Web appendix

1. Protocol 120511

We will conduct a systematic review in accordance with the recommendations from the Cochrane collaborations and the PRISMA statement. We will include only randomized controlled trials with a minimum of 100 adult diabetic patients, and a mean follow-up of at least 12 months. There will be no restrictions regarding co-morbidity or overall cardiovascular risk. Both hypertensive and normotensive patients will be accepted.

Three classes of interventions will be considered. 1) Trials comparing any blood pressure level with placebo. 2) Trials comparing any two, or more, blood pressure levels. 3) Trials evaluating specific drug doses, independent of pressure goals. Trials with combined interventions will be excluded.

Primary end points will be all cause mortality, myocardial infarction, stroke, congestive heart failure, end-stage renal disease, amputation and blindness. As secondary end points, cardiovascular and non-cardiovascular mortality will be used.

CENTRAL will be searched using MeSH terms “antihypertensive agent” and “blood pressure” combined. MEDLINE will be searched in accordance with the Cochrane Highly Sensitive Search Strategy, sensitivity-maximizing version, EMBASE according to Wong et al, -06, and their “small drop in sensitivity with a substantive gain in specificity” search strategy. Also BIOSIS will be searched for relevant conference proceedings, using the same strategy as for CENTRAL. Results from the above searches will be merged to remove duplicate records of the same publications. M.B. will review titles of all publications retrieved from this search. All relevant abstracts will be examined by M.B. and B.C to identify potentially relevant trials. The reference lists of relevant systematic reviews and guidelines will be browsed to identify any trial not identified in our own search. Also authors of relevant publications will be contacted, to reveal any unpublished material. M.B and B.C will then, independently, examine the potentially relevant publications in detail to make the final decision on study inclusion. This decision will be based on the trials meeting the inclusion criteria. Any disagreements will be resolved by discussion. Both reviewers will extract data into specially designed data collection forms independently. These forms will include data on all outcomes defined above and information permitting risk of bias evaluation according to the below.

Risk of bias will be assessed using the Cochrane Collaboration´s tool for assessing risk of bias. This tool take into consideration six domains, 1) sequence generation, 2) allocation concealment, 3) blinding, 4) incomplete outcome data, 5) selective outcome reporting, and 6) other sources of bias, including early stop and baseline imbalance.

Analysis will be based upon risk ratio for each of the outcomes measured. We will analyse the outcomes in relation to blood pressure in a number of ways.:

1) Blood pressure reached – trials will be analysed in groups based on the mean systolic blood pressure achieved in the intervention group. The different groups will preliminarily be those <130, <135 and <140.
2) Baseline pressure – trials will be grouped according to baseline systolic pressure in the intervention group. The preliminary groups will be those <130, <140 and <150.
3) Meta regression, correlating relative risk, for a number of outcomes, and systolic blood pressure difference between groups, will be performed if suitable.

Sensitivity-analysis will be performed, excluding patients with manifest cardiovascular disease, such as earlier myocardial infarction or stroke and diagnosed congestive heart failure. Also the impact of trials with high risk of bias, and trials stopped early will be explored in this way. We will also try to analyse data stratified according to mortality rate in the placebo group to assess if a certain cardiovascular risk justifies other treatment regimen.

Heterogeneity will be considered using forest plot and standard statistic methods such as chi-squared test and quantifying inconsistency. If there is evidence of heterogeneity analyses will be performed using random effects models. Possible causes of heterogeneity will be explored. Reporting bias will be assessed using funnel plots and contour enhanced funnel plots.

2. Search strategies

a) MEDLINE

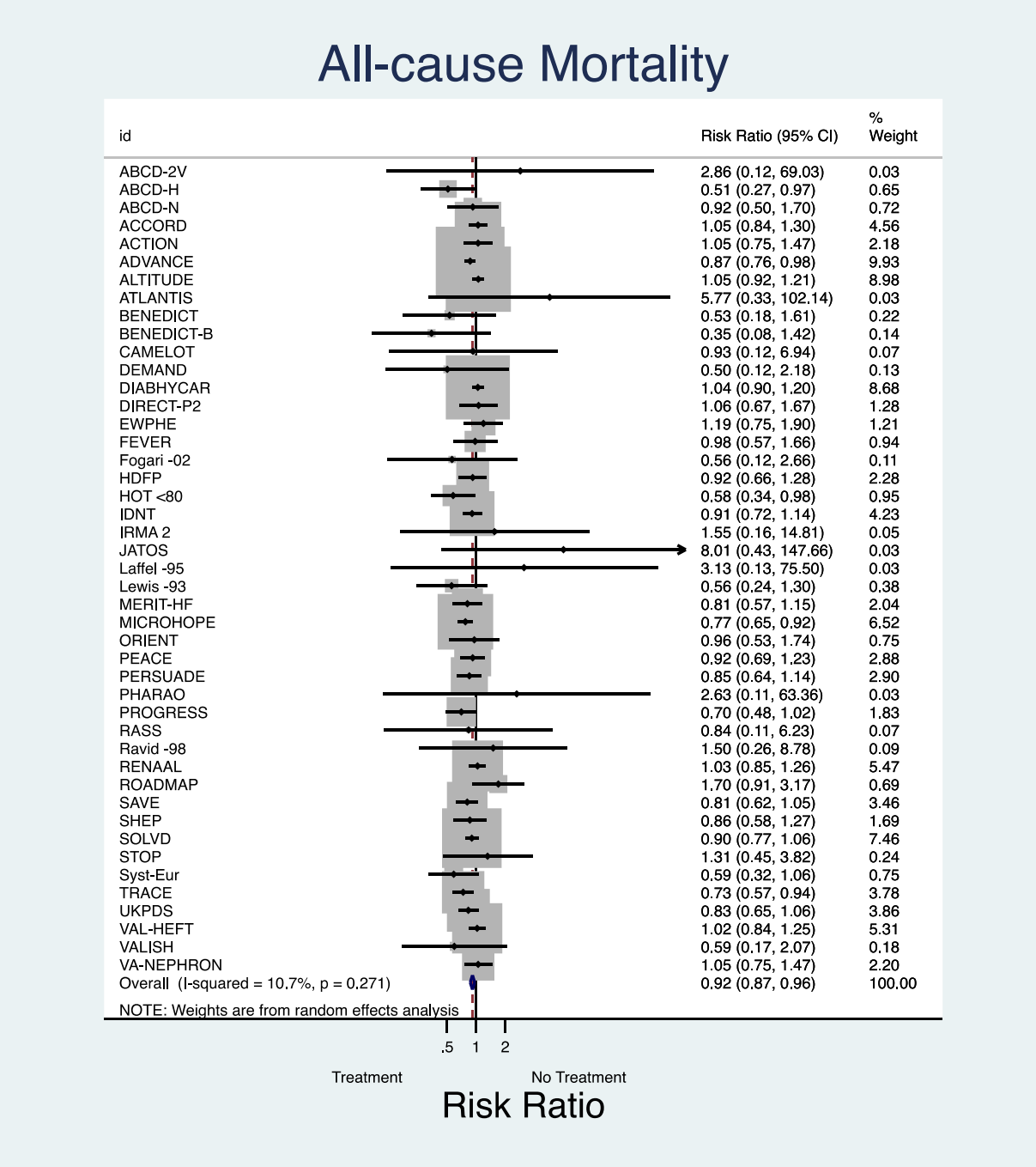
1	Randomized controlled trial [pt]
2	Controlled clinical trial [pt]
3	Randomized [tiab]
4	Placebo [tiab]
5	drug therapy [sh]
6	Randomly [tiab]
7	Trial [tiab]
8	Groups [tiab]
9	1 or 2 or 3 or 4 or 5 or 6 or 7 or 8
10	animals not (humans and animals)
11	9 not 10
12	Antihypertensive agents
13	Blood pressure
14	11 and 12 and 13

b) EMBASE

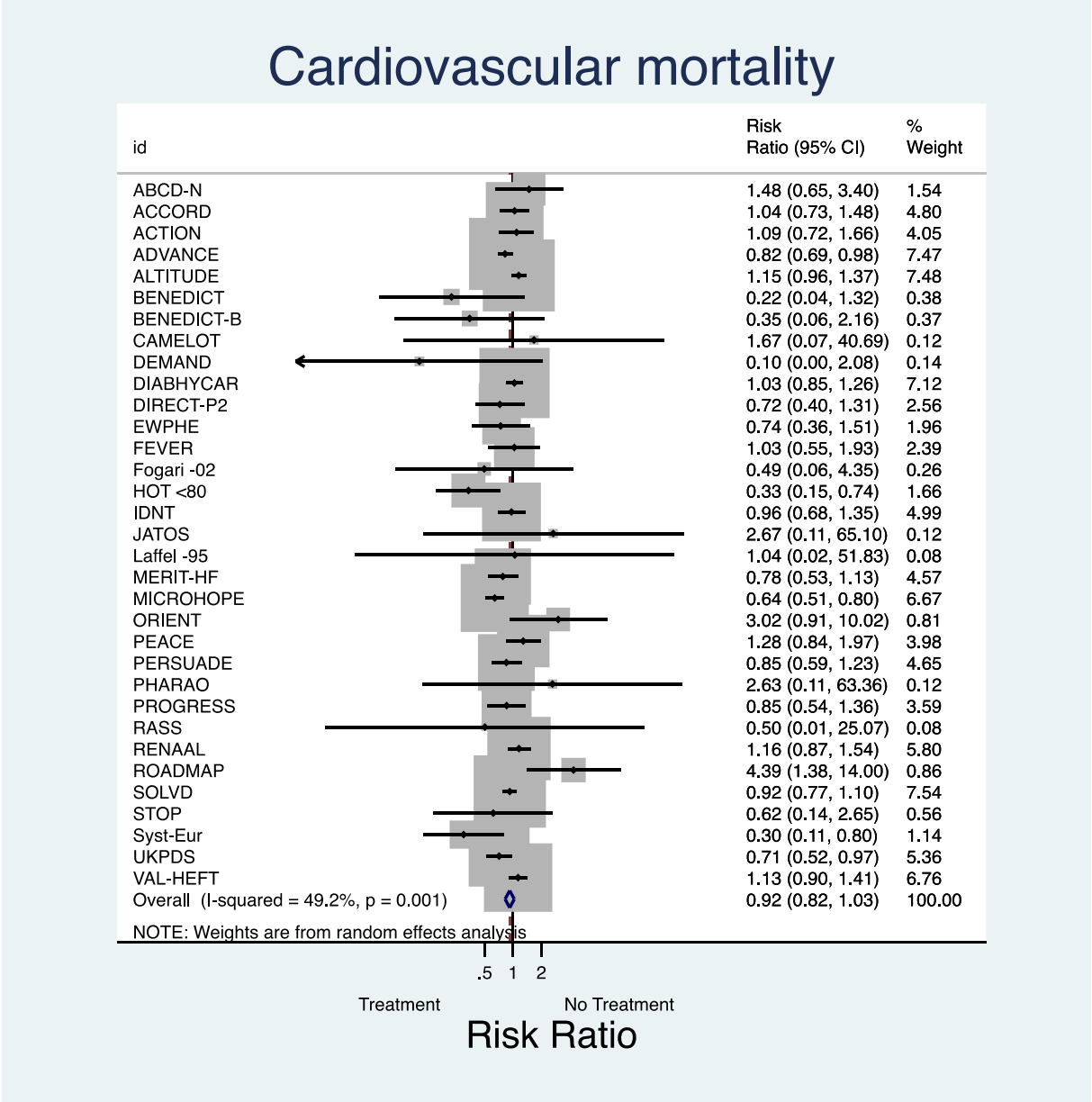
1	"antihypertensive agent".af.
2	"diabetes mellitus".af.
3	diabetes.ab.
4	diabetes.ti.
5	"antihypertensive agent".ti.
6	"antihypertensive agent".ab.
7	1 or 5 or 6
8	2 or 3 or 4
9	7 and 8
10	(random or "controlled clinical trial" or "multicenter study" or "phase 3 clinical trial" or "phase 4 clinical trial").af. or "clinical trial".ab. or "clinical trial".ti.
11	'treatment outcome'.af.
12	10 or 11
13	(randomized controlled trial or controlled clinical trial).af.
14	12 or 13
15	9 and 14

3. Results – Non-stratified meta-analyses

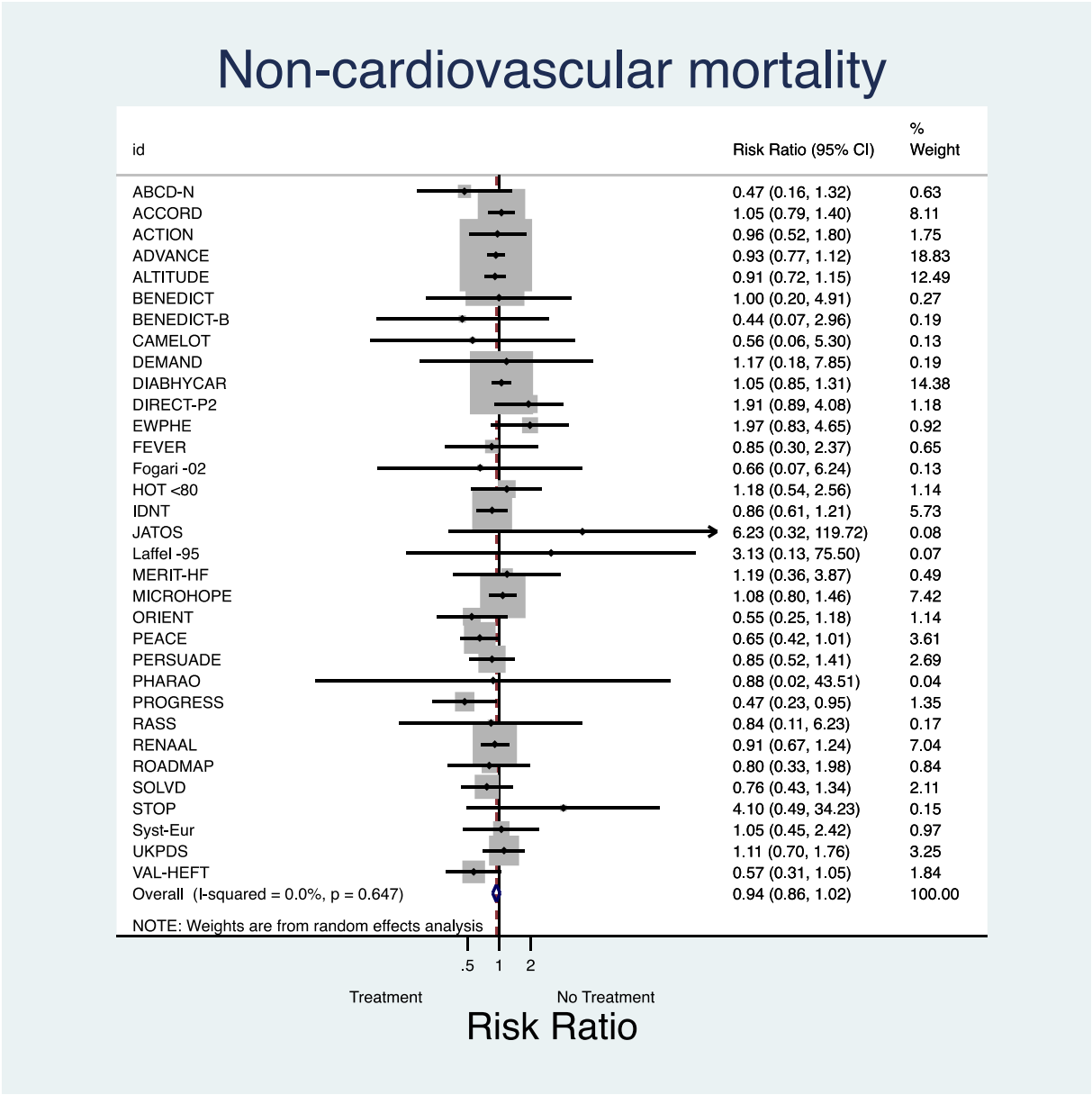
a) Forest plots



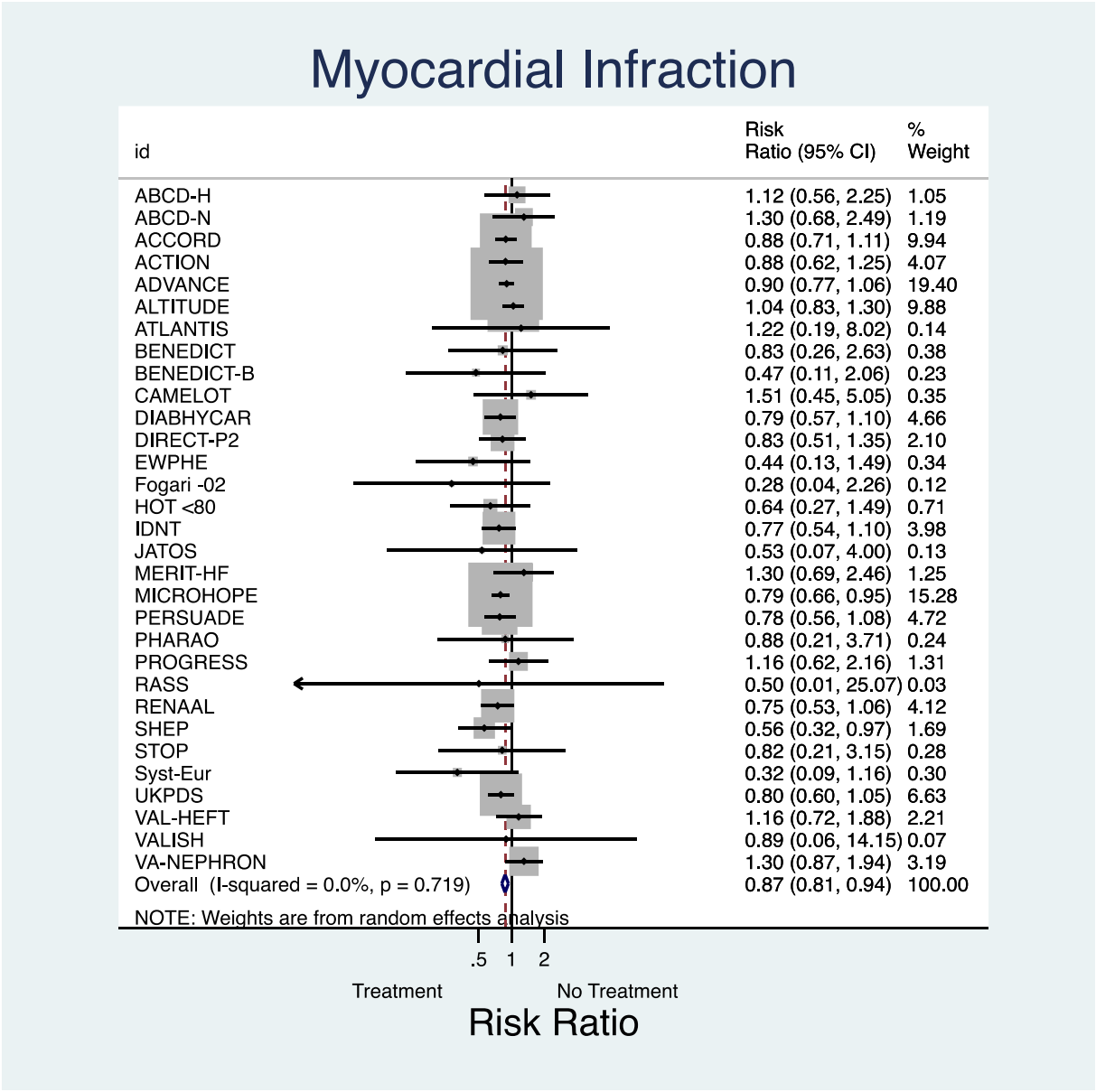
Forest plot showing relative risk of all-cause mortality in meta-analysis. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analysis (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity.



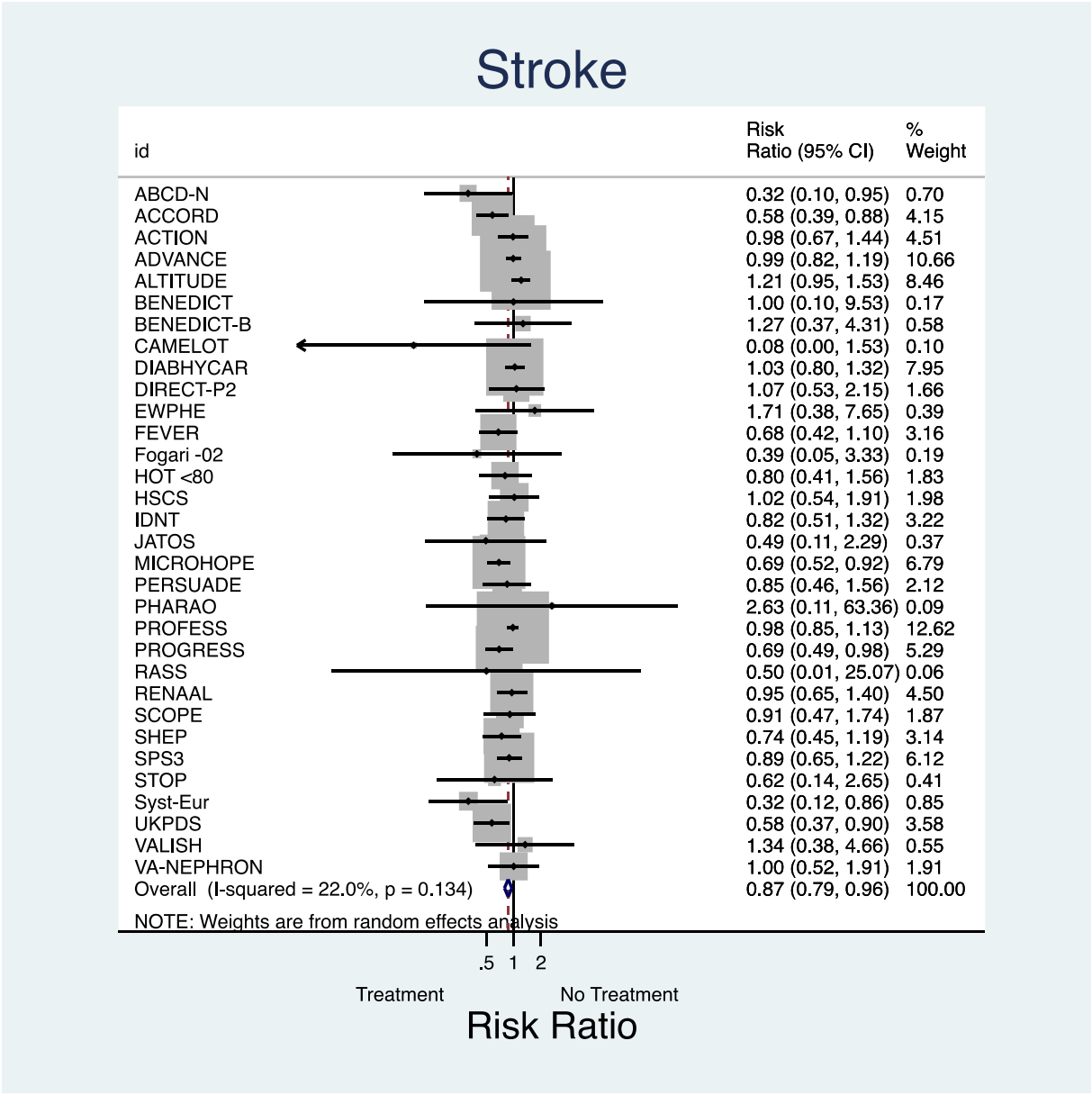
Forest plot showing relative risk of cardiovascular mortality in meta-analysis. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analysis (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity.



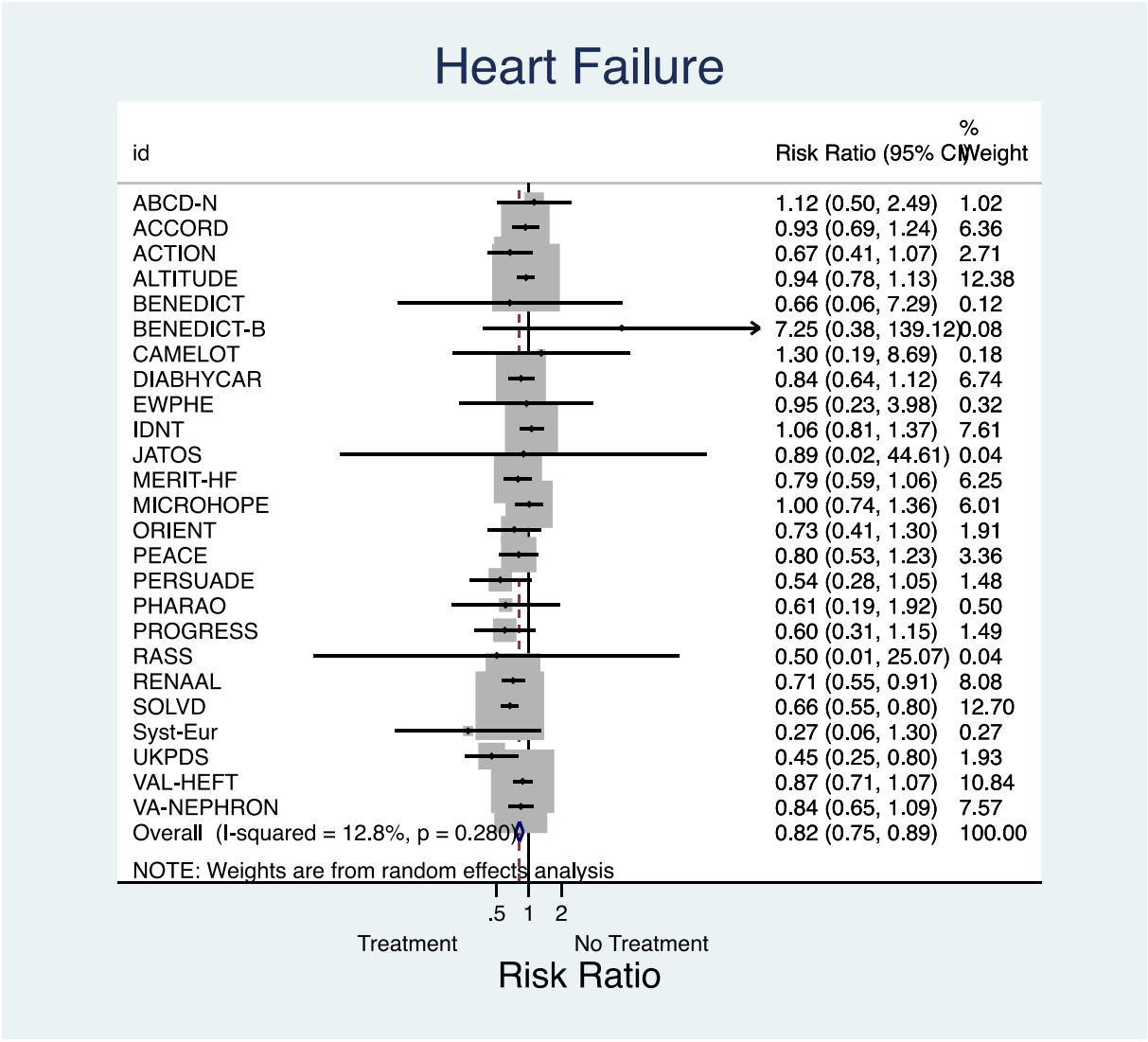
Forest plot showing relative risk of non-cardiovascular mortality in meta-analysis. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analysis (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity.



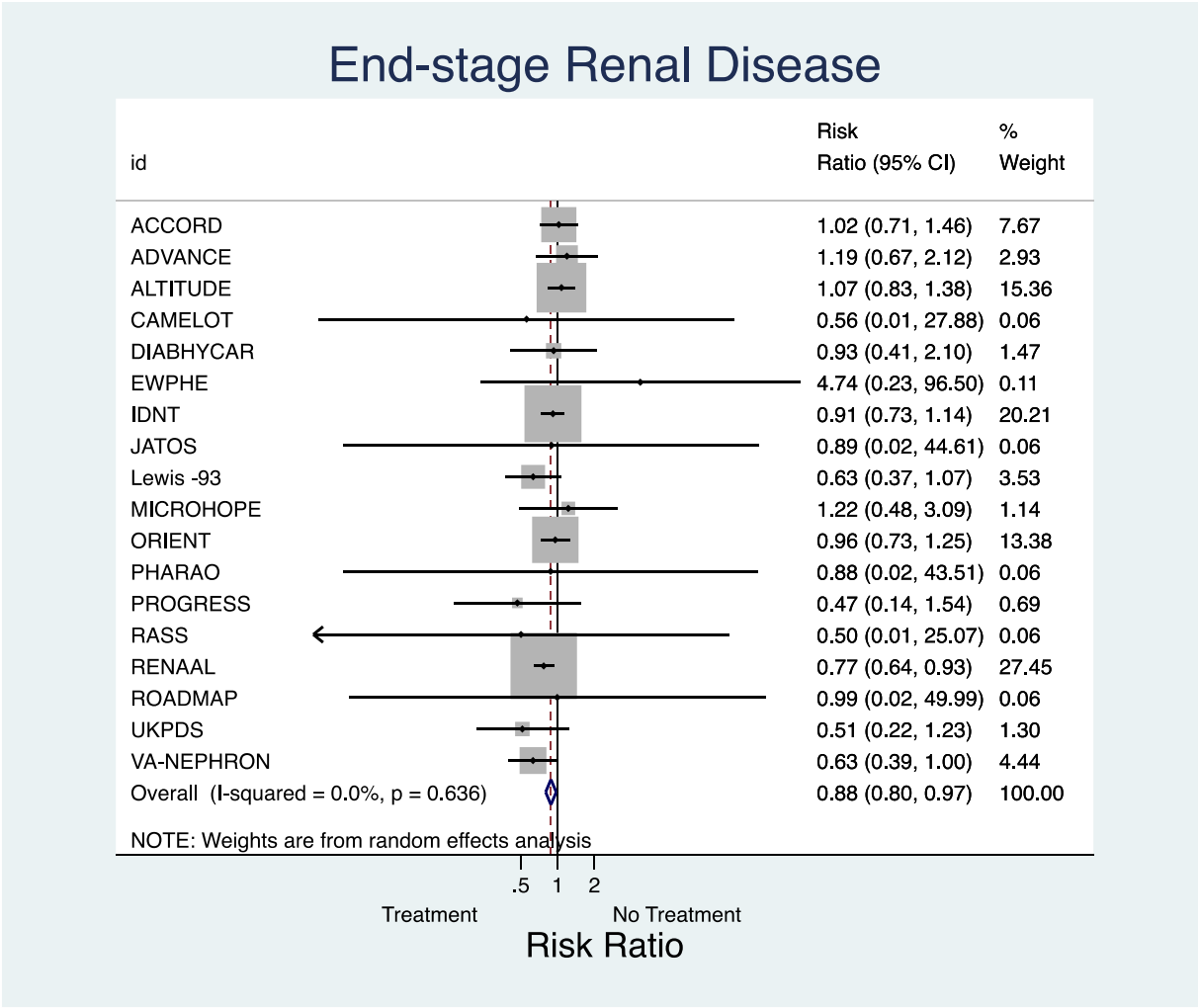
Forest plot showing relative risk of myocardial infarction in meta-analysis. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analysis (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity.



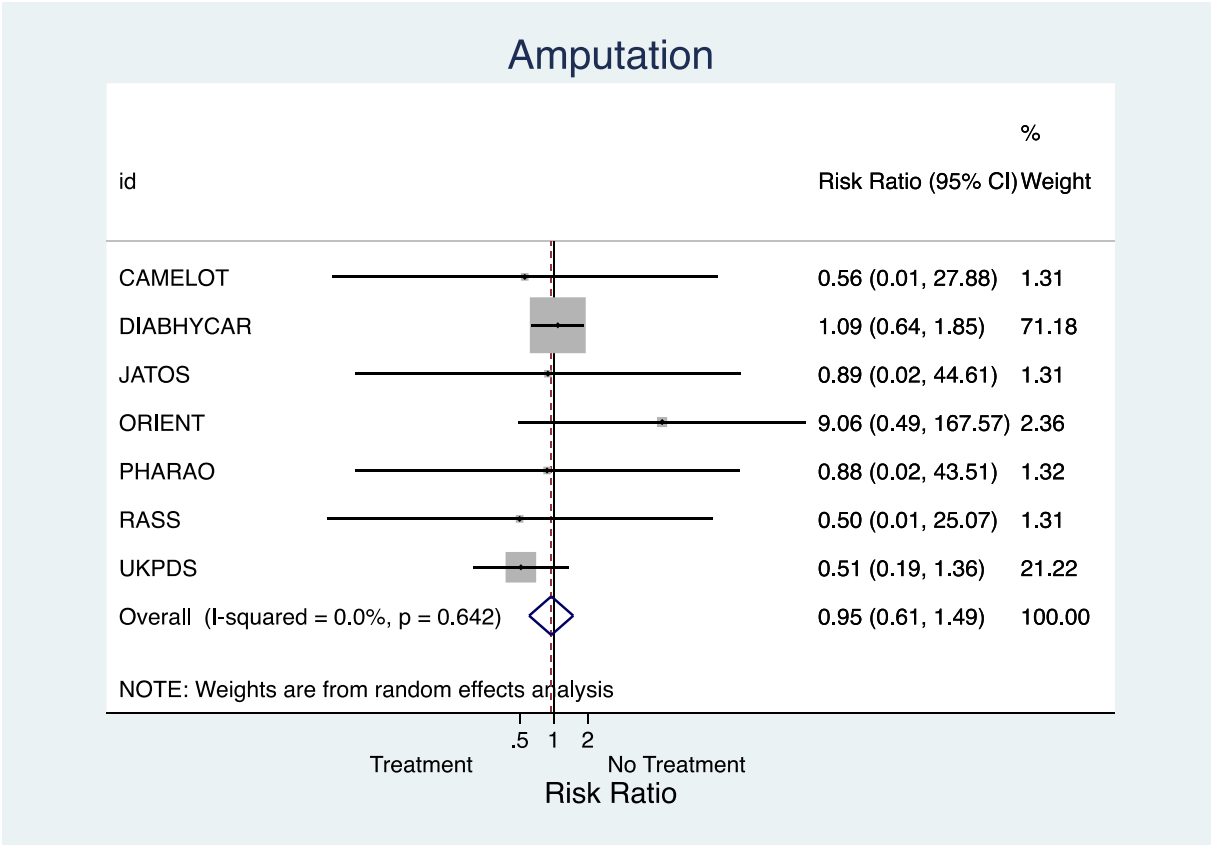
Forest plot showing relative risk of stroke in meta-analysis. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analysis (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity.

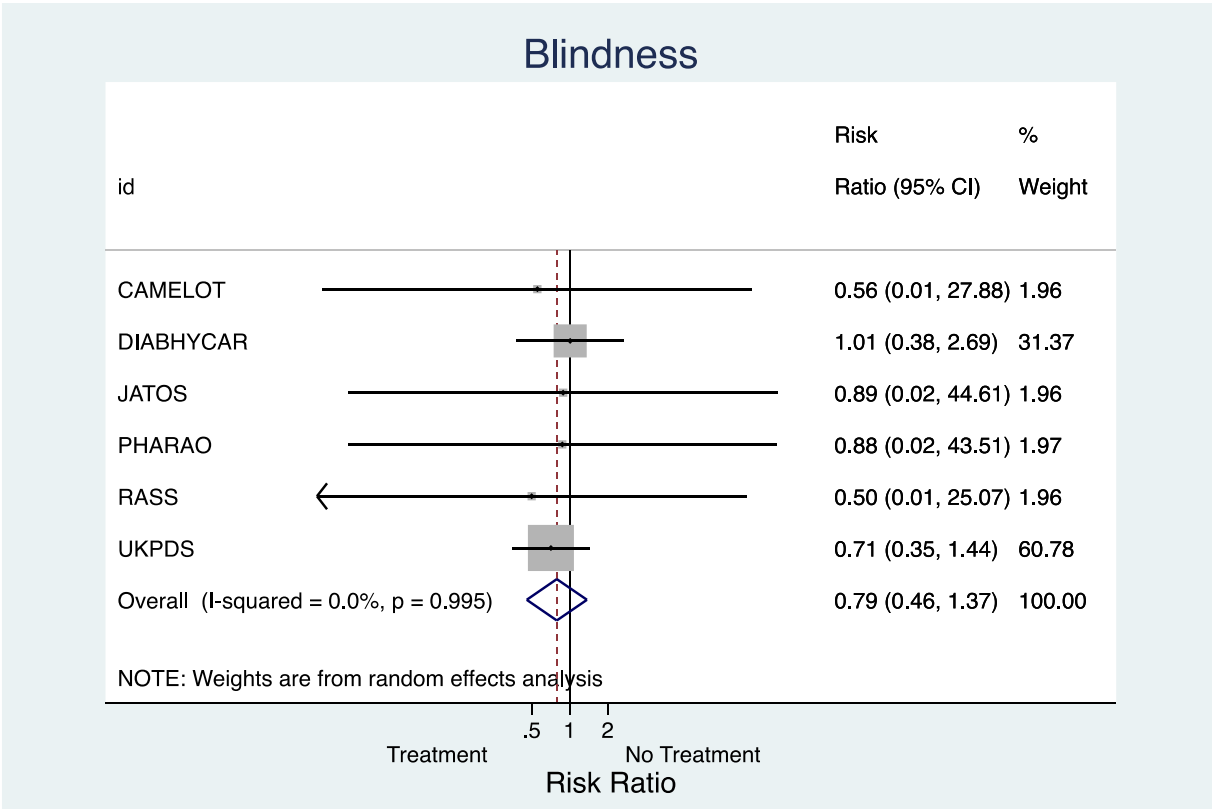


Forest plot showing relative risk of heart failure in meta-analysis. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analysis (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity.



Forest plot showing relative risk of end-stage renal disease in meta-analysis. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analysis (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity.





Forest plots showing relative risk of amputation and blindness in meta-analyses. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analysis (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity.

b) Summary table

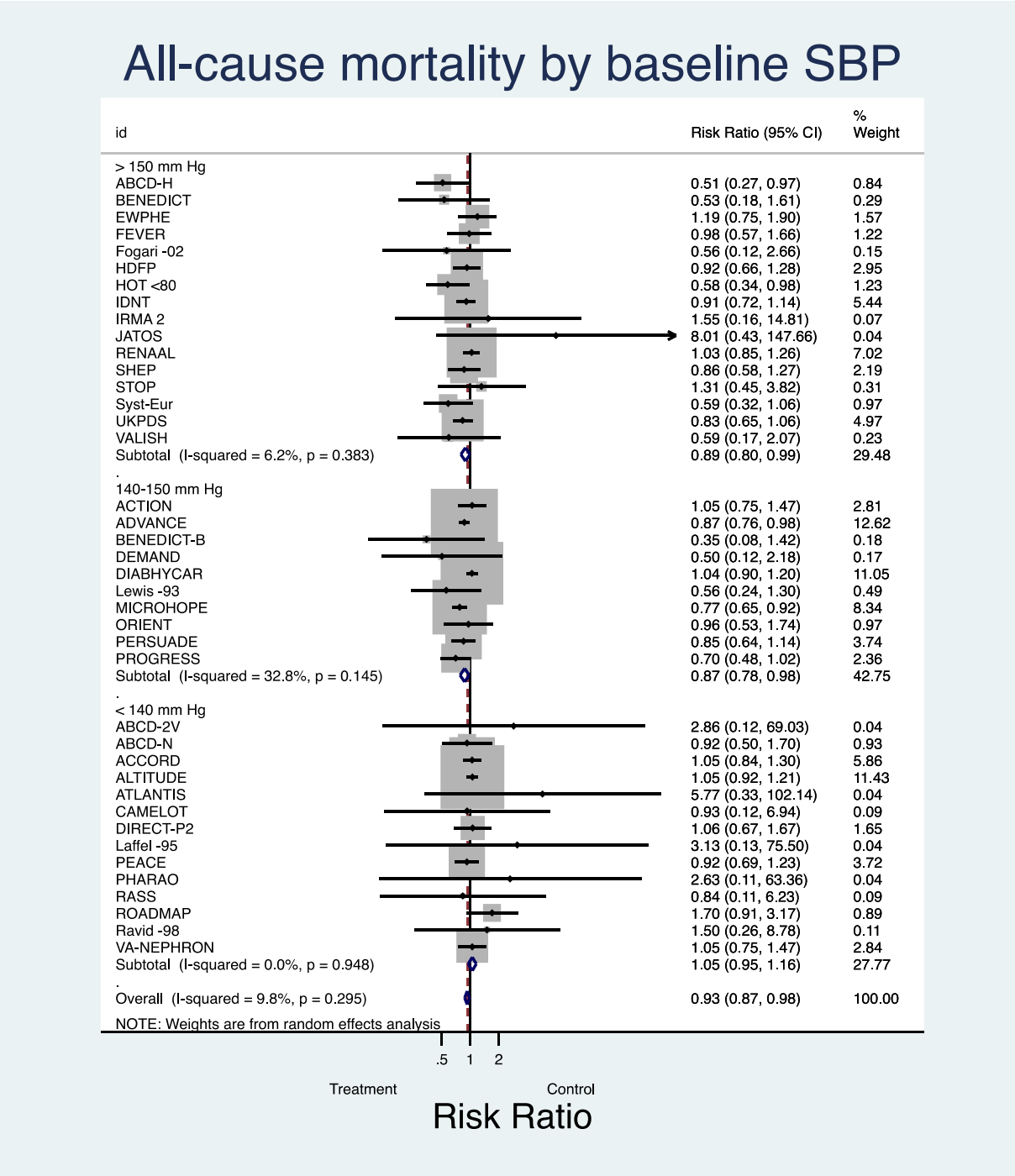
Outcome	**Included trials (n)**	**Patients with DM (n)**	**RR (95% CI)**
All-cause mortality	45	66 130	0.92 (0.87 to 0.96)
Cardiovascular mortality	33	59 956	0.92 (0.82 to1.03) [a]
Non-cardiovascular mortality	33	59 956	0.94 (0.86 to 1.02)
Myocardial infraction	31	53 512	0.87 (0.81 to 0.94)
Stroke	32	59 490	0.87 (0.79 to 0.96)
Heart failure	25	40 196	0.82 (0.75 to 0.89)
End-stage renal disease	18	47 439	0.88 (0.80 to 0.97)
Amputation	7	7 748	0.95 (0.61 to 1.49)
Blindness	6	7 171	0.79 (0.46 to 1.37)

[a] significant heterogeneity, I^2 = 49 %, p = 0.001

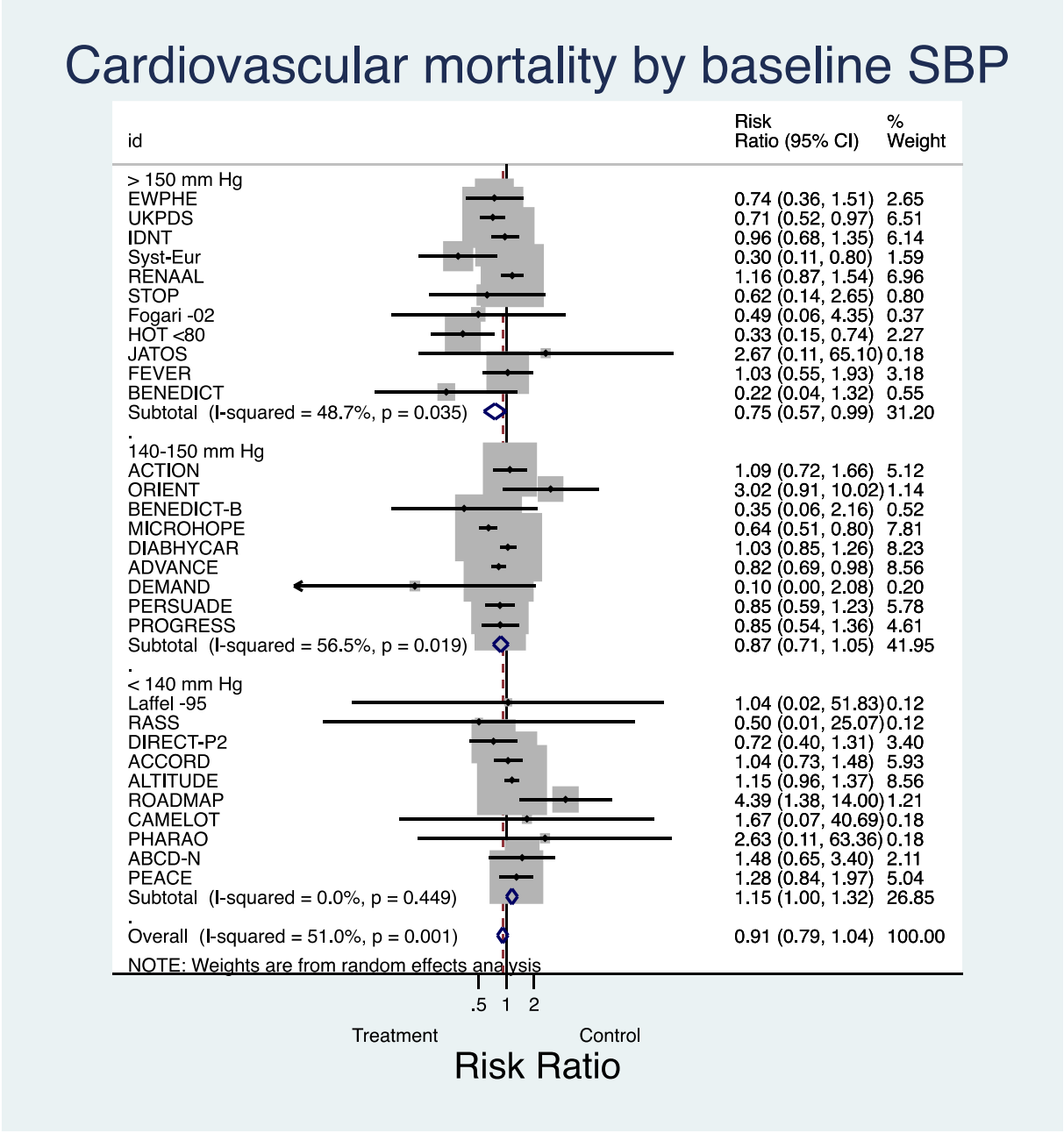
RR = relative risk, CI = confidence intervall

4. Results - Stratified meta-analyses

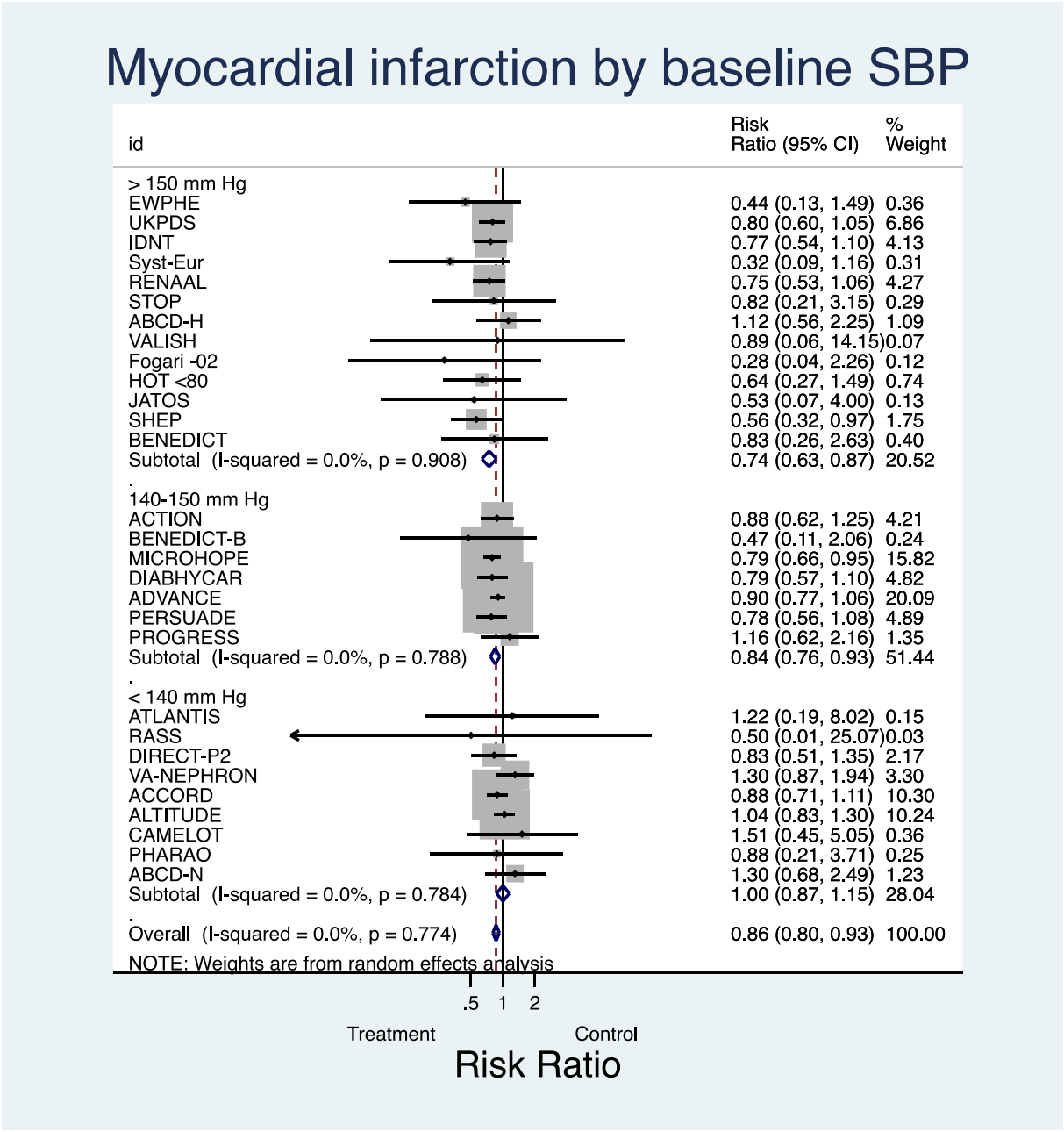
a) Baseline SBP – forest plots



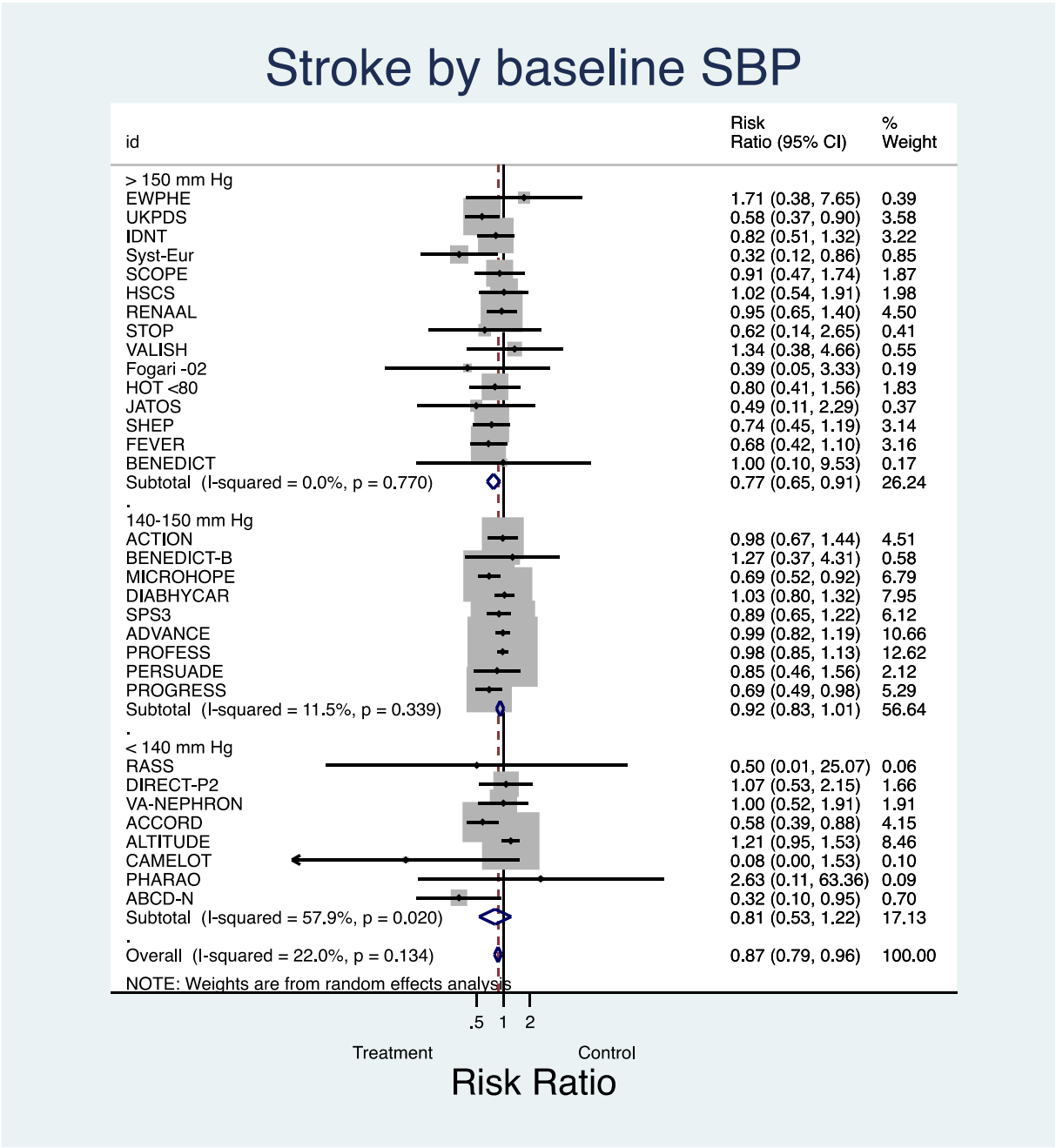
Forest plot showing relative risk of all-cause mortality in meta-analysis, stratified by baseline systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).



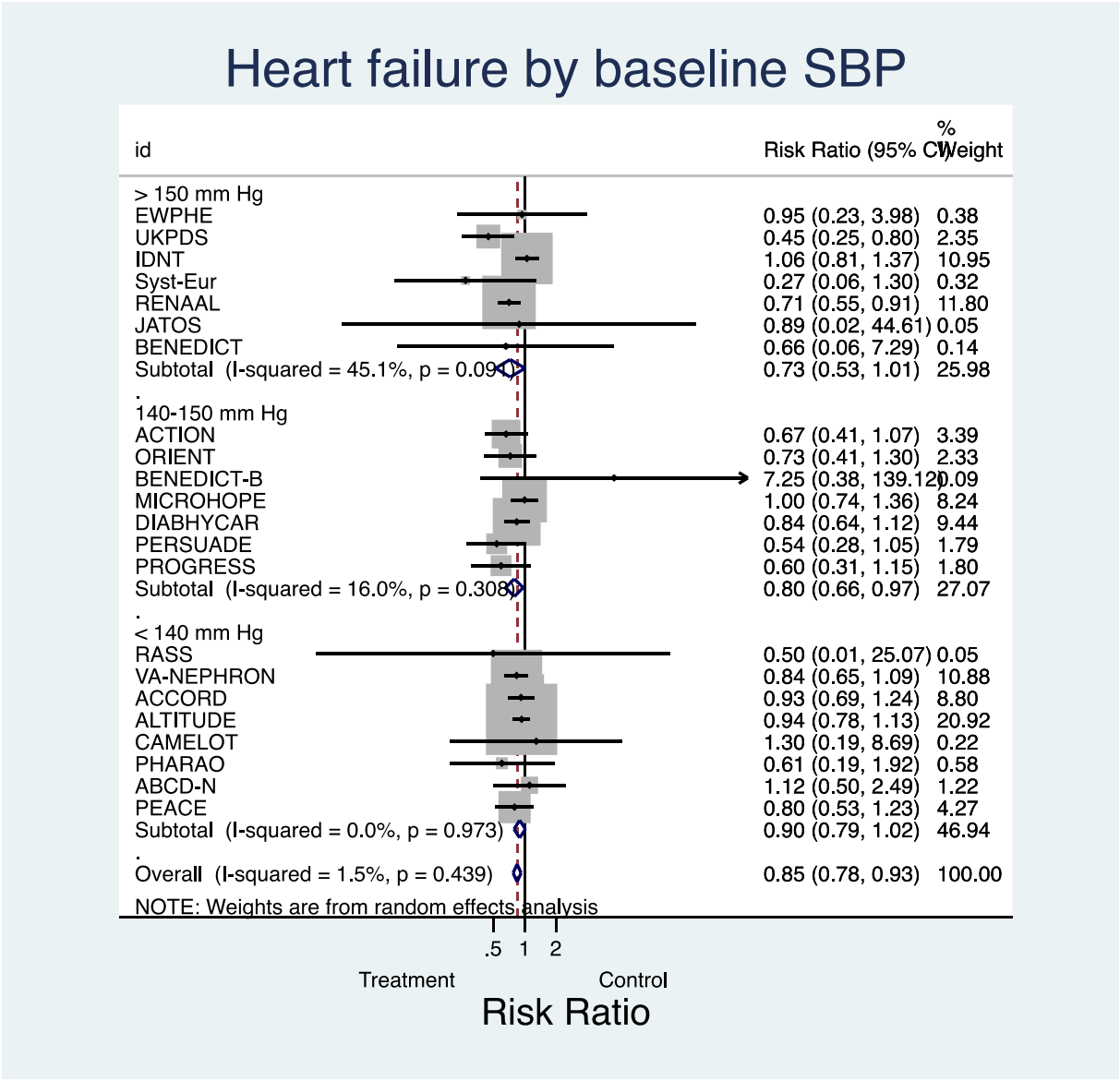
Forest plot showing relative risk of cardiovascular mortality in meta-analysis, stratified by baseline systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).



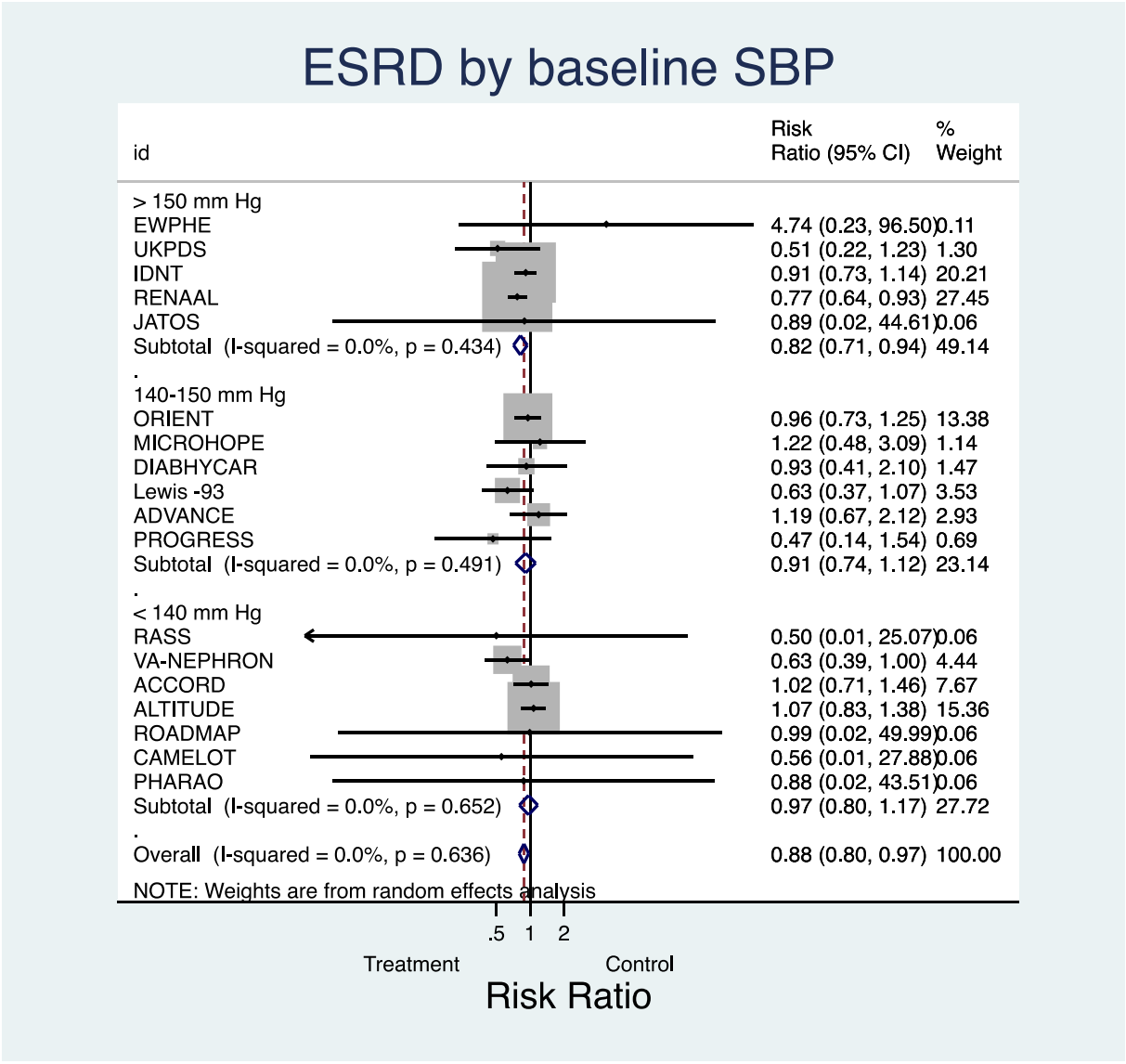
Forest plot showing relative risk of myocardial infarction in meta-analysis, stratified by baseline systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).



Forest plot showing relative risk of stroke in meta-analysis, stratified by baseline systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).



Forest plot showing relative risk of heart failure in meta-analysis, stratified by baseline systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).



Forest plot showing relative risk of end-stage renal disease (ESRD) in meta-analysis, stratified by baseline systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).

b) Baseline SBP – summary table

Baseline SBP > 150 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	16	12 824	0.89 (0.80 to 0.99)
Cardiovascular mortality	11	9 073	0.75 (0.57 to 0.99)[a]
Myocardial infraction	13	9 914	0.74 (0.63 to 0.87)
Stroke	15	11 444	0.77 (0.65 to 0.91)
Heart failure	7	6 510	0.73 (0.53 to 1.01)
End-stage renal disease	5	4 814	0.82 (0.71 to 0.94)

[a] significant heterogeneity, I^2 = 49 %, p = 0.035

Baseline SBP 140-150 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	10	24 652	0.87 (0.78 to 0.98)
Cardiovascular mortality	9	24 243	0.87 (0.71 to 1.05)[a]
Myocardial infraction	7	23 286	0.84 (0.76 to 0.93)
Stroke	9	30 135	0.92 (0.83 to 1.01)
Heart failure	7	12 723	0.80 (0.66 to 0.97)
End-stage renal disease	6	21 376	0.91 (0.74 to 1.12)

[a] significant heterogeneity, I^2 = 57 %, p = 0.019

Baseline SBP < 140 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	14	24 350	1.05 (0.95 to 1.16)
Cardiovascular mortality	10	22 439	1.15 (1.00 to 1.32)
Myocardial infraction	9	18 051	1.00 (0.87 to 1.15)
Stroke	8	17 911	0.81 (0.53 to 1.22)[a]
Heart failure	8	17 392	0.90 (0.79 to 1.02)
End-stage renal disease	7	19 973	0.97 (0.80 to 1.17)

[a] significant heterogeneity, I^2 = 58 %, p=0.020

SBP = systolic blood pressure, DM = diabetes mellitus, RR = relative risk, CI = confidence interval

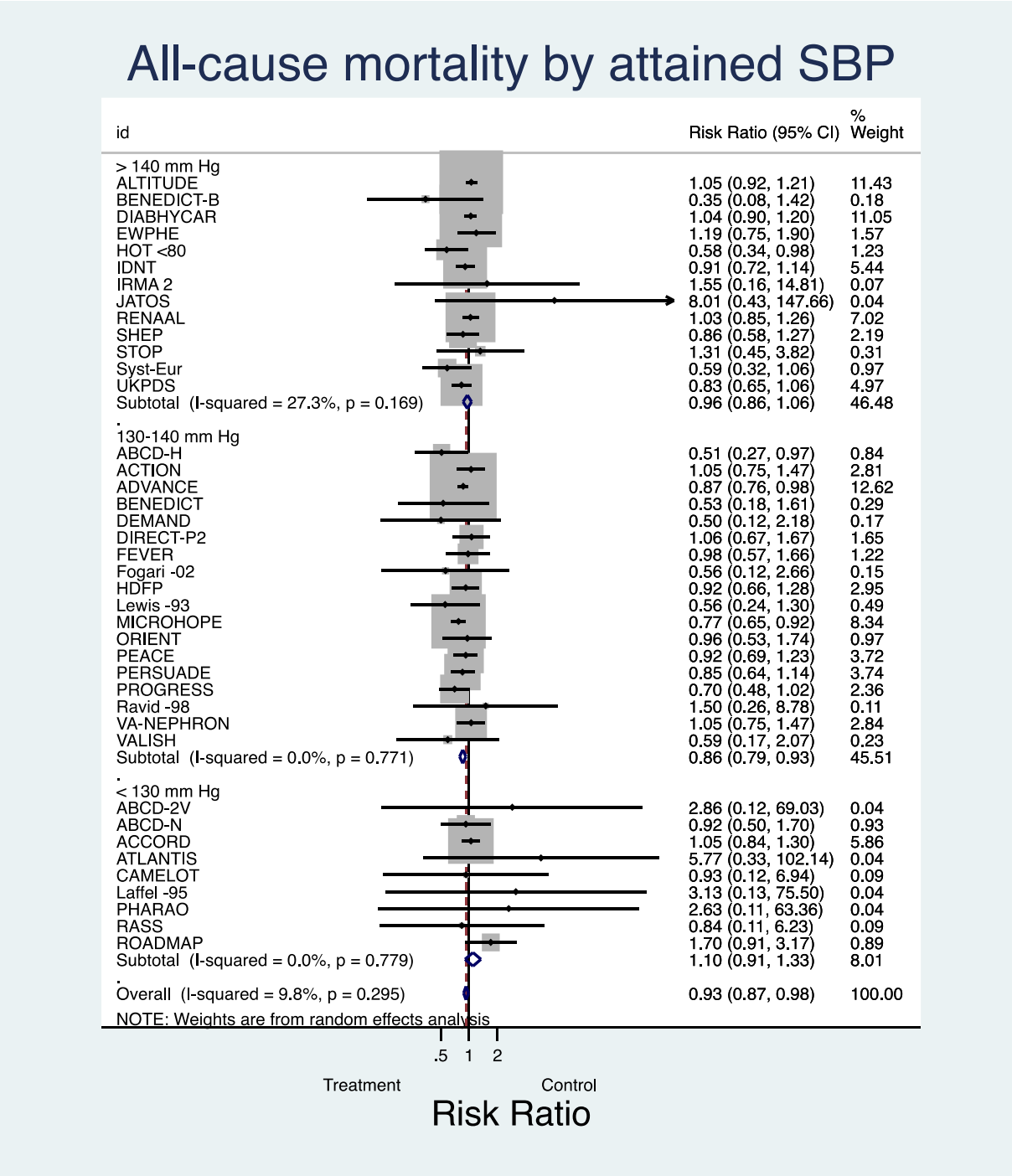
c) Baseline SBP – meta-regression analyses

Outcome	**Relative Risk (95 % CI)** [a]	**P-value**
Mortality	1.04 (0.98 to 1.10)	0.151
Cardiovascular mortality	1.15 (1.03 to 1.29)	0.015
Myocardial infarction	1.12 (1.03 to 1.22)	0.011
Stroke	1.07 (0.98 to 1.18)	0.137
Heart Failure	1.05 (0.93 to 1.20)	0.401
End-stage renal disease	1.05 (0.90 to 1.22)	0.496

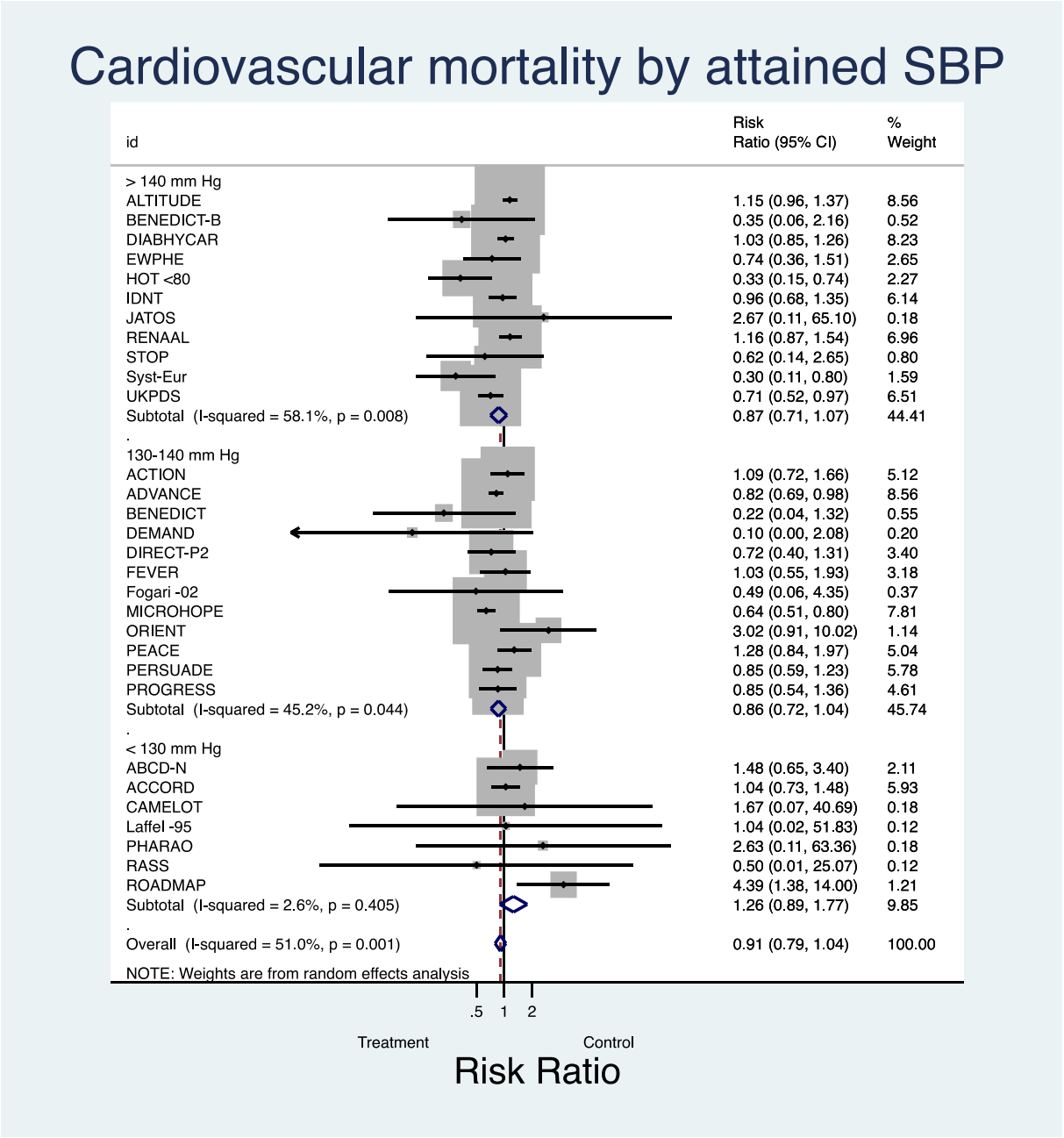
[a] expressed as change in treatment effect for each 10 mm Hg lower baseline SBP.

SBP = systolic blood pressure, CI = confidence interval

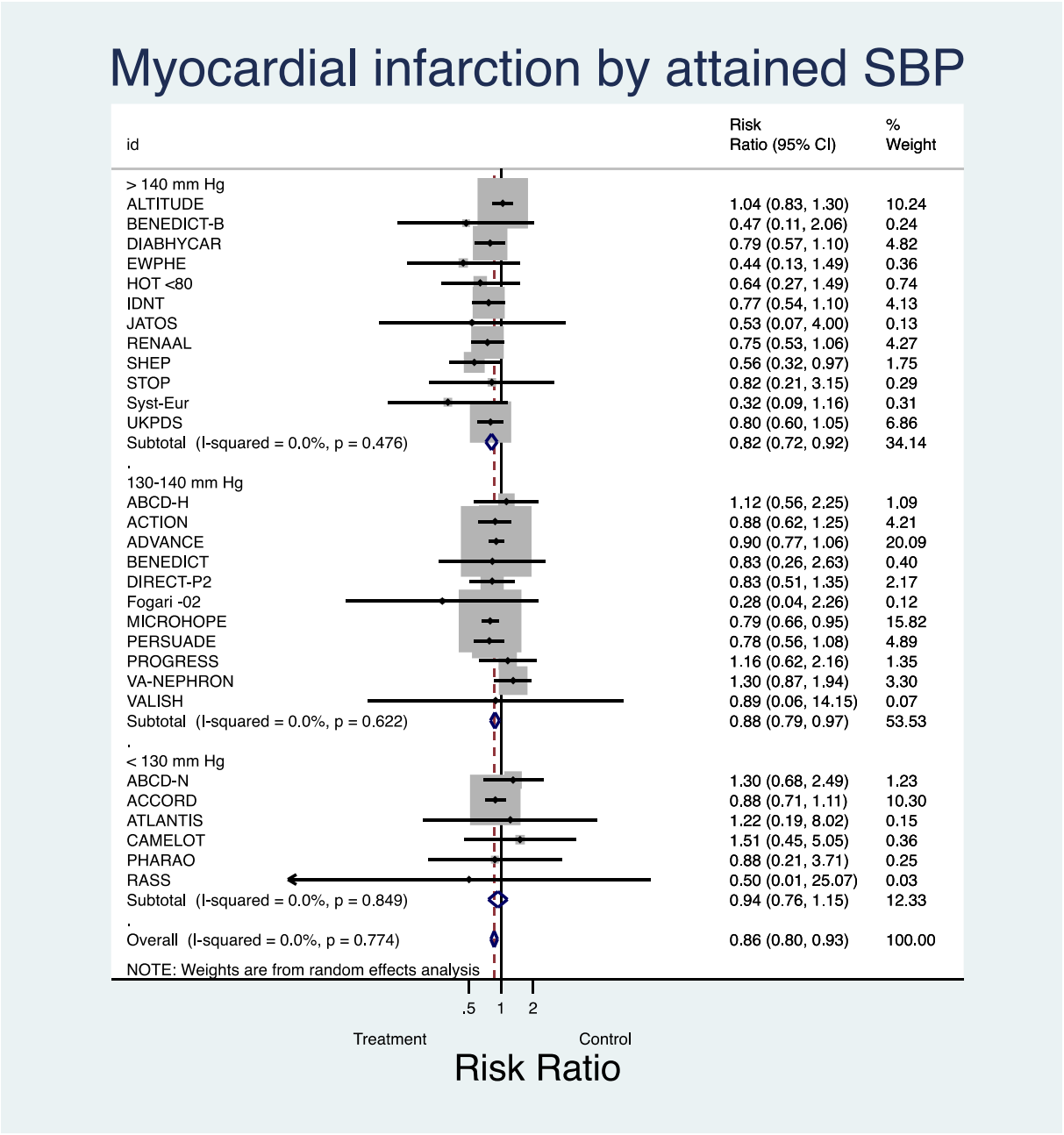
d) Attained SBP – forest plots



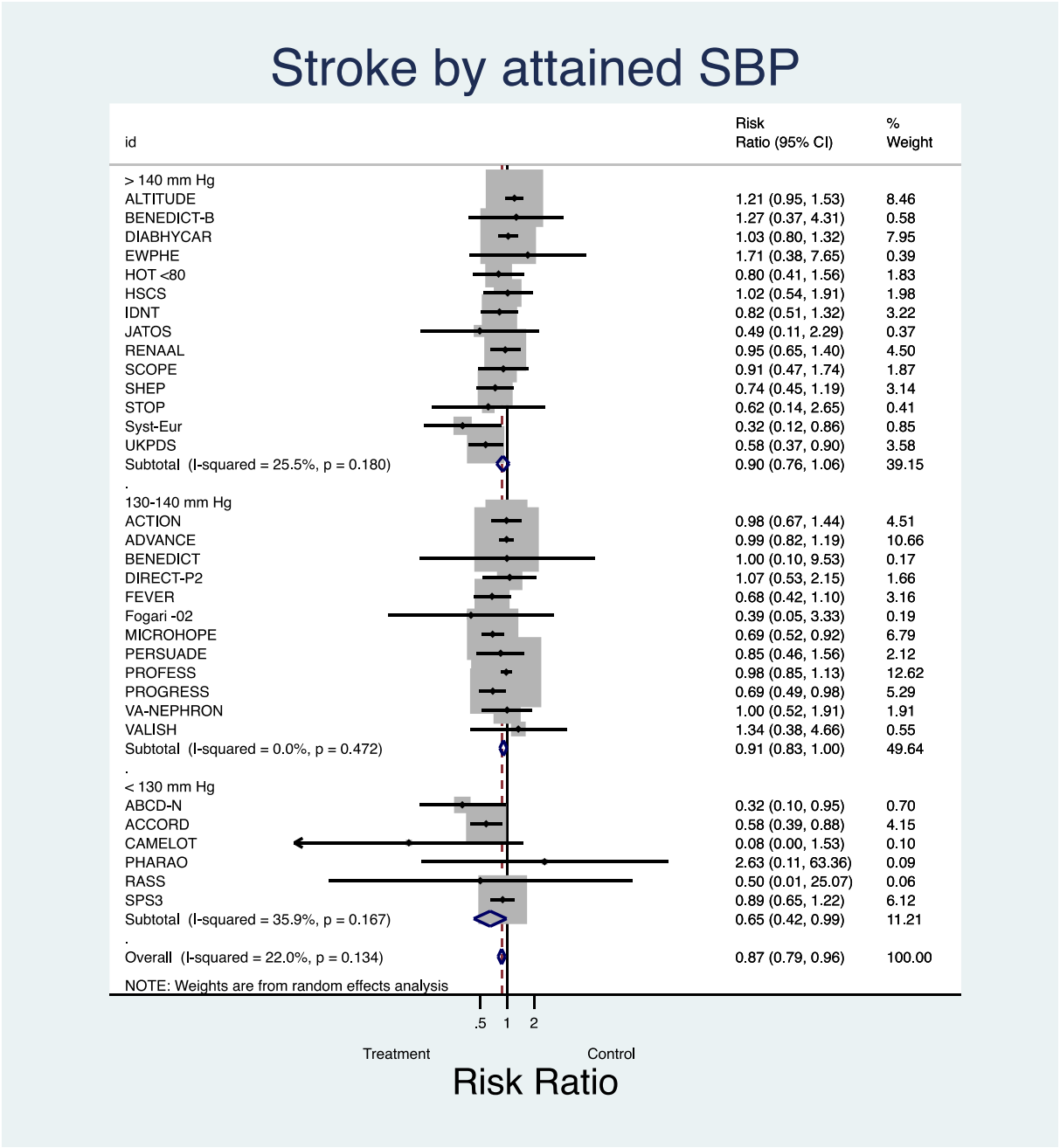
Forest plot showing relative risk of all-cause mortality in meta-analysis, stratified by attained systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).



Forest plot showing relative risk of cardiovascular mortality in meta-analysis, stratified by attained systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).

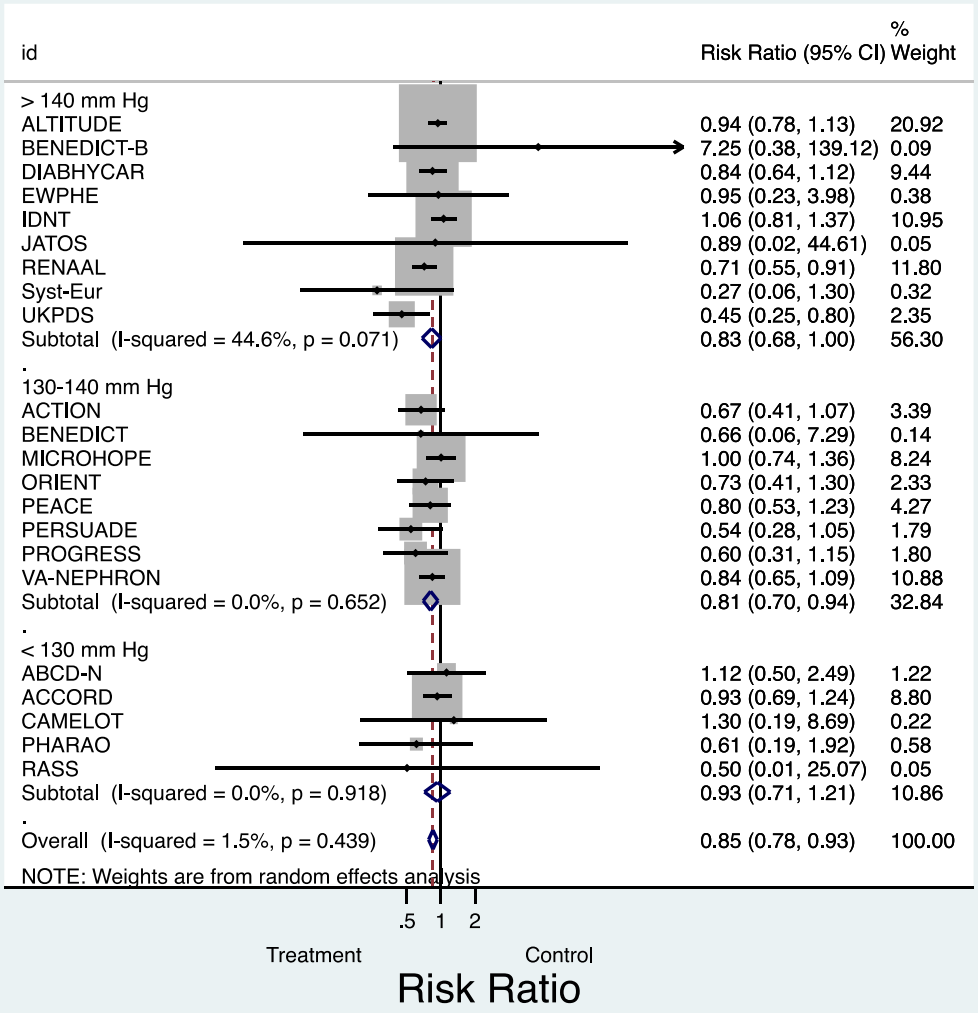


Forest plot showing relative risk of myocardial infarction in meta-analysis, stratified by attained systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).

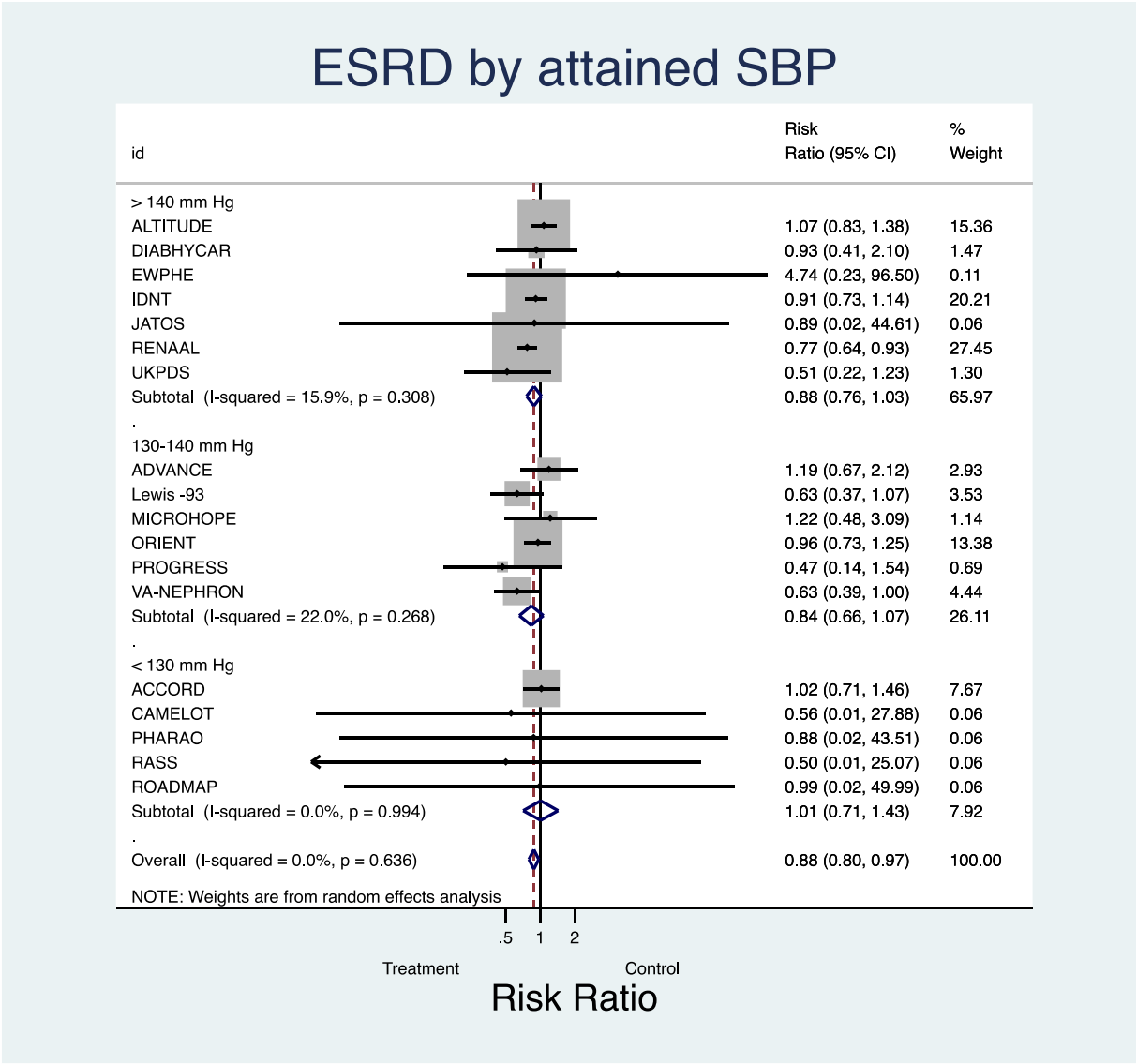


Forest plot showing relative risk of stroke in meta-analysis, stratified by attained systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).

Heart failure by attained SBP



Forest plot showing relative risk of heart failure in meta-analysis, stratified by attained systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).



Forest plot showing relative risk of end-stage renal disease (ESRD) in meta-analysis, stratified by attained systolic blood pressure (SBP), excluding trials including predominantly patients with heart failure. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analyses for each blood pressure strata, and for all strata combined (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity. Heterogeneity is measured for each stratum separately, and for all strata combined (bottom).

e) Attained SBP – summary table

Attained SBP > 140 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	13	21 876	0.96 (0.86 to 1.06)
Cardiovascular mortality	11	20 703	0.87 (0.71 to 1.07)[a]
Myocardial infraction	12	21 286	0.82 (0.72 to 0.92)
Stroke	14	22 045	0.90 (0.76 to 1.06)
Heart failure	9	19 060	0.83 (0.68 to 1.00)
End-stage renal disease	7	18 287	0.88 (0.76 to 1.03)

[a] significant heterogeneity, I^2 = 58 %, p = 0.008

Attained SBP 130-140 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	18	28 900	0.86 (0.79 to 0.93)
Cardiovascular mortality	12	25 095	0.86 (0.72 to 1.04)[a]
Myocardial infraction	11	23 828	0.88 (0.79 to 0.97)
Stroke	12	30 342	0.91 (0.83 to 1.00)
Heart failure	8	11 568	0.81 (0.70 to 0.94)
End-stage renal disease	6	17 912	0.84 (0.66 to 1.07)

[a] significant heterogeneity, I^2 = 45 %, p = 0.044

Attained SBP < 130 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	9	11 050	1.10 (0.91 to 1.33)
Cardiovascular mortality	7	10 587	1.26 (0.89 to 1.77)
Myocardial infraction	6	6 137	0.94 (0.76 to 1.15)
Stroke	6	7 103	0.65 (0.42 to 0.99)
Heart failure	5	5 997	0.93 (0.71 to 1.21)
End-stage renal disease	5	9 964	1.01 (0.71 to 1.43)

SBP = systolic blood pressure, DM = diabetes mellitus, RR = relative risk, CI = confidence interval

f) Attained SBP – meta-regression analyses

Outcome	**Relative Risk (95 % CI)** [a]	**P-value**
Mortality	1.02 (0.93 to 1.12)	0.624
Cardiovascular mortality	1.20 (0.99 to 1.44)	0.059
Myocardial infarction	1.09 (0.98 to 1.21)	0.100
Stroke	0.97 (0.82 to 1.13)	0.659
Heart Failure	1.05 (0.90 to 1.22)	0.544
End-stage renal disease	1.02 (0.85 to 1.24)	0.787

[a] expressed as change in treatment effect for each 10 mm Hg lower attained SBP.

SBP = systolic blood pressure, CI = confidence interval

g) Baseline DBP – summary table

Baseline DBP > 90 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	9	6 591	0.85 (0.73 to 1.00)
Cardiovascular mortality	6	4 452	0.70 (0.55 to 0.89)
Myocardial infraction	6	3 681	0.79 (0.62 to 1.00)
Stroke	8	5 211	0.74 (0.58 to 0.94)
Heart failure	2	1 259	0.50 (0.29 to 0.85)
End-stage renal disease	2	1 259	0.96 (0.14 to 6.76)

Baseline DBP 80-90 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	16	25 779	0.90 (0.82 to 0.99)
Cardiovascular mortality	13	24 842	0.91 (0.78 to 1.07)
Myocardial infraction	13	24 861	0.85 (0.76 to 0.95)
Stroke	14	30 604	0.92 (0.83 to 1.03)
Heart failure	11	13 322	0.81 (0.67 to 0.97)
End-stage renal disease	8	20 912	0.83 (0.72 to 0.94)

Baseline DBP < 80 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	15	29 456	0.97 (0.89 to 1.06)
Cardiovascular mortality	11	27 091	1.08 (0.82 to 1.41)[a]
Myocardial infraction	10	22 709	0.90 (0.79 to 1.02)
Stroke	10	23 675	0.86 (0.70 to 1.05)[b]
Heart failure	9	22 044	0.89 (0.80 to 1.00)
End-stage renal disease	8	23 992	0.97 (0.83 to 1.13)

[a] significant heterogeneity, I^2 = 66 %, p = 0.001
[b] significant heterogeneity, I^2 = 49 %, p = 0.04

DBP = diastolic blood pressure, DM = diabetes mellitus, RR = relative risk, CI = confidence interval

h) Baseline DBP – meta-regression analyses

Outcome	**Relative Risk (95 % CI)** [a]	**P-value**
Mortality	1.08 (0.99 to 1.18)	0.074
Cardiovascular mortality	1.28 (1.05 to 1.55)	0.013
Myocardial infarction	1.11 (0.98 to 1.26)	0.102
Stroke	1.09 (0.93 to 1.27)	0.287
Heart Failure	1.11 (0.90 to 1.36)	0.298
End-stage renal disease	1.13 (0.88 to 1.44)	0.309

[a] expressed as change in treatment effect for each 10 mm Hg lower baseline DBP.

DBP = systolic blood pressure, CI = confidence interval

i) Attained DBP – summary table

Attained DBP > 80 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	13	13 092	0.95 (0.86 to 1.06)
Cardiovascular mortality	10	11 229	0.71 (0.53 to 0.97)
Myocardial infraction	8	9 608	0.76 (0.63 to 0.93)
Stroke	10	11 011	0.87 (0.73 to 1.04)
Heart failure	5	7 656	0.72 (0.45 to 1.15)
End-stage renal disease	3	6 171	0.77 (0.39 to 1.52)

Attained DBP 75-80 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	13	14 059	0.86 (0.75 to 0.98)
Cardiovascular mortality	10	13 040	0.85 (0.69 to 1.05)[a]
Myocardial infraction	12	13 650	0.81 (0.72 to 0.91)
Stroke	12	19 380	0.86 (0.75 to 0.97)
Heart failure	9	11 135	0.79 (0.65 to 0.96)
End-stage renal disease	7	8 437	0.81 (0.71 to 0.93)

[a] significant heterogeneity, I^2 = 50 %, p = 0.035

Attained DBP < 75 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	14	34 675	0.97 (0.89 to 1.04)
Cardiovascular mortality	10	32 116	1.16 (0.92 to 1.47)[a]
Myocardial infraction	9	27 993	0.95 (0.84 to 1.07)
Stroke	10	29 099	0.87 (0.70 to 1.08)[b]
Heart failure	8	17 834	0.90 (0.79 to 1.01)
End-stage renal disease	8	31 555	0.98 (0.84 to 1.14)

[a] significant heterogeneity, I^2 = 52 %, p = 0.028
[b] significant heterogeneity, I^2 = 50 %, p = 0.037

DBP = diastolic blood pressure, DM = diabetes mellitus, RR = relative risk, CI = confidence interval

j) Attained DBP – meta-regression analyses

Outcome	**Relative Risk (95 % CI)** [a]	**P-value**
Mortality	1.07 (0.93 to 1.23)	0.320
Cardiovascular mortality	1.35 (0.98 to 1.86)	0.062
Myocardial infarction	1.13 (0.96 to 1.33)	0.129
Stroke	0.95 (0.75 to 1.21)	0.680
Heart Failure	1.11 (0.90 to 1.36)	0.298
End-stage renal disease	1.11 (0.88 to 1.41)	0.358

[a] expressed as change in treatment effect for each 10 mm Hg lower attained DBP.

DBP = systolic blood pressure, CI = confidence interval

k) SBP difference between groups during treatment – summary table

SBP difference > 6 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	12	10 175	0.91 (0.80 to 1.02)
Cardiovascular mortality	9	8 319	0.82 (0.66 to 1.01)
Myocardial infraction	9	8 759	0.82 (0.68 to 0.99)
Stroke	11	10 027	0.70 (0.58 to 0.83)
Heart failure	6	7 725	0.71 (0.50 to 1.02)
End-stage renal disease	4	6 753	0.79 (0.46 to 1.36)

SBP difference 3-6 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	16	30 547	0.87 (0.79 to 0.97)
Cardiovascular mortality	12	29 409	0.88 (0.71 to 1.10)[a]
Myocardial infraction	12	24 153	0.84 (0.76 to 0.93)
Stroke	13	31 124	0.92 (0.83 to 1.01)
Heart failure	7	9 175	0.90 (0.75 to 1.08)
End-stage renal disease	7	22 147	0.96 (0.81 to 1.12)

[a] significant heterogeneity, I^2 = 58 %, p = 0.006

SBP difference < 3 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	12	21 104	1.02 (0.94 to 1.11)
Cardiovascular mortality	9	18 657	1.10 (0.96 to 1.26)
Myocardial infraction	8	18 339	0.94 (0.81 to 1.09)
Stroke	8	18 339	1.09 (0.94 to 1.27)
Heart failure	9	19 725	0.84 (0.75 to 0.94)
End-stage renal disease	7	17 263	0.82 (0.69 to 0.98)

SBP = systolic blood pressure, DM = diabetes mellitus, RR = relative risk, CI = confidence interval

l) DBP difference between groups during treatment – summary table

DBP difference > 4 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	12	9 699	0.91 (0.80 to 1.03)
Cardiovascular mortality	8	7 827	0.85 (0.70 to 1.03)
Myocardial infraction	8	8 154	0.88 (0.76 to 1.03)
Stroke	9	8 952	0.71 (0.59 to 0.86)
Heart failure	5	7 233	0.75 (0.53 to 1.06)
End-stage renal disease	4	6 753	0.79 (0.46 to 1.36)

DBP difference 2-4 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	10	18 582	0.86 (0.78 to 0.95)
Cardiovascular mortality	7	17 450	0.73 (0.53 to 1.00)[a]
Myocardial infraction	9	18 173	0.84 (0.74 to 0.96)
Stroke	9	23 776	0.95 (0.85 to 1.05)
Heart failure	5	4 809	0.83 (0.57 to 1.19)
End-stage renal disease	4	13 549	0.89 (0.74 to 1.08)

[a] significant heterogeneity, I^2 = 56 %, p = 0.034

DBP difference < 2 mmHg

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	18	33 545	0.97 (0.90 to 1.06)
Cardiovascular mortality	15	31 108	1.02 (0.83 to 1.25)[a]
Myocardial infraction	12	24 924	0.87 (0.78 to 0.96)
Stroke	14	26 762	0.94 (0.81 to 1.08)
Heart failure	12	24 583	0.85 (0.77 to 0.94)
End-stage renal disease	10	25 861	0.87 (0.77 to 0.99)

[a] significant heterogeneity, I^2 = 60 %, p = 0.001

DBP = diastolic blood pressure, DM = diabetes mellitus, RR = relative risk, CI = confidence interval

5. Results – sensitivity analyses

a) Excluding DIRECT-P2

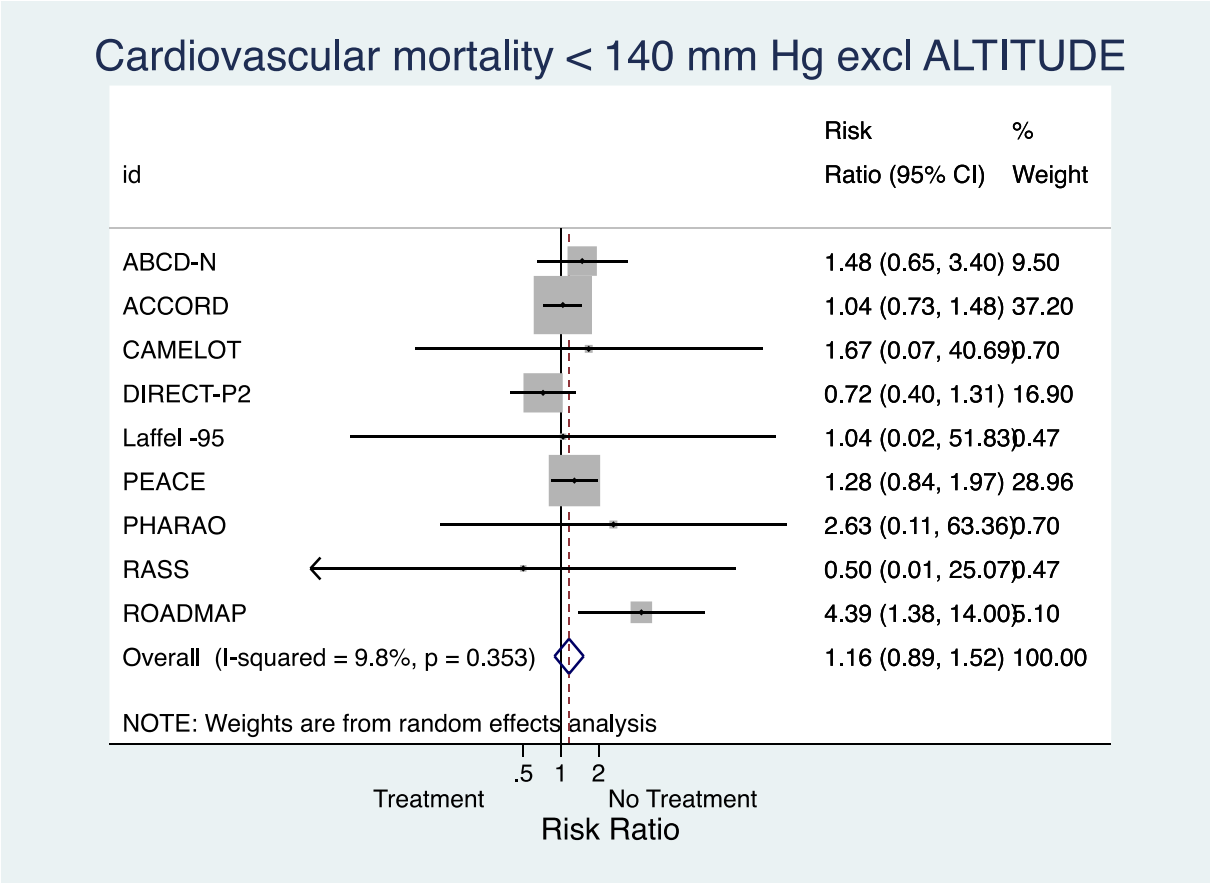
Baseline SBP < 140 mm Hg without DIRECT-P2

Outcome	Included trials (n)	Patients with DM	RR (95% CI)
All-cause mortality	13	22 445	1.05 (0.95 to 1.16)
Cardiovascular mortality	9	20 534	1.18 (1.02 to 1.36)
Myocardial infraction	8	16 146	1.02 (0.88 to 1.17)
Stroke	7	16 006	0.75 (0.45 to 1.23)[a]
Heart failure	8	17 392	0.90 (0.79 to 1.02)
End-stage renal disease	7	19 973	0.97 (0.80 to 1.17)

[a] significant heterogeneity, I^2 = 64 %, p=0.011

SBP = systolic blood pressure, DM = diabetes mellitus, RR = relative risk, CI = confidence interval

b) Excluding ALTITUDE from cardiovascular mortality analysis



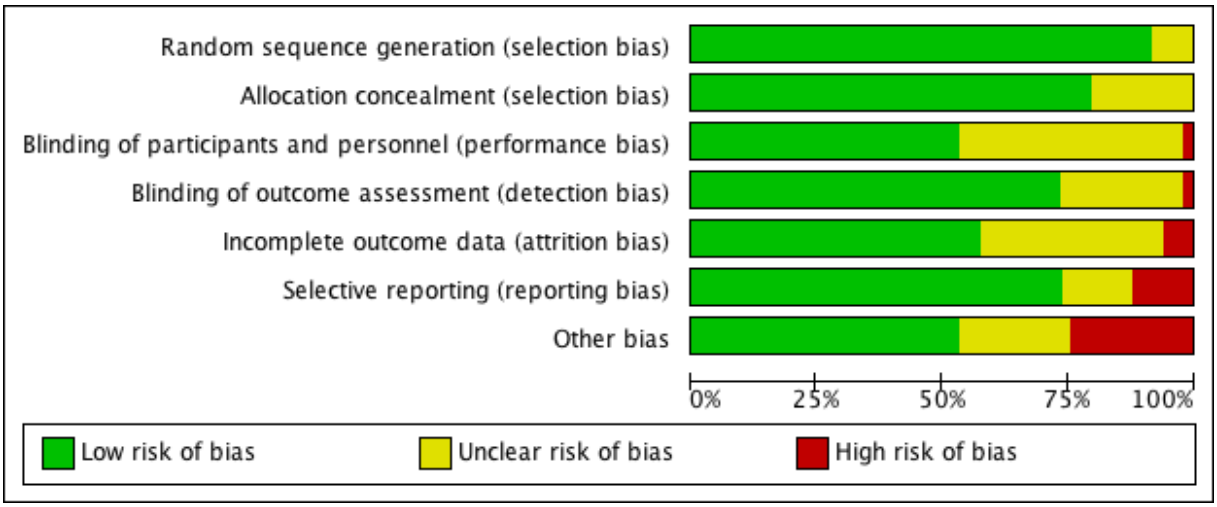
Forest plot showing relative risk of cardiovascular mortality in meta-analysis of trials with baseline systolic blood pressure, excluding ALTITUDE. Black dots represent relative risk in each trial, black lines represent confidence intervals (CI) in each trial, and grey squares represent the weight given each trial in the meta-analysis. Blue diamonds represent the results from the meta-analysis (bottom). I-squared is a measure of heterogeneity, and the following p-value represents the significance of that heterogeneity.

5. Risk of bias

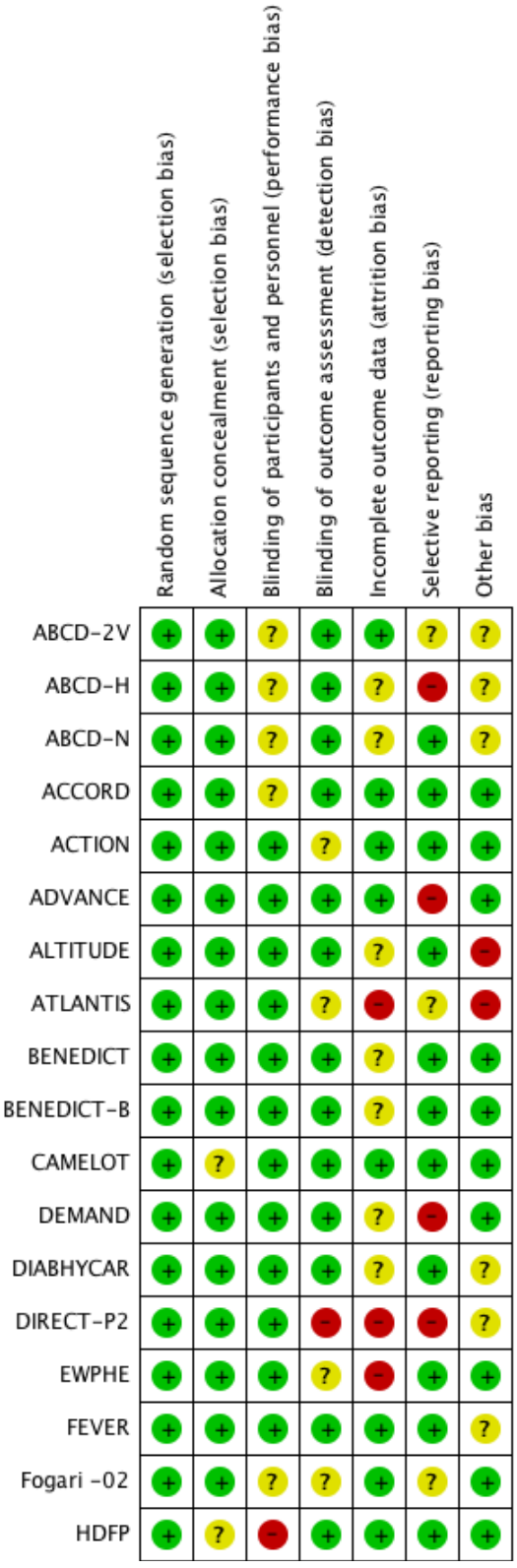
Risk of bias was generally considered low or unclear across domains. The most common reason for judging unclear risk of bias was lack of reporting. High risk of bias was present in at least one domain in 19 of 49 trials. The most common reasons for judging high risk of bias was that trials were stopped early because of treatment effects, that they were confined to heart failure patients with anticipated treatment effect besides that of BP lowering, or that sponsors were involved in the design of the trial, interpretation of the results, and writing of the report. All these concerns are represented in the domain *other sources of bias*, and was present in twelve trials in total. Trials confined to heart failure patients were excluded from the stratified analyses. Trials stopped early and trials subject to sponsor involvement were mostly trials in the higher BP range, hence potentially overestimating the effect in these strata, but not affecting low BP analyses. Selective reporting was suspected in six trials. This was a combination of outcomes specified in the study protocol, but not being reported in the publication, and outcomes being reported in ways that could not be included in the meta-analyses. Because this problem was present in only about one tenth of all studies, and it was spread across different outcomes, it was not judged to affect the overall results. We found one study, judged to have high risk of bias on three domains (DIRECT-P2), with potential for detection bias, attrition bias and reporting bias. Excluding this trial from the analyses shifted the point estimate and confidence intervals for CV mortality and myocardial infarction slightly more towards harm in the stratified analyses with baseline SBP < 140 mm Hg.

Funnel plots were made for all trials combined for each outcome studied, and for mortality in each SBP strata (web appendix). The overall plots for all-cause mortality and myocardial infarction showed potential asymmetry, judged by visual inspection. However, this could be explained by expected differences in treatment effect in different SBP strata, and was not present in stratified analyses. Also, asymmetry was non-significant using Egger´s and Begg´s tests.

a) Summary graph across domains



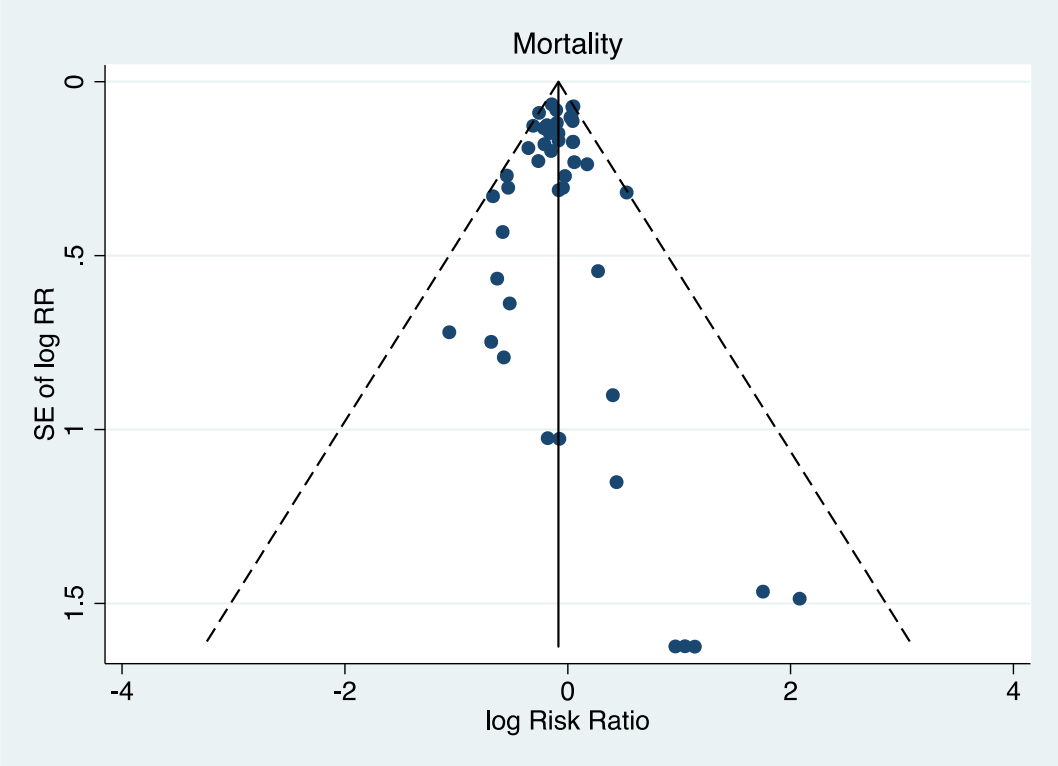
b) Individual study table

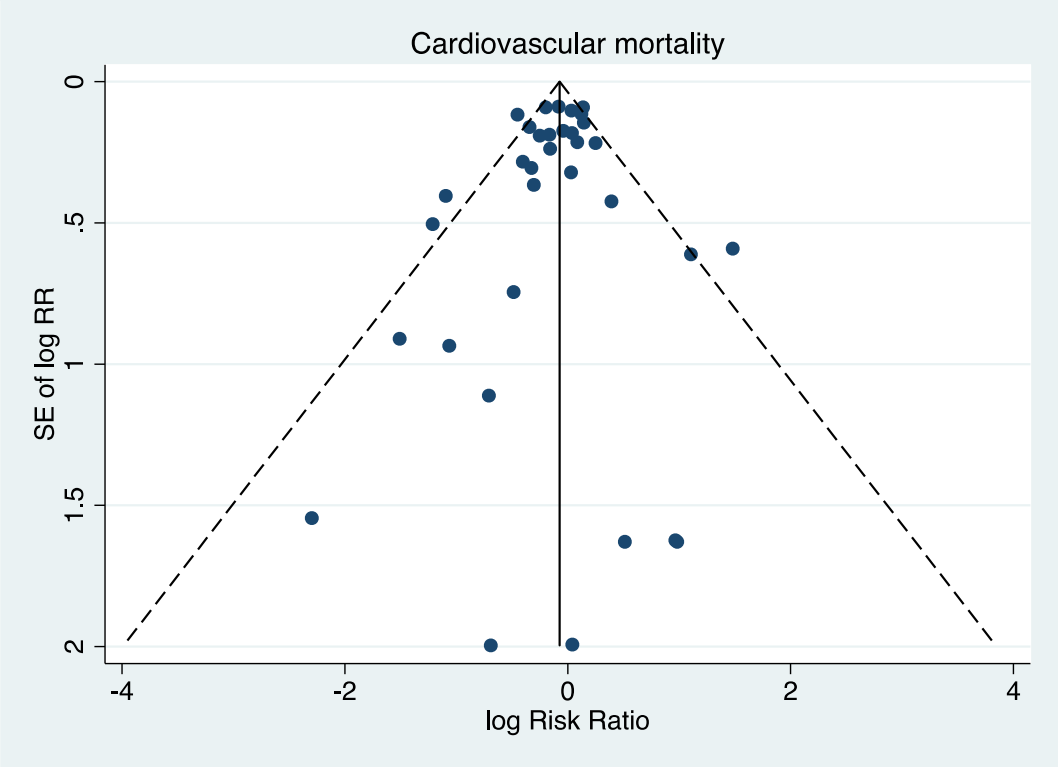


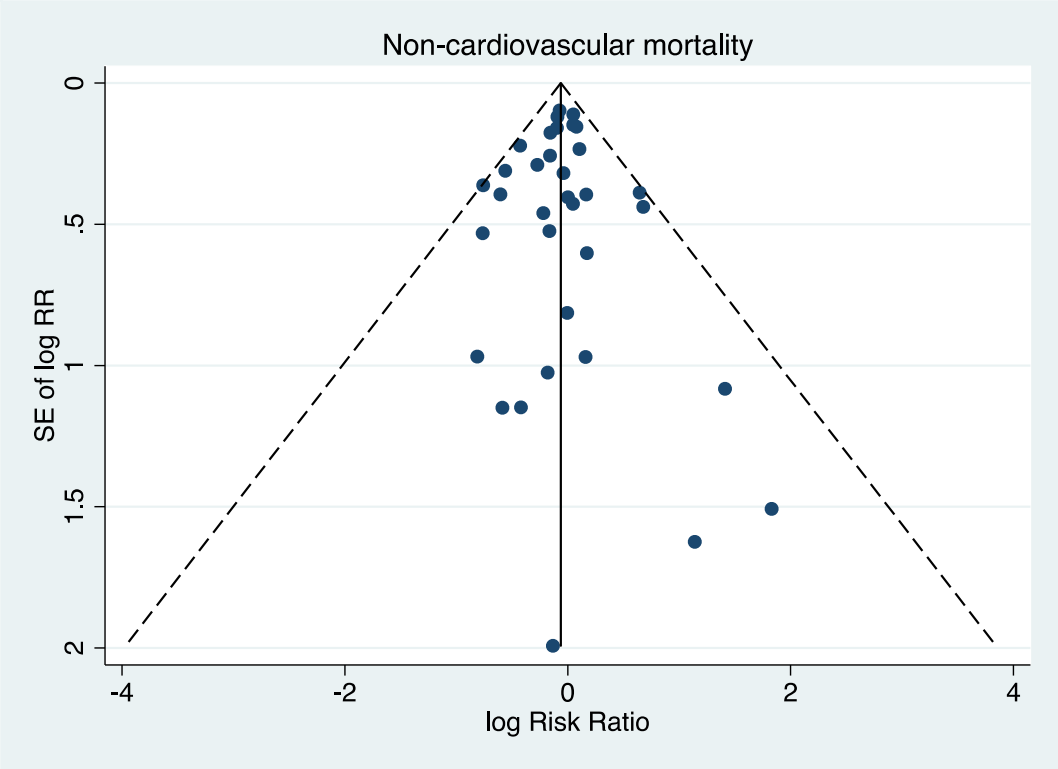
Green dots represent low risk of bias. Yellow dots represent unclear risk of bias. Red dots represent high risk of bias. In the *other bias* category we systematically judged if trials were stopped early, if there were extensive sponsor involvement, if there were major changes to the protocol, and if there were clinically significant baseline imbalances between groups.

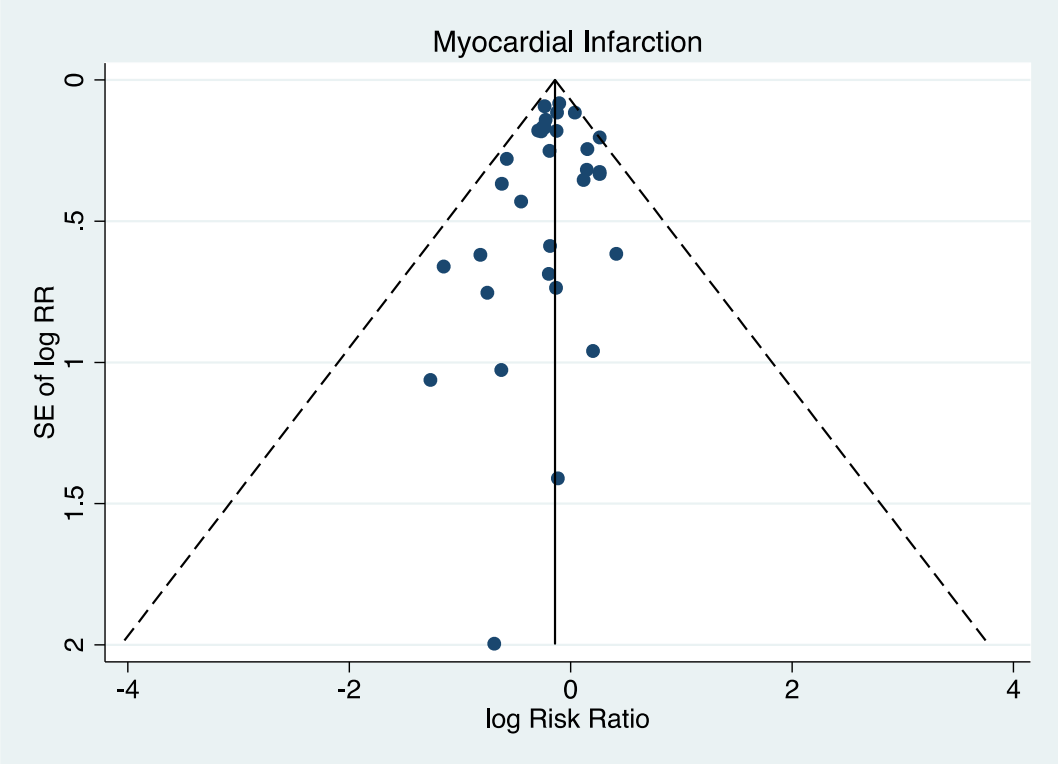
7. Funnel plots

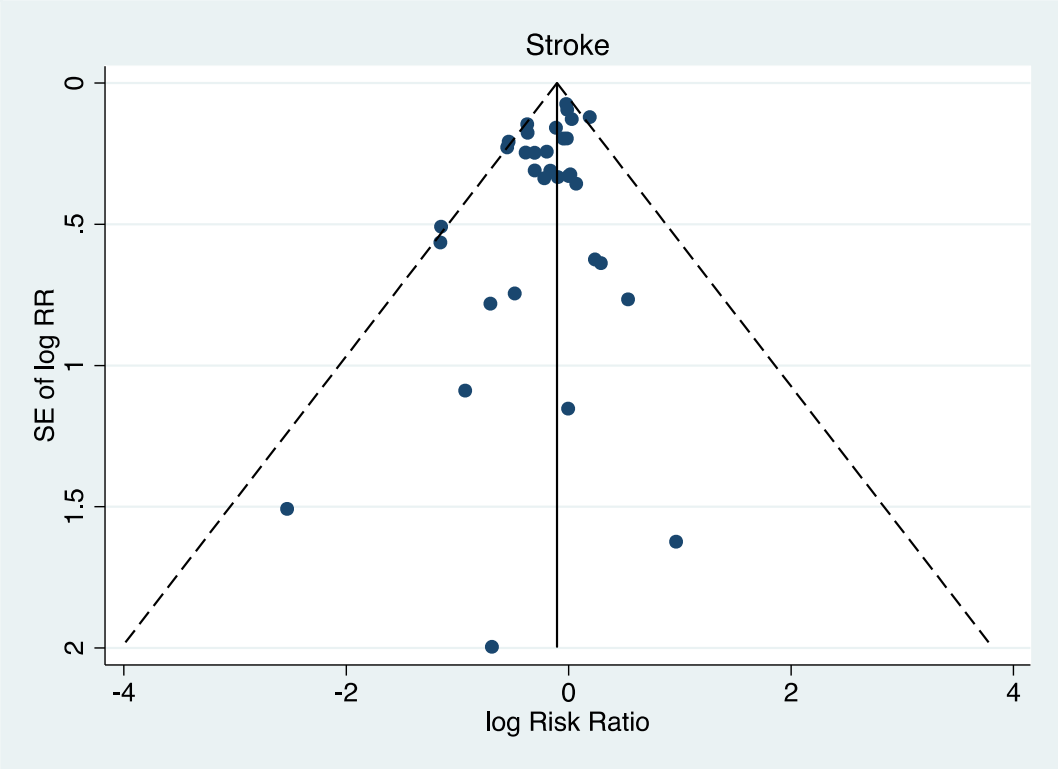
a) All trials for each outcome

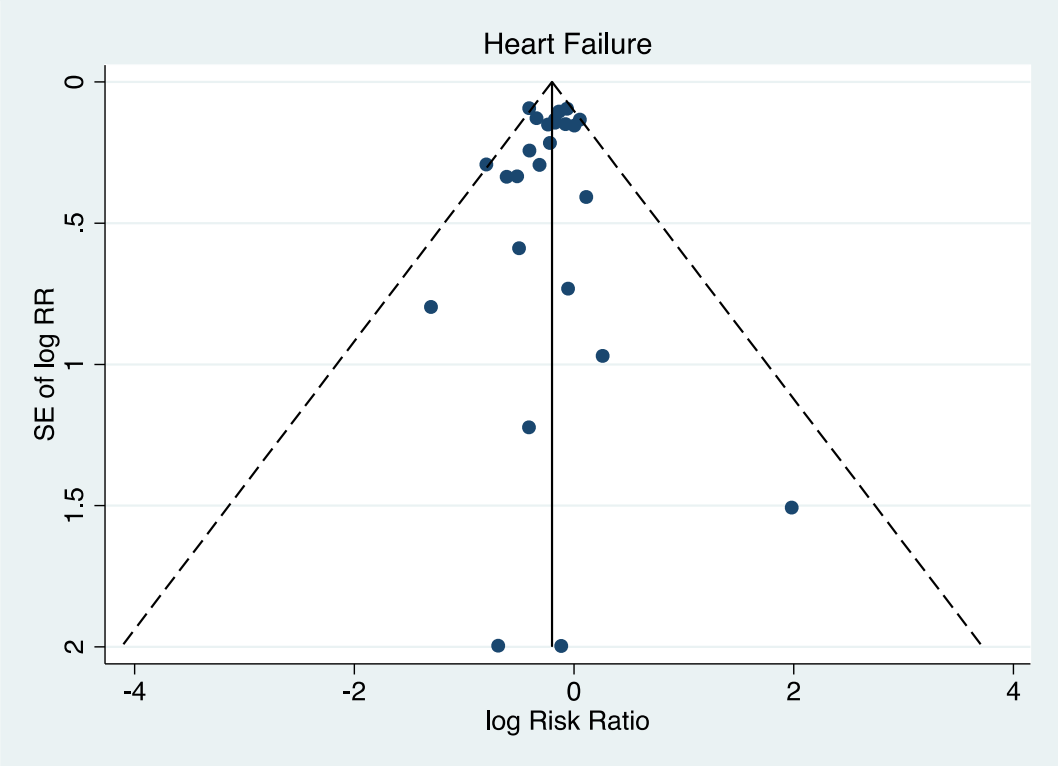


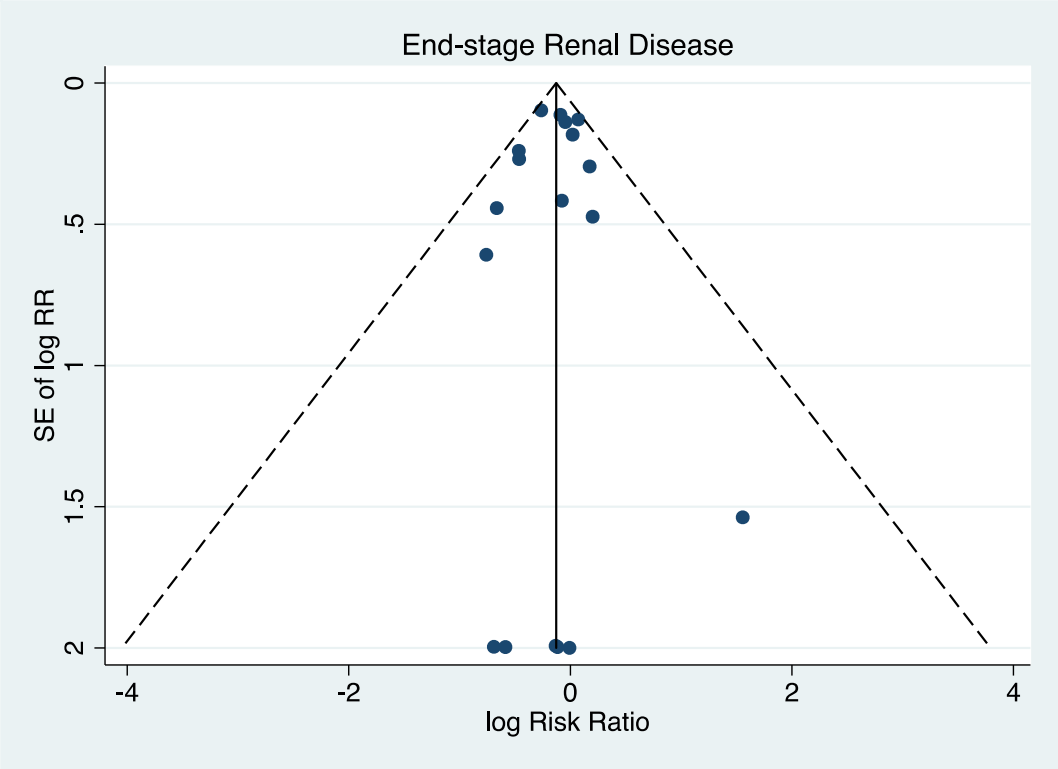


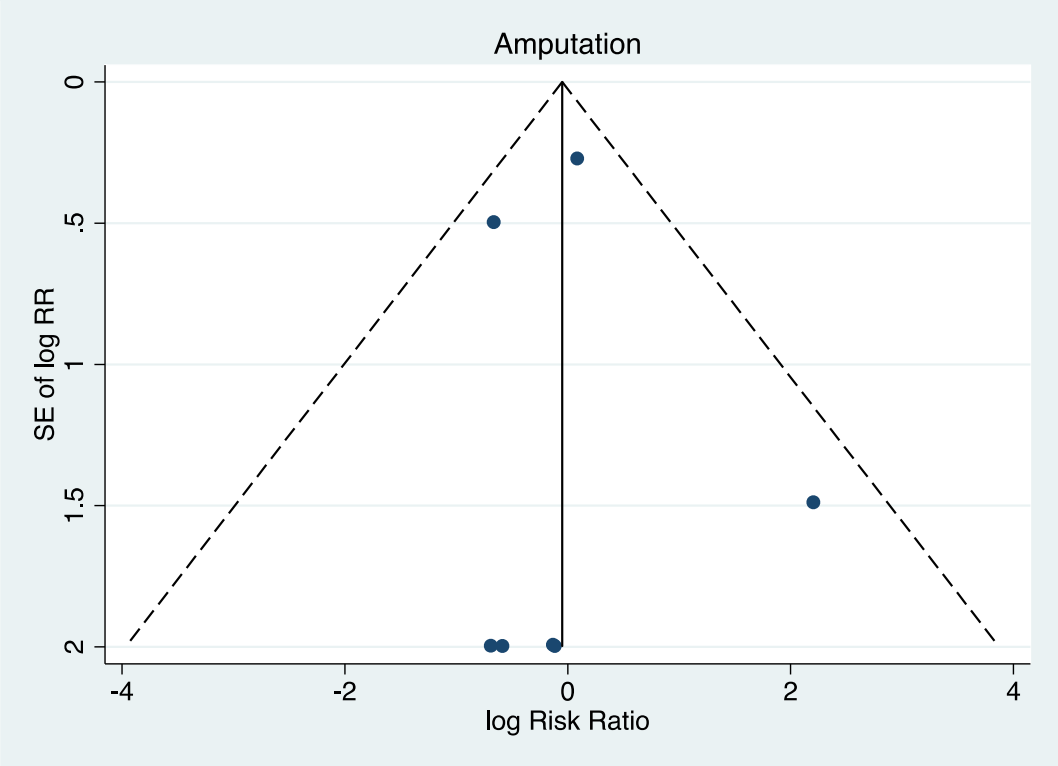

Non-cardiovascular mortality
SE of log RR
0
.5
1
1.5
2
-4
-2
0
2
4
log Risk Ratio

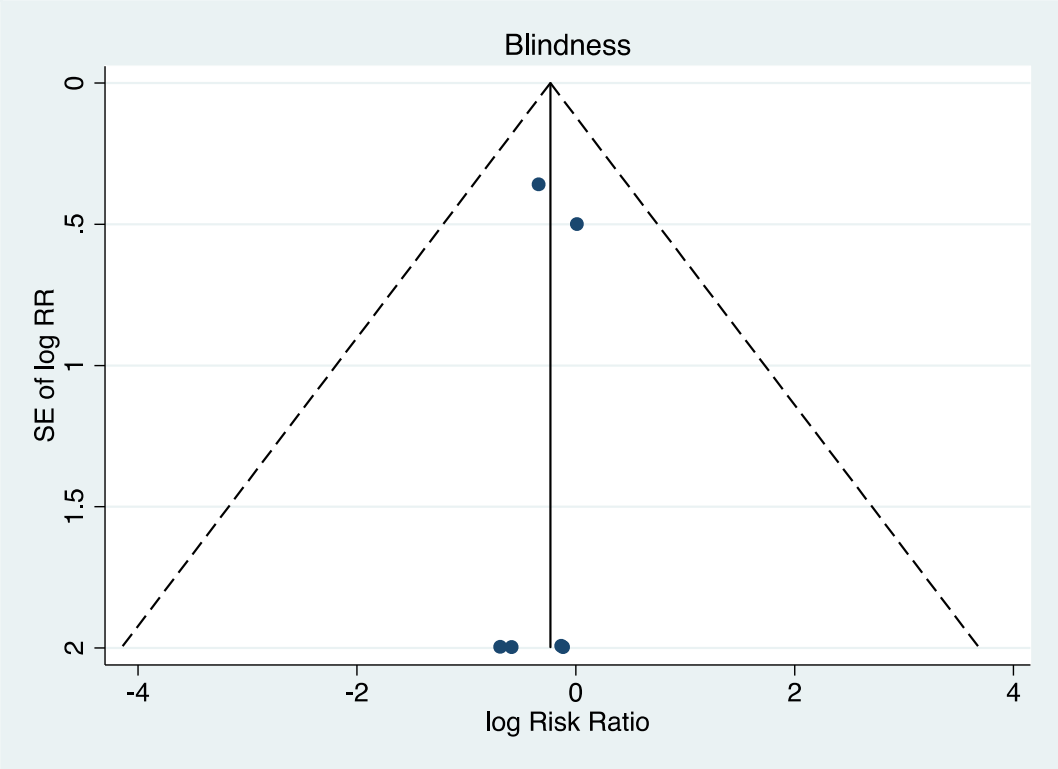

Myocardial Infarction
SE of log RR
0
.5
1
1.5
2
-4
-2
0
2
4
log Risk Ratio


Stroke
SE of log RR
0
.5
1
1.5
2
-4
-2
0
2
4
log Risk Ratio


Heart Failure
SE of log RR
0
.5
1
1.5
2
-4
-2
0
2
4
log Risk Ratio

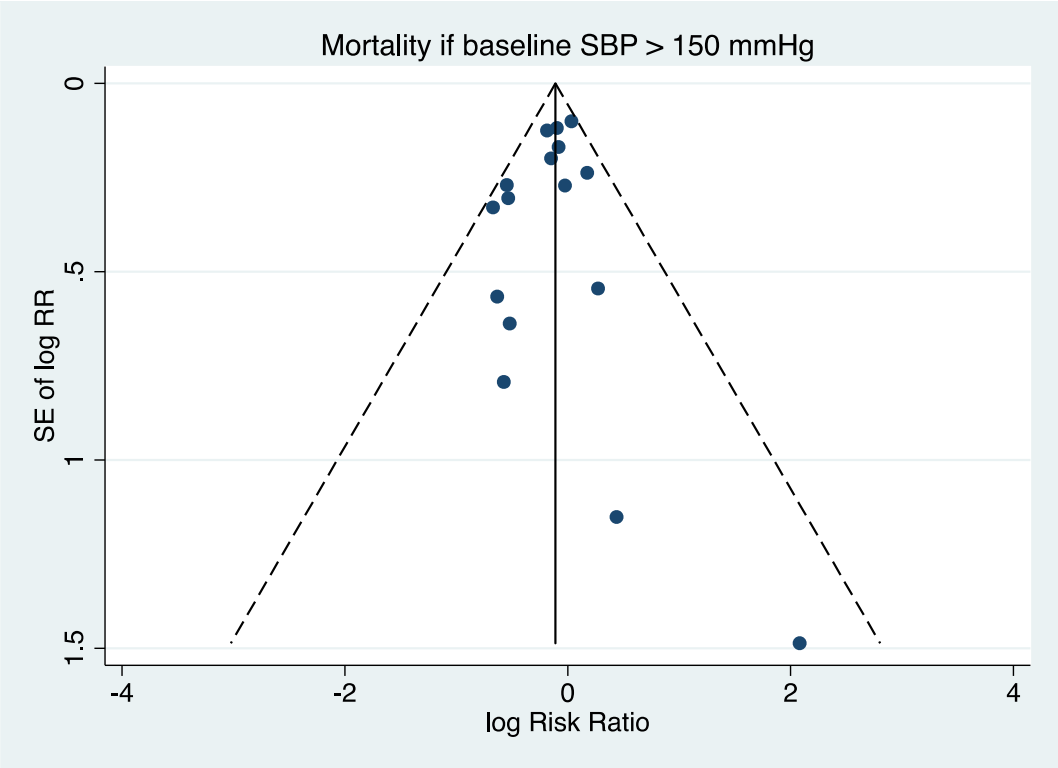

End-stage Renal Disease
SE of log RR
0
.5
1
1.5
2
-4
-2
0
2
4
log Risk Ratio

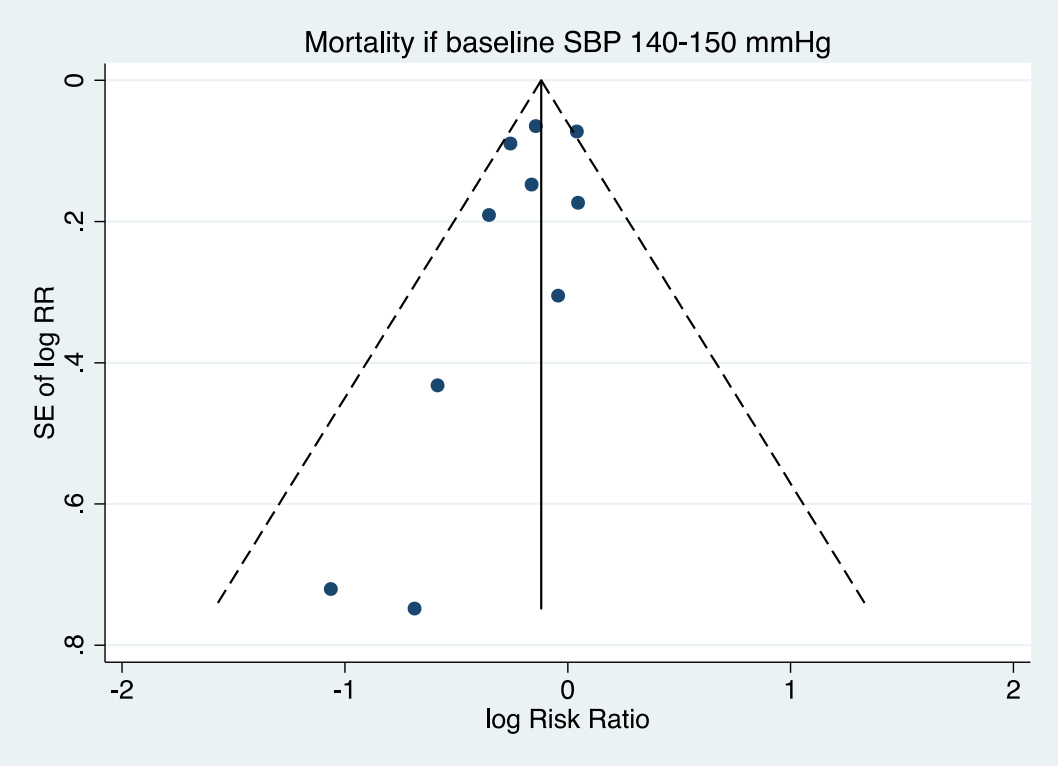

Amputation
SE of log RR
0
.5
1
1.5
2
-4
-2
0
2
4
log Risk Ratio

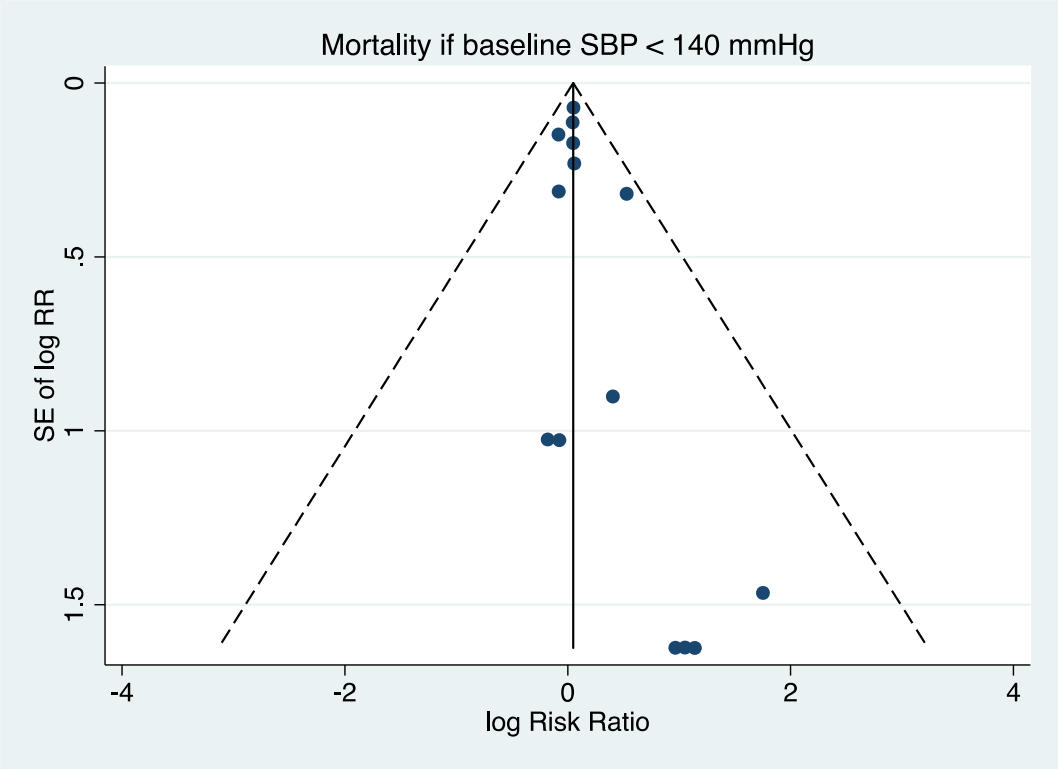


SE = standard error, RR = relative risk, log indicates logarithmic scale. Each dot represents one trial.

b) For mortality across baseline SBP strata

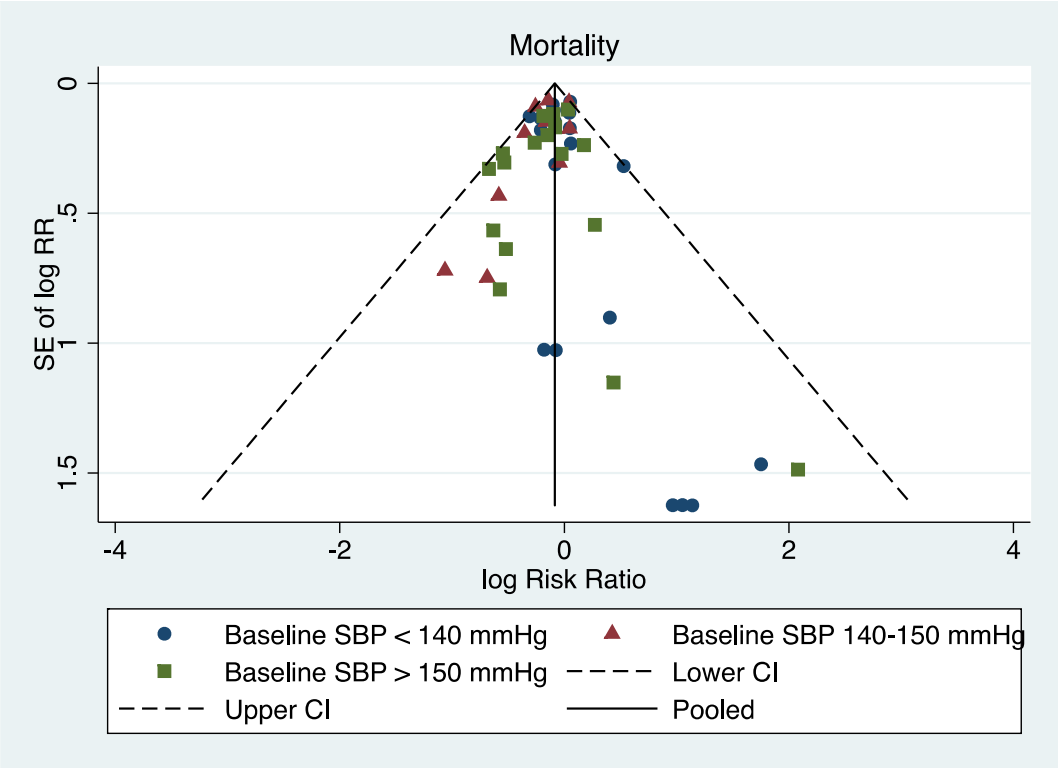


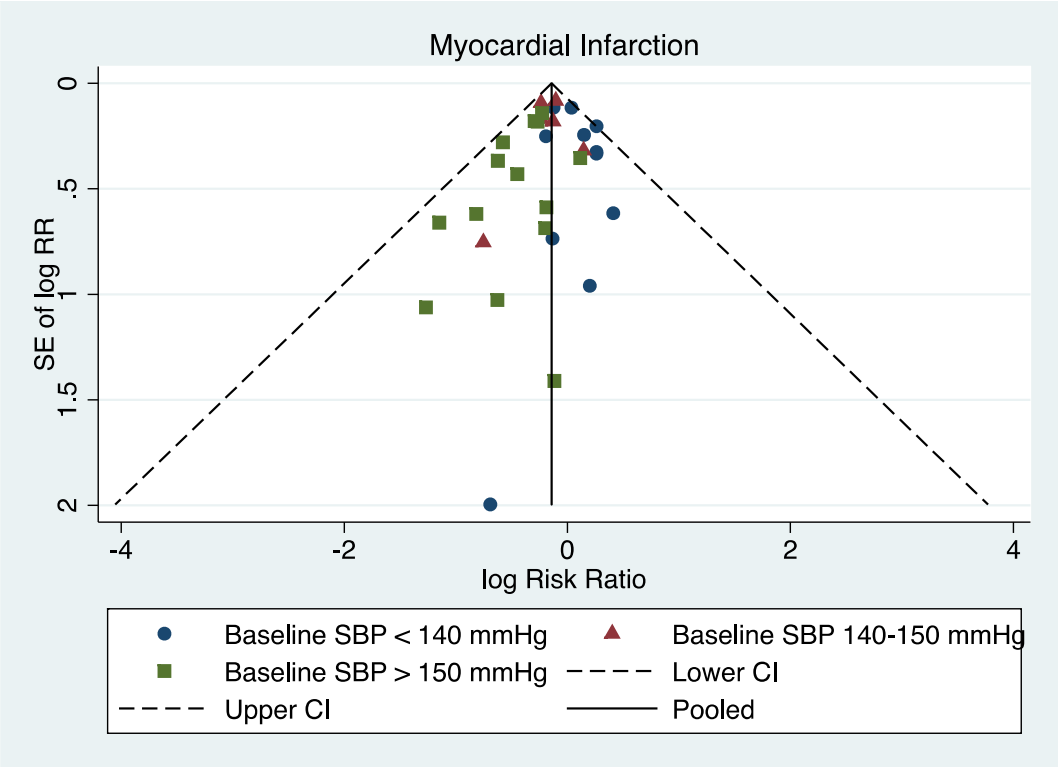




SE = standard error, RR = relative risk, SBP = systolic blood pressure, log indicates logarithmic scale. Each dot represents one trial.

c) Ad-hoc analyses of mortality and myocardial infarction, categorized by SBP strata





SE = standard error, RR = relative risk, SBP = systolic blood pressure, CI = confidence interval, log indicates logarithmic scale. Each dot, circle or triangle represents one trial.