Peripheral edema associated with calcium channel blockers: incidence and withdrawal rate – a meta-analysis of randomized trials

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Objective **Peripheral edema is considered to be a common and annoying adverse effect of calcium channel blockers (CCBs). It has been thought to occur secondary to arteriolar dilatation causing intracapillary hypertension and fluid extravasation. We aimed to evaluate the incidence and withdrawal rate of peripheral edema with CCBs.**

Methods **A systematic search was made in *PubMed*, *EMBASE* and *CENTRAL* from 1980 to January 2011 for randomized clinical trials reporting peripheral edema with CCBs in patients with hypertension. Trials enrolling at least 100 patients in the CCB arm and lasting at least 4 weeks were included in the analysis. Both the incidence and withdrawal rate due to edema were pooled by weighing each trial by the inverse of the variance. Head-to-head comparison was done to evaluate the risk of edema between newer lipophilic dihydropyridine (DHP) CCBs and older DHPs.**

Results **One hundred and six studies with 99 469 participants, mean age 56 ± 6 years, satisfied our inclusion criteria and were included in this analysis. The weighted incidence of peripheral edema was significantly higher in the CCBs group when compared with controls/placebo (10.7 vs. 3.2%, $P<0.0001$). Similarly, the withdrawal rate due to edema was higher in patients on CCBs compared with control/placebo (2.1 vs. 0.5%, $P<0.0001$). Both the incidence of edema and patient withdrawal rate due to edema increased with the duration of therapy with CCBs reaching 24 and 5%, respectively, after 6 months. The risk of peripheral edema with lipophilic DHPs was 57% lower than with traditional DHPs (relative risk 0.43; 95% confidence interval 0.34–0.53; $P<0.0001$). Incidence of peripheral edema in patients on DHPs was 12.3% compared with 3.1% with non-DHPs ($P<0.0001$). Edema with high-dose CCBs (defined as more than half the usual maximal dose) was 2.8 times higher than that with low-dose CCBs (16.1 vs. 5.7%, $P<0.0001$).**

Conclusion **The incidence of peripheral edema progressively increased with duration of CCB therapy up to 6 months. Over the long term, more than 5% of patients discontinued CCBs because of this adverse effect. Edema rates were lower with both non-DHPs and lipophilic DHPs.**

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Abbreviations: CCB, calcium channel blocker; DHP, dihydropyridine; PDR, physician desk reference

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Introduction

Calcium channel blockers (CCBs) are one of the classes of drugs recommended for initial treatment of hypertension. In addition to their powerful and consistent antihypertensive effect, CCBs have the advantage of once daily dosing and not causing any metabolic abnormalities. They act by preferential peripheral arteriolar vasodilatation. As shown by Zanchetti *et al.* [1], peripheral edema is considered to be the most common dose-dependent adverse effect of CCBs, which varies among various CCBs and increases with duration of therapy [2]. It has been thought to occur due to precapillary sphincter causing intracapillary hypertension and extravasation of fluids [3]. Incidence of edema is found to vary from 1.8 to 10.8% as reported in the physician desk reference (PDR) and Food and Drug Administration website [4] or vary more widely from 7 to 33% in various clinical trials [5–8]. Not infrequently, peripheral edema is the reason for withdrawal from CCBs [2,9,10].

The aim of our analysis was three-fold: to evaluate the incidence and withdrawal rate of edema overall, to assess the effect of treatment duration on edema incidence; and to compare the incidence of edema among lipophilic dihyropyridine (DHP) CCBs, older traditional DHPs and non-DHPs.

Methods

Search strategy

A systematic search was made in *PubMed*, *EMBASE* and Cochrane Central Register of Controlled trials using the key terms 'calcium channel blockers' OR 'calcium

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antagonists' OR 'CCBs' OR using the names of all individual CCBs. We limited our search to randomized clinical trials in humans and in peer-reviewed journals from 1980 to January 2011. We checked the reference lists of the reviewed articles and original studies identified by electronic search to find potentially eligible articles. No language restriction was applied. Trials in the abstract form without a published manuscript were not considered for the analysis. Authors of articles were contacted when results were unclear or when relevant data were not reported.

Data extraction

Two authors (N.H., R.S.B.) searched the data independently and in duplicate. Disagreements were resolved by consensus. We extracted the baseline characteristics of the study population, sample size, type of medication used along with the dose, study duration, incidence and withdrawal rate due to peripheral edema. Information was obtained regarding the method of assessing peripheral edema in each trial (self-reported, by symptom questionnaire or measurement of ankle edema by examiner). All types of edema like ankle edema or swelling, lower leg swelling, lower extremity edema and pretibial edema were considered as peripheral edema for the purpose of analysis.

Selection criteria

Eligible trials had to fulfill the following criteria for inclusion: randomized clinical trial with comparison of regimen based on CCBs with other agents including placebo; cohort enrolled with hypertension; sample size of at least 100 patients in the CCB arm; duration of trial of at least 4 weeks; and reporting data on peripheral edema. Studies in patients with coronary artery disease or heart failure were excluded from this analysis. Studies involving mibefradil were excluded, as it was withdrawn from the market due to its potential for drug interactions.

Quality assessment and subgroup analysis

The quality of studies were assessed using the methods recommended by the Cochrane Collaboration tools for assessing risk of bias based on seven components [11]. For each component, studies were described as low, high or unclear risk of bias. Studies with low risk of bias for seven of seven components were considered as low risk, those for six of seven components as intermediate risk and those for less than six of seven components as high risk for bias studies.

Subgroup analysis was performed based on the duration of therapy, DHPs vs. non-DHPs, newer lipophilic DHPs vs. older DHPs and the dose of CCB (high-dose vs. low-dose). Lacidipine, lercanidipine and manidipine were considered as newer lipophilic DHPs, whereas amlodipine, barnidipine, felodipine, isradipine, nicardipine, nifedipine, nimodipine, nitrendipine and pranidipine were considered as older DHPs. High-dose CCB was defined as more than half the usual maximal dose of CCB. Difference between the subgroups was estimated on the basis of tests for interaction [12].

Statistical analysis

The statistical analysis was done in line with recommendations from the Cochrane Collaboration and the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [13] using Review Manager (RevMan) version 5.0.25. The incidence of peripheral edema was pooled together for both CCBs and their controls, by weighing the rate by the inverse of the variance of each trial. In addition to placebo, control group comprised of all the antihypertensives including angiotensin-converting enzyme (ACE) inhibitors, angiotensin receptor blockers, beta-blockers, calcium channel blockers, direct renin inhibitors and thiazides. Head-to-head comparison was made between older DHPs and newer lipophilic DHPs where data were available. Heterogeneity was assessed using the I^2 statistics. I^2 is the proportion of total variation observed between the trials attributable to differences between trials rather than sampling error (chance) and we considered I^2 less than 25% as low and I^2 more than 75% as high. If trials were homogenous, a fixed-effect model was used to calculate pooled effect sizes; otherwise, a random-effect model of DerSimonian and Laird [14] was applied to calculate overall differences. All analyses were performed using the intention-to-treat principle. Publication bias was estimated visually by funnel plots, and or using the Begg's test and the weighted regression test of Egger [15].

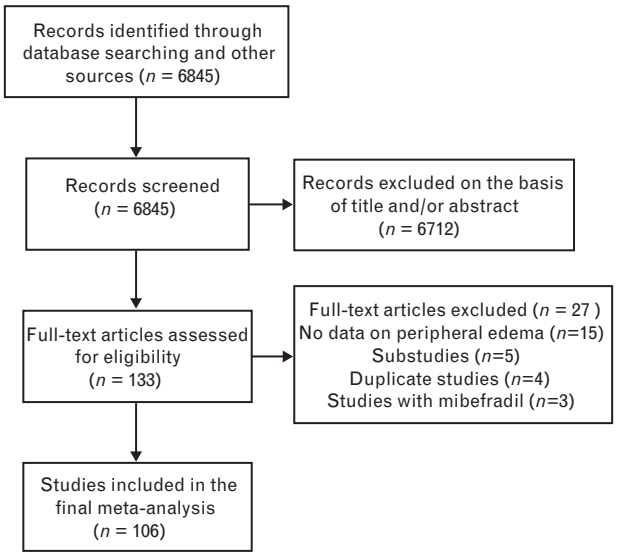
Results

Baseline characteristics

We identified 6845 articles, out of which 133 were retrieved and reviewed for possible inclusion (Fig. 1). One hundred and six studies (1–2, 5–10, 16–113) with the total of 99 469 patients, mean age 56 ± 6 years, 56% men and the mean duration of 6 months, fulfilled the inclusion criteria and were included in the analysis (Table 1). Of these 106 trials (125 comparison arms), amlodipine was used in 52 trials, nifedipine in 21, diltiazem in 12, felodipine in nine, isradipine in eight, lacidipine in seven, lercandipine in five, verapamil in three, nitrendipine and nisoldipine in two and barnidipine, manidipine, nicardipine and pranidipine in one each. Thirty-nine trials with 22 977 patients reported data on withdrawal due to peripheral edema. Six trials with the total of 2648 patients reported edema rates in head-to-head comparison of newer lipophilic DHPs (lacidipine, lercanidipine and manidipine) compared to older, traditional DHPs.

Of the 106 trials, only 16 trials were high risk for bias, whereas the rest were low–intermediate risk for bias.

Fig. 1



Selection of studies.

There was no evidence for publication bias in any of the analyses. In addition to being self-reported by patients in all trials, peripheral edema was evaluated by patient questionnaire in 11 trials and by measurement of ankle edema in four trials.

Incidence of peripheral edema

Nine thousand, three hundred and twenty-two of 47 879 patients on CCBs over the mean duration of 27 weeks reported peripheral edema with the weighted incidence of 10.7% [95% confidence interval (CI) 10.6–10.9] compared with 3282 of 43 208 patients in control group with the incidence of 3.2% (95% CI 3.1–3.3).

Patient withdrawal due to peripheral edema

Five hundred and eighteen of 12 091 patients withdrew due to edema on CCBs (2.1%; 95% CI 1.9–2.2) compared with 19 of 7125 patients in control group (0.5%; 95% CI 0.36–0.58).

Calcium channel blocker type and peripheral edema

Dihydropyridines and nondihydropyridines

Incidence of peripheral edema was significantly higher with DHPs (12.3%; 95% CI 12.2–12.5) compared with non-DHPs (3.1%; 95% CI 2.8–3.4; $P < 0.0001$). Similarly, patient withdrawal due to edema was significantly higher with DHPs (2.4%; 95% CI 2.2–2.5) compared with non-DHPs (0.6%; 95% CI 0.35–0.85; $P < 0.0001$).

Newer lipophilic vs. older traditional dihydropyridines

The risk of peripheral edema with newer DHPs was 57% lower than with older DHPs [relative risk (RR) 0.43; 95% CI 0.34–0.53; $P < 0.0001$] (Fig. 2). Similarly, the risk of withdrawal due to edema was 78% lower with newer DHPs compared with older DHPs (RR 0.22; 95% CI 0.12–0.40; $P < 0.0001$). Weighted incidence of peripheral edema with older DHPs was 14.4% (95% CI 13.4–15.3) compared with 6.4% (95% CI 5.8–7.0) with lipophilic DHPs. All newer DHPs seemed similar in efficacy with lower edema rates. There was no evidence of heterogeneity in this comparison and test of publication bias was negative (Egger's $P = 0.78$).

Duration of calcium channel blocker therapy and peripheral edema

Incidence of peripheral edema was found to be 2.3% on 4 weeks CCB therapy and increased with duration of CCB therapy to 6% on 5–12 weeks of CCB, 10.8% on 13–26 weeks of CCB and 23.8% on over 26 weeks of CCBs. Similarly, patient withdrawal due to edema increased with increase in duration of CCB therapy from 1% (4 weeks CCB) to 5.5% with long-term use (Fig. 3).

Dosage of calcium channel blockers and peripheral edema

Incidence of edema was significantly higher in patients on high-dose CCB (16.1%; 95% CI 15.9–16.3) when compared with low-dose CCB (5.7%; 95% CI 5.5–5.9; $P < 0.0001$). In both the groups, the incidence of edema increased with the duration of therapy with higher rates of edema in the high-dose CCB group (Fig. 4).

Discussion

The present study documents that both the incidence of edema and patient withdrawal due to edema was distinctly higher than reported in the PDR. Around 25% patients on CCBs were found to have peripheral edema, and among those with edema, 25% was found to withdraw from CCB due to edema. Edema rates were dose dependent and found to increase with duration of therapy for a period of up to 6 months. The rates were higher with traditional DHPs compared with lipophilic DHPs or non-DHPs.

Peripheral edema is thought to result from preferential arteriolar dilatation, thus increasing the pressure gradient between arteriolar and venule capillaries, leading to extravasation of intravascular fluid [114,115]. Principal determinants of capillary fluid filtration into interstitium are intracapillary pressure, interstitial oncotic pressures, capillary permeability and lymphatic drainage. Precapillary vasoconstriction is selectively diminished by CCBs, increasing intracapillary pressure thereby filtering capillary fluid into interstitium causing peripheral edema [114,115].

Compliance with CCB therapy may be hampered by adverse effects, which is especially true for CCB-related peripheral edema. Several measures can be taken to reduce this adverse effect: reducing the dose of DHPs has been associated with reduced rates of edema,

Table 1 Baseline characteristics[a]

Study	Total patients	Mean age (in years)	Men (%)	Follow-up (months)	Comparison groups with dose	Type of edema defined in the study	Reporting of edema
AASK [16]	1094	55	61	48	Amlodipine 5–10 mg vs. metoprolol 50–200 mg vs. ramipril 2.5–10 mg	Edema	Self-reported
ANCHOR [17]	208	50	53	1.5	Nisoldipine 10–30 mg vs. placebo	Peripheral edema	Self-reported
ASCOT-BPLA [7]	19257	63	77	66	Amlodipine 5–10 mg vs. atenolol 50–100 mg	Peripheral edema	Self-reported
Bittar *et al.* [18]	239	51	53	3	Diltiazem 180–360 mg vs. mibefradil 50–100 mg	Leg edema	Self-reported
Carr *et al.* [19]	388	47	46	1.5	Nifedipine 20–150 mg vs. placebo	Edema	Self-reported
Cherubini *et al.* [20]	324	73	33	6	Lacidipine 2–4 mg vs. lercandipine 5–10 mg vs. nifedipine 30–60 mg	Edema	Self-reported
Chrysant and Cohen [21]	402	56	75	1.5	Isradipine 5–20 mg vs. placebo	Ankle edema	Self-reported
Chrysant *et al.* [22]	440	52	64	2	Amlodipine 5 mg vs. olmesartan 20 mg vs. placebo	Peripheral edema	Self-reported
Chrysant *et al.* [23]	812	51	58	1.5	Amlodipine 10 mg vs. amlodipine/benazepril 10/20–40 mg	Edema	Self-reported
Chrysant *et al.* [24]	1940	54	54	2	Amlodipine 5–10 mg vs. olmesartan 10–40 mg vs. amlodipine/olmesartan 5–10/10–40 mg vs. placebo	Peripheral edema	Self-reported
Cocco *et al.* [25]	178	60	71	1.25	Isradipine 1–5 mg vs. placebo	Edema	Self-reported and questionnaire
Cushman *et al.* [26]	891	54	68	3	Dilitazem ER 120–180 mg vs. enalapril 5 mg vs. diltiazem/enalapril 120–180/5 mg vs. placebo	Edema	Self-reported
Destro *et al.* [27]	646	58	49	2	Amlodipine 10 mg vs. amlodipine/valsartan 10/160 mg	Peripheral edema	Self-reported
Drummond *et al.* [28]	545	54	54	1.5	Amlodipine 5 mg vs. amlodipine 10 mg vs. amlodipine/aliskiren 5/150 mg	Peripheral edema	Self-reported
Emeriau *et al.* [29]	524	73	37	4	Amlodipine 5 mg vs. indapamide 1.5 mg vs. hydrochlorothiazide 25 mg	Leg edema	Self-reported
Esnault *et al.* [30]	263	58	60	36	Amlodipine 5–10 mg vs. enalapril 5–20 mg	Peripheral edema	Self-reported
Fagan *et al.* [31] 1994	227	50	78	1.5	Felodipine 5–10 mg vs. nifedipine 30–90 mg	Peripheral edema	Self-reported
Farsang [32]	303	56	50	3	Amlodipine 5–10 mg vs. zofenopril 30–60 mg	Edema	Self-reported
Felicetta *et al.* [33]	229	48	71	1	Diltiazem ER 90–540 mg vs. placebo	Peripheral edema	Self-reported
Fiddes *et al.* [34]	350	65	45	3	Diltiazem XR 240–480 mg vs. placebo	Peripheral edema	Self-reported
Flack *et al.* [35]	572	54	40	3	Amlodipine 10 mg vs. amlodipine/valsartan 10/160 mg	Peripheral edema	Self-reported
Fletcher *et al.* [36]	540	54	57	6	Nifedipine 40–80 mg vs. atenolol 50–100 mg vs. cilazapril 2.5–5 mg	Edema	Self-reported
Fogari *et al.* [37]	203	55	57	2	Amlodipine 10 mg vs. candesartan/HCTZ 16/12.5 mg	Ankle edema	Self-reported and measured by examiner
Franco *et al.* [38]	343	55	29	2	Amlodipine 10 mg vs. valsartan/HCTZ 160/12.5 mg	Peripheral edema	Self-reported
Frick *et al.* [39] 1989	205	49	60	2	Amlodipine 1.25–10 mg vs. placebo	Edema	Self-reported
Frishman *et al.* [40]	265	53	53	6.5	Diltiazem 240–360 mg vs. HCTZ 25–50 mg	Edema	Self-reported
Glasser *et al.* [41]	228	56	54	2	Nifedipine GITS 60 mg vs. nifedipine CC 60 mg	Peripheral edema	Self-reported
Glasser *et al.* [42]	478	52	63	1.75	Diltiazem ER 120–480 mg vs. placebo	Lower limb edema	Self-reported
Gradman *et al.* [43]	707	54	65	2	Felodipine 2.5–10 mg vs. enalapril 5–20 mg vs. felodipine/enalapril 2.5–10/5–20 mg vs. placebo	Peripheral edema	Self-reported
Graney [44]	275	51	65	1	Diltiazem 120–480 mg vs. placebo	Peripheral edema	Self-reported
Hall *et al.* [45]	163	50	37	2	Amlodipine 5–10 mg vs. nifedipine CC 30–60 mg vs. nifedipine GITS 30–60 mg	Ankle edema	Self-reported and questionnaire
Hart and Holwerda [46]	190	56	65	1.5	Barnidipine 10–30 mg vs. placebo	Peripheral edema	Self-reported
Heagerty *et al.* [47]	410	55	50	2	Nifedipine 20–40 mg vs. placebo	Edema	Self-reported
Hermans *et al.* [48]	205	57	42	1.5	Amlodipine 5 mg vs. isradipine 5 mg	Ankle edema	Self-reported and questionnaire
Hollenberg *et al.* [49]	269	68	47	6	Amlodipine 2.5–10 mg vs. eplerenone 50–200 mg	Edema	Self-reported and questionnaire
Holtzman *et al.* [50]	252	66	88	2	Isradipine 5–10 mg vs. HCTZ 25–50 mg	Edema	Self-reported
INSIGHT [9]	6321	65	46	54	Nifedipine GITS 30–60 mg vs. HCTZ/amiloride 25–50/2.5–5 mg	Peripheral edema	Self-reported
Isles and Kitchin [51]	200	64	41	1.5	Nifedipine GITS 20 mg vs. bendrofluazide 2.5 mg	Peripheral edema	Self-reported
Jamerson *et al.* [52]	364	55	46	3	Amlodipine 5–10 mg vs. amlodipine/benazepril 5–10/20 mg	Peripheral edema	Self-reported, questionnaire and measured by examiner
James *et al.* [53]	533	57	47	5	Lacidipine 4–6 mg vs. atenolol 50–100 mg	Edema	Self-reported
James *et al.* [54]	465	55	52	4	Lercanidipine 10–20 mg vs. losartan 50–100 mg	Peripheral edema	Self-reported
Jensen [55]	219	56	54	2	Felodipine 5–10 mg vs. lisinopril 10–20 mg	Edema	Self-reported
Jern *et al.* [56]	549	52	NR	2	Isradipine 2.5–5 mg vs. atenolol 50–100 mg	Edema	Self-reported
Karch *et al.* [57]	296	54	59	3	Amlodipine 5–10 mg vs. mibefradil 50–100 mg	Leg edema	Self-reported
Ke *et al.* [58]	698	54	65	1.5	Amlodipine 5 mg vs. amlodipine/valsartan 5/80 mg	Peripheral edema	Self-reported
Kelly *et al.* [59]	156	56	49	4	Diltiazem 120–360 mg vs. placebo	Ankle edema	Self-reported
Kloner *et al.* [60]	251	54	55	2	Amlodipine 10 mg vs. candesartan 32 mg	Peripheral edema	Self-reported and measured by examiner
Koylan *et al.* [61]	983	54	43	6	Any CCB vs. any ACE inhibitor vs. irbesartan 75–300 mg	Ankle edema	Self-reported

(*continued overleaf*)

Table 1 (*continued*)

Study	Total patients	Mean age (in years)	Men (%)	Follow-up (months)	Comparison groups with dose	Type of edema defined in the study	Reporting of edema
Kuschnir *et al.* [62]	300	56	48	2	Nifedipine 20 mg vs. losartan 50 mg vs. nifedipine/losartan 20/50 mg	Peripheral edema	Self-reported
Leonetti [63]	435	51	61	12	Lacidipine 4–6 mg vs. nifedipine 40–80 mg	Peripheral edema	Self-reported
Leonetti *et al.* [2]	828	70	48	12	Amlodipine 5–10 mg vs. lacidipine 2–4 mg vs. lercandipine 10–20 mg	Edema	Self-reported and questionnaire
Liedholm and Melander [64]	151	51	97	4	Felodipine 10–20 mg vs. placebo	Ankle edema	Self-reported
Littlejohn *et al.* [5]	1078	53	52	2	Amlodipine 2.5–10 mg vs. telmisartan 20–80 mg vs. amlodipine/telmisartan 2.5–10/20–80 mg vs. placebo	Peripheral edema	Self-reported
London *et al.* [65] (X-CELLENT)	1758	59	51	3	Amlodipine 5 mg vs. candesartan 8 mg vs. indapamide 1.5 mg vs. placebo	Peripheral edema	Self-reported
Malacco *et al.* [66] (SHELL)	1882	72	39	32	Lacidipine 4–6 mg vs. chlorthalidone 12.5–25 mg	Pretibial edema	Self-reported
Malacco *et al.* [67]	421	69	45	6	Amlodipine 5–10 mg vs. valsartan 80–160 mg	Peripheral edema	Self-reported
Mallion *et al.* [68]	382	74	43	6	Nitrendipine 20–40 mg vs. olmesartan 20–40 mg	Peripheral edema	Self-reported
Marin-Iranzo *et al.* [69]	245	56	56	1.5	Amlodipine 10 mg vs. nitrendipine/enalapril 20/10 mg	Ankle edema	Self-reported
Massie *et al.* [70]	201	54	64	3	Diltiazem 360 mg vs. mibefradil 100 mg	Leg edema	Self-reported
McClennen and Wilson *et al.* [71]	220	71	39	2	Felodipine 2.5–5 mg vs. triamterene/HCTZ 25/12.5 mg	Edema	Self-reported
McMahon and Reder *et al.* [72]	221	55	57	1.5	Verapamil 60–480 mg vs. placebo	Edema	Self-reported
Mehta *et al.* [73]	210	53	53	1	Amlodipine 1.25–10 mg vs. placebo	Peripheral edema	Self-reported
Messerli *et al.* [74]	631	54	64	1.5	Verapamil 240 mg vs. trandolapril 4 mg vs. verapamil/trandolapril 240/4 mg vs. placebo	Edema	Self-reported
Messerli *et al.* [75]	1079	53	64	2	Amlodipine 5–10 mg vs. nifedipine 30–60 mg	Peripheral edema	Self-reported
Messerli *et al.* [76]	847	55	61	2	Amlodipine 5 mg vs. amlodipine/atorvastatin vs. atorvastatin vs. placebo	Peripheral edema	Self-reported
Millar-Craig *et al.* [77]	222	71	40	4	Lacidipine 2–4 mg vs. lercandipine 10–20 mg	Peripheral edema	Self-reported
Miranda *et al.* [78] (ATAR)	265	59	40	4.5	Amlodipine 2.5–10 mg vs. amlodipine/ramipril 2.5–10/2.5–10 mg	Peripheral edema	Self-reported and measured by examiner
Musatti *et al.* [79]	269	54	55	3	Nifedipine SR 50–100 mg vs. nifedipine 40–80 mg	Leg edema	Self-reported
Neldam and Edwards [80]	1000	69	42	3.5	Amlodipine 10 mg vs. telmisartan 80 mg	Peripheral edema	Self-reported
Neutel *et al.* [81] (SELECT)	505	67	39	2	Amlodipine 5 mg vs. benazepril 20 mg vs. amlodipine/benazepril 5/20 mg	Peripheral edema	Self-reported
Ongtengco *et al.* [82]	222	50	52	3	Amlodipine 5–10 mg vs. nifedipine 30–60 mg	Peripheral edema	Self-reported
Os *et al.* [83]	828	54	49	2.5	Nifedipine 20–40 mg vs. lisinopril 10–20 mg	Edema	Self-reported and questionnaire
Palatini *et al.* [84]	690	54	55	3	Amlodipine 5–10 mg vs. valsartan/HCTZ 80/12.5 mg	Leg edema	Self-reported
Philipp *et al.* [6]	3155	55	52	2	Amlodipine 2.5–10 mg vs. valsartan 40–320 mg vs. amlodipine/vlasartan 2.5–10/40–320 mg vs. placebo	Peripheral edema	Self-reported
Pittrow *et al.* [85]	405	55	66	1.5	Isradipine 2.5–5 mg vs. spirapril 3–6 mg vs. isradipine/spirapril 2.5/3 mg vs. placebo	Ankle edema	Self-reported and questionnaire
Poisson *et al.* [86]	642	58	56	3	Felodipine 2.5 mg vs. ramipril 2.5 mg vs. felodipine/ramipril 2.5/2.5 mg vs. placebo	Peripheral edema	Self-reported
Pool *et al.* [87]	309	52	52	2.25	Diltiazem 120–360 mg vs. placebo	Edema	Self-reported
Pool *et al.* [88]	451	54	63	2	Amlodipine 5 mg vs. benazepril 10 mg vs. amlodipine/benazepril 5/10 mg vs. placebo	Peripheral edema	Self-reported
Preston *et al.* [89]	1660	58	53	2	Amlodipine 5–10 mg vs. placebo	Peripheral edema	Self-reported
Redon-Mas *et al.* [90]	418	55	47	1	Verapamil 240 mg LSI vs. verapamil 240 mg HSI	Ankle swelling	Self-reported
Rizzini *et al.* [91]	247	69	39	5	Lacidipine 4 mg vs. nifedipine 40 mg vs. atenolol 50 mg vs. HCTZ 25 mg	Peripheral edema	Self-reported
Romito *et al.* [92]	325	57	46	2	Felodipine 10–20 mg vs. lercandipine 10–20 mg vs. nifedipine 30–60 mg	Edema	Self-reported
Rosenthal *et al.* [93]	176	52	55	1	Prandipine 1–8 mg vs. placebo	Edema	Self-reported and questionnaire
Ruddy and Fodor [94]	278	53	65	2	Nisoldipine CC 10–40 mg vs. lisinopril 5–20 mg	Peripheral edema	Self-reported
Ruilope *et al.* [95] (VAST)	1079	61	47	6	Amlodipine 10 mg vs. valsartan/HCTZ 160/12.5–25 mg	Leg edema	Self-reported
Sharma *et al.* [96]	210	50	68	3	Amlodipine 5 mg vs. amlodipine/telmisartan 5/40 mg	Peripheral edema	Self-reported
Schrader *et al.* [10]	1183	65	52	2	Amlodipine 10 mg vs. amlodipine/valsartan 5/160 mg	Peripheral edema	Self-reported
Schunkert *et al.* [97]	944	54	53	2	Amlodipine 10 mg vs. amlodipine/valsartan 10/160 mg	Peripheral edema	Self-reported
Shepherd *et al.* [98]	203	52	72	1.25	Isradipine 5–20 mg vs. placebo	Ankle edema	Self-reported
STOP 2 [99]	6614	76	33	60	Felodipine or isradipine 2.5 mg vs. lisinopril or enalapril 10 mg vs. beta-blockers or diuretics	Ankle edema	Self-reported
TOMHS [100]	902	54	62	12	Amlodipine 5 mg vs. acebutolol 400 mg vs. chlorthalidone 15 mg vs. doxazosin 2 mg vs. enalapril 5 mg vs. placebo	Ankle swelling	Self-reported
VALUE [8]	15245	67	58	60	Amlodipine 5–10 mg vs. valsartan 80–160 mg	Peripheral edema	Self-reported
van der Does and Euler [101]	320	55	48	3	Nifedipine 40–80 mg vs. imidapril 5–10 mg	Peripheral edema	Self-reported

(*continued*)

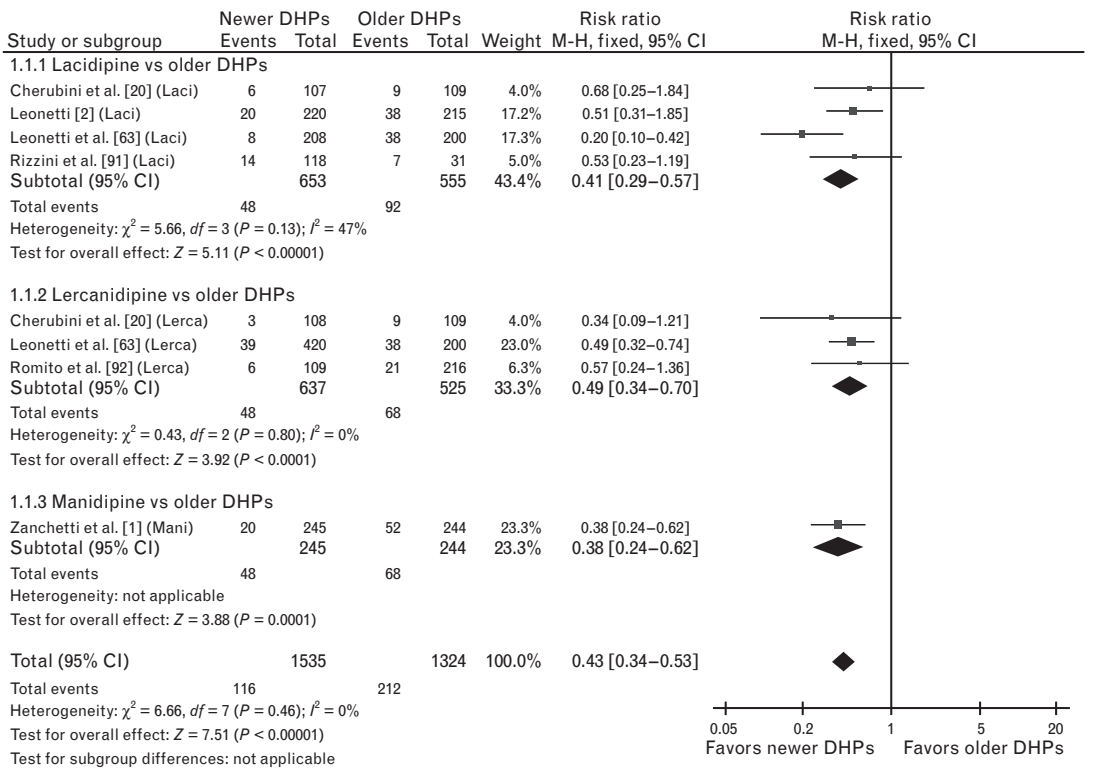
Table 1 (*continued*)

Study	Total patients	Mean age (in years)	Men (%)	Follow-up (months)	Comparison groups with dose	Type of edema defined in the study	Reporting of edema
Van Neuten *et al.* [102]	420	54	53	3	Nifedipine 40 mg vs. nebivolol 5 mg	Peripheral edema	Self-reported
Viskoper *et al.* [103]	239	54	58	3	Amlodipine 10 mg vs. mibefradil 100 mg	Leg edema	Self-reported
Volpe *et al.* [104]	857	68	34	4.5	Amlodipine 5–10 mg vs. losartan 50–100 mg	Lower extremity edema	Self-reported and questionnaire
Volpe *et al.* [105]	755	56	61	2	Amlodipine 5 mg vs. amlodipine/olmesartan 5/10–40 mg	Peripheral edema	Self-reported
Weir *et al.* [106]	223	54	60	3	Nifedipine 30–90 mg vs. losartan/HCTZ 50/25 mg	Edema	Self-reported
Weir *et al.* [107]	482	49	48	3	Amlodipine 10 mg vs. valsartan/HCTZ 160/12.5 mg	Peripheral edema	Self-reported
Wester *et al.* [108]	183	53	48	1	Felodipine ER 5–20 mg vs. placebo	Peripheral edema	Self-reported and questionnaire
White *et al.* [109]	269	68	47	6	Amlodipine 2.5–10 mg vs. eplerenone 50–200 mg	Peripheral edema	Self-reported
White *et al.* [110]	261	55	61	3.5	Diltiazem ER 240–540 mg vs. ramipril 5–20 mg	Lower limb edema	Self-reported
Wright *et al.* [111]	262	50	44	3	Amlodipine 5–10 mg vs. diltiazem 360–540 mg	Lower limb edema	Self-reported
Zanchetti *et al.* [1]	489	51	54	12	Amlodipine 5–10 mg vs. manidipine 10–20 mg	Ankle edema	Self-reported
Zannad and Boivin [112]	212	55	39	1.5	Amlodipine 5 mg vs. felodipine/metoprolol 5/50 mg	Peripheral edema	Self-reported
Zidek *et al.* [113]	207	54	54	2	Amlodipine 5–10 mg vs. nifedipine 30–60 mg	Edema	Self-reported

ACE, angiotensin-converting enzyme; ATAR, Assessment of combination Therapy of Amlodipine/Ramipril; CCB, calcium channel blocker; ER, extended release; FISH, Finnish Isradipine Study in Hypertension; LSI, low salt intake; HCTZ, hydrochlorothiazide; HSI, high salt intake; MG, microgranules; OP, osmotic pump; pts, patients; SELECT, Systolic Evaluation of Lotrel Efficacy and Comparative Therapies; STOP, Swedish Trial in Old Patients with hypertension; TOMHS, The Treatment of Mild Hypertension Study group; VALUE, Valsartan Antihypertensive Long-term Use Evaluation Trial; VAST, Valsartan/HCTZ versus Amlodipine in STage II hypertensive patients.
[a] All studies had baseline patient population with hypertension without coronary artery disease or heart failure.

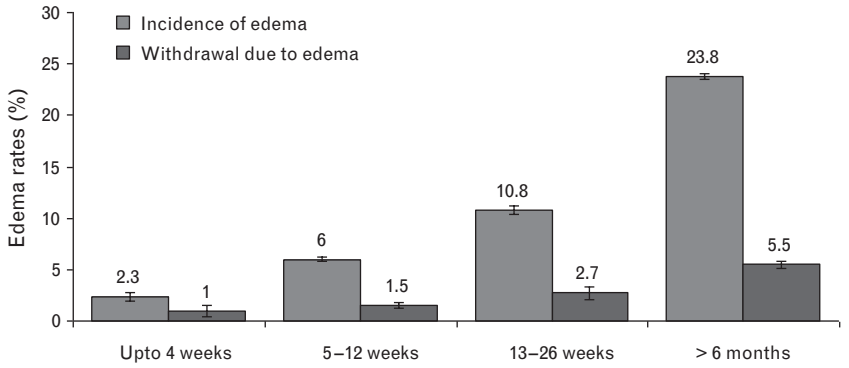
switching to a lipophilic CCB will also significantly reduce the rate of edema, in our database by 57%, several studies have shown the benefit of adding all inhibitors of the rennin–angiotensin system (RAS) to CCBs in reducing the edema rates, the addition of a diuretic is not usually very effective, as CCB-related edema is not caused by a sodium/fluid overload [116]. In contrast, the addition of ACE inhibitors or ARBs will reduce peripheral edema by decreasing postcapillary resistance, thus normalizing intracapillary pressure and reducing

Fig. 2



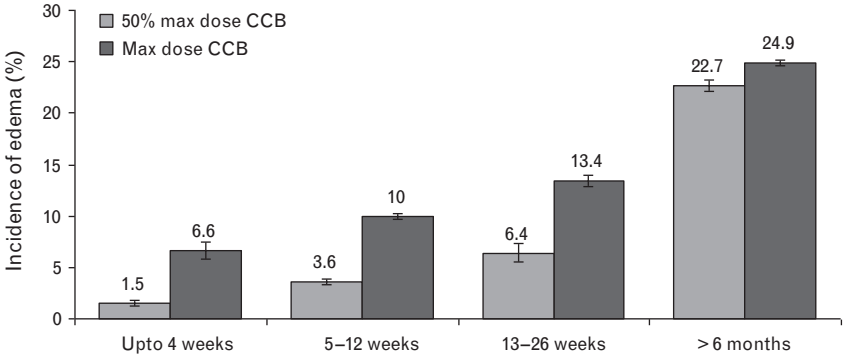
Head-to-head comparison of newer lipophilic dihydropyridines (DHPs) with older dihydropyridines on incidence of peripheral edema.

Fig. 3



Weighted incidence of peripheral edema and patient withdrawal due to edema. Error bars represent 95% confidence intervals.

Fig. 4



Weighted incidence of edema with high-dose and low-dose calcium channel blockers, stratified based on duration of therapy. Error bars represent 95% confidence intervals.

fluid extravasation. A recent meta-analysis [117] of 25 randomized controlled trials with 17 206 patients comparing CCB monotherapy to CCB/RAS blocker combination showed that the incidence of peripheral edema with CCB/RAS blocker combination was 38% lower than with CCB monotherapy ($P < 0.0001$). Similarly, the risk of withdrawal due to peripheral edema was 62% lower with CCB/RAS blocker combination compared with CCB monotherapy ($P < 0.0001$). On indirect comparison, ACE inhibitors were significantly more efficacious than angiotensin receptor blockers in reducing the incidence of edema. Newer lipophilic DHPs act by binding strongly to the lipid bilayer of cell membranes close to the calcium channel from where it is slowly released, thus giving gradual onset and 24-h duration despite short plasma half-life of 2–5 h [118,119]. This might be the reason for its lesser proneness to edema. Combination of ACE inhibitor or angiotensin receptor blocker with newer lipophilic DHPs may further reduce peripheral edema [120].

Of note, incidence of peripheral edema in our analysis was found to be considerably higher than reported in the PDR. Physicians and patient alike should become familiar with this common adverse effect of CCBs, which must be clearly distinguished from peripheral edema associated with heart failure.

Limitations

As with other meta-analyses, given the lack of data in each trial, we did not adjust our analysis for adherence to therapy. Also, the results are subject to limitations inherent to any meta-analysis based on pooling of data from different trials with different duration, different definitions for peripheral edema and different patient groups. All the analyses were divided into subgroups based on duration of therapy, as it had significant impact on both the incidence and withdrawal due to edema. Most studies failed to report the edema rates based on sex, thus it could not be ascertained whether women have higher incidence of edema.

In conclusion, both the incidence of peripheral edema and patient withdrawal due to edema progressively increase with duration of therapy up to 6 months. Over the long term, more than 5% of patients discontinued CCBs because of this adverse effect. The incidence of peripheral edema was found to be higher for traditional DHPs and lower for both newer lipophilic DHPs and non-DHPs.

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H.M. had full access to all of the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

Study concept and design: H.M., S.B. and F.H.M.

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Analysis and interpretation of data: H.M., S.B. and F.H.M.

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