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CLINICAL PHARMACOLOGY

Do drugs interact together in cardiovascular prevention? A meta-analysis of powerful or factorial randomized controlled trials

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KEYWORDS
Meta-analysis ;
Interaction ;
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Summary
Aim of the study. — To explore whether preventive cardiovascular drugs (antihypertensive, antiplatelet, lipid lowering and hypoglycemic agents) interact together in cardiovascular prevention.
Methods. — We searched PubMed®, Web of science™, Embase and Cochrane library for powerful randomized placebo-controlled trials (> 1000 patients). We explored whether drug effect on major vascular events changed according to cross-exposure to other drug classes or to

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Major vascular event ;
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cardiovascular risk factors (hypertension or type 2 diabetes), through a meta-analysis of relative odds ratio computed by trial subgroups. A significant interaction was suggested from confidence intervals of the ratio of odds ratios, when they excluded neutral value of 1.

Results. — In total, 14 trials with 178,398 patients were included. No significant interaction was observed between co-prescribed drugs or between these medications and type 2 diabetes/hypertension status.

Conclusions. — Our meta-analysis is the first one to evaluate drug-drug and drug-hypertension/type 2 diabetes status interactions in terms of cardiovascular risks: we did not observe any significant interaction. This indirectly reinforces the rationale of using several contrasted mechanisms to address cardiovascular prevention; and allows the combination effect prediction by a simple multiplication of their odds ratios. The limited availability of data reported or obtained from authors is a strong argument in favor of data sharing.

Abbreviations

ACEI: angiotensin converting enzyme inhibitors
AHA: antihypertensive agents
APA: antiplatelet agents
CI: confidence interval
CVD: cardiovascular disease
GLP-1: glucagon-like peptide
HA: hypoglycemic agents
MVE: major vascular events
OR: odds ratio
PRISMA: Preferred Reporting Items for Systematic Reviews and Meta-Analyses
RCT: randomized controlled trial
ROR: relative odds ratio
SGLT2: sodium glucose cotransporter 2
T2D: type 2 diabetes

Introduction

Cardiovascular disease (CVD) is a major cause of disability and premature death throughout the world. The CVD guidelines recommend the use of the four major drug classes i.e. antihypertensive agents (AHA), antiplatelet agents (APA), lipid lowering drugs and hypoglycemic agents (HA) in primary or secondary prevention [1].

Aspirin [2], statins [3] and antihypertensive interventions [4] reduce the risk of CVD in various populations. These benefits apply both to patients with established CVD, i.e. in secondary prevention and to those with high risk of developing CVD, i.e. in primary prevention. On the other hand, the efficacy of HA in decreasing cardiovascular risk remained controversial [5], until glucagon-like peptide (GLP-1) agonists and SGLT2 inhibitors demonstrated a cardiovascular risk reduction against placebo. Of note, statins and antihypertensive drugs such as ACEI or beta-blockers are prescribed according to clinical situations, such as type 2 diabetes (T2D) for the former, or congestive heart failure for both, without any requirement regarding an increase of the biomarker (respectively cholesterol and blood pressure) supposed to explain their preventive effect. Aspirin prescription is decided on clinical situation, without any biomarker. Hypoglycemic drugs are the only one reserved to glucose increase according to the definition of T2D. This assertion was true until recent trials showed the benefit of gliflozins without T2D, in clinical situations such as congestive heart failure or chronic kidney disease [6–8].

These drugs are often co-prescribed for patients at risk and thus the strategy called polypill, i.e. presenting in the same pill several drug classes, was reasonably suggested for health or economic perspectives. For example, a trial showed that the use of a polypill (containing aspirin, simvastatin, and two antihypertensive drugs: lisinopril and hydrochlorothiazide) might significantly improve patients' adhesion to the program and potentially reduce the risk factors [9]. Under the assumption of no interactions, combining these three groups of molecules is much more effective than monotherapy, since it multiplies odds ratio (OR) applying to each of them. For example, if the OR of each drug class was about 0.75, a polypill combining three classes would be associated with a OR of $0.75^3 = 0.75 \times 0.75 \times 0.75 = 0.42$. The resulting relative risk reduction (1-OR) would be more than doubled compared to single prescription, from 25% to 58%. Of note, the polypill strategy relies on the hypothesis that adjusting statin or antihypertensive drugs on the level of their target biomarker, cholesterol and blood pressure respectively, has no or only a marginal impact on the size of their benefit.

In many clinical randomized controlled trials (RCTs), patients took not only the experimental drug (or the placebo) but also, for many of them, the other drug classes. Subgroup analyses from these trials according to these prescriptions could hence explore whether the association of the experimental drug (e.g. a statin) with other drugs (e.g. aspirin or antihypertensive treatment) at baseline could provide the same cardiovascular protection or not. Another way of asking this question is whether both of these treatments

when experimentally controlled in factorial 2×2 designs would interact in terms of risk prevention. Such designs were sometimes set up and allowed a formal and unbiased assessment of interaction existence between two experimentally controlled drug exposures, e.g. ALLHAT [10], ASCOTT [11] or HOPE-3 [12] for statins and AHA (statins * AHA), or HOT [13] for aspirin and intensified AHA. However, only HOPE-3 is directly relevant by its experimental design to our objectives, because it compared both experimental treatments to placebo. ALLHAT and ASCOTT compared different first-line antihypertensive drug options, and HOT compared three levels of blood pressure lowering intensity.

To our knowledge, until now nobody has explored the interactions between these drugs systematically. This systematic review and meta-analysis of powerful trials aimed to explore interactions (i) between these drugs and, when corresponding drug exposure was not reported (ii) between these drugs and diabetic or hypertensive status of participants, in terms of cardiovascular risk reduction.

Methods

Study selection

We searched for the RCTs comparing one or two of the four groups of treatments to placebo and standard treatments in primary and secondary cardiovascular prevention, and reporting subgroups results according to co-prescription or hypertension or T2D status. We selected powerful trials, in order to explore within trial subgroups results heterogeneity with some precision. We then excluded studies with a number of patients less than 1000 or a power less than 80%. All information was available on the intention-to-treat analysis.

We limited the analyses to drugs that are associated with significant benefit in cardiovascular prevention. This led us to eliminate trials on insulin, sulfonylureas, glitazones or metformin in T2D, and other cholesterol lowering drugs than statins. Antihypertensive drugs were assessed against placebo in primary prevention in hypertensive people at a time where statins and aspirin were not used in such indication.

Search strategy

We conducted the research systematically using Embase, Medline (Pubmed®), Cochrane Library, Web of science™ and clinicaltrials.gov from 1966 to December 31, 2020. We searched for studies involving human subjects, clinical trials, RCTs and/or meta-analyses and/or systematic reviews. We did not apply language restriction. We followed Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [14].

Study screening through titles and abstracts was performed by seven investigators (MF, HHL, MAG, AB, CL, EE and KY), according to the pre-specified selection criteria with cross checks between at least two investigators. Data was extracted independently and compared afterwards from included full-text articles (MF, GG, AB). Disagreements were discussed and decisions were made through consensus (with the intervention of FG when required). The following information was extracted from the studies: the first author or study name, year of publication, baseline patient characteristics, intervention and related outcomes, availability of co-prescription subgroups results. In addition to database searching, we searched manually reference lists of all included studies, meta-analyses and reviews for further potential trials and/or information validation. We contacted corresponding authors to obtain non-published data considered as relevant to this work, e.g. subgroups results.

We extracted aggregate data, number of events and number of patients in each subgroup from the studies included.

Assessment of quality

Cochrane bias criteria [15] were used to evaluate the overall quality of the articles. We considered an included trial as of high quality if all its risks of bias were low.

Outcomes

Drug effect was evaluated through major vascular events (MVE, including cardiovascular death, non-fatal stroke and non-fatal myocardial infarction).

Interaction evaluation

Our main objective was to explore the changes in drug effects according to the cross-exposure to other drug classes. If not explicitly given, exposure to these drugs was assimilated to reported risk factors such as hypertension and (or) T2D. For example, if data on interaction statin * AHA or statin * HA were not given, we examined the interaction statin * hypertension status or statin * T2D status. Doing so, we assumed that T2D and hypertension identified at the beginning of the trial were likely to be treated during the course of the trial.

We computed the OR of the treatment of interest in the available subgroups, then the relative odds ratio (ROR), i.e. the ratio of odds ratio, dividing the OR in the subgroup with the co-prescription by the OR in the subgroup without the co-prescription. We computed the variance of the logarithm of the ROR by trial [log(ROR)]. We then meta-analyzed the log(ROR) across trials, with their confidence intervals. The overall log(ROR) was the weighted average of all the log(ROR) computed at the trial level, the weight being the variance inverse. A back exponential transformation gave the ROR with their 95% confidence intervals (CI). We concluded to a significant interaction when 95% CI of ROR excluded the neutral 1 value. The absence of significant interaction could correspond to two situations: a real absence of interaction, impossible to prove, or a lack of power.

We also computed the average OR across trials within drug classes, in order to estimate the average effect of the four drug classes specifically on the trials we selected. We used RevMan (version 5.3.5) for these last computations.

Results

Search results

At the end of the bibliographic search, we identified 14 studies (Fig. 1) satisfying all selection criteria, which were included in this meta-analysis. According to Cochrane tools,

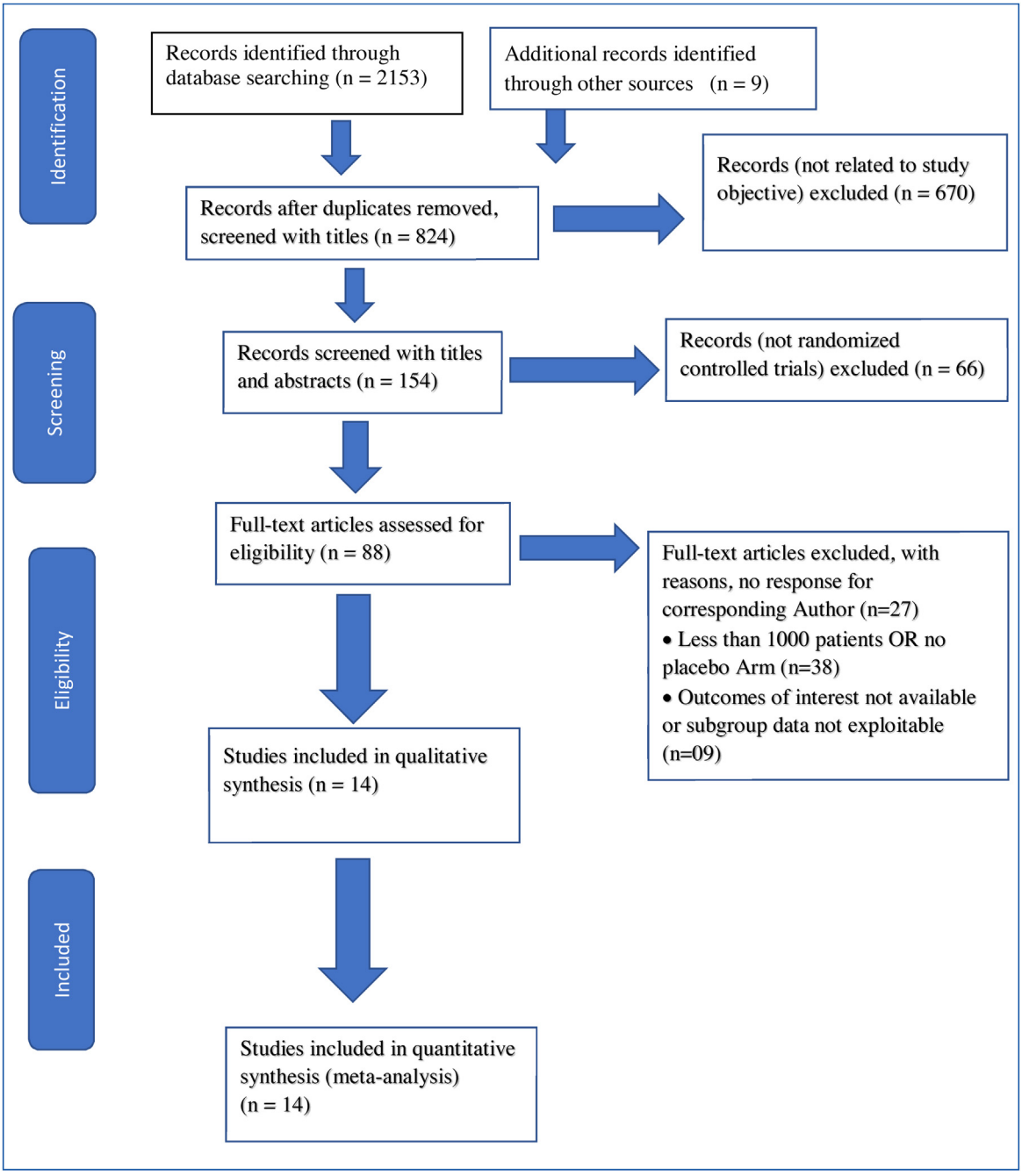

Figure 1. Flowchart of the study search.

the quality of the included trials was good, as shown in Fig. 2. A high risk of bias was attributed to EMPAREG due to the analysis performed by the sponsor. Among 178,398 patients recruited in these 14 included RCTs, the mean age was 59 years, 49% were women, 44% had hypertension, 30% had T2D and some had both risk factors (Table 1) [12,16–28].

There were 178,903 co-administrations of the drugs studied, among which 53,784 concerned APA, 45,247 statin, 64,390 AHA and 15,482 HA (Table 2) [12,16–28]. Of note, HOPE-3 is accounted twice as a factorial design, to explore the impact of statin co-prescription on the AHA preventive effect and reciprocally.

Average estimated effects in the contributive trials

The average estimates of the treatment effect by drug classes on MVE are given in the forest plots: statin reduced significantly the MVE risk (OR 0.78; 0.74–0.82, $P < 0.00001$) (Fig. 3), as did APA (OR 0.89; 0.83–0.95, $P = 0.0007$) (Fig. 4), and AHA (OR 0.82; 0.77–0.87, $P < 0.00001$) (Fig. 5). The two trials available of HA with data by subgroups of co-prescription did not show a significant benefit when considered together: OR 0.94; 0.84–1.04, $P = 0.23$ (Fig. 6).

Table 1 Trial participants' baseline characteristics.

Study	Countries	Mean follow-up, years	Population	Comparison	Concomitant drugs	Number of Participants (Exp/Pbo)	Mean age, years	Women, %
ADVANCE 2007 [16]	Australia	4.3	T2D	AHA/Pbo	Statin, aspirin	5569/5571	66	43
EMPAREG 2015 [17]	Canada	3.1	T2D	Empagliflozin 10—25 mg/Pbo	AHA, statin, aspirin	4687/2333	65	29
EUROPA 2003 [18]	France	4.2	Stable coronary disease	Perindopril 8 mg/Pbo	AHA, statin, aspirin, HA	6110/6108	60	14
HOPE 2000 [19]	Canada	3.5	High coronary risk	Ramipril 10 mg/Pbo	AHA, statin, aspirin, HA	4645/4652	66	26
HOPE-3 [12]	Canada	5.6	Moderate CV risk	Statin/Pbo AHA/Pbo	Statin, HA	3180/3168	65	46
HPS 2002 [20]	UK	5.0	High CV risk	Simvastatin 40 mg/Pbo	AHA, statin, aspirin, HA	10,269/10,267	65	65
LIPS 2001 [21]	Europe, Canada, Brazil	3.9[a]	Secondary coronary prevention	Fluvastatin 80 mg/Pbo	AHA, APA	844/833	60	16
TRACE 1995 [22]	Denmark	4.7	Secondary coronary prevention	Trandopril 1-2 mg/Pbo	AHA, aspirin	876/873	67	28
PROSPER 2002 [23]	North Europa	3.2	Primary prevention	Pravastatin 40 mg/Pbo	AHA, aspirin, HA	2891/2913	75	52
WHS 2005 [24]	USA	10.1	Primary prevention	Aspirin 100 mg/Pbo	APA	19,934/19,942	55	100
ASCEND 2018 [25]	USA	7.4	T2D	Aspirin/Pbo	AHA, statin	7740/7740	63	37
ASPREE 2018 [26]	USA, Australia	4.7	Primary prevention in healthy elderly	Aspirin/Pbo	AHA, statin	9525/9589	74	44
ELIXA 2015 [27]	USA	2.1	T2D & secondary coronary prevention	HA/Pbo	AHA, statin, aspirin, HA	3034/3034	65	31
PHS 1989 [28]	USA	5.1	Primary prevention	Aspirin 325 mg Eod/Pbo	AHA	11,037/11,034	NA	0

AHA: antihypertensive agents; APA: antiplatelet agents; CV: cardiovascular; Eod: every other day Exp: experimental; HA: hypoglycemic agents; Pbo: placebo; NA: not applicable; T2D: type 2 diabetes.

[a] Median instead of mean.

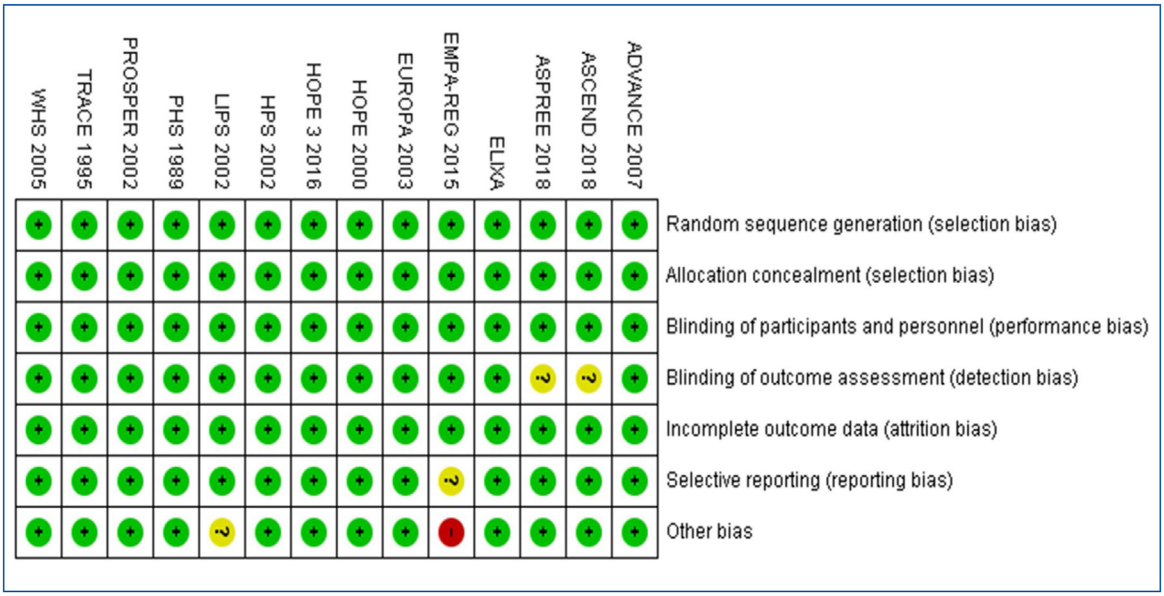

Figure 2. Quality assessment of the included trials.

Table 2 bis. Trial participants' contributive numbers.

Study	Number of participants with subgroups analysed				Number of participants with hypertension	Number of participants with T2D
	APA	HA or T2D	AHA or hypertension	Statin		
Statin trials						
HPS 2002 [20]	12,984	5963	8457	—	8457	5963
LIPS 2001 [21]	1637	202	647	—	647	202
PROSPER 2002 [23]	2104	623	3592	—	3592	623
HOPE-3 [12]	NA	NA	6356	—	4814	731
HA trials						
EMPAREG 2015 [17]	5803	—	6667	5440	6667	7020
ELIXA 2015 [27]	5917	—	4635	5627	4635	6068
AHA trials						
ADVANCE 2007 [16]	5399	NA	—	3146	7655	11,140
EUROPA 2003 [18]	11,275	1502	—	7033	3312	1502
HOPE 2000 [19]	7074	3577	—		4355	3577
HOPE-3 [12]	NA	NA	—	6361	4814	731
TRACE 1995 [22]	1591	NA	—	0	1749	27
APA trials						
WHS 2005 [24]	—	1037	10,308	NA	10,308	1037
ASCEND 2018 [25]	—	NA	NA	11,653	9533	14,569
ASPREE 2018 [26]	—	2045	14,195	5987	14,195	2057
PHS 1989 [28]	—	533	NA	NA	866	533

AHA: antihypertensive agents; APA: antiplatelet agents; HA: hypoglycemic agents; NA: not applicable; T2D: type 2 diabetes.

Statistics for interaction evaluation

The results of our search for interactions between experimental drugs and co-prescriptions are summarized in the Table 3. The cells indicate whether the experimental treatment of a given line interacts with the co-prescriptions given in columns. The diagonal cells recall the average estimate of each drug class already given above in the forest plots. Most ROR are close to 1, the range of point estimates being 0.92 to 1.10, one only being less than 0.90, at 0.89. This result concerns the modification of the effect of aspirin by the co-prescription of AHA, with a suggestion that aspirin may be more effective when prescribed with AHA. Such a positive interaction is expected to be symmetrical, making a positive interaction expected for AHA when aspirin is co-prescribed. But the reverse is observed, with a ROR of 1.10, suggesting that AHA are less effective when prescribed with aspirin: these incoherent results weaken the suggestion of an interaction between these two drug classes. None of the ROR 95% confidence intervals excludes the neutral 1 value.

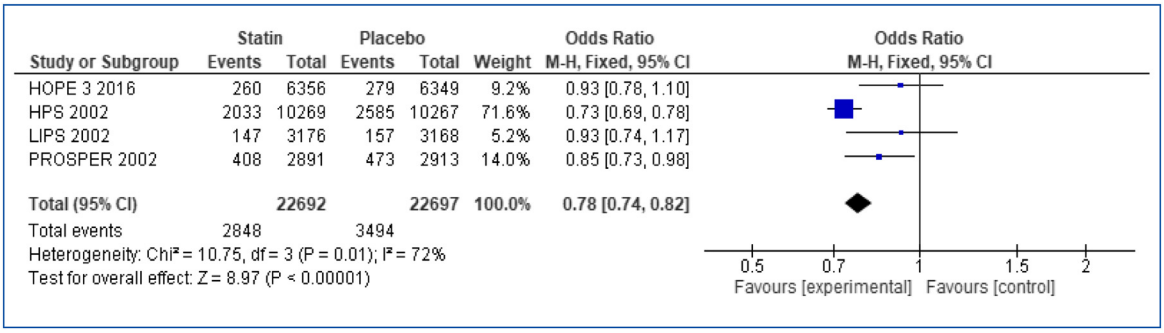

Figure 3. Forest plot of statin effect in major vascular event prevention. Forest plot of statin effect in patients with cardiovascular risk. In total, 4 out of 14 included trials allowed the effect of statin on major vascular events to be explored.

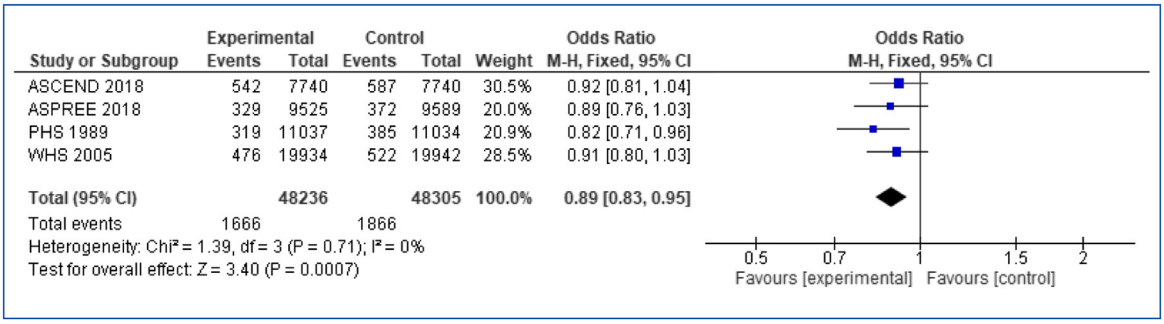

Figure 4. Forest plot of antiplatelet agent (APA) effect in major vascular event prevention. Forest plot of APA effect in patients with cardiovascular risk. In total, 4 out of 14 total included trials allowed the effect of APA on major vascular events to be explored.

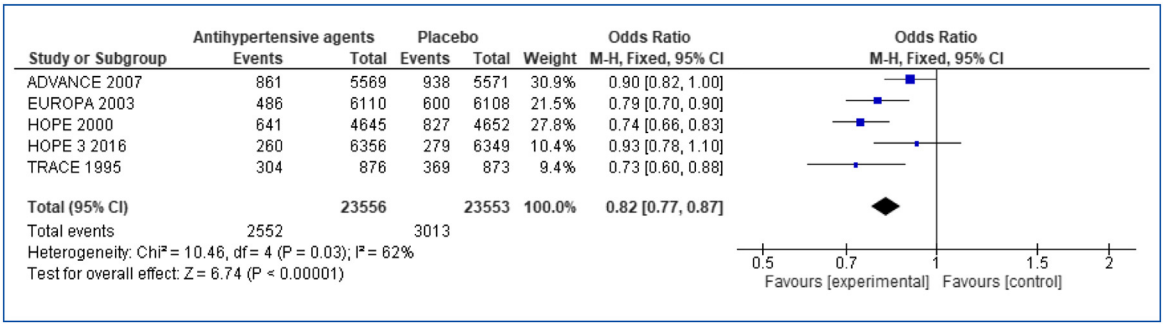

Figure 5. Forest plot of antihypertensive agent (AHA) effect in major vascular event prevention. Forest plot of AHA effect in patients with cardiovascular risk. In total, 5 out of 14 total trials allowed the effect of AHA on major vascular events to be explored.

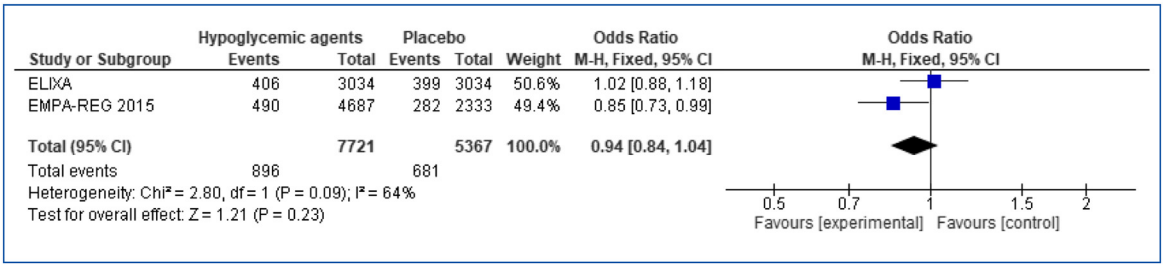

Figure 6. Forest plot of hypoglycemic agent (HA) effect in major vascular event prevention. Forest plot of HA effect in patients with cardiovascular risk. In total, 2 out of 14 included trials allowed the effect of HA on major vascular events to be explored.

Table 3 Major vascular event risk reduction (OR) are in bold in the diagonal for drug classes. The other cells display the relative odd ratios (ROR) with 95%CI for interactions.

Co-prescription: Treatment estimate	Statin	APA	AHA	HA
Statin	**0.78[0.74;0.82]**	2 studies with data 0.92 [0.81;1.04]	3 studies with data 1.00 [0.89;1.13]	3 studies with data 1.07 [0.94;1.22]
APA	2 studies with data 0.91 [0.76;1.09]	**0.89 [0.83;0.95]**	3 studies with data 0.89 [0.76;1.04]	3 studies with data 0.93 [0.71;1.22]
AHA	4 studies with data 1.04 [0.90;1.21]	2 studies with data 1.10 [0.91;1.34]	**0.82 [0.77;0.87]**	2 studies with data 0.92 [0.78;1.10]
HA	2 studies with data 0.93 [0.69;1.27]	2 studies with data 1.05 [0.73;1.52]	2 studies with data 0.94 [0.66;1.34]	**0.94 [0.84;1.04]**

AHA: antihypertensive agents; APA: antiplatelet agents; HA: hypoglycemic agents.

Discussion

Summary of main results

Our study is the first attempt to evaluate drug-drug interactions in terms of cardiovascular risk reduction. We evaluated the interactions among four cardio-preventive drug groups (APA, AHA, statin and HA) in 178,398 patients from 14 powerful RCTs, through 12 subgroups comparisons. The average estimates we obtained confirmed the efficacy of APA, AHA and statin for MVE reduction in a mixed setting of primary and secondary cardiovascular prevention (Table 3), largely illustrated elsewhere [3,29,30]. By contrast, the impact of HA was marginal and not statistically significant. We did not observe any significant interaction between experimental and co-prescribed drugs or between these medications and T2D/hypertension status, most ROR being close to 1. The strongest suggestion of a possible interaction was the change of APA effect with AHA co-prescription (Table 3), not confirmed by the change of AHA effect with APA co-prescription, observed in the opposite direction. Our work suggested that combination of these treatments was legitimate for MVE prevention, until more powerful data are available. Of note, while there was no significant drug-drug interaction demonstrated, the analyses did not suggest, in any way, that the co-administration of these agents has any added benefit or synergistic effect.

This finding is important to estimate the OR from drug combinations: assuming that there are no interactions between statin, APA and AHA leads to estimate that their simultaneous use would be associated with a reduction of about $0.78 \times 0.89 \times 0.82 = 0.57$ (Table 3) on the risk of MVE. This computation relies on the OR estimates from complete trials combining exposed and non-exposed subgroups.

Quality of evidence

We searched all classical databases (Embase, Pubmed®, Cochrane, Web of science™, clinicaltrials.gov) and we believe having covered all the most powerful related RCTs. The included trials were recent (most were conducted in 2001—2015 except TRACE [22] in 1995) and powerful (only 2 trials, LIPS [21] and TRACE [22] recruited < 5000 and > 1000 patients, the biggest one WHS consisted of 39,876 participants) (Table 1). The quality of the included studies was good: 100% low risk for selection, performance and attrition biases, 90% low risk for detection bias, > 85% low risk for reporting bias and about 80% for other bias (Fig. 2).

Limitations

Our study may present some limitations. First, publication bias exists for two reasons: (i) non-published data was not examined and only powerful trials were included; (ii) for 11 trials published but without specific subgroup data, we have contacted the authors but we received response only for a few. Of note, our main outcome, i.e. looking for interactions, was never the objective of the trials included, at the possible exception of the Heart Prevention Study, which was an unusually powerful trial aiming to resolve left questions relative to the impact of statins. The lack of preventive effect observed in the pooled results from the two included trials of HA (GLP-1 agonists and gliflozins) was not aligned with what classical meta-analyses said previously, showing about 15% reduction in MVE [31]. This illustrates that our working sample of trials does not reflect the complete landscape of cardiovascular prevention, and that better estimate of the average effects of these drug classes would be available in appropriate systematic reviews. Second, in some cases we interpreted hypertensive or diabetic status as a proxy for AHA or HA exposure. This relies on the assumption that no confusion factors intervene between hypertension/T2D status and drug exposure. Third, we assumed that initial prescription was a good surrogate for the subsequent exposure, which obviously is not completely true: even when they are supposed to be prescribed lifelong for chronic conditions that do not usually reverse, some patients stop taking these drugs due to adverse events or other reasons. Fourth, pooling pharmacological classes (e.g. diuretics or betablockers) in larger therapeutic classes could explain that we missed important interactions that would occur at the pharmacological level, but would not be apparent when observed at therapeutic class level.

When an interaction was assessed in a 2×2 factorial design, as in HOPE-3, both interacting factors were controlled and their interactions were not subject to biases. In most cases, only one treatment was controlled, with unbiased estimate of its effect, yet the co-prescriptions were not

controlled and were associated with individual characteristics, which may confound interaction search. Confounders other than individual characteristics may interfere and lead to biased results for interaction. This is likely the case for the lack of symmetry regarding the co-prescriptions of APA and AHA discussed above. In further analyses, other diseases or demographic status which may impact on the drug-drug interactions including metabolic syndrome, obesity, heart failure, kidney diseases, hepatic diseases, gender, and age (elderly) should be considered together, to reduce the risk of confusion in the search of interaction, but such analyses would require the availability of individual patient data. As well, additional statistical analyses and simulations could be further performed to look at power calculations and sample size needed to detect (and rule out) interaction.

Availability of information from trials

Among the 14 included RCTs, the most frequently assessed drug was APA (35%), followed by statin (25%), AHA (24%) and HA (16%). The sample we collected was not representative of all RCTs in the field. A more complete analysis would be possible if all RCTs systematically presented available subgroups of co-prescription results, or gave access to available individual patient data or post hoc results on request. Given the importance of possible existence of such interactions, we advocate strongly a better availability of complete RCT information, including data at the individual patient level. Serious progress was made in this prospect during the three last decades, notably under the lead of Cochrane working group devoted to these specific approaches [32].

Conclusion

Our study is the first one exploring the interactions between commonly co-administered preventive cardiovascular drugs (AHA, APA, HA, statin) in primary and secondary cardiovascular prevention, using data from the most powerful RCTs. Since we observed no significant drug-drug interaction, our meta-analysis convincingly suggests that the combinations of these four drug groups are effective for reducing MVE in high vascular risk patients. The most serious limitations could be overcome if authors and/or sponsors of randomized controlled trials made available their data at the individual patient level.

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Contribution

MF and FG were responsible for the study concept and design. HL, GG, MAG, AB, CL, EE, KY and MF acquired and extracted the data. MF, HL, AB and FG performed the analyses. HL, MF and FG drafted the manuscript. All authors revised it critically for important intellectual content.

Information about previous presentations

Part of this work was presented as:

- Poster, 26th European Society of Hypertension Meeting, Paris, June 2016 (Poster Alberto Ferrari Prize, http://www.esh2016.org/alberto-ferrari-poster-prize/).
- Oral communication, 27th World Congress of the International Union of Angiology, Lyon, October 2016.

Do drugs interact together in cardiovascular prevention? A meta-analysis of powerful of factorial randomize controlled trials. M. Fall, H. Le, M. Al-Gobari, G. Grenet, M. Cucherat, A. Dieye, F. Gueyffier.

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We got no answer from seven other trial contacts.

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Disclosure of interest

The authors declare that they have no competing interest.

Références

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