Original Article

Peripheral edema and headache associated with amlodipine treatment: a meta-analysis of randomized, placebo-controlled trials

Davor Vukadinović[a], Sean S. Scholz[a], Franz H. Messerli[b], Michael A. Weber[c], Bryan Williams[d], Michael Böhm[a], and Felix Mahfoud[a]

Objective: Use of amlodipine for treatment of arterial hypertension and stable coronary artery disease (CAD) is sometimes limited by occurrence of peripheral edema and headache. We aimed to explore the true magnitude of this phenomenon by determining the rate and placebo-adjusted rate of these side effects.

Methods: We performed a meta-analysis by including all randomized, placebo-controlled trials reporting edema and headache with amlodipine in patients with arterial hypertension and CAD. Placebo-adjusted rate (%) was determined as follows: (SE amlodipine % − SE placebo %)/ SE amlodipine %.

Results: Data from 7226 patients of 22 trials were analyzed. Rate of edema was higher on amlodipine vs. placebo (16.6 vs. 6.2%, risk ratio: 2.9, 95% CI: 2.50–3.36, $P < 0.0001$). The placebo-adjusted rate was 63%, indicating that 37% of edema cases were unrelated to amlodipine. Treatment with low/medium doses (2.5–5 mg) resulted in lower rates of edema (risk ratio: 2.01, 95% CI: 1.41–2.88, $P = 0.0001$) vs. high dose (10 mg) (risk ratio: 3.08, 95% CI 2.62–3.60, $P < 0.0001$, $P_{\text{for interaction}} = 0.03$). Incidence of headache was reduced using amlodipine vs. placebo (7.9 vs. 10.9%, risk ratio: 0.77, 95% CI: 0.65–0.90, $P = 0.002$) and was driven by use of low/medium doses (risk ratio: 0.52, 95% CI: 0.40–0.69, $P < 0.00001$ vs. risk ratio: 0.92, 95%-CI: 0.74–1.15, $P = 0.45$, for high doses, $P_{\text{for interaction}} = 0.002$).

Conclusion: Although risks of peripheral edema are three-fold higher on amlodipine, up to one-third of edema cases on amlodipine might not be induced by amlodipine. Headache is reduced on amlodipine treatment, mainly driven by use of this drug at low/medium doses.

Keywords: amlodipine, headache, meta-analysis, peripheral edema

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; AHA, American Heart Association; ARB, angiotensin receptor blocker; BP, blood pressure; CAD, coronary artery disease; CCB, calcium channel blocker; CI, confidence interval; CVD, cardiovascular disease; HCT, hydrochlorothiazide

INTRODUCTION

Calcium channel blocker (CCB) are recommended as part of first line therapy in the management of arterial hypertension [1] (class I, level of evidence A) and for angina relief in stable coronary artery disease (CAD) [2] (class I, level of evidence A). The use of amlodipine, the most commonly prescribed CCB [3], has been associated with reduced cardiovascular events in patients with normal blood pressure (BP) and CAD [4] and effectively reduced exercise-induced ischemia when used alone or in combination with beta-blockers [5,6]. In hypertensive patients, amlodipine provides greater protection against stroke and myocardial infarction, when compared with other antihypertensive drugs or placebo [7]. However, the use of amlodipine is occasionally limited by adverse side effects, such as peripheral edema and headache. Concerns about the occurrence of these side effects may deter physicians prescribing amlodipine in eligible patients despite proven benefits. In randomized, controlled clinical trials, side effects also occur on placebo treatment in a considerable number of patients. We, therefore, aimed to determine the placebo-adjusted rate of peripheral edema and headache in patients on amlodipine by conducting a comprehensive meta-analysis of randomized trials. Further, we studied whether there is a difference in the rate of placebo-adjusted edema and headache in different conditions and whether the side-effects are related to the prescribed dose of amlodipine and its inclusion in combination therapy.

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[a]Universitätsklinikum des Saarlandes, Klinik für Innere Medizin III, Homburg/Saar, Germany, [b]Department of Cardiology and Clinical Research, University Hospital, Inselspital, Freiburgstrasse, CH-3010 Bern, Switzerland, [c]State University of New York Downstate College of Medicine, Brooklyn, New York, USA and [d]Institute of Cardiovascular Science, University College London, London, UK

Correspondence to Davor Vukadinović, Universitätsklinikum des Saarlandes, Saarland University, Homburg/Saar, Klinik für Innere Medizin III, Kardiologie, Angiologie und Internistische Intensivmedizin, Kirrberger Strasse 1, IMED, D-66421 Homburg, Germany. Tel: +49 6841 16 15000; e-mail: Davor.Vukadinovic@uks.eu

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METHODS

Reporting and conducting of this meta-analysis was done following recommendations from PRISMA guidelines for meta-analysis [8] and a scientific statement from the American Heart Association (AHA) [9].

Study protocol

The analysis included randomized, placebo-controlled studies, which analyzed effects of amlodipine alone vs. placebo in patients with hypertension or coronary artery disease. These studies were required to report rates of edema and/or headache in both groups (amlodipine and placebo). The duration of follow-up had to be at least 4 weeks or longer. There was no limit for number of analyzed patients in potentially eligible studies. Studies evaluating the effects of amlodipine in patients with heart failure, or severe renal and hepatic disease were excluded. Furthermore, data from observational studies, registries, and case presentations evaluating the side effects were also not considered eligible for inclusion.

Data sources and search strategy

PUBMED, Cochrane library database, and Web of Science was searched for eligible articles published until July 2018, using the key terms 'amlodipine and edema or headache and randomized placebo blind/controlled trials' alone or in combination. We also checked the reference list from a previous published review addressing this issue [10].

Selection of studies and data abstraction

The results of the initial search were screened by two investigators (D.V. and S.S.S.) for inclusion by reviewing the title and abstract of the identified articles. Articles reporting results from randomized, placebo-controlled trials, which compared amlodipine with placebo (i.e. effect on BP reduction, relief of angina pectoris) in patients with hypertension or coronary artery disease, were reviewed. The decision to include studies in further analysis was made after consultation with a third investigator (F.M.). The following items were extracted from the studies: events of interest (peripheral edema and headache), study design, inclusion and exclusion criteria, comparators (amlodipine vs. placebo), doses of the drugs (low/medium 2.5–5 mg and high 10 mg), duration of follow-up, primary outcome, concomitant therapy, and effects on BP.

Assessment of study quality and publication bias

The quality of each included study was assessed independently by the investigators (D.V. and S.S.S.) using the Jadad score [11], as recommended by the AHA [9]. A score more than 3 is considered as high range of quality and 2 or less as low range of quality. We plotted the standard error of each trial against log risk ratio, obtaining thereby a Funnel plot. A potential presence of publication bias was assessed visually using a Funnel plot and formally using the Egger's regression asymmetry test. This was done only for main outcomes, peripheral edema and headache, between the amlodipine and placebo groups.

Statistical analysis

A meta-analysis of the summary data exploring the risk of peripheral edema and headache from the individual trials that investigated the effect of amlodipine treatment compared with placebo was performed. Differences in the occurrence of peripheral edema and headache among groups were determined and presented as risk ratios with corresponding 95% confidence intervals (CI) for each trial. Risk ratio was used as a measure of the relative risk. All assessments were based on intention-to-treat analysis. The data from each trial were pooled using fixed or random-effects models, as appropriate. Heterogeneity between the trials was assessed using Cochran's Q test and I^2 statistic. Relevant statistical heterogeneity was considered as Cochran's Q-test $P < 0.05$ and I^2 greater than 50%. In this case, we used a random-effects model. In the absence of relevant statistical heterogeneity between trials, we used the fixed-effects model to estimate combined risk ratios. Study-specific and summary risk ratios and corresponding 95% CIs together with the corresponding P-value were depicted in the Forest plots. The placebo-adjusted rate of edema/headache was calculated as the difference between the rates of side effect in patients on amlodipine and on placebo (Pla), divided by the total rate of side effect on amlodipine, as summarized in the equation: placebo-adjusted side effect on amlodipine = (side effect on amlodipine – side effect on placebo)/side effect on amlodipine. This exploratory analysis was based on the assumption that incidence of side effect on placebo represents a spontaneous rate of specific side effect in this population.

Additional subgroup analyses were performed to explore a possible moderator effect of some items on the final results. We computed the P for interaction [12] regarding effect size (risk ratios) of edema and headache between studies in the following settings: amlodipine as monotherapy vs. amlodipine in combination with an ACE-I/ARB, low/medium vs. high doses of amlodipine, patients with arterial hypertension vs. coronary artery disease. t-test was used to compare means of SBP of the two groups as appropriate. We related the prevalence of edema in low/medium-dose and high-dose subgroups with the respective mean reduction of SBP by computing the risk (% edema)/benefit (each 5-mmHg reduction of SBP) ratio in patients with hypertension. All statistical analyses were conducted by using StatsDirect version 3.0.150, RevMan 5.3. and comprehensive meta-analysis software (CMA). All P values were two-sided, with P less than 0.05 considered as significant.

RESULTS

The study selection strategy is presented in a flow diagram (Supplementary Figure S1, http://links.lww.com/HJH/B106). The initial search identified 510 articles. The medical terms used for search performance are depicted in Supplementary Table S1, http://links.lww.com/HJH/B106. After manual review of the titles and abstracts, 430 articles were excluded. The main reasons for exclusion were that amlodipine was not the objective or primary objective of the investigation, lack of randomization, and the use of amlodipine in other clinical settings. From the remaining 80 full-text reviewed trials, 58 did not meet the inclusion criteria

TABLE 1. Patient's characteristics of the included studies

Study	*N*	Comparators (*n*)	Inclusion criteria baseline characteristics	Primary outcome	Follow-up	Additional therapy
Schoeller *et al.*, 2012	47	Amlodipine[a] 10 mg (24) vs. placebo (23)	Randomized, double-blind, placebo-controlled with hypertensive (37) and nonhypertensive (10) individuals, 50–75 years, SBP 120–180 mmHg and DBP 80–110 mmHg	Evaluation of the efficacy of various methodologies for measuring pedal edema	6 weeks	No, with washout period of previous drugs
Dingemanse *et al.*, 2015	107	ACT-280778 (52) vs. amlodipine[a] (54) 10 mg vs. placebo (53)	Randomized, double-blind, placebo-controlled, 18–75 years, mild-to moderate hypertension, DBP 95–104 mmHg	Change in blood pressure	>4 weeks	No, untreated hypertension
Frishman *et al.*, 1994	82	Amlodipine[a] (41) 2.5–10 mg vs. atenolol (43) vs. placebo (41)	Randomized, double-blind, placebo-controlled, 18–75 years, essential hypertension, DBP 95–114 mmHg	Change in blood pressure	8 weeks	No, untreated hypertension
Webster *et al.*, 1987	30	Amlodipine[a] (15) 2.5–10 mg vs. placebo (15)	Randomized, double-blind, placebo-controlled, mild-to moderate hypertension, diastolic 95–114 mmHg, without antihypertensive therapy	Change in blood pressure	8 weeks	No, with washout period of previous drugs
Maclean 1994	58	Amlodipine[a] (29) 10 mg /captopril vs. placebo/captopril (29)	Randomized, double-blind, placebo-controlled, crossover design, 18–65 years, patients with uncontrolled hypertension (diastolic 100–119 mmHg) after 4 weeks on captopril	Change in blood pressure	8 weeks	No
Philipp *et al.*, 2007	797	Amlodipine[a] (460) 2.5–10 mg vs. amlodipine/valsartan (921) vs. placebo (337)	Randomized, double-blind, placebo-controlled, >18 years, with mild-to-moderate hypertension, DBP 95–110 mmHg	Change in blood pressure	8 weeks	No, with washout period of previous drugs
Kuschnir *et al.*, 1996	154	Amlodipine 5mg/benazepril (77) vs. benazepril (77) vs. amlodipine 5 mg (77) vs. placebo (77)	Randomized, double-blind, placebo-controlled, 21–80 years, essential hypertension, DBP 100–120 mmHg	Change in blood pressure	8 weeks	No, with washout period of previous drugs
Jordan *et al.*, 2007	248	Aliskiren/HCT vs. irbesartan/HCT vs. amlodipine/HCT 5–10 mg (126) vs. HCT (122)	Randomized, double-blind, placebo-controlled, obese patients without response to HCT, DBP 90–110 mmHg	Change in blood pressure	8 weeks	No, with washout period of previous drugs
Johnson *et al.*, 1992	82	Amlodipine[a] 2.5–10 mg (41) vs. atenolol (43) vs. placebo (41)	Randomized, double-blind, placebo-controlled, 18–75 years, essential hypertension, DBP 95–114 mmHg,	Change in blood pressure	8 weeks	No
Pool *et al.*, 2001	225	Amlodipine[a] 5 mg (110) vs. benazepril (116) vs. amlodipine 5mg/benazepril (110) vs. placebo (115)	Randomized, double-blind, placebo-controlled, 21–80 years, in outpatient settings, essential hypertension, DBP 100–115 mmHg	Change in blood pressure	8 weeks	No, with washout period of previous drugs
Frishman *et al.*, 1995	164	Amlodipine[a] 2.5 mg (82) vs. amlodipine 2.5/benazepril (83) vs. benazepril (85) vs. placebo (82)	Randomized, double-blind, placebo-controlled, 21–80 years, mild-to-moderate hypertension, DBP 100–115 mmHg	Change in blood pressure	8 weeks	No, with washout period of previous drugs
Glasser *et al.*, 1989	103	Amlodipine 2.5–10 mg (52) vs. placebo (51)	Randomized, double-blind, placebo-controlled, 18–75 years, all added on HCT, DBP 95–114 mmHg	Change in blood pressure	16 weeks	All patients on HCT
Chrysant *et al.*, 2008	486	Amlodipine 5–10 mg (324) vs. amlodipine/olmesartan (970) vs. olmesartan (484) vs. placebo (162)	Randomized, double-blind, placebo-controlled, >18 years, DBP 95–120 mmHg	Change in blood pressure	8 weeks	No, with washout period of previous drugs
London *et al.*, 2006	883	Amlodipine[a] 5 mg (444) vs. placebo (439) vs. indapamide (440) vs. candesartan (435)	Randomized, double-blind, placebo-controlled, 40–80 years, SBP 150–180 mmHg, DBP 95–110 mmHg	Change in blood pressure	12 weeks	Other drugs for treatment of BP were not allowed
Littlejohn *et al.*, 2009	256	Amlodipine[a] 2.5–10 mg (221) vs. placebo (35) vs. amlodipine/ telmisartan (590) vs. telmisartan (226)	Randomized, double-blind, placebo-controlled, patients with mild- to moderate hypertension, >18 years, DBP 95–119 mmHg	Change in blood pressure	8 weeks	Discontinuation of other BP lowering drugs
Mehta *et al.*, 1993	210	Amlodipine[a] 1.25–10 mg (170) vs. placebo (40)	Randomized, double-blind, placebo-controlled, 18–75 years, DBP 95–114 mmHg	Efficacy of amlodipine regarding lowering BP	4 weeks	No
Chrysant *et al.*, 2003	252	Amlodipine[a] 5 mg (186) vs. placebo (66) vs. olmesartan (188)	Patients with mild-to-moderate hypertension DBP 100–115 mmHg	Change in blood pressure	8 weeks	Discontinuation of other BP lowering drugs
Messerli *et al.*, 2006	647	Amlodipine[a] 5 mg (201) vs. amlodipine/atorvastatin (207) vs. atorvastatin (200) vs. placebo (239)	Patients with concomitant arterial hypertension and dyslipidemia and varying degree of CVD risk, 18–75 years, AE evaluated after 8 weeks of double-blind period	Efficacy and safety of coadministered amlodipine and atorvastatin on CVD	28 weeks	Previously wash out period
Ezekowitz *et al.*, 1995	101	Amlodipine[a] 5–10 mg vs. placebo	Chronic stable angina pectoris on effort, double-blind crossover design with two parallel, balanced groups	Efficacy in term of exercise capacity	8 weeks	No, with washout period of antianginal drugs
Chahine *et al.*, 1993	52	Amlodipine[a] 10 mg (24) vs. placebo (28)	Randomized, double-blind, placebo-controlled, normotensive patients with stable angina pectoris due vasospastic angina with angiographically normal coronary arteries	Assessment of efficacy and safety of amlodipine once daily in treatment of vasospastic angina	4 weeks	Only nitroglycerin sublingual was allowed
Pitt *et al.*, 2000	825	Amlodipine[a] 5–10 mg (417) vs. placebo (408)	Randomized, double-blind, placebo-controlled, patients with angiographic coronary stenosis ≤30%, 30–80 years, DBP <95 mmHg	Impact on slowing of the 3-year progression of early coronary atherosclerotic disease	36 Months	Yes (ACEi 8–10%, BB-60%, nitrates 60%, diuretic 10%)
Nissen *et al.*, 2004	1318	Amlodipine[a] 10 mg (663) vs. enalapril 20 mg (673) vs. placebo (655)	Randomized, double-blind, placebo-controlled, 30–79 years, DBP<100 mmHg, angiographic coronary lesion with stenosis >20%	Incidence of adverse CVD events	24 months	Yes (BB 74–78%, ACEi/ARB 7–12%, diuretic 30%)

ACEi, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; BB, betablocker; BP, blood pressure; CVD, cardiovascular disease; HCT, hydrochlorothiazide; *n*, number of patients analyzed in original trial; *N*, number of patients included in present meta-analysis.
[a]Once daily.

and were excluded. Twenty-two randomized, placebo-controlled trials, where the rate of peripheral edema was adequately reported, met the inclusion criteria and entered the final analysis [4,13–33]. Headache, as a side-effect, was adequately reported in 18 of the included studies, four did not provide information on headache [4,13,24,29]. Baseline patient's characteristics from the included studies are summarized in Table 1.

Peripheral edema

A total of 4069 patients on amlodipine and 3157 on placebo from 22 trials were included, whose data on rate of

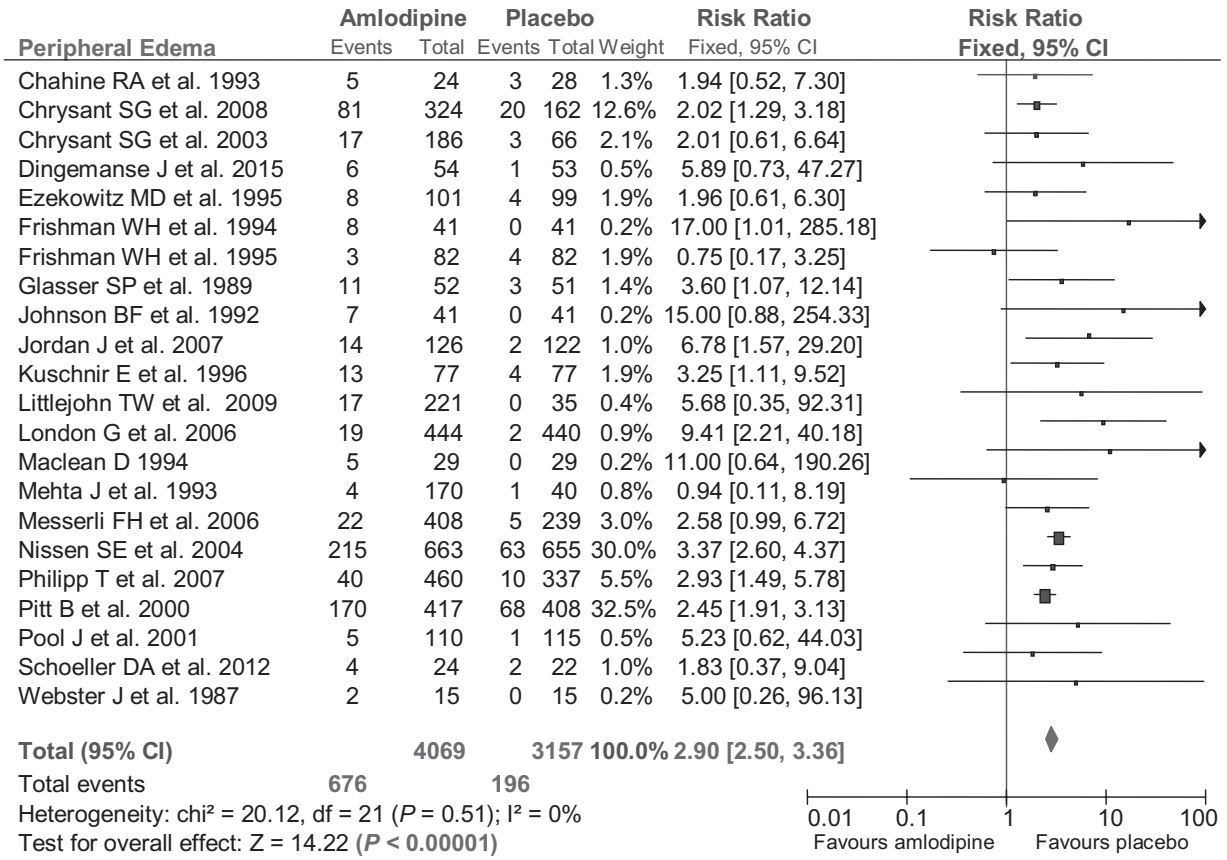

FIGURE 1 Forest plot presenting the risk ratio for peripheral edema.

peripheral edema were pooled for further analysis (Fig. 1). Peripheral edema was reported in 676 of 4069 (16.6%) patients on amlodipine and in 196 of 3157 (6.2%) patients on placebo, respectively. Patients on amlodipine had a higher risk of developing peripheral edema with a risk ratios of 2.9 (95% CI: 2.50–3.36, $P < 0.0001$) when compared with placebo (Fig. 1). The placebo-adjusted rate was 63% (Fig. 2a), indicating that in up to one-third of patients, the cause of the peripheral edema was unrelated to the use of amlodipine. Patients on low/medium doses of amlodipine had lower rates of peripheral edema than patients on high doses (5.9 vs. 28.8%) and an improved risk–benefit ratio (3.2 vs. 12.2% of edema for each 5-mmHg BP reduction). The risk ratios for peripheral edema on amlodipine vs. placebo was 2.01 for low/medium doses and 3.08 for high doses ($P_{\text{for interaction}} = 0.03$, Fig. 3). The placebo-adjusted rate was 47% for those with low/medium doses and 68% for those with high doses, respectively (Fig. 2b and c). The risk ratios for peripheral edema on amlodipine vs. placebo was no different between patients with arterial hypertension and coronary artery disease (risk ratios 3.11, 95% CI: 2.36–4.09 vs. risk ratio 2.84, 95% CI: 2.39–3.39, $P_{\text{for interaction}} = 0.6$, Supplementary Figure S2, http://links.lww.com/HJH/B106).

In six [18,19,22,23,25,27] of 22 studies, data about peripheral edema on amlodipine in combination with angiotensin-converting enzyme inhibitor (ACE-I) or angiotensin receptor blocker (ARB) were provided. In most of these six studies, low/medium doses of amlodipine (2.5–5 mg) were used (Supplementary Figure S3, http://links.lww.com/HJH/B106). In order to explore the impact of ACE-I/ARB treatment on amlodipine-related edema, the risk ratio from these six studies were compared with the low/medium dose amlodipine monotherapy studies. We found no difference in the risk ratio for edema between these two subgroups of patients ($P_{\text{for interaction}} = 0.23$, Supplementary Figure S3, http://links.lww.com/HJH/B106). Of note, the use of ACE-I/ARB on top of low/medium-dose amlodipine resulted in a greater reduction of BP than low/medium-dose amlodipine alone (Supplementary Table S2, http://links.lww.com/HJH/B106, Figure S4, http://links.lww.com/HJH/B106).

Headache

Headache as a side effect was reported in 251 of 3144 patients (7.9%) on amlodipine and in 258 of 2363 on placebo (10.9%), respectively. The risk of headache was 0.77 times lower in patients on amlodipine compared with placebo (95% CI: 0.65–0.90, $P = 0.002$, Fig. 4). Patients on low/medium doses of amlodipine had substantial lower risk of headache than patients on high doses when compared with placebo ($P_{\text{for interaction}} = 0.002$, Fig. 5). Of note, mean SBP at baseline was comparable between the two groups ($P = 0.24$). There was no difference in headache between patients with arterial hypertension and coronary artery disease (risk ratio 0.73, 95% CI: 0.59–0.90 vs. risk ratio 0.83, 95% CI: 0.64–1.08, $P_{\text{for interaction}} = 0.42$, Supplementary Figure S5, http://links.

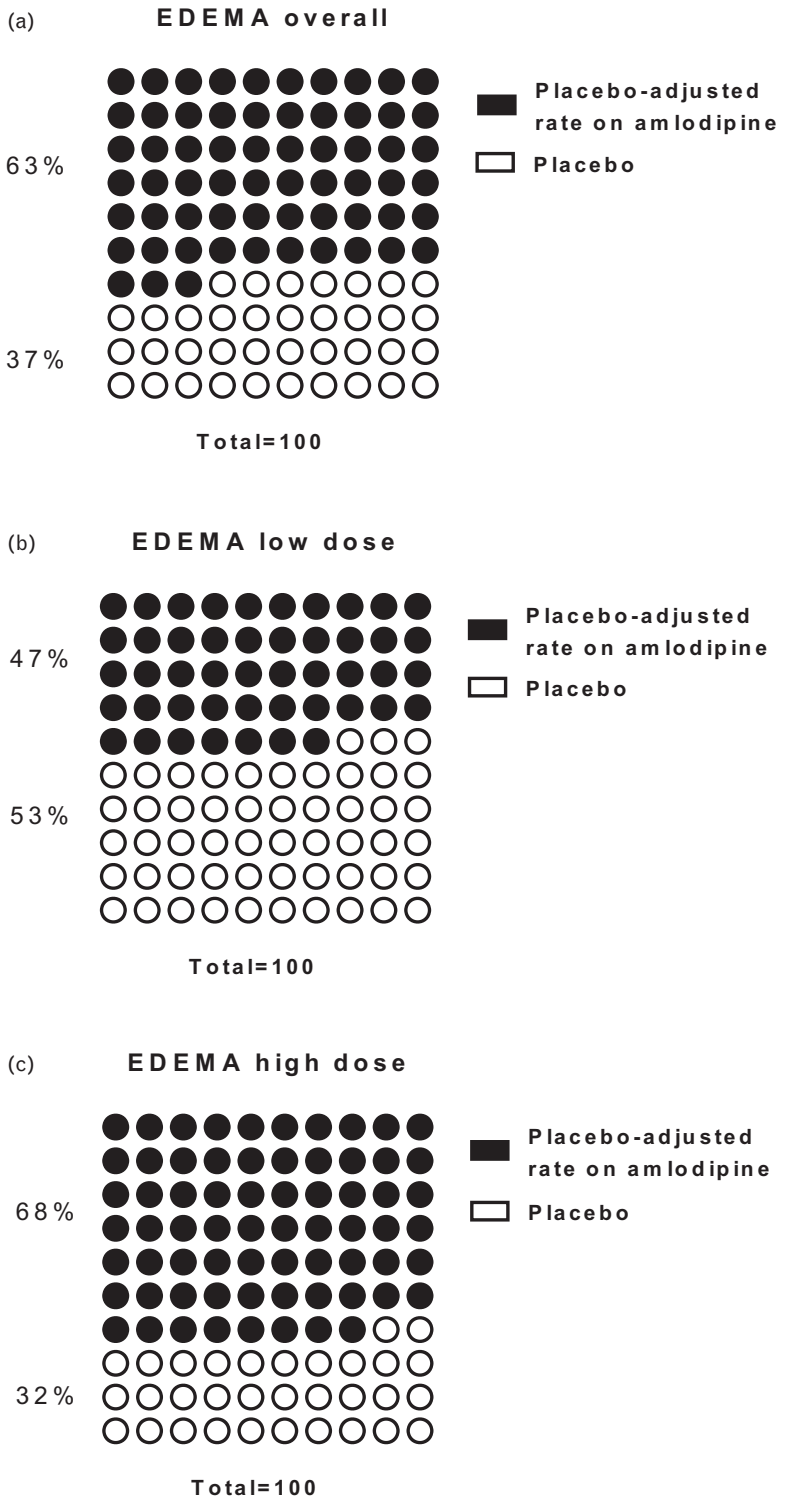

FIGURE 2 Dot plot presenting placebo-adjusted rate of peripheral edema.

lww.com/HJH/B106). There was no difference regarding risk of headache between subgroups where low/medium-dose amlodipine alone and low/medium-dose amlodipine in combination with ACE-I/ARB were used vs. placebo ($P_{\text{for interaction}} = 0.49$, Supplementary Figure S6, http://links.lww.com/HJH/B106).

Blood pressure lowering

Treatment with amlodipine resulted in significant DBP and SBP reductions compared with placebo in almost all trials (Supplementary Tables S3 and S4, http://links.lww.com/HJH/B106). Underreporting of measures of variability (SD or error) for the BP values before and after treatment with amlodipine

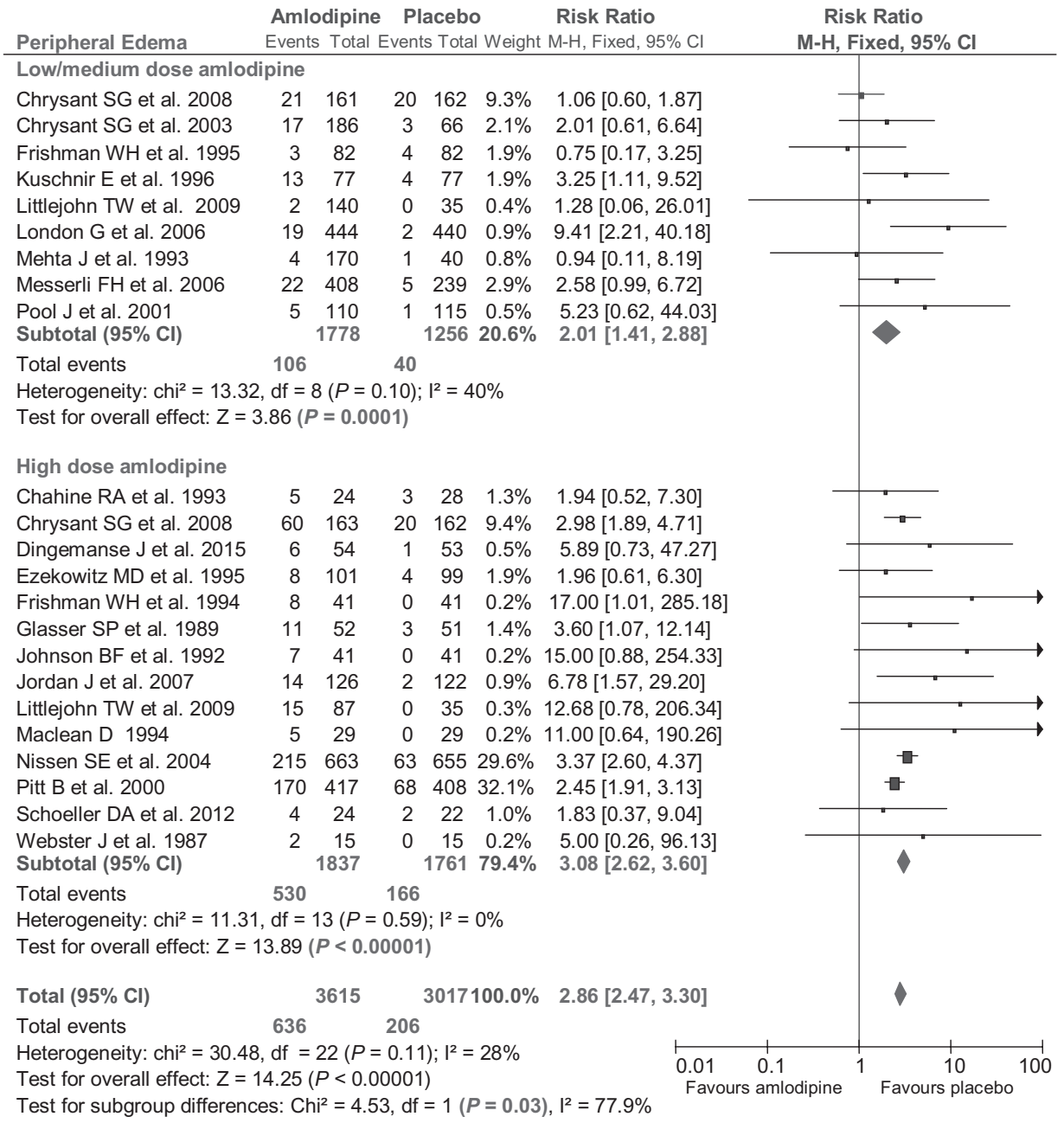

FIGURE 3 Forest plot presenting the risk ratio for peripheral edema on low/medium and high-dose amlodipine.

in most of the trials, prevented a systemic and quantitative analysis of the BP-lowering efficacy of amlodipine. Treatment with high doses of amlodipine resulted in visually and numerically more effective SBP (Supplementary Figure S7-A, http://links.lww.com/HJH/B106) and DBP (Supplementary Figure S7-B, http://links.lww.com/HJH/B106) reductions than treatment with low/medium doses.

Assessment of study quality and publication bias

According to Jadad score, all studies were assessed as high-quality trials (Supplementary Table S5, http://links.lww.com/HJH/B106). There was a high level of agreement between investigators. There was no sign of publication bias in the obtained funnel plots for peripheral edema (Egger's test $P = 0.3$, Supplementary Figure S8-A, http://links.lww.com/HJH/B106) or headache (Egger's test $P = 0.66$, Supplementary Figure S8-B, http://links.lww.com/HJH/B106).

DISCUSSION

The main findings of this meta-analysis were: the placebo-adjusted rate was 63% of all edema cases on amlodipine (16.6%) indicating that in 37% of all cases, edema were unrelated to treatment with amlodipine, low/medium doses of amlodipine were associated with less edema, but also with less effective BP reductions than high doses, co-administration of ACE-I or ARB to low/medium-dose

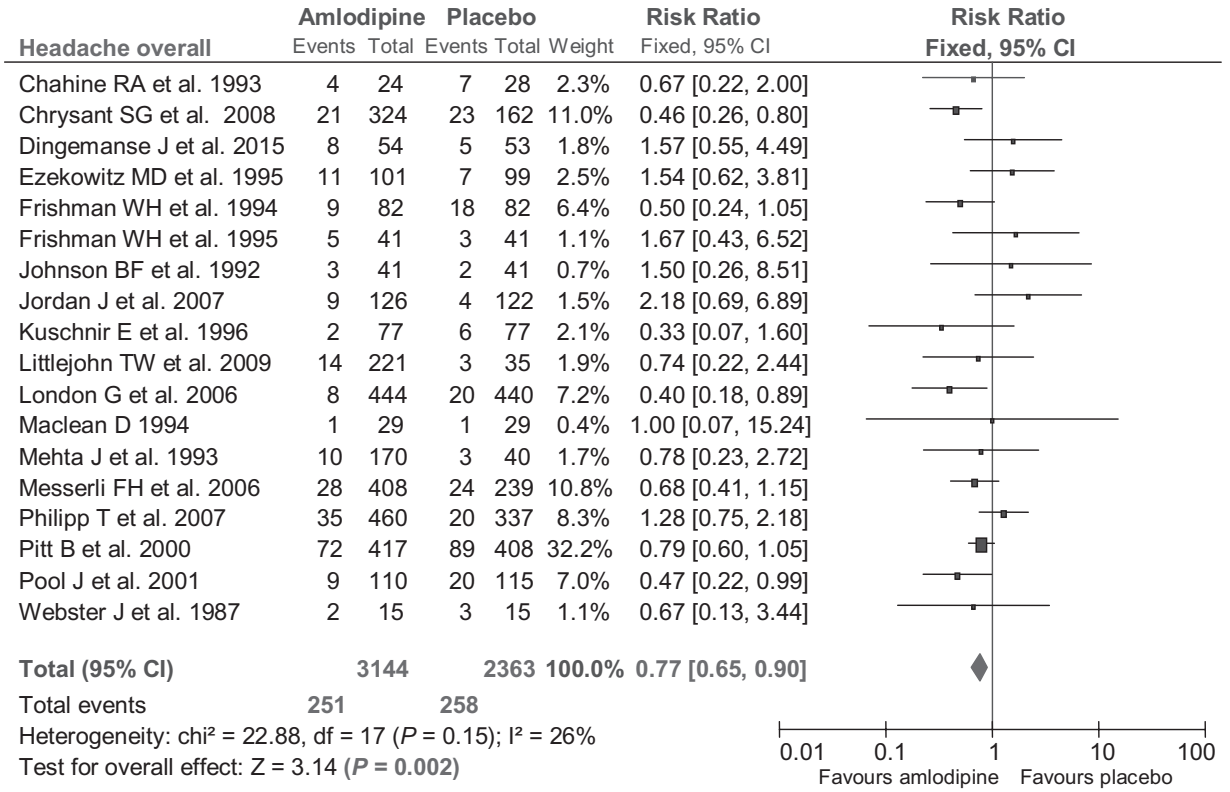

FIGURE 4 Forest plot presenting the risk ratio for headache.

amlodipine resulted in higher BP reduction with equivalent rates of edema compared with low/medium-dose amlodipine monotherapy, and headache appeared less frequently on amlodipine than on placebo but was documented only for low/medium doses of amlodipine or combination therapy in patients with hypertension but not with coronary artery disease.

Four major determinants and their balanced interplay have been identified as responsible for overall fluid homeostasis of the interstitial space of the skin (relation of the filtered interstitial fluid and its reabsorption through the lymphatic vessel to the circulation) [34]. These factors are intracapillary pressure, plasma and interstitial oncotic pressure, capillary permeability, and lymphatic drainage of interstitial fluid. Occurrence of peripheral edema on CCBs is generally assumed to be related to predominance of arteriolar dilatation, thus diminishing the venoarterial reflex [35] (postural arteriolar vasoconstriction). In turn, this leads to an increased intracapillary pressure gradient and/or capillary permeability [34]. This adverse effect is not associated with sodium retention [36]. According to our analysis, occurrence of peripheral edema represents a significant unwanted effect of treatment with amlodipine with an almost three-fold risk compared with placebo.

With an incidence of 16%, this side effect has to be expected in every fifth to sixth patient. These rates are in accordance with results from large meta-analysis on different CCBs [10]. However, our meta-analysis also indicates that a considerable number of patients (almost 40%) develop edema, that in all likelihood is not caused by the drug. This underlines that in patients with edema on amlodipine, a systematic evaluation to exclude other possible reasons for edema should be undertaken before discontinuing the drug. In general, CCBs are well tolerated with one of the lowest discontinuation rates because of adverse events among different antihypertensive drugs [37]. We showed that edema on amlodipine was less frequent with low/medium doses of amlodipine, which appears to apply for several CCBs [10]. Furthermore, for each 5-mmHg reduction in BP, one could expect lower rates of edema using a low/medium compared with high-dose of amlodipine (3.2 vs. 12.2%). Still, low/medium doses of amlodipine are associated with moderate BP reductions, which may be disadvantageous in obtaining guideline-recommended target BPs. However, our analysis has demonstrated that coadministration of ACE-I/ARB to low/medium dose of amlodipine was superior in reducing BP with equivalent rates of peripheral edema when compared with low/medium-dose amlodipine monotherapy (Supplementary Figure S4, http://links.lww.com/HJH/B106). This observation from our systematic analysis is supported by findings from randomized, double-blind, non-placebo-controlled trial [38].

Several approaches to reduce the incidence of amlodipine-induced edema have been suggested, such as use of vasodilators (i.e. nitrates or ACE-I/ARB), administration of amlodipine at bedtime, and dose reduction. Use of nitrates as vasodilators with amlodipine might lead to normalization in intracapillary pressure resulting in less edema. However, randomized, controlled studies investigating this hypothesis are lacking. Long-term administration of nitrates may require a start–stop regimen in order to avoid development of nitrate-tolerance. Administration of ACE-I [39] or ARB [40]

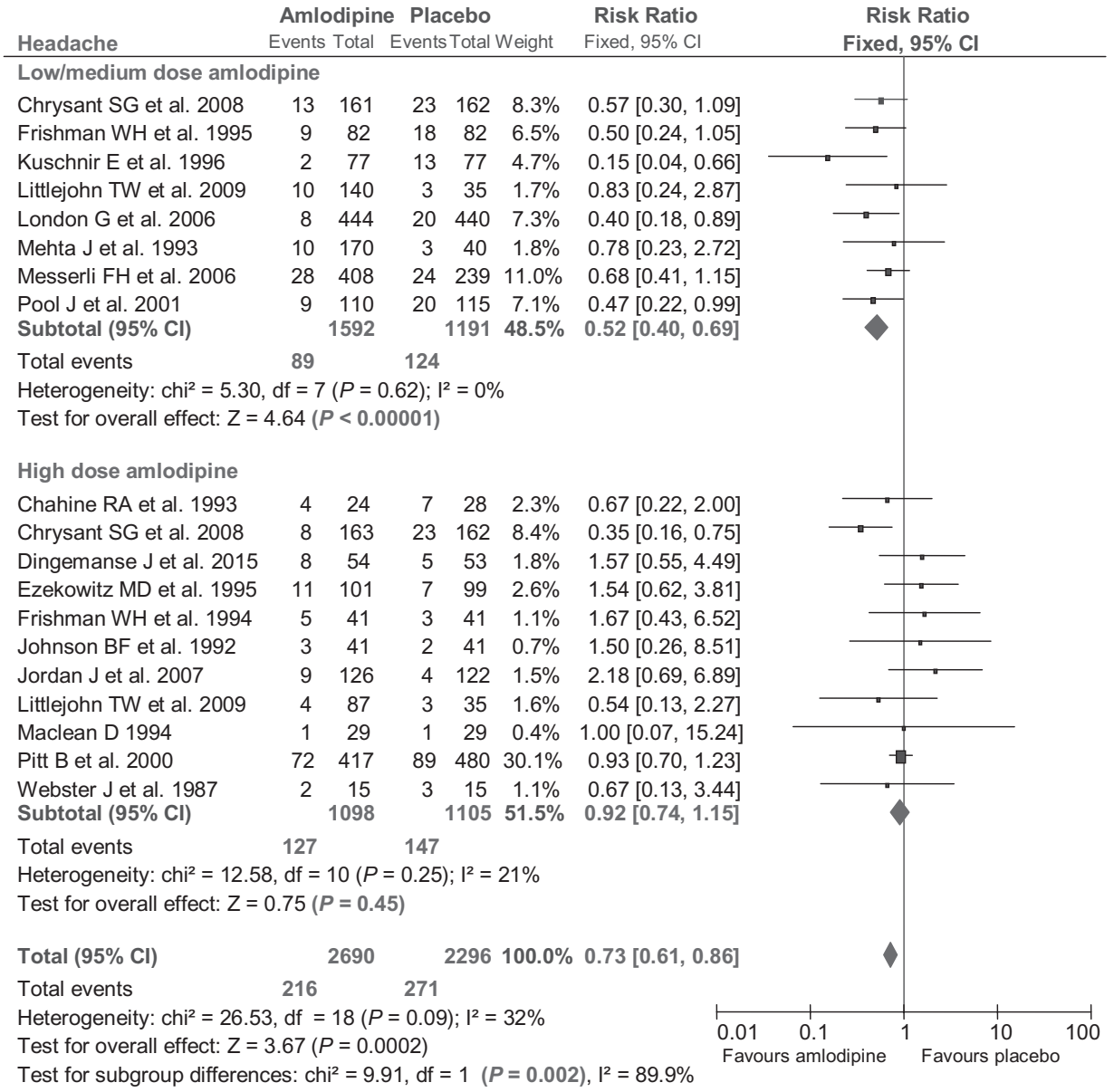

FIGURE 5 Forest plot presenting the risk ratio for headache on low-dose and high-dose amlodipine.

in combination with amlodipine resulted in less edema in direct comparison with amlodipine monotherapy, when edema were assessed with objective parameters like subcutaneous interstitial pressure and ankle volume measurements. Furthermore, these combinations were superior in blood pressure reduction compared with amlodipine monotherapy, thereby allowing reduction of the dose, which may contribute to resolution of edema, as we showed that this adverse effect is dose-dependent. Beneficial effects of add-on therapy with ACE-I/ARB in combination with amlodipine concerning edema have been supported from other randomized, double-blind studies where occurrence of edema was based on more conservative approaches, such as patient's interview (self-reported, patient's questionnaire) or physical examination [38,41]. According to the results of a small, single-center study, amlodipine-associated edema was substantially improved with addition of ACE-I/ARB rather than with diuretic (hydrochlorothiazide) [42]. This indeed supports the hypothesis that the underlying mechanism is not caused by alterations in volume load but is related to normalizing intracapillary pressure by postcapillary venous dilation produced by the renin–angiotensin blocker, thereby reducing capillary (arteriolar–venous) pressure gradient [42].

Equivalent rates of edema in patients on combination therapy with ACE-I/ARB and amlodipine and those on amlodipine monotherapy (low/medium dose of amlodipine was used in both groups), as demonstrated herein are distinct from previous findings reported in one large meta-analysis, where addition of ACE-I/ARB to CCBs decreased risk of CCBs-associated edema [43]. The findings that the risk of amlodipine-associated edema was not reduced with addition of ACE-I/ARB may be related to several major methodological differences used in our analysis in

comparison with previously published analysis [43]. The current analysis was restricted to amlodipine only (not all CCBs), included trials in which low/medium dose of amlodipine was used in both groups (monotherapy vs. combination therapy), only involved placebo-controlled trials.

Bedtime administration of amlodipine might reduce edema development by avoiding accelerating effects of upright posture on edema onset. This hypothesis is supported by evidence indicating that bedtime regimen of slow released nifedipine results in less edema compared with morning regimen [44]. Whether bedtime administration of antihypertensive therapy is associated with improved BP control remains controversial [45,46]. In the majority of trials included in our analysis, amlodipine was administered in the morning (Supplementary Table S6, http://links.lww.com/HJH/B106). There was no trial in which administration at bedtime was studied, thus allowing no comparison between these two regimens.

Occurrence of edema on amlodipine necessitates comprehensive consideration of other underlying causes, such as heart failure, liver, and kidney insufficiency. Additional causes like venous insufficiency, use of NSAIDs [47], obesity [48] or sleep apnea [49] should also be taken into consideration.

According to one meta-analysis, use of manidipine resulted in less edema compared with amlodipine [50]. However, these data should be interpreted with caution because of the relatively small number of patients and observed events of interest (i.e. peripheral edema) analyzed.

In the present meta-analysis, the incidence of headache was lower in patients with amlodipine when compared with placebo. To the best of our knowledge, this is the first analysis with pooled data from all randomized trials (in patients with arterial hypertension and coronary artery disease) indicating that the rate of headache can be beneficially affected by amlodipine. This was mainly driven by reduction of headache using low/medium doses of amlodipine (Fig. 5) in patients with hypertension. One might speculate that lower doses of amlodipine are sufficient to approach headache through BP reductions, though with a dose that is too low to induce symptomatic cerebral vasodilation. High doses had no significant effect on rate of headache, as the more effective BP reduction is caused by a more pronounced vasodilation, but it is important to note that there was no increased risk of headache with higher dose amlodipine. Thus, we can speculate that the prevention of headache is almost solely related to the observed BP reduction. These data are in line with previous studies, in which the same dose–response relationship on risk of headache has been reported for all CCBs [51]. Prevention of headache by using all four major BP-lowering drug classes (thiazides, beta-blockers, ACE-I, and ARB) indicates that there is causal relationship between high BP and headache [52].

Limitations and strengths

The observed results are very robust. Diseases, such as heart failure, severe renal or hepatic disease were considered as exclusion criteria in all trials (Supplementary Table S6, http://links.lww.com/HJH/B106), thus ensuring that the reported edema was not related to other diseases. In most of the trials, a wash-out period took place during which other medications were stopped before the study medication was given, thus minimizing the possible bias of additional drugs. In most of the analyzed trials, duration of follow-up was comparable, and lasted about 8 weeks (Table 1). In two trials [4,33], only there was a substantial longer follow-up (Table 1). In only one trial, the rates of edema and headache were reported separately in men and women, so further exploration of the data regarding sex differences were not available (Supplementary Table S6, http://links.lww.com/HJH/B106). The reporting of edema was mainly based on clinical examination or self-reported (Supplementary Table S6, http://links.lww.com/HJH/B106). Of note, in one study [13], normotensive participants were also analyzed whereas two studies [17,31] used a crossover design.

Use of amlodipine is associated with an increased risk of peripheral edema compared with placebo. Still, the placebo-adjusted rate is much lower than anticipated, stressing the importance of considering other causes for this side effect. Risk of edema decreases using low/medium doses of amlodipine, which, when used in combination with ACE-I/ARB, resulted in further reduction of BP with no additional excess in edema rates. Interestingly, the rate of headache was lower with amlodipine compared with placebo. This effect was mainly driven by the use of low/medium doses of amlodipine.

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Conflicts of interest

D.V. and S.S.S. have no conflict of interest to declare. F.H.M. currently has financial relationships with Pfizer, Servier, WebMD, American College of Cardiology, Lancet, Menarini, Sandoz, Hikma, Medtronic and Novartis. M.A.W. receives consulting fees from Medtronic, ReCor, Ablative Solutions and Johnson and Johnson. M.B. had no conflict in relation to this analysis and is supported by the Deutsche Forschungsgemeinschaft (SFB TRR 219). F.M. received speaker honoraria and consultancies fees from Berlin Chemie, Boehringer Ingelheim, Medtronic and Recor, and is supported by Deutsche Hochdruckliga, Deutsche Gesellschaft für Kardiologie and Deutsche Forschungsgemeinschaft (SFB TRR 219). B.W. receives support by the National Institute for Health Research University College London Hospitals Biomedical Research Centre.

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