# *Comparative efficacy of fixed-dose statin and antihypertensive agent combinations: a network meta-analysis of randomized controlled trials*

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## Abstract

**Background:** The concurrent administration of statins and antihypertensive agents has been associated with improved cardiovascular outcomes, although the optimal fixed-dose combination remains unclear. This meta-analysis aims to compare the blood pressure and lipid-lowering effects of various statin and antihypertensive drug combinations.

**Methods:** PubMed, Scopus, Web of Science, CENTRAL and Clinicaltrials.gov were systematically searched from inception to 20 March 2021. Randomized controlled trials evaluating the effects of statin-antihypertensive agent combinations on systolic blood pressure or serum lipids were held eligible. A random-effects frequentist model was applied to provide estimates of mean difference of percentage change.

**Results:** Overall, 18 studies were included, comprising 4,450 patients. Compared to statin monotherapy no significant difference in the percentage change of low-density lipoprotein cholesterol was achieved by adding any antihypertensive agent. Compared to amlodipine monotherapy, the addition of moderate-intensity statin resulted in a significantly greater percentage reduction of systolic blood pressure (-2.22%, 95% confidence intervals: [-3.82; -0.62]). Combined high-intensity statin and amlodipine lead to significant increase of high-density lipoprotein cholesterol (8.34%, 95% confidence intervals: [0.73; 15.95]), while effective triglyceride reduction was achieved by adding amlodipine and telmisartan to high-intensity statin (-14.68%, 95% confidence intervals: [-28.48; -0.89]). No significant difference of adverse effects was observed.

**Conclusion:** The present network meta-analysis suggests that the administration of fixed-dose combinations of statins and antihypertensive agents is safe and effective in reducing blood pressure and serum lipids. The optimal dosing strategy to prevent cardiovascular events remains to be determined.

***Key-words:*** hypertension; blood pressure; lipid-lowering; dyslipidemia; fixed-dose; polypill

## Abbreviations

ACEi (angiotensin-converting enzyme inhibitor), AED (atorvastatin equivalent dose), Amlo (amlodipine), ARB (angiotensin receptor blocker), BMI (body mass index), Cande (candesartan), CCB (calcium channel blocker), CENTRAL (Cochrane Central Register of Controlled Trials), CI (confidence intervals), CINeMA (Confidence In Network Meta-Analyses), Fima (fimasartan), HDL-C (high-density lipoprotein cholesterol), HMGR (3-hydroxy-3-methylglutaryl-coenzyme A reductase), Irbe (irbesartan), LDL-C (low-density lipoprotein cholesterol), Losa (losartan), Mani (manidipine), MD (mean difference), Olme (olmesartan), OR (odds ratio), PRISMA-NMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-analyses), Rami (ramipril), RCT (randomized controlled trial), RoB-2 (Cochrane risk of bias), SBP (systolic blood pressure), SIDE (Separating Indirect from Direct Evidence), TAE (treatment-emergent adverse effect), Telmi (telmisartan), Valsa (valsartan)

## 1. Introduction

Hypertension represents a leading cause of mortality, affecting approximately one-third of the adult population worldwide[1]. Its prevalence is rising not only in high but also in middle and low-income countries, mainly due to the ageing of the population, the increase of sedentary lifestyle and the obesity epidemic[2]. Hypertension constitutes a crucial modifiable cardiovascular risk factor and is commonly present in conjunction with comorbidities, especially diabetes mellitus and dyslipidemia[3]. Dyslipidemia predisposes to endothelial dysfunction, which in turn may disrupt the vascular integrity leading to dysregulation of vascular tone and development of hypertension[4]. As a result, concurrent therapy with blood pressure and lipid-lowering agents has been suggested to effectively mitigate the risk of atherosclerotic disease and decrease the risk of cardiovascular events[5].

Statins represent the mainstay of dyslipidemia management due to their high effectiveness in reducing low-density lipoprotein cholesterol (LDL-C) levels through the inhibition of 3-hydroxy-3-methylglutaryl-coenzyme A reductase (HMGR). Apart from their lipid-lowering properties, they present significant pleiotropic effects, such as amelioration of endothelial function, reduction of oxidative injury and modulation of innate immunity[6]. Moreover, it has been suggested that statin administration may promote blood pressure reduction, through the upregulation of nitric oxide expression, the decreased release of endothelin-1 and the improvement of vascular stiffness[7]. In this direction, evidence from meta-analyses has indicated that statin therapy is linked to a significant modest reduction of blood pressure, especially in patients with uncontrolled hypertension[8,9].

Recent research has proposed that the combined treatment with statin and antihypertensive agents is associated with significant clinical benefits, including lower risk of major cardiovascular and cerebrovascular events[10]. Nevertheless, robust evidence regarding the effects of individual drug combinations is currently lacking. The present meta-analysis aims to accumulate the available literature knowledge in the field, in order to simultaneously compare the efficacy and safety of various combinations of statins with antihypertensive agents. A network meta-analysis design is implemented to exploit both

direct and indirect evidence and assess the blood pressure and lipid-lowering effects of different dosing strategies.

## 2. Materials and methods

### 2.1. Study design

The present network meta-analysis was designed according to the PRISMA-NMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Network Meta-analyses) guidelines[11]. The protocol of the study has been prospectively registered and is available online (dx.doi.org/10.17504/protocols.io.bjxekpje). No ethical approval was needed as the study was exclusively based on already published aggregate data.

### 2.2. Eligibility criteria

The target population of the study consisted of adult patients with dyslipidemia and essential hypertension. The co-administration of a statin with antihypertensive agents was compared to statin and antihypertensive monotherapy. The primary outcomes of interest were the percentage change of LDL-C and the percentage change of systolic blood pressure (SBP). The secondary outcomes included the percentage change of high-density lipoprotein cholesterol (HDL-C) and triglycerides, the attainment of LDL-C and blood pressure goals, as well as the rate of treatment-emergent adverse effects (TAEs). Only randomized controlled trials (RCTs) were held eligible. Observational studies, case reports/series, review articles, animal and *in vitro* studies were excluded. Studies investigating polypills with more than 3 drugs or containing aspirin, studies with no standard dose of statin or antihypertensive agent, as well as those at specific populations with serious medical conditions (i.e., severe heart failure, liver failure, end-stage kidney disease) were also excluded. In addition, studies evaluating simvastatin at the dose of 80 mg were not included, given its dosing restriction due to increased myopathy risk.

### 2.3. Search strategy

The following databases were systematically searched from inception: PubMed, Scopus, Web of Science, Cochrane Central Register of Controlled Trials (CENTRAL) and

Clinicaltrials.gov. The Google Scholar database, as well as the full reference list of the included studies ("*snowball*" method[12]) were also searched to identify articles that may be not have been recognized by the primary search. The date of the last search was set at 20 March 2021. The search strategy included the combination of MeSH (Medical Subject Headings) terms ("Hydroxymethylglutaryl-CoA Reductase Inhibitors", "Antihypertensive Agents", "Angiotensin-Converting Enzyme Inhibitors", "Angiotensin Receptor Antagonists", "Calcium Channel Blockers") with a list of statins and antihypertensive agents. The full search algorithm is presented in Appendix 1.

### 2.4. Study selection

The studies of the meta-analysis were selected following 3 consecutive stages. Firstly, the titles and abstracts of the articles identified by database search were screened to assess for potential eligibility. Subsequently, all studies that were presumed to meet the pre-specified inclusion criteria were retrieved as full-texts. Then, studies that met any of the exclusion criteria were identified and were not included in the review. The process of study selection was conducted by 2 researchers independently, while any possible discrepancies were resolved through consensus.

### 2.5. Data extraction

The following data about study and patients' baseline characteristics were extracted: year of publication, country, sample size, design, eligibility criteria, interventions, timing of outcome assessment, patients' sex, median age, body mass index (BMI), smoking status, baseline SBP, LDL-C, presence of diabetes mellitus and coronary artery disease. Information about the outcomes of interest (percentage change of SBP, LDL-C, HDL-C, triglycerides, proportion of patients achieving LDL-C/blood pressure goals and TAEs) was also collected. In case data regarding the outcomes of interest were unavailable, the authors of the original studies were contacted requiring the missing information.

### 2.6. Quality assessment

The quality of the included RCTs was evaluated with the Cochrane risk of bias (RoB-2) tool[13]. The following domains were assessed for parallel trials: randomization, deviations from intended interventions, missing outcome data, measurement of the

outcome and selection of the reported results. For crossover trials, the domain of bias due to period and carryover effects was also taken into account. The credibility of evidence was judged following the CINeMA (Confidence In Network Meta-Analyses) approach[14] which takes into account within-study bias, reporting bias, indirectness, imprecision, heterogeneity and incoherence. Specifically, for the within-study bias domain, the RoB-2 score of the majority of studies was used. Reporting bias was assessed by considering the risk of publication bias by examining the asymmetry of funnel plots. Indirectness referred to the relevance of the research question of the majority of studies. The domain of imprecision was assessed by defining clinically significant effects as a 10% percent change of LDL-C or SBP; hence, it was tested whether confidence intervals crossed into the range of equivalence (percentage change between -10% and 10%). To judge heterogeneity, the 95% predictive intervals were estimated[15], while incoherence was evaluated by the significance of the SIDE (Separating Indirect from Direct Evidence) test[16]. For each domain, major, some or no concerns were assigned. Assessment of bias risk and credibility of evidence was performed by 2 researchers independently; any disagreements were resolved through discussion with all authors.

### 2.7. Definition of nodes

Nodes consisted of statins, antihypertensive agents, their combinations and placebo. Based on their dose and intensity, statins were converted to atorvastatin equivalent dose (AED) ranging from 10 to 80 mg[17]. Different doses of antihypertensive agents represented different nodes. Due to limited data on secondary outcomes (HDL-C and triglycerides), statins were classified as moderate-intensity (AED 10-20 mg) and high-intensity (AED 40-80 mg) ones, while the dose of antihypertensive agents was not taken into account. The outcomes of goals attainment and TAEs were only evaluated with pairwise meta-analysis since data inadequacy precluded the construction of connected networks.

### 2.8. Statistical analysis

Network meta-analysis was performed in R-4.0.5 (package “*netmeta”*[18]). A random-effects frequentist model was fitted by assuming a common parameter of heterogeneity across comparisons. The effect measure was the mean difference (MD), while confidence

intervals (CI) were set at 95%. When the percentage change was not directly reported, it was estimated using the delta method[19]. League tables were constructed in order to simultaneously visualize the relative effects of all interventions. Treatments were ranked according to their P-scores[20], with higher values indicating a higher probability of representing the best treatment. To identify optimal interventions, the P-scores for LDL-C of all treatments were plotted against their respective P-score for SBP. Subsequently, the geometric distance of each intervention from the ideal point ($x_0$, $y_0$), with $x_0$ corresponding to the global maximum of SBP P-scores and $y_0$ the global maximum of LDL-C P-scores, was calculated using the following equation:

$$d_i = \sqrt{(x_i - x_0)^2 + (y_i - y_0)^2} \quad (1)$$

The most suitable Pareto front point was identified by the minimization of $d_i$[21].

Heterogeneity was assessed by estimating the 95% predictive intervals in accordance with the equations proposed by IntHout et al[15]. Transitivity was judged by the distribution of potential confounders (age, sex, body mass index, baseline SBP and LDL-C) across different treatments grouped by comparison. Consistency was statistically assessed globally using the design-by-treatment interaction test[22] and locally with the SIDE test[16]. Publication bias was evaluated by constructing comparison-adjusted funnel plots and examining their asymmetry with the Egger's regression test[23] and the Thompson-Sharp test[24].

Pairwise meta-analysis of secondary outcomes was performed in R-4.0.5 (package "*metafor*"[25]) by fitting random-effects models using restricted maximum likelihood for the estimation of the tau-squared values. Estimates of odds ratios (OR) along with their 95% CI were estimated. Since the normality assumption may be challenged due to small study sample and rarity of events (i.e., TAEs), a one-stage (modified Simmons-Higgins with random-study specific effects) model was applied as a sensitivity analysis[26].

## 3. Results

### 3.1. Study selection

Literature search identified a total of 4,936 records; after deduplication and initial screening, 28 studies were retrieved as full-texts. Of them, 10 were subsequently excluded[27–36]. The reasons for exclusion were the following: absence of standard drug dosing (4 studies), partial duplication (2 studies), heterogeneous concomitant antihypertensive therapy in both groups (1 study), absence of outcomes of interest (1 study), observational design (1 study) and comparison with usual care (1 study) (Suppl. Table 1, Appendix 1). As a result, the meta-analysis was based on a cohort of 18 RCTs[37–54], including a total of 4,450 patients. The process of study selection is schematically depicted in the PRISMA flowchart (Suppl. Figure 1, Appendix 1).

### 3.2. Included studies

The methodological characteristics of the included studies are described in Table 1. All RCTs were double-blinded, while 3 of them were crossover and 15 were parallel ones. The main indication for treatment initiation was essential hypertension combined with dyslipidemia. Three studies focused on patients with insulin resistance and 1 on those with diabetes mellitus. The main reasons for exclusion were severe uncontrolled or secondary hypertension, severe dyslipidemia and serious comorbidities, such as severe heart, liver or kidney failure and recent major cardiovascular events (Suppl. Table 2, Appendix 2). Regarding statin type, rosuvastatin was administered in 11 studies, atorvastatin in 4 studies, simvastatin in 2 studies and pravastatin in 1 study. The evaluated calcium channel blockers included amlodipine (7 studies) and manidipine (1 study), while ramipril was the only angiotensin-converting enzyme inhibitor examined (1 study). Angiotensin receptor blockers were assessed in 11 studies and consisted of losartan, telmisartan, olmesartan, irbesartan, valsartan, candesartan and fimasartan. The main baseline patients' characteristics in each treatment arm are presented in Suppl. Table 3 (Appendix 2).

The majority of parallel studies were judged to be at low risk of bias; some concerns of deviations from the intended interventions were raised in 2 studies that implemented an open-label, blinded endpoint design. No concerns were raised in the domains of randomization, missing data, measurement and selection of outcomes (Suppl. Figure 2, Appendix 3). Concerning crossover studies, some concerns were assigned in the domain

of period and carryover effects since it was unclear whether the wash-out periods were effective at minimizing any carryover effects. No concerns were assigned in the remaining domains (Suppl. Figure 3, Appendix 3).

### 3.3. Primary outcomes

The available treatment combinations for the primary outcomes are schematically depicted in a Sankey diagram (Figure 1a) and the available direct comparisons are illustrated in the network plot (Figure 1b).

#### 3.3.1. LDL-C

The relative efficacy of interventions at reducing serum LDL-C levels is presented in a league table (Suppl. Table 4, Appendix 4). Compared to statin monotherapy at the AEDs of 10, 20, 40 and 80 mg, no significant difference in the percentage change of LDL-C was achieved by adding any antihypertensive agent. The credibility of evidence ranged from moderate to very low (Figure 2). Ranking of interventions indicated the combination of AED 40 mg with olmesartan 40 mg as the best treatment (P-score: 0.90), followed by the combination of AED 80 mg with irbesartan 300 mg (P-score: 0.86) and that of AED 40 mg with irbesartan 300 mg (P-score: 0.81). The comparison-adjusted funnel plot indicated no significant asymmetry (Egger's *p-value*: 0.433, Thompson-Sharp *p-value*: 0.261) (Suppl. Figure 4, Appendix 4).

#### 3.3.2. SBP

The relative effects on the percentage SBP change of all interventions are presented in the league table (Suppl. Table 5, Appendix 5). Compared to monotherapy with amlodipine 5 mg, the addition of AED 20 mg resulted in a significantly greater percentage reduction of SBP (MD: -2.2%, 95% CI: -3.82 to -0.62, moderate quality of evidence). No significant change of SBP was noted by the addition of statin regarding the remaining comparisons. The quality of evidence ranged from high to moderate for the majority of comparisons (Figure 3). Ranking of treatments demonstrated that the best intervention was AED 40 mg combined with amlodipine 5 mg and losartan 100 mg (P-score: 0.97), followed by telmisartan 80 mg with amlodipine 10 mg (P-score: 0.96) and the combination of AED 40 mg, telmisartan 80 mg and amlodipine 10 mg (P-score: 0.93). Inspection of the

comparison-adjusted funnel plot indicated no significant asymmetry (Egger's *p-value*: 0.555, Thompson-Sharp *p-value*: 0.318) (Suppl. Figure 5, Appendix 5).

### 3.3.3. Multi-objective evaluation

The relationship of LDL-C and SBP P-scores is illustrated in a scatterplot (Figure 4). The Pareto front indicated 3 potential interventions as optimum solutions: AED 40 mg with olmesartan 40 mg (P-score$_{SBP}$: 0.88, P-score$_{LDL-C}$: 0.90), AED 40 mg with amlodipine 10 mg and telmisartan 80 mg (P-score$_{SBP}$: 0.93, P-score$_{LDL-C}$: 0.72) and AED 40 mg with amlodipine 5 mg and losartan 100 mg (P-score$_{SBP}$: 0.97, P-score$_{LDL-C}$: 0.61). Among them, the combination of AED 40 mg and olmesartan 40 mg demonstrated the lowest distance from the ideal point ($d$ = 0.09).

### 3.3.4. Transitivity and consistency assessment

Comparison of the distributions of age, sex, BMI, baseline LDL-C and SBP among interventions indicated no significant differences, suggesting no threats to the transitivity assumption (Suppl. Figure 6-10, Appendix 6). Regarding the outcome of LDL-C, the design-by-treatment interaction test indicated no significant global inconsistency (Q: 31.55, *p-value*: 1). The SIDE test showed no significant difference between direct and indirect evidence in most (92.7%) comparisons with mixed evidence available (Suppl. Table 6, Appendix 7). Similarly, no significant global inconsistency was calculated for the SBP outcome (Q: 9.84, *p-value*: 1). According to the SIDE test, no significant difference of direct and indirect evidence was noted in the vast majority (98.2%) of comparisons with mixed evidence available (Suppl. Table 7, Appendix 7).

### 3.3.5. Credibility of evidence

Evaluation of the quality of evidence regarding the outcome of LDL-C change raised no major concerns of within-study bias, reporting bias and indirectness. Major concerns were assigned in the domain of incoherence in 1% of comparisons due to disagreement of direct and indirect evidence. The main reason for downgrading was imprecision in comparisons with estimated confidence intervals extending into the range of equivalence. Major concerns of heterogeneity were raised in 3.6% of comparisons due to discrepancy of 95% confidence and prediction intervals in relation to the range of equivalence.

Correspondingly, no major concerns of within-study bias, reporting bias, indirectness and incoherence were raised in comparisons of SBP change. Major concerns of imprecision and heterogeneity were assigned in a minority of comparisons (6.6% and 1.2%, respectively) (Suppl. Figure 11-12, Appendix 8).

### 3.4. Secondary outcomes

#### 3.4.1. HDL-C

The network plot depicting the direct comparisons of HDL-C change is presented in Suppl. Figure 13 (Appendix 9). The combination of high-intensity statin and amlodipine was associated with a significantly greater percentage increase of HDL-C compared to both moderate-intensity statin monotherapy (MD: 9.74%, 95% CI: 0.83 to 18.66) and high-intensity statin monotherapy (MD: 8.34%, 95% CI: 0.73 to 15.95) (Suppl. Figures 14-15, Appendix 9). Therefore, the combination of high-intensity statin and amlodipine ranked as the best treatment (P-score: 0.90), followed by high-intensity statin with telmisartan and amlodipine (P-score: 0.84), moderate-intensity statin with losartan (P-score: 0.83), high-intensity statin with telmisartan (P-score: 0.75) and moderate-intensity statin with olmesartan (P-score: 0.71).

#### 3.4.2. Triglycerides

The direct comparisons of triglyceride change are displayed in Suppl. Figure 16 (Appendix 9). Compared to moderate-intensity statin monotherapy, significantly greater triglyceride reduction was achieved by the combination of high-intensity statin with amlodipine (MD: -16.30%, 95% CI: -29.77 to -2.83), telmisartan (MD: -19.36%, 95% CI: -33.41 to -5.30) and both antihypertensive agents (MD: -22.38%, 95% CI: -38.75 to -6.01). Compared to high-intensity statin monotherapy, a greater decrease of triglyceride levels was estimated when a high-intensity statin was combined with either telmisartan (MD: -11.66%, 95% CI: -22.60 to -0.72) or telmisartan and amlodipine concomitantly (MD: -14.68%, 95% CI: -28.48 to -0.89) (Suppl. Figures 17-18, Appendix 9). As a result, the treatments ranking highest were the following: high-intensity statin with telmisartan and amlodipine (P-score: 0.94), high-intensity statin with telmisartan (P-score: 0.90),

moderate-intensity statin with olmesartan (P-score: 0.85) and high-intensity statin with amlodipine (P-score: 0.84).

### 3.4.3. LDL-C and SBP goals

The definitions of LDL-C and SBP goals are described in Suppl. Table 8 (Appendix 9). LDL-C goals followed the National Cholesterol Education Program Adult Treatment Panel III guidelines. The response of SBP was mainly detected using the Joint National Committee on Prevention, Detection, and Treatment of High Blood Pressure guidelines. No significant difference was observed between combination treatment and statin monotherapy regarding the attainment of LDL-C goal (OR: 0.96, 95% CI: 0.55 to 1.68) (Suppl Figure 19, Appendix 9). One-stage meta-analysis indicated a similar non-significant outcome (OR: 1.19, 95% CI: 0.60 to 2.98). Moreover, the achievement rate of SBP goal did not differ significantly between the combination and the antihypertensive agent monotherapy groups (OR: 1.08, 95% CI: 0.84 to 1.39) (Suppl Figure 20, Appendix 9). Sensitivity analysis with the one-stage meta-analysis model indicated a similar result (OR: 1.06, 95% CI: 0.83 to 1.46).

### 3.4.5. Adverse effects

The rate of any TAE did not differ significantly in combination treatment when compared to both statin (OR: 0.86, 95% CI: 0.42 to 1.74) and antihypertensive (OR: 1.13, 95% CI: 0.70 to 1.84) monotherapy (Suppl. Figures 21-22, Appendix 9). One-stage meta-analysis resulted in similar outcomes (OR: 0.79, 95% CI: 0.35 to 1.59 and OR: 0.90, 95% CI: 0.41 to 1.72, respectively). No significantly different risk of severe adverse effects was estimated for patients receiving combination therapy in comparison with those receiving statin (OR: 1.23, 95% CI: 0.51 to 2.99) or antihypertensive (OR: 0.96, 95% CI: 0.41 to 2.27) monotherapy (Suppl. Figures 23-24, Appendix 9). One-stage meta-analysis demonstrated no significant differences between the compared groups (OR: 1.54, 95% CI: 0.50 to 4.76 and OR: 0.94, 95% CI: 0.05 to 2.59).

## 4. Discussion

### 4.1. Summary of findings

The present network meta-analysis indicated that combination treatment resulted in comparable effects on LDL-C and SBP change with statin and antihypertensive agent monotherapy, respectively. Specifically, the concurrent administration of antihypertensive drugs and statins did not lead to a significantly greater reduction of LDL-C, compared to statin therapy alone. Regarding SBP reduction, only the combination of amlodipine 5 mg with statin (AED: 20mg) resulted in significantly greater SBP percentage change compared to antihypertensive monotherapy. The multi-objective evaluation demonstrated three treatments (statin with olmesartan, amlodipine/telmisartan and amlodipine/losartan) as optimal ones; however, the quality of evidence regarding LDL-C reduction was assessed to be low. In addition, the addition of antihypertensive agents on statin therapy did not alter the rate of treatment goal attainment and vice versa. Concerning HDL-C levels, a significantly greater percentage increase was achieved by the combination of high-intensity statin and amlodipine in comparison with statin monotherapy. Correspondingly, the percentage decrease of serum triglycerides was more prominent in patients receiving combined therapy with statin and amlodipine or telmisartan. The rate of treatment-emergent adverse effects or serious ones was similar in individuals treated with combined therapy, statin or antihypertensive agent alone.

Poor adherence to blood pressure and lipid-lowering treatment represents an important barrier to primary and secondary prevention since it has been linked to elevated risk of both cardiovascular[55] and cerebrovascular[56] events. Interestingly, low adherence to antihypertensive agents before statin initiation has been to shown to predict future discontinuation of the latter[57]. Fixed-dose drug combinations have been proposed as a therapeutic option with lower complexity, decreased cost and higher adherence. In this direction, the UMPIRE trial has demonstrated that a fixed-dose combination strategy with aspirin, statin and antihypertensive agents was linked to significantly higher medication adherence, as well as to improvements in serum LDL-C and SBP[58]. Similarly, the pragmatic randomized Polyran study has indicated that a polypill strategy was effective in reducing major cardiovascular events, without increasing the risk of toxicity[59]. The

beneficial effects of the polypill approach have been consistently reported when socioeconomically vulnerable populations were studied[60]. Importantly, the increased adherence to a single-pill combination of atorvastatin/amlodipine has been confirmed by real-world studies using prescription refill rates[61,62]. On the other hand, it should be noted that the widespread use of polypills may present a variety of risks due to the lack of individualized therapy, difficulty of dose titration and inability to identify specific drug-related adverse effects[63].

Combining statins and antihypertensive agents may raise concerns about potential interactions due to their common metabolism through the cytochrome P450. This especially applies to the combination of dihydropyridine calcium channel blockers with simvastatin, lovastatin or atorvastatin since they are substrates of CYP3A4[64]; hence, simvastatin dose has been recommended to not exceed 20 mg when combined with amlodipine, aiming to reduce the risk of myopathy[65]. In contrast, rosuvastatin undergoes minimal cytochrome metabolism and thus presents limited interactions with P450 inhibitors[66]. As a result, pharmacokinetic studies have shown that the combination of rosuvastatin and amlodipine with[67,68] or without angiotensin-receptor blockers is safe and well-tolerated[69]. It should be also noted that although angiotensin-receptor blockers are suggested to present few pharmacokinetic interactions with statins, the coadministration of fimasartan and atorvastatin has been found to increase the peak concentration of both drugs; however, the clinical significance of this interaction remains unclear[70].

From a pharmacodynamic point of view, experimental evidence has suggested that the coadministration of amlodipine and statins may result in beneficial synergistic effects[71]. More specifically, it has been proposed that the combined therapy may enhance nitric oxide bioavailability[72], improve vascular compliance[73], decrease markers of inflammation and reverse left ventricular hypertrophy[74]. On the other hand, the potential synergy of statins with angiotensin receptor blockers has been strengthened by animal studies demonstrating protective effects against atherosclerosis imitation and progression[75]. Conversely, statins have been shown to interact directly with the renin-

angiotensin-aldosterone system, mainly by reducing the synthesis of angiotensin II and downregulating the expression of angiotensin receptors[76].

It should be noted that 12 of the 18 studies of the meta-analysis were conducted in South Korea, accounting for 37.7% of the included patients. It has been established that significant differences exist in the prevalence, clinical presentation, risk factors and genetic mechanisms among different races regarding both hypertension and dyslipidemia. Response to pharmacotherapy may also differ according to ethnicity as calcium channel blockers and thiazide-type diuretics may exert significant benefits in black patients while Asians may be more prone to dry cough by the use of angiotensin converting enzyme inhibitors[77]. Correspondingly, the lipid-lowering effects of statins may differ among ethnicities, with Asians demanding generally lower doses[78]. In addition, remarkable inter-racial variability exists in drug pharmacokinetics since Asians and Caucasians tend to present different patterns of drug absorption, distribution and metabolism due to genetic polymorphisms of several enzymes, such as CYP2D6 and CYP2C[79]. As a result, further research is warranted to shed more light on the potentially differential interaction of statins with antihypertensive agents among patients of different ethnic groups.

### 4.2. Strengths and limitations of the study

The present network meta-analysis accumulated current literature knowledge about the comparative effects of statin and antihypertensive agent combinations of different doses, by exploiting both direct and indirect evidence. Strict selection criteria were applied to promote homogeneity, while only RCTs were included aiming to minimize the risk of bias. A multi-objective analysis was applied to enable the simultaneous evaluation of the intervention effects on LDL-C and SBP. The credibility of outcomes was appraised following the CINeMA method, allowing a realistic evaluation of existing evidence. On the other hand, the follow-up period of the included trials was relatively short, ranging from 8 to 12 weeks; therefore, the long-term effects of interventions remain unclear. Furthermore, statins were grouped together according to their dose and intensity in order to enable the construction of connected networks; hence, potential inter-statin differences could not be assessed. It should be also noted that data regarding secondary outcomes

were comparatively limited and thus the potential effects of antihypertensive agent dosing were taken into account.

### 4.3. Implications for current clinical practice and future research

This meta-analysis indicates that combining statins with antihypertensive agents in fixed-dose combinations does not hinder their blood pressure or lipid-lowering effects. Potential evidence of synergy was suggested for statins and amlodipine since greater improvement of blood pressure, HDL-C and triglycerides was achieved compared to monotherapy. The present outcomes supported also the benefits of triple combinations, especially those of statins with amlodipine and an angiotensin receptor blocker. Future research is needed in large scale to confirm the long-term effects of fixed-dose combinations on blood pressure and serum lipids, as well as to evaluate the impact of different dosing strategies on hard outcomes, such as major cardiovascular and cerebrovascular events. Moreover, studies aiming to assess the potential antihypertensive properties of statin should take into account dietary parameters since unrestricted salt intake has been shown to blunt their blood pressure-lowering effects[80]. It is also important to examine the efficacy and safety of alternative combination therapies; in this direction, the outcomes of the NCT04659070 trial[81] are awaited to shed light on the value of adding ezetimibe to the rosuvastatin-telmisartan combination.

## 5. Conclusions

The present network meta-analysis suggested that the administration of fixed-dose combinations of statins and antihypertensive agents in patients with dyslipidemia and uncontrolled hypertension is effective in reducing blood pressure and serum low-density lipoprotein cholesterol, without increasing the risk of adverse effects. The coadministration of statins and amlodipine with or without angiotensin receptor blockers was linked to statistically significant but clinically modest additive effects. The optimal dosing strategy that would maximize the cardiovascular benefits of statins and antihypertensive drugs remains to be determined in future randomized controlled trials.

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## Table captions

**Table 1.** Methodological characteristics of the included studies.

## Figure legends

**Figure 1.** (A) Sankey diagram of the combinations of treatments for the primary outcomes. (B) Network plot depicting the direct comparisons of interventions for the primary outcomes. The thickness of lines is proportional to the number of studies comparing the connected treatments. *CCB: calcium channel blocker; ARB: angiotensin receptor blocker; ACEi: angiotensin converting enzyme inhibitor; AED: atorvastatin equivalent dose*

**Figure 2.** Forest plot of the percentage change of low-density lipoprotein cholesterol. Mean difference expresses the comparison of statin and antihypertensive agent combination treatment with statin monotherapy. *AED: atorvastatin equivalent dose; MD: mean difference; CI: confidence intervals*

**Figure 3.** Forest plot of the percentage change of systolic blood pressure. Mean difference expresses the comparison of statin and antihypertensive agent combination with the antihypertensive agent alone. *AED: atorvastatin equivalent dose; MD: mean difference; CI: confidence intervals*

**Figure 4.** Heatmap of interventions showing the association of their P-scores for the outcome of low-density lipoprotein cholesterol and systolic blood pressure. Interventions are colored depending on their distance (*d*) from the optimal point. The Pareto front indicated the 3 highlighted treatments as optimal solutions. *LDL-C: low-density lipoprotein cholesterol; SBP: systolic blood pressure*

| Year; Author | Country | Sample size | Design | Population | Interventions | Outcome assessment | Risk of bias |
|---|---|---|---|---|---|---|---|
| 2004; Fogari | Italy | 45 | Double-blind, crossover | Hypertension, dyslipidemia & insulin resistance | Atorvastatin 20 mg, Amlodipine 5 mg, combination therapy | 12 weeks | Moderate |
| 2005; Koh | South Korea | 50 | Double-blind, crossover | Dyslipidemia & diabetes mellitus | Simvastatin 20 mg, Ramipril 10 mg, combination therapy | 8 weeks | Low |
| 2006; Messerli | USA-Canada | 816 | Double-blind, parallel | Hypertension & dyslipidemia | Atorvastatin 10 mg, Amlodipine 5 mg, combination therapy, placebo | 8 weeks | Low |
| 2007; Han | South Korea | 47 | Double-blind, crossover | Hypertension & dyslipidemia | Simvastatin 20 mg, Losartan 100 mg, combination therapy | 8 weeks | Low |
| 2007; Preston | Multinational | 1660 | Double-blind, parallel | Hypertension & dyslipidemia | Atorvastatin 10/20/40/80 mg, Amlodipine 5/10 mg, combination therapies | 8 weeks | Low |
| 2008; Divchev | Germany | 60 | Double-blind, parallel | Hypertension & coronary artery disease | Pravastatin 40 mg, Pravastatin 40 mg + Irbesartan 300 mg | 12 weeks | Low |
| 2010; Rizos | Greece | 151 | Open-label, parallel | Hypertension, dyslipidemia & insulin resistance | Rosuvastatin 10 mg + Telmisartan 80 mg, Rosuvastatin 10 mg + Irbesartan 300 mg, Rosuvastatin 10 mg + Olmesartan 20 mg | 12 weeks | Moderate |
| 2012; Liberopoulos | Greece | 40 | Open-label, parallel | Hypertension, dyslipidemia & insulin resistance | Rosuvastatin 10 mg + Olmesartan 20 mg, Rosuvastatin 10 mg + Manidipine 20 mg | 12 weeks | Moderate |
| 2015; Jang | South Korea | 123 | Double-blind, parallel | Hypertension & dyslipidemia | Rosuvastatin 20 mg, Valsartan 160 mg, combination therapy | 8 weeks | Low |
| 2016; Kim | South Korea | 223 | Double-blind, parallel | Hypertension & dyslipidemia | Atorvastatin 40/80 mg, Irbesartan 300 mg, combination therapy, placebo | 8 weeks | Low |
| 2016; Park | South Korea | 162 | Double-blind, parallel | Hypertension & dyslipidemia | Rosuvastatin 20 mg, Olmesartan 40 mg, combination therapy, placebo | 8 weeks | Low |
| 2017; Lee | South Korea | 143 | Double-blind, parallel | Hypertension & dyslipidemia | Rosuvastatin 20 mg + Losartan 100 mg, Amlodipine 5 mg + Losartan 100 mg, triple combination therapy | 8 weeks | Low |
| 2017; Rhee | South Korea | 135 | Double-blind, parallel | Hypertension & dyslipidemia | Rosuvastatin 20 mg, Fimasartan 120 mg, combination therapy | 8 weeks | Low |
| 2018; Oh | South Korea | 203 | Double-blind, parallel | Hypertension & dyslipidemia | Rosuvastatin 20 mg, Telmisartan 80 mg, combination therapy, placebo | 8 weeks | Low |
| 2019; Cho | South Korea | 212 | Double-blind, parallel | Hypertension & dyslipidemia | Rosuvastatin 20 mg, Candesartan 32 mg, combination therapy | 8 weeks | Low |
| 2019; Hong | South Korea | 144 | Double-blind, parallel | Hypertension & dyslipidemia | Rosuvastatin 20 mg + Telmisartan 80 mg, Telmisartan 80 mg + Amlodipine 10 mg, triple combination therapy | 8 weeks | Low |
| 2019; Kim | South Korea | 132 | Double-blind, parallel | Hypertension & dyslipidemia | Rosuvastatin 20 mg + Telmisartan 80 mg, Telmisartan 80 mg + Amlodipine 10 mg, combination therapy | 8 weeks | Low |
| 2020; Kim | South Korea | 104 | Double-blind, parallel | Hypertension & dyslipidemia | Rosuvastatin 20 mg, Amlodipine 10 mg, combination therapy | 8 weeks | Low |

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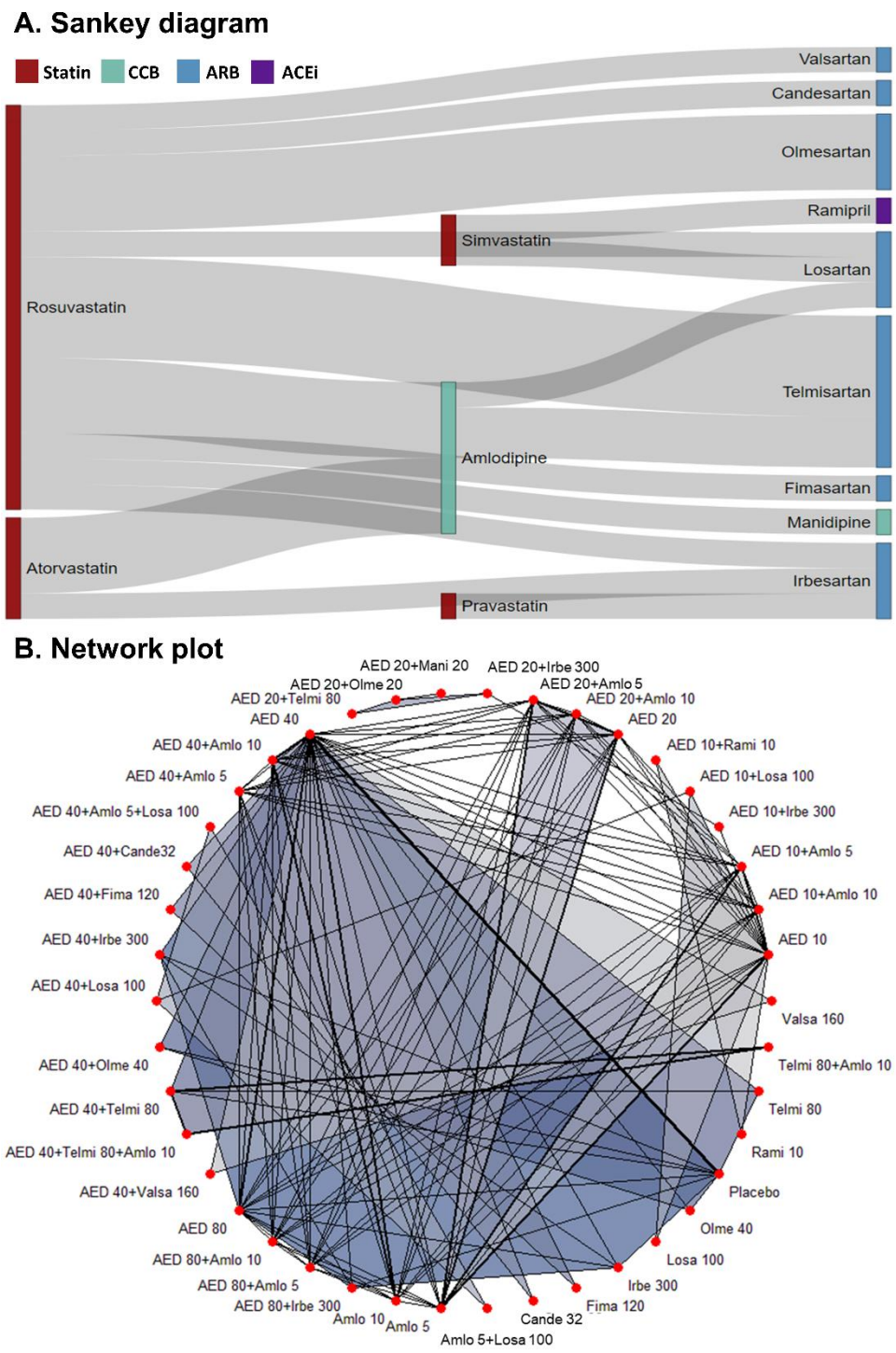


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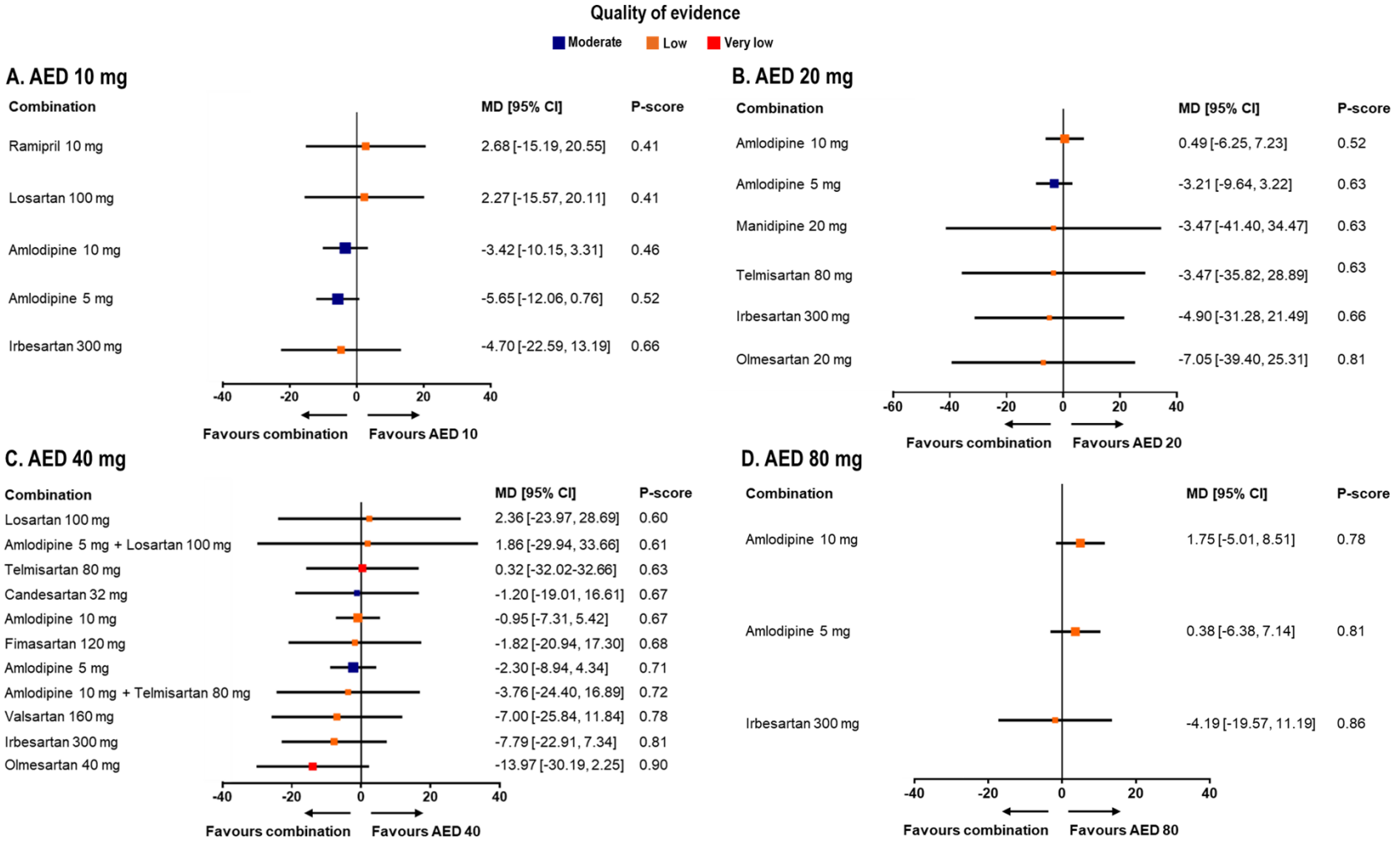


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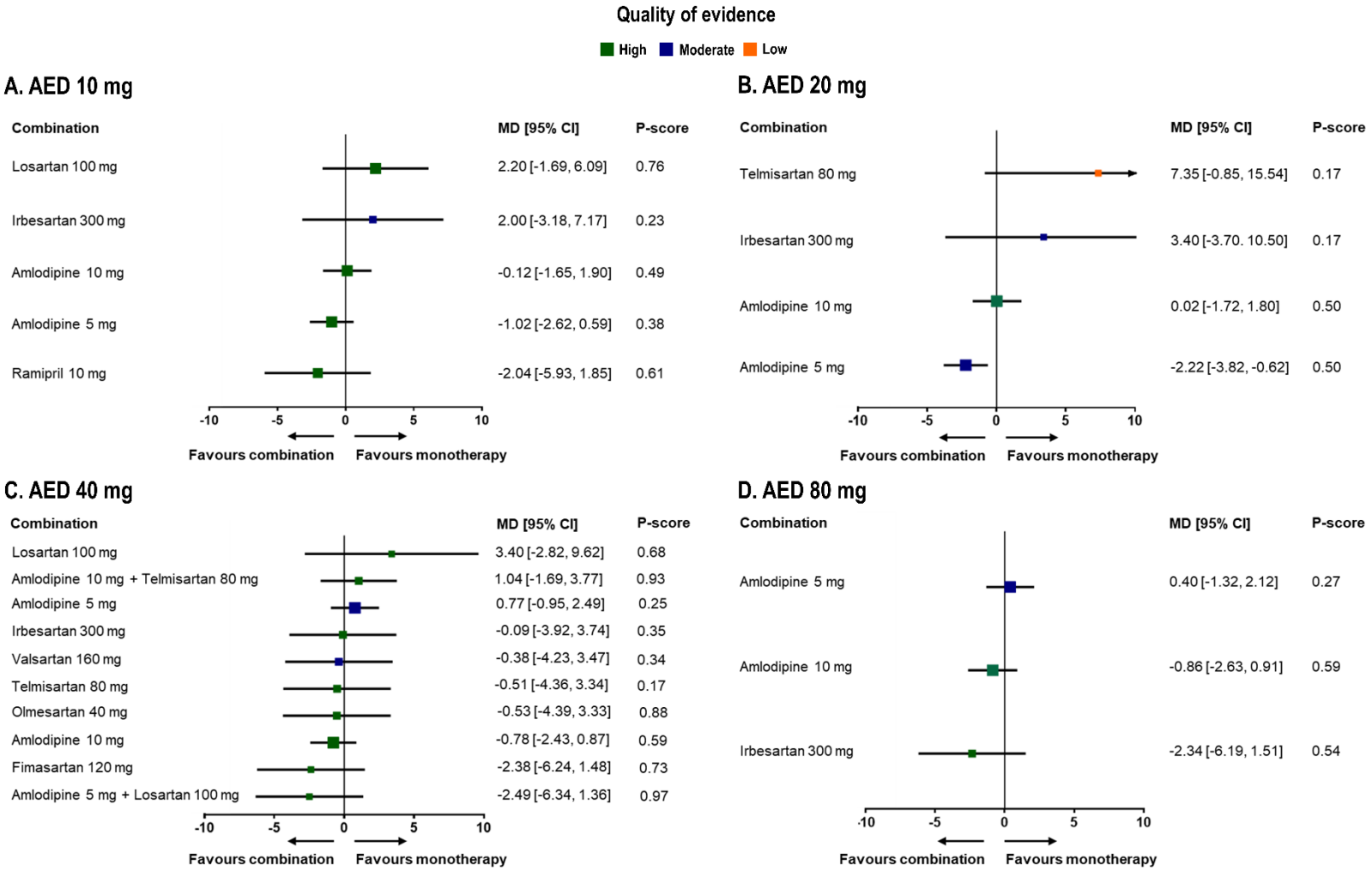


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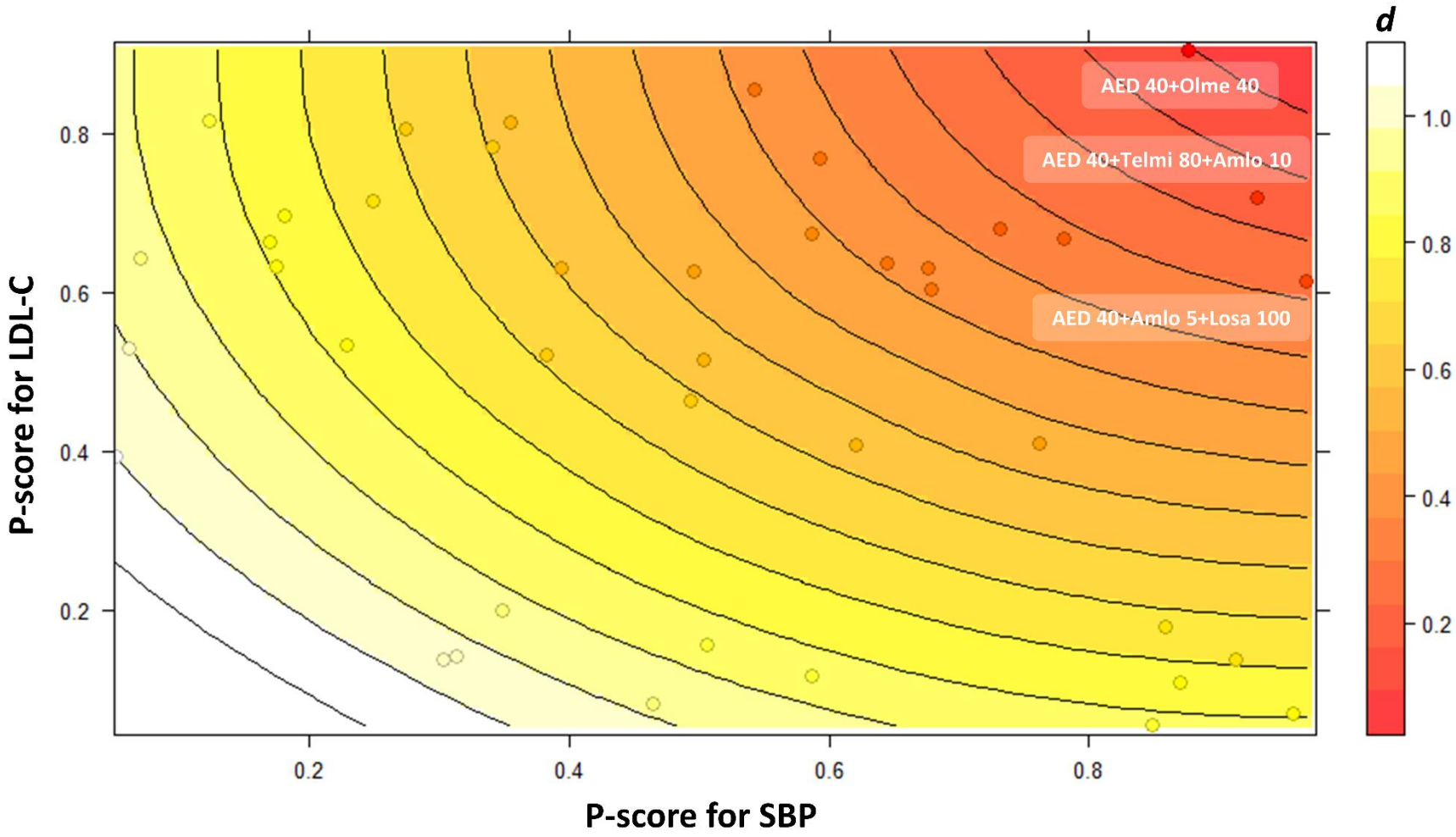


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