Hypertension Artérielle: résultats des méta-analyses et revues systématiques

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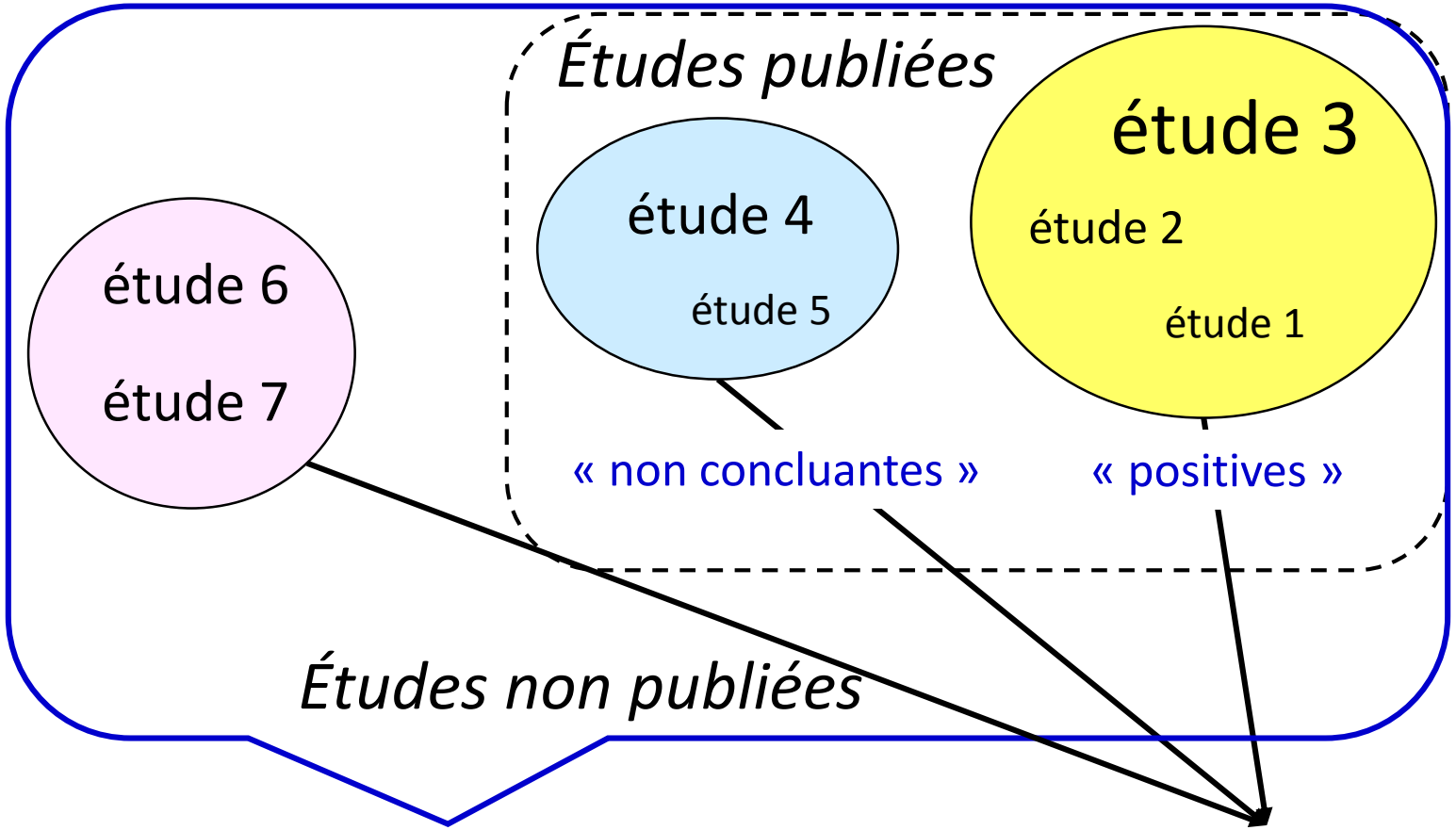
Revue systématique et Méta-analyse: définition

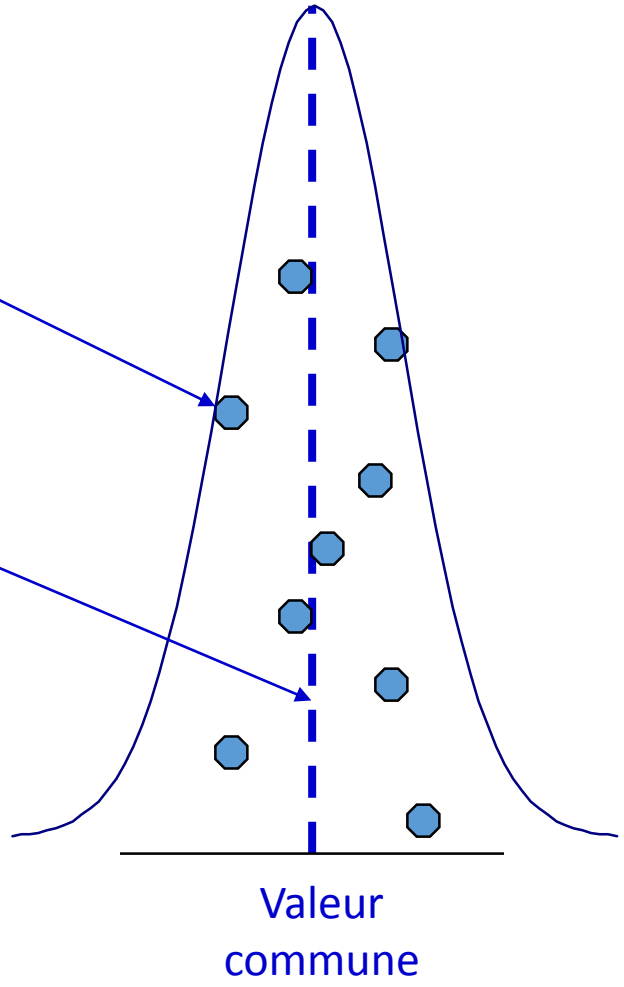


Revue Systématique:
Collecte des résultats de toutes les études réalisées – méthode explicite

Méta-analyse:
Synthèse quantitative de l'effet commun du traitement

Hypothèse - Modèle

- Les résultats des essais varient d'un essai à l'autre du fait du hasard : « estimations » de l'effet tt
- Ces résultats fluctuent de manière aléatoire autours d'une valeur commune : « vraie » effet du tt
- But de la MA : estimer cette valeur commune



Cucherat M. « Manuel pratique de méta-analyse des essais thérapeutiques » http://www.txrating.org/spc/bookma_web/frame.htm

Principe statistique

- Le but de la MA est de prendre en compte ces fluctuations dues au hasard (suppression du bruit de fond)
- et de fournir une estimation moins sujette à ces variations que l'estimation donnée par un seul essai

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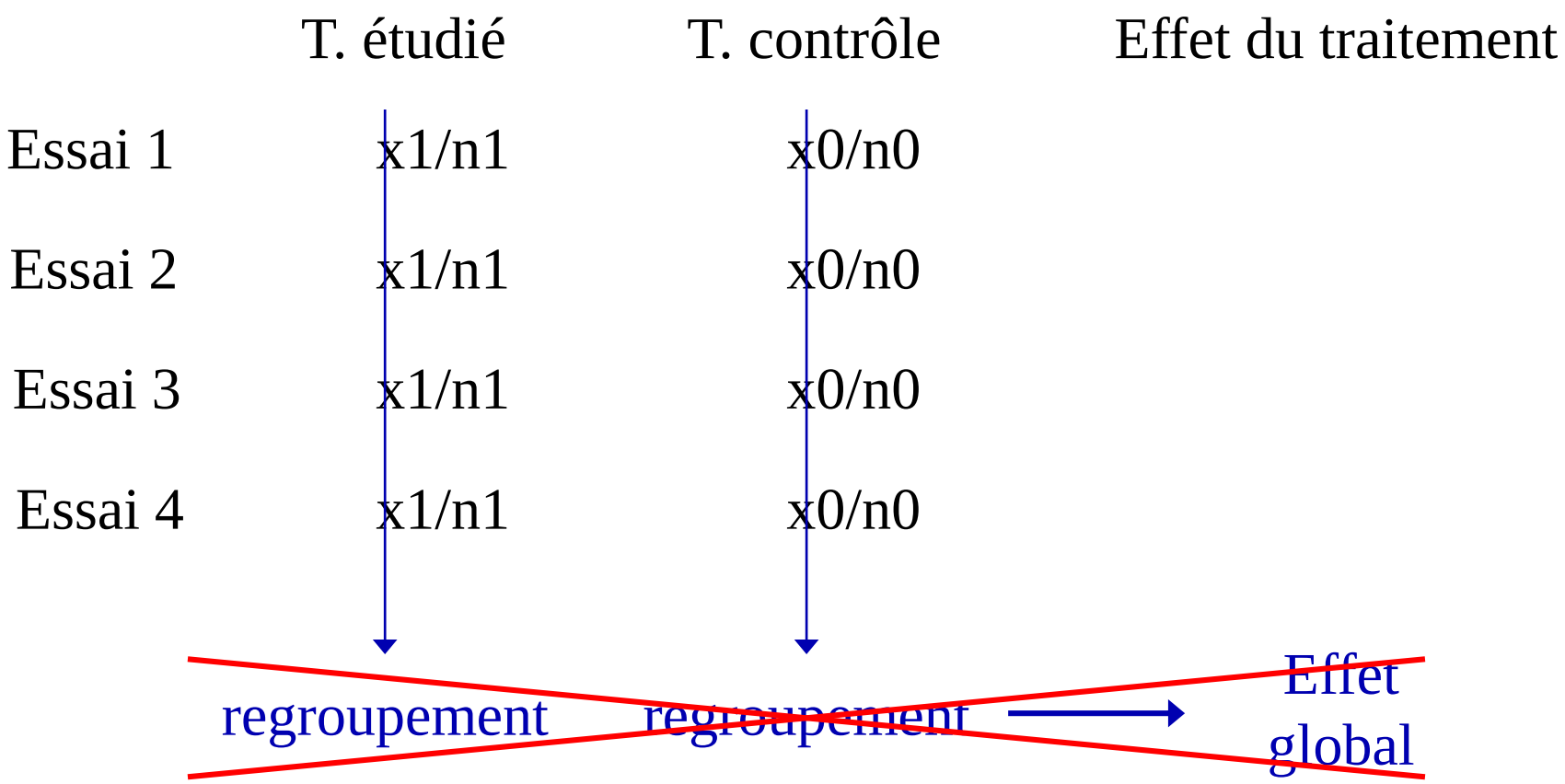
Combinaison des effets traitements incorrecte



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Paradoxe de Simpson

Essai	C	T	OR
1	18/60	36/120	**1.00**
	30%	30%	
2	84/120	42/60	**1.00**
	70%	70%	

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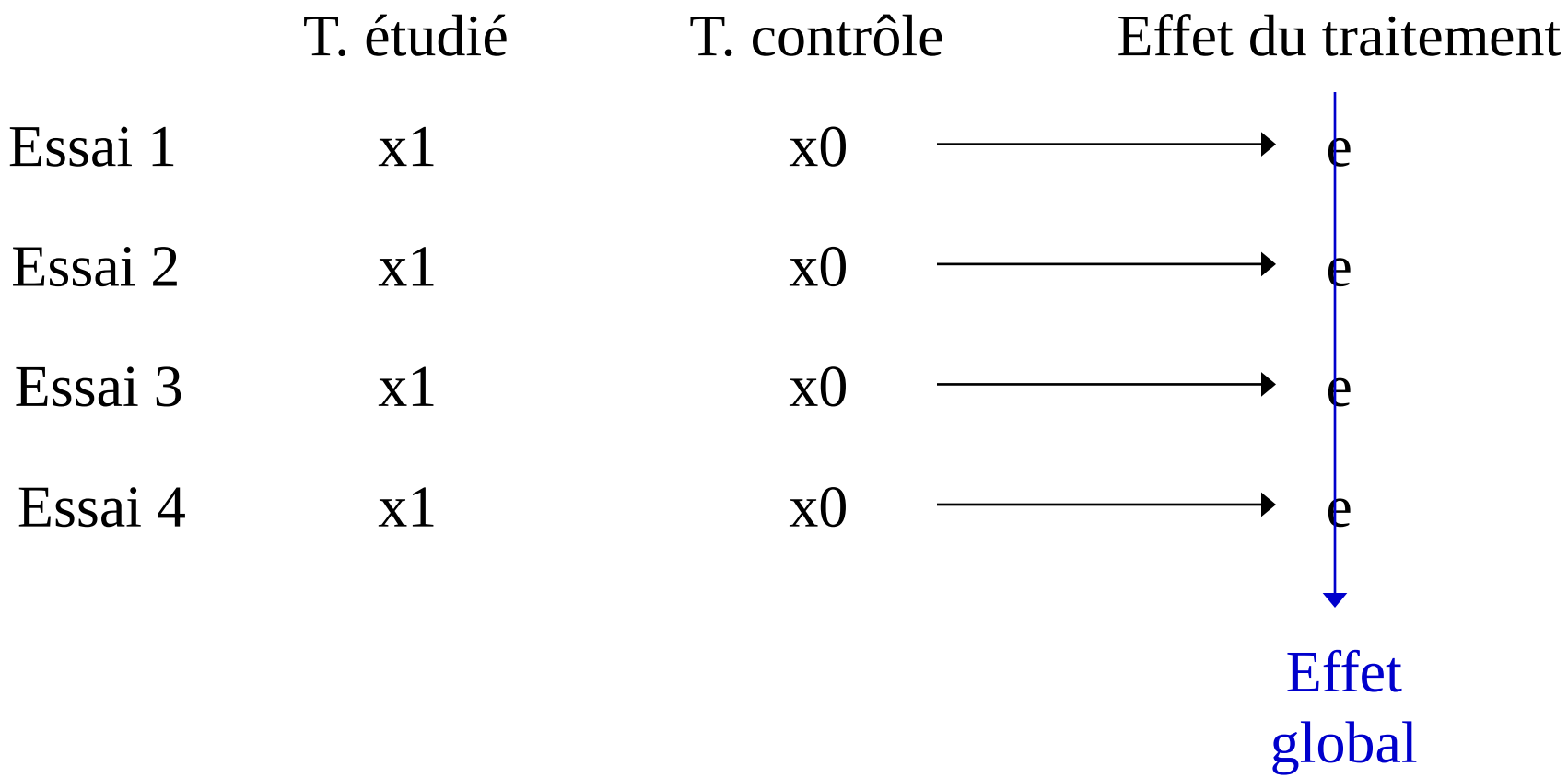
Combinaison des effets traitements correcte



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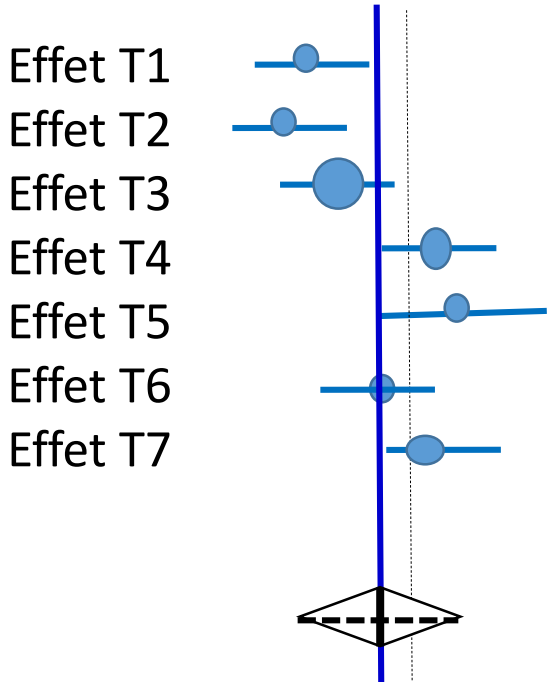
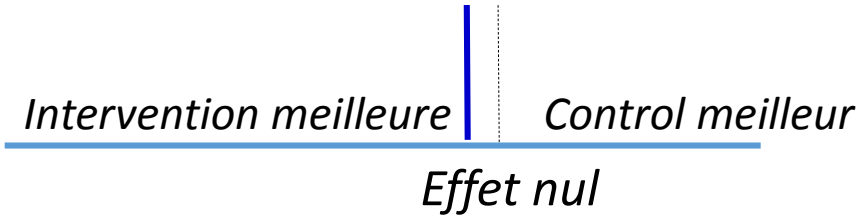
Revue systématique et Méta-analyse: hypothèses statistiques



Effet commun (IC 95%)
p-ass = NS
p-het



- Homogénéité : Modèle à effet fixe (ET1 = ET2 =… ETi)

$$\hat{T}_i \sim N(T,\ v_i^2)$$

Effet observé = Effet réel + erreur (ETi = ET + ei)

- Hétérogénéité : Modèle à effet aléatoire

$$\hat{T}_i \sim N(T, \tau^2 + v_i^2)$$

Effet observé = Effet réel + Var_inter-étude + erreur

Effet commun (IC 95%) : moyenne pondérée
Test d'association
Test d'homogénéité (hétérogénéité)

Cucherat M. « Manuel pratique de méta-analyse des essais thérapeutiques » http://www.txrating.org/spc/bookma_web/frame.htm

Hypothèse d'homogénéité

- Hypothèse omnibus
  - H0 : $\theta_1 = \theta_2 = \cdots = \theta_i$
- Hétérogénéité
  - rejet de l'hypothèse nulle
  - Acceptation de l'hypothèse alternative:

$$\exists \theta_j \, , \theta_j \neq \theta_{i \neq j}$$

Hétérogénéité

- Sous l'hypothèse d'homogénéité

$$\forall i \; \hat{\theta}_i = \theta$$

$\hat{\theta}_i - \hat{\theta}$ vaut en moyenne zéro

- Test d'hétérogénéité

$$Q = \sum w_i \left(\hat{\theta}_i - \hat{\theta} \right)^2$$

  - distance pondérée
  - nulle en cas d'homogénéité parfaite
  - Chi² à *k-1* ddl

Cucherat M. « Manuel pratique de méta-analyse des essais thérapeutiques » http://www.txrating.org/spc/bookma_web/frame.htm

I^2 (inconsistency)

- % de la variabilité totale non explicable par le hasard, du à une vraie variabilité de l'effet traitement dans les essais

$$I^2 = \max\left(0, \frac{\chi_{het}^2 - ddl}{\chi_{het}^2}\right) \times 100\%$$

- varie de 0% à 100%

- Problème d'extrapolabilité du résultat si I^2>70%

- Il existe un autre indice important tau 2
  - Lié au modèle aléatoire

Cucherat M. « Manuel pratique de méta-analyse des essais thérapeutiques » http://www.txrating.org/spc/bookma_web/frame.htm

Blood pressure lowering for prevention of cardiovascular disease and death.

Ettehad D et al. Lancet. 2016 Mar 5;387(10022):957-967. PMID: 26724178

The George Institute for Global Health, University of Oxford, Oxford, UK

- the benefits of BPLT for prevention of CVD are well established
- the extent to which these effects differ by baseline BP, presence of comorbidities, or drug class is less clear
- MEDLINE only
- 1000 patient-years FUP
- No formal protocol for this SRMA
- 123 RCT :

>600,000 patients

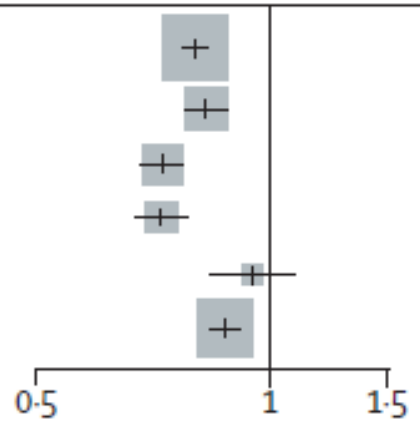
71	active treatment vs	placebo
31	different active drugs	
9	more intensive vs	less intensive BP
7	several active treatment vs	placebo
5	more intensive vs	less intensive BP and compared different active drugs

Blood pressure lowering for prevention of cardiovascular disease and death.

Ettehad D et al. Lancet. 2016 Mar 5;387(10022):957-967. PMID: 26724178

- Effect of 10 mmHg BP reduction: log(RR) x 10 / deltaBP(observed in the trial) (règle de 3)
- Validité ???

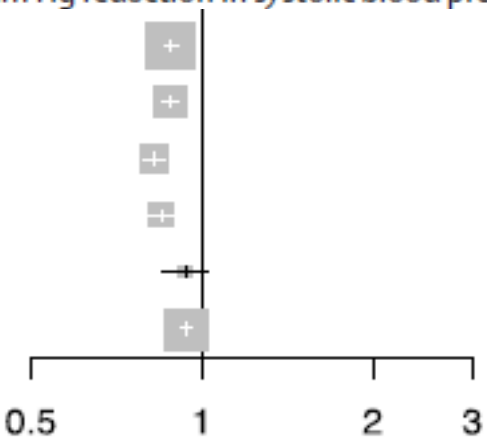
	Studies	Intervention		Control		RR (95% CI) per 10 mm Hg reduction in systolic blood pressure
		Events	Participants	Events	Participants	
Major cardiovascular events	55	13209	137319	14068	128259	0·80 (0·77–0·83)
Coronary heart disease	56	4862	136986	5301	128548	0·83 (0·78–0·88)
Stroke	54	4635	136682	5378	128641	0·73 (0·68–0·77)
Heart failure	43	3284	115411	3760	107440	0·72 (0·67–0·78)
Renal failure	16	890	39888	834	39043	0·95 (0·84–1·07)
All-cause mortality	57	9775	138298	9998	129700	0·87 (0·84–0·91)



Effets standardisés

Pertinence?

Major Cardiovascular Events	58	13774	148733	14751	139668	0.88	[0.86; 0.90]
Coronary Heart Disease	68	6165	159021	6711	150324	0.88	[0.85; 0.91]
Stroke	59	4817	150260	5653	142113	0.83	[0.79; 0.86]
Heart Failure	46	3512	121408	4023	113426	0.85	[0.81; 0.89]
Renal Failure	17	891	41609	836	40749	0.93	[0.85; 1.03]
All–cause Mortality	69	11177	160333	11448	151476	0.94	[0.92; 0.97]



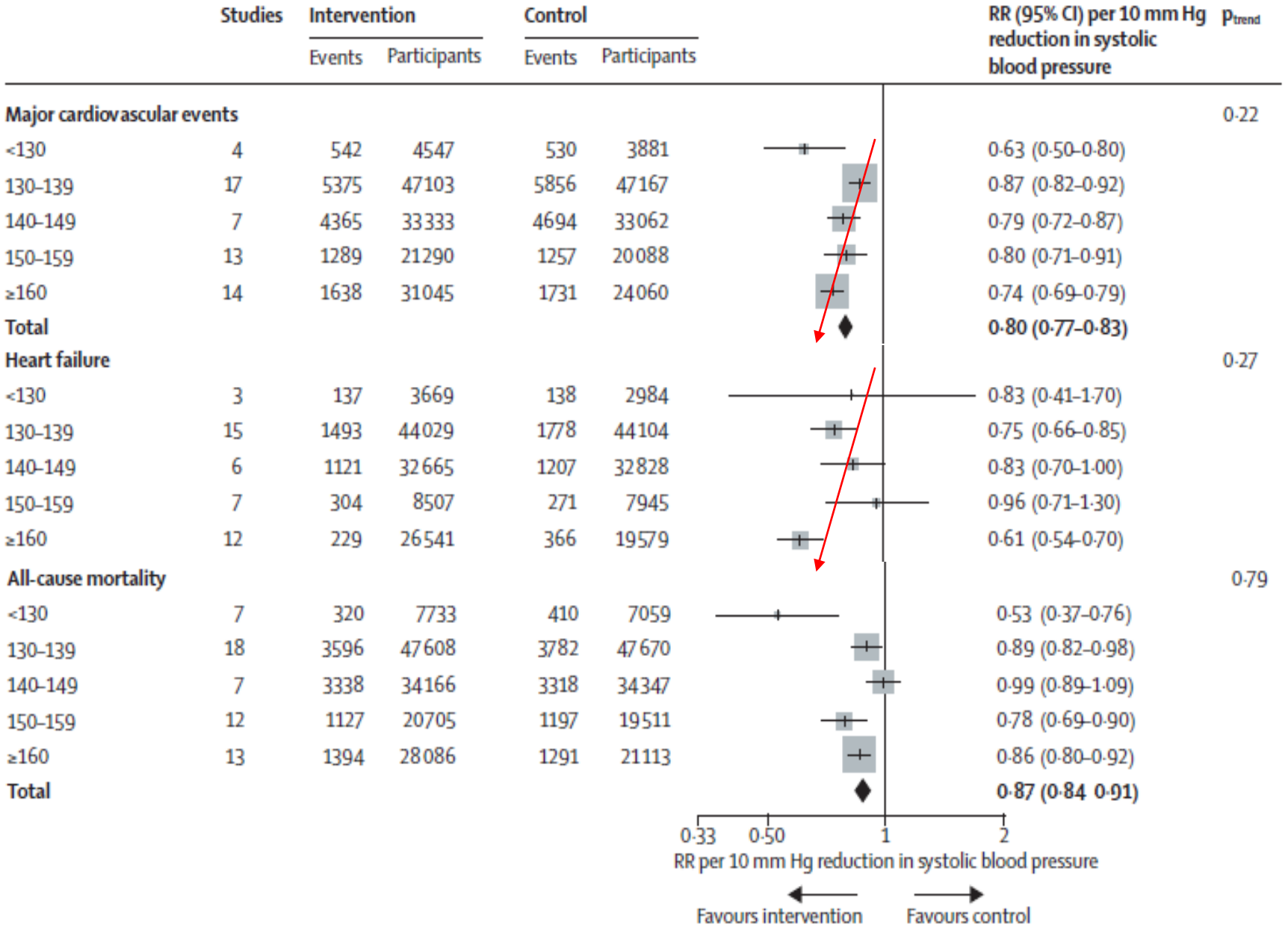
Effets non standardisés

Blood pressure lowering for prevention of cardiovascular disease and death.

Ettehad

No influence :

- of base BP
- Of comorbidities



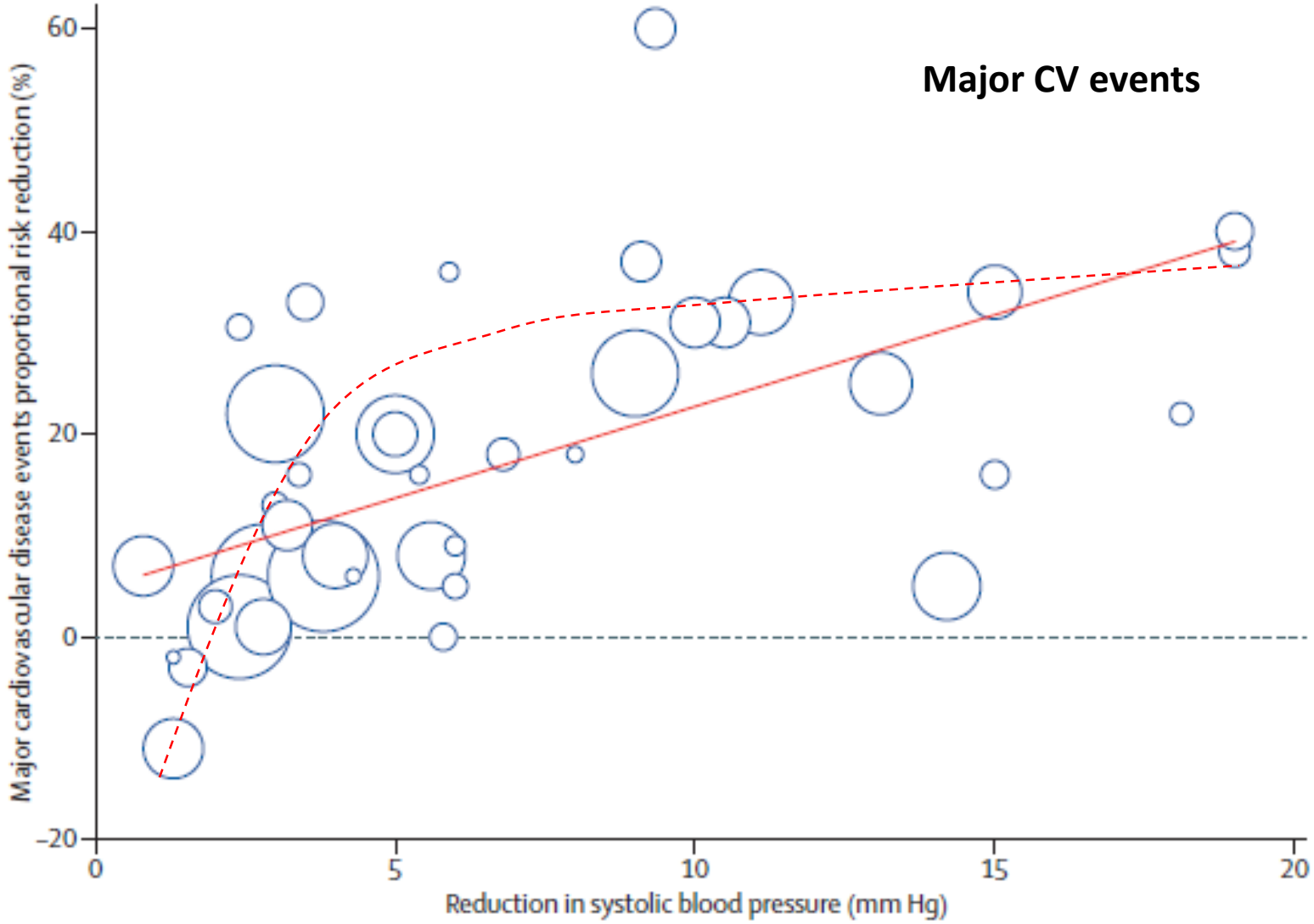
Blood pressure lowering for prevention of cardiovascular disease and death.

Ettehad D et al. Lancet. 2016 Mar 5;387(10022):957-967. PMID: 26724178

RRR not adequate for meta-regression (log OR)

Meta-regression:

- Adjusted by baseline BP
- And comorbidities: pre-existing CVD or not (HF excluded)



Blood pressure lowering for prevention

Ettehad D et al. Lancet. 2016 Mar 5;387

BB less effective than control for

- MCVE
- Stroke
- Renal failure
- All-cause mortality

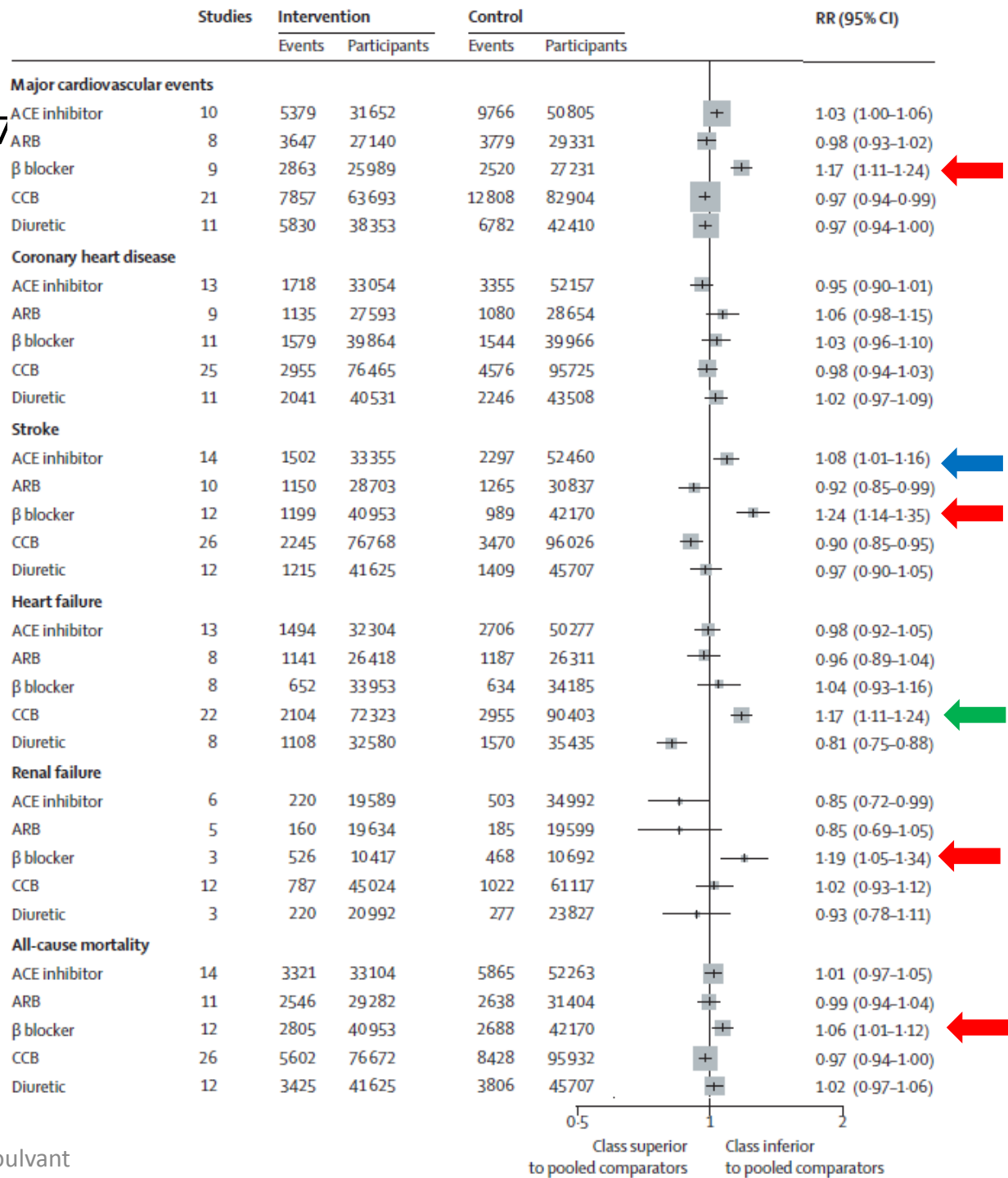
ACE-I less effective than control for

- stroke

CCB less effective than control for

- Heart failure

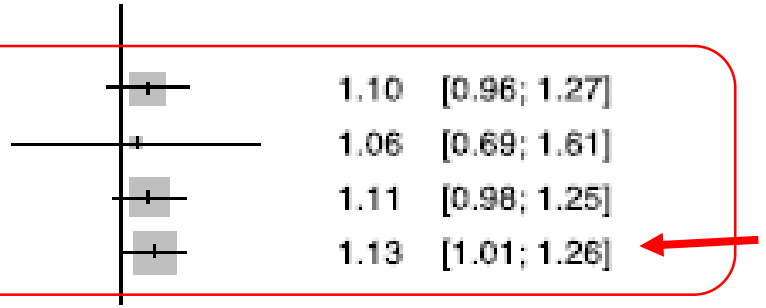
The problem: What is « control »



Blood pressure lowering for prevention of cardiovascular disease and death.

Ettehad D et al. Lancet. 2016 Mar 5;387(10022):957-967. PMID: 26724178

Subgroup	Studies	Events Intervention	Participants Intervention	Events Control	Participants Control	Relative Risk of Stroke	RR (95% CI)
ACE							
ACEi vs ARB	2	416	9748	378	9717		1.10 [0.96; 1.27]
ACEi vs BB	2	44	836	40	799		1.06 [0.69; 1.61]
ACEi vs CCB	9	560	13638	505	13748		1.11 [0.98; 1.25]
ACEi vs Diuretic	2	569	12098	782	18294		1.13 [1.01; 1.26]



inverse variance weighted fixed effects MA because heterogeneity was low and random-effects MA might apply inappropriately large weights to smaller studies: correct

ACEi vs DIU	- ALLHAT / lisinopril (very rarely used in France) / chlorthalidone (not used in France) / 55-80 years / double blind / High CV risk, 35% blacks (ACEi less effective) / RR= 1.15 [1.15-1.30] - ANBP2 / open-label, physicians unblided, events adjudicated / 65-84 years / Low CV risk / only 58% of ACEi and 62% DIU were still on tt at the end of the study / free adjustment of ttt after first line / RR= 1.02 [0.78-1.33]

Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels

Brunström M et Carlberg B. JAMA Intern Med. 2017 Nov 13. PMID: 29131895

- All trials comparing BPLT vs placebo or diff BP targets (comparable criteria with Ettehad MA)
- >1000 FUP
- No formal protocol for this SRMA
- 74 trials, ~300,000 patients; 1ry/2ry prevention trials (<50 / >50% CVD)
- Meta-regression adjusted by age, sex, diabetes N/Y (<50, >50%), trt duration
- Sensitivity: exclusion of HF trials, « true » 1ry/2ry prevention trials

Association of Blood Pressure Lowering With Mortality and Cardiovascular Disease Across Blood Pressure Levels

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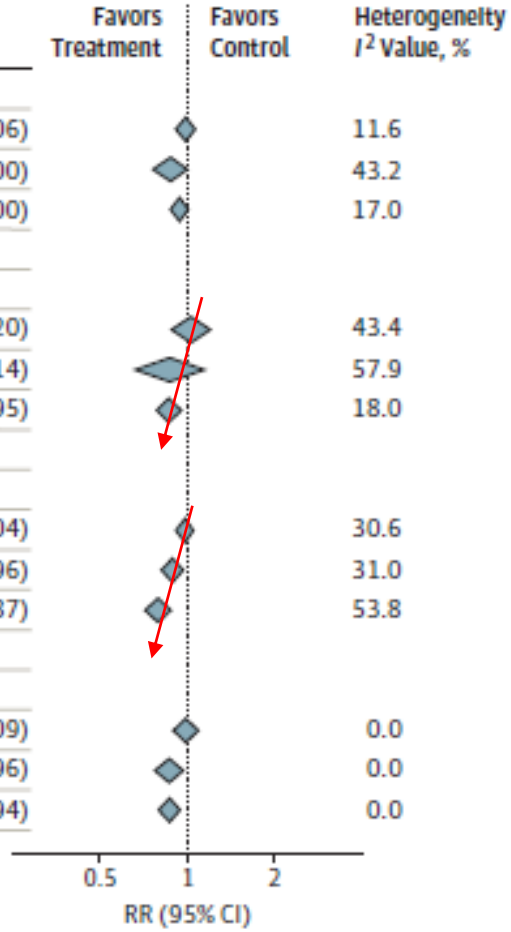
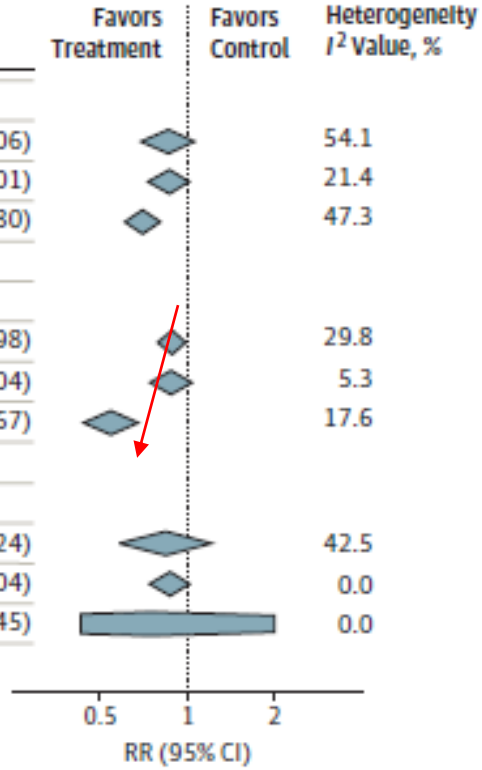
Baseline SBP, mm Hg	No. of Events/ Participants/Trials	RR (95% CI)	Heterogeneity I^2 Value, %
All-cause mortality			
<140	4897/68 816/16	0.98 (0.90-1.06)	11.6
140-159	2731/41 049/15	0.87 (0.75-1.00)	43.2
≥160	4361/79 900/18	0.93 (0.87-1.00)	17.0
SBP Interaction, *P*=.18			
Cardiovascular mortality			
<140	2633/66 480/12	1.03 (0.87-1.20)	43.4
140-159	1465/42 587/15	0.86 (0.65-1.14)	57.9
≥160	2290/78 789/17	0.85 (0.77-0.95)	18.0
SBP Interaction, *P*=.02			
Major cardiovascular events			
<140	7354/67 928/13	0.97 (0.90-1.04)	30.6
140-159	3951/43 489/16	0.88 (0.80-0.96)	31.0
≥160	4627/77 733/16	0.78 (0.70-0.87)	53.8
SBP Interaction, *P*=.004			
Coronary heart disease			
<140	1618/62 617/11	0.98 (0.88-1.09)	0.0
140-159	1369/42 543/14	0.86 (0.76-0.96)	0.0
≥160	2018/78 617/17	0.86 (0.78-0.94)	0.0
SBP Interaction, *P*=.13			



Baseline SBP, mm Hg	No. of Events/ Participants/Trials	RR (95% CI)	Heterogeneity I^2 Value, %
Stroke			
<140	1775/62 751/11	0.85 (0.68-1.06)	54.1
140-159	1429/41 641/13	0.86 (0.72-1.01)	21.4
≥160	1929/79 900/18	0.69 (0.60-0.80)	47.3
SBP Interaction, *P*=.16			
Heart failure			
<140	2261/60 879/9	0.88 (0.78-0.98)	29.8
140-159	1113/35 254/10	0.87 (0.73-1.04)	5.3
≥160	520/23 395/10	0.53 (0.42-0.67)	17.6
SBP Interaction, *P*=.005			
End-stage renal disease			
<140	488/24 512/5	0.84 (0.57-1.24)	42.5
140-159	870/32 984/7	0.88 (0.74-1.04)	0.0
≥160	32/5566/2	0.73 (0.01-6.45)	0.0
SBP Interaction, *P*=.32			



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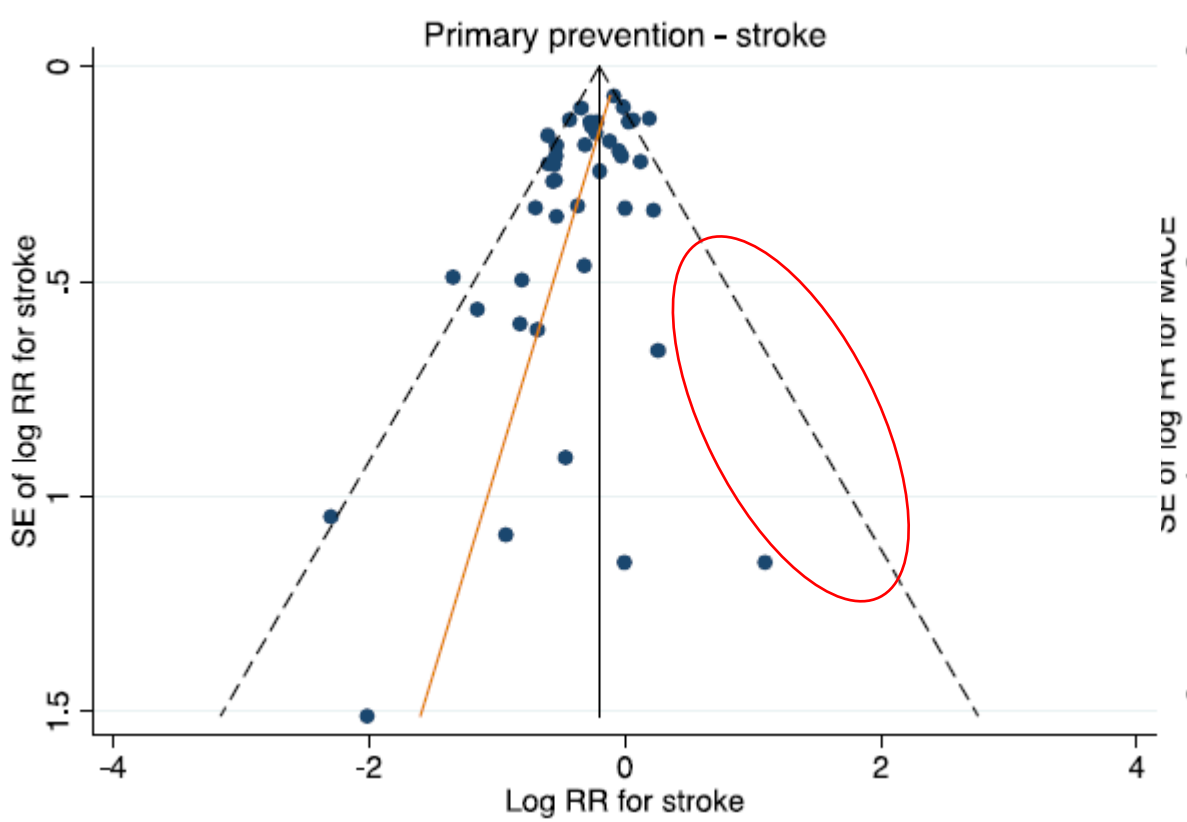
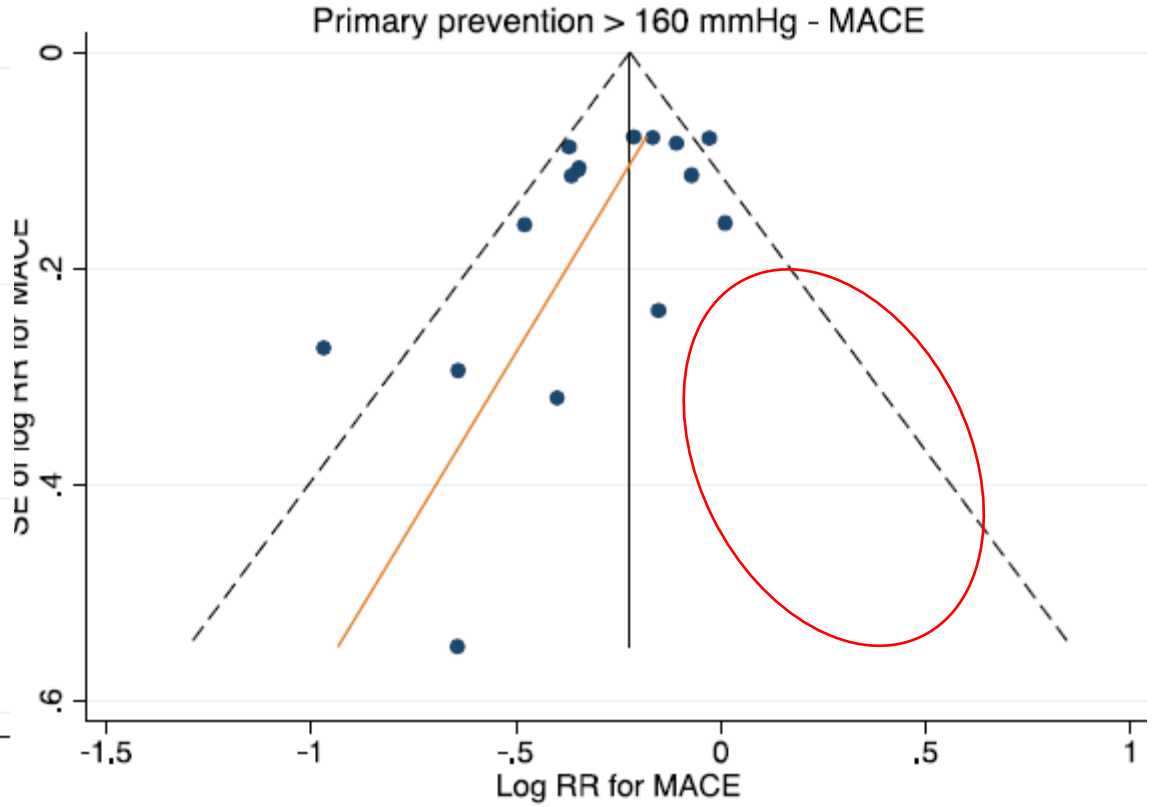


Egger´s test for small-study effect: p=0.006
Harbord´s modified test for small-study effect: p=0.007



Egger´s test for small-study effect: p=0.062
Harbord´s modified test for small-study effect: p=0.049

Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension

Monticone S et al. Lancet Diabetes Endocrinol 2017 Nov 9. PMID: 29129575
Division of Internal Medicine and Hypertension Unit, University of Turin, Italy

- Rationale for increased CV risk and TOD in PA: increased vascular inflammation, oxydative stress & fibrosis, insulin resistance…
- MEDLINE & CDSR
- PROSPERO: CRD42017073696
- Stroke/CAD main outcomes
- 31 studies comparing outcomes in PA vs essential HT, 10 prospective, 15 matched, 29 provided outcomes at diagnosis (prevalence) and only 2 provided outcomes at FUP (incidence)

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Parameter (n of studies / n of patients)	**3,838 patients with PA**	**9,284 patient with EH**
Age (years) (22/12,166)	53 [48-55]	53 [52-54]
Female gender (%) (28/12,992)	28 [26-33]	32 [31-39]
Diabetes mellitus (%) (10/8,874)	17 [15-21]	14 [9-17]
Hyperlipidemia (%) (11/9,850)	51 [42-56]	49 [4-55]
BMI (Kg/m^2) (18/9,957)	28 [22-32]	23 [21-29]
Duration of hypertension (years) (15/8,143)	8.8 [6.2-10.7]	7.2 [5.7-9.8]

Biochemical parameters (n of studies / n of patients)	**3,838 patients with PA**
Serum creatinine (µmol/L) (9/909)	79.6 [70.7-88.4]
Serum K^+ (mEq/L) (7/506)	3.3 [3.1-3.6]
PRA (ng/mL/h) (10/661)	0.3 [0.1-0.6]
Aldosterone (pmol/L) (25/3,072)	
- serum (1/99)	859 [609-1,188]
- plasma (24/2,973)	922 [663-1100]

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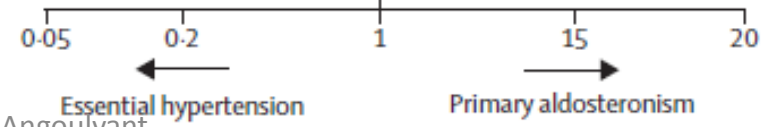
Monticone S et al. Lancet Diabetes Endocrinol 2017 Nov 9. PMID: 29129575

Division of Internal Medicine and Hypertension Unit, University of Turin, Italy

STROKE

	Primary aldosteronism		Essential hypertension			OR (95% CI)
	Events	Total	Events	Total	Weight	
Not matched studies						
Monticone at al (2017)[21]	6	99	53	1573	11·1%	1·85 (0·78–4·42)
Murata et al (2017)[17]	30	292	22	498	25·7%	2·48 (1·40–4·38)
Subtotal (95% CI)		**391**		**2071**	**36·8%**	**2·27 (1·41–3·66)**
Total events	36		75			
Heterogeneity: τ^2=0·00; χ^2=0·30, df=1 (p=0·59); I^2=0%						
Test for overall effect: Z=3·37 (p=0·0008)						
Matched studies						
Catena et al (2008)[23]	6	54	9	323	7·2%	4·36 (1·49–12·80)
Milliez et al (2015)[24]	16	124	16	465	15·9%	4·16 (2·02–8·58)
Mulatero et al (2013)[14]	20	270	28	810	23·9%	2·23 (1·24–4·04)
Takedaet al (1995)[13]	24	224	12	224	16·2%	2·12 (1·03–4·35)
Subtotal (95% CI)		**672**		**1822**	**63·2%**	**2·78 (1·93–4·00)**
Total events	66		65			
Heterogeneity: τ^2=0·00; χ^2=2·93, df=3 (p=0·40); I^2=0%						
Test for overall effect: Z=5·52 (p<0·00001)						
Total (95% CI)		**1063**		**3893**	**100·0%**	**2·58 (1·93–3·45)**
Total events	102		140			
Heterogeneity: τ^2=0·00; χ^2=3·68, df=5 (p=0·60); I^2=0%						
Test for overall effect: Z=6·43 (p<0·00001)						
Test for subgroup differences: χ^2=0·44, df=1 (p=0·51); I^2=0%						



X 2.78

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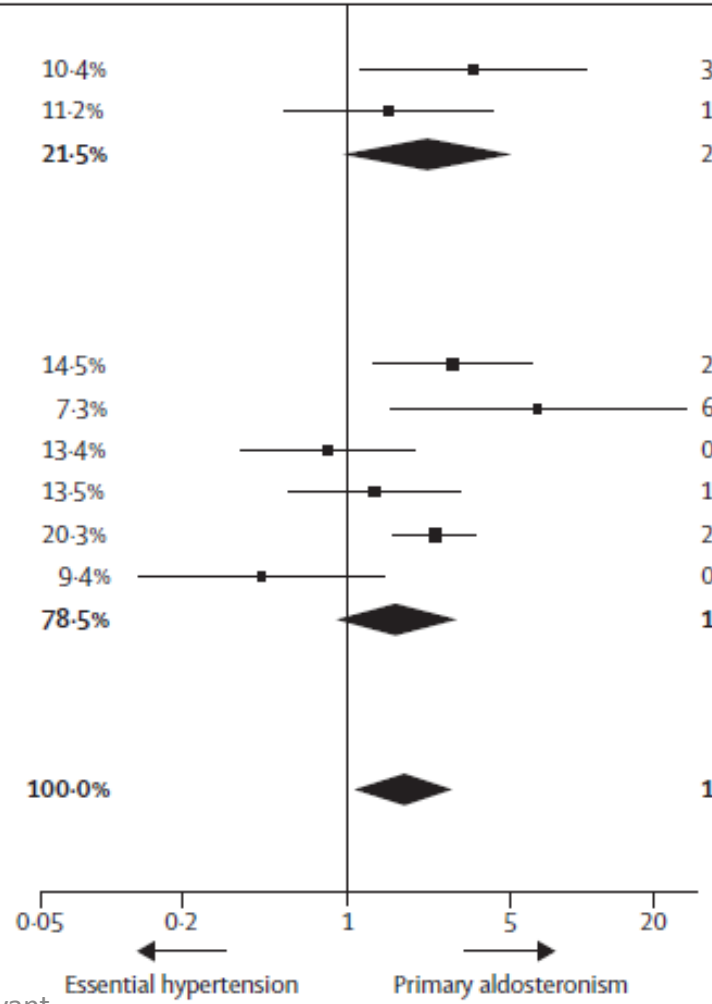
Division of Internal Medicine and Hypertension Unit, University of Turin, Italy

Coronary Artery Disease

	Primary aldosteronism		Essential hypertension			OR (95% CI)
	Events	Total	Events	Total	Weight	
Not matched studies						
Monticone et al (2017)[21]	4	99	19	1573	10·4%	3·44 (1·15–10·32)
Murata et al (2017)[22]	7	292	8	498	11·2%	1·50 (0·54–4·19)
Subtotal (95% CI)		**391**		**2071**	**21·5%**	2·22 (0·99–4·99)
Total events	11		27			
Heterogeneity: τ^2=0·05; χ^2=1·17, df=1 (p=0·28); I^2=14%						
Test for overall effect: Z=1·93 (p=0·05)						
Matched studies						
Catena et al (2008)[23]	11	54	27	323	14·5%	2·80 (1·30–6·06)
Milliez et al (2015)[24]	5	124	3	465	7·3%	6·47 (1·52–27·46)
Mulatero et al (2013)[14]	7	270	25	810	13·4%	0·84 (0·36–1·95)
Reincke et al (2012)[25]	13	281	10	281	13·5%	1·31 (0·57–3·05)
Savard et al (2013)[12]	46	459	58	1290	20·3%	2·37 (1·58–3·54)
Takeda et al (1995)[13]	4	224	9	224	9·4%	0·43 (0·13–1·43)
Subtotal (95% CI)		**1412**		**3393**	**78·5%**	**1·65 (0·92–2·95)**
Total events	86		132			
Heterogeneity: τ^2=0·33; χ^2=15·08, df=5 (p=0·01); I^2=67%						
Test for overall effect: Z=1·67 (p=0·10)						
Total (95% CI)		**1803**		**5464**	**100·0%**	**1·77 (1·10–2·83)**
Total events	97		159			
Heterogeneity: τ^2=0·24; χ^2=16·41, df=7 (p=0·02); I^2=57%						
Test for overall effect: Z=2·38 (p=0·02)						
Test for subgroup differences: χ^2=0·35, df=1 (p=0·56); I^2=0%						



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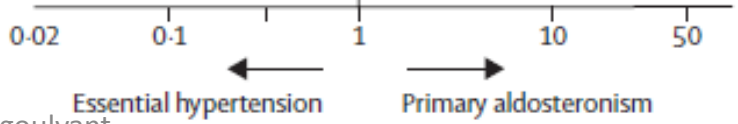
Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension

Monticone S et al. Lancet Diabetes Endocrinol 2017 Nov 9. PMID: 29129575

Division of Internal Medicine and Hypertension Unit, University of Turin, Italy

Atrial fibrillation

	Primary aldosteronism		Essential hypertension			OR (95% CI)
	Events	Total	Events	Total	Weight	
Not matched studies						
Monticone et al (2017)[21]	5	99	20	1573	14·7%	4·13 (1·52–11·25)
Murata et al (2017)[22]	8	292	12	498	16·3%	1·14 (0·46–2·82)
Rossi et al (2013)[26]	12	180	1	143	5·5%	10·13 (1·30–78·96)
Subtotal (95% CI)		**571**		**2214**	**36·5%**	**2·93 (0·91–9·47)**
Total events	25		33			
Heterogeneity: τ^2=0·66; χ^2=5·61, df=1 (p=0·06); I^2=64%						
Test for overall effect: Z=1·80 (p=0·07)						
Matched studies						
Catena et al (2008)[23]	7	54	10	323	14·6%	4·66 (1·69–12·84)
Milliez et al (2015)[24]	9	124	3	465	10·6%	12·05 (3·21–45·23)
Mulatero et al (2013)[14]	11	270	15	810	18·3%	2·25 (1·02–4·96)
Savard et al (2013)[12]	18	459	14	1290	20·0%	3·72 (1·83–7·54)
Subtotal (95% CI)		**907**		**2888**	**63·5%**	**4·01 (2·25–7·12)**
Total events	45		42			
Heterogeneity: τ^2=0·13; χ^2=4·77, df=3 (p=0·19); I^2=37%						
Test for overall effect: Z=4·72 (p<0·00001)						**3·52 (2·06–5·99)**
Total (95% CI)		**1478**		**5120**	**100·0%**	
Total events	70		75			
Heterogeneity: τ^2=0·24; χ^2=11·75, df=6 (p=0·07); I^2=49%						
Test for overall effect: Z=6·43 (p<0·00001)						
Test for subgroup differences: χ^2=0·22, df=1 (p=0·64); I^2=0%						



X 4

Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension

Monticone S et al. Lancet Diabetes Endocrinol 2017 Nov 9. PMID: 29129575

Division of Internal Medicine and Hypertension Unit, University of Turin, Italy

	low risk	medium risk	high risk	unknown
selection bias	3	20	0	8
attrition bias	28	3	0	0
adjudication bias	0	3	28	0

Main outcomes

Cardiovascular events and target organ damage in primary aldosteronism compared with essential hypertension

Monticone S et al. Lancet Diabetes Endocrinol 2017 Nov 9. PMID: 29129575
Division of Internal Medicine and Hypertension Unit, University of Turin, Italy

" In this meta-analysis of 31 studies that included 3838 patients with PA and 9284 patients with EH, we found **robust evidence** (transparency?) for a significant increase in

- cardiovascular and cerebrovascular events,
- target organ damage (left ventricular hypertrophy),
- metabolic syndrome,
- and diabetes,

in patients with primary aldosteronism compared with patients with essential hypertension »

- In the exclusive analysis of matched studies (only 3-4 studies, all retrospectives), **this association was independent from blood pressure levels, age, and sex,** suggesting that aldosterone can induce adverse cardiovascular effects through mechanisms that are at least partly independent of its effects on blood pressure

Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Reboussin DM et al. Hypertension. 2017 Nov 13. PMID: 29133355

1. Is there evidence that self-measured BP without other augmentation is superior to office-measured BP for achieving better BP control?
2. Is there evidence that self-measured BP without other augmentation is superior to office-measured BP for preventing adverse clinical outcomes that are related to elevated BP?

- Doctor Evidence: PubMed & Embase only

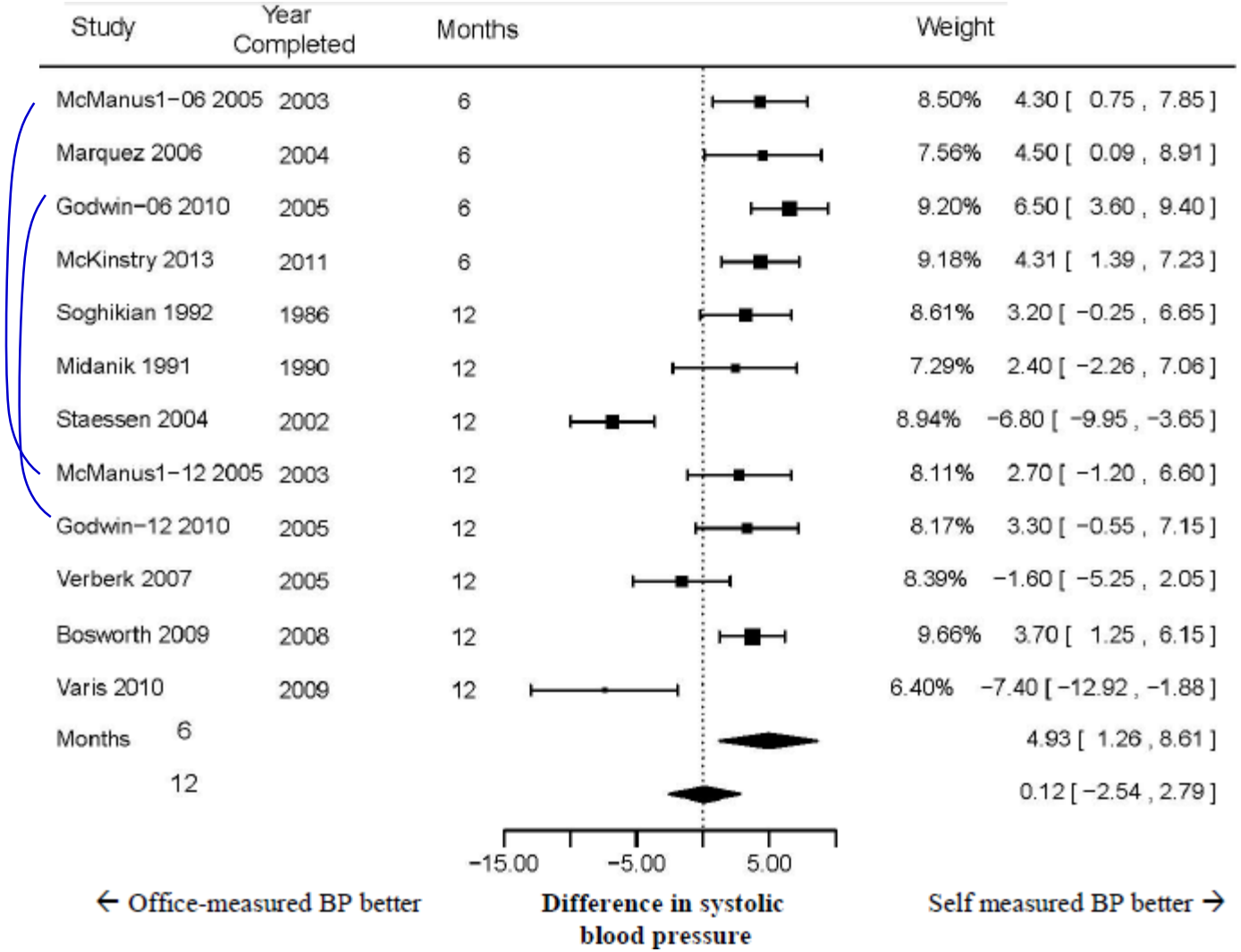
Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Reboussin DM et al. Hypertension. 2017 Nov 13. PMID: 29133355

- 10 studies; effect sizes ranged from a 7.4 mmHg worsening of systolic BP to a 6.5 mmHg improvement in **systolic BP** with self-measured BP compared with office-measured BP
- **None reported a significant intervention effect regarding % achieving BP target**

There may be some bias against publication of null and negative studies !

- Stroke, MI, and CV mortality: no data (≥4 studies) no MA
- Total mortality: 4 studies, but the number of events was small and details of how mortality data were ascertained were unclear. No significant difference; overall RR was not different from 1.0



Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Reboussin DM et al. Hypertension. 2017 Nov 13. PMID: 29133355

Limitations: Part 1

This meta-analysis has several limtations. As with any meta-analysis, we may be limited by unpublished data. There were differences in study design even among the studies that used only self-measured BP, which may have limited our ability to detect more substantial improvements in BP control with self-measured BP. We were also limited by our inability to comment on outcomes other than systolic BP, such as medication adherence, or clinical outcomes, such as end-organ damage or clinical events.

Conclusions: Part 1

In summary, we found a modest but significant improvement in systolic BP in RCTs of self-measured BP versus office-based BP . However, the improvement was not sustained for longer than 6 months. Well-run studies of self-measured BP, in conjunction with additional support, have demonstrated more substantial improvements in BP control, but study design is highly variable. Our results suggest that, for selected patients and their providers, self-measured BP may be a helpful adjunct to routine office care.

Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Reboussin DM et al. Hypertension. 2017 Nov 13. PMID: 29133355

Targets for Blood Pressure Lowering During Antihypertensive Therapy in Adults ?

- Via Doctor Evidence.
- ROB: low risk if all criteria were low risk; high risk if 1 or more criteria were high risk
- Random-effect MA if >= 3 studies: “lower vs higher”, “<130 mmHg vs higher”
- 130 mmHg: lower limit of high-normal BP and goal BP set by other guidelines for certain subpopulations
- Of the 15 included trials, 12 showed high risk of bias for the blinding of study participants and personnel
- Two studies showed high risk of bias due to inadequately addressing incomplete outcome data
- Included studies showed low or unclear risk of bias for all other domains.

Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Reboussin DM et al. Hypertension. 2017 Nov 13. PMID: 29133355

Table 2.7. Relative Risk (95% Confidence Interval) for a Given Outcome for any Intensive [Lower] Blood Pressure Target Versus any Standard [Higher] Blood Pressure Target.

Outcome	Studies included, N	Study participants included, N	Events, N (%)		RR	(95% CI)	Heterogeneity		Funnel Plot Asymmetry	
			Intensive BP target	Standard BP target			I^2 (%)	*P*-value	P-value for Kendall's Tau	P-value for Egger's Regression Test
All-cause mortality	15	49,934	952 (4.0)	1,001 (4.3)	0.89	(0.77, 1.02)	49.30	0.02	0.24	0.50
CVD mortality	10	40,266	268 (1.3)	504 (2.5)	0.86	(0.67, 1.12)	46.44	0.06	0.38	0.38
Major Cardiovascular Disease Events	7[a]	23,617	682 (5.8)	828 (7.0)	0.81	(0.70, 0.94)	41.34	0.12	0.56	0.55
Fatal or non-fatal myocardial infarction	11	31,926	415 (2.6)	419 (2.7)	0.86	(0.76, 0.99)	0.00	0.99	0.76	0.28
Fatal or non-fatal stroke	12	33,018	389 (2.3)	475 (2.9)	0.77	(0.65, 0.91)	26.43	0.18	0.74	0.41
Fatal or non-fatal heart failure	8	23,066	222 (1.9)	278 (2.4)	0.75	(0.56, 0.99)	49.12	0.06	0.55	0.72
Renal Events	8[b]	18,286	334 (3.8)	353 (4.2)	1.01	(0.89, 1.15)	0.00	0.80	1.00	0.68

Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Reboussin DM et al. Hypertension. 2017 Nov 13. PMID: 29133355

Table 2.8. Relative Risk (95% Confidence Interval) for a Given Outcome for Intensive [Lower] Blood Pressure Target <130 mm Hg Systolic Versus any Standard [Higher] Blood Pressure Target

Outcome	Studies included, N	Study participants included, N	Events, N (%)		RR	(95% CI)	Heterogeneity		Funnel Plot Asymmetry	
			Intensive BP target	Standard BP target			I^2 (%)	*P*-value	P-value for Kendall's Tau	P-value for Egger's Regression Test
All-cause mortality	9[a]	24,569	493 (4.0)	546 (4.4)	0.92	(0.79, 1.06)	15.59	0.30	0.12	0.91
CVD mortality	5[b]	19,039	117 (1.2)	145 (1.5)	0.81	(0.58, 1.14)	31.42	0.21	0.82	0.79
Major Cardiovascular Disease Events	5[a]	19,814	610 (6.2)	724 (7.3)	0.84	(0.73, 0.99)	40.70	0.15	0.82	0.82
Fatal or non-fatal myocardial infarction	6	22,077	269 (2.4)	316 (2.9)	0.85	(0.73, 1.00)	0.00	0.99	0.47	0.45
Fatal or non-fatal stroke	7	23,169	274 (2.4)	339 (2.9)	0.82	(0.70, 0.96)	0.00	0.45	1.00	0.90
Fatal or non-fatal heart failure	4	16,296	175 (2.2)	220 (2.7)	0.81	(0.58, 1.14)	53.42	0.09	1.00	0.92
Renal Events	5[b]	9,641	347 (7.4)	346 (7.0)	1.01	(0.89, 1.16)	0.00	0.99	1.00	0.48

Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Reboussin DM et al. Hypertension. 2017 Nov 13. PMID: 29133355

The results of our meta-analysis are consistent with other recent meta-analyses which demonstrate that **BP lowering** **significantly reduced the risk of cardiovascular morbidity** and **mortality** ("marginally significant reduction" 0.89, 0.77-1.02, 95%CI) regardless of meta-analytic method, comorbid condition, or mean age of study participant.

Additionally, we have shown that **BP lowering to a target of <130 mmHg** may reduce the risk of several important outcomes including risk of MI, stroke, heart failure (NS), and major cardiovascular events.

Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

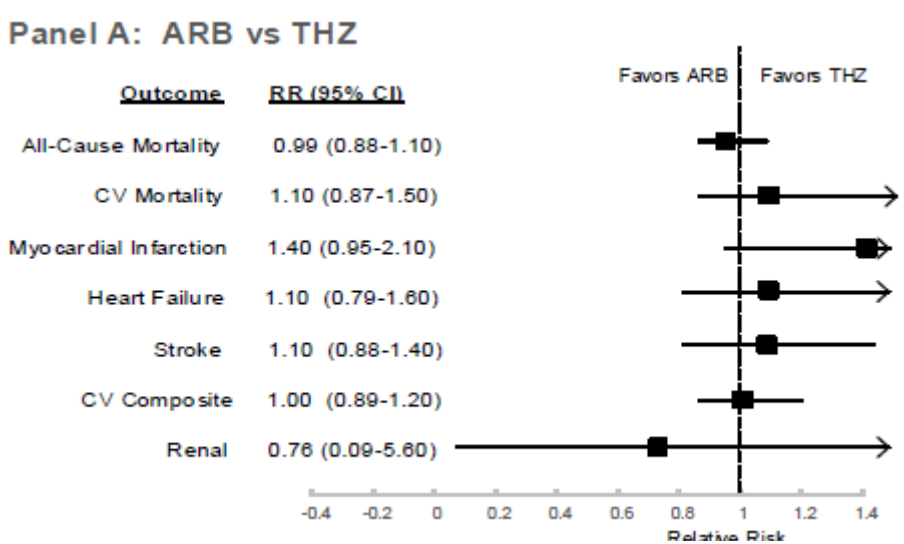
Reboussin DM et al. Hypertension. 2017 Nov 13. PMID: 29133355

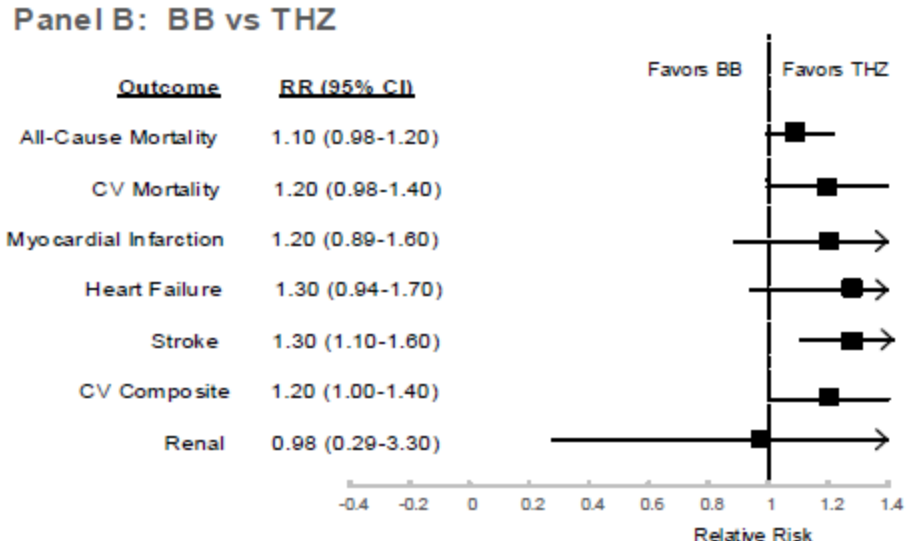
First-Line Antihypertensive Drug Class Comparisons in Adults

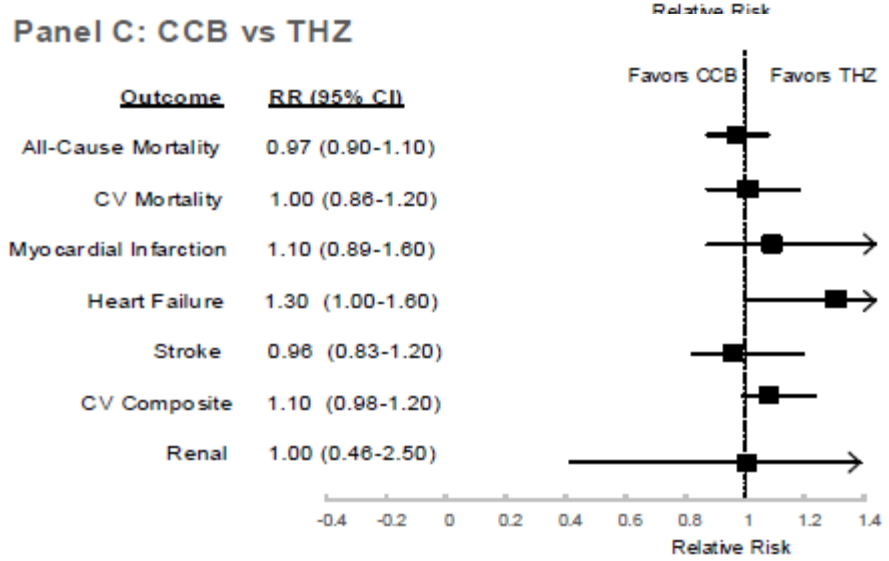
- network meta-analysis (via Doc Evidence)
- trials that compared any 2 classes of antihypertensive therapies used as first-line : thiazide and thiazide-like diuretics (THZs), ACEIs, angiotensin-receptor blockers (ARBs), calcium channel blockers (CCBs), and beta blockers.
- Our objective was to examine the comparative benefits and harms of different antihypertensive classes in adults with hypertension

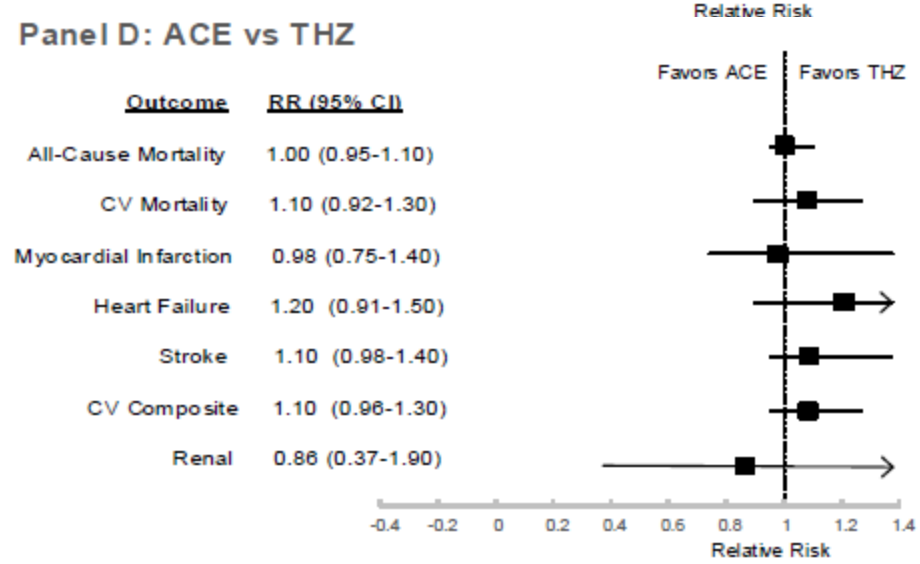
Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Pooled Network Relative risks associated with first line antihypertensive medication classes compared to THZ









Systematic Review for the 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults

Pooled Network Relative risks associated with first line antihypertensive medication classes compared to thiazides (THZ)

"In summary, we found that THZs were associated with a lower risk of many cardivoascular outcomes compared with other antihypertensive drug classes. This large and contemporary network meta-analysis supports prior findings that recommend THZs as the choice for first-line antihypertensive treatment among individuals with uncomplicated hypertension. Future studies should continue to examine whether these results are consistent across subgroups that vary by demographic or clinical characteristics. "

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	MedlineID	Authors	Reference Title	Journal	Publication Date	Study Design	Full Text	Abstract	Favourites	Sharin
1	16947782	Maini R N, Taylor...	Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist...	Arthritis and rhe...	2006 Sep	RCT Head to Head	Full Text	Abstract		
2	19019888	Nishimoto N, Miy...	Long-term safety and efficacy of tocilizumab, an anti-IL-6 receptor monoclonal antibo...	Annals of the rh...	2009 Oct	Prospective Cohort	Full Text	Abstract		

Optimal database combinations for literature searches in systematic reviews: a prospective exploratory study

Systematic Reviews

Bramer *et al. Systematic Reviews* (2017) 6:245
DOI 10.1186/s13643-017-0644-y

Wichor M. Bramer[1*], Melissa L. Rethlefsen[2], Jos Kleijnen[3,4] and Oscar H. Franco[5]

Table 4 Performance of several databases and database combinations in terms of sensitivity and precision

	# results	# includes ($N = 1746$)	Overall recall[a]	Median recall[b]	Minimum recall[c]	Percentage 100% recall[d]	Precision[e]	Number needed to read[f]
Embase (EM)	85,521	1500	85.9%	87.3%	45.8%	13.8%	1.8%	57
MEDLINE (ML)	56,340	1375	78.8%	82.9%	50.0%	8.6%	2.4%	41
Web of Science (WoS)	48,561	1189	68.1%	72.5%	13.2%	6.9%	2.4%	41
Google Scholar (GS)	10,342	601	34.4%	38.0%	8.3%	5.2%	5.8%	17
EM-ML	100,444	1621	92.8%	94.6%	66.7%	24.1%	1.6%	62
EM-WoS	104,444	1585	90.8%	93.8%	57.9%	27.6%	1.5%	66
EM-GS	91,411	1570	89.9%	93.3%	65.8%	25.9%	1.7%	58
ML-WoS	75,263	1481	84.8%	87.1%	60.0%	15.5%	2.0%	51
ML-GS	62,230	1459	83.6%	89.8%	63.2%	15.5%	2.3%	43
WoS-GS	54,451	1320	75.6%	85.7%	23.7%	13.8%	2.4%	41
EM-ML-GS	106,334	1674	95.9%	97.4%	78.9%	41.4%	1.6%	64
EM-ML-WoS	119,367	1674	95.9%	97.1%	71.1%	37.9%	1.4%	70
EM-WoS-GS	110,334	1638	93.8%	98.1%	65.8%	44.8%	1.5%	67
ML-WoS-GS	81,153	1528	87.5%	92.6%	70.0%	29.3%	1.9%	53
EM-ML-GS-WoS	125,257	1716	98.3%	100.0%	78.9%	74.1%	1.4%	73

[a]Overall recall: The total number of included references retrieved by the databases divided by the total number of included references retrieved by all databases
[b]Median recall: The median value of recall per review
[c]Minimum recall: The lowest value of recall per review
[d]Percentage 100% recall: The percentage of reviews for which the database combination retrieved all included references
[e]Precision: The number of included references divided by the total number of references retrieved
[f]Number Needed to Read: The total number of references retrieved divided by the number of included references

Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5

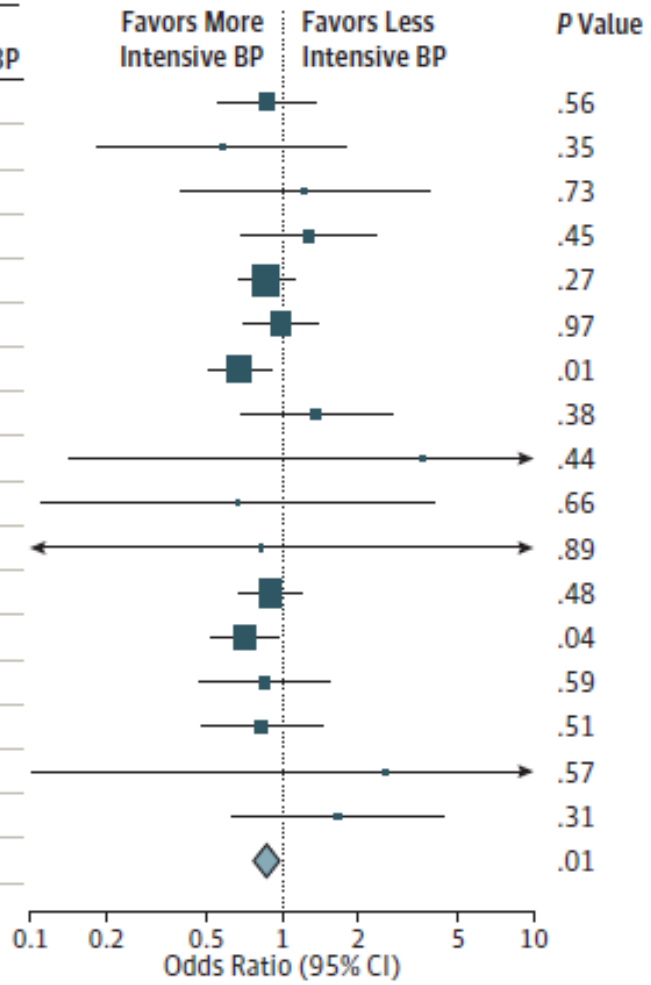
Malhotra R et al. JAMA Intern Med. 2017;177(10):1498-1505. PMID: 28873137

- MEDLINE, Cochrane Library, EMBASE, PubMed, Science Citation Index,Google Scholar, and clinicaltrials.gov
- trials comparing BPLT vs placebo or diff BP targets
- DFG <60 ml/min/1,73 m2

Random

No heterogeneity

Source	Odds Ratio (95% CI)	Score	No. of Deaths/Total No. More Intensive BP	No. of Deaths/Total No. Less Intensive BP	P Value
Wright et al,[14] 2002	0.874 (0.554-1.380)	-0.578	37/540	43/554	.56
Estacio et al,[24] 2000	0.575 (0.182-1.820)	-0.941	5/62	9/68	.35
Schrier et al,[26] 2002	1.227 (0.398-3.865)	0.349	6/57	7/80	.73
Cushman et al,[32] 2010	1.271 (0.685-2.360)	0.761	26/208	20/198	.45
Heerspink et al,[27] 2010	0.862 (0.662-1.123)	-1.102	117/1010	135/1023	.27
Lonn et al,[37] 2016	0.993 (0.699-1.410)	-0.039	49/1220	97/2399	.97
Beckett et al,[30] 2008	0.676 (0.502-0.911)	-2.570	83/788	121/816	.01
Klahr et al,[13] 1994	1.366 (0.681-2.742)	0.878	20/432	14/408	.38
Mant et al,[34] 2016	3.588 (0.140-91.945)	0.772	1/26	0/30	.44
Ruggenenti et al,[22] 2005	0.667 (0.110-4.042)	-0.441	2/167	3/168	.66
Schrier et al,[25] 2002	0.825 (0.050-13.701)	-0.134	1/41	1/34	.89
SHEP Cooperative Research Group,[28] 1991	0.900 (0.670-1.209)	-0.700	96/879	103/859	.48
Wright et al,[17] 2015	0.714 (0.519-0.982)	-2.072	70/1330	95/1316	.04
Benavente et al,[33] 2013	0.850 (0.468-1.544)	-0.534	24/216	25/195	.59
Staessen et al,[29] 1997	0.826 (0.470-1.451)	-0.665	26/242	29/228	.51
Toto et al,[23] 1995	2.566 (0.101-64.993)	0.572	1/42	0/35	.57
UK Prospective Diabetes Study Group,[35] 1998	1.667 (0.626-4.435)	1.023	20/68	7/35	.31
Overall	0.859 (0.764-0.965)	-2.560	584/7451	709/8473	.01
Heterogeneity: $\tau^2 = 0\%$; $P = .77$; $I^2 = 0\%$					



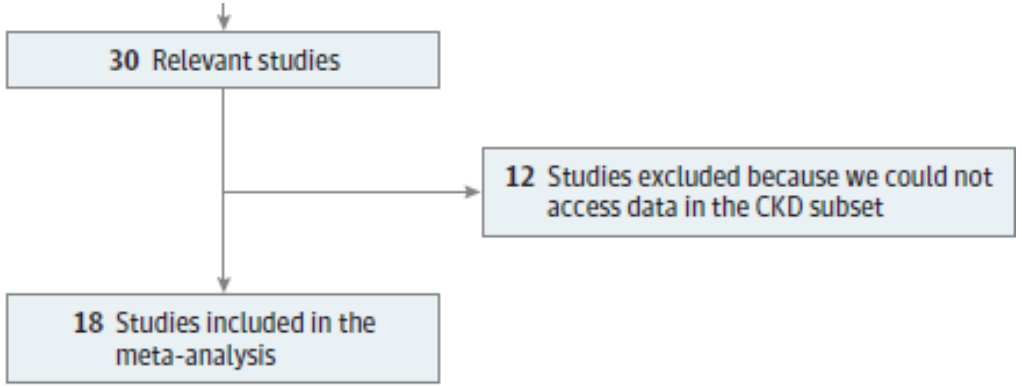
The results were similar after exclusion of SPRINT (OR, 0.88; 95%CI, 0.78-0.99; P = .05).

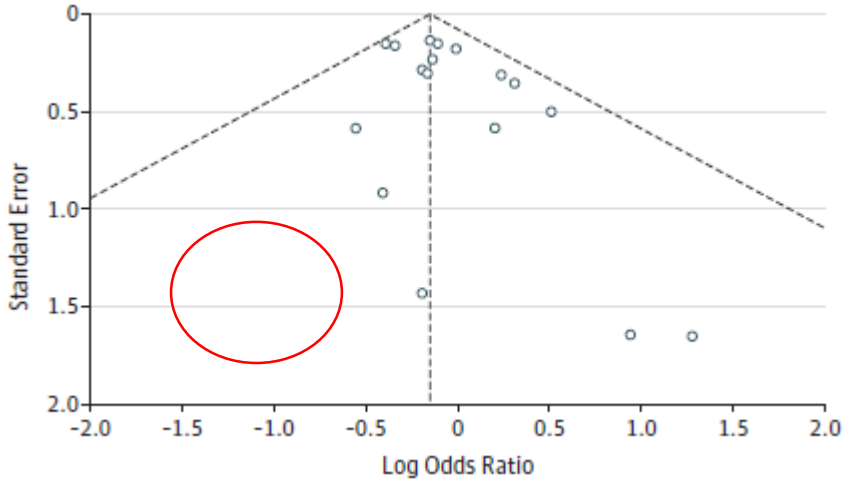
Greater mortality benefit in trials with higher differences in achieved BP across treatment arms: difference in SBP of at least 12mm Hg / OR = 0.76, trials with differences 6 to 12 / OR = 0.97, and trials those with differences <6 mmHg / OR 1.06; p-heterogeneity .06

Association Between More Intensive vs Less Intensive Blood Pressure Lowering and Risk of Mortality in Chronic Kidney Disease Stages 3 to 5

Malhotra R et al. JAMA Intern Med. 2017;177(10):1498-1505. PMID: 28873137

- Significant -14% decrease in overall mortality
- But only 18/30 studies reported results regarding mortality in subgroups of patients with low DFG



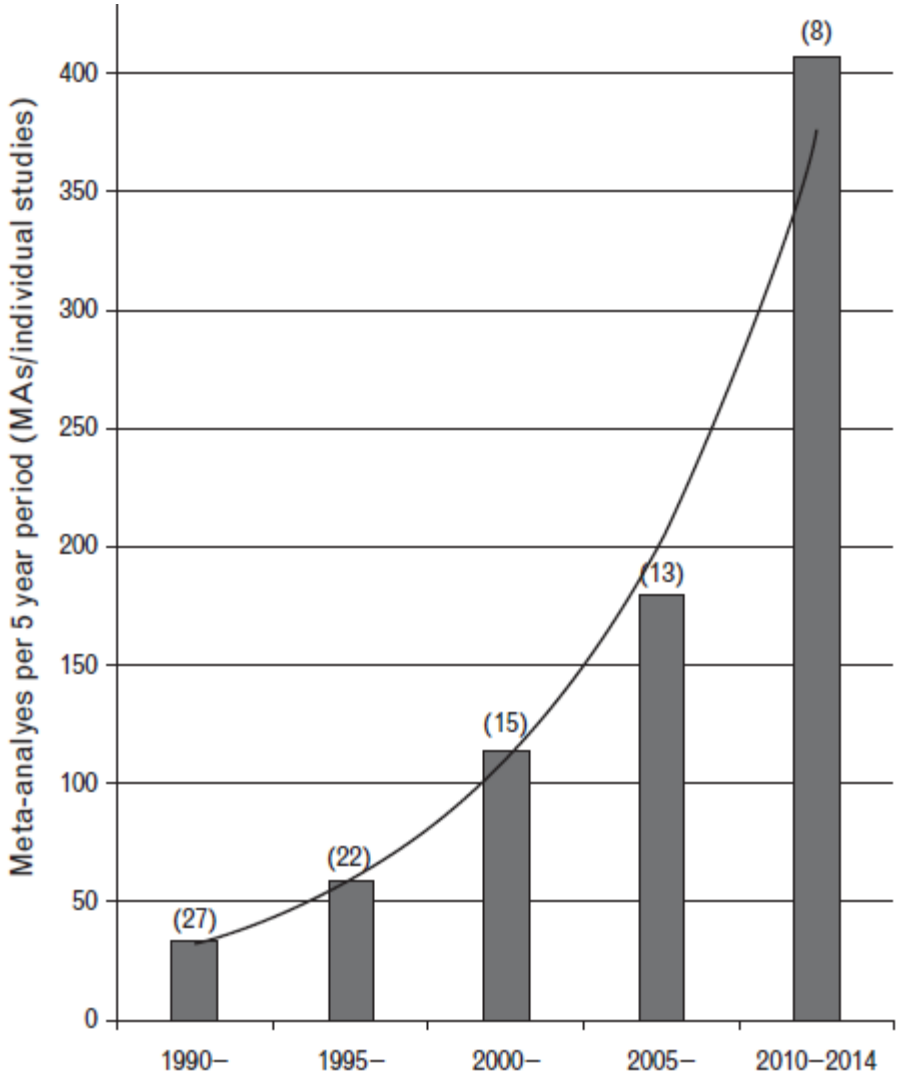


no evidence of publication bias based on visual inspection or by performing Begg and Mazumdar rank correlation (P = .23) and Egger regression (P = .08) tests

Quality of meta-analyses for randomized trials in the field of hypertension: a systematic review

Roush GC et al. J Hypertens. 2016 Dec;34(12):2305-2317. PMID: 27755384

- 25-year increase in new, study-level, hypertension-related MA from PubMed
- Parentheses contain, in the field of hypertension, the ratio of individual studies to meta-analyses.
- The increase in metaanalyses and individual studies is 12-fold and 4-fold, respectively.
- The correlation, r, between time period and the log (number of meta-analyses) is 0.997 (i.e., a nearly perfect exponential increase).
- On average, the number of MA has been doubling every 5.6 years.
- In the last 2 years, the number of these meta-analyses has average 2.1 per week.



Quality of meta-analyses for randomized trials in the field of hypertension: a systematic review

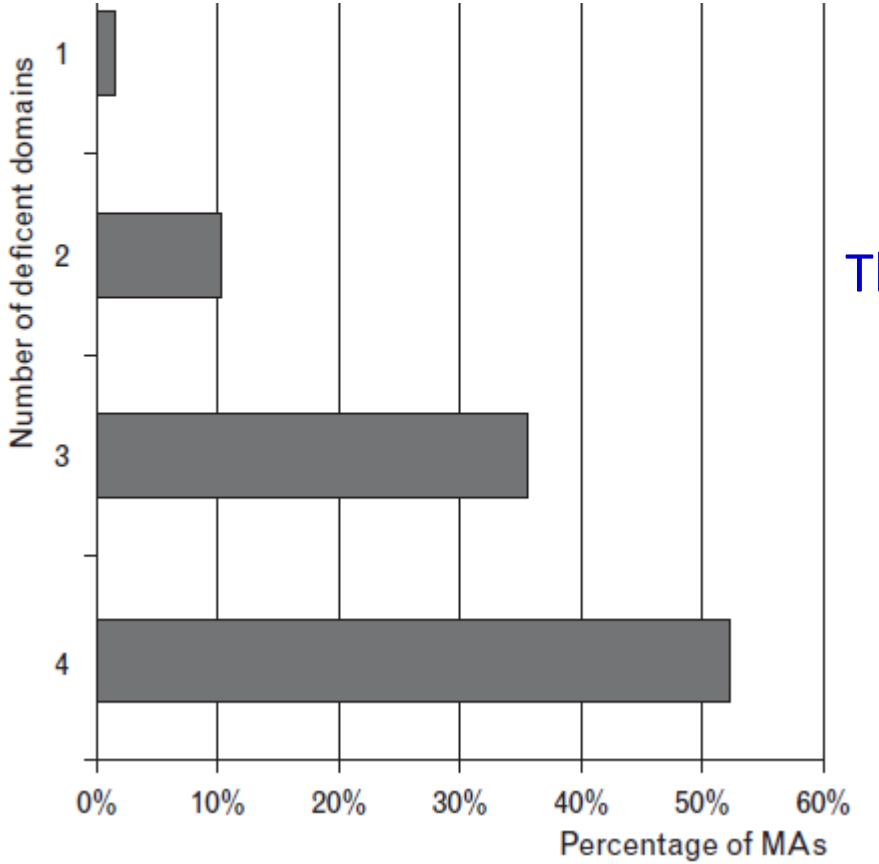
Overall study quality	
Low	16
Medium	33
High	18
Unable to tell	33
I^2 for heterogeneity	
0	16
1–24	15
25–49	15
50–74	29
75–100	24
Publication bias	
Not present	58
Present	17
Not reported	25
Test for publication bias provided	
Yes	43
No	57
Types of tests for publication bias[c]	
Egger's linear regression	34
Begg's rank correlation	7
Duvall & Tweedie's trim and fill	9
Other tests	2
Statistical power of the meta-analysis	
Calculates power (*post hoc*)	1
Acknowledges power limitation of the meta-analysis	22
No mention of power of the meta-analysis	77

- MA since 2012
- Excluded: network, IPD, meta-regression, <5 trials
- % characteristics for 143 MA retrieved (table)
- Domain 1: assessing the quality of the individual trials
  - 5 features
- Domain 2: assessing heterogeneity across trials
  - 10 features
- Domain 3: assessing publication bias
  - 5 features
- Domain 4: providing transparency for Domains 1–3 ('abstract' and 'discussion')
  - 3 features

4 domains, 23 features

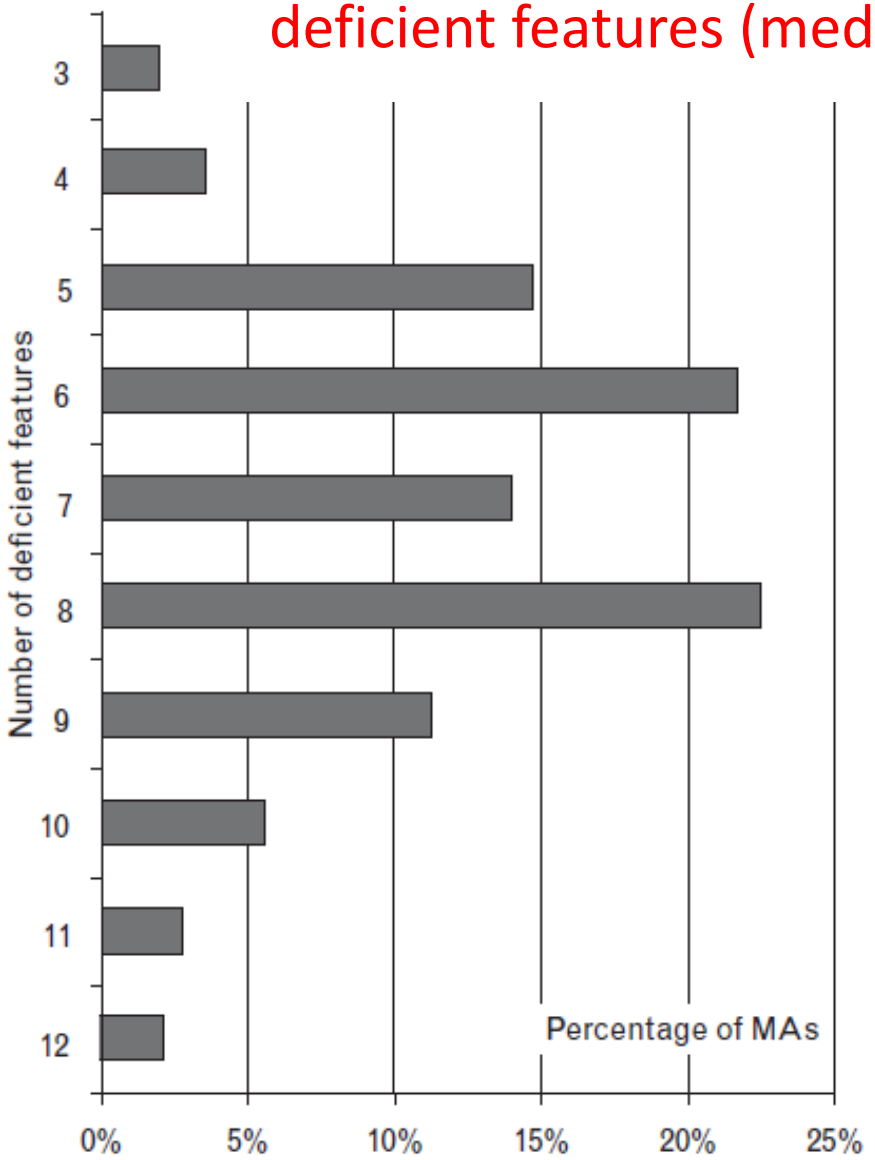
Quality of meta-analyses for randomized trials in the field of hypertension: a systematic review

- 55% of meta-analyses had all 4 domains deficient= at least one item in the domain
- 0% MA had all 4 domains deficient= half of features deficient



This was not associated with the IF of the journal

- A total of 44% MA had 8+ deficient features (median)



Quality of meta-analyses for randomized trials in the field of hypertension: a systematic review

Conclusions

- Quality did not improve over time.
- Thirty articles (21%) reported statistically significant results (P<0.05) from inappropriate DerSimonian–Laird models, whereas unreported, appropriate, Knapp–Hartung models gave statistical nonsignificance; 88% of these 30 articles reported the incorrect results in their abstracts.
- A total of 60% of all MA failed to conduct analyses in subgroups of quality when indicated, 63% failed to report Tau and Tau2, 57% omitted testing for publication bias, none conducted a cumulative analysis for publication bias, and 71–77% omitted mentioning in their abstracts problems of trial quality, heterogeneity, and publication bias.
- Deficiencies in hypertension-related meta-analyses are readily corrected and do not represent flaws inherent in the meta-analytic method

The quality of the MA depends on the quality of the studies included

GIGO phénomenon

GIGO = Garbage In → Garbage Out

'essais biaisés' → 'synthèse MA biaisée' → conclusions érronnées pour la pratique

→ MA pas une « méthode magique » permettant de gommer les biais des études

→ MA permet seulement d'en « atténuer » la portée par « dilution » par ajout d'essais de bonne qualité à des essais de mauvaise qualité

Cucherat M. « Manuel pratique de méta-analyse des essais thérapeutiques » http://www.txrating.org/spc/bookma_web/frame.htm

Meta-analysis of secure randomised controlled trials of β-blockade to prevent perioperative death in non-cardiac surgery

Bouri S et al. Heart 2014; 100:456-464

Bonne qualité

	Events	Total	Events	Total	Weight	IV, Fixed, 95% CI
Bayliff	2	49	1	50	0.8%	2.04 [0.19, 21.79]
BBSA	1	110	0	109	0.5%	2.97 [0.12, 72.19]
DIPOM	20	462	15	459	11.0%	1.32 [0.69, 2.55]
Mangano	4	99	5	101	2.9%	0.82 [0.23, 2.95]
MaVS	0	246	4	250	0.6%	0.11 [0.01, 2.09]
Neary	3	18	5	20	2.9%	0.67 [0.19, 2.40]
POBBLE	3	55	1	48	1.0%	2.62 [0.28, 24.34]
POISE	129	4174	97	4177	70.1%	1.33 [1.03, 1.73]
Yang	0	51	1	51	0.5%	0.33 [0.01, 8.00]
Subtotal (95% CI)		**5264**		**5265**	**90.1%**	**1.27 [1.01, 1.60]**
Total events	162		129			

Heterogeneity: Chi² = 5.72, df = 8 (P = 0.68); I² = 0%

Test for overall effect: Z = 2.06 (P = 0.04)

ET1 commun

Qualité douteuse

Dunkelgrun	10	533	16	533	7.8%	0.63 [0.29, 1.36]
Poldermans	2	59	9	53	2.1%	0.20 [0.05, 0.88]
Subtotal (95% CI)		**592**		**586**	**9.9%**	**0.49 [0.24, 0.97]**
Total events	12		25			

Heterogeneity: Chi² = 1.77, df = 1 (P = 0.18); I² = 44%

Test for overall effect: Z = 2.03 (P = 0.04)

ET2 commun

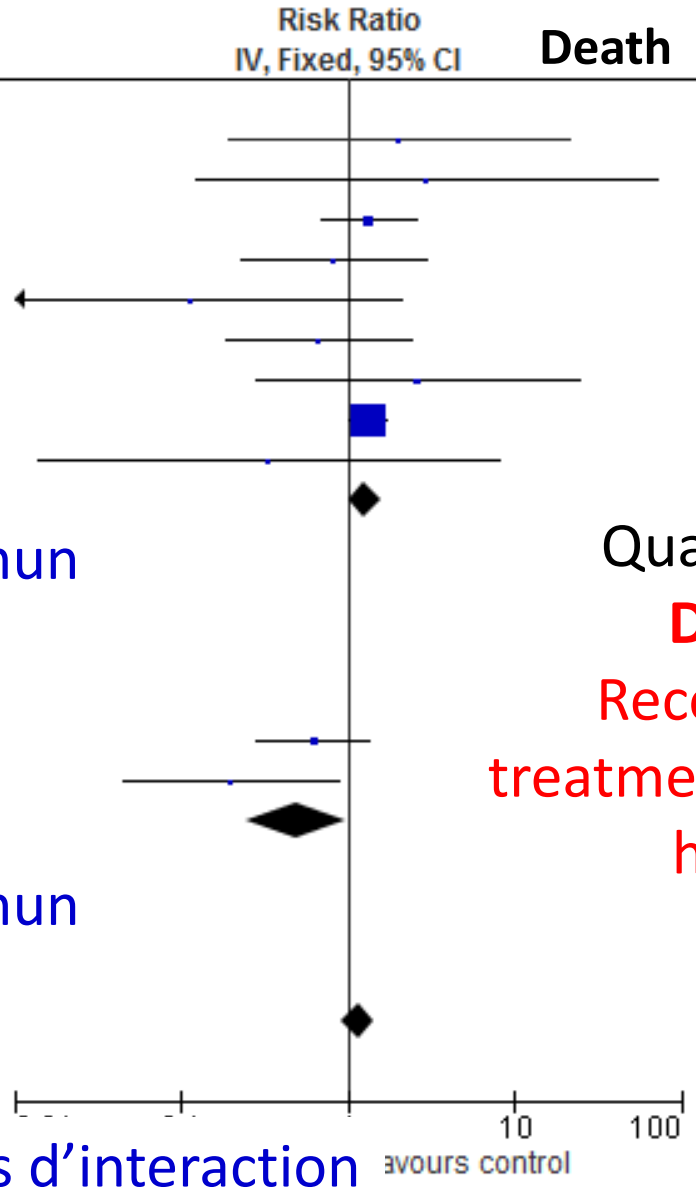
Total (95% CI)		**5856**		**5851**	**100.0%**	**1.16 [0.93, 1.44]**
Total events	174		154			

Heterogeneity: Chi² = 14.13, df = 10 (P = 0.17); I² = 29%

Test for overall effect: Z = 1.31 (P = 0.19)

Test for subgroup differences: Chi² = 6.64, df = 1 (P = 0.010), I² = 84.9%

Tests d'interaction

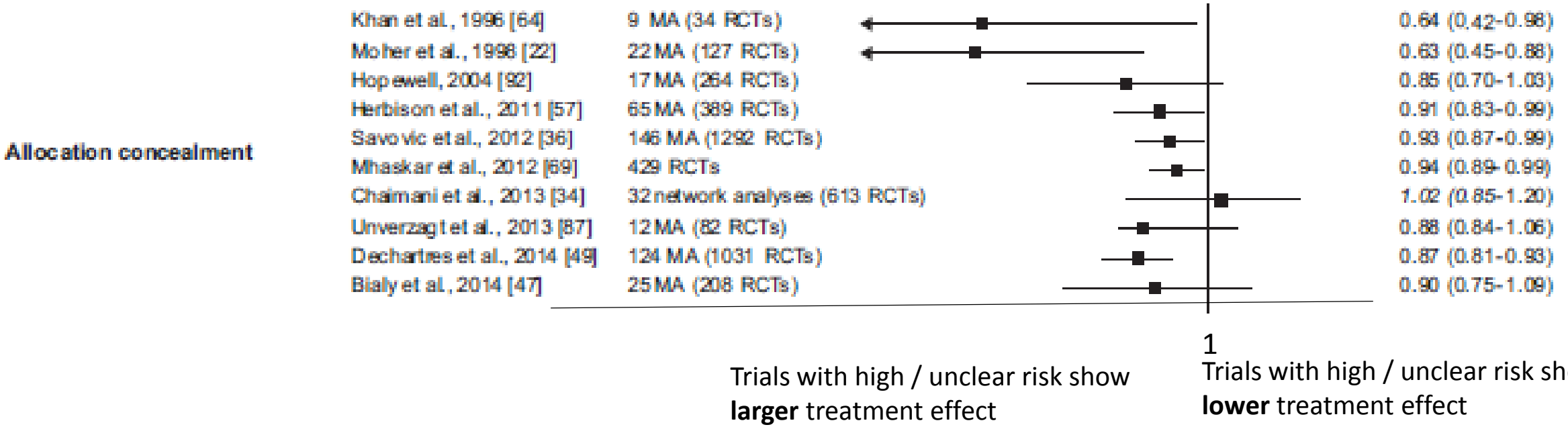


Qualitatif Bias

DANGER

Recommend a treatment that may be harmfull

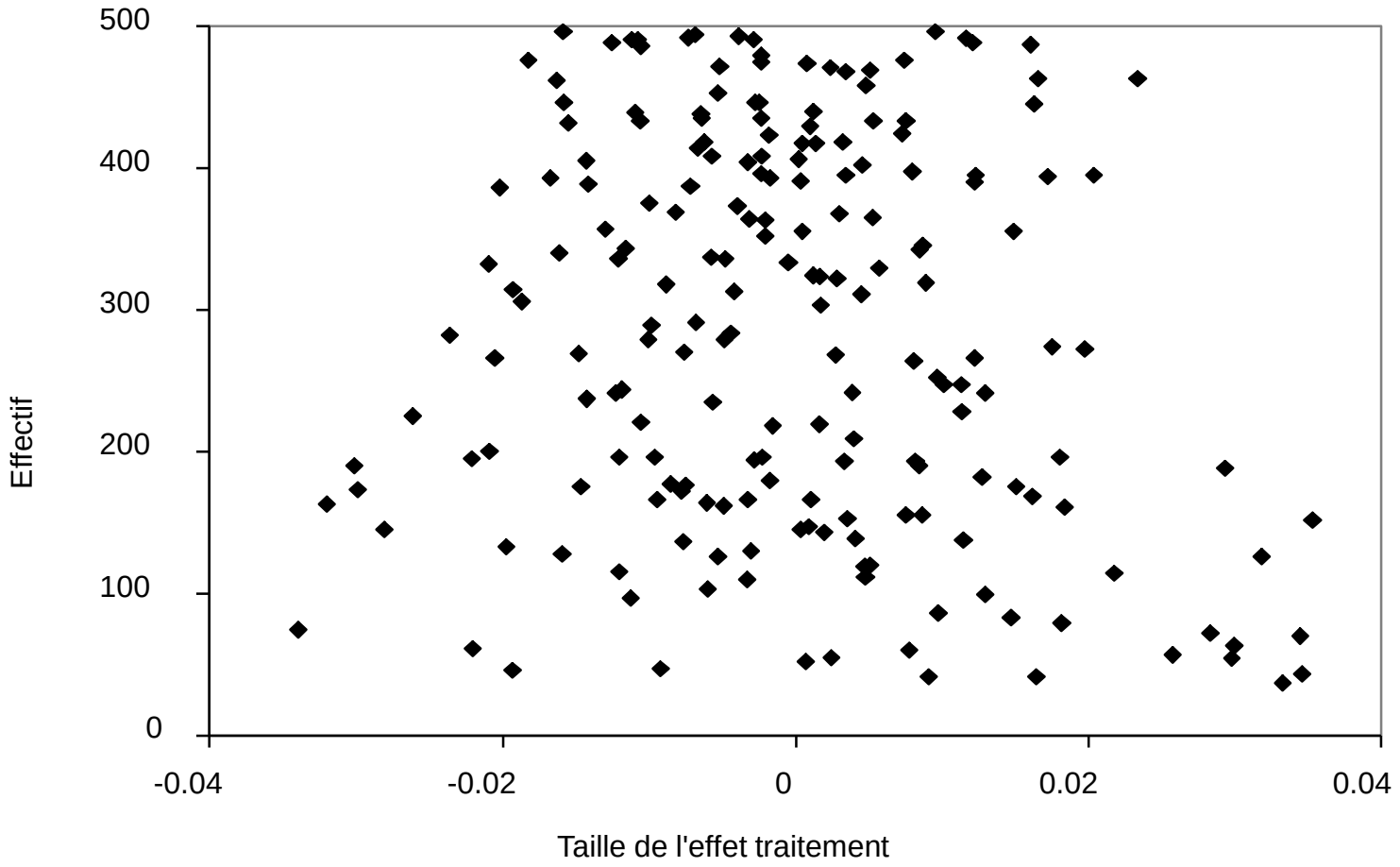
Influence of biais: allocation concealment randomisation



Dechartres A. JCE 2016

Funnel plot - sans biais de publication

- Graphique entre
  - les effets traitements
    - DR, effect size
    - Log(OR), log(RR)
  - et la taille (n)/précision (ET) des études
- Biais de publication si asymétrique



Cucherat M. « Manuel pratique de méta-analyse des essais thérapeutiques » http://www.txrating.org/spc/bookma_web/frame.htm

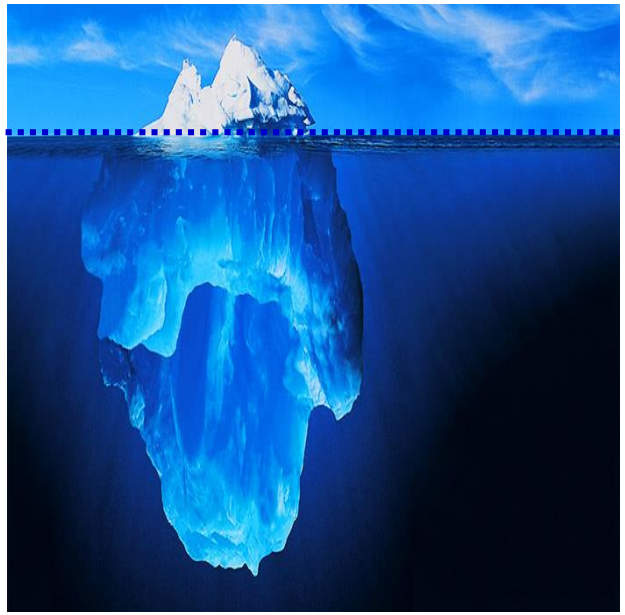
Biais de publication

ECR publiés ‘positifs’

MA ‘positive’ faussement → recommander un trt qui n’est pas réellement efficace

ECR non publiés ‘négatifs’

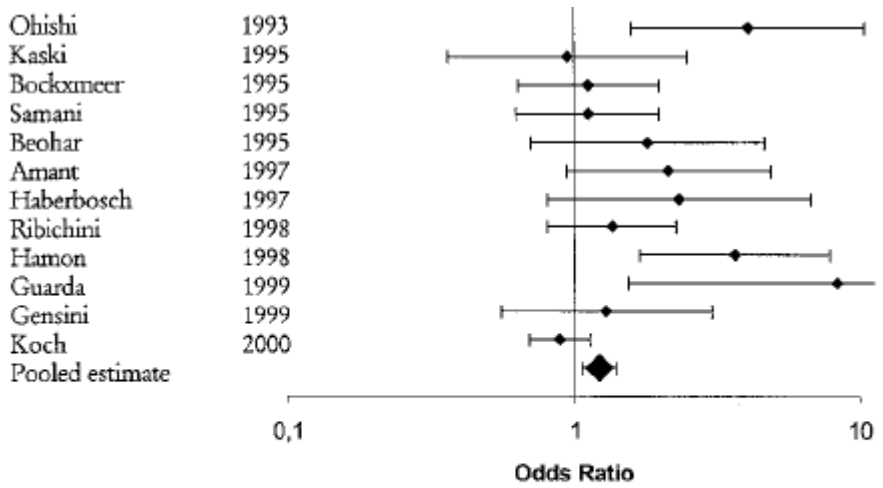
MA ne retrouvant pas d’effet



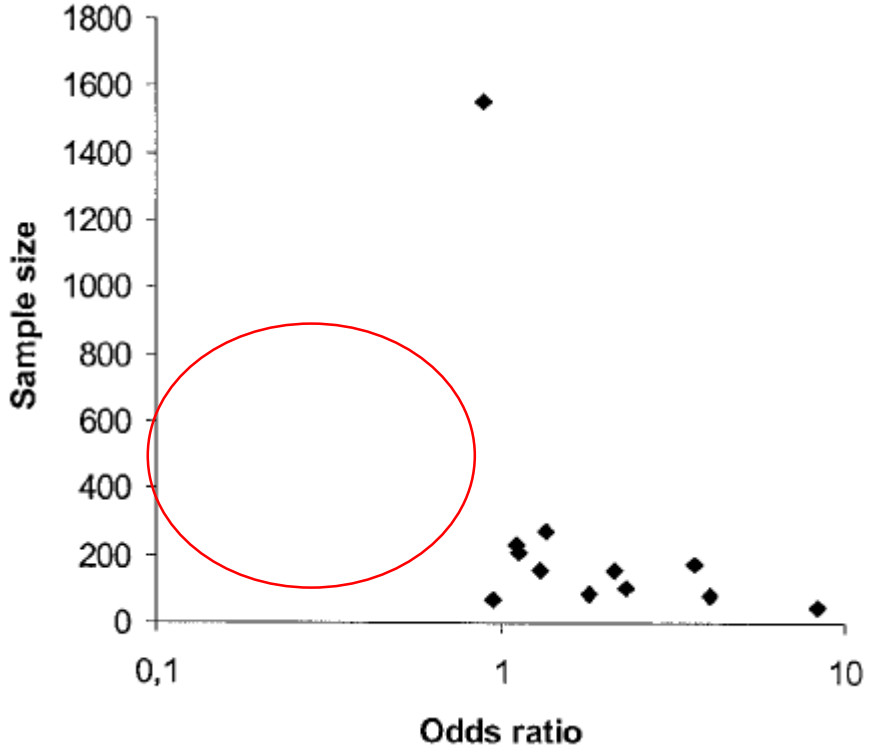
Cucherat M. « Manuel pratique de méta-analyse des essais thérapeutiques » http://www.txrating.org/spc/bookma_web/frame.htm

A meta-analysis of the angiotensin-converting enzyme gene polymorphism and restenosis after percutaneous transluminal coronary revascularization: Evidence for publication bias.

Willem R. P. Agema, et al, The Netherlands . Am Heart J 2002; 144:760-8.



Effect size per study. The individual studies are presented with odds ratios for restenosis and confidence intervals for the DD genotype versus II and *I/D* genotypes.



Funnel plot of all studies combined. The funnel plot provides a visual aid to detect publication bias. When no publication bias is present, the data should form a normal distribution. Because the distribution is skewed to the left, evidence for publication bias is present.

Cochrane Training

GRADE approach to evaluating the quality of evidence: a pathway

Topics

- Planning a review
- Analysing evidence
  - Analysing results
  - GRADE and interpreting results
  - Summary of Findings tables
- Writing a review
- Software and tools
  - GRADEPro

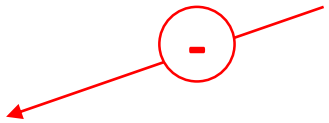
Assessing the quality of the body of evidence is a mandatory item in the Methodological standards for the conduct of new Cochrane Intervention Reviews (MECIR). GRADE is the Cochrane's recommended approach for grading the quality of evidence and the strength of recommendations. It was proposed and developed by the Grading of Recommendations, Assessment, Development and Evaluation (GRADE) Working Group.

This set of online learning resources will help you understand the GRADE approach and use it in the preparation of your Cochrane Review. The set consists of video slidecasts, a guidance document on incorporating GRADE in Cochrane Reviews, and links to additional resources, including the GRADE Handbook. Each resource is designed to be a standalone learning unit although they are presented here as a progressive learning pathway. You may choose to access the resources in any order you wish, although those new to GRADE approach may find it most productive to work through the resources in the order presented.

An introductory series of slidecasts developed by the McMaster University is a good place to start with. The series has been designed to help authors learn how to use the GRADE approach to grade the evidence in systematic reviews and create a 'Summary of findings' (SoF) table.

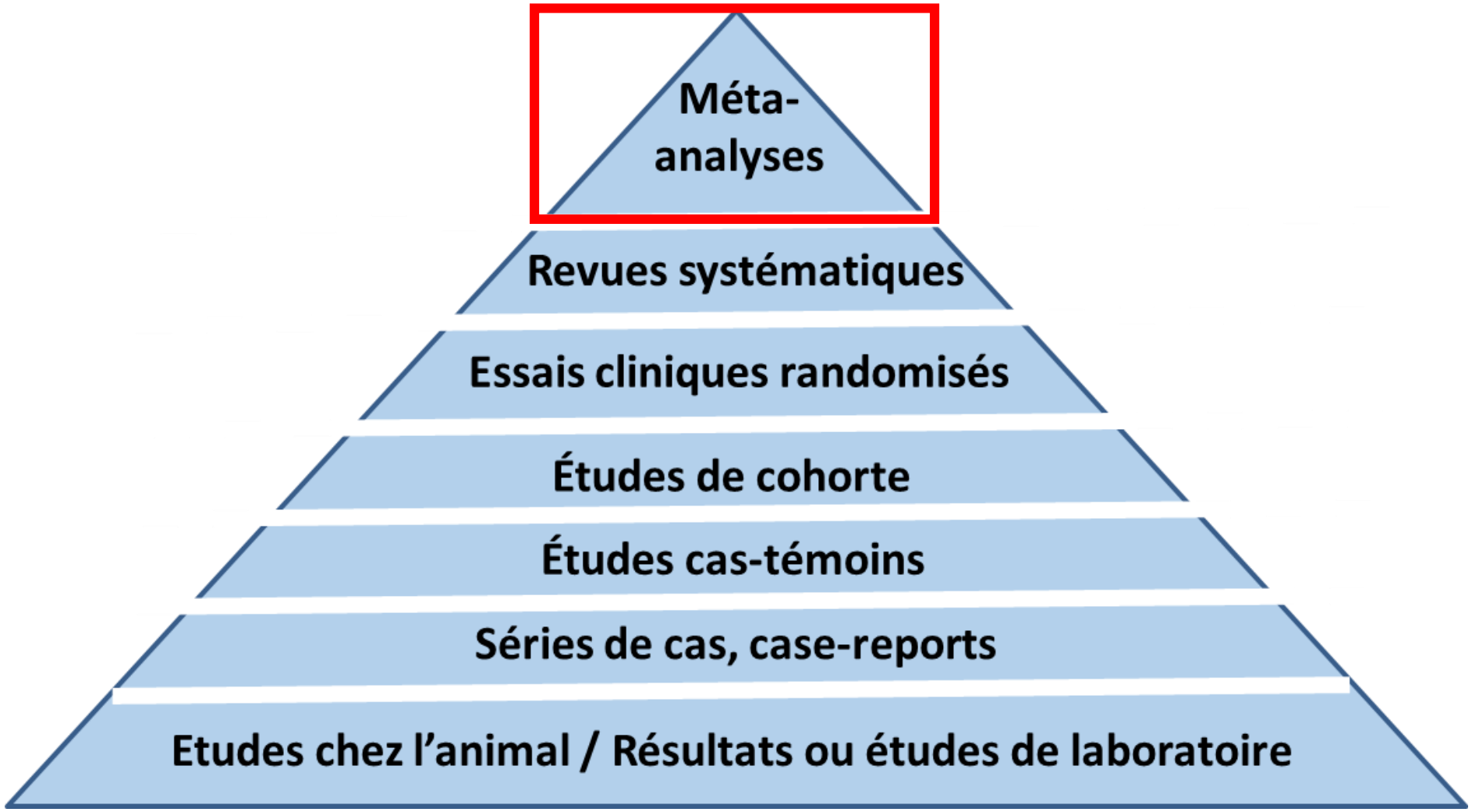
Qualité de l'évidence scientifique

System	Description
The Grading of Recommendations Assessment, Development and Evaluation GRADE	**4 Levels of quality of evidence (confidence in estimates):** • High • Moderate • Low • Very low RCTs start as high and observational studies start as low, then multiple factors that can raise or lower confidence are applied to reach a final rating. **Strength of recommendation:** 1 (strong) or 2 (weak)
American College of Cardiology Foundation/American Heart Association ACC/AHA ESC	**Certainty in evidence:** • level A evidence is derived from multiple RCTs or meta-analyses • level B is derived from a single RCT or nonrandomized studies • level C is derived from consensus opinion of experts, case studies, or standards of care **Classification of Recommendations**: Class I, Class II, , Class IIa, Class IIb, Class III



Bias within studies, inconsistency, **imprecision**, indirectness, publication bias

Pyramide du niveau de preuve



The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses

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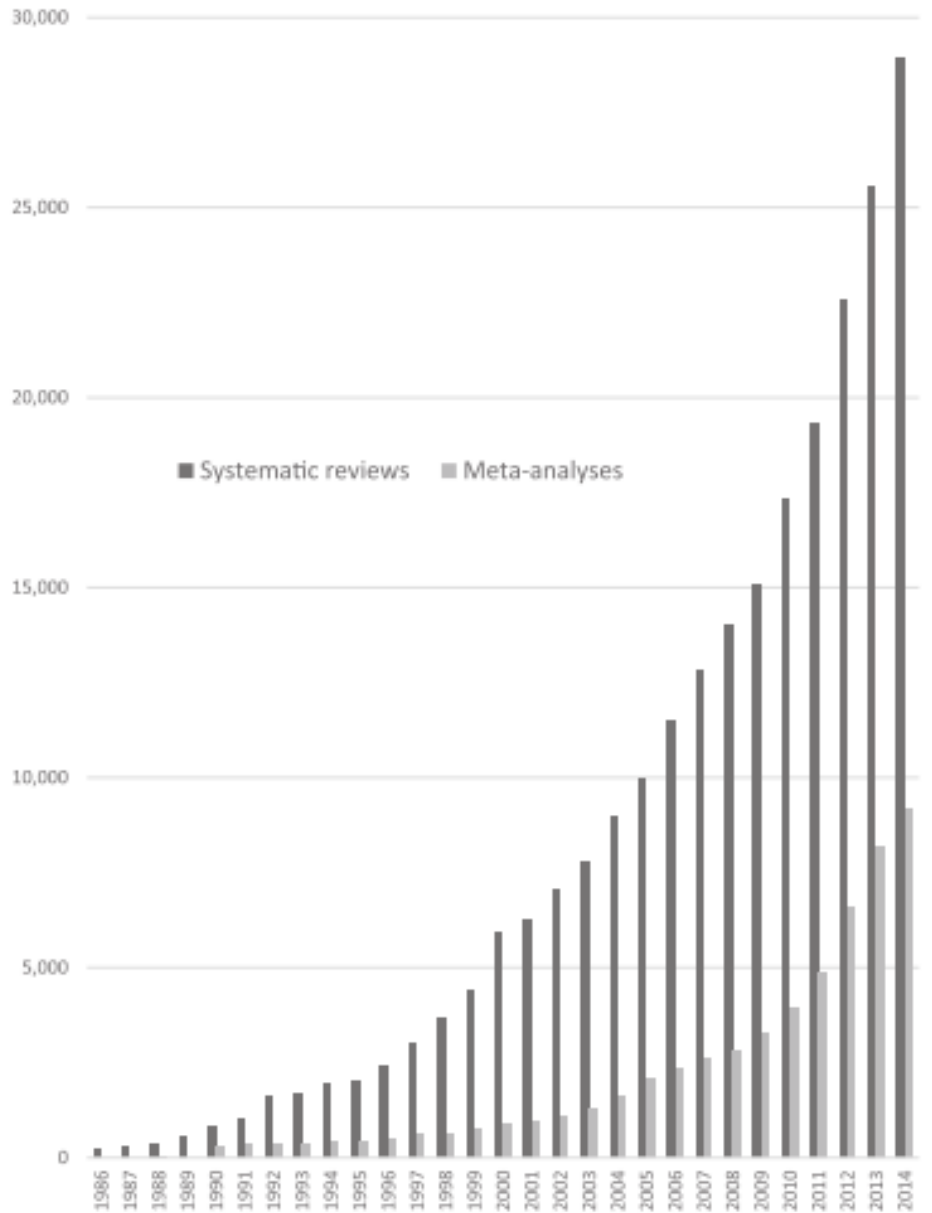
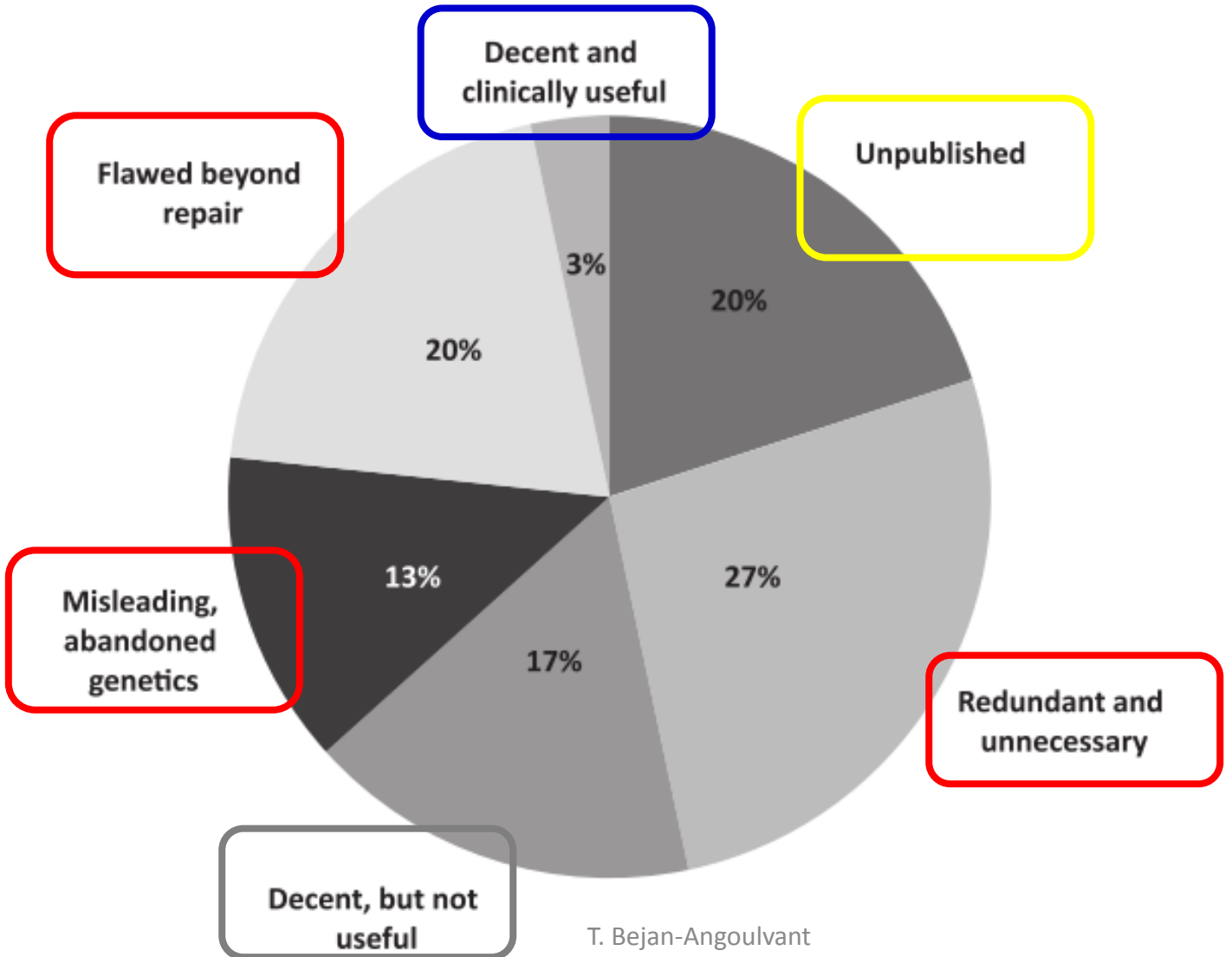
The Milbank Quarterly, Vol. 94, No. 3, 2016 (pp. 485-514)

Figure 1. Number of PubMed-Indexed Articles Published Each Year Between 1986 and 2014 That Carry the Tag "Systematic Review" or "Meta-analysis" for Type of Publication



The Mass Production of Redundant, Misleading, and Conflicted Systematic Reviews and Meta-analyses

Figure 4. A Summary Overview of Currently Produced Meta-analyses



Circulation

FRAME OF REFERENCE

Are Meta-Analyses a Form of Medical Fake News?

Thoughts About How They Should Contribute to Medical Science and Practice

Milton Packer

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Circulation. 2017;136:2097-2099
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