

Confident In Network Meta-Analysis (CINeMA)

An example from NMA on incident diabetes in clinical trials of antihypertensive drugs

Nguyen Thi Ha – MUHTA program

Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis

William J Elliott, Peter M Meyer

Domains	
P	Hypertensive patients
I and C	Anti-hypertensive agents: Angiotensin-converting enzyme (ACE) inhibitors Calcium channel blockers (CCB) Angiotensin receptor blockers (ARB) Thiazide diuretics Beta blockers
Outcome	Primary outcome: incident diabetes
Study design	SR and NMA

Lancet 2007; 369: 201–07

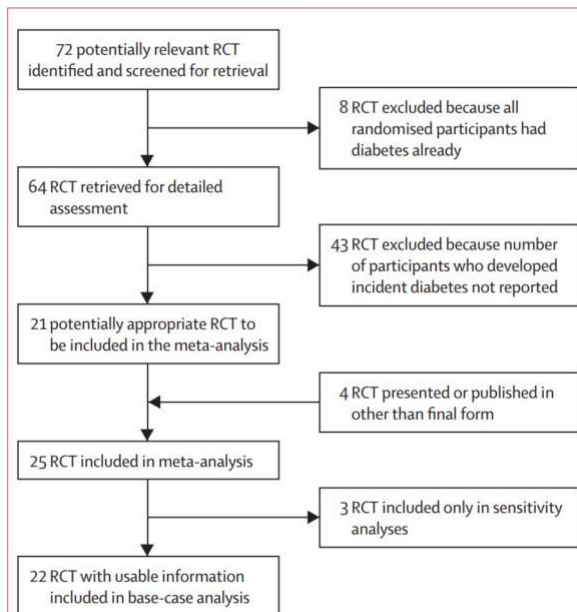


Figure 1: Summary of trial identification and selection
RCT=randomised controlled trial.

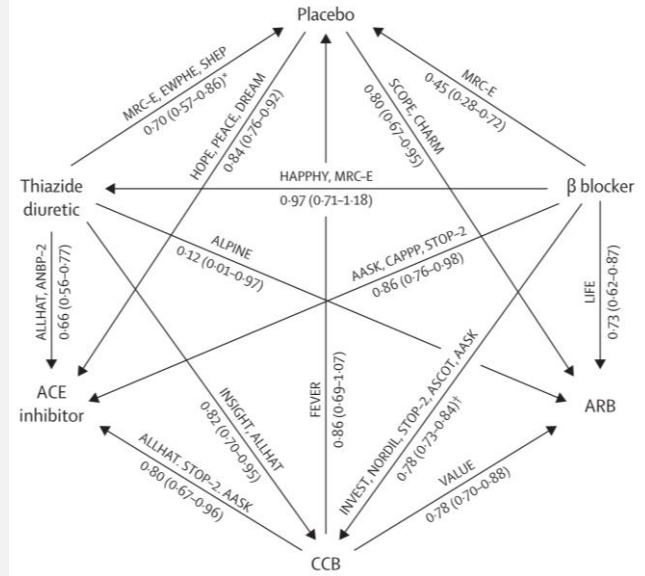


Figure 2: Network of clinical trials of antihypertensive drugs in which incident diabetes was reported

Evaluate the confidence in the results of NMA using CINeMA

<https://cinema.ispm.unibe.ch/>



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Documentation

1. DATA ACQUISITION 2. WITHIN-STUDY BIAS 3. REPORTING BIAS 4. INDIRECTNESS 5. IMPRECISION 6. HETEROGENEITY 7. INCOHERENCE 8. REPORT

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A demo dataset* can be downloaded [here](#). It is a network of six antihypertensive drugs by Elliott et al.
*Indirectness data are fictional
W. J. Elliott and P. M. Meyer. Incident diabetes in clinical trials of antihypertensive drugs: a network meta-analysis. The Lancet, 369(9557):201 – 207, 2007

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Reset CINeMA

Procedure of evaluation confidence using CINeMA

Step 1. Prepare and upload data

Step 2. Set up the NMA

Step 3. Evaluation of within-study bias

Step 4. Evaluation reporting bias

Step 5. Evaluation indirectness

Step 6. Evaluation imprecision

Step 7. Evaluation heterogeneity



Step 8. Evaluation incoherence

Step 9. Confidence rating

STEP 1: PREPARE AND UPLOAD DATA

Type of outcomes are supported: binary or continuous, NOT time-to-event or rate outcomes

File type: .csv (Microsoft Excel Comma Separated Values File) NOT .xlsx (Microsoft Excel worksheet)

Name	Date modified	Type	Size
 diabetes (2)	11/7/2021 9:36 AM	Microsoft Excel Comma Separated Values File ✓	2 KB
 diabetes (2)	11/7/2021 8:26 AM	Microsoft Excel Worksheet ✗	12 KB

Data format: Long format and wide format

STEP 1: PREPARE AND UPLOAD DATA

Binary outcomes: studyid, treatment, number of events, sample size for each arm, rob and indirectness

Binary outcomes: Long format

id	t	r	n	rob	indirectness
1	ACE	45	410	1	1
1	BBlocker	70	405	1	1
1	CCB	32	202	1	1
2	ACE	119	4096	1	1
2	CCB	154	3954	1	1

Binary outcomes:Wide format

id	t1	r1	n1	t2	r2	n2	rob	Indirectness
1	ACE	45	410	BBlocker	70	405	1	1
1	ACE	45	410	CCB	32	202	1	1
2	ACE	119	4096	CCB	154	3954	1	1
2	ACE	119	4096	Diuretic	302	6766	1	1
3	ARB	1	196	Diuretic	8	196	1	1
4	ACE	138	2800	Diuretic	200	2826	1	1

Continuous outcomes: studyid, treatment, mean, SD, sample size for each arm, rob and indirectness

Continuous outcomes: Long format

id	t	y	sd	n	rob	Indirectness
1	A	5	5	12	2	1
1	B	7	6	15	2	1
2	A	6	7	9	3	2
2	B	7	8	10	3	2

Continuous outcomes: wide format

id	t1	y1	sd1	n1	t2	y2	sd2	n2	rob	Indirectness
1	A	5	5	12	B	7	6	15	2	1
2	A	6	7	9	B	7	8	10	3	2
2	A	6	7	9	C	2	9	8	3	2
2	B	7	8	10	C	2	9	8	3	2

STEP 1: PREPARE AND UPLOAD DATA

Notes:

1. Make sure there is **NO MISSING DATA**
2. **Order the treatment arm** to support purpose of researchers:

CINeMA order treatment according to **alphabetic orders**

Example of 3 interventions: ARB, CCB and Placebo

→ Default by CINeMA: ARB vs CCB, ARB vs Placebo, CCB vs Placebo

→ Purpose of researchers: CCB vs ARB, Placebo vs ARB, Placebo vs CCB

- Rename the treatment: 1.Placebo; 2.CCB; 3.ARB
- Appearance in CINeMa: 1.Placebo vs 2.CCB, 1.Placebo vs 3.ARB; 2.CCB vs 3.ARB

Default by CINeMA

You have selected the following 15 comparisons. Confidence in the results will be graded for:

ACE vs ARB ACE vs BBLOCKER ACE vs CCB ACE vs Diuretic ACE vs Placebo ARB vs BBLOCKER ARB vs CCB ARB vs Diuretic ARB vs Placebo
BBLOCKER vs CCB BBLOCKER vs Diuretic BBLOCKER vs Placebo CCB vs Diuretic CCB vs Placebo Diuretic vs Placebo

Reordered treatment

You have selected the following 15 comparisons. Confidence in the results will be graded for:

1.Placebo vs 2.BBLOCKER 1.Placebo vs 3.CCB 1.Placebo vs 4.ARB 1.Placebo vs 5.Diuretic 1.Placebo vs 6.ACE 2.BBLOCKER vs 3.CCB 2.BBLOCKER vs 4.ARB 2.BBLOCKER vs 5.Diuretic
2.BBLOCKER vs 6.ACE 3.CCB vs 4.ARB 3.CCB vs 5.Diuretic 3.CCB vs 6.ACE 4.ARB vs 5.Diuretic 4.ARB vs 6.ACE

STEP 1: PREPARE AND UPLOAD DATA

Notes:

3. ROB and indirectness data

- (1, 2, 3) OR (L, M, H) OR (l,m,h): Low risk, some concern/moderate, high risk
- CINeMA automatically convert imported data for ROB and indirectness to 1, 2 or 3

Indirectness refer to the relevance of the included studies to the research questions

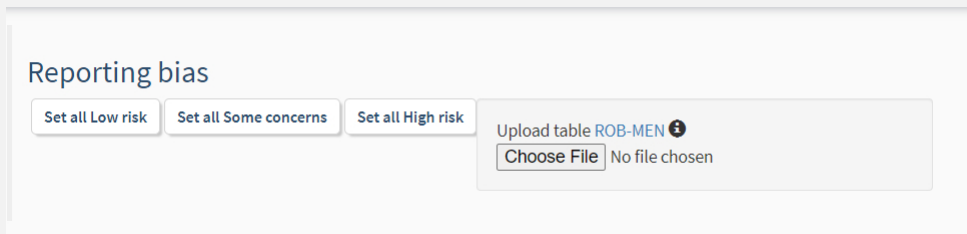
Study populations, interventions, outcomes, and study settings might not be representative of the settings, populations, or outcomes about which reviewers want to make inferences → downgrade the level of indirectness

STEP 1: PREPARE AND UPLOAD DATA

Notes:

4. Reporting bias: Not appear in the upload table but need to prepare in hand

4.1. Using web-based application in CINeMa website: Disconnected from the server



Reporting bias

Set all Low risk Set all Some concerns Set all High risk

Upload table ROB-MEN ⓘ

Choose File No file chosen

STEP 1: PREPARE AND UPLOAD DATA

Notes:

4. Reporting bias: Not appear in the upload table but need to prepare in hand

4.2. Manually prepared:

- Publication bias in individual study: Funnel plot, Eggers test, Comparison-adjusted funnel plot
- Selection of the reported results
 - Protocol, data analysis plan
 - Methodology section

CINeMA
Confidence in Network Meta-Analysis

● CONFIGURATION ● WITHIN-STUDY BIAS ● REPORTING BIAS ● INDIRECTNESS ● IMPRECISION ● HETEROGENEITY ●

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STEP 2: SET UP THE NMA

CINeMA
Confidence in Network Meta-Analysis

My Projects Documentation

CONFIGURATION ● WITHIN-STUDY BIAS ● REPORTING BIAS ● INDIRECTNESS ● IMPRECISION ● HETEROGENEITY ● INCOHERENCE ● REPORT

Network Plot

Node size by: Sample size Node color by: Risk of Bias Edge width by: Number of studies Edge color by: Average RoB

Redraw Save Plot

	study	id	t1	r1	n1	rob	indirectness	t2	r2	n2
1	AASK	1	ACE	45	410	1	1	BBBlocker	70	405
2	AASK	1	ACE	45	410	1	1	CCB	32	202
3	AASK	1	BBBlocker	70	405	1	1	CCB	32	202
4	ALLHAT	2	ACE	119	4096	1	1	CCB	154	3954
5	ALLHAT	2	ACE	119	4096	1	1	Diuretic	302	6766
6	ALLHAT	2	CCB	154	3954	1	1	Diuretic	302	6766
7	ALPINE	3	ARB	1	196	1	1	Diuretic	8	196
8	ANBP-2	4	ACE	138	2800	1	1	Diuretic	200	2826
9	ASCOT	5	BBBlocker	799	7040	1	1	CCB	567	7072
10	CAPP	6	ACE	337	5183	2	1	BBBlocker	380	5230
11	CHARM	7	ARB	163	2715	1	1	Placebo	202	2721
12	DREAM	8	ACE	449	2623	1	1	Placebo	489	2646
13	EWPH	9	Diuretic	29	416	2	1	Placebo	20	424
14	FEVER	10	CCB	177	4841	1	1	Placebo	154	4870
15	HAPPY	11	BBBlocker	86	3297	3	1	Diuretic	75	3272
16	HOPE	12	ACE	102	2837	1	1	Placebo	155	2883
17	INSIGHT	13	CCB	136	2508	1	1	Diuretic	176	2511
18	INVEST	14	BBBlocker	665	8078	1	1	CCB	569	8098
19	LIFE	15	ARB	242	4020	1	1	BBBlocker	320	3979
20	MRC	16	BBBlocker	37	1102	1	1	Diuretic	43	1081
21	MRC	16	BBBlocker	37	1102	1	1	Placebo	34	2213
22	MRC	16	Diuretic	43	1081	1	1	Placebo	34	2213

STEP 2: SET UP THE NMA

Define your analysis

Analysis model: Fixed effect ☐ Random effects ☒

Effect measure: Risk Ratio

Select intervention comparisons for evaluation

Interventions: ☒ ACE ☒ BBLOCKER ☒ CCB ☒ Diuretic ☒ ARB ☒ Placebo

Select comparisons:

Containing any of the above interventions ☐

Between the above interventions ☒

You have selected the following 15 comparisons. Confidence in the results will be graded for:

ACE vs ARB ACE vs BBLOCKER ACE vs CCB ACE vs Diuretic ACE vs Placebo ARB vs BBLOCKER ARB vs CCB ARB vs Diuretic ARB vs Placebo BBLOCKER vs CCB BBLOCKER vs Diuretic BBLOCKER vs Placebo CCB vs Diuretic CCB vs Placebo Diuretic vs Placebo

Analysis

STEP 2: SET UP THE NMA

You have selected the following 15 comparisons. Confidence in the results will be graded for:

ACE vs ARB ACE vs BBLOCKER ACE vs CCB ACE vs Diuretic ACE vs Placebo ARB vs BBLOCKER ARB vs CCB ARB vs Diuretic ARB vs Placebo BBLOCKER vs CCB BBLOCKER vs Diuretic BBLOCKER vs Placebo CCB vs Diuretic CCB vs Placebo Diuretic vs Placebo

Analysis is performed including all studies

STEP 3: EVALUATION OF WITHIN-STUDY BIAS

Selected rule: Average RoB

Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>
Comparison Evidence: mixed Majority RoB: Some concerns Average RoB: Some concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="Some concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>
Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: mixed Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>	Comparison Evidence: indirect Majority RoB: No concerns Average RoB: No concerns Highest RoB: Major concerns NMA judgment: <input type="button" value="No concerns"/>

STEP 4: REPORTING BIAS



☐ CONFIGURATION
 ☒ 1 WITHIN-STUDY BIAS
 ☐ **REPORTING BIAS**
☐ 3 INDIRECTNESS
 ☐ 4 IMPRECISION

Reporting bias

Upload table ROB-MEN ¹
 No file chosen

STEP 5: INDIRECTNESS

Select how to summarize indirectness across contributions for each network estimate ¹

1. Majority

2. Average

3. Highest

Comparison Evidence: mixed Majority: No concerns Average: No concerns Highest: No concerns NMA judgment: No concerns	Comparison Evidence: mixed Majority: No concerns Average: No concerns Highest: No concerns NMA judgment: No concerns	Comparison Evidence: mixed Majority: No concerns Average: No concerns Highest: No concerns NMA judgment: No concerns	Comparison Evidence: mixed Majority: No concerns Average: No concerns Highest: No concerns NMA judgment: No concerns	Comparison Evidence: mixed Majority: No concerns Average: No concerns Highest: No concerns NMA judgment: No concerns
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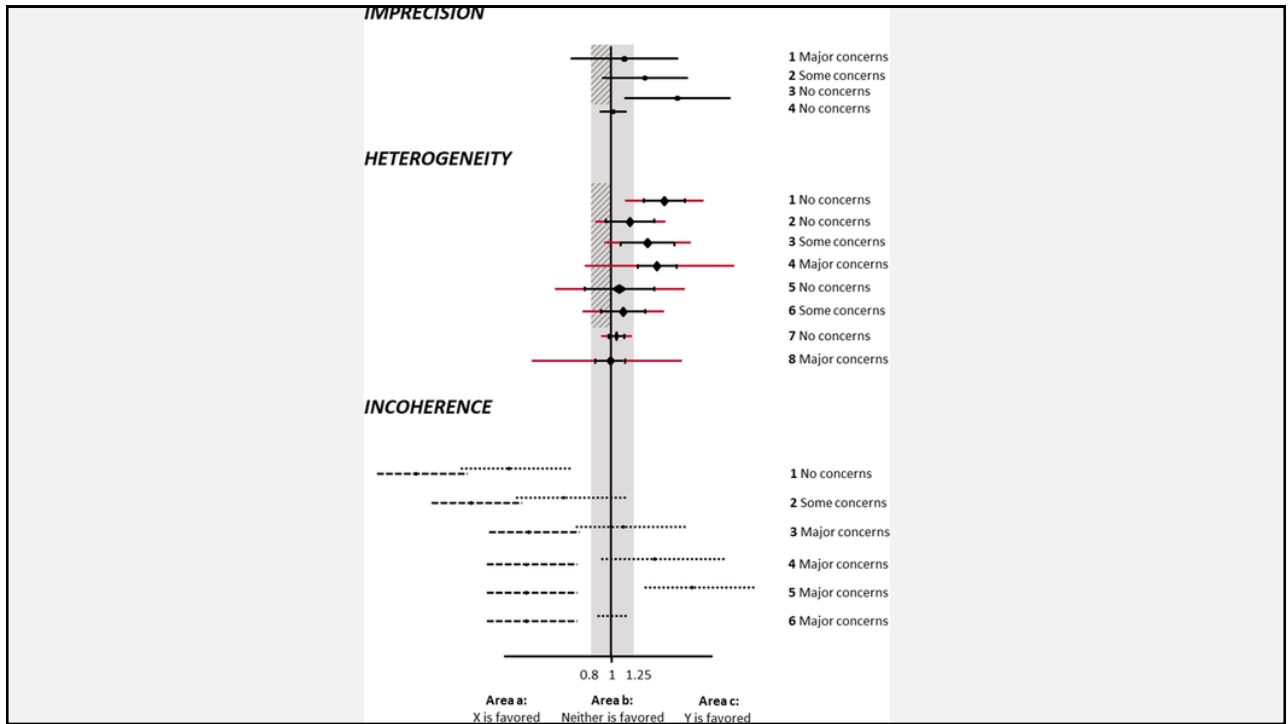
STEP 6: IMPRECISION

Imprecision

Define clinically important size of effect: Risk ratio ¹

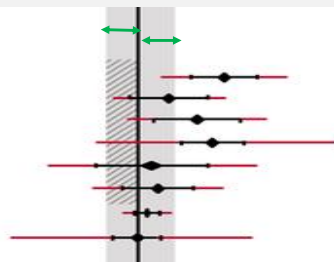
Relative effect estimates below 0.800 and above 1.250 are considered clinically important.

Comparison Evidence: mixed NMA estimate: 0.733 95% Confidence interval: (0.639,0.841) does not cross clinically important effect Imprecision judgment: No concerns	Comparison Evidence: mixed NMA estimate: 0.859 95% Confidence interval: (0.748,0.986) does not cross clinically important effect Imprecision judgment: No concerns	Comparison Evidence: mixed NMA estimate: 0.684 95% Confidence interval: (0.589,0.794) does not cross clinically important effect Imprecision judgment: No concerns	Comparison Evidence: mixed NMA estimate: 0.893 95% Confidence interval: (0.786,1.014) extends into clinically important effects Imprecision judgment: Some concerns	Comparison Evidence: mixed NMA estimate: 0.691 95% Confidence interval: (0.586,0.815) does not cross clinically important effect Imprecision judgment: No concerns
Comparison Evidence: mixed NMA estimate: 0.810 95% Confidence interval: (0.690,0.950) Confidence interval: (0.690,0.950)	Comparison Evidence: mixed NMA estimate: 0.645 95% Confidence interval: (0.532,0.783) Confidence interval: (0.532,0.783)	Comparison Evidence: mixed NMA estimate: 0.842 95% Confidence interval: (0.714,0.993) Confidence interval: (0.714,0.993)	Comparison Evidence: mixed NMA estimate: 1.171 95% Confidence interval: (1.047,1.311) Confidence interval: (1.047,1.311)	Comparison Evidence: mixed NMA estimate: 0.933 95% Confidence interval: (0.798,1.081) Confidence interval: (0.798,1.081)



STEP 7: HETEROGENEITY

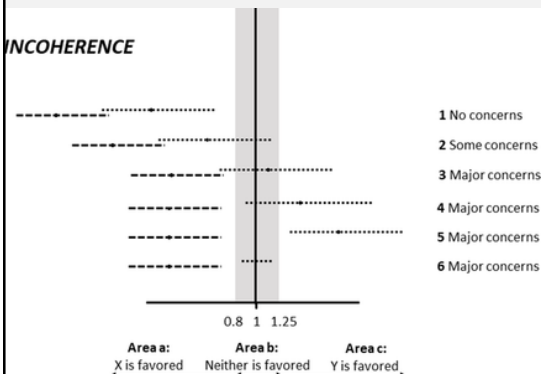
HETEROGENEITY



Heterogeneity: based on the confidence interval and prediction intervals

Number of crossings of the interval formed by the null effect and the clinically important value that favors the opposite intervention as the point estimate		Prediction intervals		
		0	1	2
Confidence intervals	0	No concerns	Some concerns	Major concerns
	1	NA	No concerns	Some concerns
	2	NA	NA	No concerns

STEP 8: INCOHERENCE



Incoherence: based on the agreement among direct and indirect evidence

Comparison	ACE:BBBlocker
Evidence: mixed	
NMA risk ratio:	0.733(0.639,0.841)
Direct risk ratio:	0.848(0.701,1.025)
Indirect risk ratio:	0.625(0.513,0.762)
Inconsistency measures	
Ratio of risk ratios:	1.357(1.031,1.786)
P value:	0.030
Incoherence judgment	Some concerns

STEP 9: CONFIDENCE RATING

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Mixed evidence									
ACE vs BBBlocker	3	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	High	
ACE vs CCB	3	No concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	High	
ACE vs Diuretic	2	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	High	
ACE vs Placebo	3	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	High	
ARB vs BBBlocker	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
ARB vs CCB	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High	
ARB vs Diuretic	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
ARB vs Placebo	2	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High	
BBBlocker vs CCB	5	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High	
BBBlocker vs Diuretic	2	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High	
BBBlocker vs Placebo	1	No concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	High	
CCB vs Diuretic	2	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High	
CCB vs Placebo	1	No concerns	Some concerns	No concerns	No concerns	Major concerns	No concerns	High	
Diuretic vs Placebo	3	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	High	
Indirect evidence									
ACE vs ARB	--	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	High	

STEP 9: CONFIDENCE RATING

Comparison	Number of Studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Mixed evidence									
ACE vs BBBlocker	3	No concerns	Low risk	No concerns	No concerns	No concerns	Some concerns	Low	Incoherence
ACE vs CCB	3	No concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Low	Reporting bias Heterogeneity
ACE vs Diuretic	2	No concerns	Some concerns	No concerns	No concerns	No concerns	No concerns	Moderate	Reporting bias
ACE vs Placebo	3	No concerns	Low risk	No concerns	Some concerns	No concerns	No concerns	Moderate	Imprecision
ARB vs BBBlocker	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
ARB vs CCB	1	Some concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Within-study bias Heterogeneity
ARB vs Diuretic	1	No concerns	Low risk	No concerns	No concerns	No concerns	No concerns	High	
ARB vs Placebo	2	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
BBBlocker vs CCB	5	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
BBBlocker vs Diuretic	2	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
BBBlocker vs Placebo	1	No concerns	Low risk	No concerns	No concerns	Some concerns	Some concerns	Low	Heterogeneity Incoherence
CCB vs Diuretic	2	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
CCB vs Placebo	1	No concerns	Some concerns	No concerns	No concerns	Some concerns	No concerns	Very low	Reporting bias Heterogeneity
Diuretic vs Placebo	3	No concerns	Low risk	No concerns	No concerns	Some concerns	No concerns	Moderate	Heterogeneity
Indirect evidence									
ACE vs ARB	--	No concerns	Low risk	No concerns	Some concerns	Some concerns	Some concerns	Very low	Imprecision Heterogeneity Incoherence

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