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Challenges in personalized evidence-based medicine, applications in type 2 diabetes

Guillaume Grenet

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Challenges in personalized evidence-based medicine, applications in type 2 diabetes

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A mon frère Xavier

« Tu n'es plus là où tu étais, mais tu es partout là où je suis. »

Victor Hugo

RESUME

Défis de la médecine personnalisée basée sur les preuves, applications dans le diabète de type 2

La médecine basée sur les preuves requiert des essais cliniques randomisés, qui permettent d'estimer un effet moyen du traitement. La personnalisation de l'estimation de l'effet du traitement nécessite l'estimation du risque spontané de la maladie (biomarqueur pronostique), la recherche de facteurs modifiant l'effet du traitement (biomarqueur théranostique). Des critères de substitution sont également proposés, dont la mesure devrait permettre d'évaluer l'effet du traitement sur l'événement clinique. La prise en charge des patients présentant un diabète de type 2 repose sur les médicaments hypoglycémiants. Plusieurs d'entre eux ont été associés à différents effets indésirables graves. Des études évaluant leur bénéfice cardiovasculaire sont nécessaires. La prise en charge de ces patients inclue également la prise en charge de l'hypertension artérielle. Celle-ci est basée sur des médicaments antihypertenseurs, dont l'intensité est ajustée au niveau de pression artérielle recherché. Cette stratégie basée sur la cible soulève plusieurs questions. Enfin, plusieurs biomarqueurs prédictifs de différents effets des médicaments hypoglycémiants ont été étudiés chez des patients présentant un diabète de type 2, avec des résultats contrastés. Une difficulté majeure dans la validation de biomarqueur théranostique est la puissance statistique nécessaire pour détecter une interaction dans un essai clinique randomisé. L'objectif de cette thèse était d'estimer les effets moyens des traitements hypoglycémiants sur les complications cardiovasculaires ; d'évaluer un potentiel critère de substitution ; et d'étudier les caractéristiques des études cliniques évaluant des biomarqueurs théranostiques.

La première partie présente une méta-analyse en réseaux comparant les effets des hypoglycémiants contemporains chez des patients avec un diabète de type 2, sur la mortalité totale, cardiovasculaire et les événements cardiovasculaires majeurs. Nous avons confirmé la supériorité des gliflozines et des agonistes du récepteur au GLP1 par rapport au traitement contrôle et aux inhibiteurs de la DPP4. Nous avons montré le besoin de comparaisons directes entre les différentes classes, notamment pour préciser la place de la metformine dans la stratégie thérapeutique. La deuxième partie présente une méta-régression évaluant l'association entre la diminution de la pression artérielle par des médicaments antihypertenseurs et les événements cardiovasculaires

majeurs. Nous avons confirmé la relation entre la baisse de la pression artérielle et le risque d'accident vasculaire cérébrale. Il n'y avait pas d'association avec la mortalité totale, la mortalité cardiovasculaire, les infarctus du myocarde. La troisième partie présente une comparaison statistique du plan expérimental en cross-over par rapport au plan en bras parallèle, concernant leur capacité à évaluer un marqueur théranostique. Nous avons montré que l'intérêt du cross-over, pour réduire le nombre de sujet nécessaire, dépend de la corrélation intra-sujet de la mesure du critère de jugement choisi, de façon similaire à l'estimation de l'effet propre du traitement.

Ce travail met en lumière le besoin de comparaisons des médicaments hypoglycémiant sur les complications cardiovasculaires, et la difficulté d'évaluer une balance bénéfice—risque d'un traitement. Des approches de méta-analyses sur données individuelles permettraient de mieux estimer l'impact du contrôle glycémique sur les complications cardiovasculaires. L'accès aux technologies de séquençage du génome à haut débit permettrait d'identifier des facteurs pronostiques et théranostiques. Finalement, nous proposons une extension du modèle d'effet, qui permet d'appréhender la balance bénéfice—risque d'un traitement en fonction de différents biomarqueurs.

L'évaluation d'un effet traitement moyen ou stratifié doit s'inscrire dans une vision globale de la balance bénéfice—risque du médicament concerné.

Mots clés

Médecine basée sur les preuves

Médecine personnalisée

Diabète de type 2

Pharmacologie clinique

ABSTRACT

Evidence based medicine requires randomized clinical trials for estimating a mean treatment effect. The personalization of this treatment effect needs prognostic biomarker for assessing the spontaneous risk of the disease and the absolute benefit of the treatment; and the search for potential theranostic biomarker, associated with a different relative treatment effect. Surrogate endpoints are also proposed, as their measure would reflect the treatment effect on the clinical outcome of interest. Taking care of patients with type 2 diabetes is based on hypoglycemic drugs. Several of them have been retrospectively associated with serious adverse events. They need to be assessed with cardiovascular outcome trials. Taking care of those patients also include handling other cardiovascular risk factor, as high blood pressure. Antihypertensive treatment is based on a “target to treat” strategy, which raise several questions. Finally, many theranostic biomarkers of the hypoglycemic drugs effect have been studied, with conflicting results. Statistical power is a high challenge in randomized trial looking for such interaction. We aimed to provide a mean treatment effect estimation of hypoglycemic drugs on cardiovascular outcomes and to explore potential tools for personalizing the treatment effect estimation.

The first part of this thesis reports a network meta-analysis assessing the contemporary hypoglycemic drugs in type 2 diabetes patients on overall mortality, cardiovascular mortality and major adverse cardiovascular events. We confirmed the superiority of SGLT2 inhibitors and of GLP1 receptor agonists compared to control and to DPP4 inhibitors. We also showed the need for direct comparison, especially for clarifying the position of metformin in the pharmacological strategy. The second part of this thesis reports a meta-regression analysis, assessing the association between the decrease in blood pressure through antihypertensive drugs and the risk of cardiovascular events. We confirmed the association between the blood pressure control and the risk of stroke, but did not find any association regarding overall mortality, cardiovascular mortality and myocardial infarction. The third part reports a statistical comparison of the parallel group design and the cross-over design, regarding their capacity to assess a potential theranostic biomarker. We showed that the advantage of the cross-over for reducing the sample size lead on the intra-subject correlation, as already known for estimating the treatment effect.

Finally, we highlighted the need for comparisons of hypoglycemic drugs for preventing macrovascular events. We emphasized pitfalls in estimating benefit—risk balance. Individual

patient data meta-analyses would help better assessing the effect of glucose control on macrovascular events. High-throughput genome sequencing technologies would help to identify both prognostic and theranostic biomarkers. Lastly, we proposed an extended version of the effect model, which allow to grasp the benefit—risk balance of a treatment, according to different biomarkers.

To conclude, assessing a mean and a stratified treatment effect should be conducted taking into account the global benefit—risk balance estimation.

Key words

Evidence-Based Medicine

Personalized Medicine

Type 2 Diabetes

Clinical Pharmacology

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ABBREVIATIONS

ADR	: Adverse Drug Reaction
ARR	: Absolute Risk Reduction
BMI	: Body Mass Index
BMJ	: British Medical Journal
BP	: Blood Pressure
CAD	: Coronary Artery Disease
CHD	: Coronary Heart Disease
CI	: Confidence Intervalle
CO	: Cross-Over
CV	: Cardiovascular
CVOT	: Cardiovascular Outcomes Trials
DPP4 inhibitors	: DiPeptidyl Peptidase-4 inhibitors
EAS	: European Atherosclerosis Society
EBM	: Evidence Based Medicine
EMA	: European Medicines Agency
ERCC1	: ERCC excision repair 1, endonuclease non-catalytic subunit
ESC	: European Society of Cardiology
F.N.A.H.	: French National Authority for Health
FDA	: U.S. Food and Drug Administration
GLP1 receptor agonists	: Glucagon Like Peptide 1 receptor agonists
HAS	: Haute Autorité de Santé
HbA1c	: Glycated Hemoglobin
HR	: Hazard Ratio
HTE	: Heterogeneity of Treatment Effect
IPD MA	: Individual Patient Data Meta Analyses
LDL	: Low-Density Lipoprotein cholesterol
MA	: Meta-Analysis
MACEs	: Major Adverse Cardiovascular Events

MI	: Myocardial Infarction
network MA	: Network Meta-Analysis
NNT	: Number Needed to Treat
OCTs	: Organic Cation Transporter Family
OR	: Odds Ratio
PG	: Parallel Group
PPAR-gamma	: Peroxisome Proliferator-Activated Receptors-gamma
RCT	: Randomized Clinical Trial
RR	: Risk Ratio
RRR	: Relative Risk Reduction
SGLT2 inhibitors	: Sodium-Glucose cotransporter 2 inhibitors
T2D	: Type 2 diabetes
TE	: Treatment Effect
TZD	: Thiazolidinediones
U.S.	: United States

SUBSTANTIAL FRENCH SUMMARY

La médecine basée sur les preuves permet de proposer au patient un traitement éprouvé. L'établissement d'une causalité entre l'intervention thérapeutique et l'effet bénéfique recherché requiert des essais cliniques randomisés, qui permettent d'estimer un effet moyen du traitement. La personnalisation de l'estimation de l'effet du traitement nécessite l'estimation du risque spontané de faire l'évènement clinique que l'on souhaite prévenir (biomarqueur 'pronostique'), la recherche de facteurs modifiant l'effet du traitement sur la survenu de cet évènement clinique (biomarqueur 'prédicatif' ou 'théranostique'). Des critères dit de substitution sont également proposés, dont la mesure devrait permettre d'évaluer l'effet du traitement sur l'évènement clinique.

La prise en charge pharmacologique des patients présentant un diabète de type 2 repose sur les médicaments hypoglycémiants. L'efficacité des médicaments hypoglycémiants est initialement évaluée par leur effet hypoglycémiant, mais plusieurs d'entre eux ont par la suite été associés à différents effets indésirables graves. Ainsi, des études évaluant leur bénéfice cardiovasculaire sont nécessaires. De nombreux essais ayant été conduit avec différentes molécules, mais essentiellement sans comparateurs actifs, des approches de méta-analyse en réseau sont nécessaires pour obtenir une synthèse quantitative et comparative de leurs effets. La prise en charge des patients présentant un diabète de type 2 repose également sur la prise en charge des autres facteurs de risque cardiovasculaire, dont l'hypertension artérielle. La prise en charge de l'hypertension artérielle est basée sur des médicaments antihypertenseurs, dont l'intensité est ajustée au niveau de pression artérielle recherché. Cette stratégie basée sur la cible de pression artérielle soulève cependant plusieurs questions. Enfin, plusieurs biomarqueurs prédictifs de différents effets de traitement hypoglycémiants ont été étudiés chez des patients présentant un diabète de type 2, avec des résultats contrastés. Une difficulté majeure dans la validation de biomarqueur théranostique est la puissance statistique nécessaire pour détecter une interaction dans un essai clinique randomisé.

L'objectif de cette thèse était d'estimer les effets moyens des médicaments hypoglycémiants chez des patients ayant un diabète de type 2, sur les complications cardiovasculaires ; puis d'évaluer un potentiel critère de substitution utilisé dans cette population ;

et enfin d'étudier les caractéristiques des études cliniques évaluant des biomarqueurs théranostiques de l'effet du traitement.

La première partie de cette thèse présente une méta-analyse en réseaux comparant les effets des hypoglycémisants contemporains sur la mortalité totale, cardiovasculaire et les événements cardiovasculaires majeurs. Nous avons confirmé la supériorité des gliflozines et des agonistes du GLP1 par rapport au groupe contrôle et aux inhibiteurs de la DPP4. Nous avons également montré le besoin de comparaisons directes entre les différentes classes, notamment pour préciser la place de la metformine dans la stratégie thérapeutique par rapport aux gliflozines et agonistes du GLP1. Cette partie est complétée d'une estimation de la balance bénéfice—risque d'une classe de médicament récents, les gliflozines, chez des patients présentant un diabète de type 2. Nous avons observé que, même en prenant en compte le risque d'amputation et le risque d'acido-cétose décrit avec ces médicaments, le bénéfice cardiovasculaire semblait rester cliniquement pertinent.

La deuxième partie de cette thèse présente une étude de méta-régression sur données agrégées, dont l'objectif était d'améliorer la caractérisation de l'association entre la diminution de la pression artérielle par des médicaments antihypertenseurs dans des essais cliniques randomisés et les événements cardiovasculaires majeurs. Nous avons confirmé la relation entre la baisse de la pression artérielle et le risque d'accident vasculaire cérébrale, mais n'avons pas observé d'association pour les autres critères de jugements étudiés : la mortalité totale, la mortalité cardiovasculaire, les infarctus du myocarde.

La troisième partie de cette thèse présente une comparaison statistique du plan expérimental en cross-over par rapport au plan en bras parallèle, concernant leur capacité à identifier une interaction entre un marqueur théranostique et l'effet du traitement. Nous avons montré que l'intérêt du cross-over, pour réduire le nombre de sujet nécessaire, dépend de la corrélation intra-sujet de la mesure du critère de jugement choisi, de façon similaire à l'estimation de l'effet propre du traitement. Cette partie inclue également une enquête de méta-recherche sur des études cliniques évaluant des biomarqueurs théranostiques pharmacogénétiques. Nous avons observé que les conclusions des études identifiées semblaient souvent excessives, au vu des méthodes rapportées.

Le travail de cette thèse a permis de mettre en lumière le besoin de comparaisons des effets des médicaments hypoglycémisants sur les complications cardiovasculaires. La difficulté d'évaluer la balance bénéfice—risque est également démontrée dans le contexte de différents médicaments hypoglycémisants. Des approches de méta-analyses sur données individuelles permettraient de mieux estimer l'impact du contrôle glycémique sur les complications cardiovasculaires. L'accès aux technologies de séquençage du génome à haut débit permettrait d'identifier des facteurs pronostiques et théranostiques, mais cela nécessite de contrôler non seulement les biais internes aux études mais également ceux liés à leur publication. Finalement, nous proposons une extension du modèle d'effet, permettant d'appréhender la balance bénéfice—risque d'un traitement en fonction de différents biomarqueurs.

Proposer une prise en charge personnalisée et fondée sur les preuves aux personnes présentant un diabète de type 2 reste un exercice difficile dans la pratique clinique quotidienne. L'évaluation d'un effet traitement moyen ou stratifié à l'aide de biomarqueurs doit s'inscrire dans une vision globale de la balance bénéfice—risque du médicament concerné.

INTRODUCTION

The Evidence Based Medicine

Claude Bernard already discussed, in 1865, the necessity to assess the efficacy of a treatment using experimental approaches [1]. Indeed, the recovery could be the simple natural evolution of a disease, and thus is not sufficient itself to prove the benefit of a treatment. Assessment of a causality, for a treatment effect (TE) but also for epidemiology, requires a highly rigorous approach, as proposed in 1965 by Austin Bradford Hill [2]. Since the first randomized trial in 1948 [3], the implementation of more and more comparative trials lead to the shift toward the evidence based medicine (EBM) paradigm [4].

Observational studies are prone to bias [5, 6]. Empirical examples illustrate false positive conclusions regarding treatment effect through epidemiological studies, eventually invalidated by randomized clinical trial (RCT) [7]. RCTs allow to estimate the TE with a low risk of bias, and to infer causality [8]. The randomization allows to allocate the treatment independently of the subject and/or the care giver, in order to avoid confusion bias. Meta-epidemiological studies have showed the importance of the random allocation – and its quality— of the treatment in trial, and of the blinding, for avoiding bias in TE estimation [9, 10]. Moreover, the use of a placebo, when possible, and the double blinding allow to avoid the placebo (and the nocebo) effect, and the intention to treat analysis allow to avoid the attrition bias, for example. However, RCTs also can be misleading. Their evidence is limited to the studied population. As any inference process, they are subject to risk of false positive results, and to false negative results. In the last decades, number of publications of RCTs has increased exponentially, leading to evidence synthesis issues.

The systematic review and meta-analysis (MA) approach help to summarize the available evidences. They also help to quantify the TE estimation, and in more diversified treated population. However, MA approaches also have their own limitations. The publication bias, which has been documented early [11], can lead to erroneous TE estimation [12]. The underlying hypothesis of a homogeneity of the TE across the included trials must also be assessed, and the statistical analysis should take into account the precision of the TE estimate from each trial [13]. MA were initially

limited to the comparison of two kind of interventions, which needed to have been directly compared in RCTs, in a “head to head” fashion (direct comparison). Then, indirect comparison using a common comparator allow to develop mixed treatment comparison [14] and finally network meta-analysis (network MA) [15], allowing to compare multiple treatments at the same time. The figure 1 illustrates the principle of adjusted indirect comparison [14]. Those new approaches can help for estimating TE, but several conditions should be assessed. For example, it is of particular importance to verify the consistency between the direct comparison and the indirect comparison [16].

RCTs and MAs allow to estimate TE with a low risk of bias and improved precision. They are helpful for assessing beneficial effects, whose impact can be assessed on *a priori* defined outcomes, with enough statistical power. However, the TE estimation regarding the risk of adverse drug reaction (ADR) remains an issue: RCTs often lack of power for rare ADR, and as those are usually not the primary endpoint, the alpha risk is not controlled for multiple testing. Several frameworks help integrating the estimation of both the benefit and the risk of a treatment [17-19].

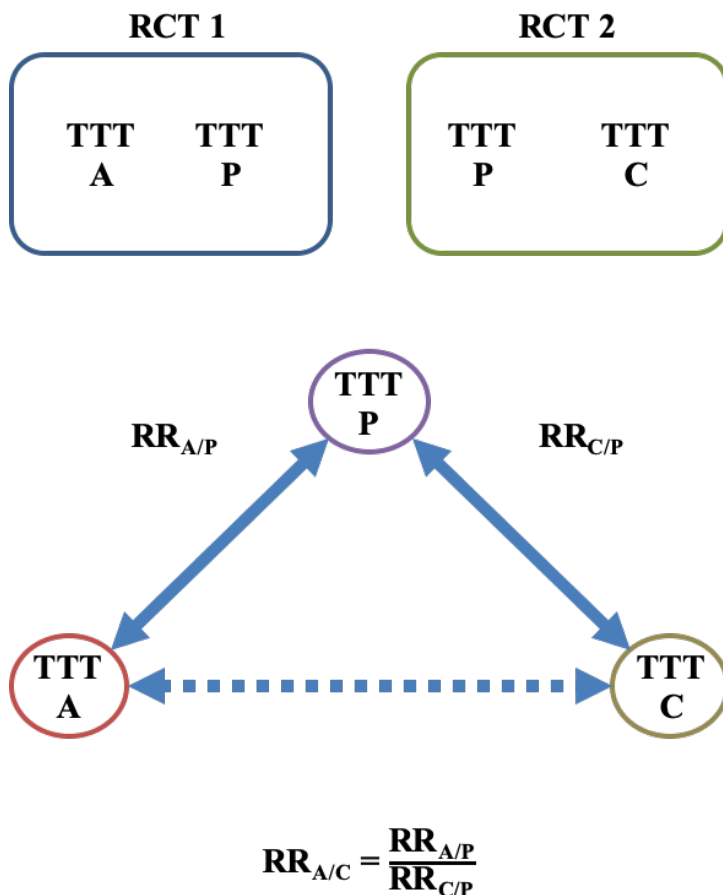


Figure 1. Indirect comparison principle, according to Bucher et al [14].

RCT: Randomized Clinical Trial; TTT: treatment ‘A’, ‘P’, ‘C’; RR: risk ratio.

The solid arrows stand for the direct comparisons; the dashed arrow for indirect comparison.

The assessment of the TE is based on the rejection of the null hypothesis of the absence of effect. Large group of subjects are needed to decrease the confidence interval of the TE estimation and to obtain enough statistical power for testing the *a priori* hypothesis. Indeed, the biological variability should be contained, in order to obtain a reliable TE estimation. Thus, estimation of the TE through RCT and MA is based on the averaging of the TE across large group of subjects and provide “only” a mean (with its confidence interval) of the TE, ignoring the heterogeneity of the TE [20] (see figure 2). Then, much criticisms haven been raised against EBM, for not taking into account the individual characteristics [21-23]. Austin Bradford Hill itself already stated that if RCT are helpful for determining the better treatment on average, they are limited for helping to choose a specific treatment for a specific subject [24].

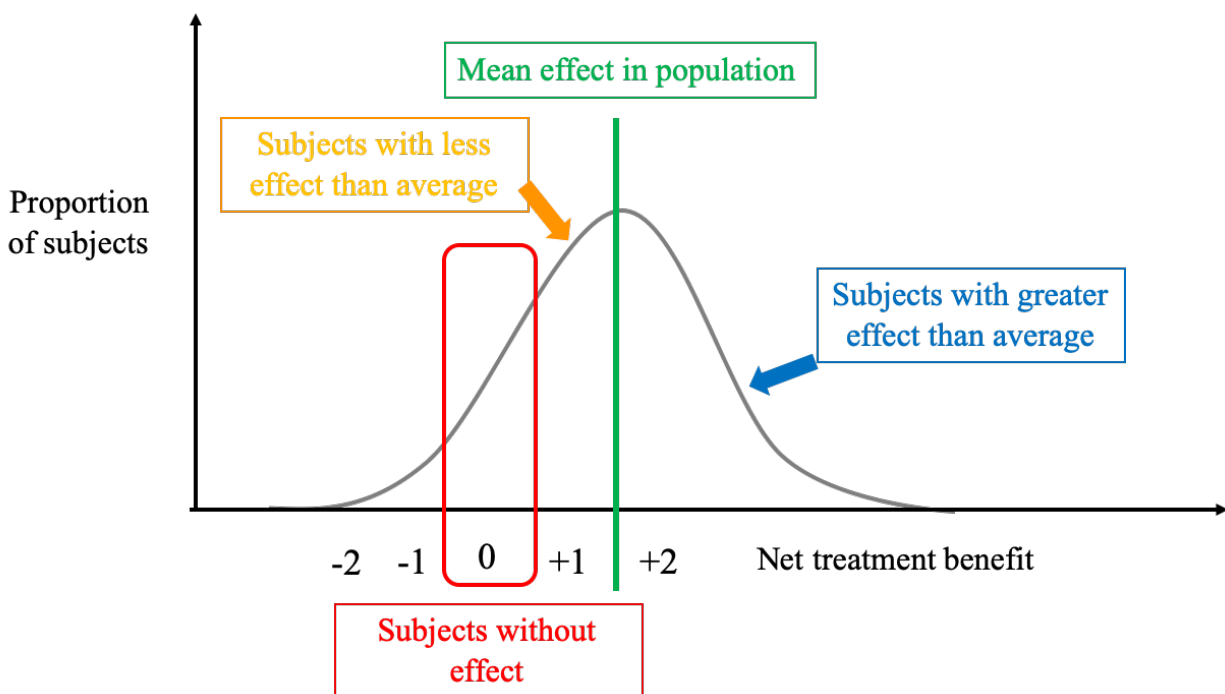


Figure 2. Distribution of treatment effects across subjects in a hypothetical population, adapted from Kravitz et al [20]. The X-axis represents the treatment benefit (arbitrary value). The mean treatment effect is indicated by the vertical green bar. Subjects to the right of the green bar derive a benefit greater than average, while those to the left derive less than an average benefit. Subjects in the red area even derive no effect from the treatment.

However, the EBM did not neglect to take into account the inter individual variability. First, its early definition includes “integrating individual clinical expertise and the best external evidence”, as “even an excellent external evidence may be inapplicable to or inappropriate for an individual patient” [25]. The integration of both the research evidence, the clinical circumstances and the patient’s preference were summarized in a now famous Venn Diagram, by Haynes *et al.* [26] (Figure 3). Moreover, there is a growing area of research concerned about TE heterogeneity (HTE for Heterogeneity of TE) and personalized EBM [27, 28].

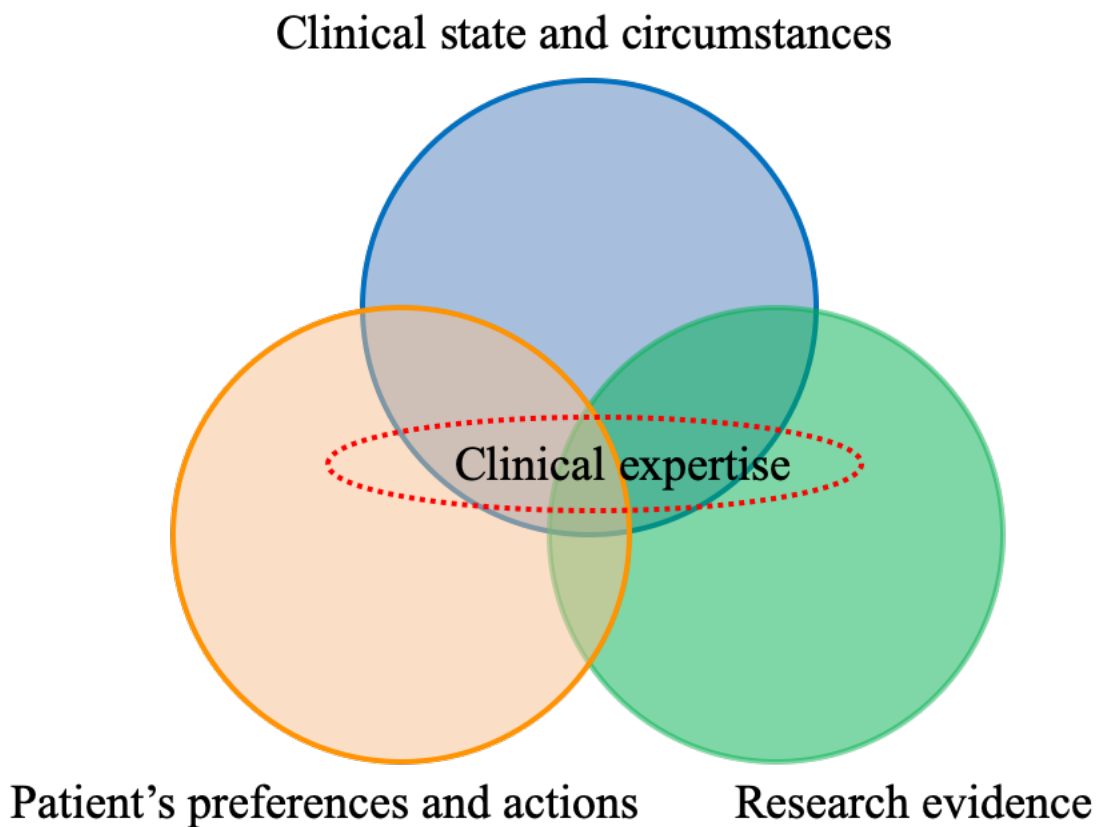


Figure 3. A model for evidence based clinical decisions, adapted from Haynes *et al* [26]

Biomarker and personalized estimation of a treatment's effect

In the last years, several definitions of the term “biomarker” have been proposed [29]. In 2001, the Biomarkers Definitions Working Group convened by the National Institutes of Health of the United States (U.S.) defined the biomarker as “A characteristic that is objectively measured and evaluated as an indicator of normal biological processes, pathogenic processes, or pharmacologic responses to a therapeutic intervention” [30]. The actual definitions used by the European Medicines Agency (EMA) is relatively large (“A biological molecule found in blood, other body fluids, or tissues that can be used to follow body processes and diseases in humans and animals”) [31]. According to the U.S. Food and Drug Administration (FDA), a biomarker can be understood as any type of measure (molecular, histologic, radiographic, or physiologic) as an indicator of a biological process, but “is not an assessment of how an individual feels, functions, or survives” [32]. The Institute of Medicine (U.S.) proposed a three step approach to evaluate biomarker: i) assessment of the analytical performance (“Analytical Validation”); ii) assessment of the association with the clinical outcome/the disease (“Qualification”); and iii) assessment of its use in a specific context (“Utilization”) [33]. Biomarkers can be associated with i) the present state of the patient (« diagnostic biomarker ») and two future state of the patient: ii) the natural evolution of a subject and/or its disease (« prognostic biomarker »); and iii) the response to the treatment (« predictive biomarker » or « theranostic » biomarker or « effect modifier ») [34].

Personalization according to the spontaneous risk, prognostic biomarker

The benefit of a treatment is often expressed on the relative scale: risk ratio (RR), odds ratio (OR) or hazard ratio (HR). Those measures are helpful to pool the estimation of the TE from different trials. However, they do not take into account the spontaneous risk of the patient to develop the disease or the outcome of interest. Absolute measures of the TE, as the absolute risk reduction (ARR), or the Number needed to treat (NNT), allow to reflect the benefit of the treatment according to the patient risk [35]. The absolute measures of the TE should be expressed within the context of a defined time-lapse [36]. ARR and NNT are especially relevant for applying TE from RCT to individual patient encountered in the clinical practice [37]. Indeed, a high heterogeneity in the spontaneous risk of the outcome of interest in clinical trials samples has been observed using multivariable prediction tool [37]. Prognostic biomarkers can help to determine the prognostic of

a patient, and therefore estimating the absolute benefit that could be expected from the treatment. Prognostic biomarkers can be identified in retrospective studies, but prospective studies and replication are needed for their validation [34]. The concept of the “effect model” refers to the relationship between the risk of an outcome of interest under treatment, as a function of its spontaneous risk, as proposed by Boissel *et al.* [38]. L’Abbé *et al.* originally used this approach to explain heterogeneity between trial results [39]. Lubsen and Tijssen extended it with the integration of a constant risk of harm, to illustrate the net benefit from a treatment [40] (see figure 4). This allows for example to choose a threshold for treating or not a patient, according to its specific risk of the disease versus the risk of a drug adverse event [41, 42]. The model was extended to integrate different risk of harm for individualizing the treatment indications [43, 44]. Since then, several examples are available, illustrating the interest of taking into account the heterogeneity of the spontaneous risk of the outcome when assessing the treatment’s benefit [28]. The estimation of the spontaneous risk of outcome can be modelled using multivariate models. To stratify the subjects included in their trial, Thune *et al.* used a prognostic score integrating the value of a dozen of clinical and/or electrocardiographic parameters [45]. They observed no benefit of the tested invasive strategy with primary angioplasty in the subjects identified as low risk by the prognostic score, but a significant decrease of mortality in the high-risk patients [45]. Prognostic score can also be modelled using omics data [46]. Similarly, prognostic score can be used for exploring the heterogeneity in risk of event which could be increased by the treatment. In a trial assessing dual antiplatelet therapy after percutaneous coronary intervention, Costa *et al.* stratified the population according to their bleeding risk, using a simple five variable risk score [47]. They observed an important change in the harm—benefit balance of the intervention [47]. Finally, two scores can be used to stratify patients both for the risk of an efficacy endpoint and for the risk of a safety endpoint [48, 49].

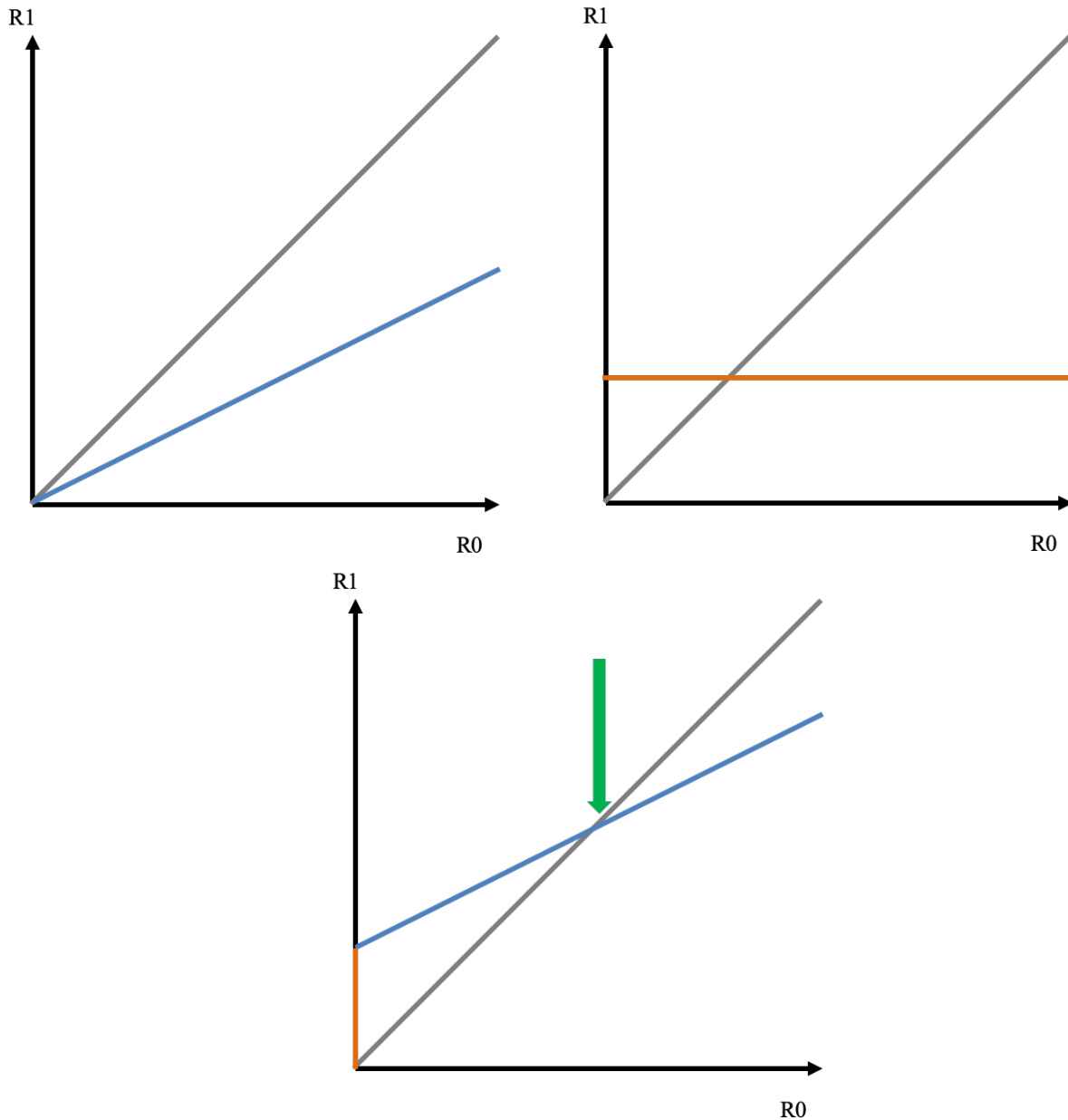


Figure 4. Effect model for the net benefit, adapted from Lubsen et al [40]. The X-axis represents the spontaneous risk of event (R_0), the Y-axis the risk under treatment (R_1). The grey diagonal stands for the absence of treatment effect ($R_0=R_1$). The blue line represents the treatment effect for the efficacy endpoint (top left). The orange line represents the risk of harm due to the treatment, here supposed constant (top right). Finally, benefit and harm are combined: the intersection with the diagonal is the threshold (green arrow) of basal risk of event from which the treatment displays a net benefit (down).

Personalization according to the treatment's response, predictive / theranostic biomarker

Heterogeneity of the TE usually reflects the modification of the TE on the relative scale, *i.e.* a different RR/HR/OR. Some authors refer to HTE on both the relative and the absolute scales [28]. We focus on effect modifier of the TE on the relative scale. If observational longitudinal cohorts of treated patients are adapted for claiming a prognostic biomarker, the demonstration of a theranostic value of a biomarker include its « effect modifier » characteristics, *i.e.* to demonstrate the interaction between the biomarker and the treatment effect. Such predictiveness of the treatment's effect would allow to identify which patient will benefit from the treatment. True « predictive » biomarker need rigorous experimental design to be claimed. Biomarkers are still often called « predictive » of the treatment effect, whenever they have been assessed in « treatment only » cohort [50]. At first, candidates could be identified in sub-group analysis of RCTs. However, sub-groups analyses are prone to false results (see following section). Then, the predictive value of the selected candidate should be validated in a « interaction trial », *i.e.* in an RCT in which the randomization is stratified according to the status of the biomarker [34]. Then, the treatment effect can be compared across the group of biomarker's statuses, to show the presence of a treatment effect in one group but not in the other. The example of ERCC1 (ERCC excision repair 1, endonuclease non-catalytic subunit) reminds the importance of the validation of the interaction through a stratified RCT. Briefly, several studies suggested that the tumoral expression of ERCC1 was a marker of efficacy of platinum-based chemotherapy in non-small cell lung cancer, but without using a stratified design [51]. Eventually, a stratified RCT was conducted, and did not observe any predictive value of this biomarker, whenever the tested treatment showed clinical benefit [52]. Indeed, such biomarker candidates should be confirmed—or refuted—with high level of proof, for avoiding potentially dramatic therapeutic abstention. However, this stringency brings sample size issues, as already described in the parallel group design [53, 54].

Finally, one could model together the prognostic risk and integrate interaction terms with treatment effect [55]. The SYNTAX trial compared two revascularization strategies. A risk score of the outcome of interest was modelled using eight variables as both prognostic variables and effect modifiers (in treatment interaction terms). Stratification using this score displayed important

differences in TE [55]. This could allow to target the most favorable treatment, according to the expected benefit and harm.

Regarding both prognostic and theranostic biomarkers, specific randomized trials assessing their clinical utility could be important for validation. The pharmacogenetic testing for warfarin dosing illustrates the difficulties for showing clinical utility [56]. On the other hand, the predictive effect of the HLA-B*5701 genetic variant for hypersensitivity reaction to Abacavir illustrates a clear success in validating a clinical useful theranostic biomarker [57]. However, true biomarkers could fail to demonstrate a clinical utility if for example they are very rare in the studied population. More research are needed in the exploration and validation of biomarker [34].

We did not discuss the targeted therapy. As they have been developed to treat a specific pathophysiological mechanism, the mutation they target are expected to be predictive of the TE. However, the SHIVA trial failed to show a benefit when personalizing the treatment according to tumor molecular profiling, but outside their indications [58]. Figure 5 (5.A and 5.B) summarizes different experimental designs and their interpretations.

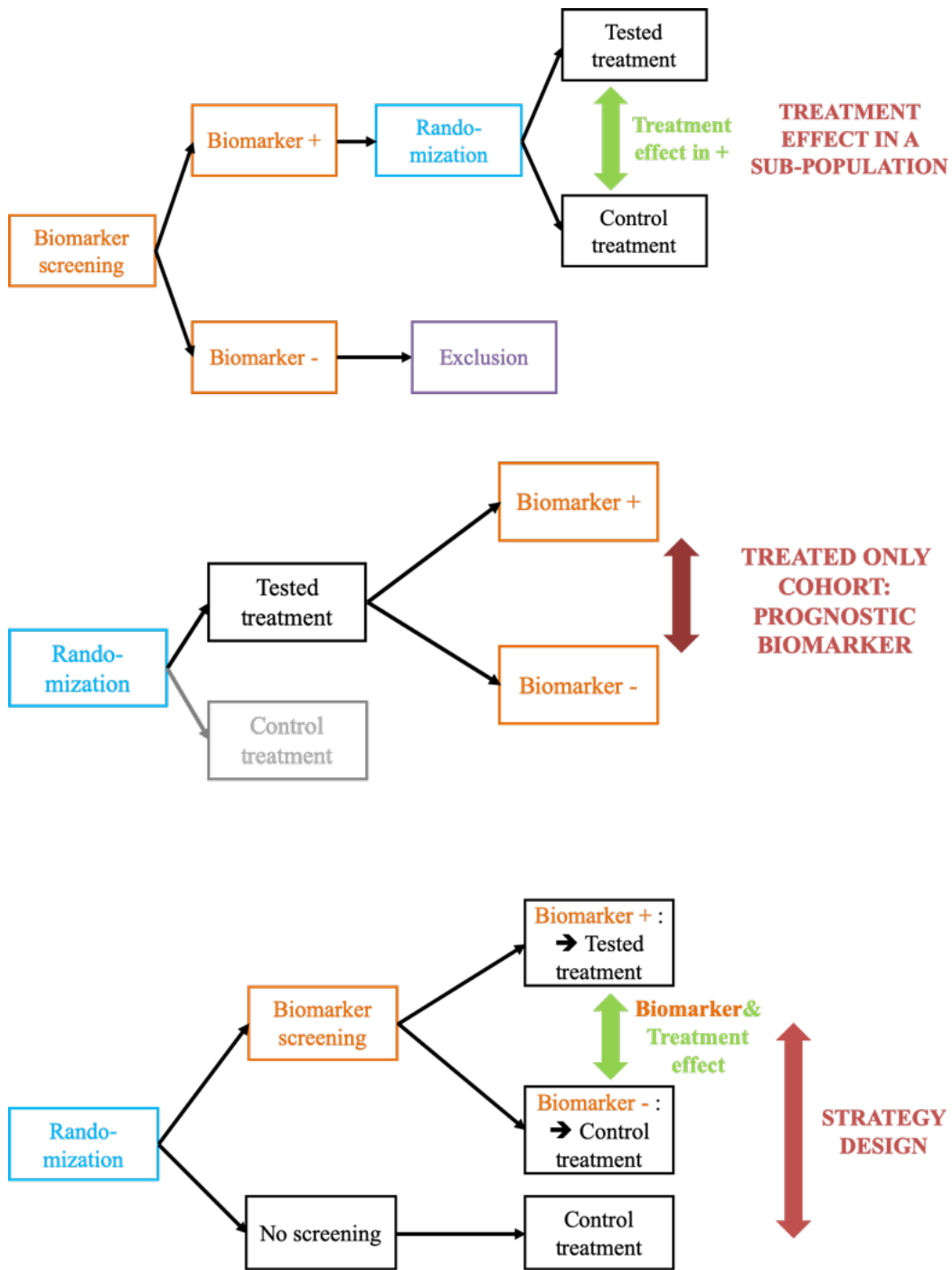


Fig 5.A. Designs not assessing a treatment – biomarker interaction per se.

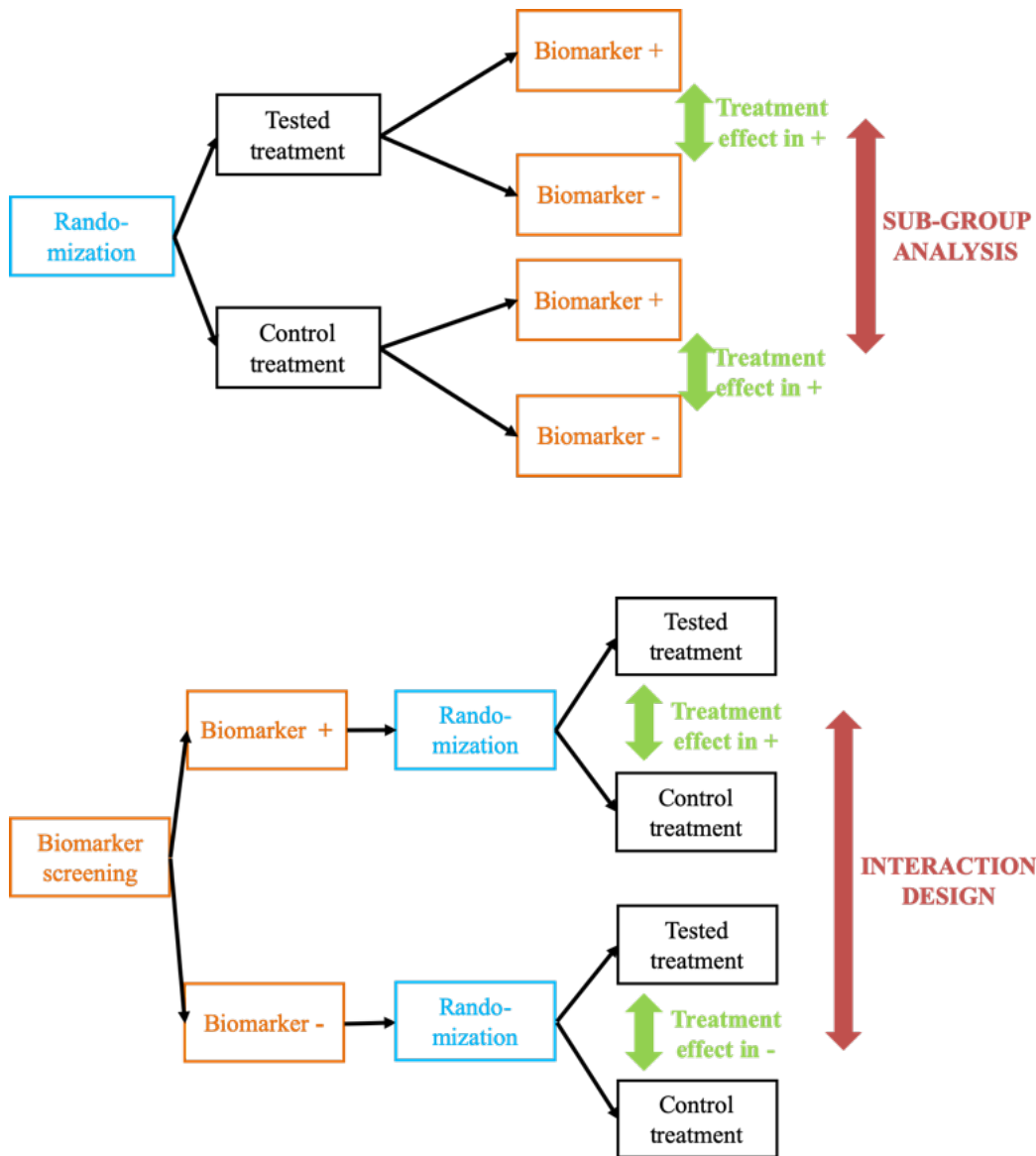


Fig 5.B. Designs assessing a treatment – biomarker interaction (see the “Warning about the sub-group analyses” section for the assessment of an interaction with the sub-group analysis).

Figure 5. Different designs assess different types of biomarkers. “+” refers to the presence of the biomarker, “-“ to its absence.

Warning about the sub-group analyses

Sub-group analysis can be helpful for identifying biomarker, whose are needed for stratifying the patients, both for the spontaneous risk and/or the response to the treatment. Once a trial is conducted, sub-group are easily made, and can lead to new hypothesis. Such analyses are widely reported in clinical trials. However, sub-group analyses are at high risk of false positive results, through multiple testing without adjustment. Thus, most positive exploratory sub-groups analyses are false [28]. Positive confirmatory sub-groups are often overestimated [28]. Sub-groups analyses are prone to false negative results as well. Indeed, when a sub-groups analysis did not show any difference in TE, this would likely be because of a lack of statistical power for testing interaction [53]. Sub-groups analysis suggesting no TE in a particular population can lead to wrong therapeutic abstention [59]. Sub-groups analyses are also prone to spin of conclusion [60]. Some authors suggest to abandon “one-variable-at-a-time” sub-groups analysis, and move towards multiple variables risk model [28]. Finally, the research for biomarker should also fit in the hypothetico-deductive approach.

Personalization according to the treatment’s response, surrogate endpoint

A surrogate endpoint is a specific kind of biomarker: the effect of an intervention should be similar on the surrogate as on the clinical outcome of interest [61]. The FDA defines it as “a substitute for a direct measure of how a patient feels, functions, or survives. A surrogate endpoint [...] is expected to predict that clinical benefit.” [62]. Surrogate endpoint can be very helpful by reducing the sample size in early phase of drug development. However, careful examination of their validity in predicting the clinical benefit is highly needed. Many historic examples are available for illustrating failure in drug’s evaluation because of false surrogate endpoints [63]. The figure 6, adapted from Fleming et al, illustrates the reasons for failure of surrogate endpoints [63]. Indeed, surrogate can be falsely negative, when the clinical outcome is in fact improved by the treatment, through another pathway [64]. But more importantly, several historic examples showed a well impact on the surrogate, but a negative effect, *i.e.* harmful, on clinical outcomes. After a myocardial infarct, a correlation was found between ventricular arrhythmia and the risk of death. Therefore, anti-arrhythmic drugs were widely prescribed in those patients: through their effect on ventricular arrhythmia, they were supposed to be beneficial regarding mortality. Actually, the CAST

trial eventually revealed their lethal effect in this population [65]. There are numbers of publications about the evaluation of candidate biomarker for being surrogate endpoint [61, 63, 66-69]. The FDA defines three levels of surrogate, according to their level of proof: “Candidate”, “Reasonably likely”, “Validated” [62]. Ciani *et al.* recently summarized a hierarchy of evidence for surrogate validations, see Table 1 [61]. It should be noted that a surrogate must not be considered as ‘validated’ itself, *i.e.* in general, but always in a specific context, for a specific intervention in a given clinical situation, and cannot be extrapolated to another intervention [67]. Moreover, assessing a treatment with a surrogate could be associated with an overestimation of the effect size of the TE [70]. In the oncologic area, it has recently been showed that most clinical trials evaluating surrogate found low correlation with survival [71]. Finally, surrogacy imputation remains a current issue [72].

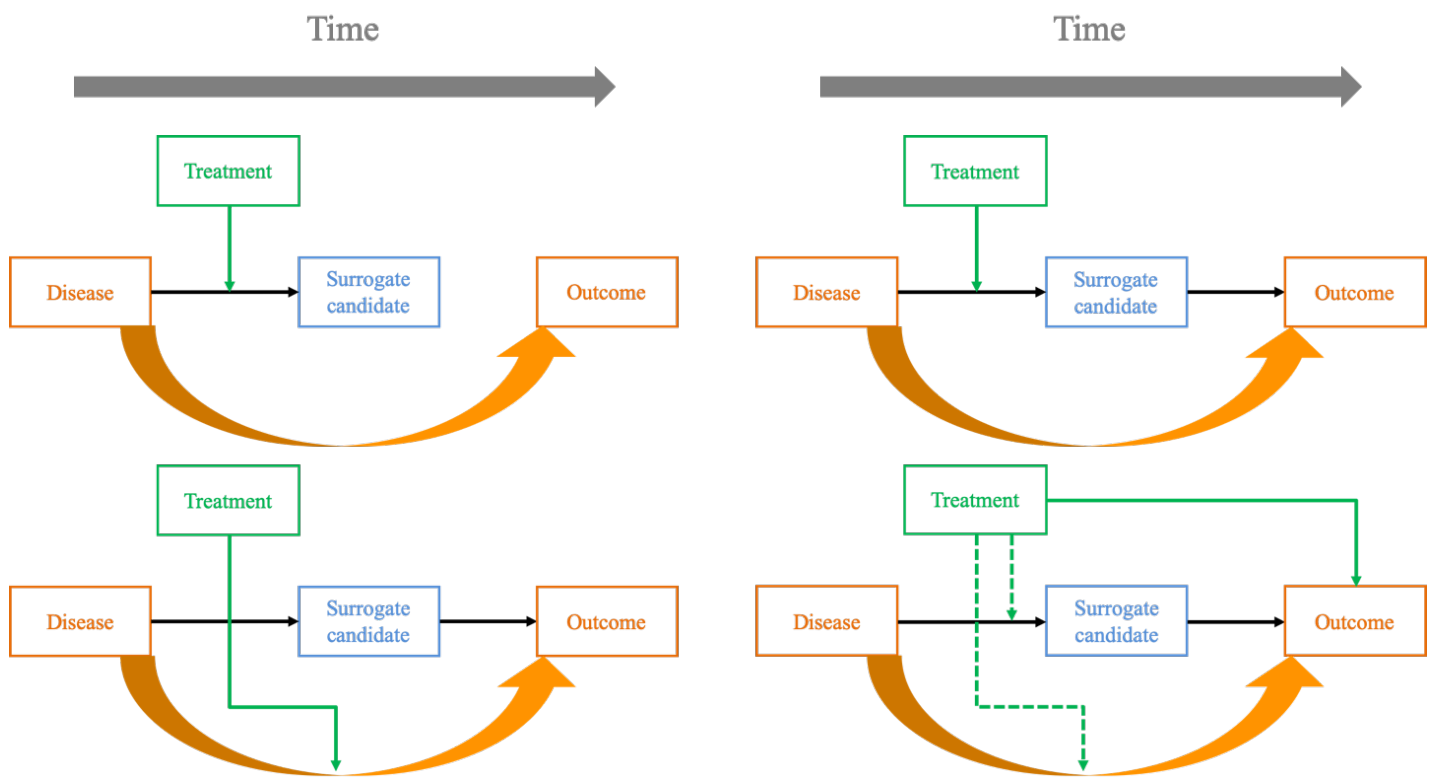


Figure 6. Reasons for failure of surrogate end points, adapted from Fleming et al [63] (up left: surrogate is not in the pathway of the disease; up right: the treatment affects the pathway of the surrogate, but other pathways exist; down left: the treatment acts through another pathway; down right: the treatment acts through mechanisms of action independent of the disease process and the surrogate. Dotted lines illustrate mechanisms of action that might exist).

Level of evidence	Requirement	Source of evidence
1	Treatment effect on surrogate corresponds to treatment effect on final outcome	Randomized controlled trials showing that changes in the surrogate are associated with commensurate changes in the final outcome
2	Consistent association between surrogate and final outcome	Epidemiological/observational studies
3	Biological plausibility of relation between surrogate and final outcome	Pathophysiological studies and understanding of the disease process

Table 1. Hierarchy of evidence for surrogate end point validity, adapted from Ciani et al [61].

Furthermore, a recent epidemiological approach appears to be helpful for testing surrogacy [73, 74]. The Mendelian randomization use the hazard of the genetic distribution during the meiosis for providing robust information when assessing causality, like a ‘natural randomization’, under several hypotheses [75]. Briefly, it searches for a relationship between a genetic factor and a clinical outcome of interest. The genetic factor should be known to be associated with an intermediate outcome of interest, a modifiable risk factor of the disease, but should not be directly associated with the clinical outcome. Therefore, if the genetic factor and the clinical outcome are associated, this would be through the intermediate outcome, thus supporting its causality in the occurrence of the clinical outcome of interest [76].

The blood level of Low-Density Lipoprotein cholesterol (LDL) illustrates well the difficulty of using surrogate endpoint for personalizing the clinical practice, despite all the evidences accumulated in this area. The recent guidelines of the European Society of Cardiology (ESC) and the European Atherosclerosis Society (EAS) for the management of dyslipidemias recommend LDL targets [77]. First, many different approaches consistently showed the LDL as causal in CV disease, as mendelian randomization study [78]. Moreover, individual patient data meta analyses (IPD MA) confirmed a dose-dependent reduction in cardiovascular (CV) events with LDL lowering agents [79], and the surrogacy of LDL has been documented [80]. Finally, an individual variability in the LDL response to dietary and pharmacological treatments has been observed. Then, using LDL target would help to individualize the CV risk reduction [77]. However, pursuing a ‘target to treat’ raises several practical concerns for the physician. Would the physician treat a patient stratified at high risk of complications, but exhibiting otherwise a level of the surrogate endpoint at the recommended target? If a patient treated with the validated drug and dose appears to be below the target, should the physicians decrease the treatment, even if the lower dose has not been validated for reducing clinical outcomes? What are the adverse effects when the patient himself/herself show high stringency to get the lower he/she could, or display culpability and/or anxiety because he/she fell, he/she fails to reach the recommended number? Furthermore, the choice of the target itself raises several issues. Should an absolute value be used, as in the European guidelines [77], or a relative value of the reduction, as in the U.S guidelines [81]? Even with the same scale, different guidelines recommend different absolute value [77, 81]: how to decide the optimal goal, how far should we get? Moreover, the European guidelines acknowledge themselves that “RCTs have not examined different LDL-C goals systematically, but felt that it was appropriate to look at the totality of the evidence” [77]. However, using extrapolation for assessing potential benefit expose the patient to an unknown—and potentially higher—risk of adverse event, which could negative the benefit—risk balance, as we will see in the following section, applied to type 2 diabetes. The question of the blood pressure level as a target is addressed in the article constituting the second part of this thesis.

EBM and personalized medicine in type 2 diabetes

Pharmacology of type 2 diabetes and EBM

Type 2 diabetes (T2D) is a public health issue. Its incidence is dramatically increasing in the world, from around 100 million people in 1980 to around 400 million in 2014 [82]. This metabolic disease is characterized by hyperglycemia, as a consequence of a functional impairment in insulin secretion, insulin action or both [83]. Its complex physiopathology implicates both genetic and environmental risk factors [84]. Long term hyperglycemia is associated with an increased risk of micro- and macrovascular outcomes [82]. Its management includes lifestyle health care, hypoglycemic treatment, control of other CV risk factors, weight loss medications and metabolic surgery [85]. Up to now, the use of hypoglycemic drugs was justified regarding their effect on glycemic control. Many hypoglycemic drug classes are now available and can be classified according to their mechanism of action, as illustrated in figure 7. Metformin, the only biguanide available, represent the first line therapy for T2D [86]. Metformin decrease the insulin-resistance, especially through its reduction of hepatic glucose production. Lactic acidosis is its more feared side effect; therefore, metformin is contraindicated in case of organ insufficiency. The other insulin-sensitizers are the thiazolidinediones (TZD, or glitazones): the rosiglitazone and the pioglitazone. They act as agonist of the Peroxisome Proliferator-Activated Receptors-gamma (PPAR-gamma) transcription factor. On another side, the incretinomimetics, named after the incretin effect, increase the secretion of insulin, but in a glucose dependent manner. They are represented by oral drugs, the DiPeptidyl Peptidase-4 inhibitors (DPP4 inhibitors), and injectable medications, the Glucagon Like Peptide 1 receptor agonists (GLP1 receptor agonists). Other insulin secretagogues are the sulfonylureas and the glinides, but they act independently of the available glucose. Then, they particularly exposed the patient to the risk of hypoglycemia and weight gain, as do the insulin analogs. Two other hypoglycemic drugs act on the input and the output of glucose: the alpha glucosidase inhibitors decrease the intestinal absorption of glucose, and the Sodium-Glucose cotransporter 2 inhibitors (SGLT2 inhibitors) increase its renal excretion. Other drug classes are also available, depending on the country (Bile acid sequestrants, Dopamine-2 agonists). The history of hypoglycemic drugs is full of illustrations of the need for EBM.

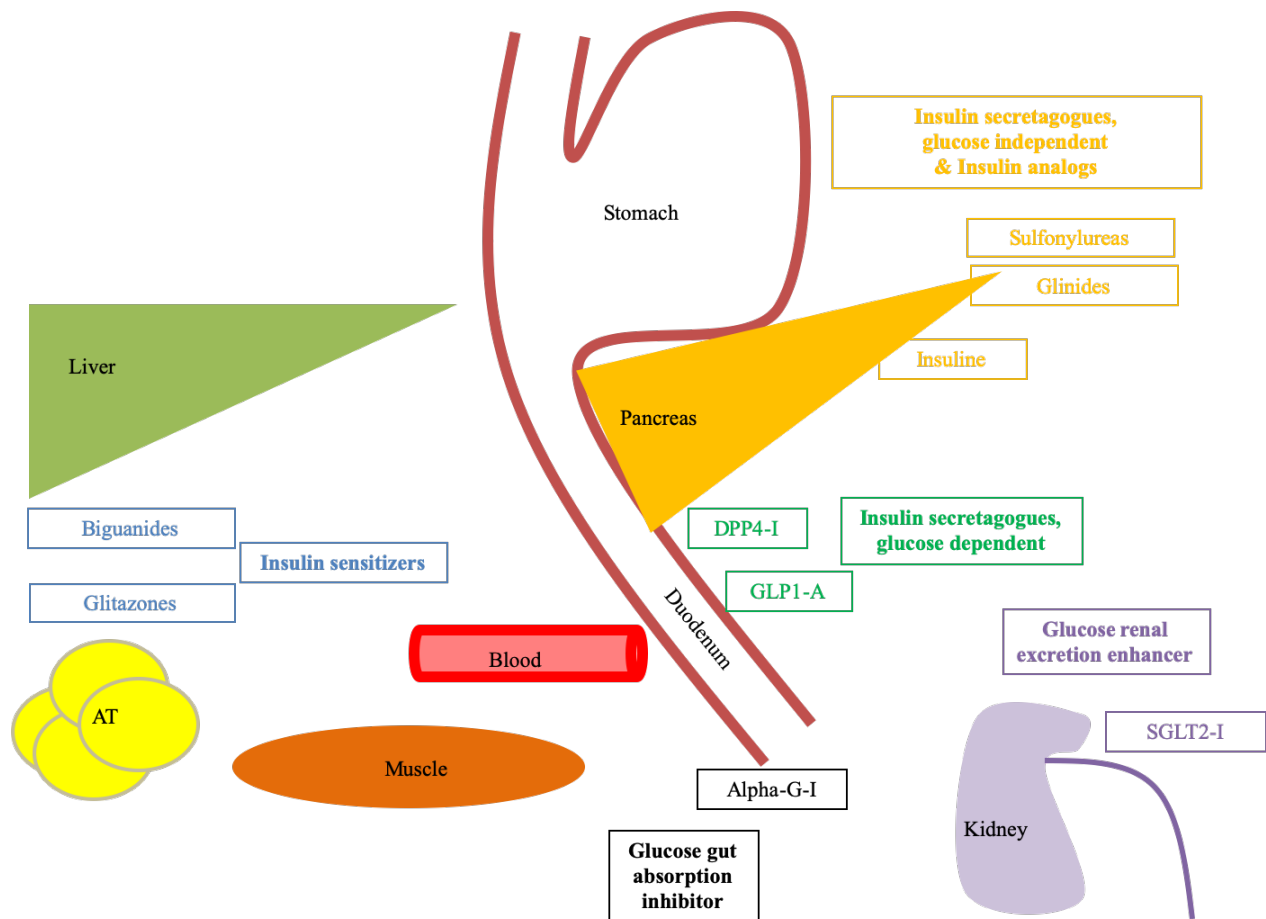


Figure 7. The main hypoglycemic drug classes.

AT: adipose tissue. Alpha-G-I: alpha glucosidase inhibitor. DPP4-I: DPP4 inhibitors. GLP1-A: GLP1 receptor agonists. SGLT2-I: SGLT2 inhibitors.

Cardiovascular diseases remain the leading cause of death in people with DT2 [85]. Thus, we focused here on the effect of glucose lowering drugs on prevention of macrovascular complications. However, assessing their effect on microvascular complications also is a matter of interest. Coca *et al.* showed that intensive glucose control was associated with a decreased risk of micro- and macroalbuminuria, but evidences regarding clinical renal outcomes (end stage renal disease, ...) were lacking [87]. However, recent data suggests nephroprotection properties of the last hypoglycemic drug classes [88], especially SGLT2 inhibitors [89] and GLP1 receptor agonists [90]. Regarding the risk of retinopathy, Tang *et al.* recently observed an association between the decrease in glycated hemoglobin (HbA1c) and the risk of retinopathy in a meta-regression of RCT [91]. They also observed an increased risk of retinopathy with sulfonylureas compared to placebo

and SGLT2 inhibitors using a network meta-analysis of RCT [91]. At last, evidence regarding neuropathy are still lacking [92].

During the 1960s, the UGDP trial [93] was one of the first RCTs conducted [94]. Two decade before the CAST trial, the UGDP already illustrated the danger of intermediate endpoint. Tolbutamide and phenformin were largely prescribed, as benefits were expected regarding their effect on blood glucose level. However, the UGDP trial showed an increased in mortality for both of them. A scientific debate has been ongoing for years, regarding the methodological tool – innovative at this time— as ‘intention to treat’ analysis they used, and the impact of disequilibria in baseline characteristics despite randomization [93, 95]. Those unexpected results lead to a huge health scandal, even reaching the Supreme Court of the United States of America [94]. Both tolbutamide and phenformin were eventually withdraw from the market.

In 1976, a few years after the release of the UGDP trial, the benfluorex obtained a market authorization in France, as add on therapy for hyperlipidemia and for diabetes with obesity [96]. Indeed, the appetite suppressant properties of this amphetamine derivative was used as weight control treatment, also in an off-label fashion. Already in 1996, an increased risk of pulmonary hypertension was observed with other amphetamine related weight control drugs, fenfluramine [97], leading to its removal. However, the benfluorex remained on the market. Another decade after, Frachon et al showed an increase in risk of unexplained valvular heart disease associated with the use of benfluorex in a case control study [98]. Finally, three decades after its authorization, the benfluorex was withdrawn in France [96]. As benfluorex and fenfluramine, other drugs seem to cause valvular heart disease through their agonist action on 5-HT_{2B} serotonergic receptors [99].

In 1998, the UKPDS 34 trial found a decrease in the risk of death associated with the use of metformin [100]. Since, this biguanide has become the first pharmacological line of diabetes treatment guidelines. However, the same UKPDS 34 trial also observed an increased risk of death with the use of metformin on top of sulfonylureas [100]. Despite these conflicting results, metformin and sulfonylureas remind an important combination in the therapeutic strategy for many decades, still recommended in second line in France by official guidelines of the French National

Authority for Health (HAS for 'Haute Autorité de Santé) (on top of lifestyle care) [101]. Finally, the example of the UKPDS 34 trial illustrated a possible citation bias [102].

In 2007, a meta-analysis showed a cardiotoxicity associated with the rosiglitazone [103], which was then withdrawal from the market in France. Then, public authority required to demonstrate cardiovascular safety for hypoglycemic agents [104]. The area of CardioVascular Outcomes Trials (CVOT) was really opened with the DPP4 inhibitors. Non inferiority trials against placebo was the design of choice. Non-inferiority trial against placebo regarding Major Adverse Cardiovascular Events (MACEs) is highly paradoxical, given the acceptance of a loss of efficacy inherent to the choice of a non-inferiority margin. Initially, the non-inferiority margin was 1.8 [104], *i.e.* accepting an increase in risk of MACE of 80% compared to placebo, as "safe". Fortunately, most of those trials were also powered enough for testing superiority.

Since 2015, the last hypoglycemic drugs, the SGLT2 inhibitors and the GLP1 receptor agonists, eventually showed clinical benefits on macrovascular events in RCTs [105-107]. The first article included in this thesis and its protocol (Appendix 1) summarize the recent developments in CVOT of hypoglycemic drugs and their meta-analyses. Finally, the assessment of the intensification of glycemic control with recent RCTs (ACCORD, ADVANCE and the VADT trials) [108-110], highlighted the necessity of personalizing the glycated hemoglobin (HbA1c) target according to the patient.

Personalizing health care in type 2 diabetes

International guidelines of T2D management include more and more personalized perspective [85, 111]. First, the clinical characteristics of the patient should be considered for proposing a tailored care [85]. Indeed, patients with previous CV disease especially will benefit from SGLT2 inhibitors and/or GLP1 receptor agonist. If the patient is fragile regarding the risk of hypoglycemia, incretin, SGLT2 inhibitor or TZD, if available, should be considered. If the need of the patient is to control or to lose weight, GLP1 agonist or SGLT2 inhibitor will be helpful. Socio-economic arguments are also relevant, depending on the country, and can lead to prefer sulfonylurea or TZD [85]. Finally, a new debate arise regarding the respective place of metformin

and SGLT2 inhibitors or GLP1 receptor agonist, with conflicting recommendations [85, 111]. The personalized HbA1c target will be discussed in the surrogate section.

Prognostic factor for personalizing treatment in type 2 diabetes

One way to personalize diabetes care is to stratify the spontaneous risk of outcome, for assessing absolute benefit of treatment [112]. Vijan *et al.* simulated the absolute benefit of intensified glucose control, by applying the relative risk reduction (RRR) of several outcomes – micro- and macro vascular–, observed in RCT, on virtual population [113]. They modelled the absolute benefit for a reduction of the HbA1c from 8.5% to 7% in different phenotypes: from diagnosis of T2D at 45 years old to diagnosis at 75 years old. Their simulation suggested that less than 1% of patients diagnosed at 65 years old, or older, would have benefit for microvascular outcomes within their lifetime. However, the number needed to treat (NNT) for non-fatal myocardial infarction (MI) remained more consistent across the phenotypes. They also discussed the time horizon needed to benefit from intensive glucose control. The UKPDS 33 trial observed a benefit on microvascular endpoint after ≈ 9 years of intensive treatment [114]. On the other hand, patients hospitalized for heart failure for the first time exhibit a 70% 5-year mortality rate [115, 116]. Thus, taking into account the global prognostic of the patient can help to prevent overtreatment [112]. Moreover, the risk of adverse event also exhibits some diversity. Therefore, estimating the personalized risk of safety endpoint can help to better estimate the individualized benefit—harm balance of a treatment in a group of patient [28]. The IRIS trial showed a decrease in risk of recurrent ischemic event (MI or stroke) with pioglitazone (in non-diabetic patients but with insulin resistance), but with an increased risk of fracture [117]. Viscoli *et al.* proposed a simple score of fracture's risks, to discriminate subject at high versus low risk of fracture, and estimated the effect of pioglitazone within fracture risk strata. Pioglitazone prevented six CV events per serious fracture in the low risk of fracture strata. However, pioglitazone prevented only one CV event per serious fracture in the high risk of fracture strata [118].

Theranostic factor for personalizing treatment in type 2 diabetes

Around half of newly treated patients with metformin do not reach sufficient response to HbA1c target [119]. One other way to personalize diabetes care is to use predictive/theranostic

biomarker of the TE. Such TE modifier may be available at different level. At the clinical level, a short duration of diabetes could be predictive of the glycemic response to metformin [119], lower body mass index (BMI) could be associated with greater glycemic response to sulfonylureas [120], obesity seems to be associated with a greater HbA1c reduction with TZD [120]. Surprisingly, a lower BMI may be associated with an improved glycemic response to metformin [119]. Similarly, an Individual Patient Data Meta-Analysis of the liraglutide clinical trial program only observed a non-clinically relevant association between baseline BMI and HbA1c reduction for liraglutide at 1.8mg [121]. At the biological level, biomarkers of higher insulin resistance appear to be associated with a decrease in glycemic response to DPP4 Inhibitors [122]. The HbA1c and blood fasting glucose at the introduction of DPP4 inhibitor also seems to explain the variability in HbA1c response to DPP4 inhibitors [123]. Such effect modifier may also be found at the genome level. With the new genome sequencing technology, there is a growing interest in pharmacogenomics, *i.e.* the search for genetic variants associated with therapeutic responses [124]. Several genetic variants have been identified in pharmacogenomics of hypoglycemic drugs [125-127]. Regarding efficacy, heritability could be responsible for around one third of the absolute HbA1c decrease with metformin [128]. Genes of the organic cation transporter family (OCTs), a drug transporter, the gene of an ATM serine/threonine kinase (associated with ataxia telangiectasia), and loci in the SLC2A2 gene (coding for the GLUT2 glucose transporter) have been associated with glycemic response to metformin [127]. Regarding sulfonylureas also, genes implicated both in the pharmacokinetics and genes implicated in the pharmacodynamics of the sulfonylureas have been associated with differential glycemic response: CYP2C9, a cytochrome P450 implicated in the metabolism of sulfonylureas; and genetic variants of the different sub-units ABCC8 and KCNJ11 of the ATP-sensitive potassium channel to which the sulfonylureas are targeted [127]. Some variants are also described as potentially implicated in the metabolic response to DPP4 inhibitors and GLP1 Receptor agonist [127]. Several genes have been associated with the safety of hypoglycemic drugs: the SLC22A1 gene (an OCT drug transporter) may be related to the gastrointestinal adverse effects of metformin, the CYP2C9 with the risk of hypoglycemia when using sulfonylureas. However, the available evidence for pharmacogenomics of ADR in T2D remains restricted [125]. Finally, the level of evidence for assessing effect modifier of hypoglycemic drugs remains limited.

Surrogate in type 2 diabetes

At last but not least, HbA1c is used as a surrogate for personalizing diabetes care. The last European guidelines recommend to differentiate HbA1c target according to the patients characteristics, for example from “6.0—6.5%” in young people with a recent DT2 and no CV disease—“if achieved without significant hypoglycemia”—, to 8 even 9% in elderly patients with multiple comorbidities, limited life expectancy [111]. The prognostic effect of HbA1c on mortality has been confirmed in large epidemiologic study [129] and meta-analyses of observational data [130, 131]. Some mendelian randomization studies have recently assessed the relationships between diabetes and/or glycemic exposure and long-term CV events, supporting the causality of long-term hyperglycemia exposure and macrovascular outcomes. Ahmad *et al.* observed a small association between multiple genetic variants associated to T2D and Coronary Heart Disease (CHD) risk [132]. Ross *et al.* reported a relationship between nine genetic variants associated with HbA1c and risk of Coronary Artery Disease (CAD) [133]; Leong *et al.* reported similar results using 50 genetic variants associated to HbA1c [134]. The translation of intensive glucose control effect in type 1 diabetes [135] to type 2 diabetes patients remains unclear. However, the demonstration of its theranostic value and clinical utility in type 2 diabetes has been discussed [136, 137]. Intensification trials have showed conflicting results. The ADVANCE trial suggested a reduction in new or worsening nephropathy, mainly in microalbuminuria, when achieving 6.5 versus 7.3% of HbA1c [108]. The VADT trial also suggested beneficial effect only on progression of albuminuria when achieving 6.9% of HbA1c versus 8.4%. However, the ACCORD trial observed an increase in mortality when pursuing a HbA1c target below 6.0% (achieved: 6.4% versus 7.5%) [110]. Meta-analyses of the intensification trials showed some macro-vascular benefit: around 15% decrease of the risk of non-fatal MI for a decrease of 1% of the HbA1c, and a decrease of microalbuminuria; but with an increased risk of hypoglycemia [138, 139]. Meta-regression using aggregated data of RCT showed conflicting results regarding the association between HbA1c reduction and CV risk reduction [137, 140]. A recent meta-regression including both the last CVOT up to February 2019 and intensive glucose control trials suggested an association between HbA1c decrease and risk of MACE [141]. However, meta-regression on aggregated data exhibits several limits, including the ecological bias. Indeed, correlations observed in meta-regressions should be seen as observational and do not have the level of evidence of RCT for assessing causality, especially using aggregate data [142]. A recent Individual Patient Data Meta-analysis suggested

benefits of HbA1c decrease on microvascular events, but mainly on intermediate endpoints [92]. Furthermore, the long term follow up of UKPDS [143] (and of DCCT/EDIC trials in type 1 diabetes [144]) have suggested a long term beneficial effect of glucose control even after the period of intensive glucose control. This has led to the hypothesis of a legacy effect, *i.e.* a metabolic memory, translating the early glucose control in prolonged benefits. However, the last follow up of intensive glucose control in DT2 did not confirmed such post-treatment effect [145]. Withdrawal RCT would help to better assess the potential of such “delayed surrogate” [146].

PROBLEMATIC AND OBJECTIVE

Personalized and evidence-based medicine in type 2 diabetes remains a challenge. We aimed to provide a mean treatment effect estimation of hypoglycemic drugs on cardiovascular outcomes; and exploring potential tools for personalizing the treatment effect estimation. This thesis is structured in three parts: i) estimating a mean TE, ii) assessing a surrogate, iii) evaluating trials designed for effect modifier assessment. We worked at a meta-research level and at a clinical trial level.

Several hypoglycemic drugs are now available, with different level of proof of their efficacy on CV outcomes. However, how they compared to each other remain unclear. We aimed to provide a global assessment of each contemporary hypoglycemic drug classes. Using all the available evidence through a network meta-analysis approach would help to estimate the mean TE of each hypoglycemic drug classes, compared to control and to each other. This part is presented in the first published article of the thesis. This part is completed by an assessment of the benefit—risk balance of the SGLT2 inhibitors.

Taking care of patient with T2D include taking care of the other CV risk factor. High blood pressure (BP) remains an issue in patients with T2D, with conflicting recommendations regarding the level of BP to target. We aimed to update and extend the characterization of the relationship between BP control and CV outcomes in T2D. Using all the available evidence through a meta-regression analysis approach would help to assess a surrogate endpoint at a meta level. This part is presented in the second published article of this thesis.

Finally, identification of theranostic biomarker in clinical trial is highly limited by the need for statistical power to detect such interaction. Power of sub-group analyses is already well described for parallel group (PG) design. Pros and cons of cross-over (CO) design compared to parallel group is already well known for estimating the TE. We aimed to assess the pros and cons of the CO design compared to the PG design for testing such theranostic biomarker. This part is presented in the third published article of this thesis. This part is completed by a short meta-epidemiological survey assessing the reporting in pharmacogenetic studies.

FIRST PART.

MEAN TREATMENT EFFECT ESTIMATION OF HYPOGLYCEMIC DRUG CLASSES

The first part is divided in two sections.

In the first section, we applied state of the art meta-analytic approach to take into account all the available evidence for comparing several drug classes, *i.e.* a network meta-analysis, which help to integrate both direct and indirect comparisons. Applying this tool to hypoglycemic drug classes, it allows us to provide mean TE estimation for different outcomes of interest:

- Efficacy and safety outcomes:
 - Overall mortality,
 - Cardiovascular mortality,
- Efficacy outcomes:
 - Major Adverse Cardiovascular Events (MACE),
 - Myocardial infarction,
 - Stroke,
- Safety outcomes:
 - Serious hypoglycemia,
 - Serious adverse events.

In the second section, we completed this part with a benefit—risk balance estimation of the SGLT2 inhibitors.

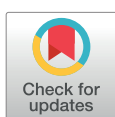
First part – first section. Distinct assessments of benefit and risk: a network meta-analysis

This section reports the original research “GLUcose COntrol Safety & Efficacy in type 2 DIabetes, a NETwork meta-analysis (GLUCOSE DINET)”. The protocol was previously registered in the PROSPERO database (CRD42016043823) [147]. The published article of the rationale and design of the study is available in appendix 1 [148].

RESEARCH ARTICLE

GLUcose COntrol Safety & Efficacy in type 2 Dlabetes, a systematic review and NETwork meta-analysis

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Abstract

Background

The last international consensus on the management of type 2 diabetes (T2D) recommends SGLT-2 inhibitors or GLP-1 agonists for patients with clinical cardiovascular (CV) disease; metformin remains the first-line glucose lowering medication. Last studies suggested beneficial effects of SGLT-2 inhibitors or GLP-1 agonists compared to DPP-4 inhibitors, in secondary CV prevention. Recently, a potential benefit of SGLT-2 inhibitors in primary CV prevention also has been suggested. However, no comparison of all the new and the old hypoglycemic drugs is available on CV outcomes. We aimed to compare the effects of old and new hypoglycemic drugs in T2D, on major adverse cardiovascular events (MACE) and mortality.

Methods and findings

We conducted a systematic review and network meta-analysis of clinical trials. Randomized trials, blinded or not, assessing contemporary hypoglycemic drugs on mortality or MACE in patients with T2D, were searched for in Medline, the Cochrane Central Register of Controlled Trials (CENTRAL), and ClinicalTrials.gov. References screening and data extraction were done by multiple observers. Each drug was analyzed according to its therapeutic class. A random Bayesian network meta-analysis model was used. The primary outcomes

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Abbreviations: BMI, Body mass index; CV, Cardiovascular; CVD, Cardiovascular diseases; FDA, Food and Drug Administration; HbA1c, Glycated hemoglobin; MACE, Major Adverse Cardiovascular Event; OR, Odds ratio; RCTs, Randomized clinical trials; SUCRA, Surface Under the Cumulative Ranking Curve; T2D, Type 2 Diabetes.

were overall mortality, cardiovascular mortality, and MACE. Severe adverse events and severe hypoglycemia were also recorded.

175,966 patients in 34 trials from 1970 to 2018 were included. No trials evaluating gli-nides or alpha glucosidase inhibitors were found. 17 trials included a majority of patients with previous cardiovascular history, 16 trials a majority of patients without. Compared to control, SGLT-2 inhibitors were associated with a decreased risk of overall mortality (OR = 0.84 [95% CrI: 0.74; 0.95]), SGLT-2 inhibitors and GLP-1 agonists with a decreased risk of MACE (OR = 0.89 [95% CrI: 0.81; 0.98] and OR = 0.88 [95% CrI: 0.81; 0.95], respectively). Compared to DPP-4 inhibitors, SGLT-2 inhibitors were associated with a decreased risk of overall mortality (OR = 0.82 [95% CrI: 0.69; 0.98]), GLP-1 agonists with a decreased risk of MACE (OR = 0.88 [95% CrI: 0.79; 0.99]). Insulin was also associated with an increased risk of MACE compared to GLP-1 agonists (OR = 1.19 [95% CrI: 1.01; 1.42]). Insulin and sulfonylureas were associated with an increased risk of severe hypoglycemia. In the trials including a majority of patients without previous CV history, the comparisons of SGLT-2 inhibitors, metformin and control did not showed significant differences on primary outcomes. We limited our analysis at the therapeutic class level.

Conclusions

SGLT-2 inhibitors and GLP-1 agonists have the most beneficial effects, especially in T2D patients with previous CV diseases. Direct comparisons of SGLT-2 inhibitors, GLP-1 agonists and metformin are needed, notably in primary CV prevention.

Trial registration

PROSPERO [CRD42016043823](https://doi.org/10.1186/17454219).

Introduction

Type 2 diabetes (T2D) is a public health issue, with a dramatically increasing incidence in the world. Cardiovascular diseases (CVD) are the main cause of mortality in T2D patients. Many hypoglycemic drugs are currently available; their benefits have been evaluated with conflicting results. Network meta-analysis allows several treatments to be compared through direct and indirect comparisons. Previous network meta analyses on hypoglycemic drugs were focused on intermediate outcomes, such as glycated hemoglobin (HbA1c), or did not compare the effect of the drugs on mortality or major adverse cardiovascular events (MACE) in the absence of data [1]. Since then, new clinical trials assessing SGLT-2 inhibitors or GLP-1 receptor agonists showed promising results on mortality or on cardiovascular outcomes (EMPARE-G-OUTCOME [2], CANVAS-Program [3], LEADER [4], SUSTAIN-6 [5]), allowing Zheng et al to show a lower mortality rate with SGLT-2 inhibitors or GLP-1 receptor agonists compared to control or DPP-4 inhibitors, mainly in secondary cardiovascular prevention [6]. The last international consensus recommends SGLT-2 inhibitors or GLP-1 receptor agonists for patients with clinical cardiovascular disease; metformin remains the first-line therapy for glucose lowering medication [7]. However, the last cardiovascular outcome trial assessing a GLP-1 receptor agonists did not showed a decreased risk of overall mortality [8]. Following the recently published DECLARE TIMI 58 trial [9], a meta-analysis suggested a potential benefit

of SGLT-2 inhibitors in primary cardiovascular prevention, but did not include GLP-1 receptor agonists or metformin [10]. Most of hypoglycemic drugs have not been directly compared in head to head clinical trials. Up to now, no comparison of all the new and the old hypoglycemic drugs is available on major cardiovascular outcomes. The purpose of this study was to compare all the currently available hypoglycemic drug classes on major adverse cardiovascular events (MACE) and on mortality in patients with T2D, through a network meta-analysis approach of randomized clinical trials.

Protocol registration number

PROSPERO CRD42016043823

Methods

Methods have been previously described [11]. This meta-analysis was conducted following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement and its extension for reviews incorporating network meta-analyses (S1 Fig) [12].

Search strategy and selection criteria

Randomized clinical trials (RCTs), double-blind or open, including patients with type 2 diabetes, evaluating a specific contemporary hypoglycemic drug through clinically relevant outcomes (as primary or secondary outcomes) have been included. Clinically relevant outcomes considered here were: overall mortality, cardiovascular mortality, MACE (myocardial infarction–MI–, acute coronary syndrome, or stroke) and diabetic microangiopathy (new or worsening) that is clinically symptomatic or leading to a therapeutic intervention such as surgery, photocoagulation, or dialysis. Trials which used drugs which have been withdrawn from the market (such as phenformin and tolbutamide) were not included. Trials comparing drugs of the same therapeutic class and glucose lowering treatment intensifications without specific drugs were excluded.

English language published trials were searched in PubMed and Central databases, without time restriction, up to March 2016 (see S1 Table). Unpublished and other on-going trials were searched through references of published meta-analyses, ClinicalTrials.gov, congress abstracts. On-going trials of potential interest were followed until November 2018 for final results. The study selection, data extraction and risk of bias assessment were performed by at least two independent reviewers (GG and SR, GN, FaG, AG or TL), consensus was reached in the case of disagreements. Studies were first screened on the basis of their titles and abstracts, then included based on the full text. The quality of the studies was assessed using the Cochrane Collaboration's tool for assessing risk of bias in RCTs [13]. Summary estimates of the treatment effect and summary of patients' characteristics (age, gender, cardiovascular risk factors) were extracted.

Outcomes of the meta-analysis

Primary outcomes of this analysis were: overall mortality, cardiovascular mortality, and major adverse cardiovascular events (MACE: cardiovascular death, non-fatal MI, and non-fatal stroke), as described in the protocol [11]. For MACE, proxies have been used for 10 studies among the 27 trials with available data (see S2 Table). Diabetic microangiopathy was a pre-specified secondary outcome, but its reporting in the included studies was heterogeneous and not available in many studies. Instead, detailed results on macrovascular outcomes (all and non-fatal MI, all and non-fatal stroke) were retrieved. Serious adverse events and severe

hypoglycemia were also reported as secondary outcomes. For Serious adverse events, reported definitions are presented in supplementary [S3 Table](#).

Data analysis

Each drug (including each drug dose) was analyzed according to its therapeutic class: biguanide (metformin), alpha glucosidase inhibitors, sulfonylureas, glitazones, glinides, insulin, DPP-4 inhibitors, GLP-1 receptor agonists, and SGLT-2 inhibitors. Placebo, diet control and active control without specific drug classes were considered together as control treatment. A random Bayesian network meta-analysis model was used [14]. The prior distribution was chosen as non-informative, the posterior distribution was estimated using Markov Chain Monte Carlo method [15]. The treatment effect estimate was presented for the network estimation and for the direct comparison, when available, through odds ratio (OR) and its 95% credible interval (95% CrI). Ranking probability and the surface under the cumulative ranking (SUCRA) values were estimated for ranking the drug classes [16]. Sensitivity analyses after considering only double-blind studies and according to two potential effect modifiers, high versus low baseline cardiovascular risk and high versus low glycemic contrast during the study, were conducted. The level of baseline cardiovascular risk of the trial was defined using the proportion of subjects with previous cardiovascular events. Trials below the mean proportion across all trials defined the subset of trials of 'low cardiovascular risk'; trials above the mean proportion defined the subset of trials of 'high cardiovascular risk'. Glycemic contrast during the study was defined by the HbA1c difference across arms of the trial. Trials below the mean HbA1c difference across all trials defined the subset of trials of "low glycemic contrast", trials above the mean HbA1c difference defined the subset of trials of "high glycemic contrast". Heterogeneity was analyzed using the I^2 . Inconsistency of the network was searched for, using the Node-splitting analysis of inconsistency of the Gemtc package [17]. Analyses have been conducted using R [18] (version 3.3.1) and JAGS [19] with the Gemtc package [17] (version 0.8–2). Meta package [20] was used to illustrate the treatment effect at the trial level.

Results

Bibliographic search and included trials

The bibliographic search retrieved 3,459 citations. The selection process is presented in [Fig 1](#). Thirty-four trials with 175,966 patients were included [2–5, 8, 9, 21–46]. We did not retrieve trials evaluating alpha glucose inhibitors or glinides. UKPDS34 [25] was considered as two trials, UKPDS34a and UKPDS34b [47]. For UGDP [23], UKPDS33 [24] and TIDE [37] trials, arms with the same drug class were summed up. For UGDP, the tolbutamide group was not included. For the ORIGIN study [36], in which more than 80% of subjects had T2D, only data from the T2D sub-group were used when available, data of the whole trial otherwise. The CANVAS-program [3] was considered as two trials, CANVAS and CANVAS-R. Indeed, given a marked difference in the baseline risk between the two cohorts, their pooling was subject to the Simpson's paradox. We were unable to obtain results of the PPAR study [21] despite having contacted the authors. Data of the recent trial CARMELINA were limited to the public information [22].

Baseline characteristics of included trials are presented in [Table 1](#). Included trials were published over a span of 48 years (from 1970 to 2018). Percentage of males ranged from 29 to 77.6%, percentage of patients i) with high blood pressure or receiving antihypertensive drugs ranged from 11.6 to 95.1%, ii) with dyslipidemia or receiving statins treatment ranged from 0.1 to 92.8% (low use of lipid lowering drugs in UKPDS), iii) receiving antiplatelet treatment ranged from 40.2 to 98.3%, and percentage of current smokers at inclusion ranged from 10.2

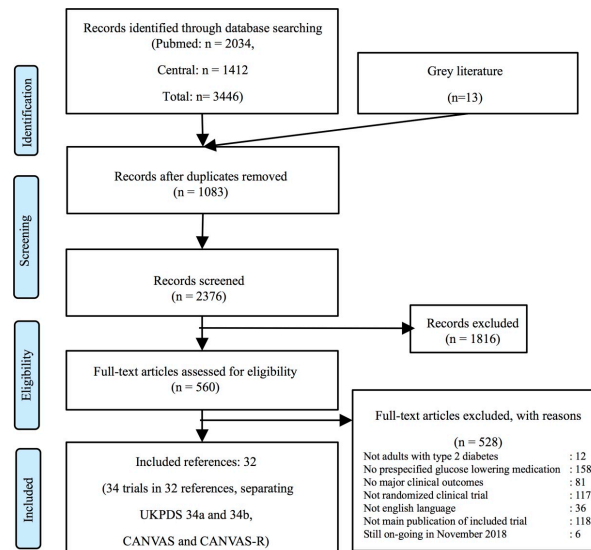


Fig 1. Flow diagram of bibliographic search (following PRISMA guidelines).

<https://doi.org/10.1371/journal.pone.0217701.g001>

to 49.6%. Mean age ranged from 53+/-8.5 to 69+/-7.1 years, mean duration of diabetes from around 0 (UKPDS) to 14.7+/-9.5 years, mean HbA1c at inclusion from 6.3+/-1.3 to 8.8 +/-1.7%, mean body mass index (BMI) at inclusion from 23.9+/-3.1 to 32.5+/-6.3 kg.m⁻². 20 (59%) trials were double-blinded. The summary of the risk of bias assessments and details for each study are presented in supplementary S2 Fig. Only 12 and seven trials provided details on clinical retinopathy and clinical nephropathy, respectively (18 trials for nephropathy when including biological outcomes).

Primary outcomes

Overall mortality. Thirty studies contributed to this analysis, including 12,203 deaths. Each active drug class had direct comparisons with control. The comparison network and forest plots of the direct comparisons are shown in supplementary S3A Fig_Network, S3A Fig_DPP-4_I VERSUS CONTROL, S3A Fig_GLITAZONES VERSUS CONTROL, S3A Fig_GLP-1_A VERSUS CONTROL, S3A Fig_INSULIN VERSUS CONTROL, S3A Fig_METFORMIN VERSUS CONTROL, S3A Fig_SGLT-2_I VERSUS CONTROL, S3A Fig_SULFONYLUREA VERSUS CONTROL, S3A Fig_SULFONYLUREA VERSUS GLITAZONES, S3A Fig_INSULIN VERSUS SULFONYLUREA, S3A Fig_METFORMIN VERSUS SULFONYLUREA. SGLT-2 inhibitors only were associated with a decreased risk of overall mortality compared to control (OR = 0.84 [95% CrI: 0.74; 0.95]) and compared to DPP-4 inhibitors (OR = 0.82 [95% CrI: 0.69; 0.98]). SUCRA values suggested that SGLT-2 inhibitors have the higher probability to be the most efficient treatment (SUCRA = 0.86). SUCRA values for metformin and GLP-1 receptor agonists were relatively similar (0.72 and 0.67, respectively). SUCRA values, summary of the network treatment estimates for each pair of comparisons and for the direct treatment estimates, when available, are summarized in Table 2.

Table 1. Baseline characteristics of included trials.

	Year of publication	Blinding	Male	HBP	Lipd	APT	Smoker	Age (year)	Diabetes duration (year)	HbA1c	BMI
DPP-4_I VERSUS CONTROL											
CARMELINA [22]	2018	DB	62.9	95.1	71.8	68.3	10.2	65.8 (9.1)	14.7 (9.5)	7.9 (1.0)	31.3 (5.3)
EXAMINE [35]	2013	DB	67.8	83	90.4	97.2	13.7	61	7.2	8 (1.1)	28.7
SAVOR.TIMI.53 [40]	2013	DB	66.9	81.8	71.2	75.2	13.4	65 (8.6)	10.3	8 (1.4)	31.1 (5.6)
TECOS [42]	2015	DB	70.7	78.4	79.5	78.2	11.4	65.5 (8)	11.6 (8.1)	7.2 (0.5)	30.2 (5.6)
GLITAZONES VERSUS CONTROL											
J.SPIRIT [44]	2015	O	NA	NA	NA	NA	NA	NA	NA	NA	NA
Kaku.2009 [32]	2009	O	62.5	69	71	NA	45.2	58	NA	7.6	26.7
Lee.2013 [39]	2013	NA	73.6	57	73.5	98.3	49.6	61.1 (9.1)	5.8 (6.7)	7.8 (1.7)	23.9 (3.1)
PROactive [27]	2005	DB	66.1	75.4	42.9	83.9	13.8	61.8	8	8.1 (1.41)	30.9 (4.8)
PROFIT.J [41]	2014	O	64.6	60.8	43.6	NA	NA	69 (7.1)	11.3 (8.9)	7.4 (0.9)	24.2 (3.3)
RECORD [31]	2009	O	51.6	65.6	34.1	NA	15.7	58.4 (8.2)	7.1 (4.9)	7.9 (0.7)	31.5 (4.7)
TIDE [37]	2012	DB	58.8	88.2	76.4	55.4	12.5	66.4 (6.6)	8.8 (6.8)	7.4 (0.9)	30.6 (5.3)
GLP-1_A VERSUS CONTROL											
ELIXA [43]	2015	DB	69.3	76.3	92.8	97.5	11.7	60.2 (9.6)	9.3 (8.2)	7.7 (1.3)	30.1 (5.7)
EXSCEL [45]	2017	DB	62	90.3	73.5	63.6	11.6	62*	12 (7;18)*	8(7.3;8.9)*	31.8*
HARMONY [8]	2018	DB	69	86.5	84.1	77.1	15.8	64.2 (8.7)	14.1 (8.8)	8.7 (1.5)	32.3 (5.9)
LEADER [4]	2016	DB	64.2	92.3	75.6	67.7	NA	64.3 (7.2)	12.8	8.7	32.5 (6.3)
SUSTAIN.6 [5]	2016	DB	60.7	93.5	76.5	NA	NA	64.6 (7.4)	13.9 (8.1)	8.7 (1.5)	NA
INSULIN VERSUS CONTROL											
ORIGIN [36]	2012	O	65	79.5	53.8	69.2	12.4	63.5 (7.8)	5.4 (6)	6.4	29.9 (5.2)
UGDP [23]	1970	NA	29	32.3	13.1	NA	NA	NA	NA	NA	NA
UKPDS.33 [24]	1998	O	62	11.6	0.1	NA	31	54 (8)	0	6.3 (1.3)	27.3 (5.1)
METFORMIN VERSUS CONTROL											
COSMIC [26]	2005	O	49.4	NA	NA	NA	NA	58.5 (13)	4.8 (6)	NA	NA
HOME [33]	2009	DB	45.6	43	16.1	NA	24.9	61.5 (10.5)	NA	7.9 (1.2)	30 (5)
UKPDS.34a [25]	1998	O	46.5	15.5	0.2	NA	25	53 (8.5)	0	7.2 (1.5)	31.7 (4.8)
UKPDS.34b [25]	1998	O	60	24.5	0.2	NA	26.5	58.5 (8.5)	0	7.5 (1.8)	29.5 (5.5)
SGLT-2_I VERSUS CONTROL											
CANVAS [3]	2017	DB	66.1	87.6	72.3	71.6	17.9	62.4 (8)	13.4 (7.5)	8.2 (0.9)	32.1 (6.2)
CANVASR [3]	2017	DB	62.8	91.7	76.9	75.1	17.7	64 (8.4)	13.7 (7.9)	8.3 (1)	31.9 (5.7)
DECLARE.TIMI.58 [9]	2018	DB	62.6	NA	75	61.1	NA	64 (6.8)	11 (6;16)*	8.3 (1.2)	32 (6)
EMPAREG [2]	2015	DB	71.4	95	81.1	NA	NA	63.1 (8.7)	NA	8.1 (0.8)	30.6 (5.2)
SULFONYLUREA VERSUS CONTROL											
ADVANCE [30]	2008	O	57.5	75.1	NA	NA	NA	66 (6)	8 (6.3)	7.5 (1.6)	28 (5)
UKPDS.33 [24]	(see previous description)										
GLITAZONES VERSUS SULFONYLUREA											

(Continued)

Table 1. (Continued)

	Year of publication	Blinding	Male	HBP	Lipd	APT	Smoker	Age (year)	Diabetes duration (year)	HbA1c	BMI
APPROACH [34]	2010	DB	67.9	80.1	75.9	83.2	16.6	61 (8.7)	4.8	7.2 (0.8)	29.6 (5.4)
PERISCOPE [29]	2008	DB	67.4	86.8	81.2	90.1	15.3	59.9 (9.2)	5.9	7.4 (1)	32 (5.2)
Giles.2008 [28]	2008	DB	73.6	NA	NA	NA	NA	63.8 (9.7)	11.8 (9.3)	8.8 (1.7)	29.6 (5.3)
PPAR.Study [21]	NA	O	NA	NA	NA	NA	NA	NA	NA	NA	NA
TOSCA.IT [46]	2017	O	58.5	70	57.3	40.2	17.6	62.3 (6.5)	8.4 (5.7)	7.7 (0.5)	30.3 (4.5)
INSULIN VERSUS SULFONYLUREA											
UKPDS.33 [24]	(see previous description)										
METFORMIN VERSUS SULFONYLUREA											
SPREAD.DIMCAD [38]	2013	DB	77.6	69.4	63.9	83.5	37.5	63.3	5.6 (5.1)	7.6 (1.7)	25.1 (3)

“_i” stands for inhibitor, “_a” stands for agonist. Percentages from the whole trial (or the mean of the arms if not available) for high blood pressure or antihypertensive drugs (HBP), dyslipidemia or statines (Lipd), antiplatelet treatment (APT) and current smoker (Smoker); mean and standard deviation from the whole trial (or the mean of the arms if not available) for age, diabetes duration, baseline HbA1c and baseline body mass index (BMI, kg.m-2). When mean and standard deviation were not available, median and interquartile range (IQR) were used, indicated with “**”).

<https://doi.org/10.1371/journal.pone.0217701.t001>

Cardiovascular mortality. Twenty-seven studies contributed to the analysis for cardiovascular mortality, including 6,221 cardiovascular deaths. Each active drug class had direct comparisons against control. The comparison network and forest plots of the direct comparisons are shown in supplementary [S3B Fig_Network](#), [S3B Fig_DPP-4_I VERSUS CONTROL](#), [S3B Fig_GLITAZONES VERSUS CONTROL](#), [S3B Fig_GLP-1_A VERSUS CONTROL](#), [S3B Fig_INSULIN VERSUS CONTROL](#), [S3B Fig_METFORMIN VERSUS CONTROL](#), [S3B Fig_SGLT-2_I VERSUS CONTROL](#), [S3B Fig_SULFONYLUREA VERSUS CONTROL](#), [S3B Fig_SULFONYLUREA VERSUS GLITAZONES](#), [S3B Fig_INSULIN VERSUS SULFONYLUREA](#), [S3B Fig_METFORMIN VERSUS SULFONYLUREA](#). No significant differences were observed in the network comparisons. SUCRA values suggested SGLT-2 inhibitors have the

Table 2. Treatment effect estimates for overall mortality.

control ; 0.2 (0.89;1.15)	1.02 (0.89;1.15)	0.93 (0.79;1.09)	0.9 (0.81;1)	0.96 (0.83;1.09)	0.86 (0.67;1.1)	0.84 (0.74;0.95)	0.95 (0.83;1.09)
1.02 (0.89;1.15)	dpp4_i ; 0.16 (0.74;1.12)	0.91 (0.74;1.12)	0.88 (0.75;1.05)	0.94 (0.78;1.12)	0.84 (0.64;1.12)	0.82 (0.69;0.98)	0.93 (0.77;1.13)
0.88 (0.46;1.39)		glitazones ; 0.53 (0.8;1.18)	0.97 (0.8;1.18)	1.03 (0.83;1.27)	0.93 (0.69;1.25)	0.91 (0.73;1.11)	1.03 (0.84;1.25)
0.89 (0.81;1)			glp1_a ; 0.67 (0.88;1.25)	1.07 (0.88;1.25)	0.96 (0.73;1.26)	0.94 (0.79;1.1)	1.06 (0.88;1.26)
0.96 (0.82;1.1)				insulin ; 0.42 (0.68;1.2)	0.9 (0.68;1.2)	0.88 (0.74;1.06)	0.99 (0.84;1.2)
0.97 (0.63;1.53)					metformin ; 0.72 (0.74;1.3)	0.98 (0.74;1.3)	1.11 (0.83;1.46)
0.84 (0.67;1.05)						sglt2_i ; 0.86 (0.94;1.37)	1.13 (0.94;1.37)
0.94 (0.83;1.07)		0.89 (0.56;1.4)		1.01 (0.81;1.25)	2.28 (0.64;8.63)		sulfonylureas ; 0.44

The diagonal contains the drug class and its SUCRA value. Treatment effect are OR with its 95% credible interval. Above the diagonal: estimates from the network meta-analysis, OR < 1 is in favor of the column; below the diagonal: estimates from the direct comparison, when available, OR < 1 is in favor of the row.

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Table 3. Treatment effect estimates for cardiovascular mortality.

control ; 0.24	0.99 (0.8;1.19)	0.92 (0.71;1.21)	0.89 (0.76;1.05)	0.95 (0.7;1.3)	0.91 (0.65;1.27)	0.83 (0.69;1)	0.92 (0.74;1.16)
0.99 (0.85;1.14)	dpp4_i ; 0.31	0.94 (0.68;1.32)	0.9 (0.71;1.18)	0.96 (0.68;1.4)	0.92 (0.63;1.36)	0.84 (0.65;1.11)	0.93 (0.7;1.28)
0.91 (0.4;2.07)		glitazones ; 0.51	0.96 (0.71;1.31)	1.03 (0.69;1.53)	0.98 (0.64;1.5)	0.9 (0.64;1.23)	0.99 (0.71;1.39)
0.89 (0.78;1.02)			glp1_a ; 0.63	1.07 (0.76;1.5)	1.02 (0.7;1.47)	0.94 (0.72;1.18)	1.03 (0.78;1.37)
0.93 (0.73;1.19)				insulin ; 0.43	0.95 (0.61;1.49)	0.87 (0.61;1.24)	0.96 (0.7;1.34)
1.15 (0.5;3)					metformin ; 0.55	0.92 (0.62;1.34)	1.01 (0.69;1.5)
0.83 (0.61;1.12)						sglt2_i ; 0.8	1.1 (0.83;1.5)
0.9 (0.75;1.08)		0.79 (0.27;2.15)		0.76 (0.61;0.95)	1.72 (0.54;5.52)		Sulfonylureas ; 0.53

The diagonal contains the drug class and its SUCRA value. Treatment effect are OR with its 95% credible interval. Above the diagonal: estimates from the network meta-analysis, OR < 1 is in favor of the column; below the diagonal: estimates from the direct comparison, when available, OR < 1 is in favor of the row.

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higher probability to be the most efficient treatment (SUCRA = 0.8), followed by GLP-1 receptor agonists and metformin (0.63 and 0.55, respectively). SUCRA values, network and direct comparisons are summarized in Table 3.

Major adverse cardiovascular events (MACE). Twenty-seven studies contributed to the analysis for MACE, including 17,188 MACEs. Details regarding the number of events are presented in S5 Table. Each active drug class had direct comparisons against control. The comparison network and forest plot of the direct comparisons are shown in supplementary S3C Fig_Network, S3C Fig_DPP-4_I VERSUS CONTROL, S3C Fig_GLITAZONES VERSUS CONTROL, S3C Fig_GLP-1_A VERSUS CONTROL, S3C Fig_INSULIN VERSUS CONTROL, S3C Fig_METFORMIN VERSUS CONTROL, S3C Fig_SGLT-2_I VERSUS CONTROL, S3C Fig_SULFONYLUREA VERSUS CONTROL, S3C Fig_SULFONYLUREA VERSUS GLITAZONES, S3C Fig_INSULIN VERSUS SULFONYLUREA, S3C Fig_METFORMIN VERSUS SULFONYLUREA. Compared to control, only SGLT-2 inhibitors and GLP-1 receptor agonists were associated with a decreased risk of MACE (OR = 0.89 [95% CrI: 0.81; 0.98] and OR = 0.88 [95% CrI: 0.81; 0.95], respectively). Compared to DPP-4 inhibitors, only GLP-1 receptor agonists were associated with a decreased risk of MACE (OR = 0.88 [95% CrI: 0.79; 0.99]). Insulin was also associated with an increased risk of MACE compared to GLP-1 receptor agonists (OR = 1.19 [95% CrI: 1.01; 1.42]). SUCRA values suggested GLP-1 receptor agonists have the higher probability to be the most efficient treatment (SUCRA = 0.76), followed by metformin and SGLT-2 inhibitors (SUCRA values: 0.75 and 0.71, respectively). SUCRA values, network and direct comparisons are summarized in Table 4. Ranking probability curve for MACE is presented in the supplementary S4 Fig.

Secondary outcomes

Regarding the risk of MI, metformin was almost associated with a decreased risk of non-fatal MI compared to control (OR = 0.66 [95% CrI: 0.44; 1]). Regarding the risk of stroke, glitazones were associated with a decreased risk of all strokes compared to control and DPP-4 inhibitors (OR = 0.74 [95% CrI: 0.57; 0.95] and OR = 0.72 [95% CrI: 0.52; 0.98], respectively); sulfonylureas and SGLT-2 inhibitors were associated with an increased risk of stroke compared to

Table 4. Treatment effect estimates for major adverse cardiovascular events (MACE).

control ; 0.21	0.99 (0.91;1.08)	0.9 (0.79;1.03)	0.88 (0.81;0.95)	1.05 (0.9;1.21)	0.85 (0.65;1.11)	0.89 (0.81;0.98)	0.93 (0.81;1.06)
0.98 (0.92;1.05)	dpp4_i ; 0.26	0.9 (0.78;1.07)	0.88 (0.79;0.99)	1.05 (0.89;1.25)	0.85 (0.65;1.14)	0.9 (0.79;1.02)	0.94 (0.8;1.1)
0.86 (0.58;1.17)		glitazones ; 0.66	0.98 (0.83;1.14)	1.17 (0.95;1.42)	0.94 (0.71;1.27)	0.99 (0.83;1.16)	1.04 (0.87;1.22)
0.87 (0.74;1)			glp1_a ; 0.76	1.19 (1.01;1.42)	0.97 (0.73;1.29)	1.01 (0.9;1.15)	1.06 (0.91;1.24)
1.04 (0.93;1.17)				insulin ; 0.12	0.81 (0.6;1.11)	0.85 (0.71;1.01)	0.89 (0.72;1.09)
0.97 (0.65;1.44)					metformin ; 0.75	1.05 (0.79;1.39)	1.09 (0.82;1.44)
0.89 (0.79;0.99)						sglt2_i ; 0.71	1.04 (0.89;1.23)
0.93 (0.81;1.08)		0.87 (0.54;1.3)			1.62 (0.77;3.47)		sulfonylureas ; 0.53

The diagonal contains the drug class and its SUCRA value. Treatment effect are OR with its 95% credible interval. Above the diagonal: estimates from the network meta-analysis, OR < 1 is in favor of the column; below the diagonal: estimates from the direct comparison, when available, OR < 1 is in favor of the row.

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glitazones (OR = 1.53 [95% CrI: 1.13; 2.15] and OR = 1.45 [95% CrI: 1.06; 2.03], respectively). Insulin was associated with an increased risk of severe adverse events compared to all the comparison except the sulfonylureas: increased risk with insulin compared to control, DPP-4 inhibitors, glitazones, GLP-1 receptor agonists (OR = 1.32 [95% CrI: 1.05; 1.68], OR = 1.44 [95% CrI: 1.05; 1.97], OR = 1.37 [95% CrI: 1.04; 1.81], OR = 1.43 [95% CrI: 1.11; 1.85], respectively), decreased risk with metformin and SGLT-2 inhibitors compared to insulin (OR = 0.7 [95% CrI: 0.5; 0.99] and OR = 0.67 [95% CrI: 0.51; 0.87], respectively). Insulin and sulfonylureas both were associated with an increased risk of severe hypoglycemia compared to all the other comparison except the metformin: i) increased risk with insulin compared to control, DPP-4 inhibitors, glitazones, GLP-1 receptor agonists (OR = 3.44 [95% CrI: 1.76; 7.25], OR = 2.92 [95% CrI: 1.22; 7.64], OR = 2.99 [95% CrI: 1.17; 7.97], OR = 4.14 [95% CrI: 1.95; 10.13], respectively), ii) decreased risk with SGLT-2 inhibitors compared to insulin (OR = 0.23 [95% CrI: 0.08; 0.59]), iii) increased risk with sulfonylureas compared to control, DPP-4 inhibitors, glitazones, GLP-1 receptor agonists and SGLT-2 inhibitors (OR = 2.9 [95% CrI: 1.68; 6.25], OR = 2.45 [95% CrI: 1.18; 6.61], OR = 2.52 [95% CrI: 1.22; 6.32], OR = 3.49 [95% CrI: 1.82; 8.94], OR = 3.71 [95% CrI: 1.62; 11] respectively). For secondary outcomes, treatment effect estimates against control are summarized in [Table 5](#).

Statistical assessment

Convergences were reached for all the analyses. Residual deviance was globally acceptable (for overall mortality, ratio of Dbar/number of data points was 1.074). Heterogeneity of the treatment effect was globally low (I^2 for overall mortality: 8%). Network consistency was globally satisfying. For overall mortality, the network estimation of metformin against sulfonylurea was inconsistent with the direct comparison (see [discussion](#)).

Sensitivity analyses

When restricting the analysis to double-blinded studies only, the decreased risk of overall mortality with SGLT-2 and of MACE with SGLT-2 and GLP-1 agonist remained, but treatment estimation were not interpretable for metformin and sulfonylureas due to inconsistency.

Table 5. Summary of treatment effect compared to control for secondary outcomes.

	All.MI	Non.fatal.MI	All.Stroke	Non.fatal.Stroke	SAE	Sev.Hypo
dpp4_i	0.95 (0.78;1.15)	1.01 (0.85;1.2)	1.03 (0.85;1.26)	0.92 (0.69;1.21)	0.92 (0.75;1.12)	1.18 (0.67;2.06)
glitazones	1.18 (0.78;1.78)	0.91 (0.74;1.11)	0.74 (0.57;0.95)	0.78 (0.55;1.11)	0.97 (0.83;1.12)	1.15 (0.58;2.33)
glp1_a	0.91 (0.79;1.02)	0.94 (0.83;1.05)	0.89 (0.77;1.04)	0.88 (0.73;1.06)	0.93 (0.85;1.01)	0.83 (0.52;1.23)
insulin	0.98 (0.79;1.2)	0.95 (0.68;1.31)	0.99 (0.8;1.19)	0.71 (0.43;1.14)	1.32 (1.05;1.68)	3.44 (1.76;7.25)
metformin	0.8 (0.6;1.1)	0.66 (0.44;1)	0.73 (0.46;1.1)	0.62 (0.36;1.03)	0.93 (0.73;1.19)	1.34 (0.31;5.63)
sglt2_i	0.88 (0.72;1.07)	0.87 (0.73;1.04)	1.07 (0.88;1.31)	1.04 (0.82;1.31)	0.88 (0.77;1.01)	0.78 (0.39;1.55)
sulfonylureas	0.87 (0.65;1.16)	0.93 (0.76;1.13)	1.13 (0.95;1.39)	1.02 (0.8;1.28)	1.03 (0.86;1.17)	2.9 (1.68;6.25)

MI: myocardial infarction; SAE: serious adverse events; Sev.hypo: severe hypoglycemia; “_i” stands for inhibitor, “_a” stands for agonist.

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The mean prevalence of previous cardiovascular history at baseline across all trials was 54.9% +/- 29.4 (see supplementary S4 Table). There were 17 trials in the subgroup with a majority of patient with previous CV history (‘high CV risk’ subgroup), and 16 trials in the subgroup with a majority of patient without previous CV history (‘low CV risk’ subgroup). There was no trial comparing metformin to control in the ‘high CV risk’ subgroup. There were no GLP-1 receptor agonist trials and no DPP-4 inhibitor trials in the ‘low CV risk’ subgroup. The beneficial effects of SGLT-2 inhibitors and of GLP-1 receptor agonists remained in the ‘high CV risk’ subgroup. In the trials including a majority of patients without previous CV history, the comparisons of SGLT-2 inhibitors, metformin and control did not showed significant differences on primary outcomes. Compared to control, risk of overall mortality, CV mortality and of MACE, with SGLT-2 inhibitors, was: OR = 0.92 [95% CrI: 0.55; 1.57], OR = 0.99 [95% CrI: 0.29; 3.28], OR = 0.94 [95% CrI: 0.55; 1.6], respectively. Compared to control, risk of overall mortality, CV mortality and of MACE, with metformin, was: OR = 0.94 [95% CrI: 0.67; 1.41], OR = 1.08 [95% CrI: 0.57; 2.43], OR = 0.97 [95% CrI: 0.57; 1.56], respectively. Compared to metformin, risk of overall mortality, of CV mortality and of MACE, with SGLT-2 inhibitors was: OR = 0.99 [95% CrI: 0.5; 1.78], OR = 0.93 [95% CrI: 0.21; 3.29], OR = 0.96 [95% CrI: 0.48; 2.09], respectively.

The mean difference of HbA1c during the follow up was -0.43% +/- 0.22. Available data for defining the glycemic contrast was unfortunately heterogeneous between studies, limiting the exploration of this potential effect modifier.

Discussion

Main findings

Our study confirms the beneficial effects of SGLT-2 inhibitors and GLP-1 receptor agonist on MACEs with at least two positive independent trials. SGLT-2 inhibitors only were associated with a decreased risk of overall mortality compared to control and to DPP-4 inhibitors. GLP-1 agonists were only associated with a decreased risk of major adverse cardiovascular events compared to control, DPP-4 inhibitors and insulin. Metformin did not showed any benefits on mortality or major adverse cardiovascular events. Glitazones were associated with a decreased risk of stroke, insulin with an increased risk of serious adverse events, insulin and sulfonylureas with an increased risk of severe hypoglycemia. In the subgroup of trials including

a majority of patients without previous cardiovascular history, the comparisons of SGLT-2 inhibitors, metformin and control did not show significant differences on those outcomes. This subgroup did not include trials assessing GLP-1 agonists.

Strengths of the study

Several hypoglycemic drug classes are now available. However, only a few direct comparisons between active treatments are available. New hypoglycemic drug classes especially have been compared only to placebo for their effect on cardiovascular outcomes. Thus, in order to compare all the hypoglycemic drug classes, network meta-analyses are needed for taking into account the information from both direct and indirect comparisons. We included any hypoglycemic drug classes, old or new, whose have been assessed for major cardiovascular outcomes, for the first time in the same network meta-analysis. We also included the last powerful trials. Moreover, we conducted subgroup analyses according to the prevalence of previous CV history in each trial. Our study helps to summarize the results of clinical trials in type 2 diabetes, focusing on major cardiovascular outcomes. Regarding the SGLT-2 inhibitors, the decrease in overall mortality with SGLT-2 inhibitors is mainly driven by the EMPAREG OUTCOME trial [2]. Moreover, a potential warning signal has been observed for peripheral amputations [48]. The CANVAS Program was the pooling of the CANVAS trial and the CANVAS R trial [49]. Those trials were initially planned separately. After an unplanned interim analysis of the CANVAS trial, those two trials have been joined together to increase the power, both trials having very similar design and inclusion criteria. This has been well explicated and justified before the publication of the final results [49]. However, the results regarding overall and cardiovascular mortality are presented on the full dataset, including data which have been used for the interim analysis. Surprisingly, the effect of GLP-1 receptor agonists was no more significant for overall mortality, with the recently published HARMONY OUTCOME trial [8]. Regarding the other classes, the effect of metformin was consistent with previous meta-analyses [47]. The beneficial effect of glitazones regarding the risk of stroke has already been described [50]. The neutral effect of DPP-4 inhibitors on cardiovascular events was consistent with previous meta-analyses [51]. The increased risk of severe hypoglycemia with sulfonylureas and insulin was also consistent with their mechanism of action and previous knowledge [52]. The increased risk of severe adverse event with insulin is based on the data of ORIGIN [36]; we found neither severe adverse event data for UGDP [53] nor UKPDS 33 [24]. Therefore our results mostly reflect the increased risk of hypoglycemia as described in the ORIGIN trial. We did not assess the specific risk of cardiac insufficiency. Unfortunately, we did not find any studies evaluating alpha glucosidase inhibitors or glinides on such major clinical outcome.

Previous network meta-analyses [54–57] did not include both the old and the new hypoglycemic drug classes and the last powerful trials (EXSCEL [45], HARMONY OUTCOME [8], DECLARE TIMI 58 [9] and CARMELINA [22]). Above all, our results differ slightly from the network meta-analysis of Zheng et al [6], as the GLP-1 agonist were no more associated with a decrease in overall mortality, due to the latest HARMONY OUTCOME trial. Moreover, our results challenge the recently suggested benefit of SGLT-2 inhibitors in primary cardiovascular prevention [10], as we did not show a significant effect of SGLT-2 inhibitors compared to control and metformin on major CV outcomes, in trials including a majority of patients without previous CV history.

Limitations

Our study has some limitations. We included double-blinded and open clinical trials, which lead to a risk of bias. Unfortunately, there were many open trials in T2D in the last decades.

However, the sensitivity analysis restricted to the double-blinded studies was consistent with the main results. We included trials from 1970 to 2018. New hypoglycemic drugs were not assessed in the same medical context as old hypoglycemic drugs. The research of glycemic equipoise between arms in the recent trials could interfere with the interpretation of the results. Old hypoglycemic drugs have also been evaluated mostly in subjects with a shorter duration of type 2 diabetes, while the complications occur after several years of hyperglycemia. We limited our analysis on macroangiopathy. They are not the only complications of T2D patients, but they are the main cause of death in this population. We planned to address microvascular complications, but their reporting was not homogenous enough to allow the analysis. We also limited our analysis at the therapeutic class level. Treatment effect heterogeneity within classes has been described notably for glitazones and sulfonylureas, and our analysis could hide specific molecular effects by averaging the drug class effect. Pooling rosiglitazone and pioglitazone trials could have hidden some beneficial effect of pioglitazone [58] because of the negative cardiovascular effects of rosiglitazone [59]. Moreover, the sulfonylureas were mainly studied through the ADVANCE study [30], which compared a specific sulfonylurea against active hypoglycemic drugs including other sulfonylureas. Unfortunately, available data did not allow assessing the specific molecular effect. We planned to use the SUCRA values for ranking the drugs, but it does not take into consideration the upper bound of the credible interval. Thus it resulted for example in a better ranking of Metformin compared to SGLT-2 inhibitors for MACE, whereas metformin's effect was not significant. Slight inconsistency has been observed for metformin. This seems to be due to the direct comparison of metformin against sulfonylureas in the SPREAD DIMCAD trial [38]. Moreover, some drug classes have not been studied in certain populations (no DPP-4 inhibitors or GLP-1 agonist trials in the 'low CV risk' subgroup), which limit the assessment of the transitivity assumption. Sensitivity analysis did not allow identification of glycemic contrast during the trials as potential effect modifiers. Previous meta-regression looking for an association between HbA1c decrease and clinical events showed conflicting results [60, 61]. Unfortunately, the reporting of the glycemic exposure in included trials was not well standardized, and the available data were heterogeneous.

Implications

SGLT-2 inhibitors and GLP-1 receptor agonists are recommended for patients with clinical cardiovascular disease [7]. It has been recently suggested that SGLT-2 inhibitors could also be helpful in primary CV prevention [10], but metformin remained the first-line therapy for glucose lowering medication in the last international guidelines [7]. Our study challenges the suggested benefit of SGLT-2 inhibitors in primary cardiovascular prevention, as we did not observe significant difference on overall mortality or MACE between SGLT-2 inhibitors, metformin and control. Thus, our results showed the need for direct comparisons of SGLT-2 inhibitors, GLP-1 agonists and metformin, notably in primary cardiovascular prevention. Moreover, integration in network meta-analysis of supplementary active direct comparisons as the CAROLINA trial [62] will be helpful to better compare the hypoglycemic drugs. Integration of other comparison of SGLT-2 inhibitors to placebo as the VERTIS CV trials [63] will also be helpful, as the effect of SGLT-2 on mortality is mostly driven by the EMPAREG-OUTCOME, and as the decrease in overall mortality with GLP-1 agonist was no more significant with the HARMONY OUTCOMES trial. Likewise, further meta-analyses are needed for assessing the relative effect of glucose lowering drugs on microangiopathy, and for assessing the heterogeneity in the treatment effect within therapeutic classes. Finally, it would be interesting to model the cost efficiency of hypoglycemic drugs with those treatment effect estimations.

Conclusion

Hypoglycemic drugs are used to control glycaemia and reduce diabetic complications in tens of millions of people worldwide. This study helps to summarize factual knowledge of those therapeutic classes on major clinical outcomes. SGLT-2 inhibitors and GLP-1 receptor agonists appear to have the most beneficial effects on MACE, especially in type 2 diabetic patients with previous cardiovascular diseases.

Supporting information

S1 Fig. PRISMA network meta-analysis checklist of GLUCOSE DINET.

(DOCX)

S2 Fig. Risk of bias assessment (A: summary, B: details).

(DOCX)

S3 Fig. Network and forest plot for the primary outcomes.

(DOCX)

S4 Fig. Probability curves of each drug classes to be ranked best treatment to the last effective for major adverse cardiovascular events.

(DOCX)

S1 Table. Search strategy used for medline.

(DOCX)

S2 Table. Definitions of the major adverse cardiovascular events (MACE) outcome for each trial.

(DOCX)

S3 Table. Reported definitions of the serious adverse event (SAE) outcome used for each trial.

(DOCX)

S4 Table. Baseline cardiovascular risk groups for the sensitivity analysis.

(DOCX)

S5 Table. Dataset GLUCOSE DINET.

(XLSX)

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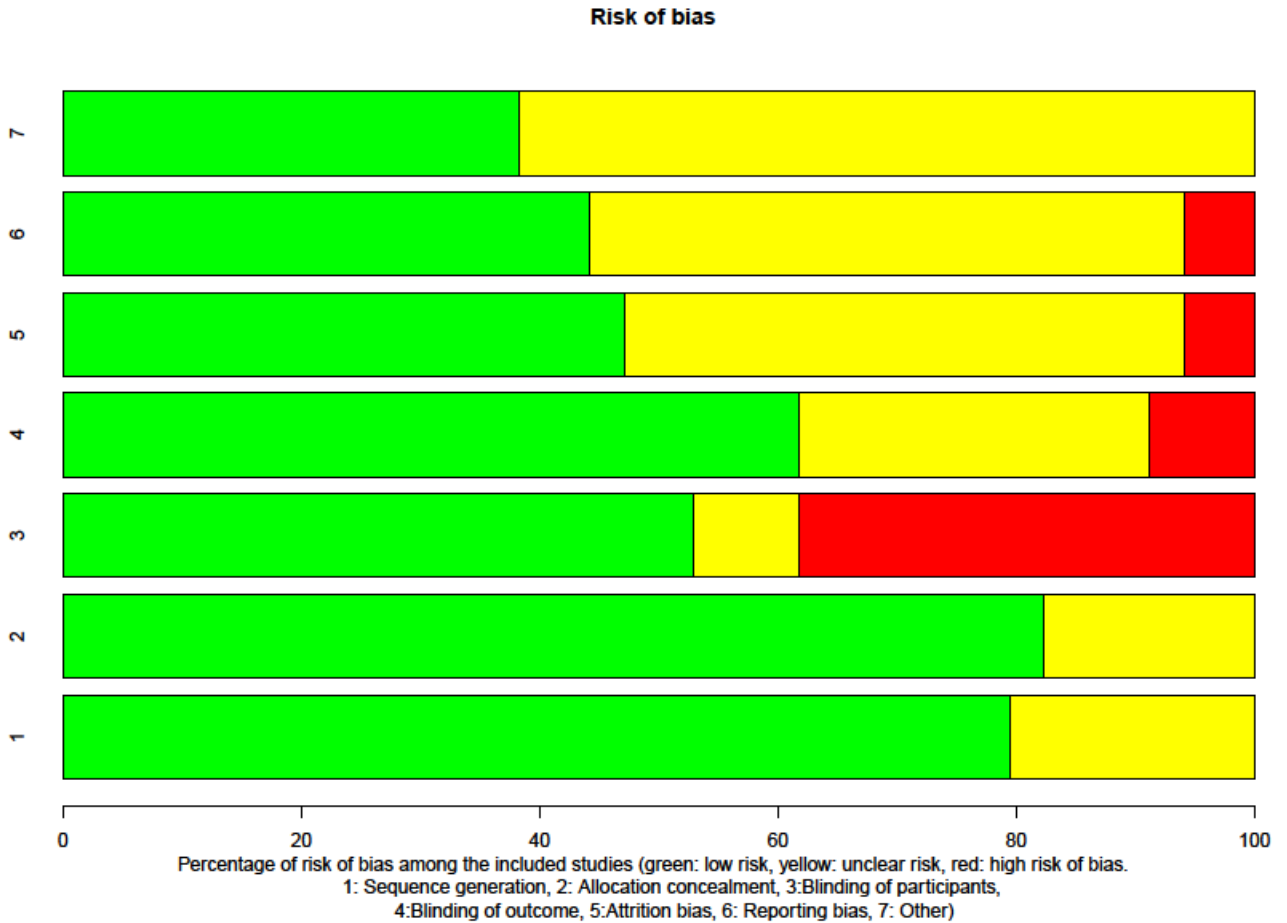
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Supporting information

Some supporting information are provided in the Appendix 2.

Risk of bias assessment (A: summary, B: details).



A. Summary of risk of bias assessment.

	1	2	3	4	5	6	7
ADVANCE	L	L	H	U	L	U	U
APPROACH	L	L	L	L	L	L	L
CANVAS1	L	L	L	L	U	U	L
CANVASR	L	L	L	L	U	H	L
CARMELINA	L	L	L	L	L	U	U
COSMIC	L	L	L	L	U	U	U
DECLARE.TIMI.58	L	L	L	L	U	L	L
ELIXA	L	L	L	L	L	L	L
EMPAREG	L	L	L	L	U	U	L
EXAMINE	L	L	L	L	L	L	U
EXSCEL	L	L	U	L	L	L	U
HARMONY	L	L	L	L	U	H	U
HOME	U	U	H	H	U	U	U
J.SPIRIT	L	L	L	L	L	L	L
LEADER	L	L	H	U	L	L	U
ORIGIN tot	L	L	H	U	L	L	U
PERISCOPE	U	L	L	L	L	L	U
Pio.Kaku.2009	U	U	H	U	U	U	U
Pio.post.stent.Lee.2013	U	U	U	U	U	U	U
PioGLy.mCD.GILES.2008	U	U	U	L	H	U	U
PPAR.Study	U	U	H	H	U	U	U
PROactive	L	L	L	L	L	U	L
PROFIT.J	U	U	H	H	H	U	U
RECORD	L	L	H	U	U	U	L
SAVOR.TIMI.53	L	L	L	L	L	L	L
SPREAD.DIMCAD	L	L	L	U	L	U	U
SUSTAIN.6	L	L	L	L	L	U	L
TECOS	L	L	L	L	L	L	L
TIDE	L	L	L	L	L	U	U
TOSCA.IT	L	L	H	L	U	U	L
UGDP	L	L	H	L	U	L	U
UKPDS.33	L	L	H	U	U	L	U
UKPDS.34a	L	L	H	U	U	L	U
UKPDS.34b	L	L	H	U	U	L	U

B. Risk of bias assessment, for each included study

(L: low risk of bias, U: unclear, H: high.

1: Sequence generation, 2: Allocation

concealment, 3: Blinding of participants, 4: Blind-

ing of outcome, 5: Attrition bias, 6: Reporting

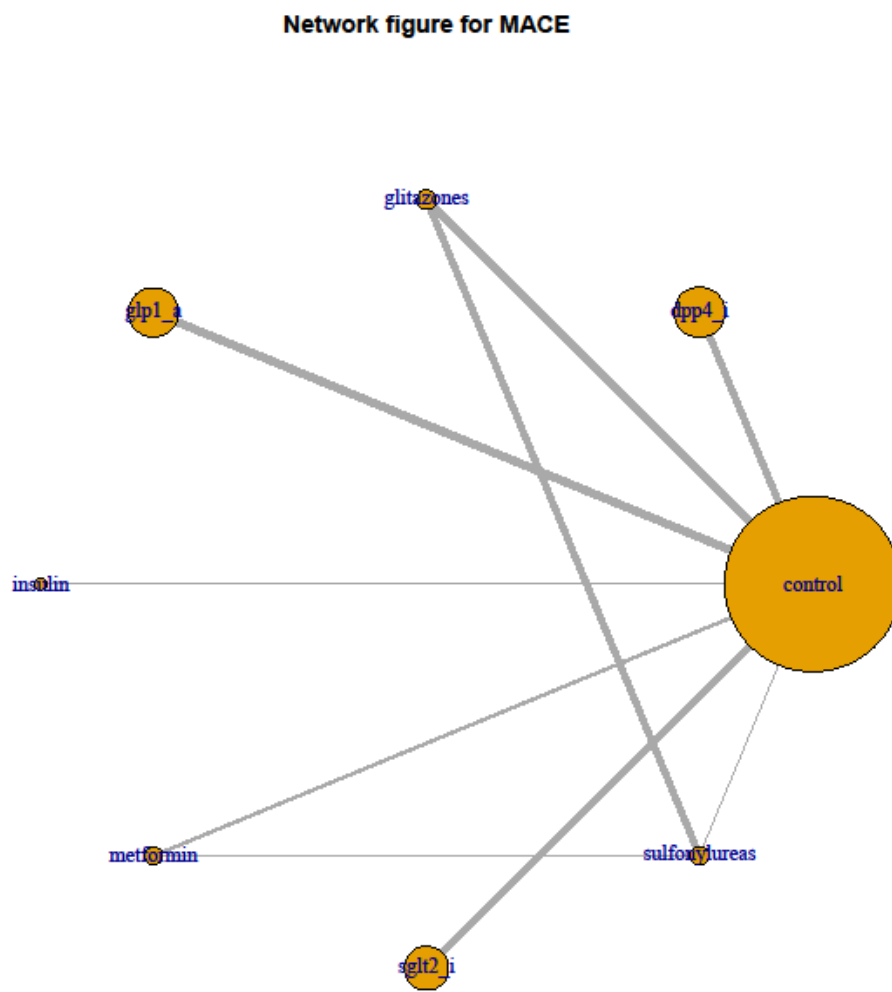
bias, 7: Other risk of bias)

Network figures and forest plots of direct comparisons for Major Adverse Cardiovascular Events

Only the network figure and the forest plots for the Major Adverse Cardiovascular Events (MACEs) are displayed here. The network figure and the forest plots for the other primary outcomes are provided in Appendix 2.

Network figure

Each node represents a drug class, each edge a direct comparison. This network included 27 randomized trials. On 168 068 subjects, 17 188 presented the outcome.

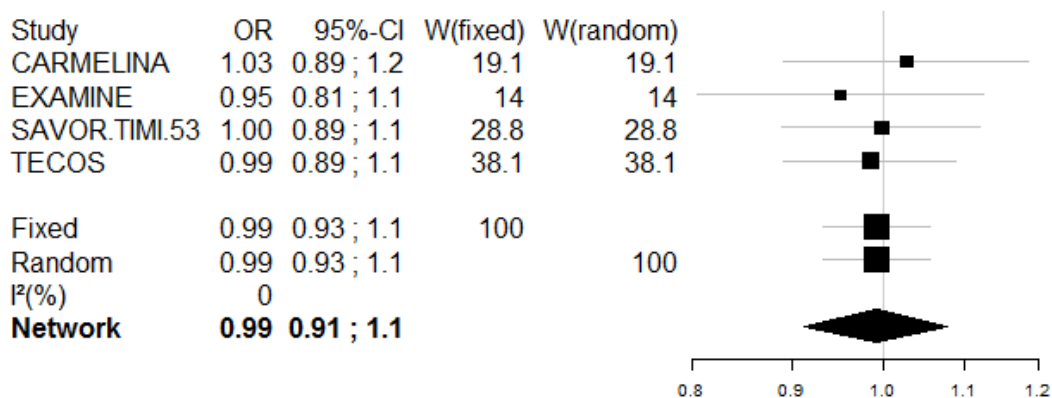


Edge width is based on the number of randomized trials, node size on the sample size.

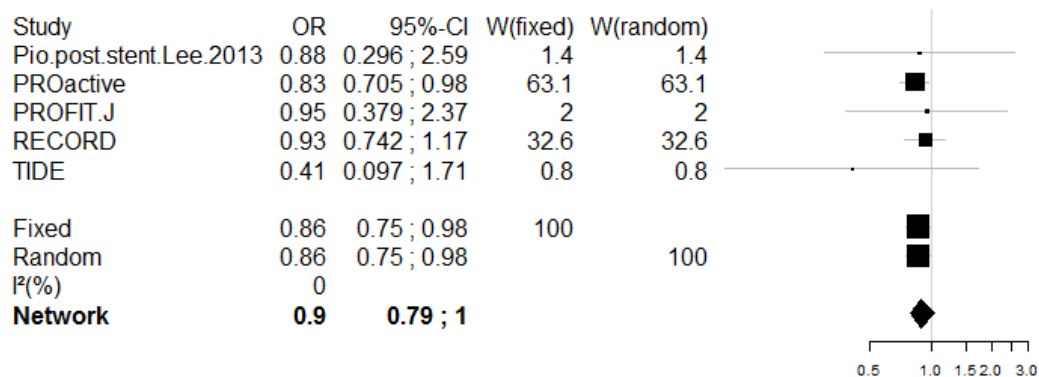
Forest plots of the Major Adverse Cardiovascular Events (MACE) for each direct comparison

The diamond in the forest plot stands for the network estimation of the TE (OR and its 95%CI) ('Network's line); the squares stand for i) the TE estimate in the corresponding trial (on line with its name), and ii) the TE estimate using direct meta-analysis with both fixed and random model ('Fixed' and 'Random', respectively). 'W' stands for the weight of each trial in the corresponding direct meta-analysis.

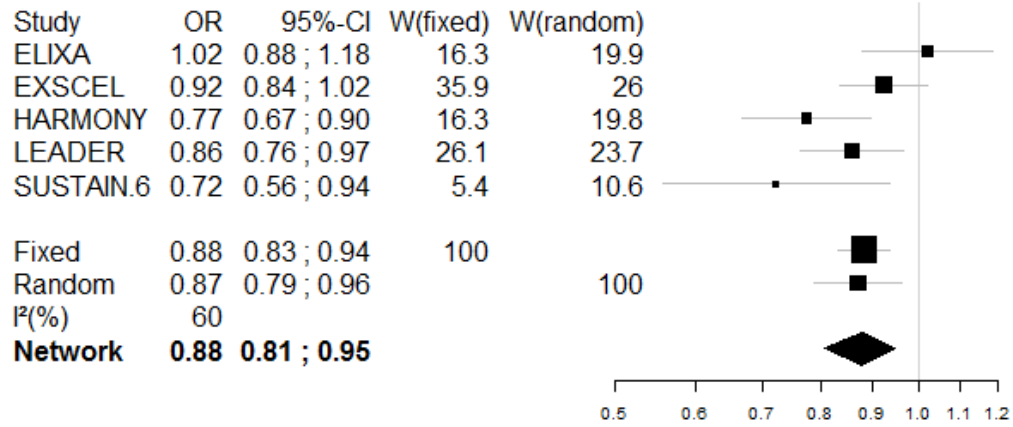
DPP-4_I VERSUS CONTROL



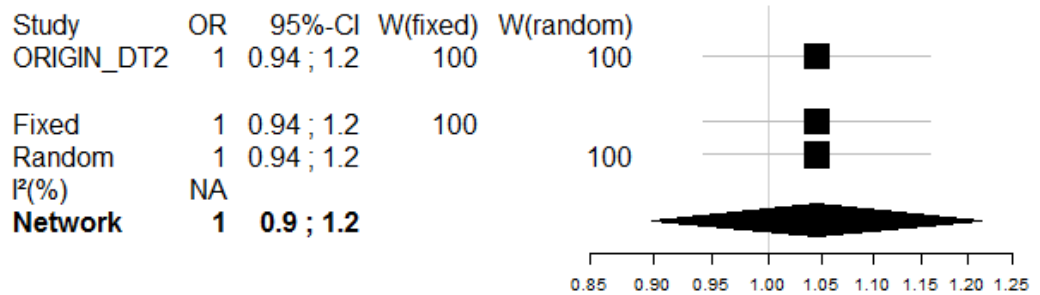
GLITAZONES VERSUS CONTROL



GLP-1_A VERSUS CONTROL

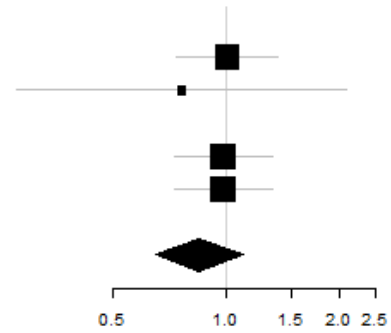


INSULIN VERSUS CONTROL



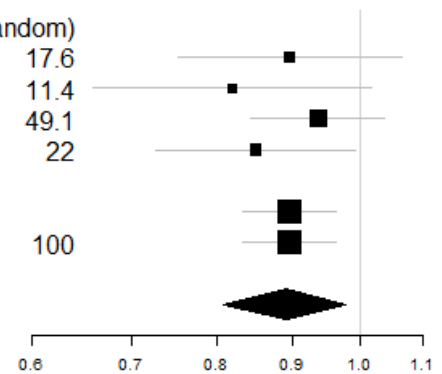
METFORMIN VERSUS CONTROL

Study	OR	95%-CI	W(fixed)	W(random)
COSMIC	1.01	0.74 ; 1.4	91.2	91.2
HOME	0.76	0.28 ; 2.1	8.8	8.8
Fixed	0.98	0.73 ; 1.3	100	
Random	0.98	0.73 ; 1.3		100
I ² (%)	0			
Network	0.85	0.65 ; 1.1		



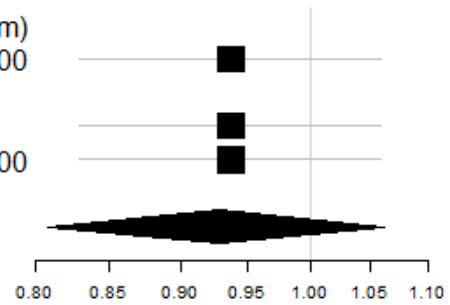
SGLT-2_I VERSUS CONTROL

Study	OR	95%-CI	W(fixed)	W(random)
CANVAS1	0.90	0.75 ; 1.07	17.6	17.6
CANVASR	0.82	0.66 ; 1.02	11.4	11.4
DECLARE.TIMI.58	0.94	0.84 ; 1.04	49.1	49.1
EMPAREG	0.85	0.73 ; 0.99	22	22
Fixed	0.89	0.83 ; 0.96	100	
Random	0.89	0.83 ; 0.96		100
I ² (%)	0			
Network	0.89	0.81 ; 0.98		



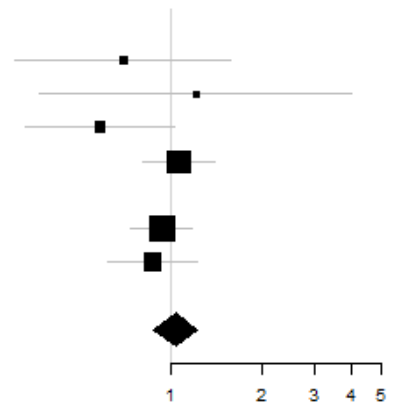
SULFONYLUREA VERSUS CONTROL

Study	OR	95%-CI	W(fixed)	W(random)
ADVANCE	0.94	0.83 ; 1.1	100	100
Fixed	0.94	0.83 ; 1.1	100	
Random	0.94	0.83 ; 1.1		100
I ² (%)	NA			
Network	0.93	0.81 ; 1.1		

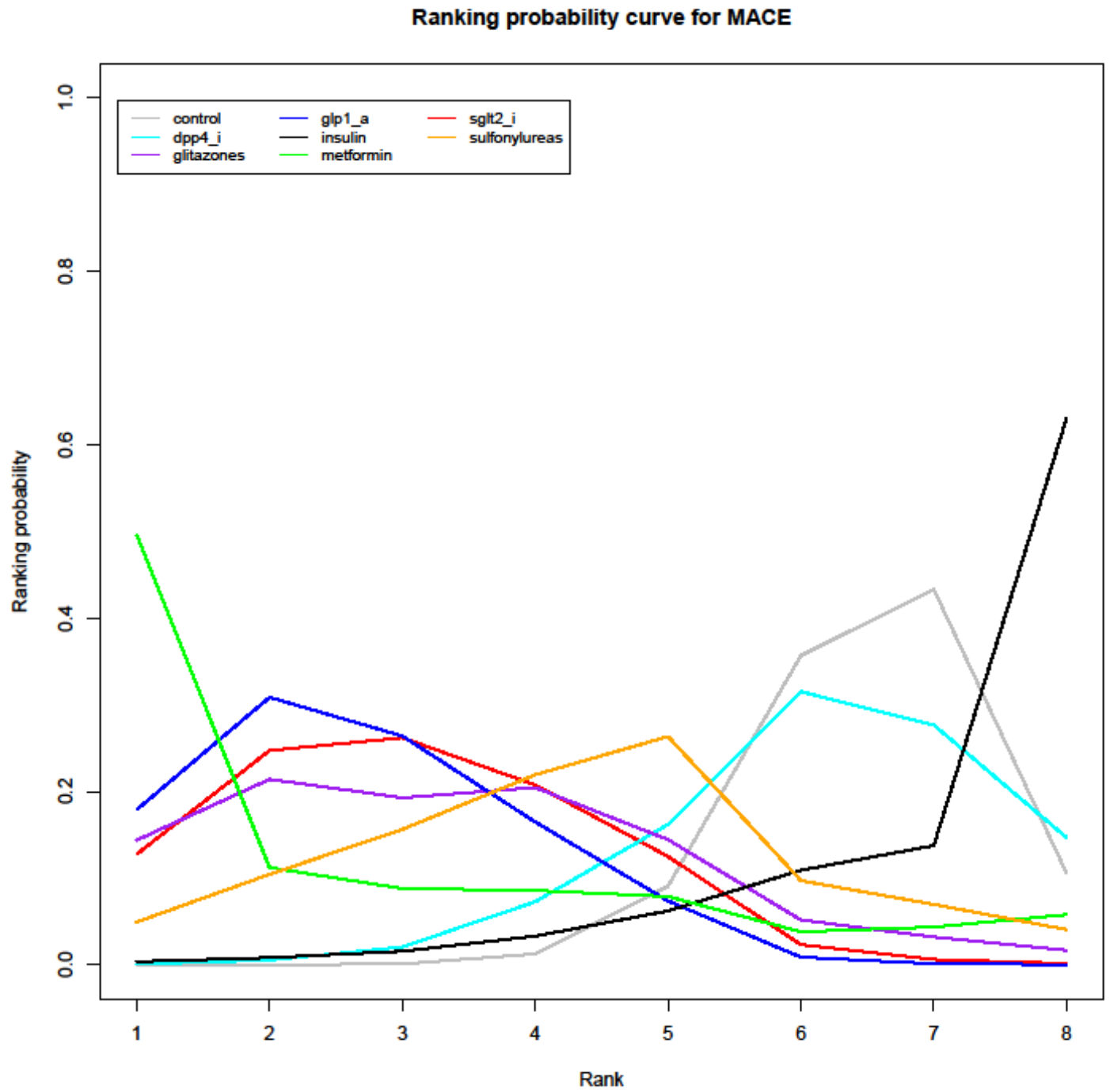


SULFONYLUREA VERSUS GLITAZONES

	OR	95%-CI	W(fixed)	W(random)
APPROACH	0.69	0.30 ; 1.6	8.1	14.2
PERISCOPE	1.21	0.36 ; 4.0	3.8	7.4
PioGLy.mCD.GILES.2008	0.58	0.33 ; 1.0	16.9	25
TOSCA.IT	1.06	0.80 ; 1.4	71.1	53.3
Fixed	0.93	0.74 ; 1.2	100	
Random	0.87	0.62 ; 1.2		100
I ² (%)	28			
Network	1	0.87 ; 1.2		



Probability curves of each drug classes to be ranked best treatment (rank = 1) to the last effective (rank = 8), for major adverse cardiovascular events (MACE).



First part – Second section. Benefit—risk balance assessment of SGLT2 inhibitors

The following has been submitted for a fast response to the British Medical Journal (BMJ). The BMJ's fast response are "electronic comments to the editor". The editor did not select it for letter article: the following has **not** been published in the BMJ. However, it does contribute to illustrate the work achieved during this thesis.

It can be found here: <https://www.bmj.com/content/363/bmj.k4365/rr-1>

This work is NOT a published article in the British Medical Journal. This work is an “electronic comments to the editor” regarding the following article:

“Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study”, BMJ 2018; 363 doi: <https://doi.org/10.1136/bmj.k4365> [149].

Article Related content Article metrics Rapid responses **Response**

Re: Sodium glucose cotransporter 2 inhibitors and risk of serious adverse events: nationwide register based cohort study

Sodium glucose cotransporter 2 (SGLT2) inhibitors have been associated with cardiovascular (CV) benefits in randomized clinical trials (RCTs) [1]. However, specific safety issues remain unclear. Ueda et al. observed an increased risk of lower limb amputation and of diabetic ketoacidosis with the use of SGLT2 inhibitors compared to glucagon-like peptide 1 (GLP1) receptor agonists (incidence rate 2.7 vs. 1.1 events per 1000 person years, HR 2.32 [95% CI 1.37; 3.91], and 1.3 vs. 0.6, HR = 2.14 [1.01; 4.52], respectively) [2].

Ueda et al. reported an original analysis of nationwide registers from Sweden and Denmark, to assess the risk of seven serious adverse events when using SGLT2 inhibitors. They used a propensity score matched cohort of 34 426 new users of SGLT2 inhibitors or GLP1 receptor agonists. Their results suggested potential harmful effects of SGLT2 inhibitors. We examined these results at the light of those of 3 powerful RCTs [3-5] assessing SGLT2 inhibitors in patients with type 2 diabetes, to discuss the agreement between observational and experimental data, taking into account the benefit/risk balance estimations.

First, the three CV outcomes RCTs assessing SGLT2 inhibitors [3-5] showed conflicting results regarding the risk of amputation. In the CANVAS Program [3], patients randomized to canagliflozin displayed higher rates of lower limb amputation (HR 1.97 [95% CI 1.41; 2.75]). In the EMPAREG OUTCOME trial [4, 6] and in the

DECLARE TIMI 58 trial [5], the risk of amputation was not increased in the SGLT2 inhibitor group compared to placebo (HR=1.00 [95% CI 0.70; 1.44] and 1.09 [95% CI 0.84; 1.40], respectively); these confidence intervals excluding the HR estimated in CANVAS. As expected, the meta-analysis of the risk increase of amputation in those 3 RCTs displayed a significant heterogeneity ($I^2 = 77%$, supplementary figure available on request). The meta-analysis of the risk increase of diabetic ketoacidosis was consistent across the 3 RCTs (RR = 2.14 [95% IC 1.24; 3.71], $I^2 = 0%$, supplementary figure available on request).

Second, the treatment effect estimation through those three randomized, double-blinded, placebo controlled trials has a high level of evidence and a lower risk of bias than from pharmaco-epidemiological study. Diabetic ketoacidosis was a pre-specified safety outcome in all 3 RCTs; amputations were adverse events of interest in the CANVAS Program trial [3], collected retro- and prospectively in the DECLARE TIMI 58 trial [5], and searched for in post hoc analysis in the EMPAREG OUTCOME trial [6].

Third, register-based cohort are usually helpful as they allow big sample size and then to overcome the limit of statistical power for safety issue in RCT regarding rare events. However, the study of Ueda et al. included 17 213 patients treated with SGLT2 inhibitors, 61% with dapagliflozin, 38% with empagliflozin and only 1% with canagliflozin. The three CV RCTs pooled results on 19 056 patients treated with SGLT2 inhibitors, i.e. a similar sample size. However, the power of the study of Ueda et al. was considerably lower than the meta-analysis of the 3 RCTs, with only 62 amputations and 30 diabetic ketoacidosis against 552 and 62 in the meta-analysis, respectively (supplementary figure available on request).

Fourth, the meta-analysis of Zelniker et al. showed a decreased risk of major adverse cardiovascular events (MACE) and of CV death or hospitalization for heart failure with SGLT2 inhibitors (HR = 0.89 [95% CI 0.83; 0.96] and HR = 0.77 [95% CI 0.71; 0.84], respectively) [1]. The absolute risk difference for amputation, diabetic ketoacidosis, MACE and hospitalization for heart failure, estimated from the 3 RCTs, suggested a favorable benefit/risk balance for the SGLT2 inhibitors, even when taking into account the risk of amputation and of diabetic ketoacidosis (Table available on request).

To conclude, Ueda et al. suggested a risk of amputations with SGLT2 inhibitors, but the meta-analysis of more powerful RCTs excluded a class effect. The risk of diabetic ketoacidosis seemed to be related to the class, but did not offset the CV benefits. Pharmaco-epidemiology approach could help to identify safety signal, but its potentially biased estimation should be interpreted with caution. When both approaches disagree, as long as they are powerful enough, RCTs results dominate due to their higher level of evidence.

27 November 2018

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Here, they advocate not to drop out drugs with positive benefit-risk balances.

Supplementary figure: Forest plot showing the effect of SGLT2 Inhibitors on risk of amputation and of diabetic ketoacidosis, through meta-analysis of the CANVAS Program, DECLARE TIMI 58 and EMPAREG OUTCOME trials (available on request)

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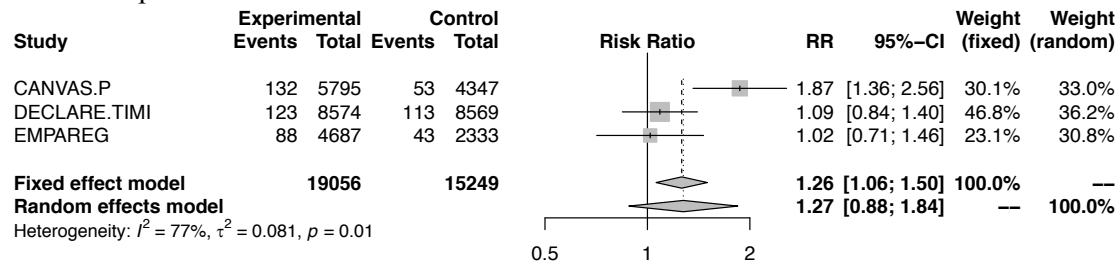
Competing interests: GG has received support for travel to scientific meetings from Novo Nordisk, Lilly and is a member of the association « Association des toxicologues ». MC has received consulting fees from Boehringer Ingelheim, SANOFI, and speaker honoraria from SANOFI. In the last five years, FG received for his institution fees from Portola Pharmaceuticals for central reading of ultrasound records, from Neurochlore for DSMB coordination, from EryTech Pharma for modeling projects, from RCTs and Steve Consultant for exploring French social security database.

Supporting information

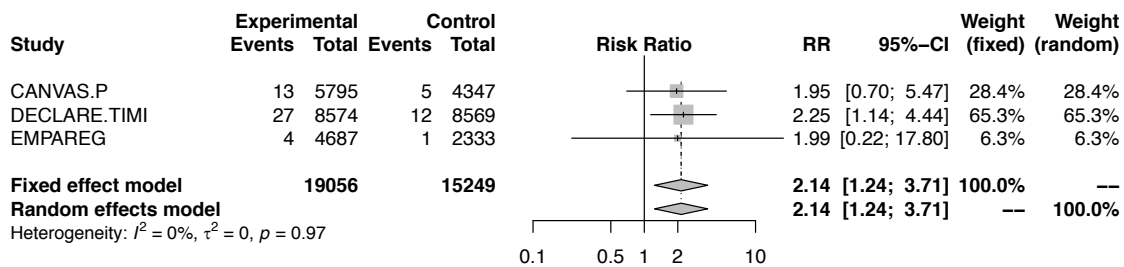
Forest plot of the effect of SGLT2 inhibitors on risk of amputation (up) and of diabetic ketoacidosis (down).

The diamonds in the forest plot stand for the estimate (OR and its 95%CI) using direct meta-analysis with both fixed and random model; the squares stand for the TE estimate in the corresponding trial.

Risk of amputation



Risk of diabetic ketoacidosis



Comparison of the absolute difference of safety and efficacy events, with SGLT2 inhibitors compared to placebo.

	Absolute difference in rate per 1000 patients-year			
	Amputation	Diabetic ketoacidosis	MACE	Hospitalization for heart failure
CANVAS Program	2,9*	0,3	-4,6*	-3,2*
DECLARE TIMI 58	0,3	0,4*	-1,6	-2,3*
EMPAREG OUTCOME	0,1	0,1	-6,5*	-5,1*

Table. Absolute difference in rate per 1000 patients-year of safety and efficacy outcomes (MACE: major adverse cardiovascular events, * $p < 0.05$)

SECOND PART.

ASSESSMENT OF THE BLOOD PRESSURE AS A SURROGATE

In the second part, we used a meta-regression approach of aggregates data of randomized clinical trials for characterizing the relationship between the reduction of blood pressure and the cardiovascular risk, with antihypertensive treatment, in patients with type 2 diabetes. This could help assessing surrogate endpoint for personalizing the treatment effect estimation.



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Original article

Association between difference in blood pressure reduction and risk of cardiovascular events in a type 2 diabetes population: A meta-regression analysis

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ABSTRACT

Aim. – Recent US recommendations indicate a target blood pressure (BP) of 130/80 mmHg for patients with type 2 diabetes (T2D). Our aim was to characterize the association between risk of cardiovascular events and differences in BP decreases in randomized trials of a T2D population.

Methods. – A systematic search was made for randomized clinical trials assessing the effects of antihypertensive treatments in T2D patients on mortality, and fatal and non-fatal cardiovascular events, using a meta-regression technique to explore the influence of BP decreases on treatment effects.

Results. – A total of 88,503 patients from 44 randomized trials were included. There was no significant association between BP decreases and risk of all-cause or cardiovascular mortality, cardiovascular events or myocardial infarction. However, stroke risk was influenced by BP decreases: compared with no reduction, a 10-mmHg reduction in systolic BP was associated with a relative odds ratio (OR) decrease of 33% (OR: 0.67, 95% CI: 0.54–0.82), and a 5-mmHg diastolic BP reduction was associated with a relative OR decrease of 38% (OR: 0.62, 95% CI: 0.50–0.76). Restricting the analysis to double-blind studies did not change the results for diastolic BP.

Conclusion. – A reduction in BP lowers the risk of stroke, but does not appear to affect the risk of other cardiovascular events in a T2D population.

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Introduction

High blood pressure (BP) is a major cardiovascular (CV) risk factor and, in the general population, the CV benefits of

antihypertensive drugs may be partially explained by the different BP values achieved [1]. Indeed, BP decrease has been proposed as a surrogate endpoint of risk of stroke [2]. When BP is reduced, it appears to influence mainly the risk of stroke compared with other CV outcomes [3]. However, even for stroke, systolic BP (SBP) reduction explains only half of the risk reduction in the general population [4]. In the past, based on a subgroup analysis of the Hypertension Optimal Treatment (HOT) trial in diabetes patients, more stringent BP targets were recommended for patients with type 2 diabetes (T2D) compared with the general population [5,6]. However, as this BP target for the diabetes population became a subject of debate [7–9], eventually the same BP target as for the general population was proposed [10,11]. Yet, since those

Abbreviations: ACC, American College of Cardiology; ACE, Angiotensin-converting enzyme; AHA, American Heart Association; BP, Blood Pressure; CV, Cardiovascular; CVD, Cardiovascular Disease; DBP, Diastolic Blood Pressure; FDA, Food and Drug Administration; OR, Odds Ratio; RCT(s), Randomized Clinical Trial(s); REML, Restricted Maximum Likelihood; SBP, Systolic Blood Pressure; T2D, Type 2 Diabetes.

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recommendations were made, meta-analyses have shown some discrepancies among BP targets for CV prevention in T2D patients. Bangalore et al. [12] described an association between more intensive treatment targeting an SBP of 135 mmHg and a decrease in macrovascular events, while Reboldi et al. [13] confirmed that BP reduction appeared to lower the risk of stroke, but not the risk of myocardial infarction. A meta-analysis by Emdin et al. [14] suggested a decrease in risk of mortality for every 10-mmHg SBP reduction, whereas Brunström and Carlberg [15] reported an increased risk of CV death, but no benefit when baseline SBP was < 140 mmHg. In the general population, it has been suggested that lowering SBP to < 130 mmHg might be beneficial [16,17], but other meta-analyses found conflicting results [18]. Recently, the American College of Cardiology (ACC) and American Heart Association (AHA) recommended reducing BP to < 130/80 mmHg for patients with T2D [19].

The meta-regression approach investigates whether particular covariates (potential effect modifiers) might explain some of the differences in treatment effects observed across multiple studies [20,21], and explores whether any of the considered outcomes are influenced by BP changes [22]. In T2D populations, recent studies have focused on the influence of either baseline BP or achieved BP in intensive-treatment groups [12,15], or used a standardized approach (log of the risk of outcome multiplied by [10 mmHg/systolic BP reduction]) [14] which could bias the results [23]. In a previous study of differences in baseline and achieved BP in active-treatment vs control groups in T2D populations, outcomes were limited to myocardial infarction and stroke [13]. Our present study updates that exploration with more recent trials, and extends the analysis to overall and CV mortality as well as CV events.

Thus, the purpose of this study was to characterize the association between intensity of BP reduction and magnitude of clinical benefit on several CV events in T2D patients.

Material and methods

As no protocol has been previously published, the present study is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA; Appendix A.1; see supplementary materials associated with this article online).

Eligibility criteria

Only studies fulfilling the inclusion criteria described below, following the PICO (population/problem, intervention/exposure, comparison, outcome) framework, were eligible for inclusion in our analysis.

Participants

Only patients aged ≥ 18 years with T2D were included. The diagnosis of T2D had to have been established using either standard criteria or, if necessary, the author's definition. Studies that included patients on dialysis, patients with solid organ transplants, pregnant women, patients with impaired glucose tolerance or impaired fasting glucose, or the metabolic syndrome only, were excluded.

Interventions

Eligible interventions were any antihypertensive drugs, such as beta-blockers, angiotensin-converting enzyme (ACE) inhibitors, sartans (angiotensin receptor blockers), calcium-channel blockers, diuretics and intensive antihypertensive treatments. In trials combining the intervention of interest with another intervention, only data for the intervention of interest were included if the subgroup met our inclusion criteria. For example, in the Action in

Diabetes and Vascular Disease: Preterax and Diamicron Modified-Release Controlled Evaluation (ADVANCE) trial, only data from the antihypertensive groups were considered and, in the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT), only data from the diabetes subgroup were included.

Comparisons

All comparisons against a control group (placebo, active treatment, usual care) were included.

Outcomes

Trials designed to evaluate CV events as either their primary or secondary endpoints were included, whereas trials reporting CV events for safety purposes only were not. The considered outcomes were: total deaths; CV deaths; CV events (CVEs); all myocardial infarctions (MIs; fatal, non-fatal); all strokes (fatal, non-fatal); major microvascular events; and major combined macrovascular and microvascular events.

Study design

Only parallel-group randomized clinical trials (RCTs) were included.

Outcomes of meta-analysis

Outcomes of this analysis were total deaths, CV deaths, CVEs, all MIs (fatal, non-fatal), all strokes (fatal, non-fatal), major microvascular events, and major combined macrovascular and microvascular events.

Information sources and search strategy

Published trials were identified through a computerized search of: (i) Medline (PubMed, www.pubmed.org, from inception to 1 March 2016); (ii) Embase (www.embase.com); and (iii) the Cochrane Central Register of Controlled Trials (CENTRAL). Our search terms comprised disease terms, a study design filter and drug terms. The study design filters were designed to identify placebo-controlled or head-to-head RCTs using a combination of index and free-text terms. The PubMed database was searched using a specific sensitive strategy (as described by Haynes et al. [24]), including type of "randomized clinical trial" and MeSH terms (Appendix A.2; see supplementary materials associated with this article online). Unpublished trials were searched for in: (i) abstracts and presentations from appropriate conferences (using the ISI Web of Knowledge database that indexes conference proceedings); (ii) reference lists from studies, reviews and meta-analyses obtained from the PubMed search; and (iii) the Internet, including websites dedicated to the dissemination of results from clinical trials (Medscape) and the US Food and Drug Administration (FDA), and those maintained by drug manufacturers, including product information sheets. Also included were trials published only in abstract form to limit the influence of potentially relevant trials unpublished when completed. When an abstract from proceedings and a full paper referred to the same trial, only the full article was included in our analysis. When two or more papers used the same data, only the most complete report was used.

Study selection, data collection and risk of bias assessment in individual studies

Study selection was performed by three independent reviewers (M.C., G.G., H.H.L.), among whom a consensus had to be reached in cases of disagreement. The study flow diagram (Appendix A.3; see

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Table 1
Characteristics of the trials included in the meta-regression analysis.

Trial	Blinding	Sample size (N)	Treatment 1	Treatment 2
ABCD 2V, 2006	Assessment ^a	66 vs 63	Intensive DBP control (< 75 mmHg) with valsartan	Moderate BP control (DBP 80–90 mmHg, SBP < 140 mmHg), placebo
ABCD Hypertension, 1998	Double	235 vs 235	Nisoldipine	Enalapril
ABCD Normotensives, 1993	Open	237 vs 243	Intensive (10 mmHg below baseline) DBP control	Moderate (80–89 mmHg) DBP control
ACCOMPLISH	Double	1432 vs 1410	Benazepril + amlodipine	Benazepril + hydrochlorothiazide
ACCORD BP, 2010	Open	2363 vs 2371	Intensive	Standard
ACTION	Double	565 vs 545	Nifedipine	Placebo
ADVANCE	Double	5569 vs 5571	Low-dose fixed combination of perindopril + indapamide	Placebo
ALLHAT (amlodipine vs chlor)	Double	2664 vs 4498	Amlodipine	Chlorthalidone
ALLHAT (lisi vs chlor)	Double	2431 vs 4498	Lisinopril	Chlorthalidone
Trial	Blinding	Sample size (N)	Treatment 1	Treatment 2
ASCOT (subgroup), 2008	Double	2565 vs 2572	Amlodipine + added perindopril	Atenolol + added thiazide
CAPP	Assessment ^a	309 vs 263	Captopril	Thiazide diuretic or beta-blocker
Chan, 1992	Double	50 vs 52	Enalapril	Nifedipine
DETAIL	Double	120 vs 130	Telmisartan	Enalapril
DIABHYCAR	Double	2443 vs 2469	Ramipril	Placebo
DREAM	Open	2623 vs 2646	Ramipril	Placebo
EUROPA (PERSUADE substudy)	Double	721 vs 781	Perindopril	Placebo
FACET	Open	191 vs 189	Amlodipine	Fosinopril
Fogari et al., 2002	Open	103 vs 104	Amlodipine	Amlodipine + fosinopril
Fogari et al., 2002	Open	102 vs 104	Fosinopril	Amlodipine + fosinopril
GEMINI	Double	498 vs 737	Carvedilol	Metoprolol
GUARD, 2008	Double	166 vs 166	Benazepril + amlodipine	Benazepril + hydrochlorothiazide
Trial	Blinding	Sample size (N)	Treatment 1	Treatment 2
HOPE	Double	1808 vs 1759	Ramipril	Placebo
HOT	Open	499 vs 500	Target DBP ≤ 80 mmHg	Target DBP ≤ 90 mmHg
IDNT (irbesartan vs amlodipine)	Double	579 vs 567	Irbesartan	Amlodipine
IDNT amlodipine	Double	567 vs 569	Amlodipine	Placebo
IDNT irbesartan	Double	579 vs 569	Irbesartan	Placebo
INSIGHT	Double	649 vs 653	Nifedipine	Co-amilozide hydrochlorothiazide + amiloride
INVEST (subgroup), 2003	Open	3169 vs 3231	Calcium antagonist strategy (verapamil sustained-release)	Non-calcium antagonist strategy (atenolol)
IPDM	Double	195 vs 201	Irbesartan	Placebo
JMIC-B	Open	199 vs 173	Nifedipine	ACEI
LIFE	Double	586 vs 609	Losartan	Atenolol
MERIT-HF	Double	495 vs 490	Metoprolol	Placebo
Trial	Blinding	Sample size (N)	Treatment 1	Treatment 2
NAGOYA HEART, 2011	Open	575 vs 575	BP-lowering based on valsartan	BP-lowering based on amlodipine
NORDIL	Open	351 vs 376	Diltiazem	Thiazide diuretic or beta-blocker at step 1
ORIENT	Double	288; 289	Olmesartan	Placebo
PROFESS	Double	2840 vs 2903	Telmisartan	Placebo
PROGRESS (diabetic subgroup)	Double	393 vs 368	Perindopril	Placebo
RENAAL	Double	751 vs 762	Losartan	Placebo
ROADMAP	Double	2232; 2215	Olmesartan	Placebo
SANDS	Open	252 vs 247	Aggressive SBP control ≤ 115 mmHg (DBP ≤ 75 mmHg)	Standard SBP control ≤ 130 mmHg (DBP ≤ 85 mmHg)
SCAT	Double	25 vs 25	Enalapril	Placebo
SCOPE (diabetic subgroup), 2003	Double	313 vs 284	Candesartan	Control
SHEP	Double	283 vs 300	Chlorthalidone + atenolol or reserpine	Placebo
Trial	Blinding	Sample size (N)	Treatment 1	Treatment 2
SOLVD	Double	646 vs 664	Enalapril	Placebo
STOP-2 (ACEI vs CCB) (diabetic subgroup), 2000	Assessment ^a	235 vs 231	ACEI	Calcium antagonists
STOP-2 ACEI (diabetic subgroup), 2000	Assessment ^a	235 vs 253	ACEI	Conventional (diuretic or beta-blocker)
STOP-2 CCB (diabetic subgroup), 2000	Assessment ^a	231 vs 253	Calcium antagonists	Conventional (diuretic or beta-blocker)
Syst-Eur (diabetic subgroup), 1999	Double	252 vs 240	Calcium-channel blocker	Placebo
UKPDS 38	Open	758 vs 390	Target < 150/85 mmHg (captopril or atenolol as main treatment)	Target < 180/105 mmHg (avoiding ACEIs or beta-blockers)
UKPDS 39	Open	400 vs 358	Captopril	Atenolol

DBP/SBP: diastolic/systolic blood pressure; BP: blood pressure; ACEI: angiotensin-converting enzyme inhibitor.

^a Open design with blinded assessment of outcomes; number of subjects in each group the same as in treatment description.

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supplementary materials associated with this article online) shows that detailed inclusion criteria, treatment type and duration of follow-up were extracted (as available) from each individual study. The blinding design of the study was also evaluated.

Statistical methods

Our analysis used weighted meta-regression of the logarithm (log) of the odds ratio (OR) against differences in BP reduction, defined as the difference in BP change (expressed as mmHg) during the trial (final value minus baseline value) between active-treatment and control (active control or placebo, depending on the study) groups. If not available, the difference in final BP values was used.

Also used were the restricted maximum likelihood (REML) estimator [25], weighted log OR and an additive between-study variance component (ϵ^2) to take into account residual heterogeneity, such that $y_i = \log(\text{OR}_i) = N(\alpha + \beta x_i, \sigma_i + \epsilon^2)$, where σ_i is the variance of the log OR within trial i , ϵ^2 is the between-study variance, β is the slope and represents change in the log OR of the considered endpoint per each 1-unit change in BP reduction x_i , and α is the log OR at a BP reduction of zero (intercept). The weight of the trials was defined as $\omega_i = 1/\sigma_i$.

EASYMA [26] with R [27] software was used in our analyses. For each CV outcome, the analysis was run twice [for SBP and for diastolic BP (DBP) values]. Sensitivity analyses restricted to double-blind studies only were also conducted. No correction for multiple testing was applied.

Risk of publication bias

Funnel plots were used to assess the risk of publication bias [28].

Results

A total of 44 RCTs, involving a total of 88,503 patients, were included in our analysis. ACE inhibitors were used as either first or second line treatment in 20 arms, calcium-channel blockers in 16 arms, sartans in 12, beta-blockers in 12 and diuretics in 11. Non-specific intensive strategies were also included (four trials). The average study sample size was 1948 patients (range: 50–11,140), and the first study was published in 1992. Among our RCTs, 28 were double-blind, 13 were unblinded (open), and three were open, but blinded when assessing the outcome (not taken into account in the sensitivity analysis). Three trials were unpublished. Table 1 summarizes the main characteristics of the included trials.

Meta-regression showed a significant relationship between SBP reduction and the log(OR) of stroke, but not for the other outcomes (total mortality, CV mortality, CVEs and MIs). Equations and P values of regression are summarized in Table 2. The effect of SBP reduction on the log(OR) of those outcomes is illustrated in Fig. 1. The significant ($P=0.01$) relationship between risk of stroke and SBP reduction was $\log(\text{OR}) = -0.0192 + (0.0386 \times [\text{SBP}$

reduction]). Compared with no BP reduction, every 10-mmHg SBP reduction was associated with a relative 33% decrease in risk of stroke [OR: 0.67, 95% confidence interval (CI): 0.54–0.82].

Meta-regression also revealed a significant relationship between DBP and the log(OR) of stroke, but not for the other outcomes (total mortality, CV mortality, CVEs, MIs). Equations and P values of regression are summarized in Table 2. The effect of DBP reduction on the log(OR) of those outcomes is illustrated in Fig. 2. The significant ($P=0.001$) relationship between risk of stroke and DBP reduction was $\log(\text{OR}) = -0.0013 + (0.0969 \times [\text{DBP}$ reduction]). Compared with no BP reduction, every 5-mmHg reduction in DBP was associated with a relative 38% decrease in risk of stroke (OR: 0.62, 95% CI: 0.50–0.76).

Regarding microvascular outcomes, their reporting in the eligible studies did not allow for meta-regression analysis to be conducted. Sensitivity analyses were restricted to double-blind studies and so included only 28 trials. The relationship between DBP reduction and the log(OR) of stroke remained significant ($P=0.04$) with no correction for multiple testing (Appendix A.4; see supplementary materials associated with this article online). Funnel plots showed no evidence of potential publication biases (Appendix A.5; see supplementary materials associated with this article online).

Discussion

Decreases in BP do not appear to influence the risk of all-cause or CV mortality, CVEs or MIs. Our present results suggest, however, that lowering BP does affect the risk of stroke. This association was observed with both SBP and DBP reductions, but persisted on sensitivity analyses restricted to double-blind RCTs for DBP only. In fact, our findings confirm the results of Reboldi et al. [13], albeit extended to total and CV deaths, and CVEs. In a T2D patient population, Bangalore et al. [12] suggested a linear relationship between stroke risk and achieved SBP in the intensive-treatment group, while Brunström et al. [15] suggested an increased risk of CV mortality with baseline SBP < 140 mmHg. Emdin et al. [14] suggested an association between lowering SBP and decreases in mortality, CV disease, coronary heart disease and stroke. However, for their results, they standardized risk according to BP-lowering (log of risk was multiplied by [10 mmHg/SBP reduction]) [14], which may have overestimated the overall effect, as recently described [23]. For this reason, Brunström et al. [15] proposed that, before using such a standardized approach, a linear relationship within trials between different risk factors (differences in BP evolution) and treatment effects on the outcome of interest should be determined first. Our study suggested that such a relationship was observed only for risk of stroke, and not for risk of mortality or risk of CVEs.

Our study has some limitations. Open clinical trials were included, resulting in a risk of bias. Unfortunately, open trials of diabetes were common during the last few decades. Also, our analysis focused on severe clinical outcomes that were

Table 2
Summary of meta-regression of log(OR) of outcomes for systolic (SBP) and diastolic blood pressure (DBP) reductions.

Outcome	Comparisons (N)		Equation		P	
	SBP	DBP	SBP	DBP	SBP	DBP
Total deaths	26	25	$-0.142 + (-0.0094)^* X$	$-0.1408 + (-0.0205)^* X$	0.423	0.437
CV deaths	17	16	$-0.1118 + (-0.0094)^* X$	$-0.158 + (-0.0416)^* X$	0.645	0.327
CV events	21	21	$-0.0839 + (0.0109)^* X$	$-0.0736 + (0.0293)^* X$	0.372	0.249
MI	25	24	$-0.1101 + (-0.0023)^* X$	$-0.1392 + (-0.0175)^* X$	0.887	0.609
Stroke	27	26	$-0.0192 + (0.0386)^* X$	$-0.0013 + (0.0969)^* X$	0.01*	0.001*

In equations, "X" stands for difference in blood pressure reduction in mmHg; CV: cardiovascular; MI: myocardial infarction. *Nominal $P < 0.05$.

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mostly CV-related and not the only complications found in T2D patients, but nonetheless representative of the main causes of death in such a population. In addition, it was not possible to explore the risk of haemorrhagic vs ischaemic stroke or CV risk at baseline, and microvascular complications were not explored due to a lack of data. Furthermore, the definition of outcomes may

have differed across the included studies, with some studies reporting the number of non-fatal strokes and others the number of fatal strokes. Moreover, exact details concerning BP evolution across different treatment groups were not always available, leading to a smaller number of analyzed studies. Likewise, it was not possible to take into account the heterogeneity of BP

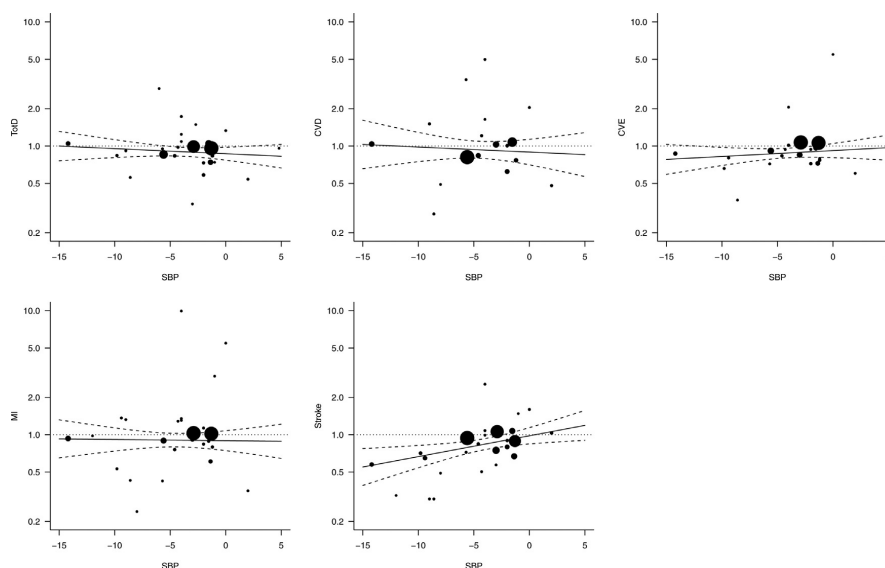


Fig. 1. Regression plots of the odds ratio (OR; log scale) for each outcome against differences in systolic blood pressure (SBP). Each black point represents a comparison (size varies according to weight); the solid line represents the meta-regression line, the dashed line its 95% confidence interval, and the dotted line the null effect on outcome (OR = 1). TotD: total deaths; CVD: cardiovascular deaths; CVE: cardiovascular events; MI: myocardial infarction.

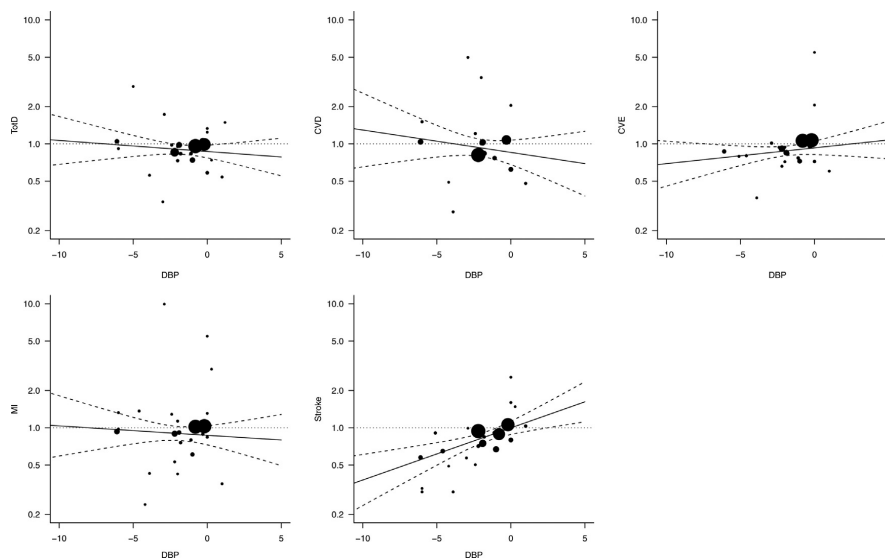


Fig. 2. Regression plot of the odds ratio (OR; log scale) for each outcome against differences in diastolic blood pressure (DBP). Each black point represents a comparison (size varies according to weight); the solid line represents the meta-regression line, the dashed line its 95% confidence interval, and the dotted line the null effect on outcome (OR = 1). TotD: total deaths; CVD: cardiovascular deaths; CVE: cardiovascular events; MI: myocardial infarction.

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measurements. Our study could only analyze aggregate data and could not explore individual patients' data. Thus, the possibility that the association between the OR of stroke and BP decreases might be due to an ecological bias cannot be excluded. Also, meta-regression approaches are not protected against confusion bias, and meta-analyses at the individual data level would be helpful in future studies. On the other hand, false-negative results for the other outcomes due to a lack of power also cannot be excluded. Finally, it has been observed that BP variability itself could be a predictor of risk of stroke [29].

Recent recommendations of the ACC and AHA [19] have revealed some disagreement with the recent Position Statement of the American Diabetes Association [30] regarding BP targets in patients with T2D. Indeed, our present results and the current literature appear to suggest heterogeneity of organ sensitivity to BP decreases. This observation could lead to BP targets being adapted according to the individual patient's characteristics with a personalized medicine perspective. For example, the association between stroke and BP appears to be stronger in Asian populations, leading Park et al. [31] to propose a specific BP target of 130/80 mmHg in Asians.

Conclusion

Our present study confirms the potential association between BP-lowering and risk of stroke, but not for other CV events in a T2D population. Nevertheless, our findings contribute towards clarifying the effect of BP decreases in reducing CV risk in T2D patients, and quantitative estimates of this association could lead to more precise models of the public-health benefits of BP-lowering treatments in such a patient population.

Ethics

Ethics approval and consent to participate: not applicable.
Consent for publication: not applicable.

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Contribution

M.C. proposed the idea of the review, and made substantial contributions to the conception and design of the protocol. M.C., G.G. and H.H.L. performed the study search and selection, and contributed to the data acquisition and analyses. G.G. wrote the article. M.C., H.H.L., F.G., T.B.-A., S.E., P.M., R.B. and B.K. have been involved in revising the manuscript critically for important intellectual content.

All authors read and approved the final manuscript.

Disclosure of interest

G.G. has received support for travel to scientific meetings from Novo Nordisk and Eli Lilly.

H.H.L. is receiving a salary from Claude Bernard Lyon 1 University (scholarship of French Ministry of Higher Education & Research) for her three-year PhD at the UMR 5558 CNRS.

M.C. has received consulting fees from Boehringer Ingelheim and Sanofi, and speaker honoraria from Sanofi.

In the last five years, F.G. received fees for his institution from Portola Pharmaceuticals for central reading of ultrasound records, from Neurochlore for DSMB coordination, from Erytech Pharma for

modelling projects, and from RCTs and Steve Consultant for exploring the French social security database.

P.M.(1) or his institution (2) has received honoraria (talks and/or trials and/or consultancies) or support for travel to scientific meetings(3) from Novo Nordisk1, MSD1, Amgen2, AMT/Chiesi2, AstraZeneca/BMS2, Eli Lilly2, MSD2, Novo Nordisk2, Novartis2, Olympus2, Pierre Fabre2, Regeneron2, Sanofi2, Servier2, AstraZeneca3, Boehringer Ingelheim3, BMS3, Janssen3, MSD3, Eli Lilly3 and Sanofi3.

The authors T.B.-A., S.E., R.B., B.K. declare that they have no competing interest.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at <https://doi.org/10.1016/j.diabet.2019.05.003>.

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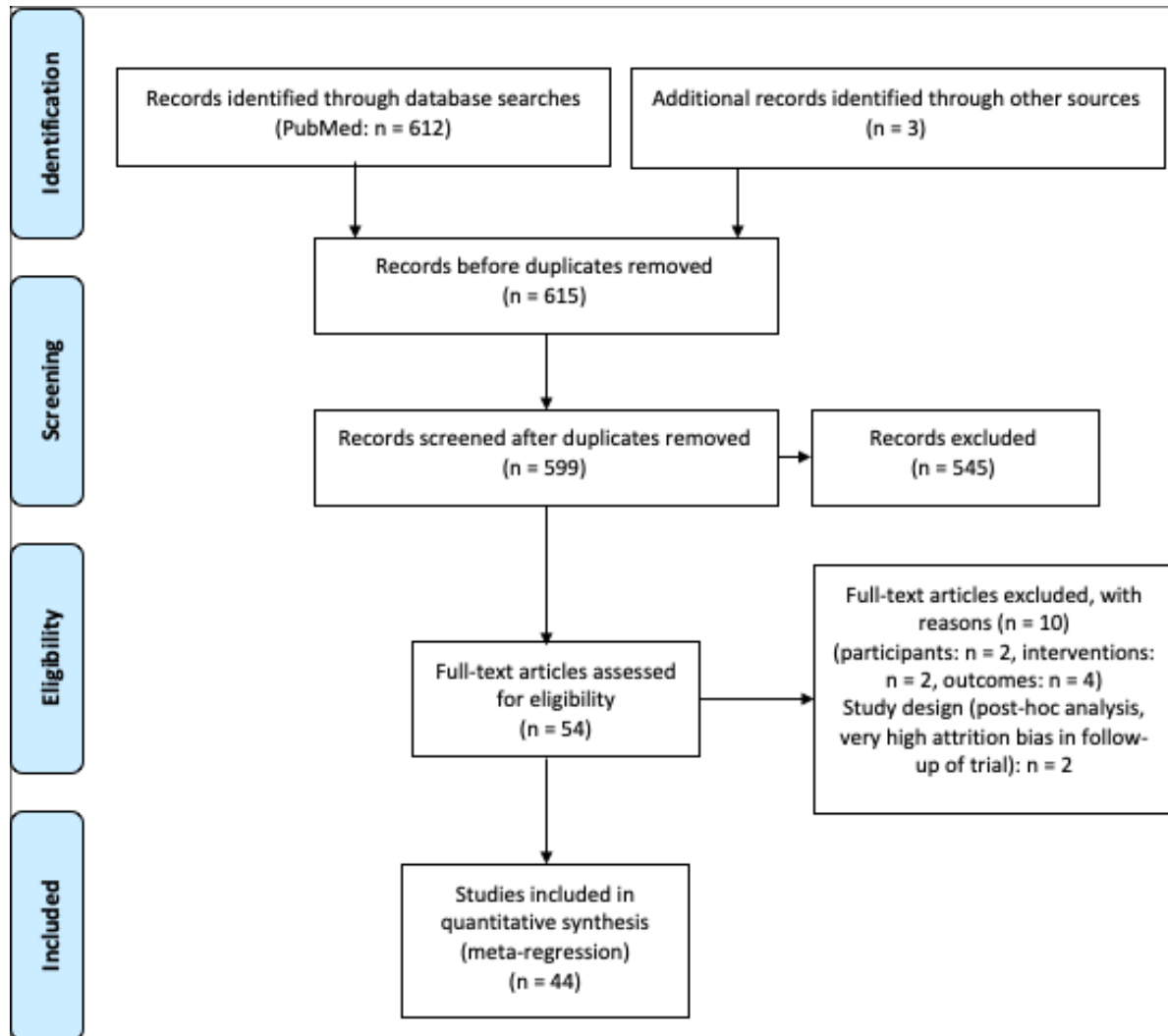
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Supporting information

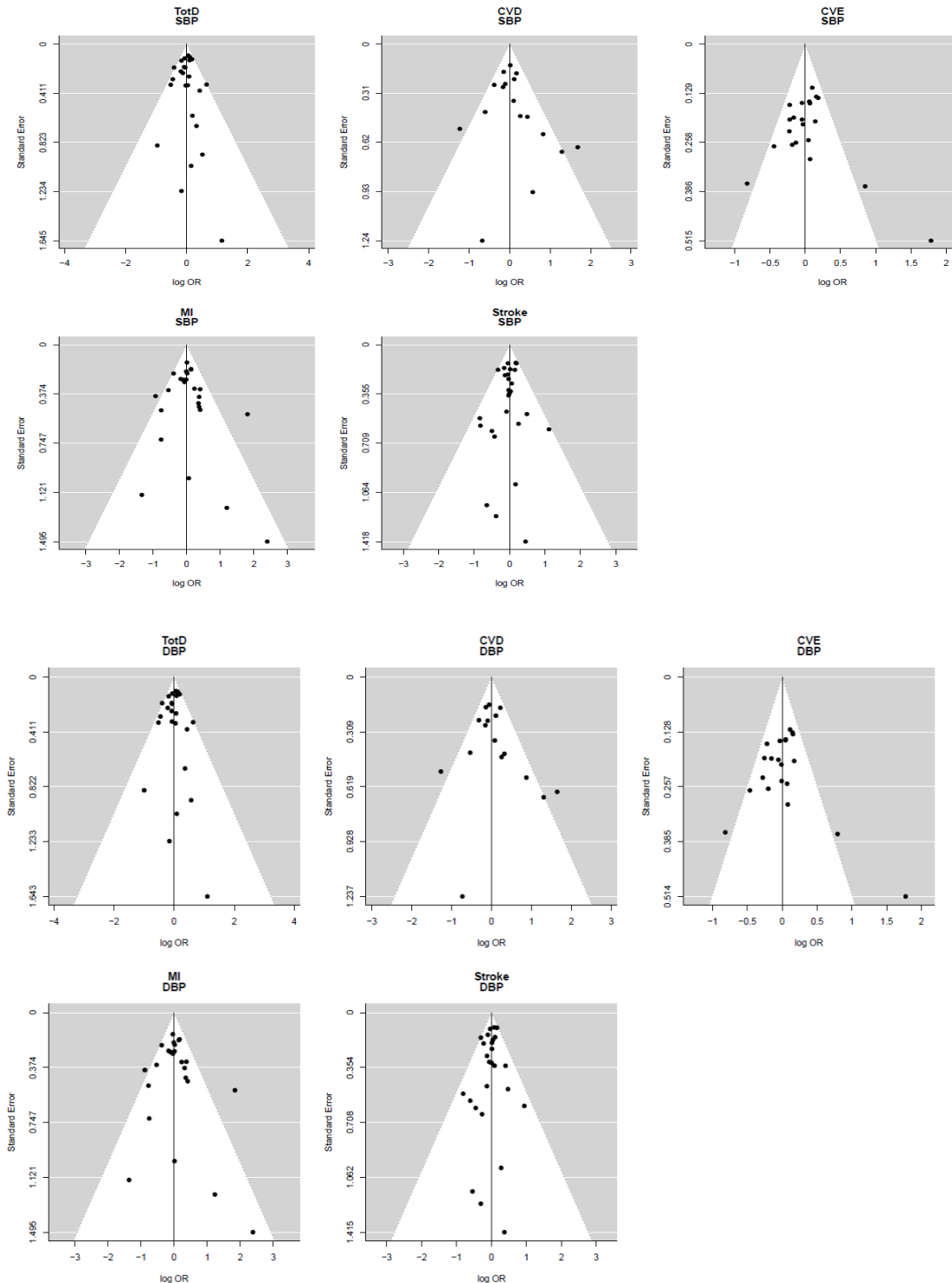
Some supporting information are provided in the Appendix 3.

Flow diagram of the systematic review



Assessment of publication bias: funnel plot.

X-axis: treatment effect estimation log (OR), Y-axis: standard error of the estimation. Each point stand for a trial. SBP/DBP: systolic/diastolic blood pressure; TotD: total deaths; CVD: cardiovascular deaths; CVE: cardiovascular event; MI: myocardial infarction



Sensitivity analysis restricted to blinded trials only

Summary of meta-regression of log(OR) of outcomes for systolic (SBP) and diastolic blood pressure (DBP) reductions

Outcome	Comparisons (n)		Equation		<i>p value</i>	
	SBP	DBP	SBP	DBP	SBP	DBP
Total deaths	19	18	$-0.069 + (0.0135) * X$	$-0.0736 + (0.0307) * X$	0.529	0.539
CV deaths	11	10	$0.0265 + (0.0383) * X$	$-0.1142 + (-0.0078) * X$	0.409	0.943
CV events	16	16	$-0.0475 + (0.0279) * X$	$-0.0618 + (0.0493) * X$	0.133	0.152
MI	18	17	$0.0134 + (0.0335) * X$	$-0.0501 + (0.0427) * X$	0.248	0.51
Stroke	19	18	$-0.0331 + (0.0327) * X$	$-0.0223 + (0.0805) * X$	0.135	0.04

In equations, 'X' stands for differences in blood pressure reduction in mmHg;

CV: cardiovascular; MI: myocardial infarction

THIRD PART.

TRIALS ASSESSING THERANOSTIC BIOMARKER: DESIGNS AND REPORTING.

The third part is divided in two sections.

In the first section, we developed a statistical comparison of two experimental designs for testing theranostic biomarker, in the case of a stratified randomization. This could help designing clinical trial for testing candidate effect modifier, which would allow to stratify the treatment effect estimation.

In the second section, we report a meta-epidemiological survey assessing pharmacogenetic studies. We provided a critical appraisal of the reporting of pharmacogenetic associations in RCT and assess the quality of the methodology for claiming predictive effect of a genetic variant. This section presents the poster communication summarizing this survey.

Third part – First section. Comparison of two experimental designs for testing theranostic biomarkers

Comparison of crossover and parallel-group designs for the identification of a binary predictive biomarker of the treatment effect

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Abstract

Pros and cons of crossover design are well known for estimating the treatment effect compared to parallel-group design, but remain unclear for identifying and estimating an interaction between a potential biomarker and the treatment effect. Such 'predictive' biomarkers, or 'effect modifiers', help to predict the response to specific treatments. The purpose of this report was to better characterize the advantages and disadvantages of crossover versus parallel-group design to identify predictive biomarkers. The treatment effect, the effect of a binary biomarker and their interaction were modelled using a linear model. The intra-subject correlation in the crossover design was taken into account through an intra-class correlation coefficient. The variance-covariance matrix of the parameters was derived and compared. For both trial designs, the variance of the parameter estimating an interaction between the treatment effect and a potential predictive biomarker corresponds to the variance of the parameter estimating the treatment effect, multiplied by the inverse of the frequency of the candidate biomarker. The ratio of the variance of the interaction parameter in the crossover to the variance estimated in the parallel-group design depends on the complement of the intra-class correlation coefficient. When planning a clinical trial including a search for candidate biomarker, the frequency of the candidate biomarker helps design the sample size, and the intra-subject correlation of the outcome should be taken into account for choosing between parallel-group and crossover designs.

KEYWORDS

crossover trial, parallel-group trial, predictive biomarker, statistical power

1 | INTRODUCTION

Biomarkers can be useful in the personalized medicine perspective. Prognostic biomarkers help predict the course of

a disease in a defined population, irrespective of treatment, whereas predictive biomarkers or effect modifiers are needed to predict the effect of a specific treatment.¹ Such theranostic biomarkers can help identifying responder patients before prescribing a drug. Randomized trials are the best setting to search for such identification, as they assess the treatment effect with the lowest risk of bias compared to other designs. Indeed, the randomization process allows inferring causality for the treatment effect. Trials are often limited

Abbreviations: CO, Crossover; N_{co} , Number of subject in the crossover design; $N_{pg,expo}$, Number of subject exposed to the tested treatment, in the parallel-group design; N_{pg} , Number of subject in the parallel-group design; PG, Parallel-group.

to the demonstration of the existence of an effect, whereas target therapies have stimulated the conduct of trials specifically designed for testing such interaction. Different designs of randomized trials are available, with specific pros and cons.² The crossover (CO) design can decrease the number of subjects needed for estimating the treatment effect, as already described.³⁻⁷ Indeed, the treatment effect is estimated through intra-subject comparison in the CO design, usually leading to a decreased variability of the measure of the outcome. However, the advantages of the CO design, compared to parallel-group (PG) design, for identifying an interaction between the treatment effect and a potential predictive biomarker have not yet been documented, despite the increase in publications regarding the predictive biomarkers area.^{1,8-10} Moreover, some literature studied the sample size determination for subgroup analysis for testing treatment interactions in the PG trial design,^{11,12} yet less is known regarding the CO design. The objective of this study was to examine the pros and cons of the CO trial compared to the PG trial, for assessing a binary predictive biomarker, in terms of number of subjects needed.

2 | METHODS

The materials and methods section describes (a) the delimitation of the study, (b) the linear model we used and (c) the design matrix in each design.

2.1 | Delimitations of the study

In order to compare the statistical power of each design, with the same point estimate of the parameter reflecting the interaction in both designs, we compared the variance of those estimates. Using a Wald test for testing the parameter of the interaction, the statistical power of each design is related to the variance of the estimation of the parameter of the interaction. We focused on a simple situation: a two arms PG trial and a two periods CO trial, with a 1:1 randomization, and a well-balanced frequency of the biomarker in both arms of the trial. The treatment effect and the biomarker effect were modelled with a linear regression. We analysed the variance-covariance matrix of the regression parameter for each design, which allowed us to compare the variance of the estimate of the interaction parameter under each of the two designs, according to their respective samples.

2.2 | Linear model

In order to compare the two designs, for each subject ' i ' receiving treatment ' j ', we used the same model, including a continuous variable ' y ' for the outcome assessing the effect

of the tested treatment ' t ' ignoring baseline measurement, a binary variable ' b ' reflecting the presence ($b = 1$) or the absence ($b = 0$) of the potential biomarker:

$$y_{ij} = \beta_0 + \beta_1 t_{ij} + \beta_2 b_i + \beta_3 t_{ij} \times b_i + (u_{0i} + \epsilon_{ij}) \quad (1)$$

$i \in \{1, \dots, N\}$, N : number of included subjects: N_{PG} in the PG trial, N_{CO} in the CO trial. In both designs, we restricted our work to the hypothesis of no drop-out.

$j \in \{0, 1\}$, 0 for the control treatment, 1 for the tested treatment. It should be noted that, in the CO design, each subject receives both treatment, that is has one measure of y for $j = 0$ and one other measure of y for $j = 1$. On the other hand, in the PG trial, each subject receives only one treatment, that is has only one measure of y , with $j = 0$ or $j = 1$.

y_{ij} : outcome measure of the subject ' i ' receiving treatment ' j ',

β_0 : control treatment effect,

β_1 : difference between tested and control treatment effects,

β_2 : prognostic effect of the potential biomarker,

β_3 : predictive effect of the potential biomarker,

$u_{0i} \sim N(0, \sigma_0^2)$, σ_0^2 standing for the inter-subject variability,

$\epsilon_{ij} \sim N(0, \sigma_\epsilon^2)$, σ_ϵ^2 standing for the intra-subject variability, $\sigma^2 = (\sigma_0^2 + \sigma_\epsilon^2)$.

Table 1 synthesizes the cell mean model, using q the frequency of $b = 0$, p the frequency of $b = 1$.

2.3 | Design matrix

2.3.1 | In the parallel-group trial design

In the PG trial, the design matrix $\mathbf{X}_{PG}(N_{PG}, 4)$ is:

$$\mathbf{X}_{PG} = \begin{bmatrix} 1 & 0 & b_1 & 0 \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ 1 & 0 & b_{N_{PG}/2} & 0 \\ 1 & 1 & b_{N_{PG}/2+1} & b_{N_{PG}/2+1} \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ 1 & 1 & b_{N_{PG}} & b_{N_{PG}} \end{bmatrix}$$

2.3.2 | In the crossover trial design

In the CO trial, the design matrix \mathbf{X}_{CO} includes a pair of row for each subject: one period with the tested treatment, one period with the control treatment. Considering that the treatment sequence order is randomized, we limited our analysis to the hypothesis of the absence of period effect. Considering an ideal CO trial with an adapted washout period, we also restricted our work to the hypothesis of the absence of carry-over effect. $\mathbf{X}_{CO}(2N_{CO}, 4)$ is defined as:

TABLE 1 Cell mean model of the linear regression assessing the treatment effect and the potential predictive effect of a candidate biomarker (PG: parallel group, CO: crossover)

Treatment	PG design and first period of the CO		Second period of the CO	
	Biomarker –	Biomarker +	Biomarker –	Biomarker +
$t = 0$	$\bar{y}_{i,0} = \beta_0$ ($qN/2$)	$\bar{y}_{i,1} = \beta_0 + \beta_2$ ($pN/2$)	$\bar{y}_{i,0} = \beta_0$ ($qN/2$)	$\bar{y}_{i,1} = \beta_0 + \beta_2$ ($pN/2$)
$t = 1$	$\bar{y}_{i,0} = \beta_0 + \beta_1$ ($qN/2$)	$\bar{y}_{i,1} = \beta_0 + \beta_1 + \beta_2 + \beta_3$ ($pN/2$)	$\bar{y}_{i,0} = \beta_0 + \beta_1$ ($qN/2$)	$\bar{y}_{i,1} = \beta_0 + \beta_1 + \beta_2 + \beta_3$ ($pN/2$)

N : number of included subject, p : prevalence of the potential theranostic biomarker in the included population (+) ($q = 1-p$), $t = 0$: control group, $t = 1$: tested treatment group.

$$\mathbf{X}_{\text{CO}} = \begin{bmatrix} 1 & 0 & b_1 & 0 \\ 1 & & b_1 & b_1 \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ 1 & 0 & b_i & 0 \\ 1 & 1 & b_i & b_i \\ \cdot & \cdot & \cdot & \cdot \\ \cdot & \cdot & \cdot & \cdot \\ 1 & 0 & b_{N_{\text{CO}}} & 0 \\ 1 & 0 & b_{N_{\text{CO}}} & b_{N_{\text{CO}}} \end{bmatrix}$$

The study was conducted in accordance with the Basic & Clinical Pharmacology & Toxicology policy for experimental and clinical studies.¹³

3 | RESULTS

The results section shows the variance-covariance matrix of the coefficients in each design, the comparison of the variance of the estimation of the interaction parameter, an application to a special case of interest, the comparison of the statistical power.

3.1 | Variance-covariance matrix of the coefficients

Details on the matrix calculation are available in Appendix A.

3.1.1 | In the parallel-group design

In the PG trial, the variance-covariance matrix of the fixed coefficients, $\mathbf{V}(\beta)$, estimated with the ordinary least squares method¹⁴ is $\mathbf{V}(\beta) = \sigma^2 (\mathbf{X}_{\text{PG}}^t \mathbf{X}_{\text{PG}})^{-1}$. For the model presented in Equation (1) and using the previous definition of the design matrix \mathbf{X}_{PG} :

$$\mathbf{V}(\beta) = 2\sigma^2 / [N_{\text{PG}}(1-p)] \begin{bmatrix} 1 & -1 & -1 & 1 \\ -1 & 2 & 1 & -2 \\ -1 & 1 & 1/p & -1/p \\ 1 & -2 & -1/p & 2/p \end{bmatrix}$$

3.1.2 | In the crossover design

In the CO trial, we first need to define the variance-covariance matrix of the outcome measure, Σ , for taking into account the intra-subject correlation. Assuming that the variance of all responses is identical ($\sigma^2 = (\sigma_0^2 + \sigma_\epsilon^2)$) and the within-subject covariances are equal, with a pair of column for each subject, Σ ($2N_{\text{CO}}, 2N_{\text{CO}}$) is⁶:

$$\Sigma = \sigma^2 \begin{bmatrix} 1 & \rho & & & & \\ \rho & 1 & & & & \\ & & \mathbf{0} & & & \\ & & & \cdot & & \\ \mathbf{0} & & & & & \\ & & & & & 1 & \rho \\ & & & & & \rho & 1 \end{bmatrix}$$

' ρ ' standing for the intra-subject correlation in the CO design, defined as the intra-class correlation coefficient $\rho = \sigma_0^2 / (\sigma_0^2 + \sigma_\epsilon^2)$. Then, the variance-covariance matrix of the fixed coefficients $\mathbf{V}(\beta)$ in the CO design, estimated with the generalized least squares method,¹³ is $\mathbf{V}(\beta) = (\mathbf{X}_{\text{CO}}^t \Sigma^{-1} \mathbf{X}_{\text{CO}})^{-1}$. Using the previous model defined in Equation (1) and the definition of the design matrix \mathbf{X}_{CO} :

$$\mathbf{V}(\beta) = \sigma^2 / [N_{\text{CO}}(1-p)] \begin{bmatrix} 1 & (\rho-1) & -1 & (1-\rho) \\ (\rho-1) & 2(1-\rho) & (1-\rho) & -2(1-\rho) \\ -1 & (1-\rho) & 1/p & (\rho-1)/p \\ 1-\rho & -2(1-\rho) & (\rho-1)/p & 2(1-\rho)/p \end{bmatrix}$$

3.2 | Comparison of the variance of the estimation of the interaction parameter

The variance of the fixed coefficients estimating the treatment effect and of the fixed coefficients estimating the interaction in both trial designs is summarized here:

$$\text{var}(\beta_{1\text{PG}}) = 4(\sigma_0^2 + \sigma_\epsilon^2) / [N_{\text{PG}}(1-p)]$$

$$\text{var}(\beta_{3\text{PG}}) = 4(\sigma_0^2 + \sigma_\epsilon^2) / [N_{\text{PG}}p(1-p)]$$

$$\begin{aligned}\text{var}(\beta_{1\text{CO}}) &= 2(\sigma_0^2 + \sigma_\varepsilon^2)(1-\rho) / [N_{\text{CO}}(1-p)] \\ &= 2\sigma_\varepsilon^2 / [N_{\text{CO}}(1-p)]\end{aligned}$$

$$\begin{aligned}\text{var}(\beta_{3\text{CO}}) &= 2(\sigma_0^2 + \sigma_\varepsilon^2)(1-\rho) / [N_{\text{CO}}p(1-p)] \\ &= 2\sigma_\varepsilon^2 / [N_{\text{CO}}p(1-p)]\end{aligned}$$

In both study designs, the variance of the parameter estimating an interaction between the treatment effect and a potential predictive biomarker is the product of the variance of the parameter estimating the treatment effect, multiplied by the inverse of the frequency of the candidate biomarker. The variance of the estimation of the interaction in the two designs can be compared by calculating their ratio:

$$\begin{aligned}\text{var}(\beta_{3\text{CO}}) / \text{var}(\beta_{3\text{PG}}) &= \\ (2\sigma_\varepsilon^2 / [N_{\text{CO}}p(1-p)]) / (4(\sigma_0^2 + \sigma_\varepsilon^2) / [N_{\text{PG}}p(1-p)])\end{aligned}$$

leading to:

$$\text{var}(\beta_{3\text{CO}}) = \text{var}(\beta_{3\text{PG}}) \times (1-\rho) \times N_{\text{PG}} / (2N_{\text{CO}})$$

The ratio of the variance of the interaction parameter in the CO to the variance estimated in the PG design depends on the complement of the intra-class correlation coefficient, multiplied by the ratio of their respective sample sizes.

The ratio of the Wald statistic is:

$$\begin{aligned}[\beta_{3\text{CO}}^2 / \text{var}(\beta_{3\text{CO}})] / [\beta_{3\text{PG}}^2 / \text{var}(\beta_{3\text{PG}})] &= \\ [\beta_{3\text{CO}}^2 / 2\sigma_\varepsilon^2 / [N_{\text{CO}}p(1-p)]] / [\beta_{3\text{PG}}^2 / 4(\sigma_0^2 + \sigma_\varepsilon^2) / [N_{\text{PG}}p(1-p)]] &= \\ [\beta_{3\text{CO}}^2 / \beta_{3\text{PG}}^2] \times [2N_{\text{CO}} / N_{\text{PG}}] \times [1 / (1-\rho)]\end{aligned}$$

The Wald statistic in the CO design can be expressed according to the variance of the interaction parameter of the PG design:

$$\begin{aligned}\beta_{3\text{CO}}^2 / \text{var}(\beta_{3\text{CO}}) &= \beta_{3\text{CO}}^2 / [\text{var}(\beta_{3\text{PG}}) \times (1-\rho) \times N_{\text{PG}} / (2N_{\text{CO}})] \\ &= [\beta_{3\text{CO}}^2 / \text{var}(\beta_{3\text{PG}})] \times [2N_{\text{CO}} / N_{\text{PG}}] \times [1 / (1-\rho)]\end{aligned}$$

3.3 | Application to the special case where $N_{\text{PG}} = 2N_{\text{CO}}$

In the PG trial, $N_{\text{PG}}/2$ subjects are exposed to the tested treatment; in the CO trial, N_{CO} are exposed to the tested treatment. We now declined the comparison in the special case where $N_{\text{PG}} = 2N_{\text{CO}}$, in order to consider the same number of subjects exposed to the tested treatment in a trial. This also allows equating the number of measurements taken in the two designs. In this case, the variances of β_3 estimations in both designs are equal if $(1-\rho) = 1$.

3.4 | Comparison of the statistical power

Considering the credible alternative hypothesis β_3^* , specified for the power (P) calculation to detect the interaction in the PG (P_{PG}) and in the CO (P_{CO}) trials, P_{PG} and P_{CO} are defined by:

$$\begin{aligned}P_{\text{PG}} &\approx 1 - \phi \left[\beta_3^* / \sqrt{[4\sigma^2 / [N_{\text{PG}}p(1-p)]]} - z_{\alpha/2} \right] \\ &\approx 1 - \phi \left[\beta_3^* \sqrt{[N_{\text{PG}}p(1-p)]} / 2\sigma - z_{\alpha/2} \right]\end{aligned}$$

$$\begin{aligned}P_{\text{CO}} &\approx 1 - \phi \left[\beta_3^* / \sqrt{[2\sigma^2(1-\rho) / [N_{\text{CO}}p(1-p)]]} - z_{\alpha/2} \right] \\ &\approx 1 - \phi \left[\beta_3^* / \sqrt{[4\sigma^2(1-\rho) / [N_{\text{PG}}p(1-p)]]} - z_{\alpha/2} \right] \\ &\approx 1 - \phi \left[\beta_3^* / \sqrt{[N_{\text{PG}}p(1-p)]} / [2\sigma\sqrt{(1-\rho)}] - z_{\alpha/2} \right]\end{aligned}$$

ϕ being the standard normal cumulative distribution function of an $N(0, 1)$ distribution.

3.5 | Comparison of the sample size

The type 1 error rate, α , being fixed, the numbers of patients included in each design in order to reach the same statistical power ' $1-\beta^*$ ' are:

$$\begin{aligned}N_{\text{PG}} &\approx 4\sigma^2(z_{1-\beta} + z_{1-\alpha})^2 / \beta_3^{*2} \\ N_{\text{CO}} &\approx 2\sigma^2(1-\rho)(z_{1-\beta} + z_{1-\alpha})^2 / \beta_3^{*2}\end{aligned}$$

As β_3^* estimation is independent of the study design:

$$N_{\text{CO}} / N_{\text{PG}} = [(1-\rho)/2]$$

To summarize, for both trial designs, the variance of the parameter estimating an interaction between the treatment effect and a potential predictive biomarker corresponds to the variance of the parameter estimating the treatment effect, multiplied by the inverse of the frequency of the candidate biomarker. The ratio of the variance of the interaction parameter in the crossover to the variance estimated in the parallel-group design depends on the complement of the intra-class correlation coefficient. For the same power when testing an interaction, the gain in terms of reduced needed sample size with the CO compared to the PG design depends on the complement of the intra-class correlation coefficient.

4 | DISCUSSION

The discussion section summarizes the interesting findings and the limits of the study, and highlights some issues for further research.

The search for theranostic biomarkers will help the development of the personalized medicine. However, such interactions on the treatment effect are not easy to demonstrate; large sample sizes are often required. In the same way, the CO design could help assessing a treatment with less exposed subjects in the experimental arm, and it could also help identify

such theranostic biomarkers. We compared the variances of the interaction estimates according to the trial design; this led to quantifying the potential gain in statistical power (eg in terms of number of subjects needed) with the CO trial, compared to the PG trial. We showed how the variance of the parameter estimating an interaction depends on the variance of the parameter estimating the treatment effect, and the frequency of the candidate biomarker, in both designs. We showed that the frequency of the candidate biomarker impacts the variance of the interaction estimate similarly in both design. Thus, the gain in its estimation with the CO design depends on the intra-subject correlation, as previously known for the treatment effect estimation.⁴ The estimation of the variance of the interaction effect in the CO design decreases compared to the PG design, as the intra-class correlation increases. In the special case where $N_{PG} = 2N_{CO}$, which corresponds to the same number of subjects exposed to the tested treatment, and/or the same number of measurements of the outcome, both trials are equivalent if the intra-class correlation is null, but the CO design is more effective as the intra-class correlation increases. Comparing the CO and the PG designs for estimating the treatment effect, Brown showed that the ratio of variance of the treatment effect estimation was the complement of the intra-class correlation.⁴ We completed those results by showing a similar impact of the intra-class correlation on the estimation of the interaction.

Kenward and Jones reported an intra-subject correlation typically between 0.5 and 0.9 in 15 crossover data sets.¹⁵ Thus, around 5%-25% of the sample size needed in a PG trial could be enough for identifying the same interaction in a CO design. Our results are consistent with previous analyses on the treatment effect estimation that did not compare both designs regarding the predictive biomarker interaction.

There are, however, several limits to our study. Firstly, we restricted our analysis to a simple model, without considering baseline measurement of the outcome variable, which would increase the precision of the estimation in both designs.¹⁶ Moreover, we did not take into account any carry-over effect or any drop-out rates. Carry-over is a major concern of CO study, but does not exist in PG trial. Its impact on the treatment effect estimation has already been well studied.⁴ Its impact on the comparison of CO versus PG has already been described, for the treatment effect estimation.⁷ Naturally, the presence of a carry-over effect would negatively impact the power of a CO study. However, our aim was to compare the theoretical properties of both designs themselves. Then, we needed to avoid multiple sources of difference between designs. For example, we defined the same linear model at the beginning of our analysis. Taking into account a carry-over effect would have introduced a supplementary difference in the comparison. Thus, a difference in statistical power could have resulted from the properties of the designs and/or from the carry-over effect. In a similar way, taking into account a drop-out rate would have a more

negative impact on the statistical power of the CO, as each subject is measured twice in this design. This has already been described for the estimation of the treatment effect.⁷ Again, we wanted to focus on the properties of both designs themselves and then needed to avoid other source of difference. Of course, those methodological choices limit the extrapolability of our results in real life. Then, further research is needed on this topic. We also restricted our work to the hypothesis of a well-balanced frequency of the biomarker in both arms of the trial. Finally, our study can help when planning clinical trials, both for the estimation of the sample size for interaction testing and for the choice of the design between CO and PG. However, it should be kept in mind that the estimation of the statistical power would be a simple approximation, and could be less than expected, depending on the observed values of the drop-out rate and the intra-subject correlation in real clinical trials.

5 | CONCLUSION

Clinical trials remain essential, as they allow to assess the treatment effect and to identify potential predictive biomarkers. In the personalized medicine perspective, for the construction of individual prediction model, it is needed to know the properties of those estimators and the power of a clinical trial for identifying them. We showed the relationship between the intra-subject correlations and the potential gain of the CO design for identifying such interaction. An a priori estimation of the frequency of the candidate biomarker and of the intra-subject correlation is advisable for choosing the optimal experimental design.

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CONFLICT OF INTERESTS

CBI, CBa and PR report no conflicts of interest. GG has received support for travel to scientific meetings from Novo Nordisk and Lilly and is a member of the association " Association des toxicologues." In the last five years, FG received, for his institution, fees from Portola Pharmaceuticals for central reading of ultrasound records, from Neurochlore for DSMB coordination, from EryTech Pharma for modelling projects, and from RCTs and Steve Consultant for exploring French social security database.

AUTHOR CONTRIBUTION

GG, FG and PR made substantial contributions to the conception and the design of the protocol. GG carried out the statistical

analysis, CBI checked the analysis and PR supervised the analysis. GG wrote the article. FG, PR, CBI and CBa were involved in revising the manuscript critically for important intellectual content. All authors read and approved the final manuscript.

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APPENDIX A

In the parallel-group trial design:

$$\mathbf{X}_{PG}'\mathbf{X}_{PG} = \begin{bmatrix} N_{PG} & N_{PG}/2 & pN_{PG} & pN_{PG}/2 \\ N_{PG}/2 & N_{PG}/2 & pN_{PG}/2 & pN_{PG}/2 \\ pN_{PG} & pN_{PG}/2 & pN_{PG} & pN_{PG}/2 \\ pN_{PG}/2 & pN_{PG}/2 & pN_{PG}/2 & pN_{PG}/2 \end{bmatrix}$$

$$(\mathbf{X}_{PG}'\mathbf{X}_{PG})^{-1} = 2 / [N_{PG}(1-p)] \begin{bmatrix} 1 & -1 & -1 & 1 \\ -1 & 2 & 1 & -2 \\ -1 & 1 & 1/p & -1/p \\ 1 & -2 & -1/p & 2/p \end{bmatrix}$$

In the crossover trial design, Σ^{-1} is defined as (see Piantadosi, *Clinical Trials: A Methodologic Perspective*, Wiley, 2005):

$$\Sigma^{-1} = 1 / [\sigma^2(1-\rho^2)] \begin{bmatrix} 1 & -\rho & & & & \\ -\rho & 1 & & & & \\ & & \ddots & & & \\ & & & 1 & -\rho & \\ 0 & & & -\rho & 1 & \end{bmatrix}$$

$$(\mathbf{X}_{CO}'\Sigma^{-1}) = 1 / [\sigma^2(1-\rho^2)] \begin{bmatrix} 1-\rho & 1-\rho & \dots & 1-\rho & 1-\rho \\ -\rho & 1 & \dots & -\rho & 1 \\ 0 & 0 & \dots & 1-\rho & 1-\rho \\ 0 & 0 & \dots & -\rho & 1 \end{bmatrix}$$

$$(\mathbf{X}_{CO}'\Sigma^{-1}\mathbf{X}_{CO}) = N_{CO} / [\sigma^2(1-\rho^2)] \begin{bmatrix} (1-\rho)*2 & (1-\rho) & (1-\rho)p/2 & (1-\rho)p \\ (1-\rho) & 1 & (1-\rho)p & p \\ (1-\rho)p/2 & (1-\rho)p & (1-\rho)p/2 & (1-\rho)p \\ (1-\rho)p & p & (1-\rho)p & p \end{bmatrix}$$

$$(\mathbf{X}_{CO}'\Sigma^{-1}\mathbf{X}_{CO})^{-1} = \sigma^2 / [N_{CO}(1-\rho)] \begin{bmatrix} 1 & (\rho-1) & -1 & (1-\rho) \\ (\rho-1) & 2(1-\rho) & (1-\rho) & -2(1-\rho) \\ -1 & (1-\rho) & 1/p & (\rho-1)/p \\ 1-\rho & -2(1-\rho) & (\rho-1)/p & 2(1-\rho)/p \end{bmatrix}$$

Third part – Second section. Meta-epidemiology in pharmacogenetic

Quality assessment of published pharmacogenetic association in randomized clinical trials

This poster communication has been an e-Poster at the Drug Information Association (DIA) Euro-meeting, edition 2019.

QUALITY ASSESSMENT OF PUBLISHED PHARMACOGENETIC ASSOCIATION IN RANDOMIZED CLINICAL TRIALS,

A SYSTEMATIC REVIEW

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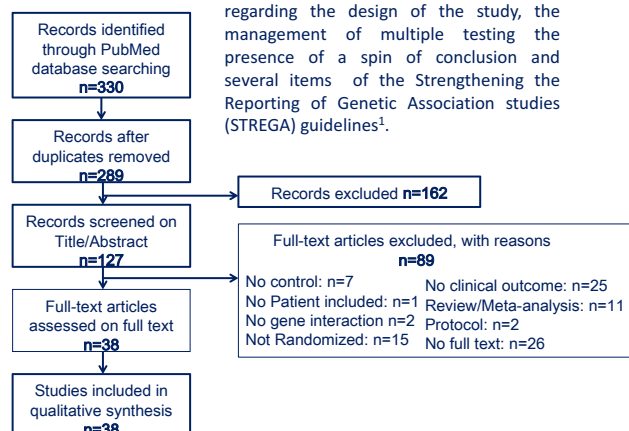


INTRODUCTION

These last few years, research in personalized medicine increased as the cost of genotyping decreased. Hence, the following of reporting guidelines may **enhance the quality and the harmonization of published studies**. Our aim was to **describe the quality of the reporting in published pharmacogenetics associations in randomized clinical trials**. This permits assessing the need for complementary specific reporting guidelines.

METHODS

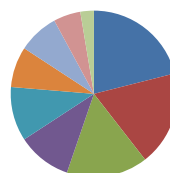
From **October 2015 to October 2018**, we systematically searched for **Randomized, Controlled, Pharmacogenetics Clinical Studies, reporting a clinical outcome in Human**, in PubMed. References were screened based on Title/Abstract, then on the full text. The following flowchart shows the results of the study selection. We extracted the data for several items of interest and provided a critical appraisal regarding the design of the study, the management of multiple testing the presence of a spin of conclusion and several items of the Strengthening the Reporting of Genetic Association studies (STREGA) guidelines¹.



1. PLoS Med. 2009;6(2):e22. PMID: 19192942

RESULTS

38 Randomized Control Trials (RCT) were included. The sample sizes ranged from 22 to 3956. Medical area of the studies were:



- Addiction
- Oncology
- Cardiovascular system
- Neurology
- Psychiatry
- Immune modulation/ internal medicine
- Nephrology
- Rheumatology
- Infectiology

The following table summarizes the reporting of the studies and our critical appraisal.

	Critical Appraisal of the reviewers	Clearly reported	Unclear or not reported
DESIGN			
Type of biomarker study design	Strategy design	26,3%	100,0%
	Interaction design	0,0%	0,0%
	Controlled sub-group analysis	50,0%	0,0%
	Nested cohort in Clinical Trial	23,7%	11,1%
Post Hoc or a priori hypothesis	A priori	60,5%	39,1%
	Post hoc	23,7%	66,7%
	Unclear	15,8%	0,0%
Blinding	Double Blind	42,1%	100,0%
	Single Blind	15,8%	100,0%
	Open Label	15,8%	100,0%
	Unclear	26,3%	0,0%
STATISTICS			
Risk α managment	Only 23,7% controlled the risk α	55,3%	44,7%
GENETICS (STREGA Recommendations)			
Statement of the number of report	First report	73,7%	39,3%
	Replication study	2,6%	100,0%
	Unclear	23,7%	0,0%
Hardy Weinberg equilibrium	On the 22 studies considering the HWE, only 5 studies reported the method used	57,9%	42,1%
Genotyping method	7,9% assessed one genetic variant 89,5% assessed several genetic variant 2,6% assessed the whole genom analysis	84,2%	15,8%
SPIN OF CONCLUSION			
		76,3%	

CONCLUSION

We observed a **low control of the alpha risk and frequent spin of conclusion**. It can bias the interpretation of the litterature. We also showed a lack of reporting of crucial items in pharmacogenetics publications, despite the existing guidelines¹. This limits the comparability of studies and showed the need for specific reporting guidelines.

DISCUSSION

Mean treatment benefit—risk balance estimation

Need for comparisons of hypoglycemic drugs

The first section of the first part of this thesis highlighted the need for direct comparisons of hypoglycemic drugs. Indeed, if the network meta-analysis approach helped to compare the DPP4 inhibitors to GLP1 receptor agonist and SGLT2 inhibitors, more statistical power is likely needed for assessing metformin to GLP1 agonist receptor and SGLT2 inhibitors. Moreover, GLP1 receptor agonists and SGLT2 inhibitors have been mainly tested in secondary CV prevention, but metformin in primary CV prevention. This become of a special interest since the last European guidelines, which challenge the first line therapy position of the metformin in particular population [111]. Likewise, only one CVOT compared an ‘old’ hypoglycemic drug, a sulfonylurea, to a ‘new’ one, a DPP4 inhibitor [150]. Unfortunately, its result was not available at the time of our study. It should also be noted that no results of the assessment of the alpha glucosidase inhibitor and the glinides on major cardiovascular events have been found to be available. Finally, since the first submission of the manuscript of our meta-analysis to PLOS ONE, four CVOT studies [150-153] have been published. Implementing living cumulative meta-analysis would be helpful for providing up to date synthesis of the evidence [154].

Challenges in the mean benefit—risk balance estimation

High level of evidence is needed when assessing efficacy. The level of proof regarding safety should be adapted as well. The pioglitazone was withdrawal from the French market, after a safety signal regarding a potential to increase the risk of bladder cancer [155]. A few years after, the safety signal seems not to be truly confirmed, and complementary arguments for its benefits have been observed [156]. Thus, some authors are calling for a come-back of pioglitazone, taking into account its several benefits and risks [157].

In the same way, a safety alert has been notified regarding potential pancreatic adverse events of GLP1 receptor agonists [158]. However, a recent meta-analysis of the powerful randomized CVOT did not observed such harm; and did confirm its CV benefits [90]. Moreover, patients with T2D have a higher spontaneous risk of pancreatitis, compared to the general population [159]. Thus, a patient with T2D may have a pancreatitis when being treated by GLP1 receptor agonist, without causal relationships between the two. Following the right “primum non nocere” principle, the US Food and Drug Administration and the European Medicines Agency stated that, “Although the totality of the data that have been reviewed provides reassurance, pancreatitis will continue to be considered a risk associated with these drugs [...]” [160]. GLP1 receptor agonist should be stopped in case of pancreatitis [161]. Thus, some patients may lose the highly proved CV benefits of those drugs for a very hypothetical risk. In contrast, the DPP4 inhibitors did not showed CV benefits, but have been associated with a significant increased risk of acute pancreatitis in CVOT [105]. Nevertheless, the two summary of product characteristics are very similar, regarding the risk of pancreatitis [161, 162]. Indeed, the level of proof required for assessing a drug depends on the level of proof of its benefit—risk balance, globally, and not separately.

In 2019, the French National Authority for Health estimated that the benefit—risk of the empagliflozin was not in favor of its use [163], notably due to a potential risk of lower limb imputation, Fournier gangrene, and ketoacidosis. As illustrated in the second section of the first part of this thesis, the CV benefits of SGLT2 inhibitors probably exceed their risks. Several methods are available for benefit risk assessment, especially at the trial level [18, 164]. RCTs allow a non-biased estimation of the benefit but remain limited for safety assessment. Integrating data from different type of studies for estimating the benefit—risk balance at a meta-analytic level remains a challenge [165].

Perspectives of evidence based personalized medicine in type 2 diabetes

Surrogate and ‘treat to target’ strategy

The second part of this thesis highlighted some difficulties in assessing surrogate endpoint using meta-regression approach. The limitation of the analysis to the aggregate data of each trial exposed the result to the ecological bias. Individual Patient Data Meta-analysis (IPD-MA) can help to overcome this issue [166]. Indeed, it allow to unravel subject-heterogeneity and study-heterogeneity for estimating the TE [167]. Different approaches are proposed for conducting IPD-MA [167, 168]. If necessary, both IPD and aggregate data could be integrated in the analysis [169]. Finally, network MA and IPD-MA methods can be combined, for searching treatment-covariate interaction in a multiple treatment comparison [170].

In T2D field, a collaborative group has already published an IPD-MA focused on impact of glucose control on microvascular complications [92], yet IPD-MA regarding macrovascular complications remains needed. Moreover, different surrogate candidates are potentially actionable. The glucose control was traditionally assessed using the HbA1c level, but the new technology as the Continuous Glucose Monitoring System allow using other measures of glucose variability in the future [171]. Apart from the blood pressure, and the LDL level, albuminuria may also be a surrogate of interest, as recently suggested for end stage renal disease [172]. Interestingly, some drugs impact several surrogates simultaneously: for example, the SGLT2 inhibitors and the GLP1 receptor agonists also decrease arterial blood pressure [173, 174]. However, although we observed an association between the decrease of blood pressure through antihypertensive drug and the risk of stroke, the SGLT2 inhibitors do not seems to decrease the risk of stroke in our meta-analysis and other [175].

The level of proof of the target-based strategies remains restricted. Hard target such as 6.0% of HbA1c [111] in primary cardiovascular prevention in healthy people are extrapolated goals and may be associated with more harm than benefit [110]. They should be taken very cautiously, the “*primum non nocere*” principle applying first. Moreover, the numerical value of the target itself should not become an absolute treatment’s goal, and lifestyle cardiovascular risk factor should be addressed in priority. However, the higher prognostic effect of an elevated HbA1c above 8%

legitimizes a therapeutic intervention, even based on limited level of evidence, except for patients exhibiting particular fragility.

Theranostic biomarker: perspectives in the genomic medicine

The level of proof regarding mean benefit effects of pharmacological treatments have increased. However, so-called “predictive” biomarkers are still often assessed with a low level of proof. One increasing challenge is the availability of efficient medicine, but whose use would be misled by false indications and/or counter-indications. In the last decade, the emergence of new gene sequencing technology had allowed an intensive search for genetic biomarker, nurturing the hope for a genomic/predictive/personalized medicine [176]. However, the use of omics data lead to the risk of false positive results and an optimism bias [177]. The burden of publication in this area contribute to the reproducibility crisis [178-180]. Publication bias has been showed both for genetic association studies [181] and observational studies assessing adverse drug event [182]. Publication bias in pharmacogenetic studies is therefore highly suspected. Also, the use of multiple screening can lead to overdiagnosis [183].

Indeed, EBM’s principles are not only still valid in the genomic area but highly needed [184, 185]. Research is ongoing looking at validation’s tool of such effect modifier [186]. 36 criteria for claiming effect modification has been reported so far, of which test for interaction, *a priori* hypothesis and providing a causal explanation were frequently reported [186]. Finally, genomic can help both for better estimating the risk of a disease or an outcome of a subject [187] and identifying subjects exhibiting specific responses to drugs [124, 188]. Using polygenic scores [189] would help individualizing the treatment benefit—risk balance estimation. The figure 8 extended the effect model to schematize the impact of different prognostic and theranostic factors on the TE estimation.

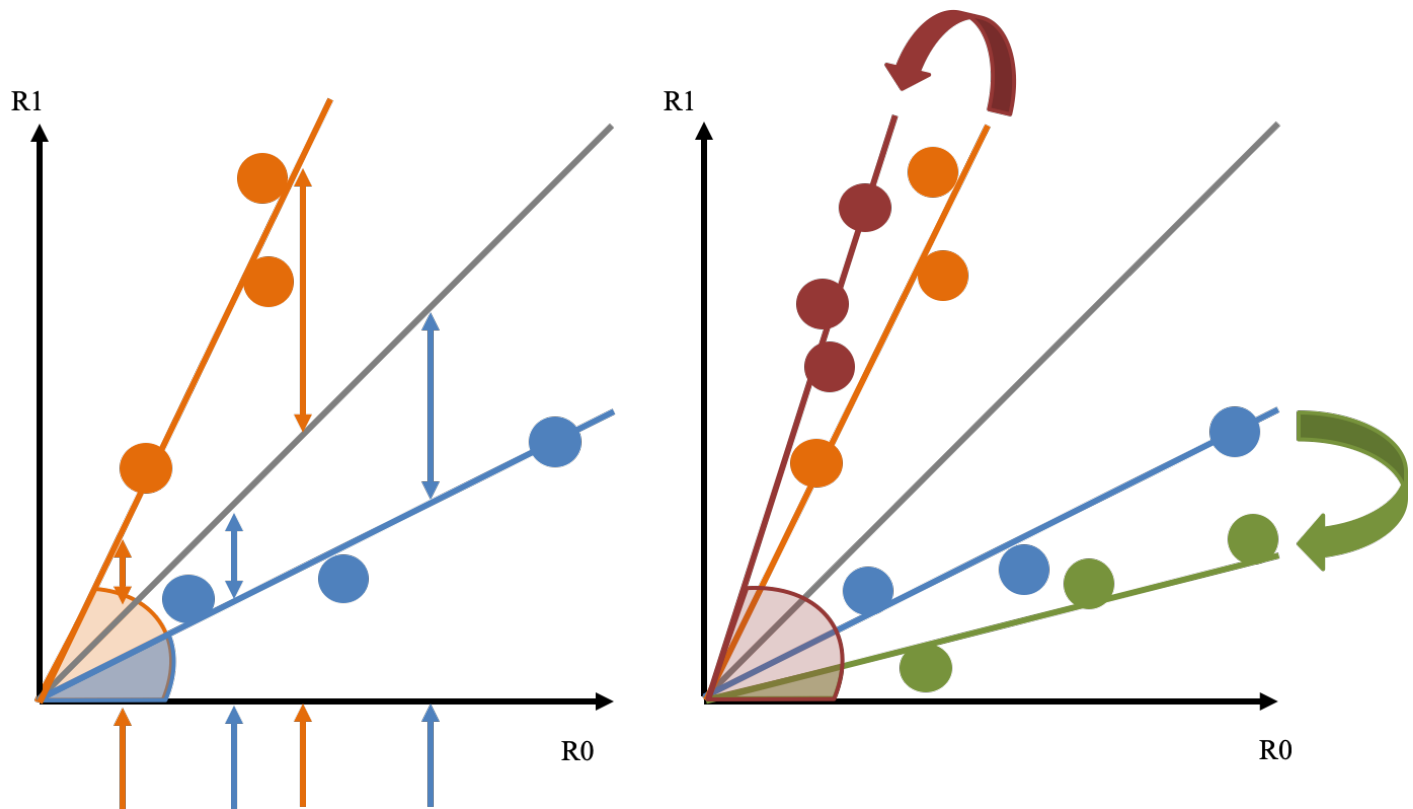


Figure 8. Effect model for a personalized benefit—risk balance estimation.

X-axis: spontaneous risk of event ($R0$); Y-axis: risk of event under treatment ($R1$). Each circle stands for the estimate of one trial, regarding one endpoint. Blue and orange are estimation of efficacy and safety endpoints, respectively. The grey diagonal represents the absence of treatment effect ($R0=R1$). The blue and the orange line represent the meta-analyses of studies for each event, their slope being the treatment effect on the relative scale. On the left: the blue and orange one-sided arrows represent different prognostic factor for efficacy and safety endpoints, respectively. The blue and orange double-sided arrows represent the absolute effect (difference in risk between treated and untreated group) of the treatment for efficacy and safety event, respectively, for different level of prognostic factor. The net benefit could be calculated by their difference. On the right: the green and red circles and lines stand for the estimation in presence of an effect modifier; the large green and red arrows simply explicit the change in relative risk of events under treatment with the presence of the theranostic biomarker.

CONCLUSION

Evidence based personalized medicine for patients with type 2 diabetes remains challenging in everyday clinical practice. There is still need for improvement, even if, fortunately, the progress in health care had allow a decrease in diabetes complication over the year [190]. One role of the physician is to inform the patient of the risk of the natural evolution of the disease, of the benefit—risk balance of the treatment, and of the uncertainties regarding both of them, in order to allow the person to make his/her own choice, taking into account his/her own belief.

Using a network meta-analysis approach, we showed that only the SGLT2 inhibitors and the GLP1 receptor agonist displayed a high level of proof for reducing cardiovascular events, challenging the place of metformin. However, the use of SGLT2 inhibitors and GLP1 receptor agonist is constrained because of safety signal of lower level of evidence. Using a meta-regression approach, we explored the impact of a surrogate on cardiovascular outcomes, highlighting the limits of the “target to treat” strategy for personalizing the treatment intensity. Finally, we provided a statistical comparison of two experimental designs for assessing theranostic biomarkers, which could help conducting clinical research in the future.

Assessing a mean and a stratified treatment effect should be conducted taking into account the global benefit—risk balance estimation. The personalized medicine may also extend to the integration of the individual gut microbiome in clinical care [191]. The recent development in machine learning may also help to further identify theranostic biomarker [192], as recently illustrated in the search for predictive factor of mortality under intensive glucose control in the ACCORD trial [193].

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APPENDIX

Appendix 1. Rational and design of the network meta-analysis ‘GLUCOSE DINET’

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REVIEW ARTICLE

Protocol of GLUCOSE CONTROL Safety and Efficacy in type 2 DIABETES, a NETWORK meta-analysis: GLUCOSE DINET protocol—Rational and design

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ABSTRACT

The aim of this study was to propose a ranking of the currently available antidiabetic drugs, regarding vascular clinical outcomes, in patients with type 2 diabetes, through a network meta-analysis approach. Randomized clinical trials, regardless of the blinding design, testing contemporary antidiabetic drugs, and considering clinically relevant outcomes in patients with type 2 diabetes mellitus will be included. The primary outcomes of this analysis will be overall mortality, cardiovascular mortality, and major cardiovascular events. Diabetic microangiopathy will be a secondary outcome. Adverse events, hypoglycemia, weight evolution, bariatric surgery, and discontinuation of the treatment will also be recorded. Each drug will be analyzed according to its therapeutic class: biguanide, alpha-glucosidase inhibitors, sulfonylureas, glitazones, glinides, insulin, DPP-4 inhibitors, GLP-1 analogs, and gliflozins. The treatment effect of each drug class will be compared using pairwise meta-analysis and a Bayesian random model network meta-analysis. Sensitivity analyses will be conducted according to the quality of the studies and the glycemic control. The report will follow the PRISMA checklist for network meta-analysis. Results of the search strategy and of the study selection will be presented in a PRISMA compliant flowchart. The treatment effects will be summarized with odds ratio (OR) estimates and their 95% credible intervals. A ranking of the drugs will be proposed. Our network meta-analysis should allow a clinically relevant ranking of the contemporary antidiabetic drugs.

INTRODUCTION

Type 2 diabetes (T2D) is a public health issue, with a dramatically increasing incidence in the world.

Cardiovascular diseases (CVD) are the main cause of mortality in patients with T2D. Many antidiabetic drugs are currently available. The benefit of some of these drugs on patients' outcomes has been evaluated

in meta-analyses with conflicting results. Several meta-analyses of intensive vs. standard blood glucose control have shown a decrease in nonfatal myocardial infarction and no conclusive effect on overall or cardiovascular mortality [1–3]. The effect of metformin on cardiovascular (CV) prevention, recommended as the first-line drug in all guidelines for T2D glucose-lowering therapy, has been challenged. The results of meta-analyses depend on whether they include the UK Prospective Diabetes Study (UKPDS 34) group of non-obese patients treated with sulfonylureas alone. Without this group, metformin is found to reduce CV events but does not if it is included in the meta-analyses. No convincing results are available regarding the impact of insulin or sulfonylureas on cardiovascular outcomes.

Since the last published international guidelines [4], new antidiabetic drugs have become available. These drugs help control glycemia, but their impact on cardiovascular complications is not clear. Two powerful trials—SAVOR [5] and TECOS [6]—calculated their sample size for superiority regarding cardiovascular events but without observing any major difference in HbA1c control between the intervention and the placebo groups. Another trial—EXAMINE [7]—calculated their sample size for noninferiority but with an observed small glycemic control difference. All three trials did not show any specific effect of DPP4 inhibitors compared with placebo on neither major cardiovascular events nor mortality. Gliflozin showed promising results on cardiovascular outcomes in one powerful clinical trial [8]. Two powerful clinical trials have recently shown a beneficial effect of GLP1 agonist on cardiovascular events (LEADER [9] and SUSTAIN 6 [10]).

New tools for indirect and mixed treatment comparisons, such as network meta-analyses, have become available. Traditional meta-analyses use direct ('head-to-head') comparisons between two treatments compared within the same clinical trials. When no direct comparisons are available, indirect comparisons allow the comparison of two treatments through a third common comparator. Although direct comparisons remain the gold standard in treatment evaluation, indirect comparisons can also add to the information provided by direct comparisons, by improving the treatment effect estimate (mixed treatment comparison). In most cases, results of indirect comparisons are consistent with results obtained by direct comparisons [11]. Network meta-analyses allow to compare several treatments, through direct and indirect comparisons. In the treatment network graph, nodes (points) stand for the

treatments and edges (lines between the points) for the available direct comparisons.

Many glucose-lowering treatments are currently available. Regarding cardiovascular prevention, the choice can be difficult for physicians due to a lack of direct comparisons. Network meta-analyses can help summarize all available evidence. A bibliographic search (on PubMed) for meta-analyses in type 2 diabetes resulted in more than 900 references, which decreased to more than 200 references when mortality or cardiovascular outcome was specified, and to around 30 for the specific use of a network meta-analysis approach. Several network meta-analyses of antidiabetic drugs have already been conducted. However, they focus on specific drug classes [12,13], on intermediate outcome such as glycated hemoglobin (HbA1c) or blood lipid level controls rather than mortality, cardiovascular diseases and diabetic complications, and/or on specific questions (second- or third-line therapy) [14–17], as illustrated in *Table I*.

One network meta-analysis published in 2011 tried to compare hypoglycemic drugs on mortality and cardiovascular events focusing only on second-line therapy. They did not find enough data to proceed to the analysis [15]. One recent network meta-analysis, published in 2016, was conducted on mortality and cardiovascular events, but did not include the last three powerful trials EMPAREG, LEADER, and SUSTAIN 6 [18]. We believe that the last available trials will add enough information to the overall comparison of these drugs on hard clinical judgment.

The purpose of this study was to propose a ranking of the currently available antidiabetic drugs, regarding vascular clinical outcomes, in patients with T2D, through a network meta-analysis approach.

METHODS

Eligibility criteria

Only studies fulfilling the inclusion criteria, described below following the PICOS structure, will be eligible for this meta-analysis.

Participants

Only subjects aged 18 and over with T2D will be included. The diagnosis of T2D should have been established using standard criteria or, if necessary, by the definition of T2D given by the author in the corresponding clinical trial. Exclusion criteria are dialysis, transplantation, pregnancy, impaired glucose tolerance,

Table 1 Characteristics of recent network meta-analysis on hypoglycemic drugs in type 2 diabetes (not exhaustive).

PMID	year	1st author	Outcomes	N of included RCT	Comments
27434443	2016	Palmer	Cardiovascular mortality, all-cause mortality, serious adverse events, myocardial infarction, stroke [...]	301	Monotherapy, or added to metformin or added to metformin and sulfonylurea. Do not include EMPAREG, LEADER, SUSTAIN 6
26104021	2015	Mearns	HbA1c, blood pressure, genital or urinary infections	20	Third-line therapy (added to metformin and sulfonylurea)
25919293	2015	Mearns	HbA1c, body weight, blood pressure, hypoglycemia, urinary, and genital tract infection	62	Second-line therapy (added to metformin)
25762228	2015	Jia	HbA1c, fasting blood glucose	in process	Protocol (registered in Prospero)
25109773	2014	Zintzaras	HbA1c, hypoglycemia	NA (full text not accessible)	indirect judgement criteria
24805140	2014	Dai	Change in LDL, HDL, triglyceride, and total cholesterol	18	Dual combinations of antidiabetic drugs
24237939	2014	Goring	HbA1c, weight, blood pressure, hypoglycemia	6	Second-line therapy (added to metformin)
22486990	2012	Liu	HbA1c, hypoglycemia, body weight	39	Second-line therapy (added to metformin)
21576535	2011	Gross	HbA1c, hypoglycemia, body weight	18	Third-line therapy (added to metformin and sulfonylurea)
22046219	2011	Micimosh	HbA1c, body weight, hypoglycemia, quality of life, long-term diabetes-related complications, serious adverse drug events, and mortality	49	Not enough data for mortality and cardiovascular disease, in second-line therapy

N, number; RCT, randomized clinical trial.

impaired fasting glucose, and metabolic syndrome without T2D. For studies including patients with T2D and other types of population, if data are available, only the T2D subgroup will be included.

Interventions

Eligible interventions will be any contemporary antidiabetic drugs, that is, biguanide, alpha-glucosidase inhibitors, sulfonylureas, thiazolidinediones (pioglitazone and rosiglitazone), glinides, insulin, DPP-4 inhibitors, GLP-1 analogs, and gliflozins. Drugs which are not on the market any longer (as, for example, phenformin and tolbutamide) will be excluded. For factorial designs, only data of the intervention of interest will be included. Glucose-lowering treatment intensification without specific drugs and acute interventions will not be included.

Comparisons

All comparisons between active treatments and vs. placebo, as monotherapy or add-on, will be included. Comparisons within the same therapeutic class will be excluded (see 'Planned method of analyses').

Outcomes

Only studies with clinically relevant outcomes (as primary or secondary outcomes) will be included. Clinically relevant outcomes considered here are as follows: overall mortality, cardiovascular mortality, major cardiovascular events, and diabetic microangiopathy (new or worsening). Major cardiovascular events considered here are as follows: myocardial infarction or acute coronary syndrome, stroke, and arteriopathy of the lower limbs. Diabetic microangiopathy considered here includes the following: retinopathy, nephropathy, and neuropathy. All these outcomes should be clinically relevant, that is, clinically symptomatic, or leading to a therapeutic intervention such as surgery, photocoagulation, or dialysis. HbA1c, blood glucose, and fructosamine level, isolated serum creatinine or albuminuria changes, weight, body mass index (BMI), and hip/waist ratio will not be considered as clinically relevant outcomes. Efficacy and/or safety studies will be included.

Study design

Only parallel-group randomized controlled trials (RCTs) will be included, regardless of the blinding design.

Outcomes of the meta-analysis

The primary outcomes of this analysis will be overall mortality, cardiovascular mortality, and major

cardiovascular events. Diabetic microangiopathy will be a secondary outcome. Their definitions are given in the 'Outcome' section. Adverse events, hypoglycemia, weight evolution, bariatric surgery, and discontinuation of the treatment will also be recorded.

Information sources and search strategy

English-language RCTs will be searched in PubMed and Central databases, without time restriction. EMBASE will not be used as Halladay *et al.* showed that the expected gain is only modest [19]. Complementary sources will be used, especially to identify unpublished trials: reference lists of published meta-analyses, ClinicalTrials.gov, EU Clinical Trials Register, the Food and Drug Administration (FDA) website, and experts' knowledge.

The search strategy will be defined by (i) patient's condition (i.e., T2D), (ii) studied drugs (i.e., antidiabetics), (iii) measured outcomes, and (iv) study design. For the latter, the specific search strategy of RCTs defined in the Cochrane Handbook will be used [20]. We will exclude literature reviews. Each parameter will be defined by several MeSH terms and/or free text in titles and abstracts. The search strategy will be available in the appendix.

Study selection, data collection process, and risk of bias assessment in individual studies

The study selection, data extraction, and risk of bias assessment will be carried out by at least two independent reviewers. In case of disagreements, consensus will be reached with a third person. Studies will be screened on the basis of their titles and abstracts. Eligible studies will then be reviewed on their full texts. For each excluded study, reason(s) for exclusion will be given.

Extracted data items will include the following: quality items, characteristics of the studies and their patients, and the outcomes of interest. Authors will be contacted in case of missing data. The quality of the studies will be assessed using the Cochrane Collaboration's tool for assessing risk of bias in RCTs [21]. A summary of the quality assessment will be available in the appendix.

Geometry of the network

The structure of the network will be illustrated through a network graph, indicating the number of available RCTs for each direct comparison.

Summary measures

OR with its 95% credible interval will be the principal summary measure for the primary and secondary

outcomes. Additional summary measures will include the ranking of the therapeutic classes.

Planned method of analysis

Each drug (including each drug dose) will be analyzed according to its therapeutic class: biguanide, alpha-glucosidase inhibitors, sulfonylureas, glitazones, glinides, insulin, DPP-4 inhibitors, GLP-1 analogs, and gliflozins. The treatment effect of each drug class will be compared using pairwise meta-analyses and a Bayesian random model network meta-analysis [22]. A random model will be used due to the expected heterogeneity between trials. The prior distribution will be chosen as noninformative. The posterior distribution will be estimated using a Markov chain Monte Carlo method [23].

Network assessment

Inconsistency of the network will be searched for, using local and global approaches [24]. Distribution of the treatment effect modifiers across the comparisons will be evaluated to assess the transitivity assumption [24].

Drug ranking

According to their probability of being at each rank of efficacy, the different drug classes will be ranked using the surface under the cumulative ranking curve (SUCRA) [25].

Additional analyses

Sensitivity analyses will be conducted according to the quality of the studies (especially open vs. blinded RCTs), according to the glycemic control (RCTs in which achieved HbA1c blood levels were different vs. RCTs without difference in HbA1c between the intervention group and the control group), and according to the level of cardiovascular risk at baseline. If treatment effect modifiers are identified, subgroup analyses will be conducted.

Risk of bias across studies

A funnel plot will be used to assess the risk of publication bias, with corresponding measures of the probability of lack of publication bias.

Software

Analyses will be conducted using R [26] and WinBUGS [27] software.

RESULTS

The report will follow the PRISMA checklist for network meta-analyses [28]. Results of the search strategy and the study selection will be presented in a PRISMA compliant flowchart [29]. Study characteristics will be summarized, as shown in *Table II*. Treatment effects will be summarized with OR estimates and their 95% credible intervals. A ranking of the therapeutic classes will be proposed.

DISCUSSION

Type 2 diabetes has an increasing public health impact in the world. Network meta-analyses are still exploratory analyses, but they allow the use of all available information, thus leading to more informed drug prescriptions. A very interesting question in this network meta-analysis will be the ranking of metformin, regarding the recent results for gliflozins and GLP1 agonists.

The main potential limit of this analysis will possibly be the lack of data, as inconsistency between direct and indirect comparisons seems to be higher with fewer trials [11]. Moreover, when a meta-analysis showed no effect, a lack of power, in terms of number of subject and/or duration of the studies, is still one of the possible explanations. The meta-analysis is then helpful as it shows the insufficiency of the available data used to prescribe drugs.

One other limit is the inclusion of open clinical trials leading to a risk of bias. Unfortunately, the frequency of open trials in diabetes mellitus in the last decades is high. However, a sensitivity analysis is planned to investigate the impact of those open trials in our analysis.

Other limits are the potential effect modifiers, like the possible difference in the cardiovascular baseline risk of the included subjects. For example, patients were at high cardiovascular risk in LEADER and EMPAREG but not in UKPDS. Moreover, there was no difference in glycemic control between the groups in some studies. Those possible effect modifiers will be investigated using sensitivity analyses instead of integrating those parameters in the model. The interpretation of complex models remains a difficult issue, and we do not expect to have enough data.

We focus on severe clinical outcomes, mainly cardiovascular. They are not the only complications of patients with T2D, but they are the main cause of

Table II Characteristics of included studies.

	Study i		
Year			
Blinded (DB, SB, O)			
Line therapy (1, 2, 3)			
Mean of follow-up, years			
Group	Intervention	Control	Total
Drug			
Patients, <i>n</i>			
Male, <i>n</i> (%)			
Mean age (SD), years			
Mean diabetes duration (SD), years			
Patients with previous cardiovascular events, <i>n</i> (%)			
Patients without previous cardiovascular events, <i>n</i> (%)			
Patients without previous cardiovascular events, with diabetic microangiopathy, <i>n</i> (%)			
Patients without previous cardiovascular events, without diabetic microangiopathy, <i>n</i> (%)			
Patients with high blood pressure (treated or not), <i>n</i> (%)			
Patients with dyslipidemia (treated or not), <i>n</i> (%)			
Patients with antiplatelet treatment, <i>n</i> (%)			
Current smoker at inclusion (%)			
Mean baseline HbA1c level (SD), %			
Mean change in HbA1c level (SD), %			
Mean baseline BMI level (SD), kg/m ²			
Mean change in weight (SD), kg			

DB, double blinded; SB, single blinded; O, open; SD, standard deviation.

death in this population. We also plan to look at microvascular complications, but those outcomes could be subject to reporting bias in cardiovascular trials.

We limit our study at the therapeutic class level for this first analysis, but it would be interesting to look at the heterogeneity in the treatment effect within therapeutic classes in further analyses, notably for glitazones and sulfonylureas.

CONCLUSION

Up to now, there is no clear picture to help us distinguish which of these therapeutic classes are most contributing to the prevention of complications in diabetes. These drugs are used to control glycemia and reduce diabetic complications in tens of millions of people

worldwide, and in over two million in France. Our network meta-analysis should allow a clinically relevant drug ranking of the contemporary antidiabetic therapeutic classes.

DECLARATIONS

Ethics approval and consent to participate: not applicable.

Consent for publication: not applicable.

Availability of data and material: not applicable.

COMPETING INTERESTS

AL, SR, GN, TL, AM, CC: No conflict of interests.

GG has received support for travel to scientific meetings from Novo Nordisk, Lilly.

MC has received consulting fees from Boehringer Ingelheim, SANOFI, and speaker honoraria from SANOFI.

PM⁽¹⁾ or his institution⁽²⁾ has received honoraria (talks and/or trials and/or consultancies) or support for travel to scientific meetings⁽³⁾ from Novo Nordisk¹, MSD¹, Amgen², AMT/Chiesi², Astra Zeneca/BMS², Lilly², MSD², Novo Nordisk², Novartis², Olympus², Pierre Fabre², Regeneron², Sanofi², Servier², Astra Zeneca³, Boehringer³, BMS³, Janssen³, MSD³, Lilly³, Sanofi³.

FG⁽¹⁾ or his institution⁽²⁾ has received further honoraria (Speaker fees, Consultancy, Advisory Board fees, Investigator, Committee Member) from Teva Pharmaceutical Industries², Portola Pharmaceuticals², Bristol-Myers Squibb².

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AUTHORS' CONTRIBUTIONS

FG proposed the idea of the review. GG, AL, MC, and FG made substantial contributions to the conception and the design of the protocol. GG wrote the article. CC, PM, AL, MC, and FG have been involved in revising the manuscript critically for important intellectual content. GG, SR, GN, TL, and AM started the search of studies. All authors read and approved the final manuscript.

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ABBREVIATIONS

BMI – body mass index

CV – cardiovascular

CVD – cardiovascular diseases

FDA – Food and Drug Administration

HbA1c – glycated hemoglobin

OR – odds ratio

PICOS – participants, interventions, control, outcome, study design

PRISMA – preferred reporting items for systematic reviews and meta-analyses

RCTs – randomized clinical trials

SUCRA – surface under the cumulative ranking curve

T2D – type 2 diabetes

UKPDS – UK Prospective Diabetes Study

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Appendix 2. Complementary supporting information of the network meta-analysis GLUCOSE DINET

S1 Checklist. PRISMA network meta-analysis checklist of GLUCOSE DINET.

Section/Topic	Item #	Checklist Item	Reported on Page #
TITLE			
Title	1	Identify the report as a systematic review <i>incorporating a network meta-analysis (or related form of meta-analysis)</i> .	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: Background: main objectives Methods: data sources; study eligibility criteria, participants, and interventions; study appraisal; and <i>synthesis methods, such as network meta-analysis</i> . Results: number of studies and participants identified; summary estimates with corresponding confidence/credible intervals; <i>treatment rankings may also be discussed. Authors may choose to summarize pairwise comparisons against a chosen treatment included in their analyses for brevity.</i> Discussion/Conclusions: limitations; conclusions and implications of findings. Other: primary source of funding; systematic review registration number with registry name.	3
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known, <i>including mention of why a network meta-analysis has been conducted</i> .	5
Objectives	4	Provide an explicit statement of questions being addressed, with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	5-6
METHODS			
Protocol and registration	5	Indicate whether a review protocol exists and if and where it can be accessed (e.g., Web address); and, if available, provide registration information, including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale. <i>Clearly describe eligible treatments included in the treatment network, and note whether any have been clustered or merged into the same node (with justification)</i> .	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	6-7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	S1 Table
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	6-7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	6-7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	7
Geometry of the network	S1	Describe methods used to explore the geometry of the treatment network under study and potential biases related to it. This should include how the evidence base has been graphically summarized for presentation, and what characteristics were compiled and used to describe the evidence base to readers.	S3 Appendix
Risk of bias within individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	7
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means). <i>Also describe the use of additional summary measures assessed, such as treatment rankings and surface under the cumulative ranking curve (SUCRA) values, as well as modified approaches used to present summary findings from meta-analyses.</i>	7-8
Planned methods of analysis	14	Describe the methods of handling data and combining results of studies for each network meta-analysis. This should include, but not be limited to: <ul style="list-style-type: none"> • <i>Handling of multi-arm trials;</i> • <i>Selection of variance structure;</i> • <i>Selection of prior distributions in Bayesian analyses; and</i> • <i>Assessment of model fit.</i> 	7--8
Assessment of Inconsistency	S2	Describe the statistical methods used to evaluate the agreement of direct and indirect evidence in the treatment network(s) studied. Describe efforts taken to address its presence when found.	7-8

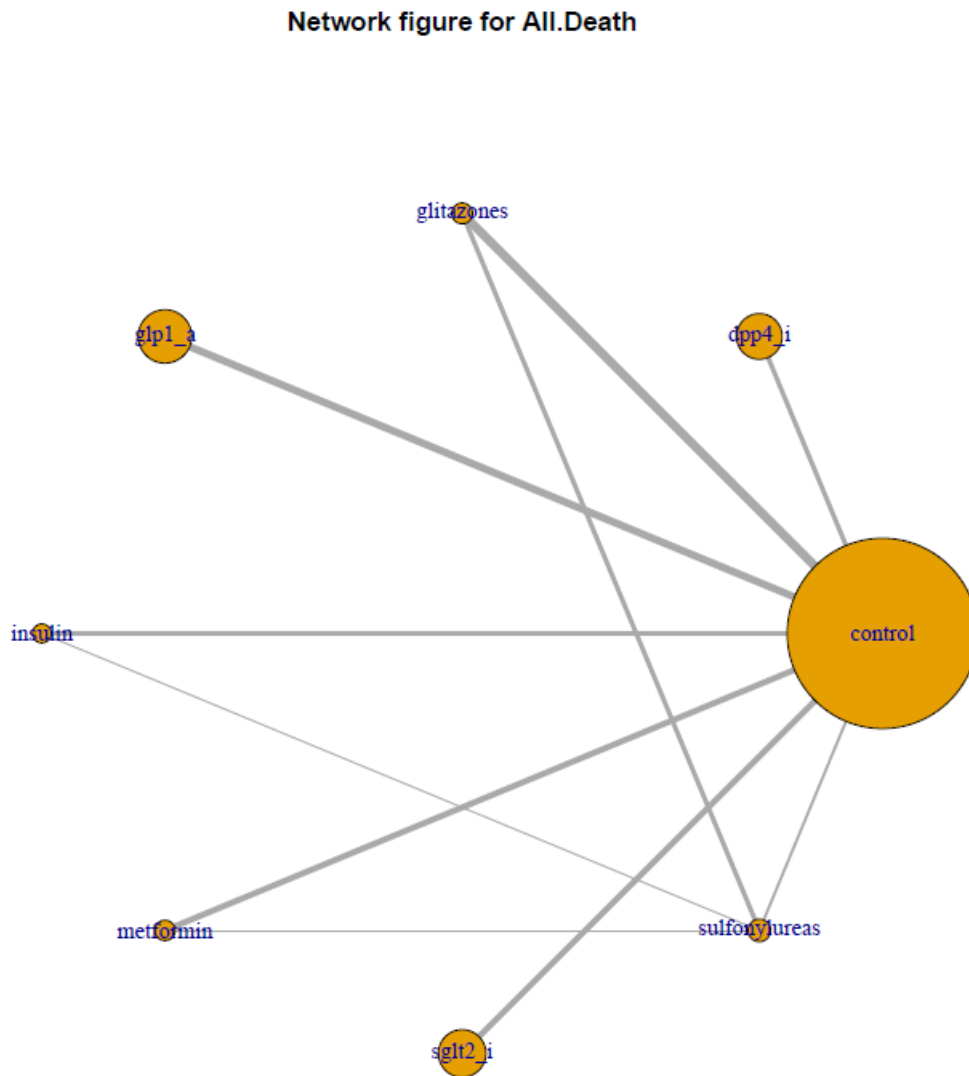
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	7
Additional analyses	16	Describe methods of additional analyses if done, indicating which were pre-specified. This may include, but not be limited to, the following: <ul style="list-style-type: none"> • Sensitivity or subgroup analyses; • Meta-regression analyses; • <i>Alternative formulations of the treatment network; and</i> • <i>Use of alternative prior distributions for Bayesian analyses (if applicable).</i> 	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Fig 1
Presentation of network structure	S3	Provide a network graph of the included studies to enable visualization of the geometry of the treatment network.	S3 Appendix
Summary of network geometry	S4	Provide a brief overview of characteristics of the treatment network. This may include commentary on the abundance of trials and randomized patients for the different interventions and pairwise comparisons in the network, gaps of evidence in the treatment network, and potential biases reflected by the network structure.	9
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment.	S2 Appendix
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: 1) simple summary data for each intervention group, and 2) effect estimates and confidence intervals. <i>Modified approaches may be needed to deal with information from larger networks.</i>	S5 Table
Synthesis of results	21	Present results of each meta-analysis done, including confidence/credible intervals. <i>In larger networks, authors may focus on comparisons versus a particular comparator (e.g. placebo or standard care), with full findings presented in an appendix. League tables and forest plots may be considered to summarize pairwise comparisons.</i> If additional summary measures were explored (such as treatment rankings), these should also be presented.	Table 2
Exploration for inconsistency	S5	Describe results from investigations of inconsistency. This may include such information as measures of model fit to compare consistency and inconsistency models, <i>P</i> values from statistical tests, or summary of inconsistency estimates from different parts of the treatment network.	10
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies for the evidence base being studied.	9-10
Results of additional analyses	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression analyses, <i>alternative network geometries studied, alternative choice of prior distributions for Bayesian analyses, and so forth</i>).	11-12
DISCUSSION			
Summary of evidence	24	Summarize the main findings, including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy-makers).	14-15
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review level (e.g., incomplete retrieval of identified research, reporting bias). <i>Comment on the validity of the assumptions, such as transitivity and consistency. Comment on any concerns regarding network geometry (e.g., avoidance of certain comparisons).</i>	16-17
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	17-18
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review. This should also include information regarding whether funding has been received from manufacturers of treatments in the network and/or whether some of the authors are content experts with professional conflicts of interest that could affect use of treatments in the network.	20

S3 Fig. Network figures for the primary outcomes and forest plots of the direct comparisons

A. Overall mortality

This network included 30 randomized trials. On 168 332 subjects, 12 203 presented the outcome.

S3A Fig_Network:

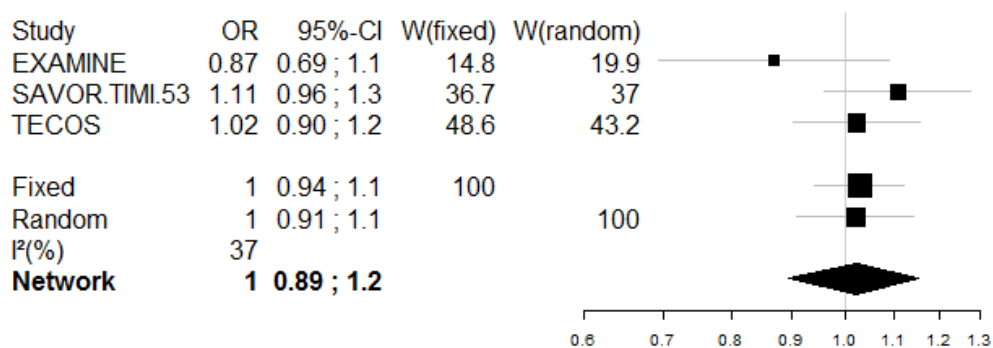


Edge width is based on the number of randomized trials, node size on the sample size.

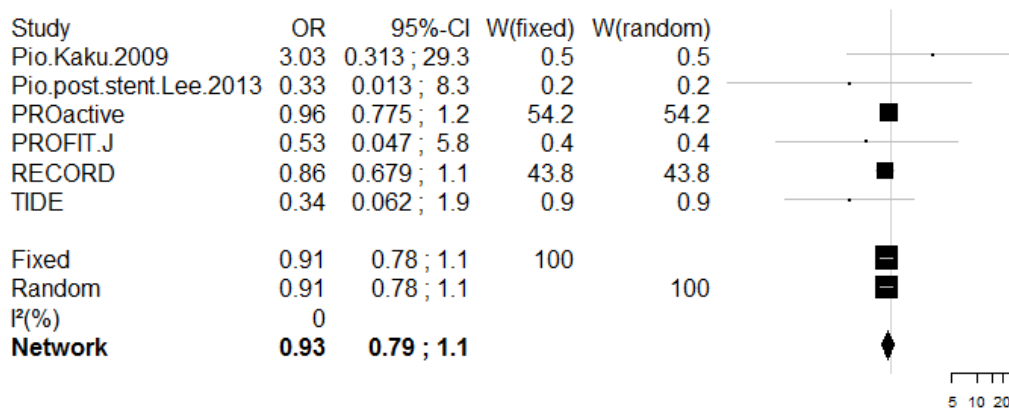
Forest plots of the overall mortality for each direct comparison:

The diamond in the forest plot stands for the network estimation of the TE (OR and its 95%CI) ('Network's line'); the squares stand for i) the TE estimate in the corresponding trial (on line with its name), and ii) the TE estimate using direct meta-analysis with both fixed and random model ('Fixed' and 'Random', respectively). 'W' stands for the weight of each trial in the corresponding direct meta-analysis.

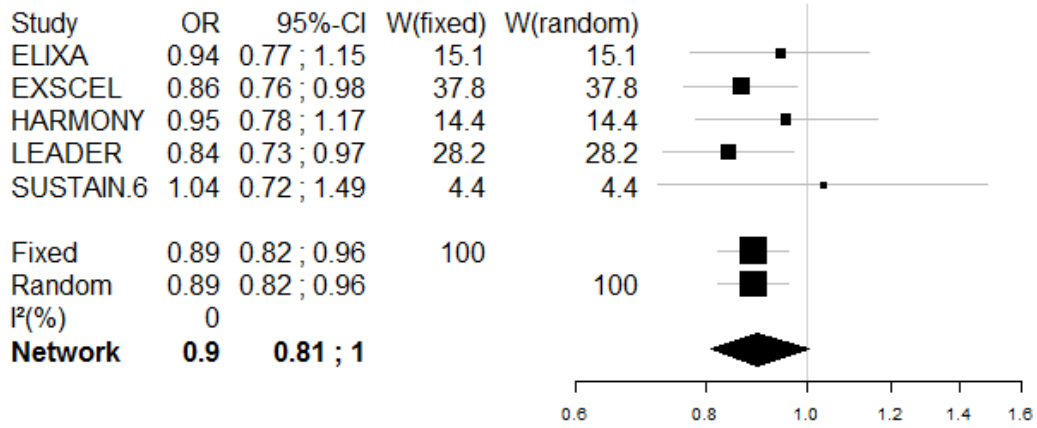
S3A Fig_DPP-4_I VERSUS CONTRO



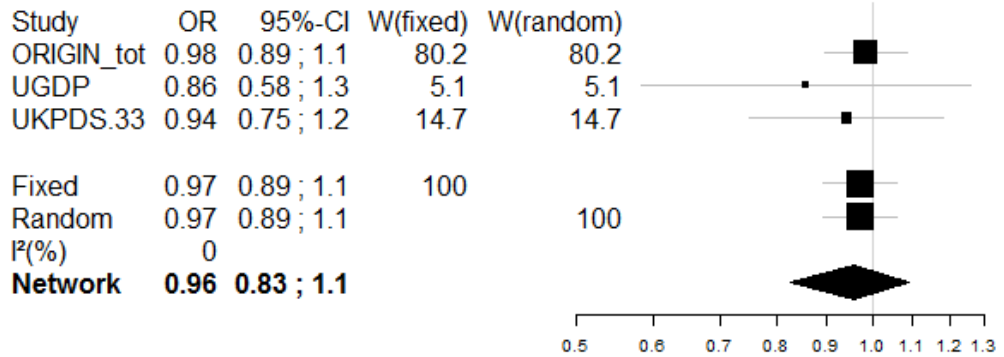
S3A Fig_GLITAZONES VERSUS CONTROL



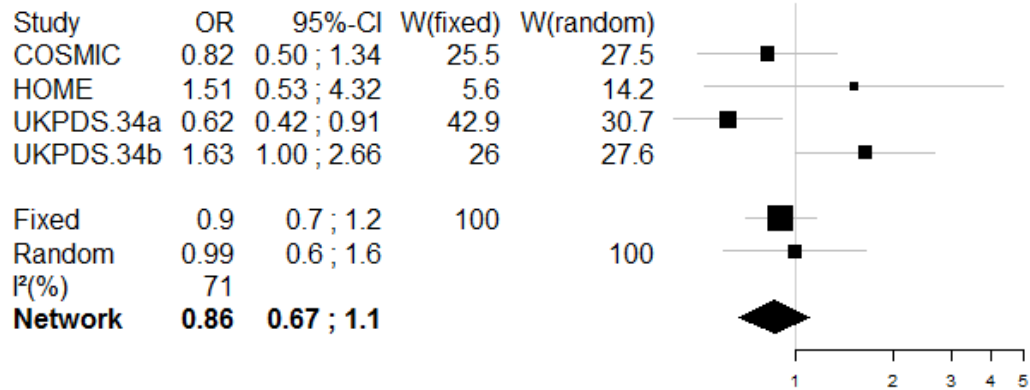
S3A Fig_GLP-1_A VERSUS CONTROL



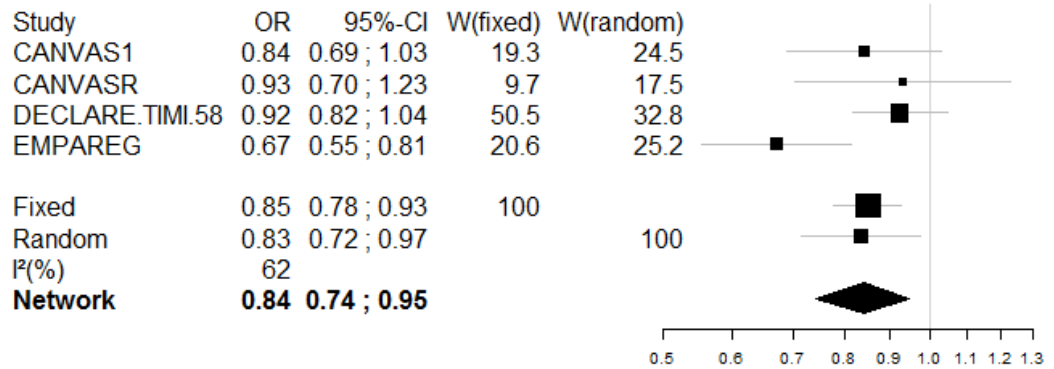
S3A Fig_INSULIN VERSUS CONTROL



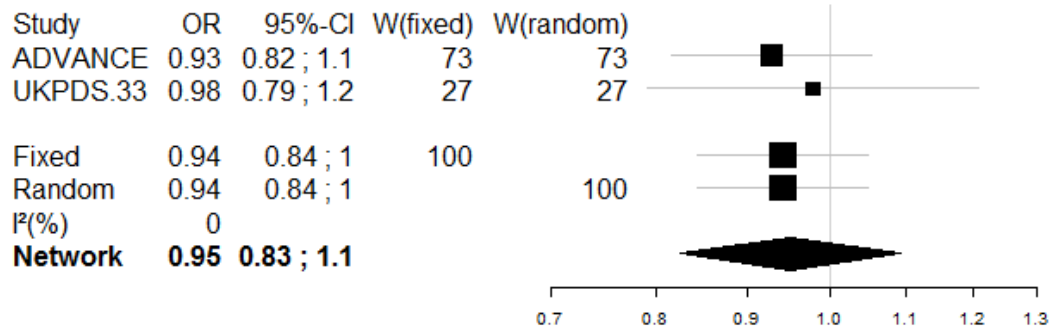
S3A Fig_METFORMIN VERSUS CONTROL



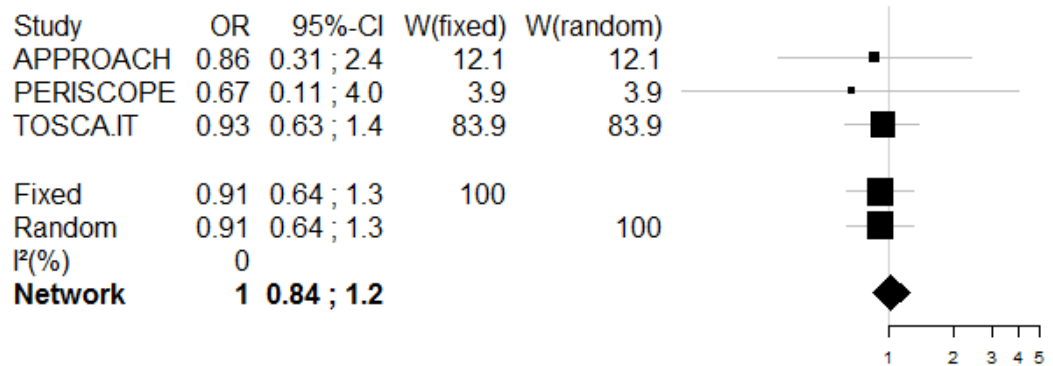
S3A Fig_SGLT-2_I VERSUS CONTROL



S3A Fig_SULFONYLUREA VERSUS CONTROL



S3A Fig_SULFONYLUREA VERSUS GLITAZONES

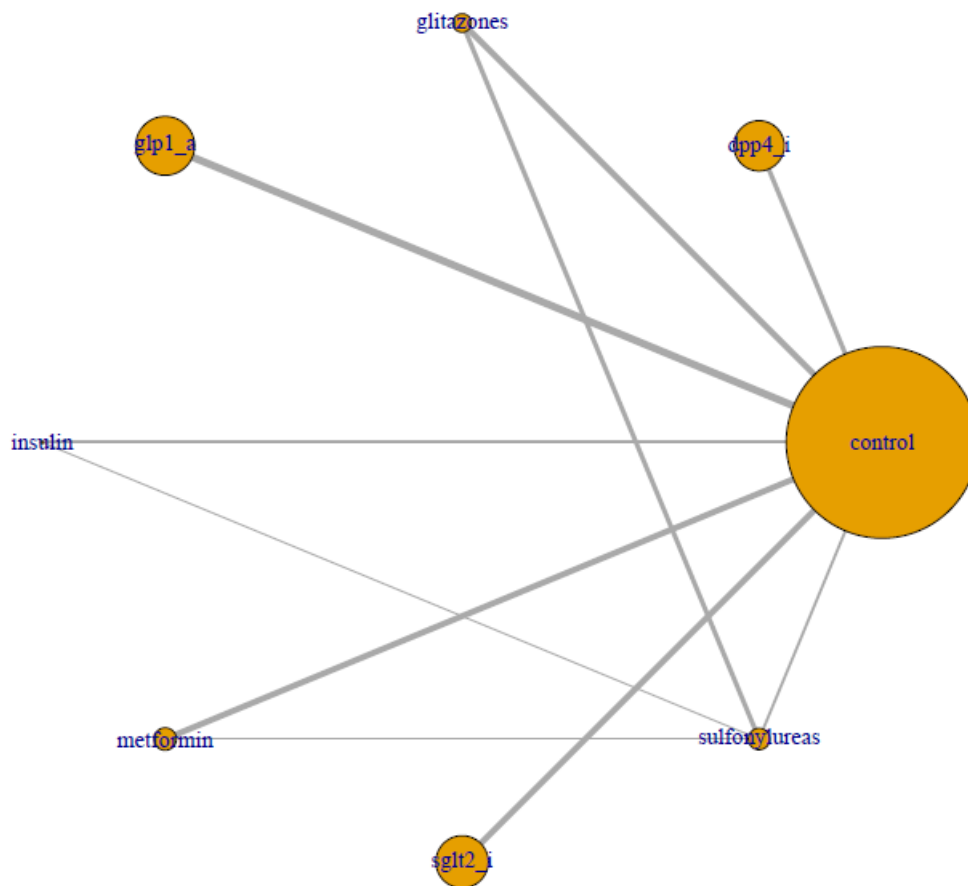


B. Cardiovascular mortality

This network included 27 randomized trials. On 152 642 subjects, 6 221 presented the outcome.

S3B Fig_Network:

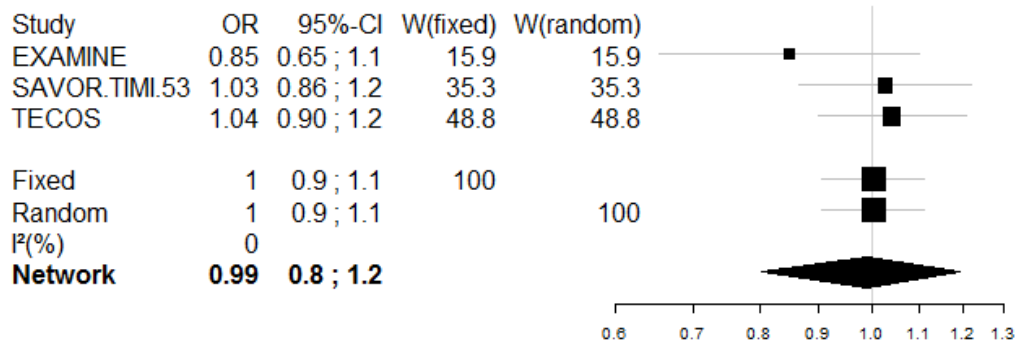
Network figure for CV.Death



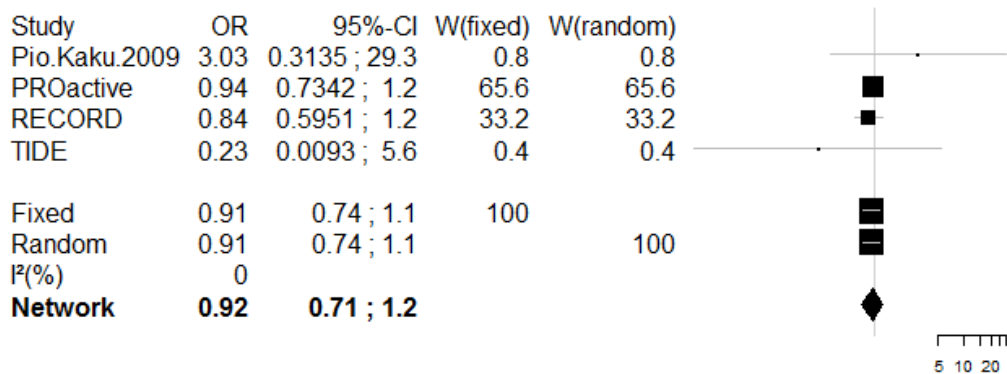
Edge width is based on the number of randomized trials, node size on the sample size.

Forest plots of the cardiovascular mortality for each direct comparison:

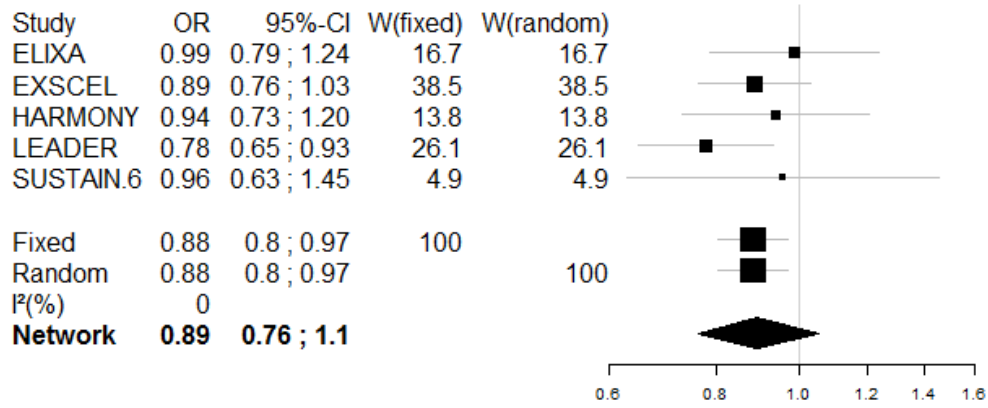
S3B Fig_DPP-4_I VERSUS CONTROL



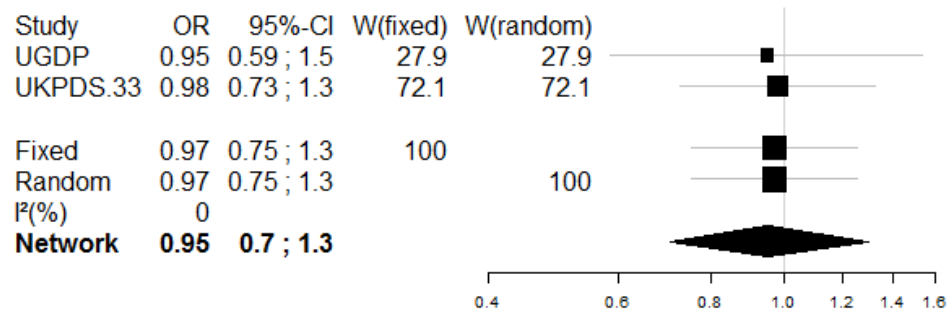
S3B Fig_GLITAZONES VERSUS CONTROL



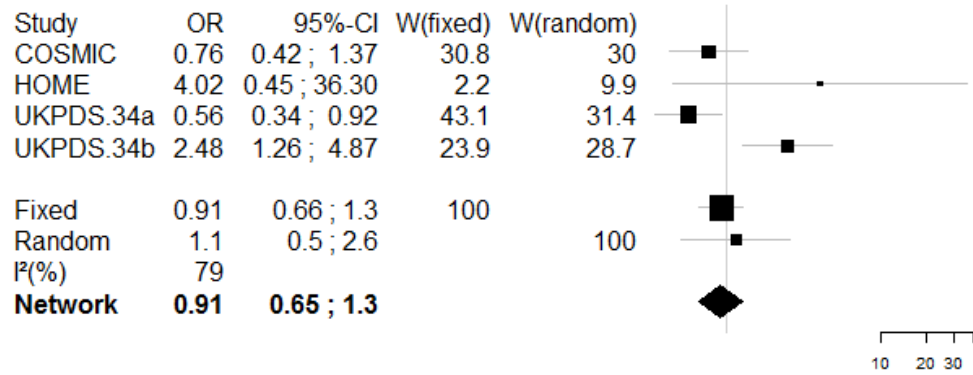
S3B Fig_GLP-1_A VERSUS CONTROL



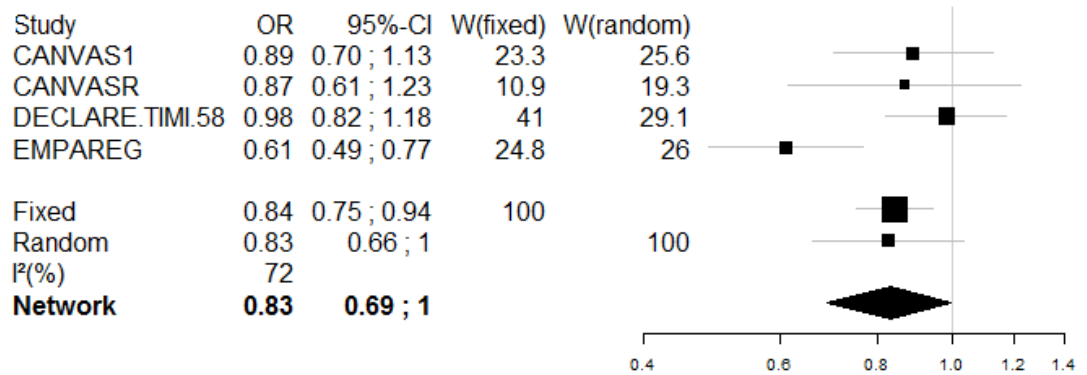
S3B Fig_INSULIN VERSUS CONTROL



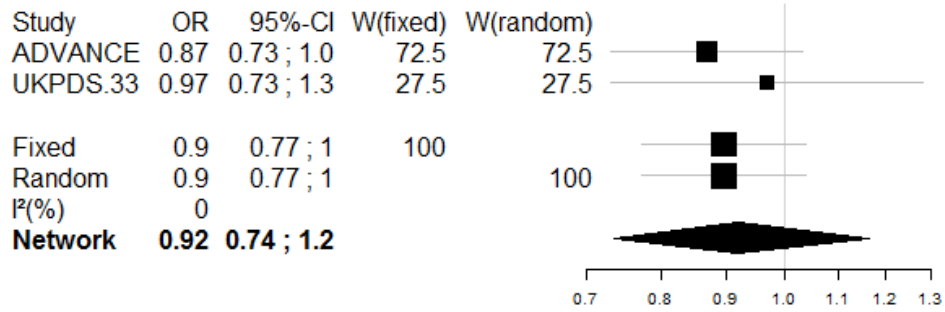
S3B Fig_METFORMIN VERSUS CONTROL



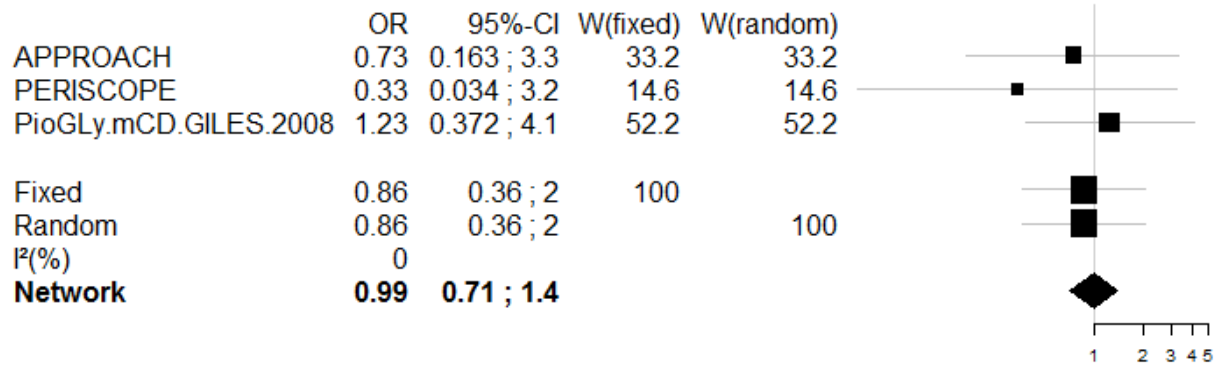
S3B Fig_SGLT-2_I VERSUS CONTROL



S3B Fig_SULFONYLUREA VERSUS CONTROL



S3B Fig_SULFONYLUREA VERSUS GLITAZONES



S1 Table. Search strategy used for Medline

Patients	"diabetes mellitus, type 2"[MeSH Terms] OR type 2 diabetes mellitus[Title/Abstract] OR type 2 diabetes[Title/Abstract] OR "diabetes mellitus"[MeSH Terms] OR "diabetes mellitus"[Title/Abstract] OR "non-insulin-dependent diabetes mellitus"[Title/Abstract] OR "non insulin dependent diabetes mellitus"[Title/Abstract] OR "NIDDM"[Title/Abstract]
	AND
Intervention	hypoglycaemic agents[Title/Abstract] OR hypoglycemic agents[Pharmacological Action] OR "hypoglycemic agents"[MeSH Terms] OR "hypoglycemic agents"[Title/Abstract] OR "hypoglycemic agent"[Title/Abstract] OR "glycaemic control"[Title/Abstract] OR "glycemic control"[Title/Abstract] OR "glucose control"[Title/Abstract]
	AND
Type of study	(randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms:noexp] OR randomly[tiab] OR trial[ti]) NOT (animals[mh] NOT humans[mh])
	AND
Outcome	"mortality"[Subheading] OR mortality[Title/Abstract] OR "mortality"[MeSH Terms] OR "cardiovascular diseases"[MeSH Terms] OR "cardiovascular diseases"[Title/Abstract] OR "cardiovascular disease"[Title/Abstract]
	NOT
Type of studies excluded	review[Publication Type] OR meta analysis[Publication Type] OR meta-analysis[Publication Type]

S2 Table. Definitions of the major adverse cardiovascular events (MACE) outcome for each trial. When not available, proxy was used as defined in the table. CV: cardiovascular, MI: myocardial infarction, SAE: serious adverse event, PCI: percutaneous coronary intervention, HF: heart failure

Study	"MACE" outcome	"MACE" outcome reported definitions
ADVANCE	MACE	CV death and non-fatal MI and non-fatal stroke
APPROACH	MACE	CV death, non-fatal MI, or non-fatal stroke
CANVAS	MACE	CV mortality, non-fatal MI, non- fatal stroke
CANVASR	MACE	CV mortality, non-fatal MI, non- fatal stroke
CARMELINA	MACE	CV mortality, non-fatal MI, non- fatal stroke
COSMIC	proxy	SAE Cardiac disorders, including coronary artery disease, chest pain, congestive cardiac failure, myocardial infarction +/- cerebrovascular accident?
DECLARE TIMI 58	MACE	CV death, myocardial infarction, or ischemic stroke
ELIXA	proxy	Death from CV causes, non-fatal stroke, non-fatal MI, or unstable angina
EMPAREG	MACE	Death from CV causes, non-fatal MI, or non-fatal stroke
EXAMINE	MACE	Death from CV causes, non-fatal MI, or non-fatal stroke
EXSCEL	MACE	Death from CV causes, non-fatal MI, or non-fatal stroke
HARMONY	MACE	Death from CV causes, non-fatal MI, or non-fatal stroke
HOME	proxy	CV intervention (peripheral arterial reconstruction, percutaneous transluminal coronary angioplasty, and coronary artery bypass graft)
J-SPIRIT	NA	
LEADER	MACE	Death from CV causes, non-fatal (including silent) MI, or non-fatal stroke
ORIGIN	MACE	CV death, non-fatal MI, non-fatal stroke
PERISCOPE	MACE	CV death, non-fatal MI, or non-fatal stroke
Kaku.2009	proxy	Death, acute MI excluding silent MI, or stroke
Lee.2013	proxy	Death, MI, re-PCI TLR (target lesion revascularisation), and TVR (target vessel revascularization), stent thrombosis
Giles.2008	proxy	CV mortality and hospitalization or ER (emergency room) visit for HF
PPAR.Study	NA	

PROactive	proxy	Death, non-fatal MI excluding silent MI, stroke
PROFIT-J	proxy	All death, non-fatal stroke, non-fatal MI
RECORD	MACE	CV death, MI, or stroke
SAOR. TIMI.53	MACE	CV death, non-fatal MI, or non-fatal ischemic stroke
SPREAD- DIMCAD	proxy	Non-fatal MI, non-fatal stroke or arterial revascularization by percutaneous transluminal coronary angioplasty (PTCA) or by coronary artery bypass graft, death from a CV cause, and death from any cause
SUSTAIN.6	MACE	Death from CV causes, non-fatal MI, or non-fatal stroke
TECOS	proxy	CV death, non-fatal MI, non-fatal stroke, or hospitalization for unstable angina
TIDE	MACE	MI, stroke or CV death
TOSCA.IT	proxy	All-cause mortality, non-fatal MI (including silent MI), non-fatal stroke, unplanned coronary revascularization
UGDP	NA	
UKPDS.33	NA	
UKPDS.34a	NA	

S3 Table. Reported definitions of the serious adverse event (SAE) outcome used for each trial. AE: adverse event. SAE: serious adverse events

Study	Severe/serious adverse events reported definitions
ADVANCE	Hospitalization
APPROACH	NA
CANVAS	NA (Event rate per 1000 patient/year for the CANVAS Programme)
CANVASR	NA (Event rate per 1000 patient/year for the CANVAS Programme)
CARMELINA	NA
COSMIC	Any fatal, life-threatening, permanently or substantially disabling events, resulted in permanent or significant disability or incapacity, required or prolonged hospitalization, important event that jeopardized the patient or required intervention to prevent a serious outcome, a congenital abnormality, a cancer, an overdose of medication, or drug dependency or drug abuse.
DECLARE TIMI	Serious adverse event
ELIXA	MedDRA version 15.0
EMPAREG	Any SAE
EXAMINE	Any SAE
EXSCEL	Any SAE
HARMONY	Serious Adverse Events by System Organ Class in subjects who took at least one dose of study drug in Appendix (Malignancies included in Neoplasms)
HOME	NA
J-SPIRIT	NA
LEADER	SAE
ORIGIN	Aside from hypoglycemia and cancer, SAE were captured if considered related to a study drug.
PERISCOPE	Total, SAE
Kaku.2009	"Other SAE"
Lee.2013	NA
Giles.2008	SAE (>1.5%)
PPAR.Study	NA
PROactive	Any SAE, non-endpoint events
PROFIT-J	NA
RECORD	NA
SAVOR.TIMI.53	NA
SPREAD-DIMCAD	NA

SUSTAIN.6	SAE (death, a life-threatening episode, hospitalization or prolongation of existing hospitalization, a persistent or substantial disability or incapacity, or an event otherwise considered to be an important medical event)
TECOS	NA
TIDE	Total, Serious Adverse Events
TOSCA.IT	SAE (death, a life-threatening episode, hospital admission or prolongation of existing hospital admission, or a persistent or substantial disability)
UGDP	NA
UKPDS.33	NA
UKPDS.34a	NA
UKPDS.34b	NA

S4 Table. Baseline cardiovascular (CV) risk groups (Grp) for the sensitivity analysis. ‘H’ stands for “high cardiovascular risk at baseline”, ‘L’ for “low cardiovascular risk at baseline”.

ACS: acute coronary syndrome, STEMI: ST elevation myocardial infarction, NSTEMI: non- ST elevation myocardial infarction, AP: angina pectoris, PCI: percutaneous coronary intervention, CABG: coronary artery bypass graft, TIA: transient ischemic attack, MI: myocardial infarction.

Study	CV Grp	CV history (%)	CV history definitions
ELIXA	H	99.8	Qualifying ACS event: NSTEMI, STEMI, Unstable angina
EXAMINE	H	99.7	Myocardial infarction, Unstable angina requiring hospitalization
Pio.post.stent.Lee .2013	H	99.2	Stable AP, Unstable AP, NSTEMI, STEMI
EMPAREG	H	99	Established cardiovascular disease
PROactive	H	85.4	Previous myocardial infarction, Previous stroke, Symptomatic peripheral arterial obstructive disease
SAVOR.TIMI.53	H	78.6	Established atherosclerotic disease
TECOS	H	74	Prior cardiovascular disease (Myocardial infarction, >50% coronary stenosis, Prior PCI, CABG)
EXSCCEL	H	73.1	Prior CV event at randomization
LEADER	H	72.4	Established cardiovascular disease
CANVAS1	H	72.2	History of atherosclerotic vascular disease in CANVAS_P
CANVASR	H	72.2	History of atherosclerotic vascular disease in CANVAS_P
HARMONY	H	70.6	*Any of myocardial infarction, coronary artery bypass grafting, percutaneous coronary intervention, or at least 50% stenosis of coronary artery on angiography
PioGLy.mCD.GI LES.2008	H	68.1	NA
SUSTAIN.6	H	58.8	established cardiovascular disease without chronic kidney disease
ORIGIN_tot	H	58.8	Prior cardiovascular event

SPREAD-DIMCAD	H	58.6	History of myocardial infarction
CARMELINA	H	57	Defined as albuminuria and prevalent macrovascular disease
DECLARE.TIMI.58	L	40.6	17,160 patients, including 10,186 without atherosclerotic cardiovascular disease
APPROACH	L	38	A total of 38% presented with acute coronary syndrome
TIDE	L	34.5	Cardiovascular disease
ADVANCE	L	32.2	History of major macrovascular disease
HOME	L	31.7	HOME 2002 : Diabetic complications Cardiovascular : 31.7%
PROFIT-J	L	31.6	silent cerebral infarction. Ohter previous CV disease: unknown
PERISCOPE	L	28.2	Prior myocardial infarction
RECORD	L	17.4	Ischaemic heart disease at baseline
TOSCA.IT	L	11	Previous cardiovascular disease
J-SPIRIT	L	10	Previous stroke (previous MI : 0)
UGDP	L	10	History of angina pectoris or of significant ECG abnormality
Pio.Kaku.2009	L	8.5	History of CV events (Stroke excluding TIA, angina pectoris, myocardial infarction and coronary intervention procedure)
UKPDS.33	L	NA	early diabetes
UKPDS.34a	L	NA	early diabetes
UKPDS.34b	L	NA	early diabetes
COSMIC	L	NA	type 2 diabetic patients suboptimally controlled on diet or sulfonylurea
PPAR.Study	NA	NA	NA
Mean		54.9	
S.D		29.4	
Median		58.8	

Appendix 3. Complementary supporting information of the meta-regression

Appendix A.2

Search strategy

PubMed – specific strategy:

(“Antihypertensive Agents” [MeSH Terms]) AND (“Hypertension” [MeSH Terms] AND “Diabetes Mellitus” [MeSH Terms]) AND (Randomized Controlled Trial[ptyp])

PubMed – sensible strategy:

(Antihypertensive Agents [MeSH Terms] OR Antihypertensive Agents [TIAB] OR Antihypertensive Agents [TIAB] OR Antihypertensive Agents [TIAB] OR Antihypertensive Drugs [TIAB] OR Antihypertensive Drugs [TIAB] OR Antihypertensives [TIAB] OR Antihypertensives [TIAB] OR Antihypertensive Drugs [TIAB] OR Antihypertensives [TIAB]) AND (Hypertension [MeSH Terms] OR Hypertension [TIAB] OR High Blood Pressure [TIAB] OR High Blood Pressures [TIAB] OR Diabetes Mellitus [MeSH Terms] OR Diabetes Mellitus [TIAB]) AND (“clinical” [TIAB] AND “trial” [TIAB]) OR “clinical trials” [MeSH Terms] OR “clinical trial” [Publication Type] OR “random*” [TIAB] OR “random allocation” [MeSH Terms] OR “therapeutic use” [MeSH subheading])

Appendix A.1 PRISMA 2009 checklist

Section/topic	#	Checklist item	page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	4
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes and study design (PICOS).	5
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address) and, if available, provide registration information including registration number.	6
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	6
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	Appendix A.1
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review and, if applicable, included in the meta-analysis).	8
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	8
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	8
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	8

Section/topic	#	Checklist item	Reported on page #
Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	8
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	Appendix B
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	Table 1
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	Table 1
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	NA
Synthesis of results	21	Present the main results of the review. If meta-analyses are done, include for each, confidence intervals and measures of consistency	Table 2
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	Table 1
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	Table A.3
DISCUSSION			
Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	11
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	11-12
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	12
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	13

LIST OF PUBLICATIONS – ORAL AND POSTER

COMMUNICATIONS

First author publications

Included in the thesis

- **G Grenet**, S Ribault, GB Nguyen, F Glais, A Metge, T Linet, B Kassai, C Cornu, T Bejan-Angoulvant, S Erpeldinger, R Boussageon, A Gouraud, F Bonnet, M Cucherat, P Moulin, F Gueyffier. GLUcose COntrol Safety & Efficacy in type 2 DIabetes, a systematic review and NETwork meta-analysis, PLoS One. 2019 Jun 25;14(6):e0217701. doi: 10.1371/journal.pone.0217701
- **G Grenet**, HH Le, T Bejan-Angoulvant, S Erpeldinger, R Boussageon, B Kassai, P Moulin, F Gueyffier, M Cucherat. Association between difference in blood pressure reduction and risk of cardiovascular events in a type 2 diabetes population: A meta-regression analysis, Diabetes Metab. 2019 May 28. pii: S1262-3636(19)30085-0. doi: 10.1016/j.diabet.2019.05.003. [Epub ahead of print]
- **G Grenet**, C Blanc, C Bardel, F Gueyffier P Roy. Comparison of cross-over and parallel group designs for the identification of a binary predictive biomarker of the treatment, Basic Clin Pharmacol Toxicol. 2019 Jul 16. doi: 10.1111/bcpt.13293. [Epub ahead of print]

Not included in the thesis

- **G Grenet**, A. Lajoinie, S. Ribault, G. B. Nguyen, T. Linet, A. Metge, C. Cornu, M. Cucherat, P. Moulin, F. Gueyffier. Protocol of GLUcose COntrol Safety and Efficacy in type 2 DIabetes, a NETwork meta-analysis: GLUCOSE DINET protocol-Rational and design. Fundam Clin Pharmacol. 2017 Jun;31(3):258-264. doi: 10.1111/fcp.12263

Other publications

- C Betry, E Meugnier, M Pflieger, **G Grenet**, S Hercberg, P Galan, E Kesse-Guyot, H Vidal, M Laville. High expression of CPT1b in skeletal muscle in metabolically healthy older subjects. *Diabetes Metab.* 2019 Apr;45(2):152-159. doi: 10.1016/j.diabet.2018.01.018
- B Kassai, P Bouyé, B Gilbert-Dissardier, F Godart, JB Thambo, M Rossi, P Cochat, P Chirossel, S Luong, A Serusclat, I Canterino, C Mercier, M Rabilloud, C Pivot, F Pirot, T Ginhoux, S Coopman, **G Grenet**, F Gueyffier, S Di-Fillippo, A Bertholet-Thomas. BMC Pediatrics Minoxidil versus placebo in the treatment of arterial wall hypertrophy in children with Williams Beuren Syndrome: a randomized controlled trial. *BMC Pediatr.* 2019 May 28;19(1):170. doi: 10.1186/s12887-019-1544-1.
- B Laviolle, P Denèfle, F Gueyffier, the participants of Giens XXXIV Round Table “Translational research”, E Bégué, P Bilbault, H Espérou, F Gaillard-Bigot, **G Grenet**, JF Guérin, C Guillot, PH Longerey, J Morere, O Perche, L Perrier, D Sanlaville, J Thevenon, N Varoqueaux. The contribution of genomics in the medicine of tomorrow, clinical applications and issues, *Therapie.* 2019 Feb;74(1):9-15. doi: 10.1016/j.therap.2018.11.012
- B Kassai, F Glais, **G Grenet**, C Cornu, KA Nguyen. Reducing waste in pediatric clinical research. *Therapie.* 2018 Apr;73(2):181-184. doi: 10.1016/j.therap.2017.11.013
- P Janiaud, F Glais, **G Grenet**, A Lajoinie, C Cornu, B Kassai. Use of available clinical evidence to extrapolate drug effects from adults to children, *Therapie.* 2018 Apr;73(2):119-125. doi: 10.1016/j.therap.2017.11.007

Oral Communications

- GLUCOSE CONTROL Safety & Efficacy in type 2 Diabetes, a systematic review and Network meta-analysis, Annual Meeting of French Society of Pharmacology and Therapeutics, 2018
- Association between difference in blood pressure reduction and risk of cardiovascular events in a type 2 diabetes population: A meta-regression analysis, Annual Meeting of French Society of Pharmacology and Therapeutics, 2019
- Minoxidil versus placebo in the treatment of arterial wall hypertrophy in children with Williams Beuren Syndrome: a randomized controlled trial., International meeting on Williams-Beuren syndrome, 2017

Poster Communications

- Quality assessment of published pharmacogenetic association in randomized clinical trials, e-poster at the Drug Information Association (DIA) Euro-meeting, edition 2019
- A review of genetic variants related to edema risk using PPAR agonists in type 2 diabetes, e-poster at the Drug Information Association (DIA) Euro-meeting, edition 2018
- Diphtherine® in therapeutic care of chemical burn: to recommend or not to recommend? French Society of Clinical Toxicology, 2019
- Toxicité cardiaque du paracétamol? French Society of Clinical Toxicology, 2018
- GLUCOSE CONTROL Safety & Efficacy in type 2 Diabetes, a systematic review and Network meta-analysis, Congress of the European Association for Clinical Pharmacology and Therapeutics, 2019 (EACPT2019)