116) Diabetics subgroup	68 (39/29)	Pravastatin 40mg vs. placebo	DB	CV morbi-mortality	4.9	54
Total T2D patients	79 310					

CV: Cardiovascular; DB: Double Blind

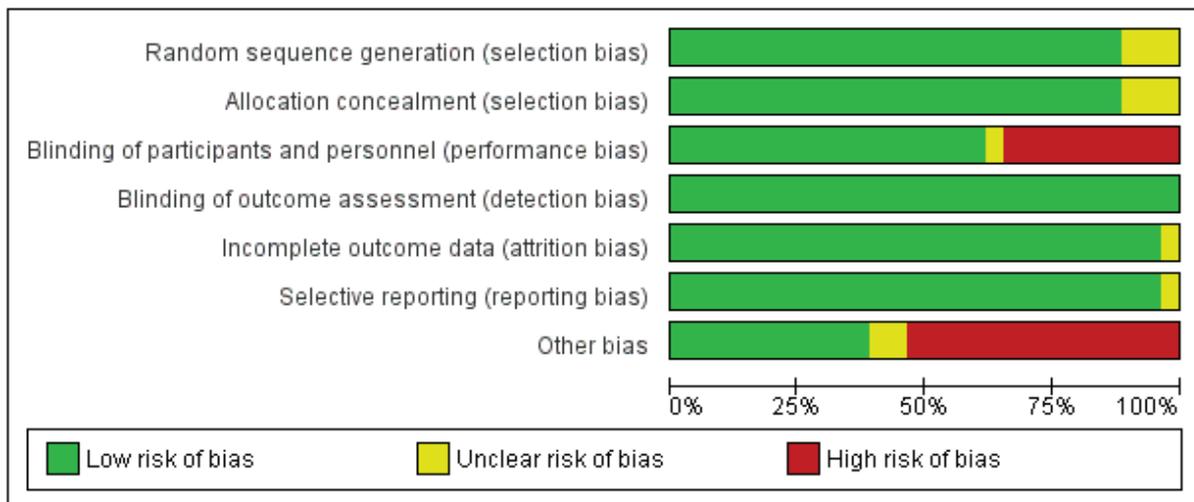


Figure 7. Risk of bias graph. Review authors' judgements about each risk of bias item presented as percentages across all 26 included RCTs.

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
4D 2005	+	+	+	+	+	+	?
ACCORD 2008	+	+	-	+	+	+	+
ADVANCE 2008	+	+	+	+	+	+	+
ALTITUDE 2012	?	?	+	+	+	+	+
ASPEN 2006	?	?	+	+	+	+	?
CARDS 2004	+	+	+	+	+	+	+
DIABHYCAR 2004	+	+	+	+	+	+	-
EMPAREG 2015	+	+	+	+	+	+	-
ETDRS 1992	+	?	+	+	+	+	+
EWPHE 1985	?	+	+	+	+	+	+
HOME 2009	+	+	+	+	?	+	-
HOPE 2004	+	+	+	+	+	+	-
JPAD 2016	+	+	-	+	+	+	+
MRFIT 1982	+	+	-	+	+	+	-
ROADMAP 2011	+	+	+	+	+	+	+
SHEP 1996	+	+	+	+	+	+	+
STOP-2 1999	+	+	+	+	+	+	+
SYSTEUR 1999	+	+	+	+	+	+	-
UGBP A 1976	+	+	?	+	+	?	-
UGBP B 1982	+	+	-	+	+	+	-
UKPDS 33 1998	+	+	-	+	+	+	-
UKPDS 34 1998	+	+	-	+	+	+	-
UKPDS38, 1998	+	+	-	+	+	+	-
VA CSDM 1995	+	+	-	+	+	+	-
VADT 2009	+	+	-	+	+	+	-
WOSCOP 1985	+	+	+	+	+	+	-

Figure 8. Risk of bias summary. Review authors' judgements about each risk of bias item for each included study

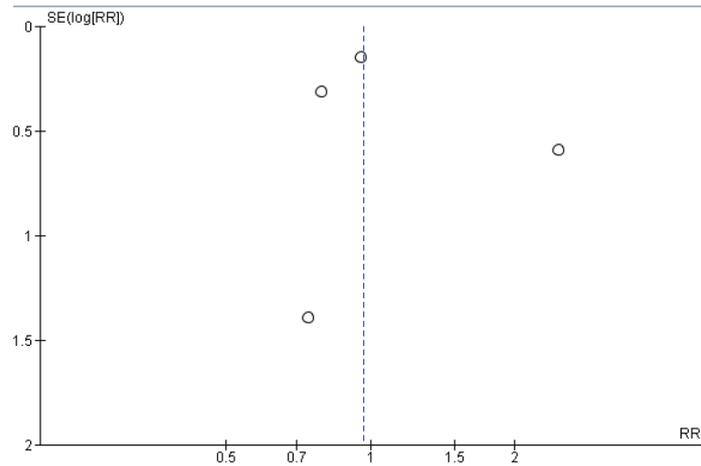
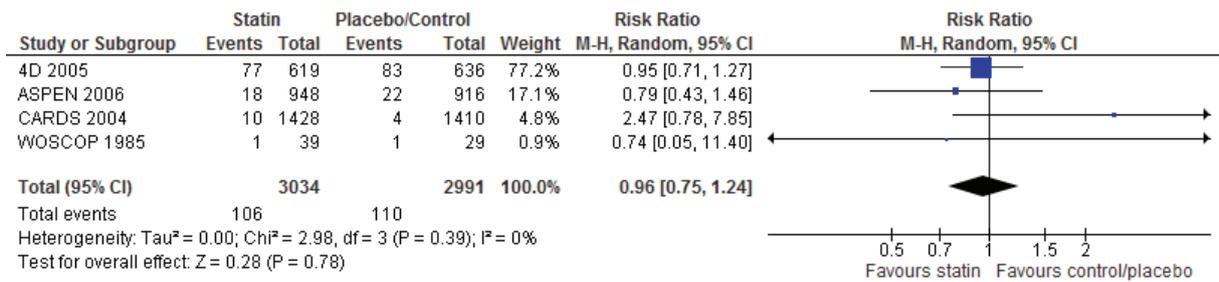


Figure 9. Effect of statins on sudden cardiac death prevention in type 2 diabetes (Forest plot for treatment effect & funnel plot for publication bias, *idem* for figure 11-18)

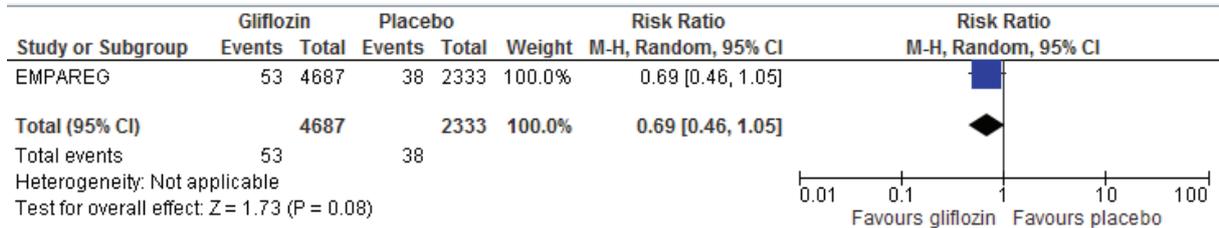


Figure 10. Effect of empagliflozin on sudden cardiac death prevention in type 2 diabetes

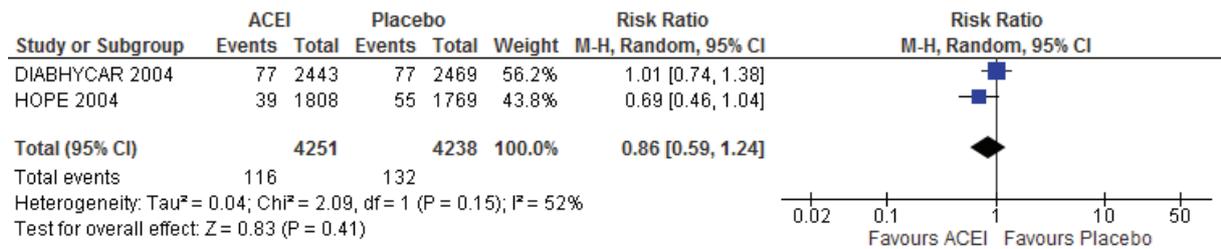


Figure 11. Effect of ACE inhibitors on sudden cardiac death prevention in type 2 diabetes

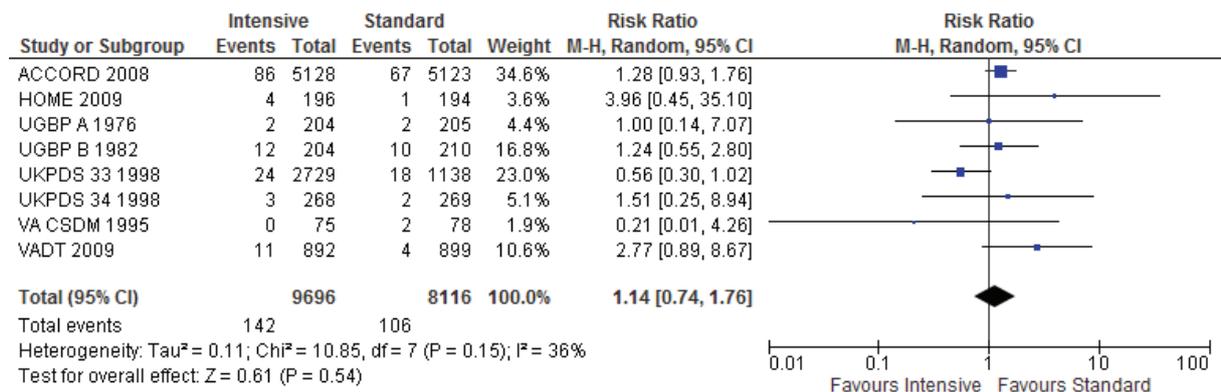


Figure 12. Effect of intensive glycemic control on sudden cardiac death prevention in type 2 diabetes

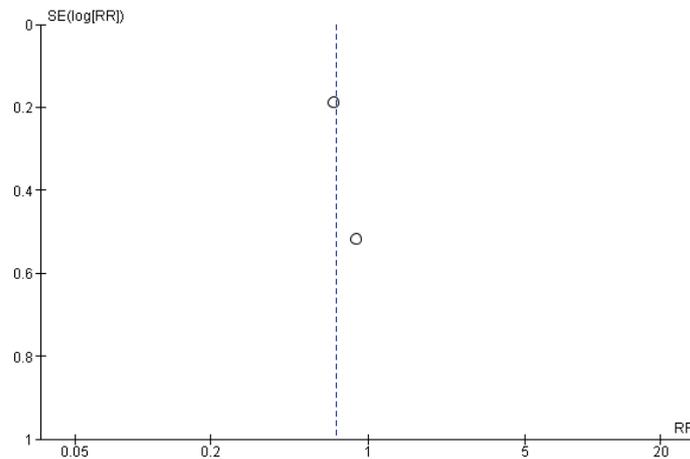
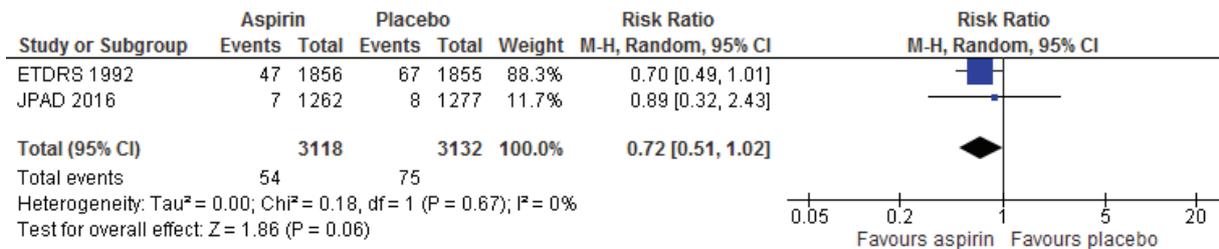


Figure 13. Effect of aspirin on sudden cardiac death prevention in type 2 diabetes

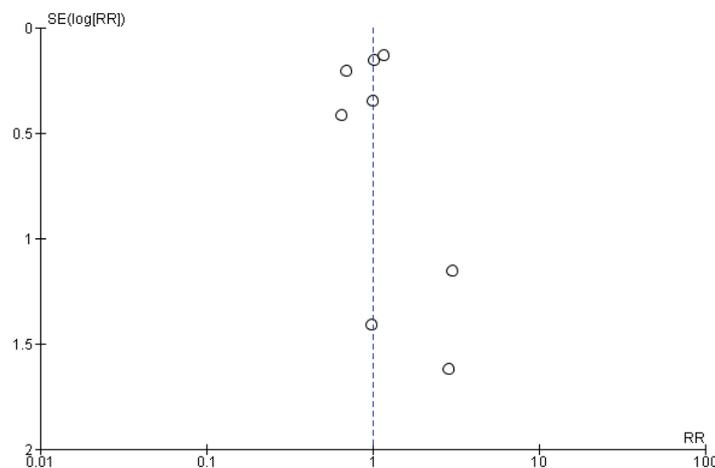
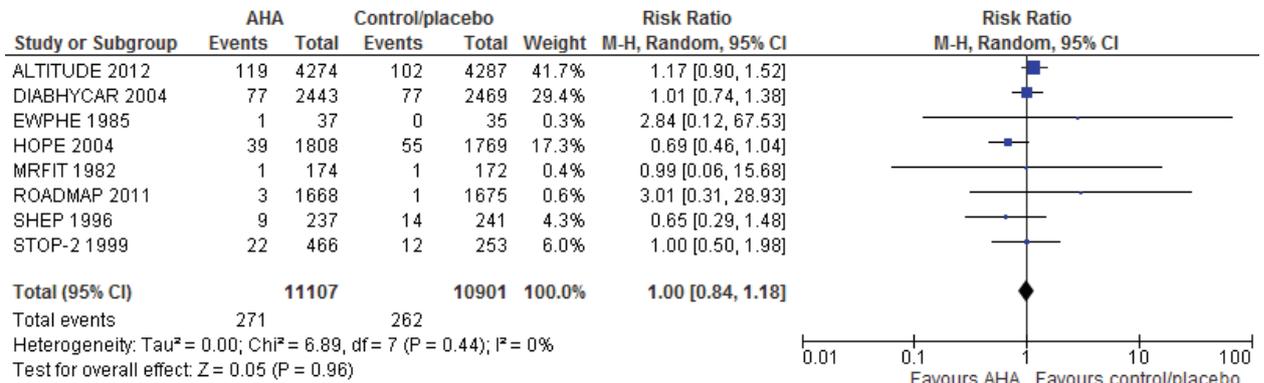


Figure 14. Effect of antihypertensive agents on sudden cardiac death prevention in type 2 diabetes

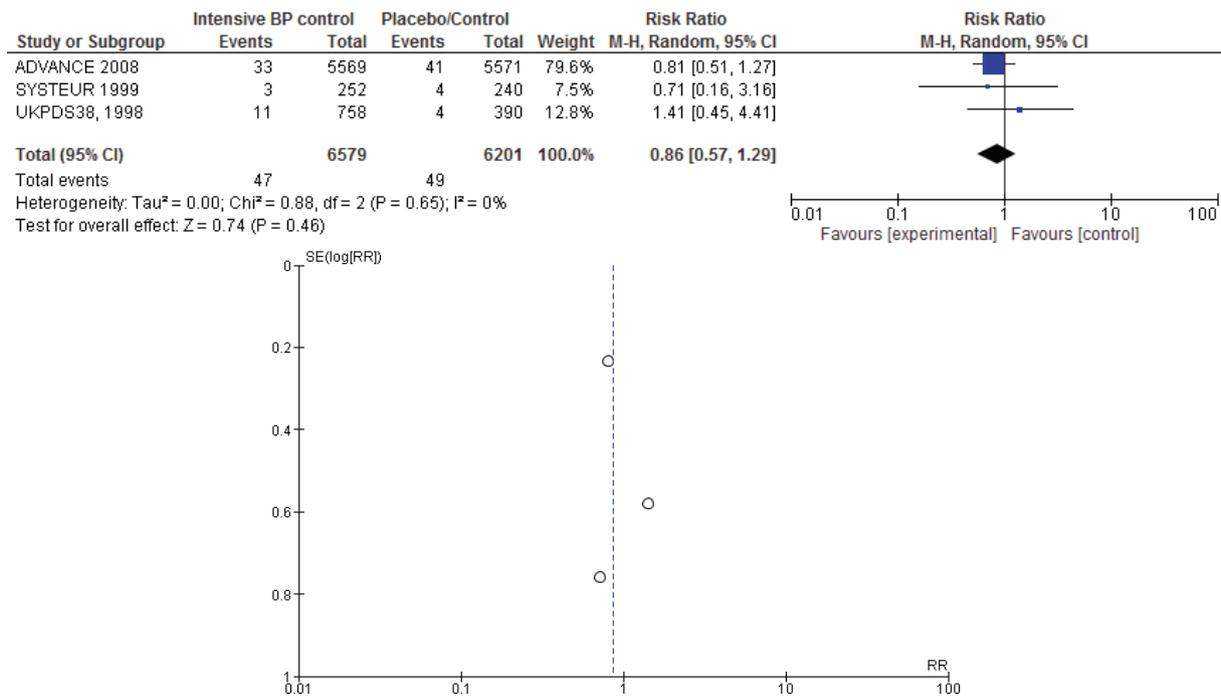


Figure 15. Effect of intensive blood pressure control on sudden cardiac death prevention in type 2 diabetes

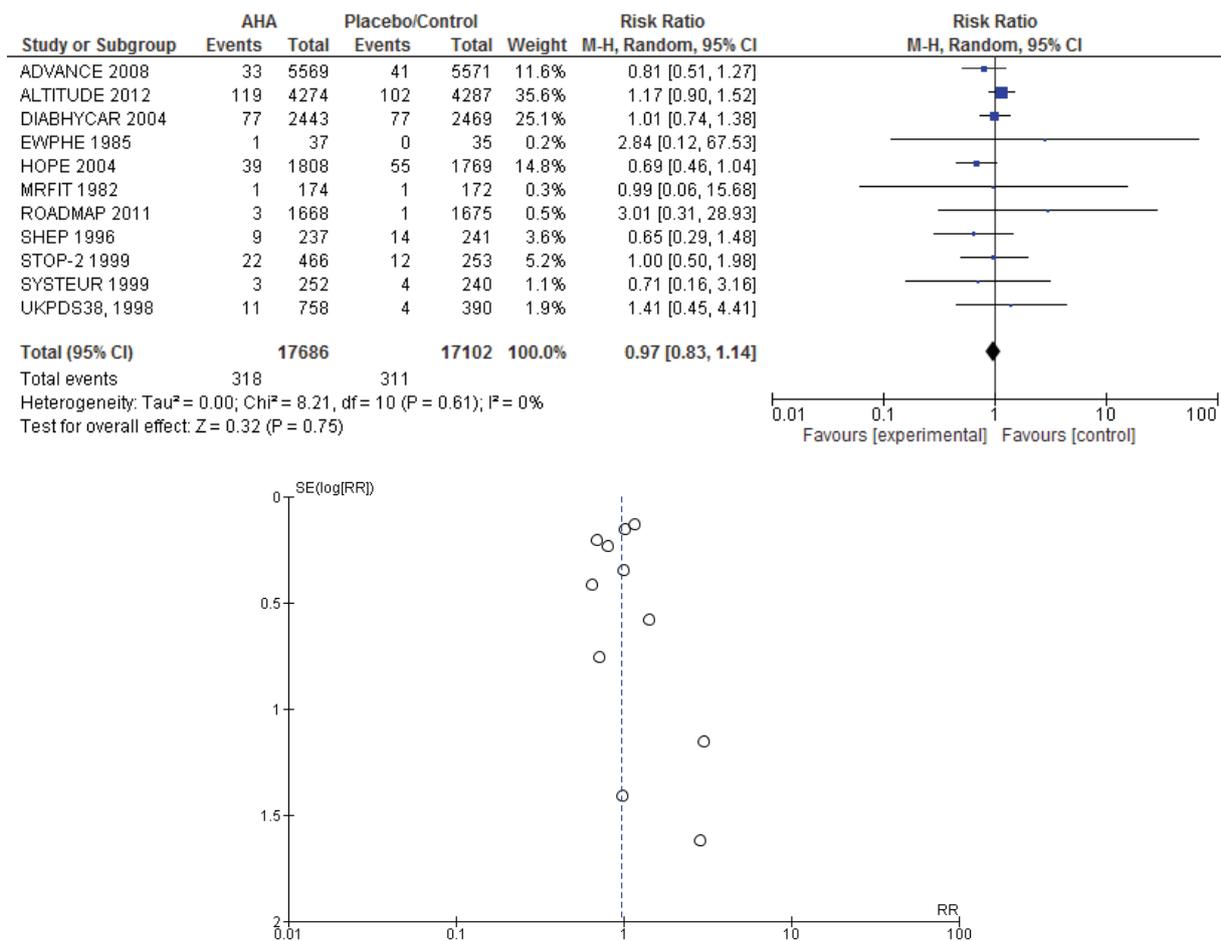


Figure 16. Effect of intensive blood pressure control and antihypertensive agents on sudden cardiac death prevention in type 2 diabetes

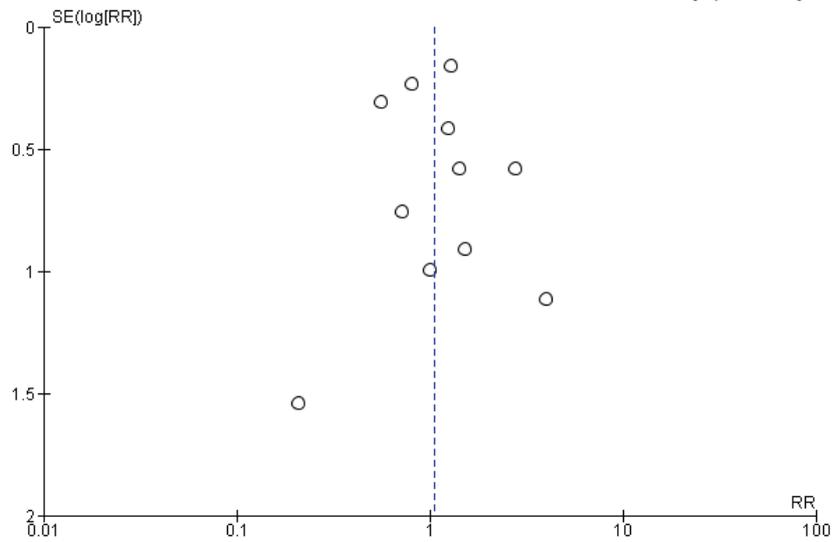
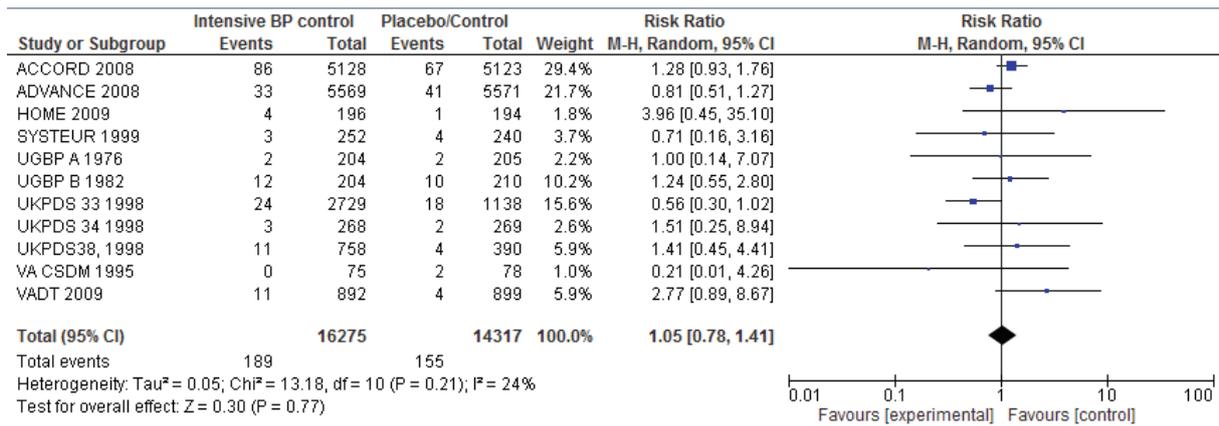


Figure 17. Effect of intensive blood pressure and glucose controls on sudden cardiac death prevention in type 2 diabetes

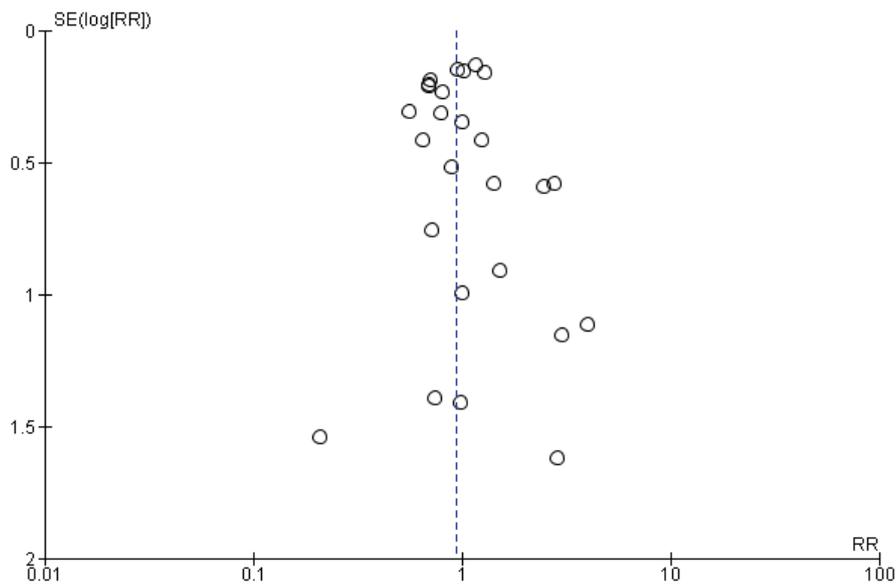
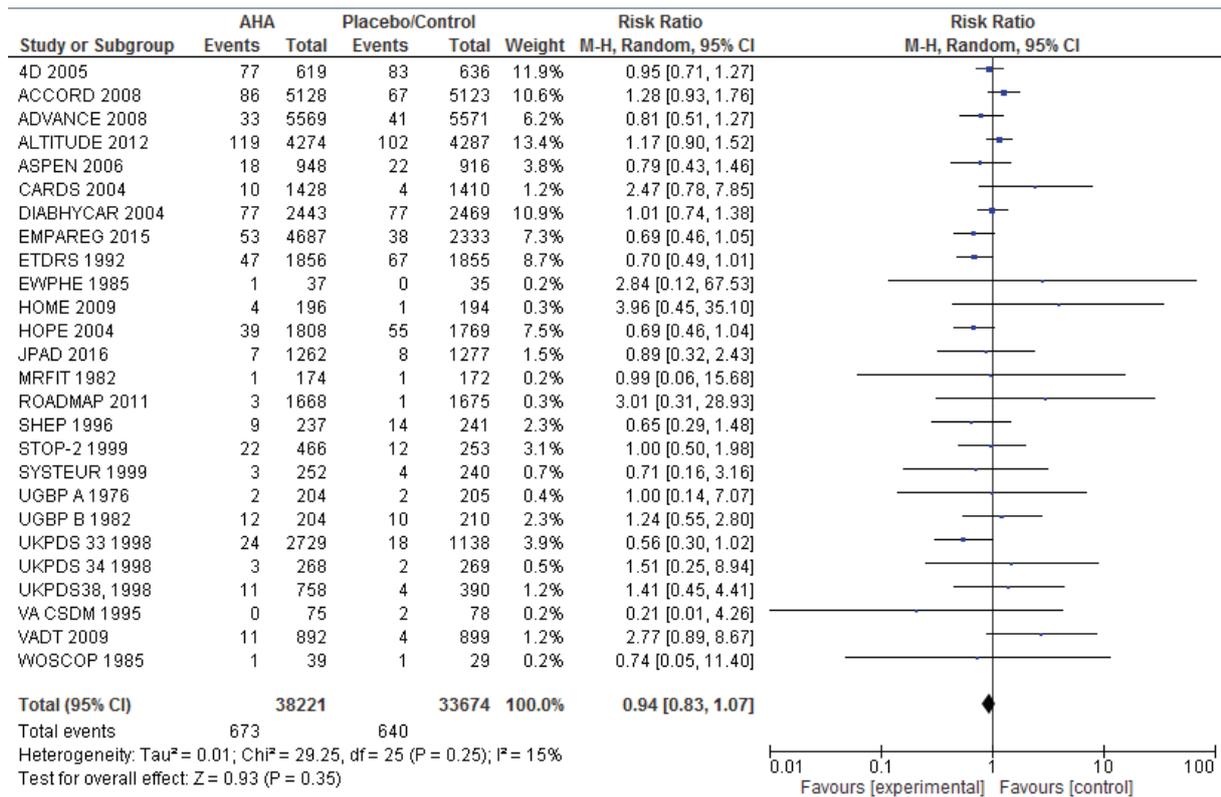


Figure 18. Effect of all treatments on sudden cardiac death prevention in type 2 diabetes

Published article 1 (proofreading version)

A SUDden death risk score in HYPertension. Based on 25,648 individual patient data from six randomized controlled trials.

J Hypertens. 2017 Jun 24. doi: 10.1097/HJH.0000000000001451

HH Le, F Subtil, M Cerou, I Marchant, M Al-Gobari, M Fall, Y Mimouni, B Kassai, Lars Lindholm, Lutgarde Thijs, **F Gueyffier**.

ERRATA in this pre-press/ pre-publication version

In the abstract, some numbers should be changed to (underlined):

In terms of discrimination performance, HYSUD model was adequate with areas under the receiver operating characteristic curve of 77.74% (confidence interval 95%, 74.13–81.35) for the derivation set, of 77.46% (74.09–80.83) for the validation set, and of 79.17% (75.94–82.40) for the whole population. And idem for the table 3 or the article.

All the trials were double blind, except Coope et al. [9] and Multiple Risk Factor Intervention Trial (MRFIT) [10], which were an open-label trial. The biggest one was MRFIT [10],...

We are sorry for these inconveniences.

The official version published in the Journal of Hypertension does not include these errors.

Published article 2

Impact of aldosterone antagonist on the sudden cardiac death in heart failure and myocardial infarction: a systematic review and meta-analysis of randomized-control trials.

PLoS ONE 11(2): e0145958. doi:10.1371/journal.pone.0145958

HH Le, C El-Khatib, M Mombled, F Guitarian, M Al-Gobari, M Fall, P Janiaud, I Marchant, M Cucherat, T Bejan-Angoulvant, **F Gueyffier**.

Review

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

Hai-Ha Le^a, Fabien Subtil^a, Marc Cerou^a, Ivanny Marchant^b, Muaamar Al-Gobari^c, Mor Fall^{a,d}, Yanis Mimouni^{a,e}, Behrouz Kassai^{a,f}, Lars Lindholm^g, Lutgarde Thijs^h, and François Gueyffier^{a,i}

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

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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 (semi-parametric 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 'time-ROC' 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

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

Covariables	Univariable analyses		Multivariable analysis (final model)	
	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- μ mol/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

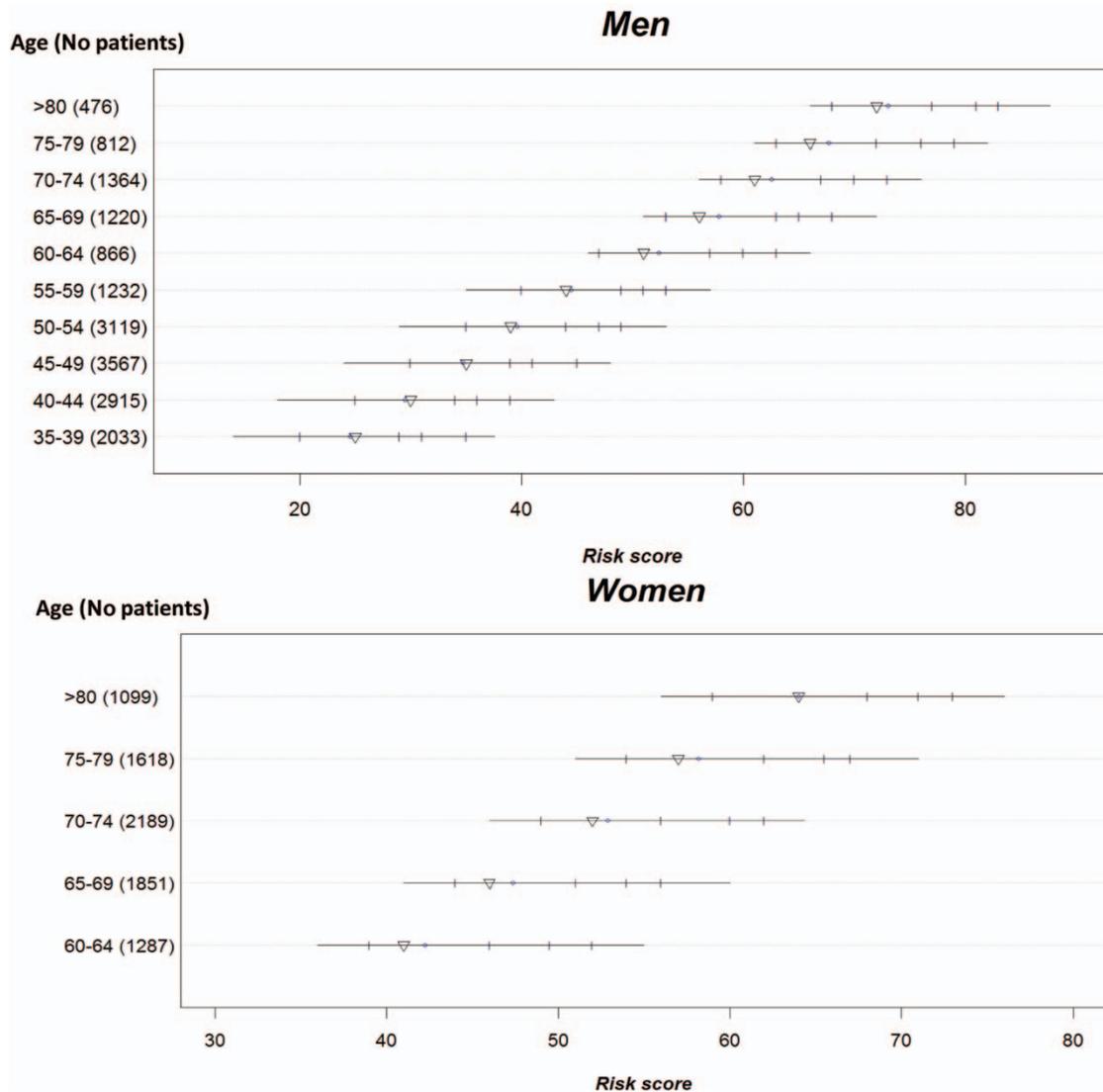


FIGURE 1 Distribution of risk scores by sex and age groups.

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,

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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 anti-arrhythmic 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 anti-hypertensive 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.

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H.H.L., F.S., M.C., M.A., M.F., E. Héning, 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.

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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.

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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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; (L)VEF, (Left Ventricular) Ejection Fraction; LVSD, Left Ventricular Systolic Dysfunction; NYHA, New York Heart 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 Heart 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 substantial 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.

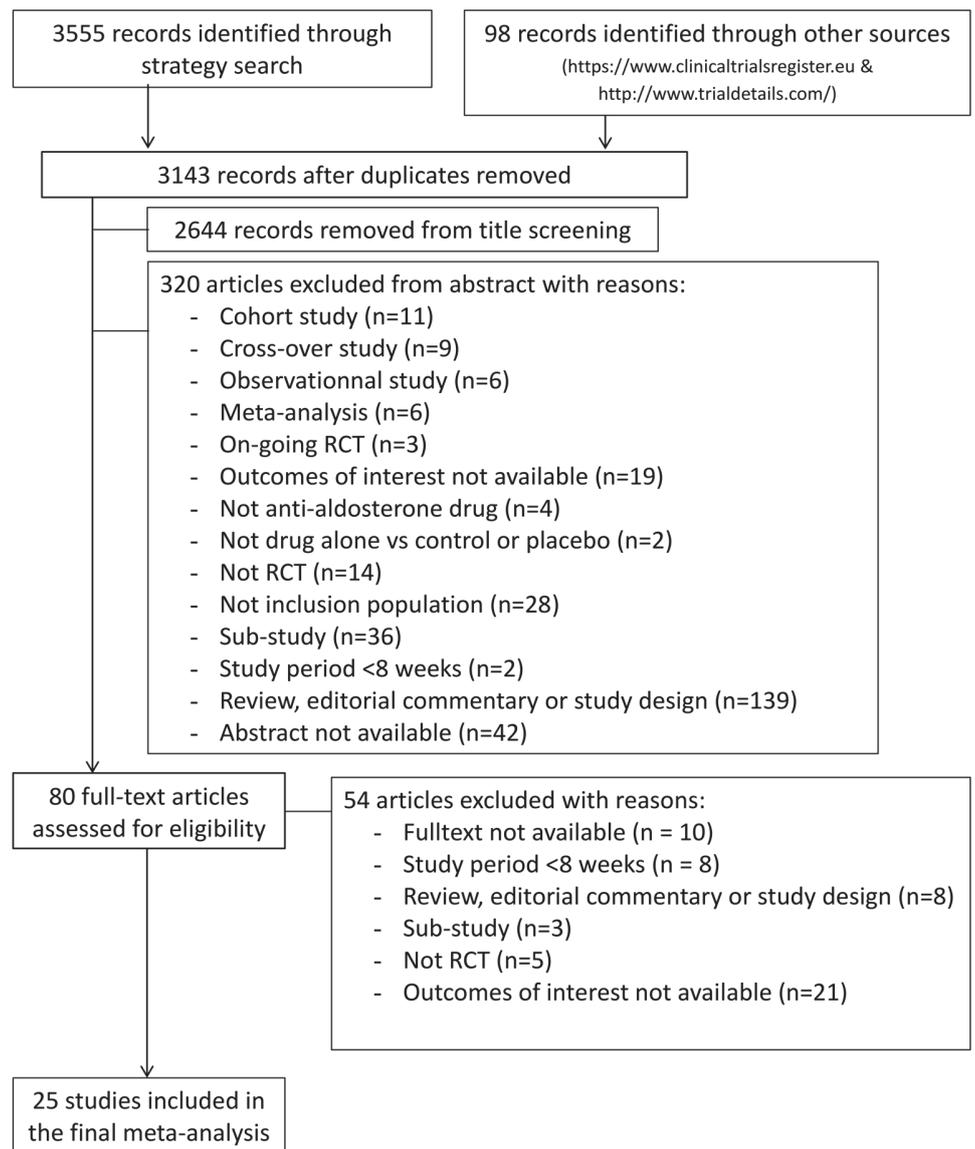


Fig 1. Study flowchart for the selection process of the final included trials.

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 Edlmann *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.

<i>Studies, (abbreviation name), year of publication</i>	<i>Patients; duration (follow-up); countries</i>	<i>Comparison</i>	<i>Study design, intention to treat analysis (ITTA)</i>	<i>Number of randomized patients (excluded during follow-up)</i>	<i>Mean age (SD)</i>	<i>Male sex (%)</i>	<i>Ischemic etiology (%)</i>	<i>Ejection fraction (%)</i>
<i>Boccanelli et al. 2009 (AREA-in-HF) [35]</i>	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)
<i>Chan et al. 2007 [56]</i>	HF; 12 months; China	Spirolactone 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)
<i>Cicoira et al. 2002 [22]</i>	HF; 12 months; Italy	Spirolactone 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)
<i>Deswal et al. 2011 (RAAM-PEF) [36]</i>	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)*
<i>Di Pasquale et al. 2005 [25]</i>	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
<i>Edelmann et al. 2013 (Aldo-DHF) [32]</i>	HFPEF; 12 months; Germany & Austria	Spirolactone 25 mg/day vs. Placebo	DB; with ITTA	213(0)/209(0)	67(8)/67(8)	48/47	NR/NR	67(8)/68(7)
<i>Gao et al. 2007 [57]</i>	HF; 6 months; China	Spirolactone 20 mg/day vs. Placebo	DB, with ITTA	58(0)/58(0)	55(13)/54(12)	64/66	50/52	42(11)/43 (10)
<i>Kayrak et al. 2010 [26]</i>	AMI; 6 months; Turkey	Spirolactone 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)*
<i>Mak et al. 2009 [23]</i>	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)
<i>Modena et al. 2001 [27]</i>	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)
<i>Montalescot et al. 2014 (REMINDER) [28]</i>	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
<i>Pitt et al. 2014 (TOPCAT) [14]</i>	HF; 3.3 years; International (6 countries)	Spirolactone (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
<i>Pitt et al. 2003 (EPHESUS) [13]</i>	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
Vizzardì 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)
Vizzardì 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; EPHEUS: 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 EPHEUS 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

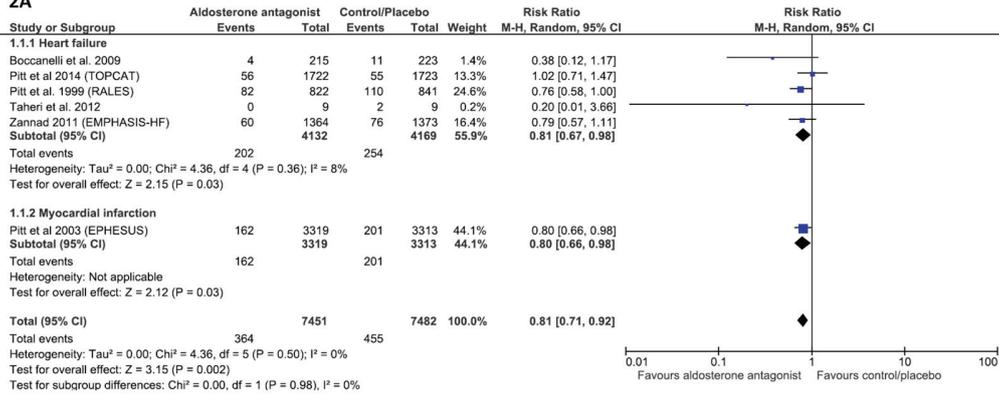
NYHA: New York Health Association; ND: Not Defined; NR: Not Reported; 221 μmol/l ~ 2.5 mg/dL.

doi:10.1371/journal.pone.0145958.t002

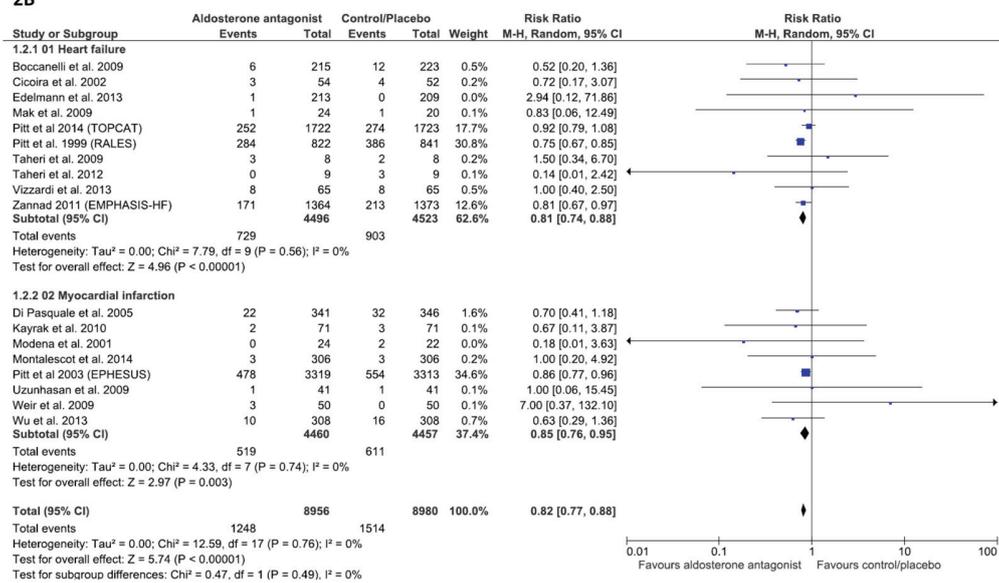
There was a significant reduction of SCD rate with AAs in patients with HF (19% SCD reduction; RR 0.81; 95% CI, 0.67–0.98; p = 0.03) or with post-MI left ventricular dysfunction (20% SCD reduction; RR 0.80; 95% CI, 0.66–0.98; p = 0.03). In total, the SCD rate was 4.88% (n = 364/7451) in those treated 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 (I² = 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 I² = 0%) (Fig 2B).

2A



2B



2C

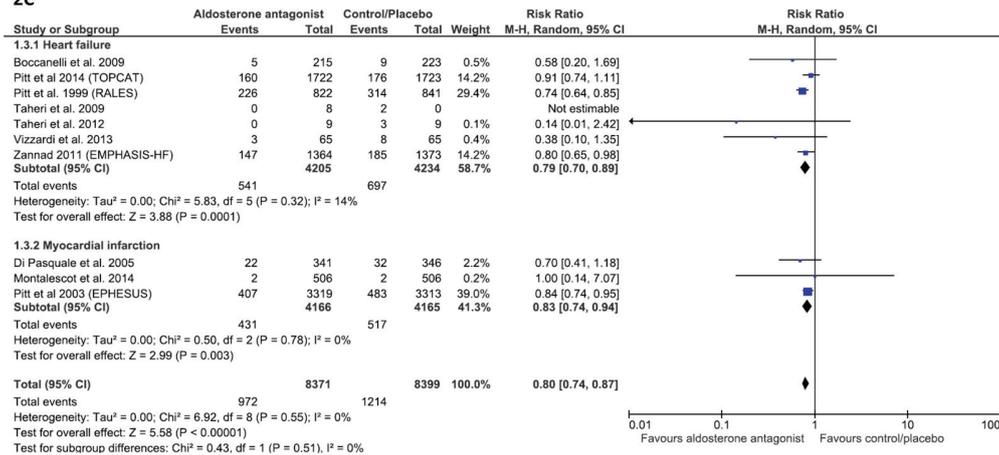


Fig 2. Efficacy of aldosterone antagonist compared with control for the prevention of (A) Sudden death, (B) All-cause mortality, and (C) Cardiovascular death in patients with heart failure or myocardial infarction.

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

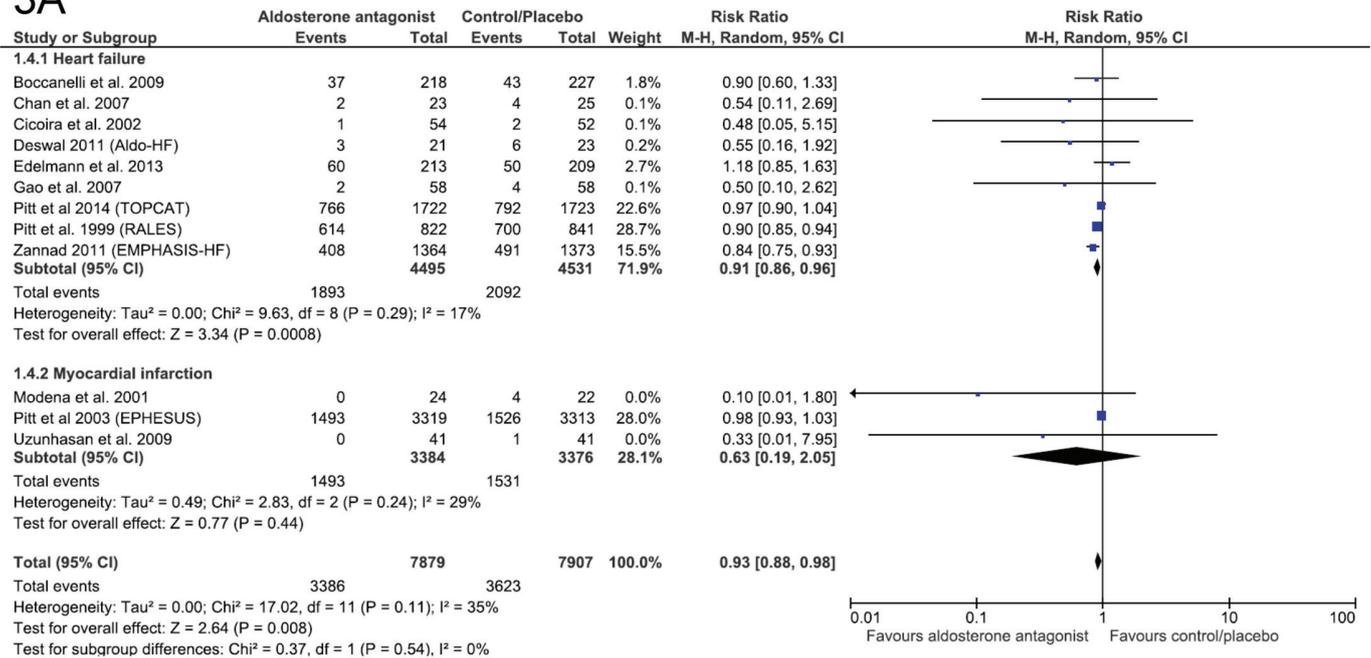
Hyperkalemia, worsening renal function and gynecomastia were the main observed side effects of AAs in the 25 included studies, as compared to placebo or control. In general, the incidence of all considered adverse events significantly doubled in patients treated with AAs, compared to those receiving placebo or reference therapy. Corresponding RRs were 1.88 (CI 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

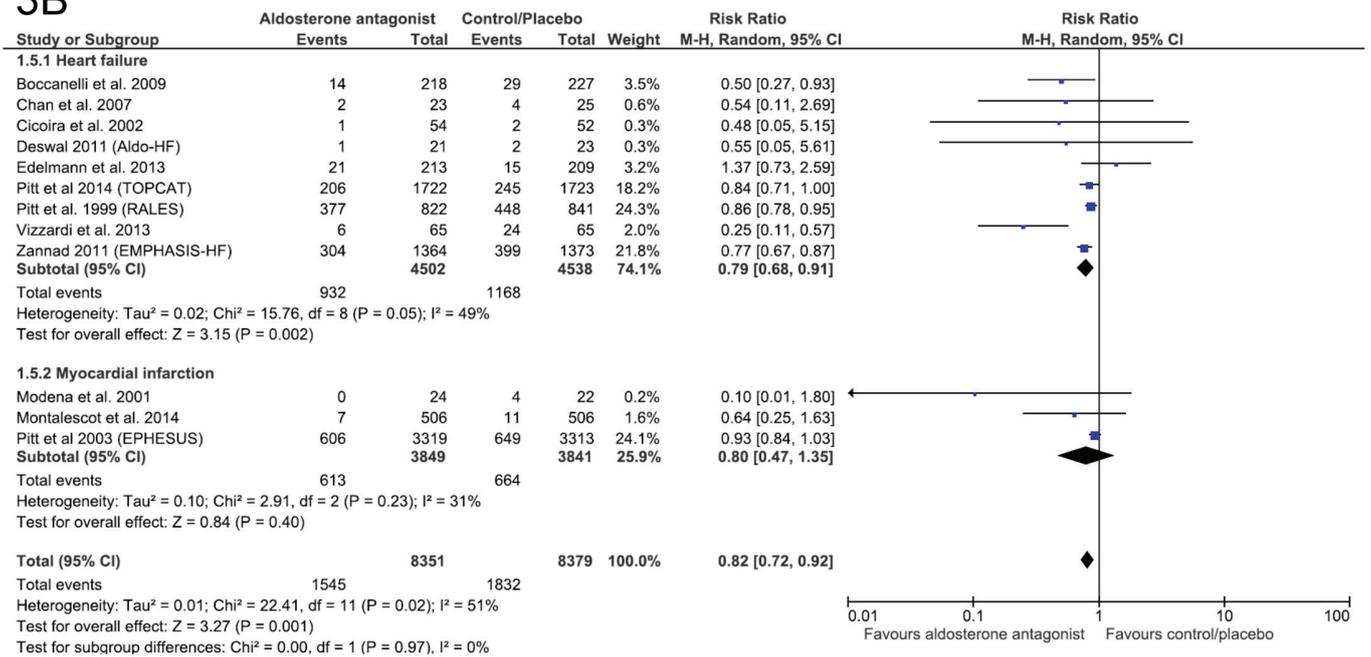


Fig 3. Efficacy of aldosterone antagonist compared to control for the prevention of (A) All-cause hospitalization and (B) Cardiovascular hospitalization in patients with heart failure or myocardial infarction.

doi:10.1371/journal.pone.0145958.g003

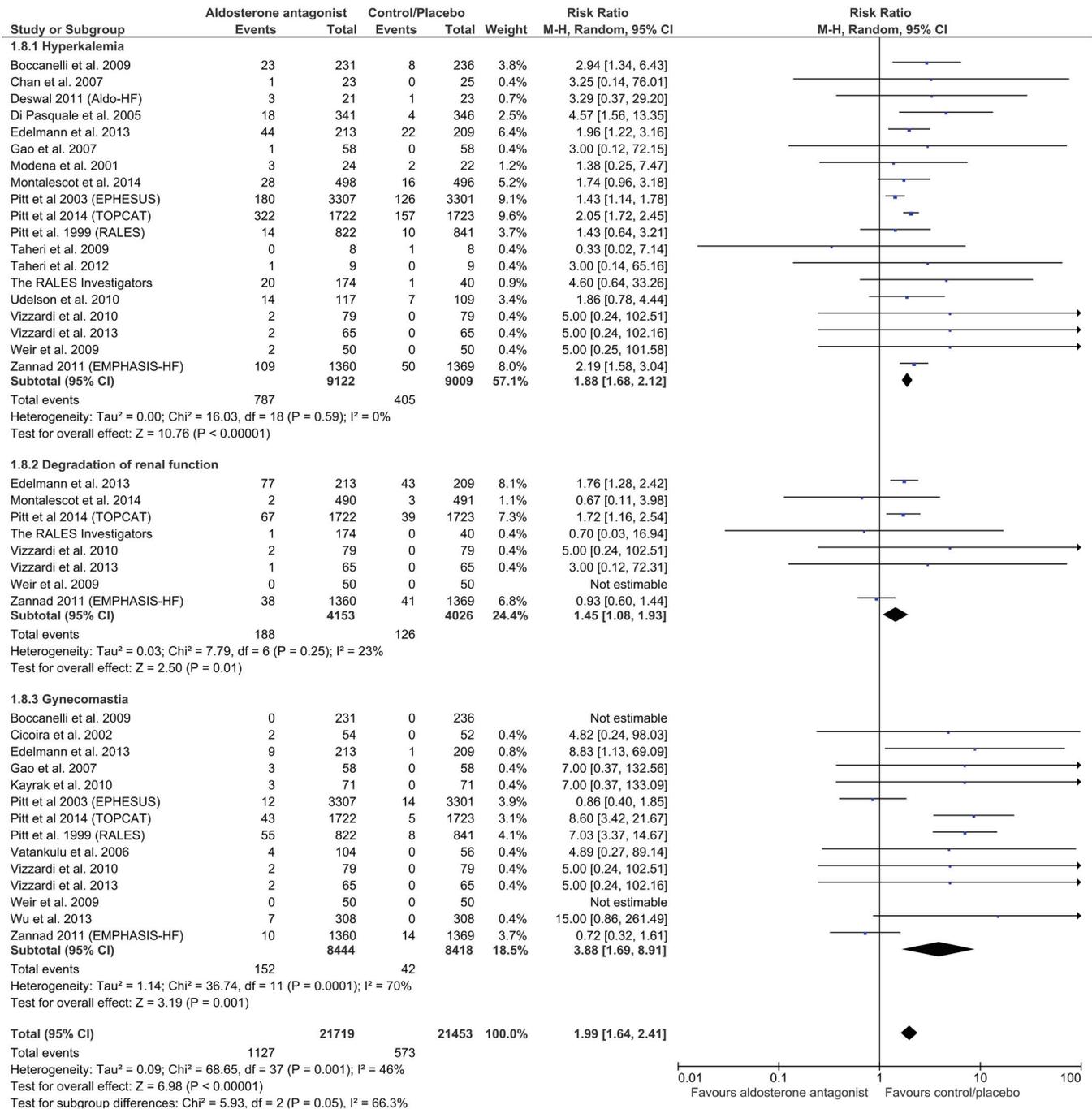


Fig 4. Incidences of adverse effects (hyperkalemia, degradation of renal function and gynecomastia) under aldosterone antagonist treatment, compared with control/placebo group, in patients with heart failure or myocardial infarction.

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.

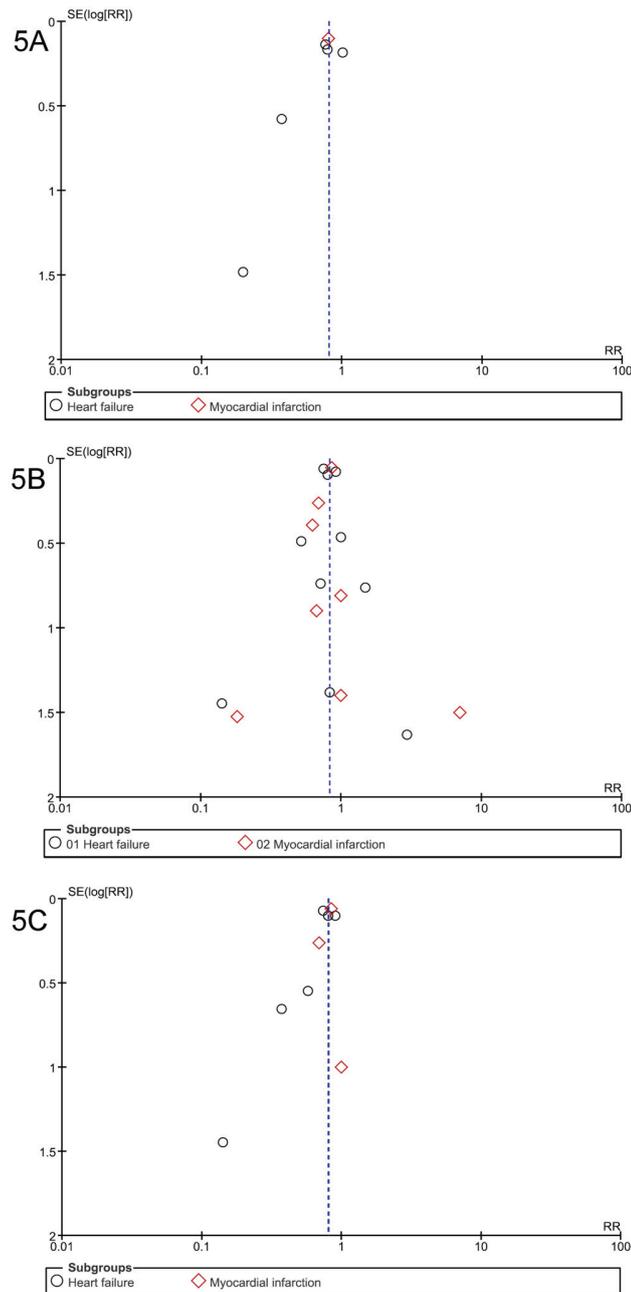


Fig 5. Funnel plot of standard error (log odds ratio) by odds ratio to evaluate publication bias for effect of aldosterone antagonist treatment in preventing (A) Sudden death, (B) All-cause mortality, and (C) Cardiovascular mortality in patients with heart failure or myocardial infarction.

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

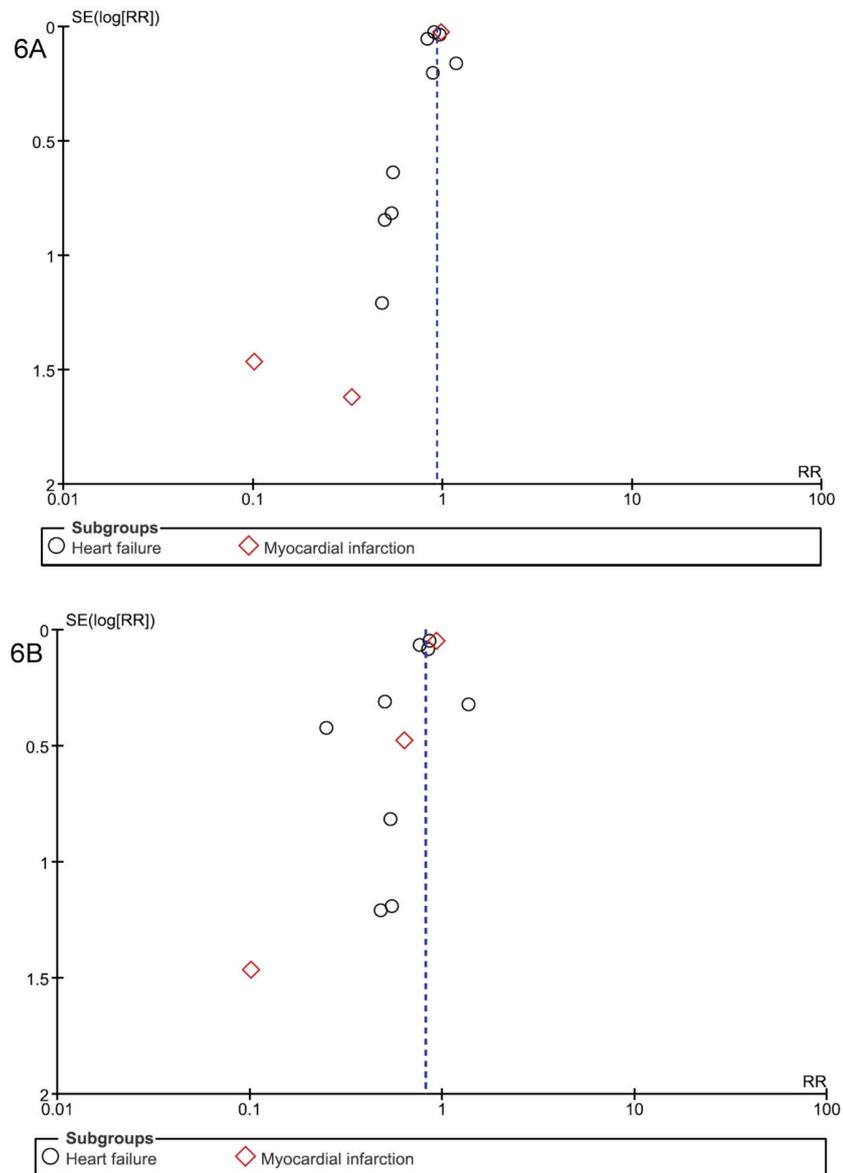


Fig 6. Funnel plot of standard error (log odds ratio) by odds ratio to evaluate publication bias for effect of aldosterone antagonist treatment in preventing (A) All-cause hospitalization and (B) Cardiovascular hospitalization in patients with heart failure or myocardial infarction.

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],

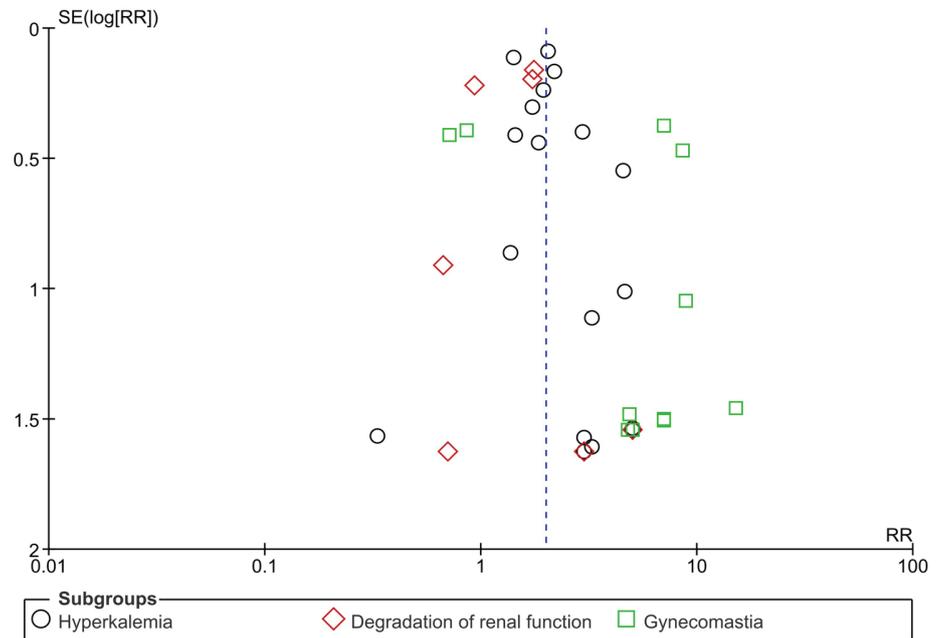


Fig 7. Funnel plot of standard error (log odds ratio) by odds ratio to evaluate publication bias for effect of aldosterone antagonist treatment in inducing common side effects (hyperkalemia, degradation of renal function, gynecomastia) in comparison with placebo/control, in patients with heart failure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

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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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