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META-ANALYSIS

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Comparative peripheral edema for dihydropyridines calcium channel blockers treatment: A systematic review and network meta-analysis

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Abstract

Dihydropyridine calcium channel blockers (DHPCCBs) are widely used to treat hypertension and chronic coronary artery disease. One common adverse effect of DHPCCBs is peripheral edema, particularly of the lower limbs. The side effect could lead to dose reduction or discontinuation of the medication. The combination of DHPCCBs and renin-angiotensin system blockers has shown to reduce the risk of DHPCCBs-associated peripheral edema compared with DHPCCBs monotherapy. We performed the current systematic review and network meta-analysis of randomized controlled trials (RCTs) to estimate the rate of peripheral edema with DHPCCBs as a class and with individual DHPCCBs and the ranking of the reduction of peripheral edema. The effects of renin-angiotensin system blockers on DHPCCBs network meta-analysis were created to analyze the ranking of the reduction of peripheral edema. A total of 3312 publications were identified and 71 studies with 56,283 patients were included. Nifedipine ranked highest in inducing peripheral edema (SUCRA 81.8%) and lacidipine (SUCRA 12.8%) ranked the least. All DHPCCBs except lacidipine resulted in higher relative risk (RR) of peripheral edema compared with placebo. Nifedipine plus angiotensin receptor blocker (SUCRA: 92.3%) did not mitigate peripheral edema and amlodipine plus angiotensin-converting enzyme inhibitors (SUCRA: 16%) reduced peripheral edema the most. Nifedipine ranked the highest and lacidipine ranked the lowest amongst DHPCCBs for developing peripheral edema when used for cardiovascular indications. The second or higher generation of DHPCCBs combination with ACEIs or ARBs or diuretics lowered the chance of peripheral edema development compared to single DHPCCB treatment.

KEYWORDS
Ace Inhibitors, Coronary Disease, Hypertension General

1 | INTRODUCTION

Dihydropyridine calcium channel blockers (DHPCCBs) are widely used to treat hypertension[1] and chronic coronary artery disease.[2] One common adverse effect of DHPCCBs is peripheral edema, particularly of the lower limbs. The rate of peripheral edema induced by DHPCCBs varies significantly from 5% to 60% with high doses[3–6] among different DHPCCBs.[7–9] The main mechanism of peripheral edema with DHPCCBs is the imbalance between precapillary and postcapillary tone, which causes intracapillary hypertension and extravasation of fluid.[10] The side effect could lead to dose reduction or discontinuation of the medication, by patient or provider, adversely affecting the compliance and thus the antihypertensive efficacy.[3,10]

Although one review has already analyzed the pooled incidence of peripheral edema with different DHPCCBs using pairwise meta-analysis,[11] the indirect network comparison of incidence of peripheral edema caused by different DHPCCBs has not been established. It would be beneficial to identify a CCB with a lower incidence of peripheral edema to minimize the risks to patients. In addition, the combination of DHPCCBs and renin-angiotensin system blockers (RASBs) was shown to reduce the risk of DHPCCBs-associated peripheral edema compared with DHPCCBs monotherapy,[3] but which combination is most likely to reduce the risk of peripheral edema has not been ranked by network meta-analysis.

In our systematic review, we performed an updated head-to-head meta-analysis, network meta-analysis of randomized controlled trials (RCTs) to estimate the rate of peripheral edema with DHPCCBs as a class and with individual DHPCCBs. Also, the effects of RASBs on DHPCCBs network meta-analysis was created to analyze the ranking of the reduction of peripheral edema.

2 | METHODS

We performed the current systematic review and network meta-analysis in accordance with a review protocol and the reporting of this systematic review was guided by to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) extension statement for reporting network meta-analysis.[12] This network meta-analysis was registered on the PROSPERO website (CRD42020163489).

2.1 | Search strategy

The medical librarian developed and executed comprehensive searches in Ovid MEDLINE, Ovid EMBASE, CINAHL, Web of Science Core Collection, Cochrane Library (Wiley), and ProQuest Dissertations & Theses Global on October 23, 2019. The search was subsequently updated on March 18, 2021. To ensure an extensive search was conducted, the search strategy included all terms related to calcium channel blockers. (Appendix I) The search was limited to English and Chinese languages.

2.2 | Study selection

2.2.1 | Inclusion and exclusion criteria

The inclusion criteria were: (1) randomized open-labeled or blinded controlled studies; (2) DHPCCBs treatment; and (3) ankle edema, lower trunk edema, peripheral edema, or leg edema reported. The excluded criteria were: (1) the same chemical ingredient of CCBs as a comparator; (2) edema before intervention; (3) no edema reported; (4) no related edema caused by CCBs; (5) no cardiovascular disease involved; and (6) edema caused by other types of drugs.

2.2.2 | Intervention/comparators

The intervention group for single agent included all CCBs with the comparator as any of other antihypertensive agents or placebo. The combination included any CCBs plus any other antihypertensive agent compared with a combination of antihypertensive agents other than CCB or placebo.

2.2.3 | Data extraction and quality assessment

Two raters independently extracted data with all basic characteristics from included trials: authors, journal, population, intervention, comparator, sample size, and drug-related peripheral edema. When insufficient information was reported in trials, authors were contacted or data were calculated according to the methods in the Cochrane Handbook for Systematic Reviews of Interventions.[13] As for the single DHPCCB network meta-analysis, we only extracted the peripheral edema counts induced by single DHPCCB treatment versus other type of single DHPCCB or single DHPCCB treatment versus placebo. When it came to the combination DHPCCB treatment, no limitation was set to extract the peripheral edema data with the combination treatment. By applying the Cochrane Collaboration's tools,[14] two raters independently appraised the quality of all included studies. One of three category judgments (high, unclear, and low risk) was assigned in each bias domain: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting, and other bias. A third researcher helped resolve differences of opinion or decisions that required further judgment.

2.3 | Statistical analysis

To build the connective relationship within multiarms and between studies, a network meta-analysis was performed. The indirect evaluations of peripheral edema risk ratios (RRs) for different single DHPCCB treatments that had not been compared head-to-head directly was determined. Also, peripheral edema RRs for different DHPCCB

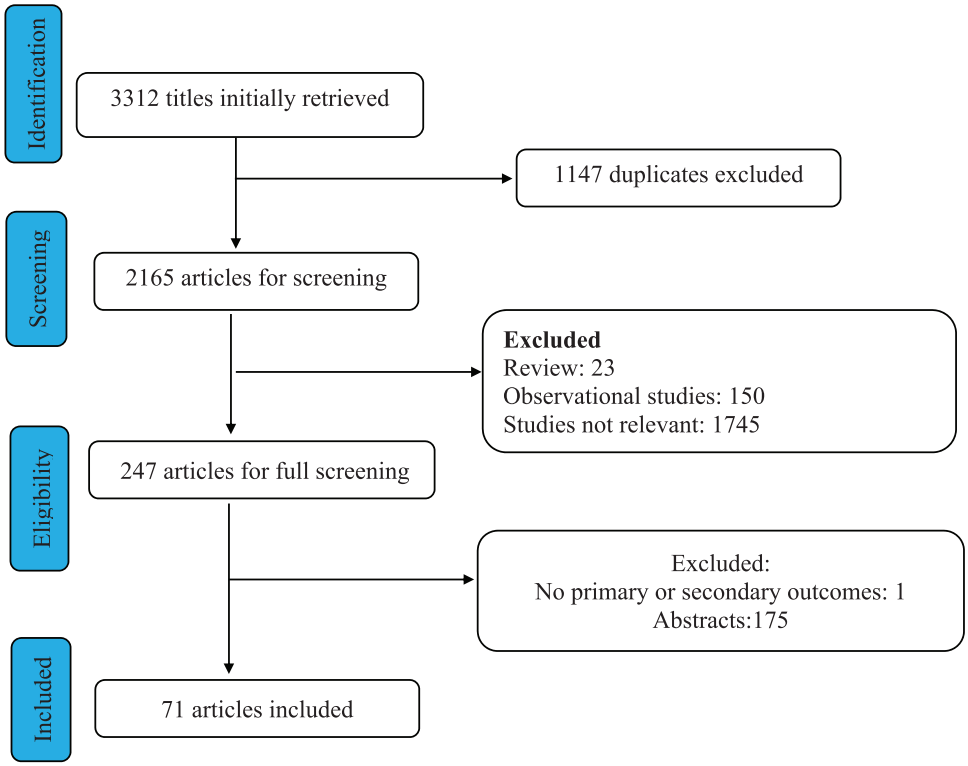

FIGURE 1 PRISMA diagram

combinations in these trials were evaluated. Using these methods, network maps of these connections and network forests of estimated RRs were created by entering every event arm data in the Stata software. In addition, different DHPCCBs or different DHPCCB combinations were ranked according to the surface under the cumulative ranking curve (SUCRA). These curves indicated the maximum probability of peripheral edema caused by one DHPCCB or DHPCCB combination and the minimum probability of peripheral edema caused by another. In the process of network meta-analysis, the global inconsistency test and node-splitting approach were used to check for inconsistency to justify using combination of direct and indirect evidence. Normally, we used the random model in the consistency test. If no heterogeneity was found in the inconsistency test, the fixed model was chosen to do the consistency test. Publication bias was estimated by comparison-adjusted funnel plots.

A two-tailed p-value $< .05$ was considered statistically significant. All the statistical analyses were performed in Stata 14.1 (Stata Corp, College Station, TX, USA).

3 | RESULTS

3.1 | Study selection

The team used Covidence (www.covidence.org), a systematic review screening tool to facilitate the screening process. In addition to subscription databases, the research team searched Google Scholar and the first 200 results were evaluated for inclusion. Reviewing the first 200 results was deemed a reasonable number to screen since there is high overlap between Web of Science and Google Scholar.[15] The research team also reviewed the reference lists of included studies.

3.2 | Characteristics of included studies

A total of 3312 publications were identified. After removing 1147 duplications, the abstracts of the remaining 2165 were screened. Ultimately, 71 studies with 56 283 patients were included. The mean age range is 50-70.8 years. Figure 1 shows the PRISMA diagram, outlining how publications funneled through the screening process. The features of the included studies are shown in Table 1. Twenty-four studies were placebo-controlled trials, and nine studies were head-to-head comparisons between different DHPCCBs (single treatment). Forty-two trials were comparisons between DHPCCB combination and single DHPCCB or alternatives. Rates of reported peripheral edema induced by single DHPCCBs treatment ranged from 0% to 77.4%. Participants with hypertension were enrolled in 94 studies, coronary artery disease in eight studies, heart failure in two studies, and nephropathy in one study. The age ranged between 18 and 85 years. The detailed treatment information of these eligible trials is listed in Table 1. Figure 2 shows the quality of eligible studies. Only the allocation concealment processes were not fulfilled in more than 75% of the trials.

TABLE 1 Basic characteristics of studies

First Author, Year	Journal	Patient characteristics, sample size	dihydropyridine CCB or dihydropyridine CCB combination	Comparator drugs	Maximal dosage	Follow-up
Bakris G, 2013[36]	Am. J. Cardiol	Population: stage 2 HTN Mean age: 60.5 yr n = 11 506 (G1 = 5744, G2 = 5762)	G1: AML/benazepril	G2: benazepril/ HCTZ	G1: 40 mg/10 mg G2: 40 mg/ 25 mg	G1: 35.7, G2: 35.6 (months)
Black HR, 2011[37]	J. Clin. Hypertens	Population: stage 2 HTN Mean age: 52.8 yr n = 443 (G1 = 223, G2 = 220)	G1: AML	G2: aliskiren / AML	G1: 10 mg G2: 300 mg/10 mg	8 weeks
Bobrie G, 2012[38]	Clin. Ther.	Population: HTN Mean age (range): 57.3 yr (19-88) n = 287 (G1 = 143, G2 = 144)	G1: AML	G2: AML/ irbesartan	G1: 10 mg G2: 150 mg/10 mg	10 weeks
Boero R, 2003[39]	AJKD	Population: nondiabetic nephropathy Mean age: 54 yr n = 69 (G1 = 36, G2 = 33)	G1: trandolapril/AML	G2: trandolapril/ verapamil	G1: 2 mg/180 mg G2: 2 mg/5 mg	8 weeks
Brown MJ, 2011[40]	Lancet	Population: HTN Mean age: 58.2 yr n = 1254 (G1 = 620, G2 = 316, G3 = 318)	G1: aliskiren / AML G2: AML	G3: aliskiren	G1: 300 mg/10 mg G2: 10 mg G3: 300 mg	32 weeks
Calhoun DA, 2009[41]	Hypertension	Population: HTN Mean age (range): 53 yr (18-85) n = 2271 (G1 = 583, G2 = 561, G3 = 568, G4 = 559)	G1: VAL/HCTZ/AML G2: HCTZ/ AML G3: VAL/AML	G4: VAL/HCTZ	G1: 320 mg/25 mg/10 mg G2: 25 mg/10 mg G3: 320 mg/10 mg G4: 320 mg/25 mg	9 weeks
Carruthers SG, 1993[42]	Clin. Invest. Med.	Population: HTN Mean age (range): 52.2 yr (22-70) n = 148 (G1 = 100, G2 = 48)	G1: felodipine	G2: placebo	G1: 20 mg	6 weeks
Chahine RA, 1993[43]	J. Am. Coll. Cardiol.	Population: CAD Mean age (range): 55.4 yr (35-71) n = 52 (G1 = 24, G2 = 28)	G1: AML	G2: placebo	G1: 10 mg	4 weeks
Chen T, 2013[44]	Chin. Med.	Population: HTN Mean age: 55.9 yr n = 176 (G1 = 86, G2 = 90)	G1: benazepril/lercanidipine	G2: benazepril	G1: 10 mg/10 mg G2: 10 mg	8 weeks
Chrysant SG, 1988[45]	Clin. Cardiol.	Population: HTN Mean age: 51.7 yr n = 43 (G1 = 33, G2 = 10)	G1: darodipine	G2: placebo	G1: 150 mg	4 weeks
Chrysant SG, 2003[46]	J. Hum. Hypertens.	Population: HTN Mean age: 52 yr n = 440 (G1 = 186, G2 = 188, G3 = 66)	G1: AML	G2: olmesartan G3: placebo	G1: 5 mg G2: 20 mg	8 weeks

(Continues)

TABLE 1 (Continued)

First Author, Year	Journal	Patient characteristics, sample size	dihydropyridine CCB or dihydropyridine CCB combination	Comparator drugs	Maximal dosage	Follow-up
Chrysant SG, 2004[47]	Am. J. Cardiol.	Population: HTN Mean age: 52.3 yr n = 329 (G1 = 164, G2 = 165)	G1: AML/benazepril	G2: benazepril	G1: 10 mg/40 mg G2: 40 mg	8 weeks
Chrysant SG, 2012[48]	Am. J. Cardiovas. Drugs	Population: HTN Mean age: 55.1 yr n = 2492 (G1 = 574, G2 = 552, G3 = 596, G4 = 580)	G1: olmesartan/AML/ HCTZ G2: AML / HCTZ G3: olmesartan/amlodipine	G4: olmesartan/ HCTZ	G1: 40 mg/10 mg/25 mg G2: 10 mg/25 mg G3: 40 mg/10 mg G4: 40 mg/25 mg	12 weeks
Cohn JN, 1997[49]	Circulation	Population: heart failure Mean age: 64 yr n = 524 (G1 = 224, G2 = 226)	G1: felodipine	G2: placebo	G1: 10 mg	18 months
DeWood MA, 1990[50]	Am. Heart J.	Population: angina pectoris Mean age: 62 yr n = 250 (G1 = 124, G2 = 126)	G1: nifedipine	G2: nicardipine	G1: 20 mg TID G2: 30 mg TID	8 weeks
Dingemanse J, 2015[51]	J. Hum. Hypertens.	Population: HTN Mean age (range): 57.1 yr (18-75) n = 107 (G1 = 54, G2 = 53)	G1: AML	G2: placebo	G1: 10 mg	4 weeks
Dominiczak AF, 2019[52]	J. Hypertens.	Population: HTN Mean age (range): 57 yr (18-75) n = 473 (G1 = 236, G2 = 237)	G1: AML/valsartan	G2: AML/ indapamide	G1: 5 mg/80 mg G2: 5 mg/1.5 mg	12 weeks
Elliott WJ, 2015[53]	JASH	Population: HTN Mean age (range): 52 yr n = 837 (G1 = 280, G2 = 279, G3 = 278)	G1: AML G2: AML/perindopril	G3: perindopril	G1: 10 mg G2: 10 mg/14 mg G3: 16 mg	42 days
Flack JM, 2009[54]	J. Hum. Hypertens.	Population: stage 2 HTN n = 572 (G1 = 286, G2 = 286)	G1: AML/valsartan	G2: AML	G1: 10 mg/160 mg G2: 10 mg	12 weeks
Fagan T, 1993[55]	Chest	Population: HTN Mean age (range): 22-75 yr n = 230 (G1 = 172, G2 = 58)	G1: nicardipine	G2: placebo	G1: 60 mg	12 weeks
Fogari R, 1997[56]	J. Cardiovasc Pharmacol.	Population: HTN not controlled with ACEI Mean age: 55 yr n = 448 (G1 = 289, G2 = 159)	G1: AML/benazepril	G2: benazepril	G1: 5 mg/10 mg G2: 10 mg	8 weeks
Frishman, WH, 1994[57]	Am. J. Cardiol.	Population: HTN n = 125 (G1 = 41, G2 = 41, G3 = 43)	G1: AML	G2: placebo G3: atenolol	G1: 10 mg G3: 100 mg	8 weeks

(Continues)

TABLE 1 (Continued)

First Author, Year	Journal	Patient characteristics, sample size	dihydropyridine CCB or dihydropyridine CCB combination	Comparator drugs	Maximal dosage	Follow-up
Frishman, WH, 1995[58]	J. Clin. Pharmacol.	Population: HTN n = 332 (G1 = 82, G2 = 83, G3 = 82, G4 = 85)	G1: AML G2: AML/benazepril	G3: placebo G4: benazepril	G1: 2.5 mg G2: 2.5 mg/10 mg G4: 10 mg	8 weeks
Frishman, WH, 2006[59]	Am. J. Hypertens	Population: HTN Mean age (range): 54 yr (25-80) n = 1087 (G1 = 228, G2 = 542, G3 = 95, G4 = 222)	G1: felodipine G2: felodipine/metoprolol	G3: placebo G4: metoprolol	G1: 20 mg G2: 20 mg/400 mg G4: 400 mg	16 weeks
Glasser SP, 1989[60]	Am. J. Hypertens	Population: HTN n = 103 (G1 = 52, G2 = 51)	G1: AML	G2: placebo	G1: 10 mg	4 weeks
Gradman AH, 1997[5]	Am. J. Cardiol	Population: HTN Mean age: 53.5 yr n = 707 (G1 = 176, G2 = 319, G3 = 79, G4 = 133)	G1: felodipine G2: felodipine/enalapril	G3: placebo G4: enalapril	G1: 20 mg G2: 20 mg/10 mg G4: 10 mg	8 weeks
Halimi JM, 2007[61]	Clin. Transplant.	Population: hypertensive renal transplant recipients n = 99 (G1 = 34, G2 = 32, G3 = 33)	G1: AML G2: AML/enalapril	G3: enalapril	G1: 10 mg G2: 10 mg/10 mg G3: 10 mg	6 months
DEFIANT II Research Group, 1997[62]	Eur. Heart J.	Population: acute MI n = 542 (G1 = 270, G2 = 272)	G1: nisoldipine	G2: placebo	G1: 40 mg	24 weeks
Hasebe N, 2005[63]	J. Hypertens.	Population: essential HTN n = 258 (G1 = 130, G2 = 128)	G1: nifendipine/candesartan	G2: candesartan	G1: 20 mg/8 mg G2: 12 mg	8 weeks
Hayoz D, 2012[64]	J. Clin. Hypertens	Population: HTN n = 135 (G1 = 63, G2 = 62)	G1: AML	G2: VAL	G1: 10 mg G2:320 mg	38 weeks
Izzo JL, 2010[65]	J. Hum. Hypertens	Population: severe HTN Mean age: 18-80 yr n = 259 (G1 = 130, G2 = 129)	G1: AML	G2: AML/ benazepril	G1: 40 mg G2: 10 mg/40 mg	6 weeks
Johnson BF, 1992[66]	Am. J. Hypertens.	Population: HTN Mean age: 57 yr n = 135 (G1 = 41, G2 = 41, G3 = 43)	G1: AML	G2: placebo G3: atenolol	G1: 10 mg G3: 100 mg	8 weeks
Kang SM, 2011[67]	Clin. Ther.	Population HTN Mean age (range): 53.7 yr (27-80) n = 185 (G1 = 93, G2 = 92)	G1: AML	G2: AML/losartan	G1: 10 mg G2: 5 mg/50 mg	8 weeks
Kario Kazuomi, 2017[68]	Circulation	Population: nocturnal BP ≥120/70 mmHg Mean age: 62.7 yr n = 411 (G1 = 203, G2 = 208)	G1: AML/irbesartan	G2: irbesartan/ TCTZ	G1: 5 mg/100 mg G2: 100 mg/1 mg	12 weeks

(Continues)

TABLE 1 (Continued)

First Author, Year	Journal	Patient characteristics, sample size	dihydropyridine CCB or dihydropyridine CCB combination	Comparator drugs	Maximal dosage	Follow-up
Ke YN, 2012[69]	Cardiovasc. Thera.	Population: hypertension Mean age: 55.9 yr n = 360 (G1 = 178, G2 = 182)	G1: nifedipine/VAL	G2: VAL	G1: 30 mg/80 mg G2: 160 mg	12 weeks
Kereiakes DJ, 2007[70]	A. J. Cardiovasc. Drugs	Population: stage 2 HTN Mean age: 55.6 yr n = 191 (G1 = 97, G2 = 94)	G1: AML/benazepril	G2: olmesartan/HCTZ	G1: 10 mg/20 mg G2: 40 mg/25 mg	12 weeks
Kes S, 2003[71]	Curr. Med. Res. Opin.	Population: HTN Mean age: 35-75 yr n = 155 (G1 = 79, G2 = 76)	G1 AML	G2: nifedipine	G1: 10 mg G2: 60 mg	12 weeks
Kirch W, 1990[72]	J. Cardiovasc. Pharmacol.	Population: essential HTN Mean age: 58.2 yr n = 86 (G1 = 65, G2 = 21)	G1: isradipine	G2: placebo	G1: 5 mg	6 weeks
Kereiakes DJ, 2012[73]	Cardiovasc Diabetol.	Population: HTN with DM or CKD Mean age: 62.6 yr n = 2492 (G1 = 628, G2 = 637, G3 = 600, G4 = 627)	G1: AML/Olmesartan	G2: olmesartan/HCTZ G3: AML/HCTZ G4: AML/Olmesartan/HCTZ	G1: 10 mg/40 mg G2: 40 mg/25 mg G3: 10 mg/25 mg G4: 10 mg/40 mg/25 mg	12 weeks
Kloner RA, 2008[74]	Ann. Pharmacother.	Population: mild HTN Mean age (range): 58.5 yr (30-75) n = 431 (G1 = 99, G2 = 120, G3 = 102, G4 = 110)	G1: AML/quinapril G2: AML/losartan	G3: losartan G4: quinapril	G1: 10 mg/40 mg G2: 10 mg/100 g G3: 100 mg G4: 40 mg	20 weeks
Kohlmann O, 2006[75]	ARQ	Population: stage 1 & 2 HTN Mean age: 52.9 yr n = 198 (G1 = 66, G2 = 66, G3 = 66)	G1: AML G2: AML/losartan	G3: losartan	G1: 10 mg G2: 5 mg/100 mg G3: 100 mg	12 weeks
Kuschnir E, 2004[76]	J. Cardiovasc. Pharmacol.	Population: stage 1 & 2 HTN Mean age (range): 56 yr (24-78) n = 300 (G1 = 100, G2 = 100, G3 = 100)	G1: nifedipine G2: nifedipine/losartan	G3: losartan	G1: 20 mg G2: 50 mg G3: 20 mg/50 mg	8 weeks
Leonetti G, 2002[9]	Blood Press.	Population: elderly HTN Mean age: 69.8 yr n = 828 (G1 = 200, G2 = 420, G3 = 208)	G1: AML G2: lercanidipine	G3: lacidipine	G1: 10 mg G2: 20 mg G3: 4 mg	Average 12 months
Lewin AJ, 2014[77]	Ethn. Dis.	Population: HTN Mean age (range): 55.1 yr n = 2491 (G1 = 628, G2 = 600, G3 = 627, G4 = 636)	G1: AML /olmesartan G2: AML/HCTZ G3: AML/olmesartan/ HCTZ	G4: olmesartan/HCTZ	G1: 10 mg/40 mg G2: 10 mg/25 mg G3: 10 mg/40 mg/25 mg G4: 40 mg/25 mg	40 weeks
Lin TH, 2013[78]	KJMS	Population: HTN Mean age (range): 53.1 yr (20-80) n = 141 (G1 = 71, G2 = 70)	G1: AML	G2: AML/olmesartan	G1: 10 mg G2: 5 mg/20 mg	8 weeks

(Continues)

TABLE 1 (Continued)

First Author, Year	Journal	Patient characteristics, sample size	dihydropyridine CCB or dihydropyridine CCB combination	Comparator drugs	Maximal dosage	Follow-up
Littlejohn III, TW, 2013[79]	J. Hum. Hypertens.	Population: HTN Mean age (range): 54.1 yr n = 1688 (G1 = 366, G2 = 726, G3 = 198, G4 = 398)	G1: AML G12: AML/aliskiren	G3: placebo G4: aliskiren	G1: 10 mg G2: 10 mg/300 mg G4: 300 mg	12 weeks
London G, 2006[80]	Am. J. Hypertens.	Population: HTN Mean age (range): 58.9 yr n = 1758 (G1 = 444, G2 = 439, G3 = 435, G4 = 440)	G1: AML	G2: placebo G3: candesartan G4: indapamide	G1: 5 mg G3: 8 mg G4: 1.5 mg	12 weeks
Lund-Johansen P, 2003[7]	J. Hypertens.	Population: postmenopause mild to moderate HTN Mean age: 60 yr n = 92 (G1 = 44, G2 = 48)	G1: AML	G2: lercanidipine	G1: 10 mg G2: 20 mg	8 weeks
Lüscher TF, 2009[81]	Eur. Heart J.	Population: stable CAD Mean age: 58 yr n = 226 (G1 = 114, G2 = 112)	G1: nifedipine	G2: placebo	G1: 60 mg	18-24 months
Millar-Carig M, 2003[8]	J. Hum. Hypertens.	Population: elderly with isolated systolic HTN Mean age (range): 70.8 yr (60-85) n = 135 (G1 = 69, G2 = 66)	G1: lacidipine	G2: lercanidipine	G1: 4 mg G2: 20 mg	21 weeks
Miranda RD, 2008[82]	Clin. Ther.	Population: stage 1 & 2 HTN Mean age (range): 58.6 yr (40-79) n = 265 (G1 = 134, G2 = 131)	G1 AML	G2: AML/ramipril	G1: 10 mg G2: 10 mg/10 mg	18 weeks
Neutel JM, 2005[83]	J. Clin. Hypertens.	Population: HTN Mean age (range): 67.7 yr n = 443 (G1 = 146, G2 = 149, G3 = 148)	G1: AML G2: AML/ benazepril	G3: benazepril	G1: 5 mg G2: 5 mg/20 mg G3: 20 mg	8 weeks
Nissen SE, 2004[84]	JAMA	Population: CAD Mean age (range): 57.7 yr (32-82) n = 1997 (G1 = 665, G2 = 657, G3 = 675)	G1: AML	G2: placebo G3: enalapril	G1: 10 mg G3: 20 mg	24 months
Ongtengco I, 2002[85]	J. Hum. Hypertens.	Population: Asian with essential HTN Mean age (range): 50.4 yr (26-75) n = 222 (G1 = 109, G2 = 113)	G1: AML	G2: nifedipine	G1: 10 mg G2: 60 mg	12 weeks
Opie LH, 1997[86]	Am. J. Hypertens.	Population: essential HTN Mean age (range): 52.3 yr (20-75) n = 206 (G1 = 148, G2 = 58)	G1: nisoldipine	G2: placebo	G1: 30 mg	6 weeks
Packer M, 2013[87]	JACC: Heart Failure	Population: heart failure Mean age (range): 59 yr n = 1654 (G1 = 827, G2 = 827)	G1: AML	G2: placebo	G1: 10 mg	Median 33 months

(Continues)

TABLE 1 (Continued)

First Author, Year	Journal	Patient characteristics, sample size	dihydropyridine CCB or dihydropyridine CCB combination	Comparator drugs	Maximal dosage	Follow-up
Parati G, 2010[88]	Clin. Ther.	Population: essential HTN Mean age (range): 55 yr (30-75 n = 68 (G1 = 34, G2 = 34)	G1: barnidipine/losartan	G2: losartan	G1: 10 mg/50 mg G2: 100 mg	12 weeks
Pepine CJ, 2003[89]	Am. J. Cardiol.	Population: stage 1-2 HTN and CAD Mean age (range): 60 yr (40-80) n = 120 (G1 = 60, G2 = 60)	G1: AML	G2: nisoldipine	G1: 10 mg G2: 40 mg	6 weeks
Philipp T, 2011[90]	JASH	Population: stage 2 HTN Mean age (range): 57 yr n = 1249 (G1 = 207, G2 = 418, G3 = 209, G4 = 415)	G1: AMG2: AML /valsartan	G3: placebo G4: VAL	G1: 10 mg G2: 10 mg/320 mg G4: 320 mg	12 weeks
Poldermans D, 2007[91]	Clin Ther	Population: stage 2 HTN Mean age (range): 57 yr n = 130 (G1 = 64, G2 = 66)	G1: AML /valsartan	G2: lisinopril/HCTZ	G1: 10 mg/160 mg G2: 20 mg/12.5 mg	6 weeks
Poole-Wilson PA, 2004[92]	Lancet	Population: stable symptomatic CAD Mean age: 63.5 yr n = 7665 (G1 = 3825, G2 = 3840)	G1: nifedipine	G2: placebo	G1: 60 mg	6 weeks
Saito Ikuo, 2006[93]	Hypertens. Res.	Population: HTN Mean age: 56.9 yr n = 513 (G1 = 250, G2 = 263)	G1: nifedipine	G2: AML	G1: 40 mg G2: 5 mg	16 weeks
Scholze J, 1999[94]	Clin. Exp. Hypertens.	Population: mild-moderate HTN Mean age (range): 50.2 yr (18-73) n = 507 (G1 = 84, G2 = 255, G3 = 43, G4 = 125)	G1: felodipine G2: felodipine/ramipril	G3: placebo G4: ramipril	G1: 10 mg G2: 10 mg/10 mg G4: 10 mg	6 weeks
Sohn IS, 2017[95]	Clin. Ther.	Population: HTN Mean age: 57.3 yr n = 425 (G1 = 106, G2 = 212, G3 = 107)	G1 AML G2: AML/candesartan	G3: candesartan	G1: 10 mg G2: 10 mg/16 mg G3: 16 mg	8 weeks
Suh, SY, 2014[96]	Clin. Ther.	Population: HTN; Mean age (range): 51.56 yr n = 190 (G1 = 97, G2 = 93)	G1: AML/losartan	G2: losartan/HCTZ	G1: 5 mg/100 mg G2: 100 mg/12.5 mg	8 weeks

(Continues)

TABLE 1 (Continued)

First Author, Year	Journal	Patient characteristics, sample size	dihydropyridine CCB or dihydropyridine CCB combination	Comparator drugs	Maximal dosage	Follow-up
Taddei S, 2003[97]	J. Cardiovasc. Pharmacol.	Population: moderate-severe HTN Mean age (range): 54.9 yr (32-68) n = 72 (G1 = 24, G2 = 24, G3 = 24)	G1: nifedipine G2: nifedipine/lisinopril	G3: lisinopril	G1: 30 mg G2: 30 mg/20 mg G3: 20 mg	14 weeks
Toto RD, 2008[98]	J. Clin. Hypertens.	Population: essential HTN with diabetes Mean age: 60.8 yr n = 304 (G1 = 152, G2 = 152)	G1: AML/benazepril	G2: tran-dolapril/verapamil	G1: 10 mg/20 mg G2: 4 mg/240 mg	36 weeks
Walker JM, 1996[99]	Int. J. Cardiol.	Population: angina Mean age: 35-57 yr n = 293 (G1 = 95, G2 = 99, G3 = 99)	G1: nifedipine	G2: ISMN G3: ISMN	G1: 90 mg G2: 60 mg G3: 100 mg	6 weeks
Wang JG, 2013[100]	Ad. Ther.	Population: HTN not adequately controlled by prior monotherapy Mean age: 54.5 yr n = 540 (G1 = 268, G2 = 272)	G1: nifedipine	G2: VAL/AML	G1: 30 mg G2: 80 mg/5 mg	12 weeks
White WB, 2003[101]	A. J. Hypertens.	Population: essential HTN; Mean age (range): 52 yr n = 178 (G1 = 95, G2 = 83)	G1: AML	G2: nisoldipine	G1: 10 mg G2: 60 mg	12 weeks
Yan P, 2014[102]	Clin. Exp. Hypertens.	Population: mild to moderate HTN; Mean age: 51 yr n = 341 (G1 = 227, G2 = 114)	G1: AML/ benazepril	G2: benazepril	G1: 5 mg/10 mg G2: 10 mg	12 weeks

Abbreviations: HTN, hypertension; CAD , coronary artery disease; MI, myocardial infarction; DM, diabetes; HCTZ, hydrochlorothiazide; AML, amlodipine; TCTZ, trichlormethiazide; VAL, valsartan; ISMN, isosorbide dinitrate.

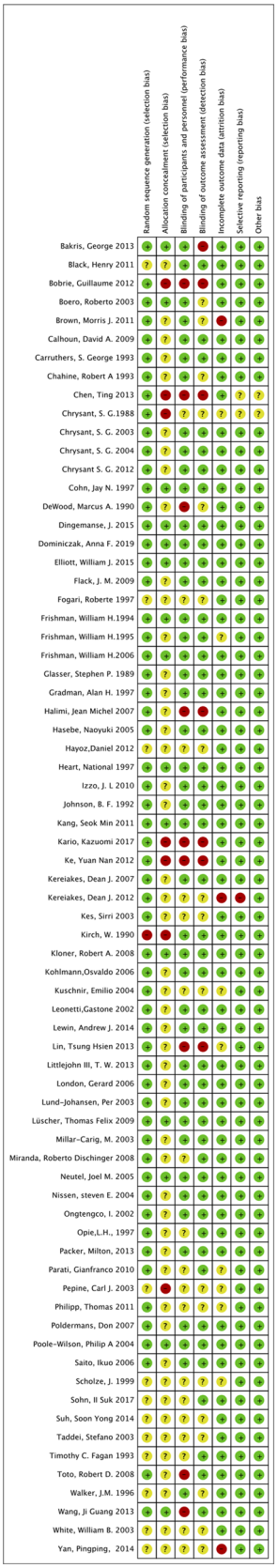

FIGURE 2 Judgments based on seven bias risk domains for all included studies

3.3 | Network plot

Network plots including single DHPCCB treatment and combined CCBs treatment were generated. Figure 3 illustrates the network maps of nine different DHPCCB comparisons (A) and 24 DHPCCB combination treatment comparisons (B).

3.4 | Single CCBs treatment network meta-analysis for peripheral edema

The direct and indirect evidence of different single CCBs was combined to analyze the network meta-analysis. In the next step, comparisons were completed between each DHPCCB drug with alternative DHPCCB drugs or placebo in the network meta-analysis based on the direct or indirect evidence. For each treatment in the network meta-analysis, the ranking indicates which of the DHPCCBs was more likely to cause peripheral edema according to their surface under the cumulative ranking curves (SUCRA). In Figure 4, nifedipine ranked as number one of inducing peripheral edema (SUCRA 81.8%). The order for the rest of the CCBs was as follows: nisoldipine (SUCRA 78.6%), nicardipine (SUCRA 77.2%), amlodipine (SUCRA 58.5%), darodipine (SUCRA 52.4%), isradipine (SUCRA 48.8%), felodipine (SUCRA 47.3%), lercanidipine (SUCRA 26.2%), and lacidipine (SUCRA 12.8%).

All DHPCCBs except lacidipine resulted in higher relative risk (RR) of peripheral edema compared with placebo. Lacidipine showed the least probability for peripheral edema, but no significance was observed between lacidipine and placebo (RR = 1.19, 95% CI: 0.38–3.75). Lercanidpine caused less probability than other types of DHPCCB (except lacidipine), and no statistical significance between lercanidipine and placebo (RR = 1.27, 95% CI: 0.48–3.33) was observed. Amlodipine, one of the most popularly prescribed DHPCCB, had 3.34 times risk of developing peripheral edema compared with placebo (RR = 3.34, 95% CI: 2.08–5.37). Similarly, compared with placebo, nifedipine (RR = 6.03, 95% CI: 2.89–12.61), nisoldipine (RR = 5.58, 95% CI: 2.41–12.94), nicardipine (RR = 5.72, 95% CI: 1.73–18.87), and felodipine (RR = 2.48, 95% CI: 1.14–5.37) showed statistically significant higher chance of peripheral edema development. Although lacidipine and lercanidipine did not show statistical significance compared with placebo, nifedipine, nisoldipine, and amlodipine had higher risk of peripheral edema than them individually (Figure 4). The 95% CI of the inconsistency factors of the existing closed-loops (Figure 4) did not exclude zero implying that there was no observed inconsistency between direct and indirect evidence.

3.5 | Combined CCBs treatment network meta-analysis for peripheral edema

The peripheral edema ranking of the combined CCBs interventions based on their SUCRA was shown in Figure 5. Among the twenty-four combination CCBs treatments, six combination interventions resulted

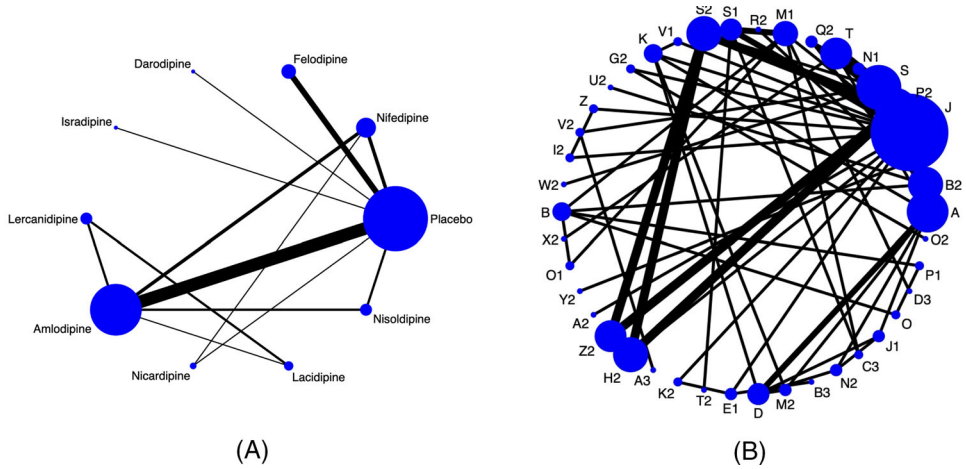

FIGURE 3 DHPCCBs treatment network map for peripheral edema. Different treatments with direct evidence are connected by the black lines. Every black line width is positively proportional to the number of trials including every pair of treatments, whereas every circle size is positively proportional to the total number of patients for each treatment. The comparison of single DHPCCB treatments and peripheral edema is showed in diagram A and the comparison of combined DHPCCBs treatment and peripheral edema is showed in diagram B

A = placebo	A2 = amlodipine + ramipril	A3 = trandolapril + amlodipine
B = nifedipine	B2 = amlodipine + valsartan	B3 = nifedipine + candesartan
C3 = amlodipine + quinapril	D = felodipine	D3 = barnidipine + losartan
E1 = candesartan	G2 = irbesartan + amlodipine	H2 = olmesartan + amlodipine
I2 = perindopril + amlodipine	J = amlodipine	J1 = ramipril
K = enalapril	K2 = candesartan + amlodipine	M1 = losartan
N1 = valsartan + hydrochlorothiazide	N2 = felodipine+ ramipril	O = lisinopril
O1 = nifedipine + losartan	O2 = irbesartan + trichlormethiazide	P1 = nifedipine + lisinopril
P2 = amlodipine + hydrochlorothiazide	Q2 = amlodipine+ valsartan + hydrochlorothiazide	R2 = lisinopril + hydrochlorothiazide
S = amlodipine + benazepril	S1 = losartan + amlodipine	S2 = olmesartan + hydrochlorothiazide
T = benazepril	T2 = losartan+ hydrochlorothiazide	U2 = amlodipine + indapamide
V1 = amlodipine + enalapril	V2 = trandolapril + verapamil	W2 = benazepril + hydrochlorothiazide
X2 = benazepril + lercanidipine	Y2 = nifedipine + valsartan	Z = perindopril
Z2 = amlodipine + olmesartan + hydrochlorothiazide		

in less chance of peripheral edema development than placebo: amlodipine plus trandolapril (RR = 1.09, 95% CI: 0.26–4.64), lercanidipine plus benazepril (RR = 1.86, 95% CI: 0.06–53.60), nifedipine plus candesartan (RR = 2.56, 95% CI: 0.07–93.97), amlodipine plus irbesartan (RR = 2.59, 95% CI: 0.12–57.27), nifedipine plus candesartan (RR = 37.94, 95% CI: 0.47–3075.24), and amlodipine plus candesartan (RR = 20.09, 95% CI: 0.98–413.19). However, no statistical significances were observed.

To address the wide CI in the combination DHPCCB network meta-analysis, the combination of treatments was grouped as classes of agents. The peripheral edema ranked in the order: nifedipine plus ARB (SUCRA: 92.3%), nifedipine plus ACEI (SUCRA: 78.8%), nifedipine (SUCRA: 74.6%), felodipine (SUCRA: 68.7%), amlodipine (SUCRA: 52.9%), amlodipine plus diuretics (SUCRA: 52.2%), felodipine plus ACEI (SUCRA: 41.8%), amlodipine plus ARB (SUCRA: 39.2%), amlodipine plus diuretics plus ARB (SUCRA: 30.2%), and amlodipine plus ACEI (SUCRA: 16%). Amlodipine plus ACEI (benazepril, perindopril, enalapril, and ramipril) performed the best among amlodipine plus ARB (losartan, irbesartan, olmesartan, valsartan, and candesartan), amlodipine plus diuretics (hydrochlorothiazide), and amlodipine single (Figure 6). Similarly, felodipine plus ACEI (enapril and ramipril) significantly reduced the risk of peripheral edema compared to single felodipine treatment. However, neither nifedipine plus ARB (losartan, candesartan, and valsartan) nor nifedipine plus ACEI (lisinopril) alleviated

Nifedipine (81.8%)	0.93 (0.31,2.75)	0.95 (0.35,2.58)	0.55 (0.25,1.24)	0.48 (0.02,10.90)	0.39 (0.02,9.42)	0.41 (0.14,1.19)	0.21 (0.07,0.67)	0.17 (0.08,0.35)	0.14 (0.04,0.52)
1.08 (0.36,3.21)	Nisoldipine (78.6%)	1.02 (0.24,4.36)	0.60 (0.27,1.34)	0.52 (0.02,12.10)	0.42 (0.02,10.44)	0.44 (0.15,1.32)	0.23 (0.07,0.74)	0.18 (0.08,0.42)	0.15 (0.04,0.57)
1.05 (0.39,2.87)	0.98 (0.23,4.15)	Nicardipine (77.2%)	0.58 (0.17,2.04)	0.51 (0.02,13.21)	0.41 (0.01,11.37)	0.43 (0.10,1.81)	0.22 (0.05,1.00)	0.17 (0.05,0.58)	0.15 (0.03,0.75)
1.81 (0.81,4.06)	1.67 (0.74,3.76)	1.71 (0.49,5.98)	Amlodipine (58.5%)	0.87 (0.04,18.71)	0.70 (0.03,16.18)	0.74 (0.31,1.75)	0.38 (0.16,0.89)	0.30 (0.19,0.48)	0.25 (0.09,0.72)
2.07 (0.09,46.81)	1.92 (0.08,44.47)	1.96 (0.08,50.97)	1.15 (0.05,24.61)	Darodipine (52.4%)	0.80 (0.01,61.40)	0.85 (0.04,19.38)	0.43 (0.02,10.45)	0.34 (0.02,7.10)	0.29 (0.01,7.37)
2.59 (0.11,62.97)	2.39 (0.10,59.78)	2.45 (0.09,68.34)	1.43 (0.06,33.14)	1.25 (0.02,95.62)	Isradipine (48.8%)	1.06 (0.04,26.07)	0.54 (0.02,14.04)	0.43 (0.02,9.57)	0.36 (0.01,9.89)
2.44 (0.84,7.09)	2.26 (0.76,6.70)	2.31 (0.55,9.67)	1.35 (0.57,3.18)	1.18 (0.05,26.82)	0.94 (0.04,23.16)	Felodipine (47.3%)	0.51 (0.15,1.72)	0.40 (0.19,0.88)	0.34 (0.09,1.32)
4.77 (1.48,15.33)	4.41 (1.36,14.33)	4.52 (1.00,20.37)	2.64 (1.12,6.19)	2.30 (0.10,55.30)	1.84 (0.07,47.70)	1.96 (0.58,6.59)	Lercanidipine (26.2%)	0.79 (0.30,2.08)	0.66 (0.27,1.63)
6.03 (2.89,12.61)	5.58 (2.41,12.94)	5.72 (1.73,18.87)	3.34 (2.08,5.37)	2.91 (0.14,60.22)	2.33 (0.10,52.13)	2.48 (1.14,5.37)	1.27 (0.48,3.33)	Placebo (16.5%)	0.84 (0.27,2.65)
7.17 (1.91,26.92)	6.64 (1.76,25.06)	6.80 (1.33,34.68)	3.97 (1.39,11.37)	3.46 (0.14,88.39)	2.77 (0.10,76.13)	2.94 (0.76,11.47)	1.51 (0.61,3.69)	1.19 (0.38,3.75)	Lacidipine (12.8%)

FIGURE 4 Single DHPCCBs interventions network meta-analysis for peripheral edema. The figure represents the relative risk with 95% confidence interval of single DHPCCBs compared with placebo. The probabilities beside the CCBs names were the treatment ranking based on SUCRA from left to right. The treatment drugs divided the figure into upper (blue colored) and lower (green colored) parts. For the lower part, the efficacy estimate was the ratio of the column defining treatment to the row defining treatment. For the upper part, the efficacy estimate was the ratio of the row defining treatment to the column defining treatment. The lower and the upper parts results were mutually reciprocal. The relative risk ratio in each treatment should be compared to the treatment to the right in the same row.

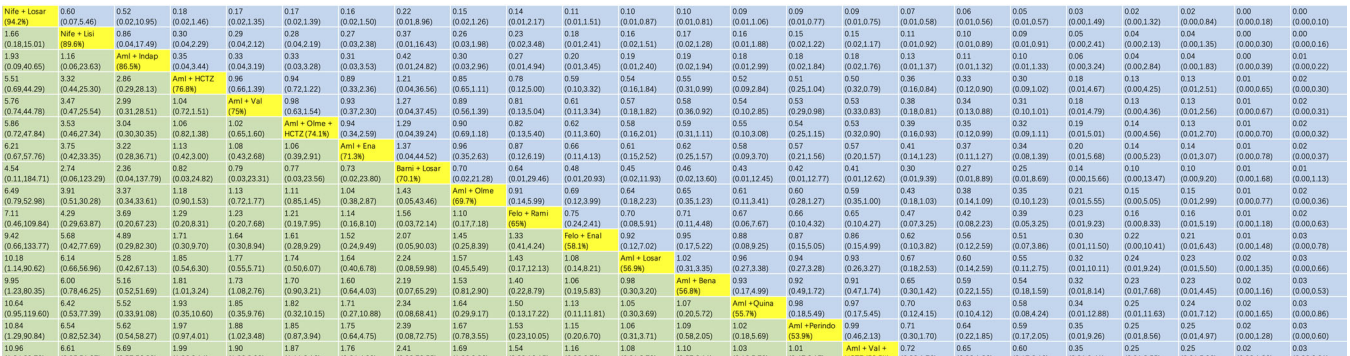

FIGURE 5 Combined DHPCCBs interventions network meta-analysis for peripheral edema. The figure represents the relative risk with 95% confidence interval of combined DHPCCBs compared with placebo. The probabilities beside the CCBs names are the treatment ranking based on SUCRA from left to right. The treatment drugs divided the figure into upper (blue colored) and lower (green colored) parts. For the lower part, the efficacy estimate was the ratio of the column defining treatment to the row defining treatment. For the upper part, the efficacy estimate was the ratio of the row defining treatment to the column defining treatment. The lower and the upper parts' results were mutually reciprocal. The relative risk ratio in each treatment should be compared to the treatment in the same row to the right.

risk of peripheral edema development based on the counts from single nifedipine treatment.

The 95% CI of the inconsistency factors of the existing closed-loops (Figure 5) did not exclude zero implying that there was no observed inconsistency between direct and indirect evidence.

3.6 | Publication bias

Comparison-adjusted funnel plots were used to verify publication bias. In Figure 7, the funnel plots were symmetrical, indicating no obvious publication bias observed.

Nifedipine+ARB (92.3%)	0.33 (0.03,4.39)	0.25 (0.03,2.20)	0.21 (0.00,10.69)	0.08 (0.01,1.24)	0.08 (0.01,1.18)	0.08 (0.00,4.30)	0.07 (0.00,1.04)	0.06 (0.00,0.95)	0.05 (0.00,0.69)	0.02 (0.00,0.40)
3.00 (0.23,39.51)	Nifedipine+ACEI (78.8%)	0.75 (0.19,3.00)	0.62 (0.02,22.10)	0.25 (0.03,2.07)	0.24 (0.03,1.98)	0.25 (0.01,8.89)	0.21 (0.03,1.73)	0.19 (0.02,1.58)	0.14 (0.02,1.16)	0.07 (0.01,0.68)
4.00 (0.46,35.16)	1.33 (0.33,5.33)	Nifedipine (74.6%)	0.82 (0.03,22.28)	0.33 (0.07,1.65)	0.32 (0.07,1.56)	0.33 (0.01,8.96)	0.29 (0.06,1.36)	0.26 (0.05,1.25)	0.18 (0.04,0.93)	0.10 (0.02,0.56)
4.85(0.09,251.77)	1.62 (0.05,57.82)	1.21 (0.04,32.79)	Felodipine (68.7%)	0.41 (0.02,7.32)	0.39 (0.02,7.20)	0.40 (0.23,0.69)	0.35 (0.02,6.32)	0.31 (0.02,5.76)	0.22 (0.01,4.06)	0.12 (0.01,1.88)
11.95 (0.81,176.91)	3.98 (0.48,32.90)	2.99 (0.61,14.69)	2.46 (0.14,44.43)	Amlodipine (52.9%)	0.96 (0.66,1.41)	0.99 (0.05,17.88)	0.85 (0.63,1.16)	0.77 (0.52,1.13)	0.55 (0.43,0.71)	0.29 (0.13,0.64)
12.40 (0.84,181.98)	4.13 (0.51,33.77)	3.10 (0.64,15.03)	2.55 (0.14,46.97)	1.04 (0.71,1.52)	Amlodipine+diuretics (52.2%)	1.02 (0.06,18.90)	0.89 (0.71,1.11)	0.80 (0.64,1.00)	0.57 (0.36,0.91)	0.30 (0.13,0.70)
12.12 (0.23,630.86)	4.04 (0.11,144.92)	3.03 (0.11,82.22)	2.50 (1.44,4.32)	1.01 (0.06,18.38)	0.98 (0.05,18.05)	Felodipine+ACEI (41.8%)	0.87 (0.05,15.85)	0.78 (0.04,14.44)	0.56 (0.03,10.20)	0.29 (0.02,4.71)
14.00 (0.96,203.61)	4.67 (0.58,37.68)	3.50 (0.73,16.70)	2.89 (0.16,52.59)	1.17 (0.86,1.59)	1.13 (0.90,1.41)	1.16 (0.06,21.17)	Amlodipine+ARB (39.2%)	0.90 (0.71,1.14)	0.65 (0.43,0.96)	0.34 (0.15,0.77)
15.51(1.06,227.94)	5.17 (0.63,42.31)	3.88 (0.80,18.83)	3.20 (0.17,58.83)	1.30 (0.88,1.91)	1.25 (1.00,1.57)	1.28 (0.07,23.68)	1.11 (0.88,1.40)	Amlodipine+DIURETICS+ARB (30.2%)	0.72 (0.45,1.14)	0.37 (0.16,0.88)
21.64 (1.44,324.26)	7.21(0.86,60.51)	5.41 (1.08,27.15)	4.46 (0.25,80.86)	1.81 (1.40,2.34)	1.75 (1.10,2.76)	1.79 (0.10,32.54)	1.55 (1.04,2.31)	1.40 (0.88,2.22)	Amlodipine+ACEI (16%)	0.52 (0.23,1.17)
41.72(2.53,688.92)	13.91 (1.47,131.84)	10.43 (1.77,61.32)	8.60 (0.53,138.66)	3.49 (1.57,7.75)	3.37 (1.42,7.98)	3.44 (0.21,55.82)	2.98 (1.29,6.86)	2.69 (1.13,6.40)	1.93 (0.85,4.36)	Placebo(3.4%)

FIGURE 6 Summary of the grouped combination DHPCCB network meta-analysis

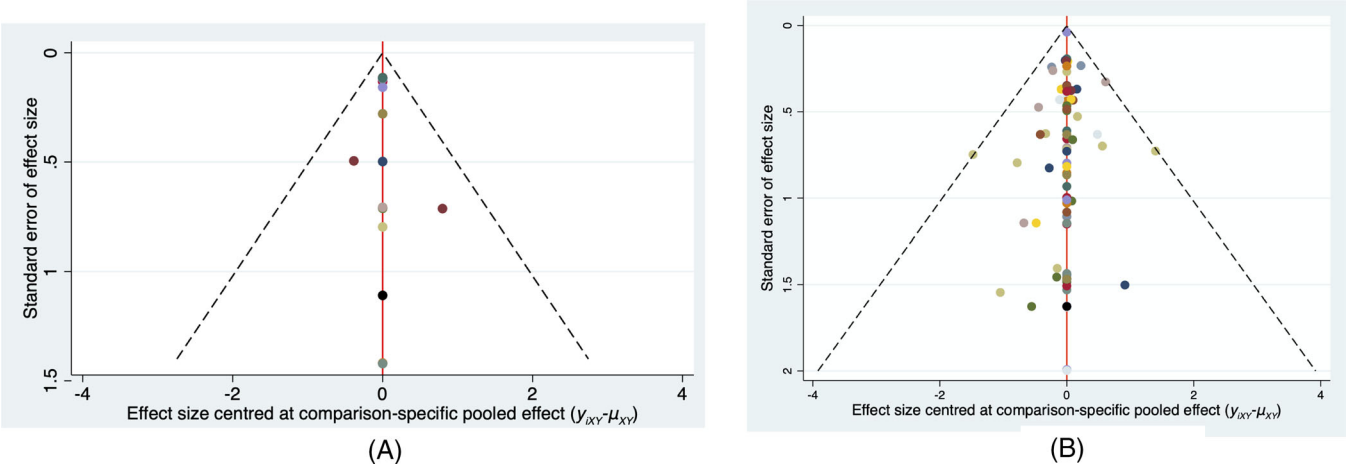

FIGURE 7 Comparison-adjusted funnel plot of peripheral edema in the network meta-analysis. A: Single DHPCCBs; B: combined DHPCCBs

4 | DISCUSSION

This is the first network meta-analysis that identifies the ranking of CCB induced peripheral edema. The 71 clinical trials included nine DHPCCBs in various doses from first to fourth generations. DHPCCB has been recommended as a monotherapy or in combination with other agents for the treatment of hypertension.[16] Currently, there are numerous CCBs available in the market to choose from. A well-known side effect from CCBs is peripheral edema which often leads to the discontinuation of the therapy. Dihydropyridine CCBs, such as nifedipine, cause peripheral edema by increasing capillary hydrostatic pressure which results in an imbalance of dilation between precapillary and postcapillary vessels.[10,17–19] The severity of the edema varies from one CCB to another and it is dose dependent.[7,20–23] In a meta-analysis, peripheral edema with high-dose CCBs which was defined as more than half the usual maximum dose was 2.8 times higher than that with low-dose CCBs (16.1 vs 5.7%, $p < .0001$) and patient withdrawal rate due to edema increased with the duration of therapy with CCBs was 5%, after 6 months.[27] The meta-analysis included 52 trials with amlodipine and 21 trials with nifedipine out of 106 trials, it showed that incidence of peripheral edema was significantly higher with dihydropyridines (12.3%; 95% CI 12.2–12.5) compared with nondihydropyridines (3.1%; 95% CI 2.8–3.4; $p < .0001$). In addition, patient withdrawal due to edema was significantly higher with dihydropyridines (2.4%; 95% CI 2.2–2.5) compared with nondihydropyridines (0.6%; 95% CI 0.35–0.85; $p < .0001$).[27]

Although risk factors such as being female, obesity, and advanced age that predispose patients to peripheral edema from a CCB are identified,[24–26,28] patients without the identified risks still develop peripheral edema. A meta-analysis showed that CCB use is 10.7 times more likely to cause peripheral edema when compared with control or placebo and the withdrawal rate due to peripheral edema was 2.1 times higher in the CCB group than control or placebo group.[11] Therefore, it is critical to identify the CCB that has the least potential to cause peripheral edema so that clinicians could avoid using it preferentially.

This network meta-analysis shows that nifedipine ranked the most likely to cause peripheral edema and lacidipine the least likely. The results from this network meta-analysis show that the DHPCCBs with more lipophilic properties are less likely to cause peripheral edema which is consistent with previous studies.[29] The lipophilic property increases from first to fourth generation of DHPCCBs. Nifedipine and nicardipine are first generation, and lacidipine is the fourth generation DHPCCB. Multiple studies show that lacidipine has a much better safety profile in terms of peripheral edema when compared with other CCBs.[9,30,31] The withdrawal rate due to peripheral edema was lowest when compared with other CCBs.[21] Lacidipine ranked lower than placebo in our network analysis as a result of an indirect estimate. Nifedipine is 7.17 times more likely to cause peripheral edema compared to lacidipine (95% CI: 1.91–26.92). Lacidipine is a new potent and long acting 1,4-dihydropyridine derivative, calcium channel blocker with vascular-selective calcium entry blocking activity. A proposed mechanism attributed to the lower incidence of peripheral edema is that it causes less arteriolar and venular vasodilation likely due to the lower sympathetic activation. As a result, it caused less venoconstriction than older dihydropyridines such as nifedipine.[32] In addition, different actions on vascular permeability and fluid extravasation may play a role in the reduction of peripheral edema.[33]

There has been an increased use of renin-angiotensin system blockers (RASBs) in combination with a CCB in the treatment of hypertension. This combination has been shown to have better blood pressure control and to reduce cardiovascular risk. In addition to the reduction in cardiovascular risk, a theoretical rationale for combining these drug classes is that RASBs decrease post capillary resistance resulting in normal intracapillary pressure and reduction in the fluid extravasation which, in turn, leads to reduced peripheral edema.[10,18,34] Evidence to support this theory includes a meta-analysis of 82 studies that demonstrated that the combination of benazepril/amlodipine resulted in lower overall rate of side effects and withdrawal compared to amlodipine monotherapy.[35]

In our network meta-analysis, the results showed neither the angiotensin converting enzyme inhibitor, nor the angiotensin receptor blocker prevented peripheral edema from nifedipine. The combination of amlodipine/losartan ranked the least in the DHPCCBs plus ARBs treatment and the combination of the amlodipine/ramipril ranked the least in the DHPCCBs plus ACEIs treatment after six combinations (amlodipine/trandolapril, lercanidipine/benazepril, nifedipine/valsartan, amlodipine/irbesartan, nifedipine/candesartan, and amlodipine/candesartan) were removed from analysis due to low event numbers as part of a sensitivity analysis. In the next step, we group the CCB ACEI and ARB and compared the interventions as a class to improve the overall certainty of our results. The first generation DHPCCB nifedipine combination with ACEIs or ARBs does not reduce the chance of developing peripheral edema compared to single nifedipine. For the upper generation DHPCCB, the combination treatments with ACEI, ARB, and diuretics decrease the risk of peripheral edema development. Amlodipine with some special ACEIs performs the best among other types of combination.

This network meta-analysis offers valuable insight on which DHPCCBs to avoid in patients with high risk of developing peripheral edema and which combination to use to mitigate the side effects in the case where DHPCCB remains the preferred or only treatment. However, there remains a high degree of uncertainty due to low overall event rates in certain comparisons and small sample sizes. Additional studies, particularly for newer CCBs, such as lacidipine, would help improve the certainty of the analysis and ranking. This network meta-analysis can also serve as the basis for considering future studies in evaluating whether certain DHPCCBs with a low incidence of peripheral edema can be tolerated in patients who previously developed peripheral edema while taking a DHPCCB with a higher incidence of peripheral edema. As for those patients who suffered from peripheral edema before and need to be prescribed DHPCCB to control blood pressure, the second or upper generation DHPCCB combination with ACEI could be considered to reduce the chance of peripheral edema and control blood pressure.

5 | CONCLUSION

Nifedipine ranked the highest and lacidipine ranked the lowest among DHPCCBs for developing peripheral edema when used for cardiovascular indications. The addition of ARB or ACEI did not reduce the prevalence of edema induced by nifedipine. The amlodipine plus ACEI (benazepril, perindopril, enalapril, and ramipril) combination ranked the lowest risk of developing edema. The chance of peripheral edema development induced by the second or upper generation DHPCCBs could be reduced by combination with ACEIs or ARBs or diuretics.

5.1 | Limitations

In our study, we did not analyze the relationship between incidence of peripheral edema and different dosages of DHPCCBs, although the titration regimen was applied in most of the included studies. Additionally, different formulations of the same DHPCCBs were compared in only one or two included papers and we could not evaluate the network differences of peripheral edema.

CONFLICTS OF INTEREST

All authors have no conflict of interest to declare

AUTHOR CONTRIBUTIONS

L.L. and H.L.B. conceived and conceptualized the research idea. J.K. conducted comprehensive searches. L.L. and H.L.B. reviewed the search, performed the screening and full text assessment. AJC resolved any conflicts. L.L. and H.L.B. completed the quality assessment and data extraction. L.L. performed the data analyses, LL and B.M. interpreted the results. L.L. and H.L.B. contributed to the draft manuscript. All authors contributed to the revisions and final proof reading.

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