Vedlegg:
Primærforebygging av hjerte- og karsykdom

Oversikt over vedlegg til rapport nr. 20 2008

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Vedlegg 1

PRIMÆRFOREBYGGING AV HJERTE- OG KARSYKDOM (KUNNSKAPSSENTERETS RAPPORT NR 20-2008)

SØKESTRATEGI / SEARCH STRATEGY

Tittel: Primær forebygging av hjerte- og karsykdommer
Prosjektansvarlig: Lise Lund Håheim og Atle Fretheim
Bibliotekar: Elizabeth Bunz og Marit Johansen
Søk og databaser:

- Medikamentelle og alternative tiltak: Cochrane Library online, Issue 4 2006, CDSR, DARE, CENTRAL. Utført 2. november 2006
- Medikamentelle tiltak: MEDLINE, Ovid 1950 to November Week 1 2007. Utført 19. november 2007
- Alternative tiltak: MEDLINE, Ovid 1950 to November Week 1 2007. Utført 19. november 2007
- Medikamentelle tiltak: EMBASE, Ovid 1980 to 2007 Week 46. Utført 21. november 2007
- Alternative tiltak: EMBASE, Ovid 1980 to 2007 Week 46. Utført 19. november 2007
- Medikamentelle og alternative tiltak: AMED (Allied and Complementary Medicine Database), Ovid 1985 to November 2007. Utført 19. november 2007

Antall referanser: 6101 titler og sammendrag.
Kommentar: Ved en eventuell oppdatering av denne rapporten vil vi revidere strategien som inkluderer databasen CENTRAL og kjøre søket så nære oppdateringsdato som mulig.

Medikamentelle og alternative tiltak

Cochrane Library - CDSR, DARE, CENTRAL

#1 MeSH descriptor Cerebrovascular Accident explode all trees in MeSH products
#2 MeSH descriptor Cerebrovascular Disorders explode all trees in MeSH products
#3 MeSH descriptor Cardiovascular Diseases explode all trees in MeSH products
#4 MeSH descriptor Heart Diseases explode all trees in MeSH products

#5 MeSH descriptor Coronary Disease explode all trees in MeSH products
#6 (#1 OR #2 OR #3 OR #4 OR #5)
#7 MeSH descriptor Antihypertensive Agents explode all trees in MeSH products
#8 MeSH descriptor Adrenergic beta-Antagonists explode all trees in MeSH products
#9 MeSH descriptor Angiotensin-Converting Enzyme Inhibitors explode all trees in MeSH products
#10 MeSH descriptor Calcium Channel Blockers explode all trees in MeSH products
#11 MeSH descriptor Diuretics explode all trees in MeSH products
#12 MeSH descriptor Anticholesteremic Agents explode all trees in MeSH products
#13 MeSH descriptor Dietary Fats explode all trees in MeSH products
#14 MeSH descriptor Hydroxymethylglutaryl-CoA Reductase Inhibitors explode all trees in MeSH products
#15 MeSH descriptor Antilipemic Agents explode all trees in MeSH products
#16 MeSH descriptor Hypoglycemic Agents explode all trees in MeSH products
#17 MeSH descriptor Exercise explode all trees in MeSH products
#18 MeSH descriptor Diet explode all trees in MeSH products
#19 MeSH descriptor Diet Therapy explode all trees in MeSH products
#20 MeSH descriptor Weight Loss explode all trees in MeSH products
#21 MeSH descriptor Complementary Therapies explode all trees in MeSH products
#22 lipid-lowering or cholesterol-lowering in All Fields or (lipid or cholesterol) and (lowering or reduc*) in All Fields or antidiabetic* or hypoglycemic* in Author, from 1800 to 2005 in all products
#23 (#7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18 OR (# AND 21) OR #20 OR #21 OR #22)
#24 MeSH descriptor Hyperlipidemia explode all trees with qualifier: DT in MeSH products
#25 MeSH descriptor Hypertension explode all trees with qualifier: DT in MeSH products
#26 MeSH descriptor Diabetes Mellitus, Type 2 explode all trees with qualifier: DT in MeSH products
#27 MeSH descriptor Albuminuria explode all trees with qualifier: DT in MeSH products
#28 MeSH descriptor Cardiomegaly explode all trees with qualifier: DT in MeSH products
#29 (#24 OR #25 OR #26 OR #27 OR #28)
#30 (#6 AND #23 AND #29)
#31 risk* or outcome or risk factors or risk assessment or treatment outcome in All Fields in all products
#32 (#30 AND #31)

Medikamentelle tiltak

MEDLINE

1. exp hyperlipidemia/dt or exp hypertension/dt or exp diabetes mellitus, type 2/dt or Albuminuria/dt or exp Cardiomegaly/dt
2. Antihypertensive Agents/
3. Adrenergic beta-Antagonists/

4. Angiotensin-Converting Enzyme Inhibitors/
5. Calcium Channel Blockers/
6. exp Diuretics/
7. Anticholesteremic Agents/
8. Hydroxymethylglutaryl-CoA Reductase Inhibitors/
9. Antilipemic Agents/
10. statin$1.tw.
11. ((lipid-lowering or (lipid adj lowering) or cholesterol-lowering or (cholesterol adj lowering)) and (agent$1 or drug$1)).tw.
12. Hypoglycemic Agents/
13. ((Antidiabetic or Hypoglycemic$1) and (drug$1 or agent$1)).tw.
14. Platelet Aggregation Inhibitors/
15. aspirin/
16. or/2-15
17. 16 and tu.fs.
18. 1 and 17
19. Cardiovascular Diseases/
20. Heart Diseases/ or Heart Arrest/
21. Heart Failure, Congestive/ or exp Angina Pectoris/
22. Coronary Disease/
23. Myocardial Ischemia/ or Myocardial Infarction/ or Shock, Cardiogenic/ or exp Myocardial Revascularization/
24. Cerebrovascular Disorders/
25. Cerebrovascular Accident/
26. Cerebral Hemorrhage/ or Brain Ischemia/ or Intracranial Hemorrhage/ or Cerebral Hemorrhage/
27. exp Brain Infarction/ or exp Cerebral Arterial Disease/ or exp "Intracranial Embolism and Thrombosis"/ or exp Cerebral Infarction/
28. Death/ or Death, Sudden/
29. or/19-28
30. or/19-28
31. 18 and 30
32. randomized controlled trial.pt.
33. Randomized Controlled Trials/
34. Random Allocation/
35. Double-Blind Method/
36. Single-Blind Method/
37. clinical trial.pt.
38. exp clinical trials/ or intervention studies/ or (intervention$ adj (stud$4 or trial$1)).tw.
39. (clinic$ adj trial$1).tw.
40. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
41. PLACEBOS/

42. placebo$.tw.
43. randomly allocated.tw.
44. random$.tw.
45. or/32-44
46. case report.tw.
47. (letter or editorial).pt.
48. historical article.pt.
49. review of reported cases.pt.
50. review, multicase.pt. or review.sh. or review.pt.
51. animal/
52. human/
53. 51 not (51 and 52)
54. or/46-50,53
55. 45 not 54
56. Meta-analysis/
57. meta analy$.tw.
58. metaanaly$.tw.
59. meta analysis.pt.
60. (systematic adj (review$1 or overview$1)).tw.
61. cochrane.tw. or 1469-493x.is.
62. or/56-61
63. 31 and 55
64. 31 and 62
65. 63 or 64

Alternative tiltak

MEDLINE

1. Exercise/ or Diet/ or Diet, Reducing/ or Weight Loss/ or Smoking cessation/
2. (physical adj activity).tw.
3. Complementary Therapies/
4. ((complementary or alternative) and (therap$3 or medicine)).tw.
5. or/1-4
6. Cardiovascular Diseases/
7. Heart Diseases/ or Heart Arrest/
8. Heart Failure, Congestive/ or exp Angina Pectoris/
9. Coronary Disease/
10. Myocardial Ischemia/ or Myocardial Infarction/ or Shock, Cardiogenic/ or exp Myocardial Revascularization/
11. Cerebrovascular Disorders/
12. Cerebrovascular Accident/
13. Cerebral Hemorrhage/ or Brain Ischemia/ or Intracranial Hemorrhage/ or Cerebral Hemorrhage/

14. exp Brain Infarction/ or exp Cerebral Arterial Disease/ or exp "Intracranial Embolism and Thrombosis"/ or exp Cerebral Infarction/
15. Death/ or Death, Sudden/
16. or/6-15
17. pc.fs. or (prevent$ or prophyla$).tw.
18. 16 and 17
19. 5 and 18
20. randomized controlled trial.pt.
21. Randomized Controlled Trials/
22. Random Allocation/
23. Double-Blind Method/
24. Single-Blind Method/
25. clinical trial.pt.
26. exp clinical trials/ or intervention studies/ or (intervention$ adj (stud$4 or trial$1)).tw.
27. (clinic$ adj trial$1).tw.
28. ((singl$ or doubl$ or treb$ or tripl$) adj (blind$3 or mask$3)).tw.
29. PLACEBOS/
30. placebo$.tw.
31. randomly allocated.tw.
32. (allocated adj2 random).tw.
33. or/20-32
34. case report.tw.
35. (letter or editorial).pt.
36. historical article.pt.
37. review of reported cases.pt.
38. review, multicase.pt. or review.sh. or review.pt.
39. animal/
40. human/
41. 39 not (39 and 40)
42. or/34-38,41
43. 33 not 42
44. Meta-analysis/
45. meta analy$.tw.
46. metaanaly$.tw.
47. meta analysis.pt.
48. (systematic adj (review$1 or overview$1)).tw.
49. cochrane.tw. or 1469-493x.is.
50. or/44-49
51. 19 and 43
52. 19 and 50
53. 51 or 52

Medikamentelle tiltak

EMBASE

1. exp Hyperlipidemia/dt or exp Hypertension/dt or exp Hypercholesterolemia/dt or exp Non Insulin Dependent Diabetes Mellitus/dt or Albuminuria/dt or Cardiomegaly/dt
2. Antihypertensive Agent/
3. Adrenergic beta-Antagonists/
4. Angiotensin-Converting Enzyme Inhibitors/
5. Calcium Channel Blockers/
6. exp Diuretics/
7. Anticholesteremic Agents/
8. Hydroxymethylglutaryl Coenzyme a Reductase Inhibitor/
9. Antilipemic Agents/
10. statin$1.tw.
11. ((lipid-lowering or (lipid adj lowering) or cholesterol-lowering or (cholesterol adj lowering)) and (agent$1 or drug$1)).tw.
12. Hypoglycemic Agent/
13. ((Antidiabetic or Hypoglycemic$1) and (drug$1 or agent$1)).tw.
14. Platelet Aggregation Inhibitors/
15. aspirin/
16. or/2-15
17. 16 and dt.fs.
18. 1 and 17
19. Cardiovascular Diseases/
20. Heart Diseases/ or Heart Arrest/
21. Heart Failure, Congestive/ or exp Angina Pectoris/
22. Coronary disease/
23. Myocardial Ischemia/ or Myocardial Infarction/ or Shock, Cardiogenic/ or exp Myocardial Revascularization/
24. Cerebrovascular Disease/
25. Cerebrovascular Accident/
26. Cerebral Hemorrhage/ or Brain Ischemia/ or Intracranial Hemorrhage/ or Intracranial Aneurysm/
27. exp Brain Infarction/ or exp Cerebral Arterial Disease/ or exp "Intracranial Embolism and Thrombosis"/ or exp Cerebral Infarction/
28. Death/ or Death, Sudden/
29. or/19-28
30. 18 and 29
31. Clinical Trial/
32. Randomized Controlled Trial/
33. Randomization/
34. Double Blind Procedure/

35. Single Blind Procedure/
36. Crossover Procedure/
37. Placebo/ or intervention studies/ or (intervention$ adj (stud$4 or trial$1)).tw.
38. placebo$.tw.
39. randomi?ed controlled trial$.tw.
40. rct.tw.
41. random allocation.tw.
42. randomly allocated.tw.
43. allocated randomly.tw.
44. (allocated adj2 random).tw.
45. single blind$.tw.
46. double blind$.tw.
47. ((treble or triple) adj blind$).tw.
48. Prospective study/
49. or/31-48
50. Case study/
51. case report.tw. or review$.mp.
52. Abstract report/
53. Letter/ or Editorial/
54. Human/
55. Nonhuman/
56. ANIMAL/
57. Animal Experiment/
58. 55 or 56 or 57
59. 58 not (58 and 54)
60. or/50-53,59
61. 49 not 60
62. Meta-analysis/
63. meta analy$.tw.
64. metaanaly$.tw.
65. Systematic Review/
66. (systematic adj (review$1 or overview$1)).tw.
67. Cochrane Library/ or cochrane.tw. or 1469-493x.is.
68. or/62-67
69. 30 and 61
70. 30 and 68
71. 69 or 70
72. 71 and risk.mp.

Alternative tiltak

EMBASE

1. Exercise/ or Diet/ or Diet, Reducing/ or Weight Loss/ or Smoking cessation/ or Weight Reduction/
2. (physical adj activity).tw.
3. Complementary Therapies/
4. ((complementary or alternative) and (therap$3 or medicine)).tw.
5. or/1-4
6. Cardiovascular Diseases/
7. Heart Diseases/ or Heart Arrest/
8. Heart Failure, Congestive/ or exp Angina Pectoris/
9. Coronary Disease/
10. Myocardial Ischemia/ or Myocardial Infarction/ or Shock, Cardiogenic/ or exp Myocardial Revascularization/
11. Cerebrovascular Disorders/
12. Cerebrovascular Accident/
13. Cerebral Hemorrhage/ or Brain Ischemia/ or Intracranial Hemorrhage/ or Cerebral Hemorrhage/
14. exp Brain Infarction/ or exp Cerebral Arterial Disease/ or exp "Intracranial Embolism and Thrombosis"/ or exp Cerebral Infarction/
15. Death/ or Death, Sudden/
16. or/6-15
17. pc.fs.
18. 16 and 17
19. 5 and 18
20. Clinical Trial/
21. Randomized Controlled Trial/
22. Randomization/
23. Double Blind Procedure/
24. Double Blind Procedure/
25. Crossover Procedure/
26. Placebo/ or intervention studies/ or (intervention$ adj (stud$4 or trial$1)).tw.
27. placebo$.tw.
28. randomi?ed controlled trial$.tw.
29. rct.tw.
30. random allocation.tw.
31. randomly allocated.tw.
32. allocated randomly.tw.
33. (allocated adj2 random).tw.
34. single blind$.tw.
35. double blind$.tw.
36. ((treble or triple) adj blind$).tw.
37. ((treble or triple) adj blind$).tw.
38. or/20-37

39. Case study/
40. case report.tw. or review$.mp.
41. Abstract report/
42. Abstract report/
43. Human/
44. Nonhuman/
45. ANIMAL/
46. Animal Experiment/
47. 44 or 45 or 46
48. 47 not (43 and 47)
49. or/39-42,48
50. 38 not 49
51. Meta-analysis/
52. meta analy$.tw.
53. metaanaly$.tw.
54. Systematic Review/
55. (systematic adj (review$1 or overview$1)).tw.
56. Cochrane Library/ or cochrane.tw. or 1469-493x.is.
57. or/51-56
58. 19 and 50
59. 19 and 57
60. 58 or 59
61. 60 and risk$.mp.

Medikamentelle og alternative tiltak

AMED

1. exp heart disease/
2. exp cerebrovascular disorders/
3. exp cerebral hemorrhage/ or exp cerebral infarction/ or exp cerebral ischemia/
4. death/ or death, sudden/
5. or/1-4
6. exp Antihypertensive Agents/
7. exp adrenergic beta receptor blockaders/
8. (Enzyme inhibitors/ and angiotensin.tw.) or ACE.tw.
9. exp Calcium Channel Blockers/
10. exp Diuretics/
11. exp dietary fats/
12. statin$1.tw.
13. ((lipid or cholesterol) and (lowering or reduc$)).tw.
14. (lipid-lowering or cholesterol-lowering).tw.
15. (antidiabetic$ or antiglycemic$).tw.
16. exp exercise/ or exp physical fitness/

17. exp physical education/ or exp physical endurance/
18. (physical adj activit$).tw.
19. exp diet/ or exp diet therapy/
20. exp diet reducing/
21. exp weight loss/
22. exp smoking/ or exp smoking cessation/
23. exp Risk/ or risk$3.tw. or Treatment Outcome/
24. exp prevention/ or prevent$ pr prophyla$.tw.
25. or/1-4
26. or/6-22
27. 23 and 24
28. 25 and 26 and 27
29. exp random allocation/
30. randomized controlled trials/
31. (random$ or rct).tw.
32. or/29-31
33. 28 and 31
34. 25 and 26 and 32

Vedlegg 2

PRIMÆRFOREBYGGING AV HJERTE- OG KARSYKDOM (KUNNSKAPSSENTERETS RAPPORT NR 20-2008)

SJEKKLISTE FOR RANDOMISERTE KONTROLLERTE FORSØK

		JA UKLART NEI
1	Er pasientene fordelt tilfeldig (randomisert) til intervensjon og kontroll?	
2	Er randomiseringen skjult (consealed random allocation)?	
3	Er pasienter og behandlere uvitende (blindet) med hensyn til hvem som fikk behandling?	
4	Er den som vurderte resultatet og evt. analyserte dataene uvitende (blindet) om hvilken behandling pasientene fikk?	
5	Er kjente konfunderende faktorer likt fordelt mellom intervensjon og kontroll?	
6	Er gruppene behandlet likt utenom intervensjonen?	
7	Er det gjort rede for alle pasientene som inngikk i forsøket og er de analysert ut fra sin opprinnelige gruppe (intention-to-treat)?	

Kvalitetsvurdering

De inkluderte studiene rangeres i forhold til tre kvalitetsklasser basert på en total vurdering av studiekvalitet og resultatenes validitet etter sjekkliste for den aktuelle studiedesign og eventuell egen statistisk vurdering.

Tabell 9. Rangering i kvalitetsklasser (i forhold til studier med tilsvarende design)	
Rang	**Kriterier**
++	Høy kvalitet/validitet. Brukes hvis alle eller de fleste kriteriene fra sjekklisten er oppfylt. Selv om noen av kriteriene ikke er oppfylt, må det være *veldig lite* sannsynlig at studiens eller oversiktens beviskraft påvirkes.
+	Middels kvalitet/validitet. Brukes hvis noen av kriteriene fra sjekklisten ikke er oppfylt og/eller der studien/oversikten ikke er adekvat beskrevet. Samlet vurdering tilsier at det er *lite* sannsynlig at studiens eller oversiktens beviskraft påvirkes.
-	Lav kvalitet/validitet. Brukes hvis få eller ingen av kriteriene fra sjekklisten er oppfylt og/eller der studien/oversikten er mangelfull beskrevet. Samlet vurdering tilsier at det er *høyst* sannsynlighet at studiens eller oversiktens beviskraft påvirkes.

Bare studier rangert til høy (++) og middels kvalitetsklasse (+) har beviskraft "god nok" til å kunne besvare eller belyse metodens kliniske effekt og utgjør således dokumentasjonsgrunnlaget i metodevurderingen. Studier rangert til lav kvalitetsklasse (-) har uakseptabel metodologisk kvalitet og for svak beviskraft til å inngå som dokumentasjonsgrunnlag i samlesyntesen.

Studiens evidensnivå:_____+(-)_____

Referanse: Harbour R, Miller J for the Scottish Intercollegiate Guidelines Network Grading Review Group. A new system for grading recommendations in evidence based guidelines. BMJ 2001;323;334-6.

Vedlegg 3

PRIMÆRFOREBYGGING AV HJERTE- OG KARSYKDOM (KUNNSKAPSSENTERETS RAPPORT NR 20-2008)

EVIDENSTABELLER (EVIDENCE-TABLES)

The tables are presented in the same order as in the main report's chapter "Resultater".

Intervention	Study, year of publication, referance number (main references)
Antitrombotics (6 studies)	BMDS 1988 (1), USPHS 1989 (2), TPT 1998 (3), HOT 1998 (4), PPP 2001 (5) , WHS (6)
Lipid lowering drugs (12 studies)	Dorr 1977 (7), LRC-CPPT 1986 (8), HHS 1987 (9), WOSCOPS 1995 (10), AFCAPS/TexCAPS 1998 (11), PROSPER 2002 (12), ALLHAT-LLT 2002 (13), ASCOT-LLA 2003 (14), CARDS 2004 (15), FIELD 2005 (16), MEGA 2006 (17), HPS 2007 (18)
Antihypertensives (43 studies)	Drug versus placebo: VA 1 1967 (19), VA 2 1970 (20), USPHSHCS 1977 (21), VA-NHLBI 1978 (22), Oslo Hypertension Study 1980 (23), ANBP 1 1980 (24), EWPHE 1985 (25), IPPPSH 1985 (26), Coope 1986 (27), MRC 1 1985 (28, 29), SHEP pilot 1989 (30), MRC 2 1992 (31), STOP 1 1991 (32), SHEP 1991 (33), SYST-EUR 1997 (34), Sun 1997 (35), HYVET-pilot 2003 (36), SCOPE 2003 (37), JIKEI 2007 (38), HYVET 2008 (39) Drug versus drug: HAPPHY 1987 (40), MRC 1 1985 (28, 29), MRC 2 1992 (31), CAPPP 1999 (41), STOP 2 1999 (42), ALLHAT 2000/2002 (43, 44), NORDIL 2000 (45), INSIGHT 2000 (46), CONVINCE 2003 (47), LIFE 2002 (48), ANBP 2 2003 (49), SHELL 2003 (50), HYVET-pilot 2003 (36), VALUE 2004 (51), ASCOT-BPLA 2005 (52), CASE-J 2008 (53) Drug versus placebo among persons with diabetes SHEP (subgroup) 1996 (54), SYST-EUR (subgroup) 2003 (55), RENAAL 2001 (56), IDNT 2001 (57, 58), DIAB-HYCAR 2004 (59), ADVANCE 2007 (60), DREAM 2006 (participants had impaired glucose tolerance) (61) Drug versus drug among persons with diabetes: STOP-2 (subgroup) 2000 (62), NORDIL 2000 (subanalysis) (45), CAPPP (subgroup) 2001 (63), LIFE (subgroup) 2002 (64), INSIGHT (subgroup) 2003 (65), UKDPS 39 1998 (66), FACET 1998 (67), ABCD 2000 (68), IDNT 2001 (57, 58), DETAIL 2004 (69)
Glucose lowering drugs (5)	Persons with lowered glucose-tolerance: STOP-NIDDM 2003 (70), DREAM 2006 (71) Type 2 diabetes: UKPDS 33 1998 (72), UKPDS 34 1998 (73), RECORD 2007 (74)
Multifactorial interventions (6 studies)	Oslo study 1981 (75), HDFP 1984 (76-78), Finnish businessmen 1985 (79, 80), MRFIT 1986 (81-83), Diabetes intervention study 1991 (84), Steno-2 2003 (85)
Food supplements (2 studies)	PPP 2001 (5), JELIS 2007 (86)

Antithrombotic drugs

BMDS 1988 (1), USPHS 1989 (2), TPT 1998 (3), HOT 1998 (4), PPP 2001 (5) , WHS (6):

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Peto, 1988, BMDS (1)
	Setting	General practice
	Country	UK
	Aim (as described in the article)	Whether 500 mg aspirin daily would reduce the incidence of and mortality from stroke, myocardial infarction, or other vascular conditions.
	Study design	RCT
	Inclusion period (year start-year end)	1978-84
	Mean follow-up (year)	6y
Intervention	Drug (pharmaceutical) in treatment arms	Aspirin
	Initial drug dose	500 mg (or 300 mg)
	Actual usage	
Population characteristics	Mean age	
	Age range	Up to age 79y
	Sex	M
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Diabetes 2%
	Concomittant medication	
	N intervention	3429
	N control	1710
	N excluded	
	N lost to follow-up	Stopped treatment: Treatment gr. 670 (19.5%), Control gr. 30 (1.8%) All were followed up for endpoints
	Discontinuance (n, percent)	24.8% (after 5 years)
	Crossover (n, percent)	
Method	Criteria for inclusion	Male british doctors residing in the UK in1978, born after 1900 who had answered a questionnaire in 1951 as part of another study, and were still listed in the 1977 Medical Directory

	Criteria for exclusion	Already on aspirin, contra indications, history of peptic ulcer, stroke or definite MI		
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Log rank		
	Power calculation description			
Results	Primary endpoint of study	Definite myocardial infarction or stroke; fatal		
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Event rates per 10000		
	Adverse events Bleed, not cerebral Peptic ulcer	Placebo 7 (0.41%) 28 (1.64%)	Aspirin 20 (0.58%) 88 (2.57%)	P-value Not significant < 0.05

Events	Control	Aspirin
	N= 1710	N= 3429
Total mortality	151	270
Nonfatal MI	45	102
Fatal MI	47	89
Nonfatal stroke	27	61
Fatal stroke	12	30

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Steering committee of USPHS, 1989, USPHS (2)
	Setting	GP
	Country	USA
	Aim (as described in the article)	To determine whether low-dose aspirin (325 mg every other day) decreases cardiovascular mortality. The other component of this study was to study betacarotene and its prevention of cancer.
	Study design	RCT, double blind, placebo controlled in a two-by-two factorial design
	Inclusion period (year start-year end)	Early termination of aspirin component of trial on December 18, 1987
	Mean follow-up (year)	60.2 months (range 45.8-77.0)
Intervention	Drug (pharmaceutical) in treatment	Aspirin

	arms			
	Initial drug dose	325 mg every other day		
	Actual usage	Aspirin 85.71%: placebo 14.23%		
Population characteristics	Mean age			
	Age range	40-84y		
	Sex	Men only		
	Ethnicity (frequency)			
	Comorbidity (frequency CVD, diabetes)			
	Concomittant medication			
	N intervention	11037		
	N control	11034		
	N excluded			
	N lost to follow-up	0.03% morbidity information		
	Discontinuance (n, percent)			
	Crossover (n, percent)			
Method	Criteria for inclusion	US physicians, 40-84y		
	Criteria for exclusion	History of MI, stroke or TIA, Cancer (except non-melanoma skin cancer), current liver or renal disease, peptic ulcer, or gout, contraindication to aspirin, current use of aspirin, other platelet-active drugs, non-steroidal inflammatory agents, current use of Vitamin A supplement.		
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)			
	Power calculation description			
Results	Primary endpoint of study	MI and stroke		
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RR		
	Adverse events	Placebo	Aspirin	P-value
	Upper gastrointestinal ulcers	138 (1.3%)	169 (1.5%)	0.08
	Bleeding problems	2248 (20.4%)	2979 (27.0%)	<0.0001
	Melena	246 (2.2%)	364 (3.3%)	<0.00001
	Transfusion	28 (0.25%)	48 (0.43%)	0.02
	Death from gastrointestinal hemorrhage	0	1 (0.009%)	-

Events	Placebo	Aspirin
	N= 11034	N= 11037
Total mortality	227	217

Nonfatal MI	213	129
Fatal MI	26	10
Nonfatal stroke	92	110
Fatal stroke	6	9

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	The Medical Research Council's General Pratice Research Framework : TPT (Thrombosis Prevention Trial), 1998 (3)
	Setting	General Practice
	Country	UK
	Aim (as described in the article)	To evaluate low intensity oral anticoagulation with warfarin and low-dose aspirin in the primary prevention of ischaemic heart disease
	Study design	RCT, multicenter, factorial
	Inclusion period (year start-year end)	1983-89 non-factorial 1989-92 factorial
	Mean follow-up (year)	Median 6.8y
Intervention	Drug (pharmaceutical) in treatment arms	Warfarin Aspirin 75 mg
	Initial drug dose	Warfarin dose according to INR
	Actual usage	
Population characteristics	Mean age	57
	Age range	45-69
	Sex	Men
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intervention	Aspirin= 2545, Warfarin = 2762
	N control	No aspirin = 2540, no warfarin = 2737
	N excluded	
	N lost to follow-up	1.1%
	Discontinuance (n, percent)	751 of active aspirin and active warfarin; 735 of active warfarin and placebo aspirin;

		735 of placebo warfarin and active aspirin; 748 of placebo warfarin and placebo aspirin			
	Crossover (n, percent)				
Method	Criteria for inclusion	Top 20-25% risk score in each practice			
	Criteria for exclusion	History of peptic ulceration, MI or stroke, contraindications for treatment			
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Log rank test; rates per 1000 person years			
	Power calculation description	Yes			
Results	Primary endpoint of study	All ischaemic heart disease = combined coronary death and fatal and nonfatal MI			
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	% proportional reduction			
	Adverse effects	Placebo	Aspirin	Warfarin	Asprin + Warfarin
	Major gastro-intestinal bleed	2 (0.16%)	6 (0.47%)	9 (0.71%)	9 (0.70%) 1 (0.08%)
	Fatal	1 (0.08%)	0	2 (0.16%)*	
	Intermediate gastrointestinal bleed	8 (0.63%)	16 (1.26%)	7 (0.55%)	9 (0.70%)

Events	Placebo	Aspirin
	N= 1272	N= 1268
Total mortality	110	113
Nonfatal MI	73	47
All MI	107	83
All stroke	26	18

Events	Placebo	Warfarin
	N= 1272	N= 1268
Total mortality	110	95
Nonfatal MI	73	64
All MI	107	83

All stroke	26	22

Events	Placebo	Warfarin+Aspirin
	N= 1272	N= 1277
Total mortality	110	103
Nonfatal MI	73	47
All MI	107	71
All stroke	26	29

* p <0.05

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Hansson, 2002, HOT (4)*
	Setting	Multi center, international study
	Country	26 countries Europe, N- and S-America, Asia
	Aim (as described in the article)	Find out whether 75 mg ASA once daily reduces the rate of major CV events without excess bleeding complications, especially stroke.
	Study design	RCT
	Inclusion period (year start-year end)	1992-1994
	Mean follow-up (year)	3.8 yrs (3.3-4.9)
Intervention	Drug (pharmaceutical) in treatment arms	75 mg aspirin (Bamycor) vs. placebo (5 mg felodipine for blood pressure red.) – at the end 78% on felodipine, 41% on ACE-inhibitor and 28% on beta-blocker
	Initial drug dose	75 mg
	Actual usage	78% compliance
Population characteristics	Mean age	61.5
	Age range	50-80
	Sex	53% M
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	1501 (8%) diabetes mellitus, 3080 (16.4%) ischaemic heart disease

	Concomittant medication			
	N intervention	9399		
	N control	9391		
	N excluded			
	N lost to follow-up	491 (2.6%) – 245 on aspirin, 246 on placebo		
	Discontinuance (n, percent)			
	Crossover (n, percent)			
Method	Criteria for inclusion	Diastolic BP 100-115 mmHg		
	Criteria for exclusion	Contraindication to aspirin		
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox proportional hazard model,		
	Power calculation description			
Results	Primary endpoint of study	Major cardiovascular events, myocardial infarction, fatal and non-fatal major bleeding		
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RR, NNT and NNH		
	Adverse effects	Placebo	Aspirin	P-value
	Fatal bleeds	8 (0.09%)	7 (0.07%)	Not significant
	Gastrointestinal	3 (0.03%)	5 (0.05%)	Not significant
	Non-fatal major bleeds	70 (0.75%)	129 (1.37%)	<0.001
	Gastrointestinal	34 (0.36%)	72 (0.77%)	Not reported

Events	Placebo	Aspirin
	N= 9391	N= 9399
Total mortality	305	284
Major cardiovascular events	368	315
All MI	127	82
All stroke	148	146
CHD mortality	140	133

*Data used for gender-specific analyses were taken from a meta-analysis by Berger et al (87)

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +

Study description	Author, year, study name	PPP group, 2001, PPP (5)
	Setting	General practice + hospital hypertension units (5.3%)
	Country	Italy
	Aim (as described in the article)	To investigate in general practice the effiCCBy of antiplatelets and antioxidants in primary prevention of cardiovascular events in people with one or more major cardiovascular risk factor
	Study design	Randomised, open, 2x2 factorial
	Inclusion period (year start-year end)	1994-98
	Mean follow-up (year)	3.6
Intervention	Drug (pharmaceutical) in treatment arms	Aspirin (ASA) 100 mg [Vitamin E]
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	65.4
	Age range	50-80+ (?)
	Sex	M 43%, F 57%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intervention	2226 (aspirin)
	N control	2269
	N excluded	
	N lost to follow-up	31
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Age equal or more than 65, one or more major risk factors (SBP >160, DBP > 95, total cholesterol > 6.4, diabetes, obesity BMI>30kg/m2, family history of MI before 55 in at least one parent or sibling)
	Criteria for exclusion	Treatment with antiplatelet therapy, chronic use of anti-inflammatory agents or anticoagulants, contra indications to aspirin, poor short term prognosis, predictable psychological or logistical difficulties
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox
	Power calculation description	Alfa 0.05, 1-beta= 90%

Results	Primary endpoint of study	Combined: CVDeath, nonfatal MI, nonfatal stroke		
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RR		
	Adverse effects ("severe and unexpected non-fatal events")	Placebo	Aspirin	P-value
	Bleeding	6 (0.26%)	24 (1.08%)	0.0008
	Gastrointestinal	5 (0.22%)	17 (0.76%)	Not reported

Events	No aspirin	Aspirin
	N= 2269	N= 2226
Total mortality	78	62
Nonfatal MI	22	15
All MI	28	19
Nonfatal stroke	18	15
All stroke	24	16
Revascularizations	29	20
Angina	67	54

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Ridker, 2005, Women's Health Study (WHS) (6)
	Setting	
	Country	USA
	Aim (as described in the article)	To see if aspirin decreased the risk of a first MI in women. WHS also included a study arm on the effect of vitamin E.
	Study design	A prospective randomised controlled trial.
	Inclusion period (year start-year end)	1992-1995.
	Mean follow-up (year)	10 years
Intervention	Drug (pharmaceutical) in treatment arms	Aspirin versus placebo
	Initial drug dose	100 mg on alternate days
	Actual usage	

Population characteristics	Mean age	54.6 / 54.6 (placebo)		
	Age range			
	Sex	W		
	Ethnicity (frequency)			
	Comorbidity (frequency CVD, diabetes)	No CVD		
	Concomittant medication			
	N intervention	19,934		
	N control	19,942		
	N excluded			
	N lost to follow-up			
	Discontinuance (n, percent)			
	Crossover (n, percent)			
Method	Criteria for inclusion	Women, 45y or older, no history of CHD or cerbrovascular disease, , cancer, or other major illness, no history of sideeffects to study medication, did not take other drugs NSADS, anticoaculants, corticosteroids, vitamin supplements(A, E or beta carotene) more than once a week		
	Criteria for exclusion			
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox		
	Power calculation description			
Results	Primary endpoint of study	Combination of major CVD, including nonfatal MI, nonfatal stroke, and death from CVD.		
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	HR, event rates		
	Adverse events	Placebo	Aspirin	P-value
	Any gastrointestinal bleeding	751 (3.8%)	910 (4.6%)	<0.001
	Requiring transfusion	91 (0.5%)	127 (0.6%)	0.02
	Peptic ulcer	413 (2.1%)	542 (2.7%)	<0.001

Events	Placebo	Aspirin
	N= 19942	N= 19934
Total mortality	642	609
Major CVD event	522	477
Stroke	266	221
MI	193	198

CVD death	126	120
Revascularization	374	389

Lipid-lowering drugs

Dorr 1977 (7), LRC-CPPT 1986 (8), HHS 1987 (9), WOSCOPS 1995 (10), AFCAPS/TexCAPS 1998 (11), PROSPER 2002 (12), ALLHAT-LLT 2002 (13), ASCOT-LLA 2003 (14), CARDS 2004 (15), FIELD 2005 (16), MEGA 2006 (17), HPS 2007 (18):

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Dorr et al., 1978, Dorr (7)
	Setting	108 clinics
	Country	The United States
	Aim (as described in the article)	To determine the effect of colestipol in hypercholesterolemic patients on serum cholesterol.
	Study design	Randomised controlled study
	Inclusion period (year start-year end)	1969-1972
	Mean follow-up (year)	3 years
Intervention	Drug (pharmaceutical) in treatment arms	5 g colestipol HCl x 3/day
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	50 y (male), 57 y (female)
	Age range	18 y and above.
	Sex	1094 men, 1184 women
	Ethnicity (frequency)	14% men non-white, 24% women non-white
	Comorbidity (frequency CVD, diabetes)	Diabetes 13% men and 18% women Coronary heart disease 31% men and 21% women Cerebrovascular accident 0,5% men and 0, 5% women
	Concomittant medication	Fore some patients: Insulin, antihypertensives, antidysrhythmics, oral hypoglycemics, diuretics, cornary artery dilators, steroid or nonsteroid antiinflammatory agents: Range <1%-11.1% for any of these drugs
	N intervention	1149
	N control	1129
	N excluded	
	N lost to follow-up	38.1%
	Discontinuance (n, percent)	
	Crossover (n, percent)	

Method	Criteria for inclusion	Patient had to be at least 18 years and to have had at least two of three biweekly fasting serum cholesterol concentrations greater than 250 mg/dl during the 6 week period before randomisation.
	Criteria for exclusion	Women of childbearing potential, patients who had received steroides, other hormones, anticoagulants, or lipid-lowering agents and patients with hypothyroidism, or hepatic, renal or haematologic disease.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Life table; Z-test
	Power calculation description	
Results	Primary endpoint of study	Total and cause specific mortality
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	GI disorders as hiatal hernia, duodenal ulcer, appendicitis not significantly different between groups. Cholelithiasis, cholecystitis, or cholecystectomy : Active gr: 7; placebo 6.

Events	Placebo	Colestipol
	N= 546	N= 548
Total mortality	27	17
Death all CVD	24	11
Death from CHD	22	9

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Rifkind, 1986, LRC-CPPT (8)
	Setting	
	Country	USA
	Aim (as described in the article)	Testing the effiCCBy of cholesterol lowering in reducing CHD in asymptomatic primary hypercholesterolemia
	Study design	Randomised, double-blind, placebo controlled
	Inclusion period (year start-year end)	Initated in 1973
	Mean follow-up (year)	Minimum 7 years
Intervention	Drug (pharmaceutical) in treatment arms	Cholestyramine
	Initial drug dose	24 grams

	Actual usage	
Population characteristics	Mean age	47.9 - 47.6
	Age range	35 -59
	Sex	Male
	Ethnicity (frequency)	NA
	Comorbidity (frequency CVD, diabetes)	None
	Concomittant medication	
	N intervention	1900
	N control	1906
	N excluded	NA
	N lost to follow-up	NA
	Discontinuance (n, percent)	NA
	Crossover (n, percent)	NA
Method	Criteria for inclusion	Total cholesterol > 265 mg/dl
	Criteria for exclusion	NA
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	NA
	Power calculation description	NA
Results	Primary endpoint of study	Coronary heart disease death and/or definitive non-fatal MI
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	% reduction
	Adverse effects	Cholestyramine group: High prevalence of abdominal discomfort, cramps, flatulence and constipation. These diminished with time and were handled with simple clinical measures.

Events	Placebo	Cholestyramine
	N= 1900	N= 1906
Primary endpoint: definite CHD and/or nonfatal MI	187	155

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Frick HM, 1987, HHS (9)
	Setting	37 clinics. Participants were employed by the Finnish postal

		services, telecommunications agency, the Finnish State Railway and five industrial companies in Finland.
	Country	Finland
	Aim (as described in the article)	To test the effiCCBy of simultaneously elevating serum levels of high-density lipoprotein (HDL) cholesterol and lowering levels of non-HDL cholesterol with gemfibrozil in reducing the risk of coronary heart disease in middle-aged men.
	Study design	Randomised controlled trial
	Inclusion period (year start-year end)	1981-1982
	Mean follow-up (year)	5 years
Intervention	Drug (pharmaceutical) in treatment arms	600 mg gemfibrozil twice daily
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	47.2 years
	Age range	43.5- 51 years
	Sex	Men
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Hypertension 14%, Diabetes 2.4% in treatment group and 2.9% in placebo group.
	Concomittant medication	
	N intervention	2051
	N control	2030
	N excluded	713
	N lost to follow-up	None
	Discontinuance (n, percent)	70.1%
	Crossover (n, percent)	
Method	Criteria for inclusion	Asymptomatic men 40-55 years with primary dyslipidemia (non-HDL cholesterol >200 mg/DL). This criterion had to be met in two successive measurements.
	Criteria for exclusion	Subjects were excluded if they had any clinical manifestations of coronary heart disease or electrocardiographic abnormalities, congestive heart failure, or any other disease that could have an influence on the study outcome.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	
	Power calculation description	
Results	Primary endpoint of study	Fatal and nonfatal myocardial infarction and cardiac death

	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Rate per 1000
	Adverse events	Gemfibrozil: Several GI side effects. Increased biliary cholesterol saturation in healthy persons which may cause more gallstones.

Events	Placebo	Gemfibrozil
	N= 2030	N= 2051
Nonfatal MI	71	45
Fatal MI	8	6
Sudden cardiac death	4	5
Total mortality	42	45

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Shepperd, 1995, WOSCOPS (10)
	Setting	Primary care/population based
	Country	West Scotland
	Aim (as described in the article)	To determine whether the administration of pravastatin to men with hypercholesterolemia and no history of myocardial infarction reduced the combined incidence of nonfatal myocardial infarction and death from coronary heart disease
	Study design	Randomised, double blind
	Inclusion period (year start-year end)	1989-95
	Mean follow-up (year)	4.9
Intervention	Drug (pharmaceutical) in treatment arms	Pravastatin
	Initial drug dose	40 mg evening
	Actual usage	-
Population characteristics	Mean age	55.2
	Age range	45-64
	Sex	M
	Ethnicity (frequency)	Not given (Caucasian)
	Comorbidity (frequency CVD, diabetes)	Angina: 5% Intermittent claudicatio: 3%

		Diabetes: 1% Minor ECG abnorm 8%
	Concomittant medication	-
	N intervention	3302
	N control	3293
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	30.8 – 29.6% (at year 5)
	Crossover (n, percent)	
Method	Criteria for inclusion	First visit nonfasting s-cholesterol: 6.5 and above Fasting LDL >4.5-6.0, no serious ECG abnormalities
	Criteria for exclusion	History of myocardial infarction, serious ECG abnormalities
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Kaplan Meier
	Power calculation description	
Results	Primary endpoint of study	Combined: nonfatal myocardial infarction or death from coronary heart disease
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RR, Risk reduction
	Adverse effects	Cancer Pravastatin 116; placebo 106 Myalgia Pravastatin 20; placebo 19 Muscle aches Pravastatin 97; placebo 102 > aspartate aminotransferase 26 / 20 > alanine aminotransferase 16 / 12

Events	Placebo	Pravastatin
	N= 3293	N= 3302
Total mortality	135	106
Nonfatal MI or death from CHD	248	174
Death all cardiovascular causes	73	50
Nonfatal MI	204	143
Death from CHD	61	41
Fatal or nonfatal stroke	51	46
Revascularizations	80	51

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Downs, 1998, AFCAPS / TexCAPS (11)
	Setting	Outpatient clinic in Texas.
	Country	The United States.
	Aim (as described in the article)	To compare lovastatin with placebo for prevention of the first acute major coronary event in men and women without clinically evident atherosclerotic cardiovascular disease and with average total cholesterol (TC) and LDL-C levels and below-average high-density lipoprotein cholesterol (HDL-C) levels.
	Study design	A randomised, double-blind, placebo-controlled trial.
	Inclusion period (year start-year end)	1990-1993
	Mean follow-up (year)	5.2 y range 0.2-7.2y
Intervention	Drug (pharmaceutical) in treatment arms	Lovastatin 20-40 mg/day
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	
	Age range	Men aged 45-73, women aged 55-73
	Sex	2805 men and 499 women in intervention group, and 2803 men and 498 women in placebo group.
	Ethnicity (frequency)	White 89%, Black 3%, Hispanic 7% in both groups.
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intervention	3304
	N control	3301
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	1%
	Crossover (n, percent)	
Method	Criteria for inclusion	Men aged 45 to 73 years and postmenopausal women aged 55 to 73 years who met the lipid criteria (TC, 4.65-6.82 mmol/L; LDL-L 3.36-4.91 mmol/L, HDL-C<- 1.16 mmol/L for men or <-1.22 mmol/L for women; and triglycerides <- 4.52 mmol/L were to be

		met at both 4 and 2 weeks prior to randomisation, with less than 15% difference in LDL-C values. In addition, participants with LDL-C values between 3.23 and 3.34 mmol/L were included when the ratio of TC to HDL-C was more than 6.0.
	Criteria for exclusion	History or symptoms of definite myocardial infarction, angina, claudication, cerebrovascular accident, or transient ischemic attack. In addition, cases of uncontrolled hypertension, secondary hyperlipidemia, or type 1 or type 2 diabetes mellitus were not included.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox
	Power calculation description	Yes
Results	Primary endpoint of study	First acute major coronary event defined as fatal or nonfatal myocardial infarction, unstable angina, or sudden cardiac death
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RR
	Adverse effects	No cases of myopathy, 3 cases of rhabdomyolysis (2 in placebo gr.)

Events	Placebo	Lovastatin
	N= 3301	N= 3304
Primary endpoint: fatal or nonfatal MI, unstable angina or sudden cardiac death	183	116
Mortality		
All MI	95	57
All CVD	255	194
All CHD	215	163
Unstable angina	87	60
Revascularizations	157	106
Fatal CVD	25	17
Fatal CHD	15	11

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +

Study description	Author, year, study name	Shepherd, PROSPER 2002 (12)
	Setting	University hospital
	Country	Scotland, Ireland, Netherlands
	Aim (as described in the article)	To test the benefits of pravastatin treatment in an elderly cohort of men and women with or at high risk of developing cardiovascular disease and stroke
	Study design	Randomised controlled trial
	Inclusion period (year start-year end)	19971999
	Mean follow-up (year)	3.2y
Intervention	Drug (pharmaceutical) in treatment arms	Pravastatin versus placebo
	Initial drug dose	40 mg per day
	Actual usage	
Population characteristics	Mean age	Placebo: 75,3 (3.4); pravastatin 75.4 (3.3)
	Age range	70-82y
	Sex	Men, placebo: 48.3%, pravastatin 48.3%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	History of vascular disease: placebo: 43.2%, pravastatin 45.2% History of MI/stroke: placebo: 13.7/11.0%, pravastatin 13.0/11.3%
	Concomittant medication	
	N intervention	2891
	N control	2913
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Men and women, aged 70-82y, had pre-existing vascular disease (coronar, cerebral, or peripheral) or raised risk of such disease due to smoking, hypertension, or diabetes.
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Kaplan, Meier
	Power calculation description	
Results	Primary endpoint of study	Combined endpoint of definite or suspect death from coronary heart disease, non-fatal MI, and fatal or non-fatal stroke assessed in the entire cohort.

	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse effects	Serious events: Pravastatin 56%, placebo 55%. No cases of rhabdomyolysis. Myalgia: pravastatin 36, placebo 32.

Events	Placebo	Pravastatin
	N= 2913	N= 2891
Coronary heart disease death or non-fatal Mi	356	292
Fatal or non-fatal strokee	131	135
PTCA and coronary by-pass	48	39
Heart failure hospitalisation	122	112
All cause mortality	306	298

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Allhat Collaborative Research Group, 2002, ALLHAT-LLT (13)
	Setting	513 primarily community-based North American clinical centres
	Country	North America
	Aim (as described in the article)	To determine whether pravastin compared with usual care reduces all cause mortality in older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor.
	Study design	Randomised, non-blinded trial.
	Inclusion period (year start-year end)	1994 through March 2002.
	Mean follow-up (year)	4.8 years
Intervention	Drug (pharmaceutical) in treatment arms	Pravastatin versus usual care
	Initial drug dose	Pravastatin 20-40 mg/dL
	Actual usage	
Population characteristics	Mean age	66.4y
	Age range	Above 55y
	Sex	49% women
	Ethnicity (frequency)	38% black and 23% Hispanic

	Comorbidity (frequency CVD, diabetes)	14% had a history of CHD and 35% had type 2 diabetes.
	Concomittant medication	
	N intervention	5170
	N control	5185
	N excluded	
	N lost to follow-up	98 in the intervention group, 108 in the control group
	Discontinuance (n, percent)	15 refused follow up in intervention group and 31 control group
	Crossover (n, percent)	
Method	Criteria for inclusion	Prior enrollment in ALLHAT (age over 55 years and stage 1 or 2 hypertension with at least 1 additional CHD risk factor).
	Criteria for exclusion	Participants who currently received lipid-lowering therapy, or large doses of niacin, probucol in last year, or where known to be intolerant of statins or have significant liver or kidney disease, or had other contraindictions for statin therapy.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Kaplan Meier and Cox
	Power calculation description	A revised sample size was estimated to provide 84% power to detect a 20% reduction in mortality.
Results	Primary endpoint of study	To determine whether pravastatin compared with usual care reduces all-cause mortality in older, moderately hypercholesterolemic, hypertensive participants with at least 1 additional CHD risk factor
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Log rank test, Hazard ratio
	Adverse effects	

Events	Usual care	Pravastatin
	N= 5185	N= 5170
Total mortality	641	631
CVD deaths	300	295
Fatal CHD and nonfatal MI	421	380
Stroke, all	231	209
Heart failure; hospitalised or death	248	243
CHD death	162	160

Quality	Study quality rating (according to check list)

assessment by the review group	High / ++	
Study description	Author, year, study name	Sever, 2003, ASCOT-LLA (14)
	Setting	Family practices
	Country	UK, Sweden, Island, Denmark, Norway
	Aim (as described in the article)	To assess the benefit of cholesterol lowering in the primary prevention of CHD in hypertensive patients who are not conventionally deemed dyslipidaemic
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	Median 3.3y. Planned for 5y but stopped early.
Intervention	Drug (pharmaceutical) in treatment arms	Atorvastatin versus placebo
	Initial drug dose	10 mg/day
	Actual usage	
Population characteristics	Mean age	A: 63.1y, P: 63.2y
	Age range	
	Sex	Women – A:18.9%, P: 18.7%
	Ethnicity (frequency)	White: A:94.6%, P: 94.7%
	Comorbidity (frequency CVD, diabetes)	Stroke: A:9.4%, P: 10.0% LVH: A:14.4%, P: 14.2% Diabetes: A: 24.3%, P: 24.8%
	Concomittant medication	
	N intervention	1258
	N control	1274
	N excluded	
	N lost to follow-up	7 / 10
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	ASCOT main inclusion criteria: 40-79y, hypertension. Three of the following factors: type 2 diabetes, male >55 y, microalbuminuria or proteinuria, smoking, ratio of plasma cholesterol to HDL cholesterol >6, premature family history of CHD, LVH, other specified anomaly on ECG, PAD, previous stroke or TIA. Total cholesterol <6.5 mmol/l
	Criteria for exclusion	Previous MI, curren treated angina, a cerebrovascular event last 3 months, fasting triglyseride >4.5mmol/l, heart failure, uncontrolled arythmia, or any other clinically important abnormality.

	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Kaplan Meier
	Power calculation description	Yes
Results	Primary endpoint of study	Combined endpoint of nonfatal MI, including so-called silent MI, and fatal CHD
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse effects	No significant differences between groups on liver-enzyme abnormalities. One non-fatal case of rhabomyolysis (atorvaststin)

Events	Placebo	Atorvastatin
	N= 5137	N= 5168
Primary endpoint: nonfatal MI and fatal CHD	154	100
Total mortality	212	185
CVD deaths	82	74
Stroke, all	121	89
Heart failure; fatal and nonfatal	36	41
Unstable angina	24	21
Stable angina	56	33
Development of diabetes	134	154
Development of renal impairement	24	31

Quality assessment by the review group	Study quality rating (according to check list) High /++	
Study description	Author, year, study name	Colhoun, 2004, CARDS (15)
	Setting	132 centers
	Country	UK and Ireland
	Aim (as described in the article)	Primary prevention of cardiovascular disease with atorvastatin in type 2 diabetes versus placebo
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	3.9y. Terminated 2 years before scheduled.
Intervention	Drug (pharmaceutical) in	Atorvastatin

	treatment arms	Additional drugs allowed while unaware of treatment allocation.
	Initial drug dose	10mg/d
	Actual usage	
Population characteristics	Mean age	Atorvastatin: 61,5y, placebo 61.8y
	Age range	
	Sex	Women: 32%/32%
	Ethnicity (frequency)	White: 95%/94%
	Comorbidity (frequency CVD, diabetes)	No documented previous history of CVD
	Concomittant medication	
	N intervention	1428
	N control	1410
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	A 9%, P 10%
	Crossover (n, percent)	
Method	Criteria for inclusion	40-75y, type 2 diabetes, one of the following: hypertension, retinopathy, maculopathy or previous photocoagulation, microalbuminuria or macroalbuminuria, current smoker
	Criteria for exclusion	Documented previous history of MI, angina, coronary vascular surgery, cerebrovascular event, or severe PAD.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Linear mixed model
	Power calculation description	Yes
Results	Primary endpoint of study	Time to first: acute coronary heart disease, coronary revacularization, or stroke
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio
	Adverse events	One or more serious events. A 19 /1.1%, P 20 /1.1% Cancer deaths: A: 20; P: 30. Cardiovascular deaths A 36 / 2.5%, P 45 /3.2%

Events	Placebo	Atorvastatin
	N= 1410	N= 1428
Total mortality	82	61
MI	77	51
Stroke	39	21

Revascularization	34	24
Unstable angina	9	7

Quality assessment by the review group	Study quality rating (according to check list) High (++)	
Study description	Author, year, study name	Keech 2005, FIELD-study (16)
	Setting	63 “centres”
	Country	Australia, New Zealand, Finland
	Aim (as described in the article)	To assess the effects on coronary morbidity and mortality of long-term treatment with fenofibrate to raise HDL-cholesterol concentrations and lower triglyceride levels in patients with type 2 diabetes and total blood cholesterol concentrations of less than 6.5 mmol/L.
	Study design	RCT
	Inclusion period (year start-year end)	1998-2000
	Mean follow-up (year)	5 years (median)
Intervention	Drug (pharmaceutical) in treatment arms	Fenofibrate Placebo
	Initial drug dose	200 mg
	Actual usage	20% had discontinued at end of study.
Population characteristics	Mean age	62 years
	Age range	50-75 years
	Sex	63% male
	Ethnicity (frequency)	93% white
	Comorbidity (frequency CVD, diabetes)	22% previous cardiovascular disease
	Concomittant medication	32% antithrombotics 35% ACE-inhibitors 20% CCBs 16% diuretics 74% antidiabetic medication
	N intervention	4895
	N control	4900
	N excluded	None after randomisation (4105 before randomisation)
	N lost to follow-up	Treatment group: 12 Placebo group: 10

	Discontinuance (n, percent)	Treatment: 20% Placebo: 19%
	Crossover (n, percent)	Not reported (but very few)
Method	Criteria for inclusion	Type 2 diabetes and aged 50-75 years. individuals had an initial plasma total-cholesterol concentration of between 3·0 mmol/L and 6·5 mmol/L, plus either a total-cholesterol/HDL-cholesterol ratio of 4·0 or more or a plasma triglyceride concentration of between 1·0 mmol/L and 5·0 mmol/L, with no clear indication for, or treatment with, lipid-modifying therapy at study entry.
	Criteria for exclusion	Renal impairment (blood creatinine >130 mol/L), known chronic liver disease or symptomatic gallbladder disease, and a cardiovascular event within the 3 months before recruitment.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox proportional hazards modelling to compute HRs
	Power calculation description	Yes
Results	Primary endpoint of study	Coronary heart disease events (coronary heart disease death plus non-fatal myocardial infarction)
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	HRs with 95% CIs
	Adverse events	DVT P: 48 / F: 67 Pulmonary embolism P: 32 / F: 53 Pancreatitis P: 23 / F: 40

Events	Placebo	Fenofibrate
	N= 4900	N=4895
All cause mortality	323	356
MI	288	256
CVD death	127	140
Stroke	175	158
Revascularizations (coronary)	364	290

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Nakamura, 2006, MEGA (17)
	Setting	

	Country	Japan
	Aim (as described in the article)	To assess whether evidence for treatment with statins derived from western populations can be extrapolated to the Japanese population.
	Study design	A prospective randomised controlled trial.
	Inclusion period (year start-year end)	1994-1999.
	Mean follow-up (year)	5.3 years
Intervention	Drug (pharmaceutical) in treatment arms	Diet plus 10-20 mg pravastatin/day
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	58
	Age range	40-70 years
	Sex	69% women in placebo group and 68% in intervention group
	Ethnicity (frequency)	Asian
	Comorbidity (frequency CVD, diabetes)	21% diabetes in both groups
	Concomittant medication	
	N intervention	3866
	N control	3966
	N excluded	
	N lost to follow-up	60 (in placebo group) and 42 (in intervention group)
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Men and postmenopausal women aged 40-70 years with a bodyweight of 40 kg or more and hypercholesterolaemia (total cholesterol 5.69-6.98 mmol/L) and were included.
	Criteria for exclusion	Familial hypercholesterolaemia and history of coronary heart disease or stroke
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Kaplan Meier, Cox
	Power calculation description	
Results	Primary endpoint of study	Incidence of CHD including fatal and nonfatal MI, angina, coronary and sudden death and revascularisation.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	

Adverse events	No difference regards cancer, non-cardiovascular deaths or serious events.. No cases of rhabdomyolysis.	
Events	Diet	Diet + pravastatin
	N= 3966	N= 3866
Total mortality	79	55
CHD	101	66
All MI	33	17
Fatal MI	3	2
Nonfatal MI	30	16
Angina	57	46
Revascularization	66	39
Stroke	62	50
All CVD	172	125

Quality assessment by the review group	Study quality rating (according to check list) High / +	
Study description	Author, year, study name	Heart Protection Study Collaborative Group, 2007, HPS (18)
	Setting	
	Country	UK
	Aim (as described in the article)	To assess the effects of a substantial LDL cholesterol reduction maintained for several years in a cohort of diabetic individuals. (We decided to utilize data from this subgroup of participants in the study since we considered this to be the most relevant available findings in light of our "primary prevention" mandate. In the whole study around 2/3 of the particpants had CVD at baseline, while this was the case for only around half of the participants in the diabetes subgroup.)
	Study design	A prospective randomised controlled trial.
	Inclusion period (year start-year end)	July 1994 to May 1997 Total included: 20,536; 5,963 with diabetes
	Mean follow-up (year)	5y
Intervention	Drug (pharmaceutical) in treatment arms	Simvastatin
	Initial drug dose	40 mg

	Actual usage	
Population characteristics	Mean age	62y
	Age range	
	Sex	70% men
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	19% prior MI, 14% other CHD, 18% other vascular.
	Concomittant medication	
	N intervention	2978
	N placebo	2985
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	Average statin use 85% intervention group; placebo group 17% took non-study statin
	Crossover (n, percent)	
Method	Criteria for inclusion	Men and women, 40-80y, nonfasting total cholesterol at least 3.5 mmol/L, had a medical history of coronary disease, PAD, cerebrovascular disease, diabetes, or treated hypertension (if also male and aged at least 65y. In this analysis we have only included participants that fulfilled the criteria for having diabetes.
	Criteria for exclusion	Their doctor considered statin therapy to be clearly indicated or contraindicated, or if they ha MI, stroke, or hospital admission for angina within previous 6 months; chronic liver disease or evidence of abnormal liver function; severe renal disease or evidence of substantially impaired renal function; inflammatory muscle disease or evidence of muscle problems; concurrent treatment with ciclosporin, fibrates, of high-dose niacin; child-bearing potential; severe heart failure; or other conditions htat might limit long-term compliance.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Logrank
	Power calculation description	
Results	Primary endpoint of study	Major vascular events = myocardial infarction, coronary death, stroke, or revascularization
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Event rate ratio
	Adverse events	Simvastatin 40 mg: well tolerated, no significant effect on liver enzymes or other adverse effects. Myopathy (muscle pain and/or weakness associated with an elevation in

		creatine kinase > x10 ULN) an estimated risk was calculated to about 1 in 10 000 patients per year with the 40 mg statin dosage used.
Events	Placebo	Simvastatin
	N= 2985	N= 2978
First major vascular event	748	601
Major coronary events	377	279
Strokes	193	149
Revacularisations	309	260

Blood pressure lowering drugs

Drug versus placebo:
VA 1 1967 (19), VA 2 1970 (20), USPHSHCS 1977 (21), VA-NHLBI 1978 (22), Oslo Hypertension Study 1980 (23), EWPHE 1985 (25), IPPPSH 1985 (26), ANBP 1 1980 (24), Coope 1986 (27), MRC 1 1985 (28, 29), SHEP pilot 1989 (30), MRC 2 1992 (31), STOP 1 1991 (32), SHEP 1991 (33), SYST-EUR 1997 (34), Sun 1997 (35), HYVET-pilot 2003 (36), SCOPE 2003 (37), JIKEI 2007 (38), HYVET 2008 (39)

Drug versus drug:
HAPPHY 1987 (40), MRC 1 1985 (28, 29), CAPPP 1999 (41), STOP 2 1999 (42), ALLHAT 2000/2002 (43, 44), NORDIL 2000 (45), INSIGHT 2000 (46), CONVINCE 2003 (47), LIFE 2002 (48), ANBP 2 2003 (49), SHELL 2003 (50), HYVET-pilot 2003 (36), VALUE 2004 (51), ASCOT-BPLA 2005 (52), CASE-J 2008 (53)

In patients with diabetes:
Drug versus placebo:
SHEP (subgroup) 1996 (54), SYST-EUR (subgroup) 2003 (55), RENAAL 2001 (56), IDNT 2001 (57, 58), DIAB-HYCAR 2004 (59), ADVANCE 2007 (60), DREAM 2006 (particiapants had impaired glucose tolerance) (61)

Drug versus drug:
STOP-2 (subgroup) 2000 (62), CAPPP (subgroup) 2001 (63), LIFE (subgroup) 2002 (64), INSIGHT (subgroup) 2003 (65), UKDPS 39 1998 (66), FACET 1998 (67), ABCD 2000 (68), DETAIL 2004 (69)

Drug versus placebo

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Veterans Administration Cooperative Study Group, 1967, VA 1 (19)
	Setting	Veteran's Hospital
	Country	USA
	Aim (as described in the article)	Effect of treatment on morbidity in hypertension in patients with diastolic blood pressure 115 through 129 mmHg
	Study design	Double blind randomised
	Inclusion period (year start-year end)	1964-1967
	Mean follow-up (year)	Ca 1.5

Intervention	Drug (pharmaceutical) in treatment arms	Hydroclorthiazide + reserpine + hydralazine hydrochloride
	Initial drug dose	100 mg + 0,2 mg + 150 mg
	Actual usage	-
Population characteristics	Mean age	51 y
	Age range	30-73
	Sex	M
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Prior thrombosis 11/143 LVH 46/143 Diabetes 13/143
	Concomittant medication	-
	N intervention	70
	N control	73
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	12 (8%)
	Crossover (n, percent)	
Method	Criteria for inclusion	Diastolic BP 115-129 mmHg
	Criteria for exclusion	BP outside study range or signs of accelerated hypertension, surgically curable hypertension, uremia, carcinoma, history of cerebral or subarachnoidal haemorrhages, dissecting aneurism or congestive heart failure
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Chi-square
	Power calculation description	
Results	Primary endpoint of study	Benefit of treating mild hypertension
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Severe headache or weakness. No cases of lupus erythematosus.

Events	Placebo	Clorthalidone + reserpine
	N = 70	N= 73
Total mortality	4	0
Myocardial infarction	2	0
Stroke	3	1

Angina pectoris	Not reported	Not reported
Heart failure	2	0
Total incidence of mortality and morbidity	27	2

Quality assessment by the review group	**Study quality rating (according to check list)** **High / ++**	
Study description	Author, year, study name	Veterans Administration Cooperative Study Group, 1970, VA 2 (20)
	Setting	Veteran's Hospital
	Country	USA
	Aim (as described in the article)	Effect of treatment on morbidity in hypertension in patients with diastolic blood pressure averaging 90 through 115 mmHg
	Study design	Double blind randomised
	Inclusion period (year start-year end)	1964-68
	Mean follow-up (year)	3.3 years for control group; 3.2 for exp. group
Intervention	Drug (pharmaceutical) in treatment arms	Hydroclorthiazide + reserpine + hydralazine hydrochloride
	Initial drug dose	50 mg + 0,1 mg + 25 mg
	Actual usage	-
Population characteristics	Mean age	52.4 / 50.5 (control /treatment groups)
	Age range	
	Sex	M
	Ethnicity (frequency)	Other 114/109; Black 81/76
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	-
	N intervention	194
	N control	186
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	15%

	Crossover (n, percent)		
Method	Criteria for inclusion	Diastolic BP 90-114 mmHg	
	Criteria for exclusion	BP outside study range and other causes as signs of accelerated hypertension, surgically curable hypertension, uremia, carcinoma, history of cerebral or subarachnoidal haemorrhages, dissecting aneurism or congestive heart failure	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Chi-square	
	Power calculation description		
Results	Primary endpoint of study	Benefit of treating mild hypertension	
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)		
	Adverse events	15 complained of side effects prior to drop out. (9 on active drugs)	

Events	Placebo	Clorthalidone + reserpine
	N = 194	N= 186
Total mortality	21	10
CVD mortality	19	8
Myocardial infarction	13	11
Stroke	20	5
Heart failure	11	0
Angina	Not reported	Not reported

Quality assessment by the review group	**Study quality rating (according to check list)** **Moderate / +**	
Study description	Author, year, study name	McFate Smith, 1977, USPHSHCS (21)
	Setting	Six health clinics
	Country	USA
	Aim (as described in the article)	To determine whether pressure lowering reduces the incidence of cardiovascular complications and death.
	Study design	RCT
	Inclusion period (year start-year end)	

	Mean follow-up (year)	7	
Intervention	Drug (pharmaceutical) in treatment arms	Chlorthiazide and rauwolfia	
	Initial drug dose	Chlorthiazide 500 mg/day Rauwolfia 100 mg/day	
	Actual usage		
Population characteristics	Mean age	44y	
	Age range		
	Sex	20% women	
	Ethnicity (frequency)	28% non-whites	
	Comorbidity (frequency CVD, diabetes)		
	Concomittant medication		
	N intervention	193	
	N control	196	
	N excluded		
	N lost to follow-up	75 persons	
	Discontinuance (n, percent)	33.9% drop-outs over 7 y. No difference between groups	
	Crossover (n, percent)		
Method	Criteria for inclusion	Up to age 55y, mean DBP over 6 weeks 90-114 mmHg	
	Criteria for exclusion	Diabetes mellitus, renal insufficiency, hypercholesterolemia (>350mg/dl), abnormal ECG, radiograph cardiomegaly, grade III or IV retinopathy, clinical history of previous arterial thrombosis or vascular insuffciency whether coronary, cerebral or peripheral, congestive heart failure, angina, valvular heart disease, secondary or correctable hypertension, known sensitivity to intervention agents.	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Sequential and life table analysis	
	Power calculation description	Yes	
Results	Primary endpoint of study	Cardiovascular complictions and death	
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)		
	Adverse events		
Events		Placebo	Clorthiazide + Rauwolfia
		N = 196	N= 193
Total mortality		4	2

Myocardial infarction	18	15
Stroke	6	1
Heart failure	2	0
Angina pectoris	Not reported	Not reported

Quality assessment by the review group	**Study quality rating (according to check list)** **High / ++**	
Study description	Author, year, study name	Perry, 1978, VA-NHLBI feasibility trial (22)
	Setting	Veteran's Hospital
	Country	USA
	Aim (as described in the article)	Not described (Title: "Effect of treatment on morbidity in hypertension")
	Study design	Double blind randomised
	Inclusion period (year start-year end)	1964-1967
	Mean follow-up (year)	2 y
Intervention	Drug (pharmaceutical) in treatment arms	Step 1:50 mg chlorthalidone Step21:100 mg chlorthalidone Step 3: same + 0.25mg reserpine
	Initial drug dose	
	Actual usage	-
Population characteristics	Mean age	
	Age range	21-50
	Sex	M+W
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	-
	N intervention	508
	N control	504
	N excluded	
	N lost to follow-up	68 active gr., 78 placebo gr.
	Discontinuance (n, percent)	8.4%

	Crossover (n, percent)	
Method	Criteria for inclusion	Diastolic BP 90-120 mmHg
	Criteria for exclusion	No CVD renal complications, willingness to cooperate
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	
	Power calculation description	
Results	Primary endpoint of study	Benefit of treating mild hypertension
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Morbid and drop out events not statistically significant. Symptomatic side effects were twice as frequentt in active group as placebo. All cases of hypokalemia and hyperuricemia in active group.

Events	Placebo	Clorthalidone + reserpine
	N = 504	N= 508
Total mortality	0	2
Myocardial infarction	5	8
Stroke	0	0
Heart failure	Not reported	Not reported
Angina pectoris	Not reported	Not reported
All CVD	13	25

Quality assessment by the review group	**Study quality rating (according to check list)** **Moderate / +**	
Study description	Author, year, study name	Helgeland, 1980, Oslo Hypertension study (23)
	Setting	Hospital, out-patient clinic
	Country	Norway
	Aim (as described in the article)	To see if drug treatment of borderline and mild hypertension in symptom-free middle-aged men could be maintained for several years without an invalidatingly high drop-out rate, and, if , if the reduction in the inidence of cardiovascular disease was of such

		and order as to justify the disadvantages for the participants and effort of the health system.
	Study design	Unblinded RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	5 ½ y
Intervention	Drug (pharmaceutical) in treatment arms	Hydrochlorothiazide 50 mg (+ methyldopa or propranolol) vs no treatment
	Initial drug dose	HCTZ 50 mg
	Actual usage	At 5 years: HCTZ alone 140 pat's; HCTZ+propranolol 100 pat's; HCTZ+methyldopa 80 pat's; other regimens 72 pat's; no drugs 3 pat's.
Population characteristics	Mean age	Intervention/control 45.3/45.2
	Age range	SD: 2.9/2.8
	Sex	All men
	Ethnicity (frequency)	Norwegians
	Comorbidity (frequency CVD, diabetes)	0%
	Concomittant medication	No psychopharmacological drugs
	N intervention	406
	N control	379
	N excluded	1544
	N lost to follow-up	13 (but all responded to questionnaire)
	Discontinuance (n, percent)	
	Crossover (n, percent)	1%/17%
Method	Criteria for inclusion	Age4-49, no previous cardiovascular disease No antihypertensive treatment No diabetes Syst BP >=150 and/or Diast BP >=95
	Criteria for exclusion	Retinopathia, renal disease, hepatic disease, psychosis, severe neurosis, regularly treated with psychopharmacological drugs, malignant disease, rheumatoid arthritis, endocrine disorder, obvious alcohol abuse and social misadjustmet, secondary hypertension, ECG changes at rest
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Chi square and t-tests
	Power calculation description	None reported
Results	Primary endpoint of study	Unclear (coronary events and cerebrovascular events?)
	Endpoints and effect estimate	Rates

	(RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	No serious drug-induced diseases. Low serum potassium level (<3,3 mmol/l) in 3.3% of thiazide treated subjects. One patient was diagnosed with diabetes. Dorwsiness and fatigue caused change in 415 receiving methyldopa to propranalol. After four years men reported fatigue, drowsiness, impotence and gout, most often in treated group. No difference for GI complaints, skin, nose, and throat symptoms.

Events	Control	Hydrochlorothiazide + methyldopa or propranalol
	N = 379	N= 406
All CVD events	34	25
Total mortality	9	10
Stroke	5	0
All CHD	13	20
Myocardial infarction	10	14
Heart failure	1	0
Angina pectoris	2	3

Quality assessment by the review group	**Study quality rating (according to check list)** **Moderate / +**	
Study description	Author, year, study name	The management committee, 1980, ANBP 1 (24)
	Setting	Four centres in Melbourne, Perth and Sydney. Participants recruited from screening centres in hospitals, public halls and a specially equipped bus.
	Country	Australia
	Aim (as described in the article)	No explicit statement
	Study design	Unblinded(?) RCT
	Inclusion period (year start-year end)	1973-79
	Mean follow-up (year)	4 years
Intervention	Drug (pharmaceutical) in treatment arms	Chlorothiazide 500 mg x 1 (increased to 500 mg x 2 and or a 2nd order drug, i.e. methlydopa, propranolol or pindolol) vs placebo

	Initial drug dose	(See above)
	Actual usage	Intervention group (N=1721): One drug: 492 Two drugs: 853 More than two: 314 Placebo group: Not reported
Population characteristics	Mean age	Intervention vs control 50.4 vs 50.4
	Age range	30 to 69 (both groups)
	Sex	1085/1721 vs 1085/1706 males
	Ethnicity (frequency)	"Australian (white) or European born"
	Comorbidity (frequency CVD, diabetes)	MI before 3 months: 6 vs 8
	Concomittant medication	Not reported
	N intervention	1721
	N control	1706
	N excluded	104 171 screened => 3931 randomised (504 of which fell in BP and were excluded) => 3427 included in "trial population"
	N lost to follow-up	42/1721 vs 46/1706
	Discontinuance (n, percent)	583/1721 vs 626/1706
	Crossover (n, percent)	Not reported
Method	Criteria for inclusion	95 < DBP < 110 and SBT < 200 (average of 4 measurements over two screening visits)
	Criteria for exclusion	Antihypertensive treatment past 3 months, Angina pectoris, MI past 3 months, Pregnancy, Taking oestrogene and rogresterone combination, Asthma, diabetes, gout, Primary cause of hypertension, Evidence of cerebrovascular disease, TIA, acute coronary insufficiency, angina pectoris, P-creatinine > 2 mg/dl Other serious complications of hypertension ECG evidence of myocardial ischemia Any potentially fatal disease Taking TCAs
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox
	Power calculation description	Yes
Results	Primary endpoint of study	Not clearly stated
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Rates
	Adverse events	Reasons for stopping in trial: Clinic withdrawal A 121, P 97 Subject withdrwal A 310, P 288

	Local doctor withdrawal A 110, P 195 Do not knw A 42, P 46	
Events	Placebo	Chlorothiazide and/or methlydopa, propranolol or pindolol
	N = 1706	N= 1721
Fatal CVD	18	8
Stroke	22	13
Total mortality	35	25
Myocaridal infarction	33	33
Heart failure	3	3
All CHD	109	98

Quality assessment by the review group	**Study quality rating (according to check list)** **High / ++**	
Study description	Author, year, study name	Amery, 1985, EWPHE (25)
	Setting	Not reported
	Country	Europe
	Aim (as described in the article)	To assess the effects of antihypertensive drug therapy in patients above the age of 60 years.
	Study design	Double blind, RCT
	Inclusion period (year start-year end)	1972-?
	Mean follow-up (year)	Intervention: 4.69 years Control: 4.63 years
Intervention	Drug (pharmaceutical) in treatment arms	Hydrochlorothiazide 25 mg and trimaterene 50 mg (doubled if needed, and methyldopa added, if needed) vs. placebo (placebo added if needed)
	Initial drug dose	See above
	Actual usage	Intervention group: 4% not taking diuretic 51% taking less than two capsules of diuretic per day 45% took two or more capusles of diuretic per day 65% not taking methyldopa

		Control group: Various dosages of placebo (specified in paper)
Population characteristics	Mean age	72±8 both groups
	Age range	See above
	Sex	Women: Intervention: 69.0% Control: 70.5%
	Ethnicity (frequency)	Not reported
	Comorbidity (frequency CVD, diabetes)	Intervention: 35% cardiovascular complications Control: 36% cardiovascular complications
	Concomittant medication	Not reported
	N intervention	416
	N control	424
	N excluded	Not reported
	N lost to follow-up	Intervention: 69/416 Control: 59/424
	Discontinuance (n, percent)	Intervention: 149/416 Control: 157/424
	Crossover (n, percent)	Not reported
Method	Criteria for inclusion	Age > 60 DBP 90 to 119 and SBP 160 to 239
	Criteria for exclusion	Curable causes for hypertension, Retinopathy grade 3 or 4, Congestive heart failure, History of cerebral or subarachnoid haemorrhage, Hepatitis, Chirrhosis, Gout, Malignancy, Diabetes mellitus requiring insulin
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Life-table analysis, Mantel cox estimates for significance testing
	Power calculation description	Not reported in main paper (possibly in ref no. 10 in paper)
Results	Primary endpoint of study	Not clearly stated
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard	Rates

	ratio 95% CI)	
	Adverse events	38 withdrew due to serious intercurrent illnesses (mainly neoplasms).

Events	Placebo	Hydrochlorothiazide + trimaterene
	N = 424	N= 416
All CVD death	93	67
Total mortality	149	135
Stroke death	31	21
Cardiac death	47	29

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author	IPPPSH Collaborative Group, 1985, IPPPSH (26)
	Setting	General practice and hospitale clinics
	Country	UK, Canada, Germany, Netherlands, Israel, Italy
	Aim (as described in the article)	To evaluate the effect of including oxprenolol in antihypertensive drug regimens.
	Study design	Double blind RCT
	Inclusion period (year start-year end)	1977-80
	Mean follow-up (year)	
Intervention	Drug (pharmaceutical) in treatment arms	Oxprenolol 160 mg (slow release) vs matching placebo (add on for both groups: increase of study medication, or other non-beta-blocker antyhypertensive drug added according to defined recommendations)
	Initial drug dose	See above
	Actual usage	Intervention group: 30% on study medication only 67% on diuretics 33% on sympatholytics and/or vasodilators Control group: 15% on study medication only 82% on diuretics 48% on sympatholytics and/or vasodilators
Population characteristics	Mean age	Men: 51.8 years Women: 52.7 years

	Age range	50 to 64
	Sex	Men: 3194/6357
	Ethnicity (frequency)	Not reported
	Comorbidity (frequency CVD, diabetes)	Without a history of MI, stroke or angina pectoris.
	Concomittant medication	
	N intervention	3185
	N control	3172
	N excluded	Patients rejected for study-participation not documented. 6708 enrolled => On blind examination of entry records, 351 were found to be ineligible, leaving 6357 who fulfilled the entry criteria
	N lost to follow-up	Intervention group: 20 Control group: 17
	Discontinuance (n, percent)	Intervention group: 771/3185 Control: 883/3172
	Crossover (n, percent)	0(?)
Method	Criteria for inclusion	40 to 64 years. DBP 100 to 125
	Criteria for exclusion	Evidence of MI or history of angina, Heart failure, Relevant cardiac valvular disease, AV block grades II and III or sick sinus syndrome, Bradycardia (<50 beats/minute), Intermittent claudication, Previous cerebrovascular accident, Insulin-dependant diabetes, Pregnancy, Obstructive airways disease or a history of bronchial asthma, renal, hepatic, gastrointestinal or any other severe disease making the patient unsuitable for a long-term study, Predictable lack of compliance.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	
	Power calculation description	Yes
Results	Primary endpoint of study	Sudden cardiac death and fatal or non-fatal definite myocardial infarction and cerebrovascular accidents
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Rates
	Adverse events	Doctor-elicited complaints (number of patients): Cold extremities: BB 114, non-BB 61 Bronchospasm/asthma BB 68, non-BB 62 Dyspnoea BB 232, non-BB 194 Heart failure BB 54, non-BB 51 Dyspepsia BB 366, non-BB 322 Bad dreams/nightmares BB 62, non-BB 52 Impotence and libido decrease BB 128, non-BB 159 Anxiety, depression, other emotional disorder BB 473, non-BB 560 Headache BB 829, non-BB 990 Dizziness BB 454, non-BB 491

		Patient self-assessment: Constipation BB 1097, non-BB 1015 Increased sweating BB 1553, non-BB 1453 Dry mouth BB 1329, non-BB 1453 Frequency of nocturia BB 1722, non-BB 1857 Fluttering and poundering in chest BB 1545, non-BB 1684
	Sub group analysis (sex, age, ethnicity)	Men and women analysed separately

Events	Placebo	Oxprenolol
	N = 3172	N= 3185
Stroke	46	45
Total mortality	114	108
MI (incl. sudden death)	107	98

Quality assessment by the review group	**Study quality rating (according to check list)** **Moderate / +**	
Study description	Author, year, study name	Coope et al, 1986, Coope (27)
	Setting	Primary care
	Country	UK
	Aim (as described in the article)	Whether treatment of hypertension in patients aged 60-79 reduced incidence of stroke or coronary disease or overall mortality
	Study design	Randomised trial, single blinded (not for outcomes)
	Inclusion period (year start-year end)	From 1978
	Mean follow-up (year)	4.4
Intervention	Drug (pharmaceutical) in treatment arms	Atenolol 100 mg Bendrofluazide 5 mg Evt. Methyldopa 500 mg
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	68.7
	Age range	60-79
	Sex	M/F

	Ethnicity (frequency)	Mostly Caucasian
	Comorbidity (frequency CVD, diabetes)	LVH 8-11% Cardiac enlargement (x-ray) 22-21%
	Concomittant medication	-
	N intervention	419
	N control	465
	N excluded	1871+1165 +302
	N lost to follow-up	-
	Discontinuance (n, percent)	-
	Crossover (n, percent)	-
Method	Criteria for inclusion	Hypertension
	Criteria for exclusion	Atrial fibrillation, AV block, ventricular failure, bronchial asthma, diabetes mellitus, or any serious concomitant disease
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	-
	Power calculation description	Not given
Results	Primary endpoint of study	Not defined (stroke)
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Rate ratio (95% CI)
	Adverse events	Moderate or severe side effects: Treatment gr /Control: Headaches T 18 mod/4 severe; C 17 mod/3 severe Tiredness T 47 mod 1 severe; C 45 mod/1 severe Breathlessness T 35 mod/11 severe; C 32 mod/5 severe Dizziness T 29 mod/5 severe; C 26 mod/4 severe Depression T 14 mod/2 severe; C 12 mod/0 severe Indigestion T 15 mod/ 5 severe; C 22 mod/5 severe Worries T 36 mod/ 4 severe ; C 36 mod/ 3 severe General illness T 24 mod/ 2 severe; C 19 mod/ 2 severe

Events	Control	Bendrofluozide and/or atenolol
	N = 465	N= 419
All CVD death	50	35
Total mortality	69	60
Stroke	39	20
Heart failure	36	22
Coronary attacks	38	35

Quality assessment by the review group	**Study quality rating (according to check list)** **Moderate / +**	
Study description	Author, year, study name	Medical research council working party, 1988 MRC 1 (28, 29)
	Setting	General practice
	Country	UK
	Aim (as described in the article)	The main aim was to determine whether drug treatment of mild hypertension (phase V diastolc pressure 90-109 mmHg) reduced the rate of stroke, of death due to hypertension, and of coronary events in men and women aged 35-64 y.
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	4.9
Intervention	Drug (pharmaceutical) in treatment arms	Bendrofluazide (n= 4297) and propranolol (n=4403) versus placebo (n=8654)
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	
	Age range	35-64y
	Sex	9048 men / 8306 women
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Ischaemic ECG: Bendrofluazide: 3.3%, propranalol 1.2%, placebo 2.2%
	Concomittant medication	
	N intervention	8700
	N placebo	8654
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Mild hypertension (DBP 90-109 mmHg)
	Criteria for exclusion	History of definite MI within last 3 months, angina, signs of cardiac failure, or ECG evidence of silent MI or left bundle branch block.
	Main statistical analysis (Logistic	Multiple logistic regression

	regression, Cox, Kaplan Meier, other)	
	Power calculation description	Yes
Results	Primary endpoint of study	Fatal and nonfatal coronary events. Fatal events were further split into sudden and not sudden death
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Results are given for both men and women together and separate.
	Adverse events	

Events	Placebo	Bendrofluozide or propranolol
	N = 8654	N= 8700
Total mortality	253	248
Stroke	109	60
Nonfatal coronary events	137	116
Fatal coronary	97	106
All CVD	352	286
CVD mortality	139	134

Quality assessment by the review group	**Study quality rating (according to check list)** **Moderate / +**	
Study description	Author, year, study name	Perry SHEP-PILOT 1989 (30)
	Setting	Five clinical centres
	Country	USA
	Aim (as described in the article)	A pilot study of the Systolic Hypertension in the Elderly Program (SHEP) to determine the effects of drug therpy for isolated systolic hypertension in the elderly for stroke and mortality
	Study design	Randomised controlled trial, double blind
	Inclusion period (year start-year end)	July 1981 – July 1982
	Mean follow-up (year)	34 months (range 29-42)
Intervention	Drug (pharmaceutical) in treatment arms	Chlorthalidone

	Initial drug dose	25 mg/day chlorthalidone
	Actual usage	
Population characteristics	Mean age	
	Age range	
	Sex	63% women
	Ethnicity (frequency)	18% nonwhite
	Comorbidity (frequency CVD, diabetes)	39% took antihypertensiva
	Concomittant medication	
	N intervention	443
	N placebo	108
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Age > 60y
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Intention-to-treat analysis, Kaplan Meier,
	Power calculation description	No (pilot study)
Results	Primary endpoint of study	Stroke
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Odds ratio
	Adverse events	No adverse effect on mood or cognition

Events	Placebo	Chlorthalidone
	N= 108	N= 443
Stroke	6	11
Myocardial infarction	4	15
Angina pectoris	3	8
Coronary artery surgery	0	1
Left ventricular failure	2	6
All CVD	10	26
Total mortality	7	32

Quality assessment by the review group	**Study quality rating (according to check list)** **Moderate / +**	
Study description	Author, year, study name	MRC working party, 1992, MRC 2 (31)
	Setting	General practices
	Country	UK
	Aim (as described in the article)	Establishing whether antihypertensive treatment in men and women aged 65-74 years reduces mortality and morbidity due to stroke and coronary heart disease and mortality from other causes
	Study design	Single blind RCT
	Inclusion period (year start-year end)	1982-87
	Mean follow-up (year)	5.8 years
Intervention	Drug (pharmaceutical) in treatment arms	Hydrochlorothiazide 25 mg + amiloride 2.5 mg (some early particpants were started on twice this dose) (add on: atenolol; nifedipine) vs atenolol 50 mg (add on : increase to 100 mg; hydrochlorothiazide; nifedipine) vs placebo
	Initial drug dose	See above
	Actual usage	Not reported
Population characteristics	Mean age	Men: 70.2 Women: 70.4
	Age range	65 to 74 years
	Sex	Men: 1836 of 4396
	Ethnicity (frequency)	Not reported
	Comorbidity (frequency CVD, diabetes)	Ischaemic ECG: Menn: Bendrofluazide: 18%, propranalol 17%, placebo 18% Kvinner: Bendrofluazide: 17%, propranalol 14%, placebo 15%
	Concomittant medication	Not reported
	N intervention	Hydrochlorothiazide: 1,081 Atenolol: 1,102
	N control	2,213
	N excluded	184,653 invitations for screening => 125,861 attended => 20,389 suitable repoeated BP measurement => 4,961 suitable for entry examination => 4,396 entered into main trial
	N lost to follow-up	About 25%
	Discontinuance (n, percent)	HCTZ group: 48%

		Atenolol group: 63% Placebo group: 53%
	Crossover (n, percent)	Not reported
Method	Criteria for inclusion	SBP 160 to 209; DBP<115
	Criteria for exclusion	Known or suspected secondary hypertension Taking antihypertensive drugs Cardiac failure or any other accepted indication for antihypertensive treatment Receiving treatment for angina pectoris History of MI or stroke within the preceding three months, Impaired renal function, Diabetes, Asthma, Any serious intervurrent disease including malignancy known to be present at the time of examination Serum potassium <3.4 or >5.0 mmol/l
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Not clearly stated
	Power calculation description	Yes
Results	Primary endpoint of study	Stroke Coronary heart disease Total mortality
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Rates
	Adverse events	Impaired glucose tolerance (D 6.9 /1000PY, P 2.7/1000 PY; gout 4.4 vs 0.1; skin disorder 3.9 vs 1.1; muscle cramp 5.2 vs 0.1; nausea 7.4 vs 1.1; dizziness 7.4 vs 1.2

Events	Placebo	Hydrochloro thiazide or atenolol
	N = 2213	N= 2183
All CVD events	309	258
Total mortality	315	301
Stroke	134	101
All coronary events	159	128
Fatal coronary	110	85
Nonfatal coronary events	49	43

Events	Placebo	Hydrochlorothiazide
	N = 2213	N= 1081

All CVD events	309	107
Total mortality	315	134
Stroke	134	45
All coronary events	159	48
Fatal coronary	110	33
Nonfatal coronary events	49	15

Events	Placebo	Atenolol
	N = 2213	N= 1102
All CVD events	309	151
Total mortality	315	167
Stroke	134	56
All coronary events	159	80
Fatal coronary	110	52
Nonfatal coronary events	49	28

Quality assessment by the review group	**Study quality rating (according to check list)** **High / ++**	
Study description	Author, year, study name	Dahlöf, 1991, STOP 1 (32)
	Setting	116 health centres
	Country	Sweden
	Aim (as described in the article)	To investigate whether the frequency of fatal and non-fatal stroke, fatal and non-fatal MI, and other cardiovascular death was affected by antihypertensive treatment in this age group (70 to 84 years).
	Study design	Double blind RCT
	Inclusion period (year start-year end)	1985 to 1990

	Mean follow-up (year)	2 years
Intervention	Drug (pharmaceutical) in treatment arms	Atenolol 50 mg or Hydrochlorothiazide 25 mg + amiloride 2.5 mg or metoprolol 100 mg or pindolol 5 mg vs placebo
	Initial drug dose	See above
	Actual usage	"Two-thirds of the actively treated patients received combined treatment"
Population characteristics	Mean age	75.7 years
	Age range	70 to 84 years
	Sex	Female: 63%
	Ethnicity (frequency)	Not reported
	Comorbidity (frequency CVD, diabetes)	Not reported (see exclusion criteria)
	Concomittant medication	Not reported
	N intervention	812
	N control	815
	N excluded	Not reported
	N lost to follow-up	None
	Discontinuance (n, percent)	Active drug: 16% Placebo group: 23%
	Crossover (n, percent)	Not reported
Method	Criteria for inclusion	70 to 84 years SBP 180 to 230 and DBP > 90 Or DBP 105 to 120
	Criteria for exclusion	Orthostatic hypotension Contraindications to any of the drugs MI or stroke in previous 12 months Angina pectoris requiring treatment with drugs other than glyceryl trinitrate Other severe incapacitating illnesses
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Mantel's test
	Power calculation description	Yes
Results	Primary endpoint of study	Stroke, MI, and other cardiovascular death
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Rates
	Adverse events	No unexpected, serious, or previously unknown side effects were evident

Events	Placebo	Diuretic and beta-blocker

	N = 815	N= 812
All MI	28	25
Total mortality	63	36
Heart failure	39	19
All stroke	53	29

Quality assessment by the review group	**Study quality rating (according to check list)** **High / ++**	
Study description	Author, year, study name	SHEP cooperative research group, 1991, SHEP (33)
	Setting	16 clinical centres
	Country	USA
	Aim (as described in the article)	The determination of whether antihypertensive drug treatment reduces risk of total stroke (nonfatal and fatal) in a multi-ethnic cohort of men and women aged 60 years or older with ISH. Subgroup analyses for: Age, sex, race, baseline SBP and whether on antihypertensive treatment at initial contact
	Study design	Double blind RCT
	Inclusion period (year start-year end)	1985-88
	Mean follow-up (year)	4.5 years
Intervention	Drug (pharmaceutical) in treatment arms	Chlorthalidone 12.5 mg vs placebo (Add on: doubling dose, atenolol/placebo, reserpine/placebo)
	Initial drug dose	See above
	Actual usage	90% in treatment group on active treatment throughout trial Majority in placebo group continued to receive no active medication throughout the trial
Population characteristics	Mean age	72 years
	Age range	
	Sex	57% women
	Ethnicity (frequency)	14% black
	Comorbidity (frequency CVD, diabetes)	History of stroke: 1.4% History of MI: 4.9% History of diabetes: 10.1%
	Concomittant medication	Not reported

	N intervention	2365
	N control	2371
	N excluded	447 291 screened =>11.6% met initial criteria => 2.7% completed baseline visit 1 => 70% of those eligible for visit 2 => 88% of those randomised
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	40-50% in placebo group
Method	Criteria for inclusion	SBP 160 to 219 and DBP < 90
	Criteria for exclusion	History and/or signs of specified cardiovascular diseases Other major diseases, e.g. cancer, alcoholic liver disease, established renal dysfunction Medical management problems
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Chi square, standard normal test, log rank test, proportional hazards regression
	Power calculation description	Yes
Results	Primary endpoint of study	Total stroke
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Rates
	Adverse events	Reported rates (%), active vs placebo groups: Faintness on standing: 12.8 vs 10.6 Feeling of unsteadiness or imbalance: 33.7 vs 32.9 Loss of consciousness/passing out: 2.2 vs 1.3 Heart beating fast or skipping beats: 7.2 vs 8.3 Heart beating unusually slowly: 3.8 vs 2.1 Chest pain or heaviness: 28.0 vs 21.3 Unusual shortness of breath: 11.9 vs 11.0 Unusual tiredness: 25.8 vs 23.8 Cold or numb hands: 13.6 vs 9.8 Ankle swelling: 19.5 vs 15.6 Unusual worry or anxiety: 25.5 vs 24.1 Trouble with memory/concentration: 26.4 vs 20.4 Depression that interfered with activities: 10.7 vs 10.6 Problems in sleeping: 26.4 vs 24.5 Nightmares: 4.2 vs 3.7 Problems in sexual function: 4.8 vs 3.2 Loss of appetite: 6.4 vs 5.5 Falls: 12.8 vs 10.4 Fractures: 2.4 v 2.0 Muscle wakness or cramping: 28.4 vs 25.9 Unusual indigestion: 10.3 vs 8.9 Change in bowel habits: 15.4 vs 11.4 Excessive thirst: 7.9 vs 6.4 Nausea or vomiting: 9.7 vs 8.2 Tarry black stools or red blood in stools: 2.2 vs 2.1

		Skin rash or bruising: 12.5 vs 10.6 Unusual joint pain: 36.4 vs 31.4 Severe headaches: 7.8 vs 8.7 Waking frequently at night to urinate: 14.4 vs 12.4 Any specified problem: 91.8 vs 86.4 Any speficied problem characterised as intolerable: 28.1 vs 20.8

Events	Placebo	Chlorthalidone
	N = 2371	N= 2365
All CVD	414	289
Total mortality	242	213
All stroke	163	106
All coronary events	184	140
Myocardial infarction (incl sudden and rapid deaths)	147	109
LVF	109	56
Revascularization	69	49

Quality assessment by the review group	**Study quality rating (according to check list)** **High / ++**	
Study description	Author, year, study name	Staessen, 1997, SYST-EUR (34)
	Setting	199 centres
	Country	Countries in East and West Europe
	Aim (as described in the article)	Risk reduction of cardiovascular events in elderly type 2 patients with isolated systolic hypertension by nitrendipine versus placebo
	Study design	RCT
	Inclusion period (year start-year end)	1990-1997. The trial was stopped in 1997
	Mean follow-up (year)	4y
Intervention	Drug (pharmaceutical) in treatment arms	Nitrendipine versus placebo
	Initial drug dose	10-40mg/day Additional treatment as necessary
	Actual usage	
Population	Mean age	Active/placebo: 70.3y / 70.2 y

characteristics	Age range	
	Sex	Women: 67.5% / 66.2%
	Ethnicity (frequency)	-
	Comorbidity (frequency CVD, diabetes)	All: Stroke 1.23%, MI 3.5%
	Concomittant medication	
	N intervention	2398
	N control	2297
	N excluded	
	N lost to follow-up	121/116
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	60y or older, diabetes, elevated blood pressureof SBP 160-219mmHg and DBP <95mmHg, no cardiovascular complications
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, log-rank test
	Power calculation description	Yes
Results	Primary endpoint of study	Stroke
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Non-cardiovascular events (all nonsignificant): Fatal and non-fatal cancer: P 14.7% (82) / A 12.4% (73) Benign neoplasms: P 3.0 (17) / A 4.0 (24) Intercurrent disease: P 31.4% (168) / A 33.1% (186) Bleeding: P 3.5% (20) / A 3.2% (19)

Events	Placebo	Nitrendipine
	N = 2297	N= 2398
All CVD	186	137
Total mortality	137	123
Myocardial infarction incl Sudden death	65	52
Fatal and nonfatal stroke	77	47
Heart failure nonfatal	43	29
Heart failure total	49	37

Renal failure	2	3

Quality assessment by the review group	**Study quality rating (according to check list)** **Moderate / +**	
Study description	Author, year, study name	Sun, 1997, Chinese study (35)
	Setting	15 medical teams cooperating
	Country	Hu Nan-provinsen, China
	Aim (as described in the article)	To test the effect of nitrendipine on lowering blood pressure to reduce stroke
	Study design	RCT, single blind
	Inclusion period (year start-year end)	
	Mean follow-up (year)	4.72y ±0.08y
Intervention	Drug (pharmaceutical) in treatment arms	Nitrendipine versus usual care
	Initial drug dose	10 mg, 3/d. As BP was reduced the dose was changed to 10 mg/d. If large sideeffects, medication could be changed to captopril.
	Actual usage	
Population characteristics	Mean age	51.8y ±0.11y
	Age range	
	Sex	1103 men and 977 women
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N nitrendipine	Group A: 1040
	N usual care	Group B: 1040
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Age>15y, SBP ≥160mmHg and /or DBP≥95mmHg

	Criteria for exclusion	Symptomatic hypertension, persons not able to cooperate, cor pulmonale, obvious problems with heart or kidneys, diabetes, MI last 6 months or stroke.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	U-test, Chi-square-test
	Power calculation description	Nei
Results	Primary endpoint of study	Stroke
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Headache : Group A 10.5%, Group B 14.6% Flush: Gr.A 6.5%, Gr B 1.8% Increased dreamactivity: Gr.A 3.0%, gr.B 3.8%

Events	Placebo	Nitrendipine
	N = 1040	N= 1040
Stroke	79	37
Total mortality	62	48

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Bulpitt, 2003, HYVET-pilot (36)
	Setting	
	Country	10 European countries
	Aim (as described in the article)	To study the risk and benefit of treating hypertension in individuals over 80y
	Study design	RCT single blind
	Inclusion period (year start-year end)	
	Mean follow-up (year)	13 months
Intervention	Drug (pharmaceutical) in treatment arms	Diuretic-based regimen usually bendroflumethiazide Angiotensin-converting enzyme inhibitor regimen usually lisinopril No treatment Diltiazem slow-release could be added to drug-treatment.
	Initial drug dose	ACE, lisinopril 2.5 mg Bendroflumethiazide 2.5mg
	Actual usage	
Population	Mean age	83.8y ±3.3y/ 83.7y ±3.0y/ 83.8y ±2.9y

characteristics	Age range	79.5y-96.1y
	Sex	Women: 62.9% / 64.0% / 63.4%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Previous MI 2.4% / 3.0% /3.5% Previous stroke 4.2% / 4.2% / 5.2%
	Concomittant medication	
	N diuretic-based regimen	426
	N angiotensin-converting enzyme inhibitor regimen	431
	N control group	426
	N lost to follow-up	9 / 7 / 8
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Age >80 y, SBP 160-219 / 90-109 mmHg
	Criteria for exclusion	Serum creatinine > 150µmol/l, accelerated hypertension, congestive heart failure requiring treatment, inability to stand, cerebral or subarachnoid haemorrhage in pst 6 months, need for blod pressure-decreasing treatment because of angina etc., gout, renal artery stenosis, dementia, condition expected to limit survival severely.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox
	Power calculation description	Not relevant to pilot trial
Results	Primary endpoint of study	Stroke, total mortality and cardiovascular, cardiac and stroke mortality.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	No patients withdrawn due to renal problems.

Events	No treatment	ACE
	N = 426	N= 431
Total mortality	22	27
CVD deaths	19	22
Stroke	18	12

Events	No treatment	Diuretic
	N = 426	N= 426
Total mortality	22	30

CVD deaths	19	23
Stroke	18	6

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Lithell. 2003, SCOPE (37)
	Setting	527 centres
	Country	15 countries, mainly in Europe
	Aim (as described in the article)	To assess whether candesartan-based hypertensive treatment in elderly patients with mildly to moderate elevated blood pressure confers a risk reduction in cardiovascular events, cognitive decline and dementia
	Study design	RCT, double blind
	Inclusion period (year start-year end)	March 1997 – January 1999
	Mean follow-up (year)	3.7y. Follow-up ended March 2002
Intervention	Drug (pharmaceutical) in treatment arms	Candesartan versus placebo
	Initial drug dose	Candesartan: Start dose 8 mg, increasing to 16 mg. Other hypertensives in both arms as needed to achieve blood pressure target
	Actual usage	
Population characteristics	Mean age	Candesartan: 76.4y, placebo 76.4y
	Age range	
	Sex	Women: Candesartan: 64.8%, placebo 64.2%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Previous MI 4.5% / 4.6%; Previous stroke 3.9% / 3.9%; diabetes 12.5% / 11.6%
	Concomittant medication	
	N intervention	2477
	N control	2460
	N excluded	
	N lost to follow-up	6 / 2
	Discontinuance (n, percent)	Due to adverse events: CA 15% / C 17%
	Crossover (n, percent)	

Method	Criteria for inclusion	70-89y, with treated or untreated hypertension, SBP 160-179 mmHg and/or 90-99 mmHg, MMSE score 24 or over
	Criteria for exclusion	Main criteria: SBP≥180 mmHg, stroke or MI within 6 months, serum creatinine > 180µmol/l in men and >140 µmol/l in women, serious concomitant diseases
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Log rank test for differences between groups
	Power calculation description	Yes
Results	Primary endpoint of study	Major cardiovascular events as cardiovascular deaths, nonfatal MI, and nonfatal stroke
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Candesartan (CA) / Control (C): Dizziness/vertigo 20.9% / 20.0% Accident/injury 18.4% / 18.4%; Back pain 10.2% / 17.1% Bronchitis 15.9% / 16.0%

Events	Placebo	Candesartan
	N=2460	N=2477
Total mortality	266	259
Stroke	115	89
Myocardial infarction	63	70

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Mochizuki, 2007, JIKEI
	Setting	Hospitals linked to the Jikei University (“tertiary care”),
	Country	Japan
	Aim (as described in the article)	To investigate whether addition of an ARB to convention cardiovascular treatment was effective in Japanes patients with cardiovascular disease.
	Study design	RCT
	Inclusion period (year start-year end)	Jan 2002 to December 2004
	Mean follow-up (year)	3.1 years
Intervention	Drug (pharmaceutical) in treatment	Valsartan

	arms	
	Initial drug dose	80 mg
	Actual usage	75 mg (average)
Population characteristics	Mean age	65 y (valsartan)/65 y (control)
	Age range	20 to 79 y
	Sex	34% female/34% female
	Ethnicity (frequency)	Not reported
	Comorbidity (frequency CVD, diabetes)	Coronary heart disesase: 33%/34% Heart failure: 11%/11%
	Concomittant medication	CCB: 67%; ACE-inhib 35%; beta-block 32%; statin 31%
	N intervention	1541
	N control	1540
	N excluded	4
	N lost to follow-up	15
	Discontinuance (n, percent)	Not reported
	Crossover (n, percent)	0
Method	Criteria for inclusion	Hypertension or coronary heart disease or heart failure; 20 to 79 y.
	Criteria for exclusion	Coronary event less than six months earlier; cerebrovascular event less 3 months earlier; S-creatinine > 265 µmol/L; potassium > 5 mmol/L; on ARB for weeks or less earlier.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox proportional hazard regression
	Power calculation description	Yes
Results	Primary endpoint of study	Composite of cardiovascular morbidity and mortality.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio (95% CI)
	Adverse events	Cancer: 7 (Valsartan)/7 (Control) Headache: 1/1 Rashes: 2/0 Zoster: 0/2 Stomach discomfort: 2/1 Palpitations: 1/2 Liver function: 2/1 Fracture: 1/2 Infraconjunctival haemorrhage: 0/2 Haemoptysis: 0/2 Dry cough: 1/1 Elevated serum potassium: 2/0 Any adverse event: 42/36

Events	Valsartan	Control
	N=1541	N=1540
Composite	92	149
Stroke or TIA	29	48
Stroke	25	43
Total mortality	28	27
New or recurrent acute MI	17	19
New occurence or exacerbation of angina, needing hospitalisation	19	53
New occurence or exacerbation of heart failure, needing hospitalisation	19	36
Transition to dilysis	7	8

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Beckett, 2008, HYVET (39)
	Setting	195 “centers“
	Country	13 countries in Western and Eastern Europe, China, Australasia, and North Africa
	Aim (as described in the article)	To resolve persistent areas of clinical uncertainty about the relative benefits and risks of antihypertensive treatment in patients 80 years of age or older.
	Study design	RCT
	Inclusion period (year start-year end)	2001 – 2007
	Mean follow-up (year)	2.1
Intervention	Drug (pharmaceutical) in treatment arms	Indapamide (perindopril as needed) vs. placebo (placebo added when needed)
	Initial drug dose	1.5 mg (2 or 4 mg perindopril)
	Actual usage	At 2 years, 25.8%, 23.9%, and 49.5% of patients in the active-treatment group were receiving indapamide alone, indapamide and perindopril (2 mg), and indapamide and perindopril (4 mg), respectively; 14.2%, 13.4%, and 71.8% of patients in the placebo group, respectively, were receiving the corresponding placebos.

Population characteristics	Mean age	83.6
	Age range	80 to 105 years
	Sex	60.5%
	Ethnicity (frequency)	Not reported. However: “Patients were recruited from Western Europe (86 patients), Eastern Europe (2144), China (1526), Australasia (19), and Tunisia (70).”
	Comorbidity (frequency CVD, diabetes)	Cardiovascular disease: 12% MI: 3% Heart failure: 3%
	Concomittant medication	Antihypertensive treatment before inclusion: 65%
	N intervention	1933
	N control	1912
	N excluded	None after randomisation
	N lost to follow-up	17
	Discontinuance (n, percent)	See “Actual dosage”, above
	Crossover (n, percent)	Not reported
Method	Criteria for inclusion	≥ 80 years with persistent systolic BP ≥ 160 mmHg
	Criteria for exclusion	Contraindication to use of the trial medications, accelerated hypertension, secondary hypertension, hemorrhagic stroke in the previous 6 months, heart failure requiring treatment with antihypertensive medication, a serum creatinine level greater than 150 μmol per liter (1.7 mg per deciliter), a serum potassium level of less than 3.5 mmol per liter or more than 5.5 mmol per liter, gout, a diagnosis of clinical dementia, and a requirement of nursing care.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Comparison of means of continuous variables: z-test; comparison of means of proportions: chi-square test; incidence rates: the log-rank test and Cox analyses. Cumulative-incidence curves were estimated by means of the Kaplan–Meier method.
	Power calculation description	Yes
Results	Primary endpoint of study	Stroke (excl. TIA)
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio (95% CI)
	Adverse effects	448 in the placebo group and 358 in the active-treatment group (P = 0.001). Only five of these events (three in the placebo group and two in the active-treatment group) were classified by the local investigator as possibly having been due to the trial medication.

Events	Indapamide	Placebo
	N=1933	N=1912

Stroke (fatal and nonfatal)	51	69
Death from any cause	196	235
MI (fatal or non-fatal)	9	12
Heart failure (fatal or nonfatal)	22	57

Drug versus drug

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Wilhelmsen, 1987, HAPPHY (40)
	Setting	184 “centres”
	Country	Europe and US
	Aim (as described in the article)	To determine whether antihypertensive tratment with beta-blockers differed from thiazide diuretic treatment with respect to the incidence of non-fatal MI, mortality from CHD, and total mortality in men with mild to moderate hypertension.
	Study design	Unblinded RCT
	Inclusion period (year start-year end)	1976-84
	Mean follow-up (year)	3.8 years
Intervention	Drug (pharmaceutical) in treatment arms	Bendroflumethiazide 5 mg or Hydrochlorothiazide 50 mg vs Atenolol 100 mg or metoprolol 200 mg Add-on for both groups: Hydralazine, spironolactone
	Initial drug dose	See above
	Actual usage	(For details see Table 4 in paper)
Population characteristics	Mean age	52.3
	Age range	40 to 64 years
	Sex	Only men
	Ethnicity (frequency)	99% caucasians
	Comorbidity (frequency CVD, diabetes)	Not reported (see exclusion criteria)
	Concomittant medication	Not reported
	N intervention	3297 (beta-blocker)
	N control	3272 (diuretic)

	N excluded	Not reported
	N lost to follow-up	64 (“equally distributed”)
	Discontinuance (n, percent)	Diuretic: 16.6% Beta-blocker: 14.1%
	Crossover (n, percent)	About 4% both groups
Method	Criteria for inclusion	Male 40 to 64 years DBP 100 to 130
	Criteria for exclusion	History of MI Angina pectoris Stroke Malignant or secondary hypertension Malignant disease Liver cirrhosis Alcoholism Other serious diseases Chronic obstrictuve lung disease Diabetes mellitus Gout Other non-hypertensive condition requiring treatment with a beta-blocker or a diuretic
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Fisher’s exact test Life table methods (Kaplan-Meier estimate) Cox regression to adjust for differences in baseline variables
	Power calculation description	Yes
Results	Primary endpoint of study	Not clearly stated
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Rates
	Adverse events	Withdrawal due to side effects: 2.4% vs 2.0%
	Sub group analysis (sex, age, ethnicity)	Separate analyses for quartiles of predicted CHD risk at entry Separate analysis for smokers

Events	Diuretic	beta-blocker
	N = 3272	N= 3297
Total mortality	101	96
Stroke	41	32
All CHD	116	132
Nonfatal MI	75	84
Fatal MI	50	54
Heart failure	22	32

Diabetes	75	86

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Medical research council working party, 1985 MRC 1 (28, 29)
	Setting	General practice
	Country	UK
	Aim (as described in the article)	The main aim was to determine whether drug treatment of mild hypertension (phase V diastolc pressure 90-109 mmHg) reduced the rate of stroke, of death due to hypertension, and of coronary events in men and women aged 35-64 y.
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	Maximum 5.5y
Intervention	Drug (pharmaceutical) in treatment arms	Bendrofluazide (n= 4297) and propranolol (n=4403) versus placebo (n=8654)
	Initial drug dose	Bendrofluazide: 10 mg Propranolol: ”up to 240 mg”
	Actual usage	
Population characteristics	Mean age	
	Age range	35-64y
	Sex	In total: 9048 men / 8306 women
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Ischaemic ECG: Bendrofluazide: 3.3%, propranalol 1.2%
	Concomittant medication	
	N bendrofluazide	4297
	N propranalol	4403
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Mild hypertension (DBP 90-109 mmHg)
	Criteria for exclusion	History of definite MI within last 3 months, angina, signs of

		cardiac failure, or ECG evidence of silent MI or left bundle branch block.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Multiple logistic regression
	Power calculation description	Yes
Results	Primary endpoint of study	Fatal and nonfatal coronary events. Fatal events were further split into sudden and not sudden death
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Results are given for both men and women together and separate.
	Adverse events	

Events	Bendrofluazide	Propranolol
	N = 4297	N= 4403
Total mortality	128	120
Stroke	18	42
CHD	119	103

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	MRC working party, 1992, MRC 2 (31)
	Setting	General practices
	Country	UK
	Aim (as described in the article)	Establishing whether antihypertensive treatment in men and women aged 65-74 years reduces mortality and morbidity due to stroke and coronary heart disease and mortality from other causes
	Study design	Single blind RCT
	Inclusion period (year start-year end)	1982-87
	Mean follow-up (year)	5.8 years
Intervention	Drug (pharmaceutical) in treatment arms	Hydrochlorothiazide 25 mg + amiloride 2.5 mg (some early particpants were started on twice this dose) (add on: atenolol; nifedipine) vs atenolol 50 mg (add on : increase to 100 mg; hydrochlorothiazide; nifedipine) vs placebo
	Initial drug dose	See above
	Actual usage	Not reported

Population characteristics	Mean age	Men: 70.2 Women: 70.4
	Age range	65 to 74 years
	Sex	Men: 1,836/4,396
	Ethnicity (frequency)	Not reported
	Comorbidity (frequency CVD, diabetes)	Ischaemic ECG: Menn: Bendrofluazide: 18%, propranalol 17%, placebo 18% Kvinner: Bendrofluazide: 17%, propranalol 14%, placebo 15%
	Concomittant medication	Not reported
	N intervention	Hydrochlorothiazide: 1,081 Atenolol: 1,102
	N control	2,213
	N excluded	184,653 invitations for screening => 125,861 attended => 20,389 suitable repoeated BP measurement => 4,961 suitable for entry examination => 4,396 entered into main trial
	N lost to follow-up	About 25%
	Discontinuance (n, percent)	HCTZ group: 48% Atenolol group: 63% Placebo group: 53%
	Crossover (n, percent)	Not reported
Method	Criteria for inclusion	SBP 160 to 209; DBP<115
	Criteria for exclusion	Known or suspected secondary hypertension Taking antihypertensive drugs Cardiac failure or any other accepted indication for antihypertensive treatment Receiving treatment for angina pectoris History of MI or stroke within the preceding three months, Impaired renal function, Diabetes, Asthma, Any serious intervurrent disease including malignancy known to be present at the time of examination Serum potassium <3.4 or >5.0 mmol/l
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Not clearly stated
	Power calculation description	Yes
Results	Primary endpoint of study	Stroke Coronary heart disease Total mortality
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Rates
	Adverse events	Impaired glucose tolerance (D 6.9 /1000PY, P 2.7/1000 PY; gout 4.4 vs 0.1; skin disorder 3.9 vs 1.1; muscle cramp 5.2 vs 0.1; nausea 7.4 vs 1.1; dizziness 7.4 vs 1.2

Events	Hydrochlorothiazide	Atenolol
	N = 1081	N= 1102
All CVD events	107	151
Total mortality	134	167
Stroke	45	56
All coronary events	48	80
Fatal coronary	33	52
Nonfatal coronary events	15	28

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Hansson, 1999, CAPPP (41)
	Setting	536 health centres
	Country	Sweden and Finland
	Aim (as described in the article)	Compare the effects of ACE inhibition and conventional therapy on cardiovascular morbidity and mortality in patients with hypertension
	Study design	RCT (“PROBE”)
	Inclusion period (year start-year end)	
	Mean follow-up (year)	6.1y
Intervention	Drug (pharmaceutical) in treatment arms	Captopril versus diuretic (hydrochlorthiazide and bendrofluazide) and beta-blocker (Atenolol /metoprolol)
	Initial drug dose	Captopril 50mg/day. Atenolol /metoprolol 50-100mg/day
	Actual usage	
Population characteristics	Mean age	Captopril 52.4y /conventional 52.7y
	Age range	
	Sex	M/F: Captopril 3016/2476; conventional 2858/2635
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	MI 40 (0.7%) / 55 (1.0%); ischaemic heart disease 64 (1.2%) /81 (1.5%); Stroke 50 (0.9%) /39 (0.7%); diabetes 309 (5.6%) / 263 (4.8%)
	Concomittant medication	
	N captopril	5492

	N coventional therapy	5493
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	25-66 y, treated or untreated primary hypertension with DBP>100mmHg on two separate occasions,
	Criteria for exclusion	Seccondary hypertension, serum creatinine >150 µmol/l, disorders that required treatment with beta-blocker
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox regression
	Power calculation description	Yes
Results	Primary endpoint of study	Composite of fatal and nonfatal MI, stroke, and other cardiovascular deaths.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	

Events	Diuretic and/or beta-blocker	Captopril
	N = 5493	N= 5492
Total mortality*	190	184
Nonfatal stroke	127	173
Fatal stroke	22	20
Total stroke*	148	189
Nonfatal MI	128	137
Fatal MI	35	27
Sudden death	14	6
Heart failure	66	75
Ischeamic heart disease	251	258
Coronary heart disease*	175	168
Diabetes	380	337

* Data from Blood Pressure Lowering Treatment Trialists' Collaboration (88)

Quality	Study quality rating (according to check list)

assessment by the review group	Moderate /+	
Study description	Author, year, study name	Hansson, 1999, STOP-2 study (42)
	Setting	312 health centres
	Country	Sweden
	Aim (as described in the article)	Compare the effects of conventional and newer antihypertensive drugs on cardiovascular mortality and morbidity in elderly patients.
	Study design	RCT
	Inclusion period (year start-year end)	September 1992 – December 1994
	Mean follow-up (year)	Follow-up until December 1998
Intervention	Drug (pharmaceutical) in treatment arms	1. Conventional: diuretic and beta-blocker (atenolol, metoprolol, pindolol, hydrocholorthiazide, amelioride. 2. ACE inhibitor: enalapril, lisinopril 3. Calcium antagonist: felodipine, isradipine
	Initial drug dose	1. Conventional: diuretic and beta-blocker (atenolol 50mg, metoprolol 100mg, pindolol 5mg, hydrocholorthiazide 25mg, amelioride 2.5mg. 2. ACE inhibitor: enalapril 10mg, lisinopril 10mg. 3. Calcium antagonist: felodipine 2.5mg, isradipine 2.5mg.
	Actual usage	
Population characteristics	Mean age	1: 76.0y /2: 76.1y / 3: 75.9y
	Age range	
	Sex	Men 1: 32.0% / 2: 33.7% / 3:34.0%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Overall: 3.1% MI, 8.0% IHD, 3.9% stroke, 10.9% diabetes mellitus
	Concomittant medication	
	N conventional	2213
	N ACE inhibitor	2205
	N calcium antagonist	2196
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	70-84y, SBP >180 and/or DBP >105 mmHg
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox regression

	Power calculation description	Yes
Results	Primary endpoint of study	Fatal stroke, fatal MI, or other fatal cardiovascular disease
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Conventional drugs (C) / ACE / CCB in%: Shortness of breath 11.8 / 7.3 / 8.5 Palpitations 2.9 / 5.3 / 7.9 Flushing 1.6 / 2.2 / 9.7 Headaches 5.7 / 7.7 / 10.0 Cold hands and feet 9.1 / 3.3 / 2.5 Slow pulse 3.7 / 0.8 / 1.4 Nightmares 5.8 / 1.4 / 2.0 Dry mouth 4.4 / 2.0 / 2.7 Ankle oedema 8.5 / 8.7 / 25.5 Insomnia 4.3 / 1.8 / 2.3 Dry cough 3.7 / 30.1 / 5.7 Dizziness 27.8 / 27.7 / 24.4

Events	Diuretic + beta-blocker	ACE
	N = 2213	N= 2205
Total mortality	369	380
All stroke	237	215
All CVD	460	437
Coronary heart disease*	199	194
Diabetes	97	93
HEART FAILURE	177	149

Events	Diuretic + beta-blocker	CCB
	N = 2213	N= 2196
Total mortality	369	362
All stroke	237	207
All CVD	460	450
Coronary heart disease*	199	221
Diabetes	97	95
HEART FAILURE	177	186

Events	ACE	CCB

	N = 2205	N= 2196
Total mortality	380	362
All stroke	215	207
All CVD	437	450
Coronary heart disease*	194	221
Diabetes	93	95
HEART FAILURE	149	186

* Data from Blood Pressure Lowering Treatment Trialists' Collaboration (88)

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	The ALLHAT research group, 2000, ALLHAT (44)
	Setting	625 centres
	Country	US and Canada
	Aim (as described in the article)	To compare the effect of doxazosin, an α-blocker, with chlorthalidone, a diuretic, on incidence of CVD in patients with hypertension
	Study design	RCT, double blind
	Inclusion period (year start-year end)	Start February 1994. Study stopped January 2000
	Mean follow-up (year)	Median 3.3y
Intervention	Drug (pharmaceutical) in treatment arms	Doxazosin versus chlorthalidone reported here. Additional drugs as required to reduce blood pressure. The study had four treatment arms.
	Initial drug dose	Doxazosin: 2, 4, and 8 mg/d Chlorthalidone: 12.5, 12.5, and 25mg/d respectively.
	Actual usage	
Population characteristics	Mean age	Doxazosin 67y Chlorthalidone 67
	Age range	
	Sex	Women: Doxazosin 47%, Chlorthalidone 46.4%
	Ethnicity (frequency)	White non-Hispanic: Chl. 47.2% /Dox. 46.4% Black non-Hispanic: 31.9% / 32.9% White Hispanic: 12.6% / 12.6% Black Hispanic: 3.3% / 3.4% Other race: 5.1% / 4.6%

	Comorbidity (frequency CVD, diabetes)	Type 2 diabetes; 35.9% / 35.1%, Atherosclerotic cardiovascular disease (ASCVD) : 45.2% / 45.5%
	Concomittant medication	
	N Chlorthalidone	15268
	N Doxazosin	9067
	N excluded	
	N lost to follow-up	501 / 338
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	55y or older, SBP at least 140mmHg, DBP at least 90mmHg, or took medication for hypertension and had at least 1 additional risk factor for CHD such as MI or stroke more than 6 months ago, left ventricular hypertrophy, type 2 diabets, current sigarette smoking, etc..
	Criteria for exclusion	History of hospitalised or treated symptomatic heart failure and /or known left ventricular ejection fraction of less than 35%.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Kaplan Meier, Log-rank test, Cox
	Power calculation description	Yes
Results	Primary endpoint of study	Fatal CHD or nonfatal MI
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RR (hazard ratio) and 95% CI
	Adverse events	

Events	Diuretic	α-blocker
	N = 15268	N= 9067
Total mortality	851	514
Stroke	351	244
CHD	608	365
Angina	1082	725
Revaskulering	502	337
HEART FAILURE	420	491

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +

Study description	Author, year, study name	Hansson, 2000, NORDIL(45)
	Setting	Health centres
	Country	Norway and Sweden
	Aim (as described in the article)	Compare the effects of diltiazem, a nonhydropyridine calcium antagonist, with that of diuretics, beta-blocker, or both on cardiovascular morbidity and mortality in hypertensive patients.
	Study design	RCT ("PROBE")
	Inclusion period (year start-year end)	
	Mean follow-up (year)	
Intervention	Drug (pharmaceutical) in treatment arms	Diltiazem versus diuretics, beta-blocker, or both. Stepped treatment in diltiazem group was ACE, then diuretic or beta-blocker, then any other antihypertensive compound. Other hypertensive compounds could be added to conventional treatment to achieve blood pressure target.
	Initial drug dose	Diltiazem 180-360 mg/day
	Actual usage	
Population characteristics	Mean age	Diltiazem 60.5y / conventional 60.3y
	Age range	
	Sex	Women: diltiazem, 51.5%, conventional 51.3%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Previous MI 2.1% /2.2% Previous IHD 2.3% / 2.6% Previous stroke 1.4% / 1.6% Diabetes mellitus 6.5% / 6.9%
	Concomittant medication	
	N diltiazem	5410
	N conventional	5471
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	50-74 y, DBP >100 mmHg, previously untreated, but could be included
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox regression, Kaplan Meier
	Power calculation description	Yes

Results	Primary endpoint of study	Combined endpoint of fatal and nonfatal stroke, MI, and other cardiovascular death
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Subgroup analyses on sex, age, and blood pressure in other publication
	Adverse events	Diltiazem (DG) / Diuretic and beta-blocker (DBB) in%: Dizziness 9.3 / 8.9; Arthralgia 7.7 / 7.1; Headaches 8.5 / 5.7; Chest discomfort 5.7 / 5.9; Coughing 5.6 / 5.4; Fatigue 4.4 / 6.5; Back pain 4.7 / 5.4; Depression 3.7 / 3.4; Abdominal pain 3.5 / 3.4; Dyspnoea 2.9 / 3.9; Myalgia 3.2 / 3.4 ; Impotence 2.3 / 3.7

Events	Diuretic + beta-blocker	Diltiazem
	N = 5471	N= 5410
Total mortality	228	231
Stroke	196	159
Fatal stroke	22	21
MI	157	183
Fatal MI	25	28
Diabetes	251	216
HEART FAILURE	53	63

Quality assessment by the review group	Study quality rating (according to check list) High /++	
Study description	Author, year, study name	Brown, 2000, INSIGHT (46)
	Setting	
	Country	Western Europe and Israel
	Aim (as described in the article)	Compare effiCCBy in preventing the major complications from hypertension of nifedipine (GITS) and co-amilozide. Prespecified subgroup analysis of patients with diabetes
	Study design	RCT
	Inclusion period (year start-year end)	September 1994 – June 1996
	Mean follow-up (year)	~ 3 ½ years
Intervention	Drug (pharmaceutical) in treatment arms	Nifedipine Co-amilozide
	Initial drug dose	Nifedipine: 30mg/d

		Co-amilozide: 25 mg hydrochlorthiazide and 2.5mg amiloride Doses increased to achieve target BP
	Actual usage	
Population characteristics	Mean age	<60y – 23%, 60-70y – 48%, >70y – 28%
	Age range	55 to 80 years
	Sex	Women 54%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	ALL: MI 6%, LVH 11%, PAD 6%
	Concomittant medication	
	N Nifedipine	3157
	N Co-amilozide	3164
	N excluded	254 (”in centres withdrawn for misconduct”)
	N lost to follow-up	149
	Discontinuance (n, percent)	No withdrawn adverse avents: N – 539; C – 304; p<0.0001 No withdrawn serious evetns: N – 198; C – 245; p=0.02
	Crossover (n, percent)	
Method	Criteria for inclusion	55-80y, hypertension, at least one additional cardiovascular risk factor
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Logistic regression, Kaplein Meier
	Power calculation description	Yes
Results	Primary endpoint of study	Composite of cardiovascular death, myocardial infarction, heart failure and stroke
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Cumulative event rate
	Adverse events	Nifedipine / Co-amilozide: Total adverse events 49% / 42%; p<0.0001 Serious adverse events 25% / 28%; p=0.02 Symptomatic adverse events: Peripheral oedema 28% / 4.3%; Syncope 1.5% / 2.8%; Headache 12% / 9.2%; Palpitation 2.5% / 2.7%; Peripheral vascular disorder 3.0% / 5.3%; Impotence 1.6% / 1.9%; Flushing 4.3% / 2.3%; Diabetes 3.0% / 4.3%; Dizziness 8.0% / 10.0%; Gout 1.3% / 2.1%; Accident injury 1.2% / 2.2%; Depression 3.9% / 5.7% Metabolic adverse events: Hypokalaemia 1.9% / 6.2%; Hyponatremia <0% / 1.9%; Hyperlipidaemia 4.0% / 6.3%; Hyperglycaemia 5.6% / 7.7%; Hyperuricaemia 1.3% / 6.4%; Impaired renal function 1.8% / 4.6%

Events	Co-amilozide	Nifedipine
	N= 3 164	N= 3 157
Total mortality	152	153
MI	84	94
Stroke	74	67
All CVD	182	200
Congestive heart failure	12	26
Angina	77	57
Diabetes	176	136
CHD mortality	28	33

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Wright, 2002, ALLHAT (43)
	Setting	623 centres
	Country	US and Canada
	Aim (as described in the article)	To determine whether the occurrence of fatal CHD or nonfatal MI is lower for high-risk patients with hypertension treated with CCB, an ACE-inhibitor, each compared with diuretic treatment.
	Study design	RCT, double blind
	Inclusion period (year start-year end)	Start February 1994 – January 1998
	Mean follow-up (year)	Planned 4-8y
Intervention	Drug (pharmaceutical) in treatment arms	Calcium channel blocker amlodipine versus angiotensin-converting enzyme inhibitor lisinopril versus chlorthalidone reported here. Additional drugs as required to reduce blood pressure. The study had four treatment arms.
	Initial drug dose	Amlodipine: 2.5-10 mg/d Lisinopril: 10-40 mg/d Chlorthalidone: 12.5 to 25mg/d.
	Actual usage	
Population characteristics	Mean age	66.9y (for all groups)
	Age range	Above 55y
	Sex	Women: 47.0% (C); 47.3% (A); 46.2% (L)
	Ethnicity (frequency)	White, non-hispanic: 47.2% (C); 47.6% (A); 47.1% (L) Black, non-hispanic: 31.9% (C); 32.2% (A); 32.3% (L)

		White hispanic: 12.5% (C); 12.2% (A); 12.5% (L) Black hispanic: 3.3% (C); 3.3% (A); 3.2% (L) Other: 5.1% (C); 4.7% (A); 4.9% (L)
	Comorbidity (frequency CVD, diabetes)	MI or stroke: 23.5% (C); 23.2 (A);: 22.7% (L) Type 2 diabetes: 36.2& (C); 36.7% (A); 35.5% (L)
	Concomittant medication	Aspirin: 35.6% (C); 36.1% (A); 36.0% (L) Estrogen replacement (women only): 17.8% (C); 17.6% (A); 17.4% (L)
	N Amlodipine	9048
	N Lisinopril	9054
	N Chlorthalidone	15255
	N lost to follow-up	A: 200 / L: 218 / C: 339
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	55y or older, SBP at least 140mmHg, DBP at least 90mmHg, or took medication for hypertension and had at least 1 additional risk factor for CHD such as MI or stroke more than 6 months ago, left ventricular hypertrophy, type 2 diabetes, current sigarette smoking, etc..
	Criteria for exclusion	History of hospitalised or treated symptomatic heart failure and /or known left ventricular ejection fraction of less than 35%.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Kaplan Meier, Log-rank test, Cox
	Power calculation description	Yes
Results	Primary endpoint of study	Fatal CHD or nonfatal MI
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RR (hazard ratio) and 95% CI
	Adverse events	6-year rate for hospitalization D / A /L : GI-bleeding 8.8% / 8.0% / 9.6% Angio-oedema 0.1% / <0.1% / 0.4%

Events	Chlorthalidone	Amlodipine
	N = 15255	N= 9048
Total mortality	2203	1256
Stroke	675	377
All CHD	2451	1466
CHD mortality	1362	798
Angina (hospitalised or treated)	1567	950

Heart failure	870	706
Diabetes	636	299
Revascularisation	1113	725

Events	Lisinopril	Amlodipine
	N = 9054	N= 9048
Total mortality	1314	1256
Stroke	457	377
All CHD	1505	1466
CHD mortality	796	798
Angina (hospitalised or treated)	1019	950
Heart failure	612	706
Diabetes	243	299
Revascularization	718	725

Events	Lisinopril	Chlorthalidone
	N = 9054	N= 15255
Total mortality	1314	2203
Stroke	457	675
All CHD	1505	2451
CHD mortality	796	1362
Angina (hospitalised or treated)	1019	1567
Heart failure	612	870
Diabetes	243	636
Revascularization	718	1113

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Black, 2003 CONVINCE (47)
	Setting	661 centres
	Country	15 countries

	Aim (as described in the article)	To determine whether initial therapy with controlled-onset extended release (COER) verapamil is equivalent to physician's choice of atenolol or hydrochlorothiazide in preventing cardiovascular disease.
	Study design	RCT double blind
	Inclusion period (year start-year end)	September 1996 to December 1998 and followed until December 31, 2000. The sponsor closed the study before unblinding the results 2 years early for commercial reasons.
	Mean follow-up (year)	3y
Intervention	Drug (pharmaceutical) in treatment arms	COER verapamil vs atenolol or hydrochlorothiazide. Other drugs added as needed.
	Initial drug dose	180 mg COER verapamil vs 50 mg atenolol or 12.5 mg hydrochlorothiazide
	Actual usage	
Population characteristics	Mean age	Active 65.6y ± 7.4y / control 65.6y ± 7.4y
	Age range	
	Sex	Men: Active 43.8% / control 44.2%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	MI: 7.5% / 7.9%, stroke 4.5% / 4.8%, type 2 diabetes 19.9% /19.7%
	Concomittant medication	
	N intervention	8241
	N control	8361
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	55y or older, at least one other risk factor in addition to hypertension
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Kaplan Maier
	Power calculation description	Yes
Results	Primary endpoint of study	Cardiovascular death
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Withdrawel due to adverse events: Verapamil (V) > Diuretic + beta-blocker (DBB) – p=0.02.

	Constipation most common: 216 (V) / 28 (DBB).	
Events	Diuretic + beta-blocker	Verapamil
	N = 8297	N= 8179
Total mortality	319	337
Stroke	118	133
All MI	166	133
Angina	190	202
Revaskularisering	166	163
Renal failure	34	27
HEART FAILURE	100	126

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Dahlöf, 2002 LIFE (48)
	Setting	
	Country	All Nordic countries, UK, US
	Aim (as described in the article)	The primary hypothesis of the LIFE study was that selective angiotensin-II type 1-receptor antagonism with losartan would be more effective than beta-blockade with atenolol in reducing cardiovascular morbidity and death in patients with essential hypertension and signs of LVH.
	Study design	RCT, double blind
	Inclusion period (year start-year end)	June 1995 to May 1997
	Mean follow-up (year)	4 .8y
Intervention	Drug (pharmaceutical) in treatment arms	Losartan (angiotensin-II antagonist) versus atenolol (beta-blocker)
	Initial drug dose	L: 50-100 mg/d; A: 50-100 mg/d Other hypertensive treatment as needed
	Actual usage	
Population characteristics	Mean age	Losartan / atenolol: 66.9y / 66.9y
	Age range	
	Sex	54% / 54% women
	Ethnicity (frequency)	White: 92% / 93% Black: 6% / 6%

		Hispanic: 1% / 1% Asian: 0.5% / 0.4% Other: 0.1% / 0.2%
	Comorbidity (frequency CVD, diabetes)	Any vacular disease: 25% (all) CHD: 16% CVD: 8% Perpheral vascular disease: 6% Diabetes: Losartan 13%
	Concomittant medication	
	N Losartan	4605
	N Atenolol	4588
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	55-80y, essential hypertension of 160-200/95-115 mmHg, ECG-defined left ventricular hypertrophy
	Criteria for exclusion	Patients with secondary hypertension; myocardial infarction or stroke within the previous 6 months; angina pectoris requiring treatment with beta-blockers or calcium-antagonists; heart failure or left ventricular ejection fraction of 40% or less; or a disorder that, in the treating physician's opinion, required treatment with losartan or another angiotensin–II type 1-receptor antagonist, atenolol or another beta-blocker, hydrochlorothiazide, or angiotensin-converting-enzyme inhibitors.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Kaplan Meier
	Power calculation description	Yes
Results	Primary endpoint of study	Composite endpoint: first occurrence of cardiovascular death, stroke or clinically evident MI
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio
	Adverse events	Total material Losartan (L) / Atenolol (A): Prespecified adverse events: Angio-oedema 0.1% / 0.2%; Bradycardia 1% / 9%; Cancer 8% / 7%; Cold extremeties 4% / 6%; Cough 3% / 2%; Dizziness 17% / 16%; Hypotension 3% / 2%; Sexual dysfunction 4% / 5%; Sleep disturbance 0.7% / 0.8% Additional common adverse events: Albuminuria 5% / 6%; Hyperglycaemia 5% / 7%; Asthenia/fatigue 15% / 17%; Back pain 12% / 10%; Chest pain 11% / 10%; Dyspnoea 10% / 14%; Lower extremity oedema 12% / 14%; Pneumonia 5% / 6%

Events	Atenolol	Losartan
	N = 4588	N= 4605
Total mortality	431	383
Stroke	309	232
CVD mortality	234	204
MI	188	198
Revaskulering	284	261
Angina	141	160
Heart failure	161	153
New diabetes	319	241

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Wing, 2003, ANBP-2 (49)
	Setting	1594 family practices
	Country	Australia
	Aim (as described in the article)	To compare patients treated with angiotensin-converting-enzyme (ACE) inhibitor versus patients treated with diuretic agents to test whether inhibition of the renin-angiotensin system confer benefit beyond the reduction of blood pressure alone. Achieve SBP reduction of 20 mmHg to less than 170 mmHg and less than 140mmHg if tolerated; reduction of DBP with at least 10mmHg to less than 90 mmHg and 80 mmHg if tolerated.
	Study design	RCT ("PROBE")
	Inclusion period (year start-year end)	
	Mean follow-up (year)	4.1y
Intervention	Drug (pharmaceutical) in treatment arms	ACE-inhibitor: Enalapril Diuretic: hydrochlorothiazide Additional drugs to achieve blood pressure target such as beta - blocker, calcium-channel blocker and alpha-blockers.
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	71.9y
	Age range	
	Sex	51% women

	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Coronary heart disease 8%, cerebrovascular disease 5%, diabetes mellitus 7%
	Concomittant medication	
	N intervention	3044
	N control	3039
	N excluded	
	N lost to follow-up	66 / 99
	Discontinuance (n, percent)	Assigned treatmen ttaken at end of trial: ACE 58%, diuretic 62%
	Crossover (n, percent)	
Method	Criteria for inclusion	65-84y, hypertension of SBP at least 160 mmHg or DBP at least 90 mmHg if SBP was at least 140mmHg, absence of cardiovascular events within the last 6 months
	Criteria for exclusion	Any life threatening diseases, contraindivcations to ACE-inhibitor or diuretic, plasma creatininge >2.5 mg/dl, malignant hypertension or dementia.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox
	Power calculation description	Yes
Results	Primary endpoint of study	All cardiovascular events or deaths from any cause.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	

Events	Diuretic	Enalapril
	N = 3039	N= 3044
Total mortality	210	195
Stroke	107	112
All CVD or death	736	695
Coronary events	195	173
CHD mortality	82	58
HEART FAILURE	78	69

Quality assessment by the review	Study quality rating (according to check list) Moderate / +

group		
Study description	Author, year, study name	Malacco, 2003, SHELL (50)
	Setting	Outpatients of 134 units
	Country	Italy
	Aim (as described in the article)	To compare the effect of lacidipine and chlorthalidone on cardiovascular outcome as a primary parameter and blood pressure as a secondary in elderly patients with isolated systolic hypertension
	Study design	RCT, single blind
	Inclusion period (year start-year end)	
	Mean follow-up (year)	Median 32 months
Intervention	Drug (pharmaceutical) in treatment arms	Chlorthalidone Lacidipine
	Initial drug dose	12.5 mg/d chlorthalidone 4 mg/d lacidipine
	Actual usage	
Population characteristics	Mean age	72.4y ±7.6y/ 72.3y ±7.5y
	Age range	
	Sex	M/F – 37.8%/62.2% and 39.6%/60.4%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	History of CVD 29.2% / 32.1%, diabetes mellitus 12.7% / 13.8%
	Concomittant medication	
	N Chlorthalidone	940
	N Lacidipine	942
	N excluded	
	N lost to follow-up	12.3% on lacidipine, 11% on chlorthalidone
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Age≥60y, SBP ≥160mmHg and DBP ≤95mmHg,
	Criteria for exclusion	Secondary hypertension, malignant hypertension, MI, myocardial revacularization or stroke within last six months, advanced renal damage with serum creatinine >2mg/dl, altered hepatic function, contraindications or hypersensitivity to the drugs employed in the study, severe concommittant disease.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Kaplan Meier

	Power calculation description	Yes
Results	Primary endpoint of study	Composite endpoint of cardiovascular and cerebrovascular events
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio 95% CI
	Adverse events	Chlorthalidone (L) / Lacidipine (L) in %: Dizziness 12.4 / 12.7; fatigue 20.5 / 13.7; Headache 6.4 / 9.6: Edema 4.9 / 14.3; Skin rush 1.6 / 4.0; Itching 3.8 / 3.7; Skeletal muscle disorder 7.9 / 6.6; Paresthesia 4.6 / 3.4; Constipation 5.7 / 4.5; Orthostatic hypotension 2.5 / 1.9; Cough 4.0 / 3.5

Events	Chlorthalidone	Lacidipine
	N = 940	N= 942
Total mortality	122	145
Stroke	38	37
MI (incl sudden death)	27	28
Revascularization	4	2
HEART FAILURE fatal/nonfatal	19	23

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Bulpitt, 2003, HYVET-pilot (36)
	Setting	
	Country	10 European countries
	Aim (as described in the article)	To study the risk and benefit of treating hypertension in individuals over 80y
	Study design	RCT single blind
	Inclusion period (year start-year end)	
	Mean follow-up (year)	13 months
Intervention	Drug (pharmaceutical) in treatment arms	Diuretic-based regimen usually bendroflumethiazide Angiotensin-converting enzyme inhibitor regimen usually lisinopril No treatment Diltiazem slow-release could be added to drug-treatment.
	Initial drug dose	ACE, lisinopril 2.5 mg

		Bendroflumethiazide 2.5mg	
	Actual usage		
Population characteristics	Mean age	83.8y ±3.3y/ 83.7y ±3.0y/ 83.8y ±2.9y	
	Age range	79.5y-96.1y	
	Sex	Women: 62.9% / 64.0% / 63.4%	
	Ethnicity (frequency)		
	Comorbidity (frequency CVD, diabetes)	Previous MI 2.4% / 3.0% /3.5% Previous stroke 4.2% / 4.2% / 5.2%	
	Concomittant medication		
	N diuretic-based regimen	426	
	N angiotensin-converting enzyme inhibitor regimen	431	
	N control group	426	
	N lost to follow-up	9 / 7 / 8	
	Discontinuance (n, percent)		
	Crossover (n, percent)		
Method	Criteria for inclusion	Age >80 y, SBP 160-219 / 90-109 mmHg	
	Criteria for exclusion	Serum creatinine > 150µmol/l, accelerated hypertension, congestive heart failure requiring treatment, inability to stand, cerebral or subarachnoid haemorrhage in pst 6 months, need for blod pressure-decreasing treatment because of angina etc., gout, renal artery stenosis, dementia, condition expected to limit survival severely.	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox,	
	Power calculation description	Not relevant to pilot trial	
Results	Primary endpoint of study	Stroke, total mortality and cardiovascular, cardiac and stroke mortality.	
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)		
	Adverse events	No patients withdrawn due to renal problems.	
Events		Diuretic	ACE
		N = 426	N= 431
Total mortality		30	27
CVD deaths		23	22
Stroke		6	12

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Julius, 2004 VALUE (51)
	Setting	
	Country	31 countries
	Aim (as described in the article)	To test the hypothesis that for the same blood-pressure control, valsartan would reduce cardiac morbidity and mortality more than amlodipine in hypertensive patients at high cardiovascular risk
	Study design	RCT, double blind
	Inclusion period (year start-year end)	
	Mean follow-up (year)	4.2y
Intervention	Drug (pharmaceutical) in treatment arms	Valsartan-based regimen vs amlodipine-based regimen
	Initial drug dose	Stepped treatment: Starting with 80mg Valsartan up to 160 mg, vs 5 mg up to 10 mg amlodipine. Additional drugs as needed.
	Actual usage	
Population characteristics	Mean age	Valsartan 67.2y ±8.2y, amlodipine 67.3y ±8.1y
	Age range	
	Sex	Women: Valsartan 42.4% , amlodipine 42.5%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Coronary heart disease 45.6% /46.0% Stroke or TIA 19.8% / 19.8%
	Concomittant medication	
	N valsartan	7649
	N atenolol	7596
	N withdrew concent	37 / 34
	N lost to follow-up	40 / 50
	Discontinuance (n, percent)	
	From closed sites	43 / 47
Method	Criteria for inclusion	50y or older, with treated or untreated hypertension and predefined combinations of cardiovascular risk factors and cardiovascular disease.
	Criteria for exclusion	Renal artery stenosis, pregnancy, acute myocardial infarction, PTCA or coronary artery bypass within the last 3 months, clinically relevant valvular disease, cerebrovascular event last 3 months, other severe disease.
	Main statistical analysis (Logistic	Cox, Kaplan Meier

	regression, Cox, Kaplan Meier, other)	
	Power calculation description	
Results	Primary endpoint of study	Composite endpoint of cardiac mortality and morbidity
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Prespecified : Valsartan (V) / Amlodipine (A): Peripheral oedema 14.9% / 32.9% Dizziness 16.5% / 14.3%; Headache 14.7% / 12.5% Fatigue 9.7% / 8.9% Additional common adverse events: Diarrhoea 8.8% / 6.8%; Angina pectoris 9.3% / 6.4%; Serious angina 4.4% / 3.1%; Other oedema 3.2% / 6.1%; Hypokalaemia 3.5% / 6.2%; Atrial fibrillation 2.4% / 2.0%; Syncope 1.7% / 1.0%

Events	Amlodipine	Valsartan
	N = 7596	N= 7649
Total mortality	818	841
All stroke	281	322
All MI	313	369
Diabetes	845	690
HEART FAILURE fatal and nonfatal	400	354

Quality assessment by the review group	Study quality rating (according to check list) High /++	
Study description	Author, year, study name	Dahlöf, 2005, ASCOT-BPLA (52)
	Setting	Regional centres/family practices
	Country	UK, Ireland, Scandinavia
	Aim (as described in the article)	Compare effect on non-fatal MI and fatal CHD of atenolol (+thiazide as needed) vs amlodipine (+perindopril as needed)
	Study design	Double blind prospective RCT
	Inclusion period (year start-year end)	1998-200
	Mean follow-up (year)	5,5 years (median)
Intervention	Drug (pharmaceutical) in treatment arms	Atenolol (+thiazide as needed) vs

		amlodipine (+ perindopril as needed)
	Initial drug dose	See treatment algorithm (tab 1 in paper)
	Actual usage	
Population characteristics	Mean age	63
	Age range	40-79
	Sex	Male: 77% Female: 23%
	Ethnicity (frequency)	White: 95%
	Comorbidity (frequency CVD, diabetes)	Diabetes: 27% Atrial fibrillation:1% Peripheral vasc disease: 6%
	Concomittant medication	Lipid lowering therapy: 10-11% Aspirin: 19%
	N intervention	9639
	N control	9618
	N excluded	?
	N lost to follow-up	49
	Discontinuance (n, percent)	60 withdrew consent
	Crossover (n, percent)	
Method	Criteria for inclusion	Untreated HT 160/100 Treated HT 140/90 + 3 additional risk factors
	Criteria for exclusion	Previous MI, CV event previous 3 months, currently treated angina, TG> 4,5, HF, uncontrolled arrhythmias
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Log Rank, Cox, Kaplan Meier
	Power calculation description	80%, two sided sign level 5%
Results	Primary endpoint of study	
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Amlodipine (AM) / Atenolol (AT): Bradycardia 0.4% / 6%; Chest pain 8% / 9%; Cough 19% / 8%; Diarrhoea 4% / 6%; Dizziness 12% / 16%; Dyspnoea 6% / 10%; Eczema 5% / 4%; Erectile dysfunction 6% / 7%; Fatigue 8% / 16%; Joint swelling 14% / 3%; Lethargy 2% / 5%; Oedema peripheral 23% / 6%; Peripheral coldness 1% / 6%; Vertigo 7% / 8%

Events	Atenolol (beta-blocker)	Amlodipine (CCB)

	N = 9618	N= 9639
Total mortality	820	738
All stroke	422	327
All CHD	852	753
Unstable angina	106	73
Chronic angina	208	205
HEART FAILURE fatal and nonfatal	159	134
Diabetes	799	567

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Ogihara, 2008, CASE-J (53)
	Setting	Not reported in article
	Country	Japan
	Aim (as described in the article)	To compare the long-term effects of candesartan (ARB) and amlodipine (CCB) on cardiovascular events in high-risk Japanese patients.
	Study design	RCT
	Inclusion period (year start-year end)	Sept 01 to Dec 02
	Mean follow-up (year)	3.2 y
Intervention	Drug (pharmaceutical) in treatment arms	Candesartan/amlodipine
	Initial drug dose	4 to 8 mg/2.5 to 5 mg
	Actual usage	Not reported
Population characteristics	Mean age	63.8 y
	Age range	Not reported
	Sex	Candesartan: 46.4%/amlodipine: 43.2%
	Ethnicity (frequency)	Not reported
	Comorbidity (frequency CVD, diabetes)	Type 2 diabetes: 42.9%/42.9% History of cerebrovascular events: 10.5%/9.6% History of cardiac events: 42.8%, 43.6% History of renal events: 24.3%/23.1%
	Concomittant medication	Only reported for ”through-out the Follow-up period”: Antihypertensives: 54.2%/42.7%

		Antihyperlipidemics: 44.6%/43.9% Anntithrombotics: 27.7%/26.4% Antianginal: 11.2%/11.9%
	N candeasartan-group	2354
	N amlodpine-group	2349
	N excluded	25
	N lost to follow-up	36
	Discontinuance (n, percent)	Not reported
	Crossover (n, percent)	Not reported
Method	Criteria for inclusion	BP > 140/90 for persons < 70y; BP > 160/90 for persons > 70y; and at least on of the following: Severe hypertension, diabetes mellitus type 2; history of stroke or TIA > 6 months ealier, left ventricular hypertrophy; angina pectoris; myocardial infarction > 6 months earlier; proteinuria or createine concentration > 1.3 mg/dL; arteriosclerotic peripheral artiery obstruction.
	Criteria for exclusion	See Hypertens Res. 2003; 26: 979-990
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Kaplan Meier method, Hazard Ratio (95% CI)
	Power calculation description	Yes
Results	Primary endpoint of study	Fatal/non-fatal cardiovascular event
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratios (95% CI)
	Adverse events	Not reported

Events	Candesartan	Amlodipine
	N=2354	N=2349
Primary composite	134	134
All-cause mortailty	73	86
Sudden death	11	15
Stroke	60	47
Acute myocardial infarction	17	18
Angina pectoris	8	14
Heart failure	20	16
Endstage renal disease	4	10

New-onset diabetes	66	104

Antihypertensives in persons with diabetes

Drug versus placebo

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Curb, 1996, SHEP (54)
	Setting	Multiple clinical and support centres
	Country	USA
	Aim (as described in the article)	To assess the effect of low-dose, diuretic-based antihypertensive treatment on major cardiovascular disease rates in older, non-insulin treated diabetic patients with isolated systolic hypertension compared with nondiabetic patients.
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	
Intervention	Drug (pharmaceutical) in treatment arms	Chlorthalidone Atenolol added (25-50 mg/d) if target blood pressure was not reached
	Initial drug dose	12.5 – 25mg/d
	Actual usage	
Population characteristics	Mean age	Active: 70.2y, placebo: 70.5y
	Age range	
	Sex	Active: 47% women, placebo: 52% women
	Ethnicity (frequency)	Active: black 18.4%, placebo 21% black
	Comorbidity (frequency CVD, diabetes)	MI: 5.3% / 5.0% Stroke: 2.1% / 2.0%
	Concomittant medication	
	N intervention	283
	N control	300
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	

	Crossover (n, percent)		
Method	Criteria for inclusion	Over 60y, men and women, isolated systolic hypertension, SBP >160mmHg ans DBP <95mmHg	
	Criteria for exclusion	Major CVD such as recent MI or stroke, other major diseases as cancer. Treatment for diabetes	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)		
	Power calculation description		
Results	Primary endpoint of study	Combined fatal and nonfatal stroke	
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)		
	Adverse events		

Events	Placebo	Diuretic
	N= 300	N= 283
Total mortality	48	39
Nonfatal MI + fatal CHD	34	18
Stroke	36	25
Major CVD	83	57

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Safar, 2003, SYST-EUR (55) Subgroup analysis on type 2 diabetes
	Setting	198 centres
	Country	Countries in East and West Europe
	Aim (as described in the article)	Risk reduction of cardiovascular events in elderly type 2 patients with isolated systolic hypertension by nitrendipine versus placebo
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	2y
Intervention	Drug (pharmaceutical) in treatment arms	Nitrendipine

	Initial drug dose	10-40mg/day Additional treatment as necessary
	Actual usage	
Population characteristics	Mean age	Population characteristics not givenin this publication
	Age range	-
	Sex	-
	Ethnicity (frequency)	-
	Comorbidity (frequency CVD, diabetes)	Diabetes. In total in SYST-EUR: Stroke 1.23%, MI 3.5%
	Concomittant medication	
	N intervention	278
	N control	269
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	60y or older, diabetes, elevated blood pressureof SBP 160-219mmHg and DBP <95mmHg, no cardiovascular complications
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, log-rank test
	Power calculation description	
Results	Primary endpoint of study	Cardiovascular mortality and total cardiovascular events
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio
	Adverse events	

Events	Placebo	Nitrendipine
	N= 269	N= 278
Total mortality	27	19
CVD mortality	16	5
Stroke	16	6
All CVD	35	15
All CHD	19	8

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Brenner, 2001, RENAAL (56)
	Setting	250 medical centres
	Country	Multinational: 28 countries
	Aim (as described in the article)	To assess the role of losartan in patients with diabetes type 2 and nephopathy versus placebo
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	3.4y: Study discontinued February 2001
Intervention	Drug (pharmaceutical) in treatment arms	Losartan: angiotensin-II receptor antagonist
	Initial drug dose	50mg once daily, increased to 100mg daily after four weeks if target blood pressure was not reached
	Actual usage	
Population characteristics	Mean age	Losartan: 60±7y, placebo 60±7
	Age range	
	Sex	Losartan, 462men and 289 women Placebo, 494 men and 268 women
	Ethnicity (frequency)	Asian – Losartan 15.6%, placebo 17.7% Black– Losartan 16.6%, placebo 13.8% White– Losartan 47.7%, placebo 49.6% Hispanic– Losartan 18.6%, placebo 17.8% Other– Losartan 1.5%, placebo 1.0%
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intervention	751
	N control	762
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	Placebo 53.5%, Losartan 46.5%
	Crossover (n, percent)	
Method	Criteria for inclusion	31-70 y, type 2 diabetes, nephropathy,
	Criteria for exclusion	Type 1 diabetes, nondiabetic renal disease, myocardial infarction or coronary artery bypass grafting within previous month, stroke or PCTA

		within last six months, TIA within last year, history of heart failure.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Kaplan Meier
	Power calculation description	
Results	Primary endpoint of study	Composite endpoint of a doubling of serum creatinine concentration, end-stage renal disease, or death
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ration
	Adverse events	Discontinuation; Losartan 46.5%, Placebo 53.5%

Events	Placebo	Losartan
	N= 762	N= 751
Total mortality	155	158
Renal failure	194	147
Composite endpoint	359	327

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Lewis, 2001, IDNT (57, 58)
	Setting	210 clinical centres
	Country	USA
	Aim (as described in the article)	Progression of nephropathy
	Study design	RCT
	Inclusion period (year start-year end)	March 1996 – February 1999
	Mean follow-up (year)	2.6y
Intervention	Drug (pharmaceutical) in treatment arms	Irbesartan, amlodipine, placebo
	Initial drug dose	Irbesartan 300 mg daily, amlodipine 10mg daily.
	Actual usage	
Population characteristics	Mean age	
	Age range	
	Sex	Men and women

	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intervention	Irbesartan: 579, amlodipin: 567
	N control	569
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	23.7% overall
	Crossover (n, percent)	
Method	Criteria for inclusion	30-70y, type 2 diabetes, hypertension, proteinuria, serum creatinine 1-3mg/dl in men and 1.2-3 in women.
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Product-limit survival curve and log-rank test, Cox
	Power calculation description	
Results	Primary endpoint of study	Primary composite endpoint of a doubling of base-line serum creatinine consentration, endstage renal disease, or death of any cause. Cardiovascular composite endpoint of death from CVD, nonfatal MI, heart failure resulting in hospitalization, cerebrovascular event, or lower limb amputation above the ankle.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Early increase in serum creatinine conc –stopped study medication. Hyperkalemis: irbesaratn 11/11.9%,Amlodipine 3 /0.5%, Placebo 2/0.4%.discontinunance overall 23.7%. Al least one serious event overall: 61% Rate of adverse events per 1000 days lowest in Irbasartan gr. Than amlodipine and placebo (p=0.002)

Events	Placebo	Amlodipine
	N= 569	N= 567
All cause mortality	93	83
Cardiovascular composite endpoint	185	161
MI	46	27
CVD death	46	37
Stroke	26	15

Heart failure	72	93
Revascularizations	36	28
End stage renal disease	101	104

Events	Placebo	Irbesartan
	N= 569	N= 579
All cause mortality	93	87
Cardiovascula composite endpoint	185	172
MI	46	44
CVD death	46	52
Stroke	26	28
Heart failure	72	60
Revascularizations	36	27
End stage renal disease	101	82

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	M Marre, 2005, DIAB-HYCAR (59)
	Setting	Mostly GP
	Country	16 European and north African countries
	Aim (as described in the article)	Investigate whether low-dose ramipril lowers CV and renal events in type II diabetics with microalb. or proteinuria
	Study design	Randomised, double blind
	Inclusion period (year start-year end)	1995-1998, follow-up to 2001
	Mean follow-up (year)	4 (median), range 3-6
Intervention	Drug (pharmaceutical) in treatment arms	Ramipril (in addition to usual treatment) versus placebo
	Initial drug dose	1.25 mg
	Actual usage	
Population characteristics	Mean age	65
	Age range	> 50
	Sex	1701+1731 M, 742+738 F

	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intervention	2443
	N control	2469
	N excluded	Twenty investigators who had included 25 patients: no data after randomisation and refused site visits
	N lost to follow-up	160 (62+98)
	Discontinuance (n, percent)	Drop-outs 678 (344+334)
	Crossover (n, percent)	
Method	Criteria for inclusion	>50 yrs, type II diabetes, >20 mg/L albuminuria in two successive samples
	Criteria for exclusion	Serum creatinin > 150 μmol/L, insulin treatment, ACE-inhibitor or AT-antagonist treatment
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Relative risk reduction. Kaplan-Meier and log-rank test. Cox model of single covariate, Chi square. Intention-to-treat
	Power calculation description	
Results	Primary endpoint of study	Combined incidence of CV death, non-fatal acute MI, stroke, heart failure requiring hospitalisation, and renal failure (req. of haemodialysis)
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio 1.03 (0.89-1.20), P=0.65 None of the components of the primary outcome was reduced
	Adverse events	Coughing: R 3.3%, P 0.9% Angio-oedema R 1, P 1 Serious adverse events: R 43.25, P 44.4% Nonserious adverse events: R 6.3%, P 4.0%

Events	Placebo	Ramipril
	N= 2469	N= 2443
Combined	377	362
CVD death	133	141
Total mortality	324	334
MI nonfatal	59	52
MI nonfatal and fatal	78	61
Stroke nonfatal	84	89

Stroke nonfatal and fatal	116	118
Heart failure	102	85
Endstage renal disease	12	11
Revascularization	201	179

Quality assessment by the review group	Study quality rating (according to check list) High/++	
Study description	Author, year, study name	ADVANCE Collaborative Group, 2007, ADVANCE (60)
	Setting	215 collaborative centres
	Country	20 countries in Asia, Australasia, Europe and North-America
	Aim (as described in the article)	To assess the effects of routine administration of and ACE-inhibitor-diuretic combination on serious vascular events in patients with diabetes, irrespective of initial blood pressure levels or the use of other blood pressure lowering drugs.
	Study design	RCT
	Inclusion period (year start-year end)	Completed June 2007
	Mean follow-up (year)	4.3 years
Intervention	Drug (pharmaceutical) in treatment arms	Perindopril (6.25 mg) + indapamide (0.625 mg) or matching placebo
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	66 years in both groups
	Age range	
	Sex	43% female in both groups
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	History of major macrovascular disease: 32% in both groups
	Concomittant medication	BP lowering drugs: 75% in both groups Aspirin: 44% in both groups Statins: 28% (P+I) and 29% (placebo) Oral hypoglycaemic drug: 91% in both groups
	N intervention	5569
	N control	5571
	N excluded	1737 (after run-in period)

	N lost to follow-up	15
	Discontinuance (n, percent)	27% in P+I group; 26% in placebo-group
	Crossover (n, percent)	Ca. 55% in placebo group on perindopril at end of follow-up
Method	Criteria for inclusion	55 years or older; diagnosed with diabetes type 2 after 30 years of age; previous history of major cardiovascular disease or at least one other risk factor for cardiovascular disease. No blood pressure criteria for inclusion.
	Criteria for exclusion	Definite indication or contraindication to any study treatment or the HbA1c target, definite indication for insulin therapy, current participation in another trial
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Unadjusted Cox proportional hazard models.
	Power calculation description	Yes
Results	Primary endpoint of study	Composite of major macrovascular and microvascular events.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RRR (95% CI)
	Adverse events	

Events	Placebo	Perindopril and indapamide
	N=5571	N=5569
Composite of major macro- and microvascular events	938	861
CVD death	257	211
Total mortality	471	408
Major coronary events	294	265
Major cerebrovascular events	218	215

Participants had impaired glucose tolerance

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	The DREAM Trial Investigators, 2006, DREAM (61)
	Setting	191 study sites
	Country	21 countries

	Aim (as described in the article)	To study if blockade of renin-angiotensin system may prevent diabetes
	Study design	Double-blind randomised study, 2x2 factorial design. This report is about Ramipril versus placebo
	Inclusion period (year start-year end)	July 2001-August 2003
	Mean follow-up (year)	Median 3y
Intervention	Drug (pharmaceutical) in treatment arms	Ramipril vs placebo
	Initial drug dose	5 mg start dose increasing to max 15 mg Ramipril
	Actual usage	
Population characteristics	Mean age	Ramipril 54.7y ; placebo 54.7y
	Age range	
	Sex	Women: Ramipril 59.7%, placebo 58.7%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	No history ofCVD
	Concomittant medication	
	N intervention	2623
	N control	2646
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	Participant decision R 17.4%, P 17.7% Cough R 9.7%, P 1.8% Advice from physician R 2.3%, P 2.5% Peripheral oedema R 1.0%, P 1.1%
	Crossover (n, percent)	
Method	Criteria for inclusion	Impaired fasting glucose levels or impaired glucose tolerance (IGT),
	Criteria for exclusion	History of CVD,diabetes, intolerance for study drug
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	
	Power calculation description	Yes
Results	Primary endpoint of study	Development of diabetes or death, whichever came first
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Cough R 9.7%, P 1.8% Peripheral oedema R 1.0%, P 1.1%

	Angio oedema R 0.1%, P 0.2%	
Events	Placebo	Ramipril
	N= 2646	N= 2623
Diabetes	489	449
Total mortality	32	31
Primary composite endpoint	517	475
MI	11	13
Stroke	8	4
CVD death	10	12
HEART FAILURE	4	12
New angina	20	24
Revascularisation	35	27

Drug versus drug

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Lindholm, 2000, STOP-2 (62)
	Setting	Health centres
	Country	Sweden
	Aim (as described in the article)	Examine the effect of treating hypertension in elderly persons with diabetes. Post-hoc analysis
	Study design	RCT; randomisation correct for this subgroup of patients with NIDDM
	Inclusion period (year start-year end)	
	Mean follow-up (year)	
Intervention	Drug (pharmaceutical) in treatment arms	Diuretic/ beta-blocker; atenolol, metoprolol, pindolol or hydrochlorthiazide plus amiloride. CCB; felodipine or isradipine Angiotensin converting enzyme (ACE); enalapril or lisinopril.
	Initial drug dose	
	Actual usage	
Population	Mean age	All 75.8y

characteristics	Age range	
	Sex	All 39.8% men
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	All: Mi 4.2%, stroke 5.0%, ischaemic heart disease 9.3%
	Concomittant medication	
	N Diuretic/ β-blocker	253
	N CCB	231
	N ACE	235
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	70-84y, diabetes mellitus,
	Criteria for exclusion	See main study description
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox
	Power calculation description	
Results	Primary endpoint of study	Prevention of cardiovascular mortality
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio
	Adverse events	

Events	Diureetic/ beta-blocker	ACE
	N= 253	N= 235
Total mortality	67	56
MI	26	17
Stroke	39	34
All CVD	82	67
Congestive heart failure	29	22
CVD mortality	45	39

Events	Diureetic/beta-blocker	CCB
	N= 253	N= 231
Total mortality	67	50
MI	26	32

Stroke	39	29
All CVD	82	69
Congestive heart failure	29	24
CVD mortality	45	33

Events	ACE	CCB
	N= 235	N= 231
Total mortality	56	50
MI	17	32
Stroke	34	29
All CVD	67	69
Congestive heart failure	22	24
CVD mortality	39	33

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Hansson, 2000, NORDIL (45)
	Setting	Health centres
	Country	Norway and Sweden
	Aim (as described in the article)	Compare the effects of diltiazem, a nonhydropyridine calcium antagonist, with that of diuretics, beta-blocker, or both on cardiovascular morbidity and mortality in hypertensive patients.
	Study design	RCT (“PROBE”)
	Inclusion period (year start-year end)	
	Mean follow-up (year)	
Intervention	Drug (pharmaceutical) in treatment arms	Diltiazem versus diuretics, beta-blocker, or both. Stepped treatment in diltiazem group was ACE, then diuretic or beta-blocker, then any other antihypertensive compound. Other hypertensive compounds could be added to conventional treatment to achieve blood pressure target.
	Initial drug dose	Diltiazem 180-360 mg/day
	Actual usage	
Population characteristics	Mean age*	Diltiazem 60.5y / conventional 60.3y
	Age range	

	Sex*	Women: diltiazem, 51.5%, conventional 51.3%
	Ethnicity (frequency)	
	Comorbidity* (frequency CVD, diabetes)	Previous MI 2.1% /2.2% Previous IHD 2.3% / 2.6% Previous stroke 1.4% / 1.6% Diabetes mellitus 6.5% / 6.9%
	Concomittant medication	
	N diltiazem	351
	N conventional	376
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	50-74 y, DBP >100 mmHg, previously untreated, but could be included
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox regression, Kaplan Meier
	Power calculation description	Yes
Results	Primary endpoint of study	Combined endpoint of fatal and nonfatal stroke, MI, and other cardiovascular death
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Subgroup analyses on sex, age, and blood pressure in other publication
	Adverse events	Diltiazem (DG) / Diuretic and beta-blocker (DBB) in%: Dizziness 9.3 / 8.9; Arthralgia 7.7 / 7.1; Headaches 8.5 / 5.7; Chest discomfort 5.7 / 5.9; Coughing 5.6 / 5.4; Fatigue 4.4 / 6.5; Back pain 4.7 / 5.4; Depression 3.7 / 3.4; Abdominal pain 3.5 / 3.4; Dyspnoea 2.9 / 3.9; Myalgia 3.2 / 3.4 ; Impotence 2.3 / 3.7

Events	Diuretic + beta-blocker	Diltiazem
	N = 376	N= 351
Total mortality	26	28
Stroke	20	20
Fatal stroke	3	1
MI	18	17

Fatal MI	2	5
Heart failure	7	13

*These figures are for all study-particiapants, not the diabetes sub-group.

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Niskanen, 2001, CAPPP (63)
	Setting	536 Health Centers
	Country	Sweden and Finland
	Aim (as described in the article)	Compare whether an ACE-inhibitor reduces the risk of cardiovascular events compared to a diuretic/beta-blocker treatment. Subgroup analysis of patients with diabetes.
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	
Intervention	Drug (pharmaceutical) in treatment arms	Captopril versus diuretic/beta-blocker
	Initial drug dose	Captopril -100mg/day
	Actual usage	
Population characteristics	Mean age	55.0y/55.7y
	Age range	
	Sex	M/F: 196/113 and 158/105
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	MI: 7 (2.3%) /5 (1.9%) , stroke 8 (2.6%) /2 (0.8)
	Concomittant medication	
	N captopril	309
	N diuretic/beta-blocker	263
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	25-66y, diabetes, untreated hypertension, DBP > 100mmHg
	Criteria for exclusion	Secondary hypertension, serum creatinine > 150µmol/l,

	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	
	Power calculation description	
Results	Primary endpoint of study	Combination of fatal and nonfatal MI and stroke as well as other CVD deaths
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	

Events	Diureetic/beta-blocker	Captopril
	N= 263	N= 309
Total mortality	34	20
MI	27	12
Stroke	19	23
All cardiac events	63	54
Primary endpoint	46	35
Heart failure	17	11

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Lindholm, 2002 LIFE (64)
	Setting	
	Country	All Nordic countries, UK, US
	Aim (as described in the article)	To determine whether losartan reduces cardiovascular event rates in lower-risk hypertensive patients; subgroup study in patients with diabetes.
	Study design	RCT, double blind
	Inclusion period (year start-year end)	June 1995 to May 1997
	Mean follow-up (year)	4 .7y
Intervention	Drug (pharmaceutical) in treatment arms	Losartan (angiotensin-II antagonist) versus atenolol (beta-blokker)
	Initial drug dose	L: 50-100 mg/d; A: 50-100 mg/d Other hypertensive treatment as needed
	Actual usage	

Population characteristics	Mean age	Losartan / atenolol: 67.4y / 67.4y	
	Age range		
	Sex	52% / 55% women	
	Ethnicity (frequency)	White: 86% / 85% Black: 11% / 12% Hispanic: 2% / 2% Asian: 0.9% / 0.8% Other: 0.2% / 0.2%	
	Comorbidity (frequency CVD, diabetes)	Any vascular disease: L: 35% (MI 24%, stroke 12%, PAD 7%) / A: 35% (MI 24%, stroke 12%, PAD 8%)	
	Concomittant medication		
	N Losartan	586	
	N Atenolol	609	
	N excluded		
	N dropped out	L: 32 / A: 36	
	Discontinuance (n, percent)		
	Crossover (n, percent)		
Method	Criteria for inclusion	55-80y, essential hypertension of 160-200/95-115 mmHg, ECG-defined left ventricular hypertrophy	
	Criteria for exclusion		
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Kaplan Meier	
	Power calculation description	Yes	
Results	Primary endpoint of study	Composite endpoint: first occurrence of cardiovascular death, stroke or clinically evident MI	
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio	
	Adverse events		

Events	Atenolol	Losartan
	N = 609	N= 586
Composite endpoint	139	103
CVD death	61	38
All stroke	65	51
All MI	50	41
Total mortality	104	63

Hospitalised for angina	30	30
Heart failure	55	32
Revascularization	70	62

Quality assessment by the review group	Study quality rating (according to check list) High /++	
Study description	Author, year, study name	Mancia, 2003, INSIGHT (65)
	Setting	
	Country	Italy
	Aim (as described in the article)	Compare outcome for cardiovascular morbidity and mortality in patients with hypertension and diabetes receiving either nifedipine or co-amilozide. Prespecified subgroup analysis of patients with diabetes
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	
Intervention	Drug (pharmaceutical) in treatment arms	Nifedipine Co-amilozide
	Initial drug dose	Nifedipine: 30mg/d Coamelioride: 25 mg hydrochlorthiazide and 2.5mg amiloride Doses increased to achieve target BP
	Actual usage	
Population characteristics	Mean age	<60y – 21%, 60-70y – 49.5%, >70y – 31.4%
	Age range	
	Sex	Women 51.8%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	ALL: MI 6.1%, LVH 11.2%, PAD 76%
	Concomittant medication	
	N Nifedipine	649
	N Co-amilozide	653
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	

	Crossover (n, percent)	
Method	Criteria for inclusion	55-80y, hypertension, at least one additional cardiovascular risk factor
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Logistic regression
	Power calculation description	Yes
Results	Primary endpoint of study	Composite of cardiovascular death, myocardial infarction, heart failure and stroke
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	

Events	Co-ameliozide	Nifedipine
	N= 653	N= 649
Total mortality	59	44
MI + sudden death	25	28
Stroke	19	17
Major CVD	49	46
Congestive heart failure	6	9
CVD mortality	19	19

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Holman, 1998, UKPDS 39 (66)
	Setting	20 diabetes centres
	Country	UK
	Aim (as described in the article)	Compare effect of tight blood pressure control with either a beta-blocker or an angiotensin converting enzyme inhibitor on macrovascular and microvascular complications of type 2 diabetes.
	Study design	RCT
	Inclusion period (year start-year end)	1987-91
	Mean follow-up (year)	9y

Intervention	Drug (pharmaceutical) in treatment arms	Atenolol - beta-blocker Captopril - angiotensin converting enzyme inhibitor. All treated with diet alone prior to study start. Additional drugs to achieve a tight BP controle as necessary
	Initial drug dose	Atenolol: 50-100 mg daily Captopril: 25-50 mg twice daily
	Actual usage	
Population characteristics	Mean age	56.3y / 56.0y
	Age range	
	Sex	Men: 51% / 57%
	Ethnicity (frequency)	White: 87% / 57%
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N Captopril	400
	N Atenolol	358
	N control	390
	N lost to follow-up	14 (1%) emigrated, 33 (3%) could not be contacted
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Type 2 diabetes, hypertension,
	Criteria for exclusion	Ketonuria > 3 mmol/l, history of MI last year, current angina or heart failure, more than one major vascular episode, serum creatinine >75 µmol/l, malignant hypertension, other relevant cause.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Kaplan Meier, Cox
	Power calculation description	
Results	Primary endpoint of study	1. clinical edpoint related to diabetes, 2. death related to diabetes, 3. death from all causes
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio
	Adverse events	Weight gain: Atenolol 3.4 kg, captopril 1.6 Kg (p=0.02)

Events	Atenolol	Captopril
	N= 358	N= 400
Total mortality	59	75
MI	46	61
Stroke	17	21

Angina	25	20
Renal failure	4	4
Heart failure	9	12
Diabetes related endpoint	118	141

Quality assessment by the review group	Study quality rating (according to check list) Moderate /+	
Study description	Author, year, study name	Tatti, 1998, FACET (67)
	Setting	Outpatients clinic
	Country	Italy
	Aim (as described in the article)	To assess treatment related differences in serum lipids and diabetes controlin hypertensive patients with type 2 diabetes.
	Study design	RCT
	Inclusion period (year start-year end)	January – December 1992
	Mean follow-up (year)	3.5y
Intervention	Drug (pharmaceutical) in treatment arms	Fosinopril – ACE inhibitor Amlodipine – Calcium channel blocker
	Initial drug dose	Fosinopril: 20mg/day (morning) Amlodipine: 10mg/day (evening)
	Actual usage	
Population characteristics	Mean age	Fosinopril: 62.8y, Amlodipine: 63.3y
	Age range	
	Sex	Fosinopril: 36.5% women, Amlodipine: 44.5% women
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	No CVD
	Concomittant medication	
	N Fosinopril	189
	N Amlodipine	191
	N excluded	
	N lost to follow-up	

	Discontinuance (n, percent)	F 36 patients, A 52 patients (p=0.06)
	Crossover (n, percent)	
Method	Criteria for inclusion	Hypertension, NIDDM
	Criteria for exclusion	History of coronary heart disease, stroke, or other morbid condition with poor prognosis, serum creatinine >1.5mmol/l, micralbuminuria >40µg/min, use of lipid lowering drugs, aspirin or antihypertensive agents other than diuretics and beta-blockers.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Kaplan Meier, Cox. Intention to treat
	Power calculation description	Yes
Results	Primary endpoint of study	Effect on serum lipids and diabetes incidence
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio
	Adverse events	Cause of discontinuance not given: F 36 patients, A 52 patients (p=0.06)

Events	Amlodipine	Fosinopril
	N= 191	N= 189
Total mortality	5	4
MI	13	10
Stroke	10	4
Hospitalization for angina	4	0
All CVD	27	14
Revascularization	3	3

Quality assessment by the review group	Study quality rating (according to check list) Moderate /+	
Study description	Author, year, study name	Schrier, 2000, ABCD (68)
	Setting	
	Country	USA
	Aim (as described in the article)	To test the hypothesis that intensive lowering of blood pressure would be associated with a reduced risk of cardiovascular events in normotensive patients with peripheral arterial disease (PAD) and type 2 diabetes. Within each group participants were randomised to either enalapril or nisoldipine (as needed in the less intensive treatment group)
	Study design	RCT

	Inclusion period (year start-year end)	
	Mean follow-up (year)	5.3y
Intervention	Drug (pharmaceutical) in treatment arms	Nisoldipine versus enalapril
	Initial drug dose	Nisoldipine,10 mg/day Enalapril, 5 mg/day
	Actual usage	
Population characteristics	Mean age	59.4y enalapril, 59.1y nisoldipine
	Age range	
	Sex	Male 53/56%
	Ethnicity (frequency)	White 74/73%, Black 8/6%, Hispanic 16/19%
	Comorbidity (frequency CVD, diabetes)	CAD: Enalapril 23%, nisoldipine 25% Stroke: Enalapril 3%, nisoldipine 3%
	Concomittant medication	
	N enalapril	246
	N nisoldipine	234
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	Adverse events: N 54 patients, E 41 patients “voluntary” N38, E 41 Death or CVD event N 50, E 41
	Crossover (n, percent)	
Method	Criteria for inclusion	40-74y, normotensive, type 2 diabetes
	Criteria for exclusion	Known allergy for dihydropyridines or ACE inhibitor, had MI or stroke within last 6 months, had coronary artery bypas surgery last 3 months, angina last 6 months, congestive heart failure, inneed of ACE or CCB, received hemo- or periotoneal dialysis, serum creatinine >3mg/dl.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Logistic regression
	Power calculation description	
Results	Primary endpoint of study	Effect of intensive versus moderate blood pressure control on change in 24-h creatinine clearance which was assessed every 6 months
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	OR
	Adverse events	Adverse events: N 54 patients, E 41 patients

Events	Nisoldipine	Enalapril

	N= 235	N= 235
All cause mortality	17	13
MI	25	5
Cerebrovascular accident	11	7
Congestive heart failure	6	5
CVD death	10	5

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Lewis, 2001, IDNT (57, 58)
	Setting	210 clinical centres
	Country	USA
	Aim (as described in the article)	Progression of nephropathy
	Study design	RCT
	Inclusion period (year start-year end)	March 1996 – February 1999
	Mean follow-up (year)	2.6y
Intervention	Drug (pharmaceutical) in treatment arms	Irbesartan, amlodipine, placebo
	Initial drug dose	Irbesartan 300 mg daily, amlodipine 10mg daily.
	Actual usage	
Population characteristics	Mean age	
	Age range	
	Sex	Men and women
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intervention	Irbesartan: 579, amlodipin: 567
	N control	569
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	23.7% overall

	Crossover (n, percent)	
Method	Criteria for inclusion	30-70y, type 2 diabetes, hypertension, proteinuria, serum creatinine 1-3mg/dl in men and 1.2-3 in women.
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Product-limit survival curve and log-rank test, Cox
	Power calculation description	
Results	Primary endpoint of study	Primary composite endpoint of a doubling of base-line serum creatinine consentration, endstage renal disease, or death of any cause. Cardiovascular composite endpoint of death from CVD, nonfatal MI, heart failure resulting in hospitalization, cerebrovascular event, or lower limb amputation above the ankle.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Early increase in serum creatinine conc. –stopped study medication. Hyperkalemias: irbesartan 11/1.9%, amlodipine 3 /0.5%, placebo 2/0.4%.discontinunance overall 23.7%. At least one serious event overall: 61% Rate of adverse events per 1000 days lower in Irbasartan gr. than in amlodipine and placebo (p=0.002)

Events	Amlodipine	Irbesartan
	N= 567	N= 579
All cause mortality	83	87
Cardiovascula composite endpoint	161	172
MI	27	44
CVD death	37	52
Stroke	15	28
Heart failure	93	60
Revascularizations	28	27
End stage renal disease	104	82

Quality assessment by the review group	Study quality rating (according to check list) Moderate /+

Study description	Author, year, study name	Barnett, 2004, DETAIL (69)
	Setting	39 centers
	Country	Nortern Europa
	Aim (as described in the article)	Compare the effect of telmisartan and enalapril on the change in the glomerular filtration rate over a five-year period
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	
Intervention	Drug (pharmaceutical) in treatment arms	Telmisartan versus Enalapril
	Initial drug dose	Telmisartan: 40-80 mg/day, Enalapril: 10-20mg/day
	Actual usage	
Population characteristics	Mean age	Telemisartan: 61.2y, Enalapril: 60.0y
	Age range	
	Sex	Telemisartan: 72.5% men, Enalapril: 73.1% men
	Ethnicity (frequency)	Telemisartan: 98.3% white Enalapril: 98.5% white
	Comorbidity (frequency CVD, diabetes)	History of CVD: Telmisartan: 49.2%, Enalapril: 48.5%
	Concomittant medication	
	N telmisartan	120
	N enalapril	130
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	Telemisartan 20 subjects, enalapril 30 subjects
	Crossover (n, percent)	
Method	Criteria for inclusion	35-80y, men and women, type 2 diabetes, diabetes had to have been treated by diet for one year, diet plus oral hypoglycaemic drugs (one year), or insulin preceded by treatment with oral agents (one year). Mild to moderate hypertension, normal renal morphology.
	Criteria for exclusion	Any condition other than cardiovascular disease that could restrict survival, allergy to the drugs used in the study.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	
	Power calculation description	Yes
Results	Primary endpoint of study	Change in glomerular filtration rate after five years

	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Serious events: T 115, E 130. No changes in routine haematologicic or blood chemical values in either group

Events	Telmisartan	Enalapril
	N= 120	N= 130
Total mortality	6	6
MI, non-fatal	9	6
Stroke	6	6
Congestive heart failure	9	7

Serum glucose reducing drugs:

Persons with impaired glucose tolerance:
STOP-NIDDM 2003 (70), DREAM 2006 (71)

Persons with type 2-diabetes:
UKPDS 33 1998 (72), UKPDS 34 1998 (73), RECORD 2007 (74)

Impaired glucose tolerance:

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Chiasson, 2003, STOP-NIDDM (70)
	Setting	Hospitals
	Country	Canada, Germany, Austria, Norway, Denmark, Sweden, Finland, Israel and Spain
	Aim (as described in the article)	To evaluate the effect of decreasing postprandial hyperglycemia with acarbose on the risk of cardiovascular disease and hypertension in patients with impaired glucose tolerance
	Study design	RCT, double blind, multicenter,
	Inclusion period (year start-year end)	
	Mean follow-up (year)	
Intervention	Drug (pharmaceutical) in treatment arms	Acarbose
	Initial drug dose	100 mg x 3/d
	Actual usage	
Population characteristics	Mean age	54,5
	Age range	
	Sex	M 49%, F 51%
	Ethnicity (frequency)	White 97%
	Comorbidity (frequency CVD, diabetes)	NA
	Concomittant medication	
	N intervention	682
	N control	686

	N excluded	61
	N lost to follow-up	
	Discontinuance (n)	341
	Crossover (n, percent)	
Method	Criteria for inclusion	Patients with impaired glucose tolerance
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Kaplan Meier
	Power calculation description	Yes
Results	Primary endpoint of study	Major cardiovascular events (CHD, CV death, congestive heart failure, cerebrovascular event and peripheral vascular disease) and hypertension (140/90)
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio
	Adverse effects	GI symptoms significantly more frequent in Acarbose gr. Of mild to moderat severiry. No seious adverse events were related to stud drug.

Events	Placebo	Acarbose
	N= 686	N= 682
Cardiovascular death	2	1
Myocardial infarction	12	1
Stroke	4	2
CVD	32	15
Angina	12	5
Revaskulering	20	11
Heart failure	2	0

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	The DREAM Trial Investigators, 2006, DREAM (71)
	Setting	191 study sites
	Country	21 countries

	Aim (as described in the article)	To assess whether rosiglitazone prevent type 2 diabetes in high risk patients
	Study design	Double-blind randomised study, 2x2 factorial design. This report is about rosiglitazone versus placebo
	Inclusion period (year start-year end)	July 2001-August 2003
	Mean follow-up (year)	Median 3y
Intervention	Drug (pharmaceutical) in treatment arms	Rosiglitazone vs placebo
	Initial drug dose	4 mg start dose increasing to max 15 mg rosiglitazone
	Actual usage	
Population characteristics	Mean age	rosiglitazone 54.7y; placebo 54.7y
	Age range	
	Sex	Women: rosiglitazone 58.3%, placebo 60.1%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	No history of CVD
	Concomittant medication	
	N intervention	2635
	N control	2636
	N excluded	
	N lost to follow-up	2%
	Discontinuance (n, percent)	Study drug: 28.3%, placebo 24.9%
	Crossover (n, percent)	
Method	Criteria for inclusion	Impaired fasting glucose levels or impaired glucose tolerance (IGT),
	Criteria for exclusion	History of CVD,diabetes, intolerance for study drug
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Kaplan Meier, wilcoxon rank-sum analysis
	Power calculation description	Yes
Results	Primary endpoint of study	Development of diabetes or death whichever came first
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio
	Adverse effect	Reason for stopping : participant refusal R 18.9% and P 16.7% oedema R 4.8%, P 1.6%.; physicians advice R 1.9%, P 1.5%; weight gain R 1.9%, P 0.6% Hypoglycaemia R 1 patient, P 3 patients.

Events	Placebo	Rosiglitazone
	N= 2634	N= 2635
Diabetes	658	280
Total mortality	33	30
Primary composite endpoint	686	306
MI	9	15
Stroke	5	7
CVD death	10	12
HEART FAILURE	2	14
New angina	20	24
Revascularization	27	35

Type 2 diabetes:

Quality assessment by the review group	Study quality rating (according to check list) Moderate/+	
Study description	Author	UKPDS Group, UKPDS 33, 1998 (72)
	Setting	Hospital clinics
	Country	UK
	Aim (as described in the article)	To compare intensive blood-glucose control policy, with sylphonylurea or insulin therapy, with conventional treatment policy with diet, on the risk of microvascular and macrovascular clinical complications.
	Study design	RCT
	Inclusion period (year start-year end)	1977 to 1991
	Mean follow-up (year)	10 years (median)
Intervention	Drug (pharmaceutical) in treatment arms	Non-overweight stratum: Insulin or sylphonylurea
	Initial drug dose	Not reported in main publication
	Actual usage	Insulin (medians): At 3 years 22 U At 6 years 28 U At 9 years 34 U At 12 years 36 U Sylphonylureas:

		Chlorpropamide 100-500 mg Glibenclamide 2.5-20 mg Glipizide 2.5-40 mg
Population characteristics	Mean age	53.3 years
	Age range	25 to 65 years
	Sex	M: 2539, F: 1508
	Ethnicity (frequency)	Caucasian: 81, Indian Asian: 10, Afro-Caribbian: 8, Other: 1
	Comorbidity (frequency CVD, diabetes)	Not reported in main publication
	Concomittant medication	More than one aspirin daily: 1.6%, Diuretic: 13% Digoxin: 1.1%, Antihypertensive: 12% Lipid lowering: 0.3%, Hormone replacement therapy or oral contraceptive: 0.8%
	N intervention / Intensive treatment	2729
	N control / Conventional treatment	1138
	N excluded	3407 (+ 342 patients in an overweight stratum reported separately)
	N lost to follow-up	167
	Discontinuance (n, percent)	Not reported
	Crossover (n, percent)	Not reported
Method	Criteria for inclusion	Newly diagnosed diabetes (fasting plasma glucose > 6 mmol/L on two mornings, 1-3 weeks apart) Age 25 to 65 years
	Criteria for exclusion	Ketonuria > 3 mmol/L S-Creatinine > 175µmol/L MI in the previous year Current angina or heart failure More than one major vascular event Rerthionpathy requiring laser treatment Malignant hypertension Uncorrected endocrine disorder Occupation that precluded insulin therapy Severe concurrent illness Inadequate understanding Unwillingness
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Life-table analyses with log-rank tests. Hazard ratios to estimate relative risks were obtained from Cox proportional-hazard models (more details in paper)
	Power calculation description	Yes
Results	Primary endpoint of study	Any diabetes related endpoint (sudden death, death from hyper- og hypoglycaemia, fatal or non-fatal MI, angina, hearh failure, stroke, renal failure, amputation, vitreous haemorrhage, retinal photocoagulation, blindness in one eye, cataract extraction); diabetes-related death (death from MI, stroke, peripheral

		vascular disease, renal disease, hyper- or hypoglycaemia, and sudden death); all-cause mortality.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Cardiovascular death	(Fatal MI + Sudden death Fatal stroke + + Death from peripheral vascular disease) I: (207+24+43+2)/2729 C: (90+18+15+3)/1138
	Adverse events	Increased weight gain in intervention-group (mean difference 3.1 kg) Proportion of patients with hypoglycaemic episode in a year was "significantly higher" in intervention-group
	Sub group analysis (sex, age, ethnicity)	-

Events	Conventional	Sylphonylureas
	N = 896	N= 1234
Total mortality	190	257
All MI	162	190
Fatal MI	80	102
Non-fatal MI	87	99
All stroke	47	78
Fatal stroke	12	25
Non-fatal stroke	38	60
Heart failure	31	46
Angina	58	92

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	UK Prospective Diabetes Study Group, 1998, UKPDS 34 (73)
	Setting	Diabetes centres
	Country	UK
	Aim (as described in the article)	Test whether addition of metformin reduces the risk of diabetes complications
	Study design	RCT

	Inclusion period (year start-year end)	1977-1991
	Mean follow-up (year)	Median 10.7 yrs
Intervention	Drug (pharmaceutical) in treatment arms	Sulfonylurea (glibenclamide, chlorpropamide), insulin, metformin. Initial three months on diet only.
	Initial drug dose	850 mg metformin
	Actual usage	850 – 1700 – 2550 mg
Population characteristics	Mean age	53
	Age range	SD 8 yrs
	Sex	45-47% M
	Ethnicity (frequency)	85-88% Caucasian
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	17-20% diuretics; 12-16% antihypertensives
	N intervention	metformin 342, insulin 409, chlorpropamide 265, glibenclamide 277
	N control	conventional (diet) 411
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	About 50% after 10 yrs
	Crossover (n, percent)	
Method	Criteria for inclusion	Newly diagnosed type 2 diabetes, 25-65 y, fasting plasma glucose > 6.0 mmol/l
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Intention to treat, life-table analyses with log-rank tests and hazard ratios, Cox prop. Hazards models
	Power calculation description	
Results	Primary endpoint of study	Sudden death, death from hyperglycaemia or hypoglycaemia, fatal or non-fatal MI, angina, heart failure, stroke, renal failure etc. (other diabetic complications)
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio
	Adverse events	Major hypoglycaemic episodes: Conventional 0.7%, chlorpropamide 1.2%, glibenclamide 1.0%, insulin 2.0%, metformin 0.6%. Any hypoglycaemic episode: Conventional 7.9%, chlorpropamide 15.2%, glibenclamide 20.5%, insulin 25.5%, metformin 8.3%.

Events	Conventional	Metformin
	N= 411	N= 342
Total mortality	89	50
Myocardial infarction	73	39
Stroke	23	12
Angina	22	21
Heart failure	17	11
Diabetes related endpoint	160	98

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Horne 2007, RECORD (interim analysis) (74)
	Setting	Not reported (“338 centres”)
	Country	Europe and Australasia.
	Aim (as described in the article)	Europe and Australasia Compare cardiovascular outcomes in patients with type 2 diabetes treated with rosiglitazone plus metformin or sulfonyurea,(rosiglitazone group) with outcomes in patients treated with metformin plus sulofonylurea (control group). Interim analysis conducted and reported due to concerns raised in recent meta-analysis.
	Study design	RCT (open-label)
	Inclusion period (year start-year end)	April 2001 to April 2003
	Mean follow-up (year)	3.75 years
Intervention	Drug (pharmaceutical) in treatment arms	Both arms: metformin or sulfonylurea. Intervention arm only: rosiglitazone.
	Initial drug dose	4 mg rosiglitazone. Metformin and sylfonylurea dosages according to local practice.
	Actual usage	Not reported.
Population characteristics	Mean age	58.5
	Age range	40 to 75 years
	Sex	51.5% males

	Ethnicity (frequency)	98.9% whites
	Comorbidity (frequency CVD, diabetes)	Hypertension: 79.4% Ischeamic heart disease: 16.5% Cerebrovascular disease: 4.5%
	Concomittant medication	Not reported.
	N intervention	2220
	N control	2227
	N excluded	2970 excluded after screening 11 excluded after randomisation (Did not receive study medication)
	N lost to follow-up	218 in intervention group, 233 in control group
	Discontinuance (n, percent)	Intervention group: 594, 27% Control group: 751, 34%
	Crossover (n, percent)	Not reported
Method	Criteria for inclusion	Diabetes type 2; 40 to 75 years; BMI > 25; glycated hemoglobin between 7% and 9% while on max dose of metformin or a sylfonlyurea..
	Criteria for exclusion	Use of other glucose-lowering drugs; hospitalization for major cardiovascular event in previous 3 months; planned cardiovascular intervention; heart failure; clinically significant hepatic disease; renal impairment; uncontrolled hypertension.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Kaplan Meier method and Hazard ratios.
	Power calculation description	Yes
Results	Primary endpoint of study	Hospitalization (for acute MI, heart failure, unstable anginc pectoris, TIA, unplanned cardiovascular revascularization, amputation of extremities, or any other cardiovascular reason) or death from cardiovascular casuses (incl. heart failure, acute MI, sudden death and caused by acute vascular events incl stroke).
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio (95% CI)
	Adverse events	

Events	Rosiglitazone	Control
	N=2220	N=2227
Composite	217	202
Cardiovascular death	29	35
Total mortality	74	80
New or recurrent acute MI	43	37

Heart failure	38	17

Multifaceted intervensions with and without drug treatment

Multiple interventions
Oslo study 1981 (75), HDFP 1984 (76-78), Finnish businessmen 1985 (79, 80), MRFIT 1986 (81-83), Diabetes intervention study 1991 (84), Steno-2 2003 (85)

Quality assessment by the review group	Study quality rating (according to check list) Moderate / 1 +	
Study description	Author, year, study name	Hjermann, 1981, Oslo Diet and Antismoking study (75)
	Setting	Outpatient clinic
	Country	Norway
	Aim (as described in the article)	To show whether lowering of serum lipids and cessation of smoking could reduce the incidence of CHD.
	Study design	Randomised controlled trial
	Inclusion period (year start-year end)	
	Mean follow-up (year)	5 years
Intervention	Drug (pharmaceutical) in treatment arms	Dietary and anti smoking advice
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	45.2
	Age range	40-49 years
	Sex	Men
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intervention	604
	N control	628
	N excluded	
	N lost to follow-up	5
	Discontinuance (n, percent)	1 from the control group and 9 from the intervention group.
	Crossover (n, percent)	
Method	Criteria for inclusion	Men were admitted to the trial if they had serum cholesterol levels of 7.5-9.8 mmol/l, coronary risk scores based on cholesterol levels,

		smoking habits, and systolic blood pressure below 150 mmHg (mean of two measurements.
	Criteria for exclusion	Chest pain on exercise, disease of the cardiovascular system, clinical diabetes, fasting blood sugar levels above 7.5 mmol/l, cancer, disabling disease, psychopathological disease, and alcoholism.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Log rank test, life table, Cox
	Power calculation description	Yes
Results	Primary endpoint of study	Cardiovascular events, fatal or nonfatal.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio
	Adverse events	

Events	Control	Intervention
	N = 628	N= 604
Total coronary events	36	19
Stroke fatal + nonfatal	3	3
Total mortality	24	16
All CVD	39	22
CVD death	15	8

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author	1979, HDFP (76-78)
	Year	1979
	RefId	2459
	Setting	Community based
	Country	USA
	Aim (as described in the article)	Primary aim: Is a systematic approach to antihypertensive therapy (stepped care) compared to community care effective in reducing risk of five-year mortality for all hypertensive adults in the community?
	Study design	Randomised trial, multi center
	Inclusion period	

	(year start-year end)	
	Mean follow-up (year)	5
Intervention	Drug (pharmaceutical) in treatment arms	Stepped care (vs community care) Goal: DBP <90 (or reduce 10 mm) Chlortalidone 25-100 mg Triamterene 50-300 mg Spironolactone 25-100 mg Reserpine 0,1 – 0,25 mg Metyldopa 500-2000 mg Hydralazine 30-200 mg Guanethidine sulfate 10-200 mg
	Initial drug dose	
	Actual usage	-
Population characteristics	Mean age	51y
	Age range	30-69
	Sex	M/F
	Ethnicity (frequency)	White men: ca 36% White women: ca 22% Black men: 18% Black women; ca 23%
	Comorbidity (frequency CVD, diabetes)	LVH ca 4% History of stroke ca 2,3% History of MI ca 5% History of diabetes ca 7%
	Concomittant medication	25%
	N intervention	5485
	N control	5455
	N excluded	
	N lost to follow-up	0,5%
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	
	Power calculation description	Level of significance 0,05, power 0,90
Results	Primary endpoint of study	All cause mortality
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RR

	Adverse events	
Events	Referrred care	Stepped care
	N = 5455	N= 5485
All-cause mortality	419	349
Angina	449	325
Fatal IHD or nonfatal MI	669	558
Stroke	158	102

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Miettinen, 1985, Finnish businessmen (79, 80)
	Setting	Institute of Occupational Health, Helsinki, and Second Department of Medicine, Helsinki
	Country	Finland
	Aim (as described in the article)	To investigate the long-term effects of multifactorial primary prevention of cardiovascular disease
	Study design	RCT
	Inclusion period (year start-year end)	1974-75
	Mean follow-up (year)	5-year trial.
Intervention	Drug (pharmaceutical) in treatment arms	Dietetic, hygienic and pharmacological treatment when indicated for the risk factors: hyperlipidemia, hypertension, smoking, obesity, and abnormal glucose tolerance. Pharmacological therapy included hypolipidemic agents (mainly probucol and clofibrate) and antihypertensive drugs (mainly diuretics and beta-blockers).
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	Intervention: 48y / control; 48y
	Age range	
	Sex	Men only
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intervention	612

	N control	610
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	3490 business executives born 1919-1934 who attended health cheque-ups in the late 1960's. 1222 of these clinically healthe men with CVD risk factors were entered into the trial.
	Criteria for exclusion	Cardiovascular disease
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox
	Power calculation description	
Results	Primary endpoint of study	Cardiovasular disease
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RR, HR
	Adverse events	

Events	Control	Intervention
	N = 610	N= 612
Stroke	8	0
Total coronary events	9	19
All cause mortality	5	10

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Grimm, 1986, MRFIT (81-83)
	Setting	
	Country	US
	Aim (as described in the article)	A long term study on the benefit of lowering risk factors for coronary heart disease mortality in middle-aged men
	Study design	RCT
	Inclusion period (year start-year end)	1972
	Mean follow-up (year)	6 y
Intervention	Drug (pharmaceutical) in	Randomised groups: Special intervention versus usual care.

	treatment arms	Special intervention involved cholesterol lowering dietary advice, behaviour modification for cigarette smoking and stepped care pharmacological approach to lower blood pressure (strating with: chlorthalidone or hydrchlorothiazide, resepine, hydralazine, guanethine).
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	Spesial intervention (SI): 46.2y Usual care (UC): 46.6y
	Age range	
	Sex	Men only
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Resting ECG abnormalities: SI: 28.4%, UC: 27.5%
	Concomittant medication	
	N intervention	6428
	N control	6438
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	< 10% attended the sixth annual visit
	Crossover (n, percent)	
Method	Criteria for inclusion	Men aged 35-57y, upper 10-15% of risk of CHD according to the Framingham coefficients, free of overt evidence of CHD
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox
	Power calculation description	
Results	Primary endpoint of study	CHD mortality
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	HR
	Adverse events	

Events	Usual care	Special intervention
	N = 6438	N = 6428
Stroke mortality*	9	11
Non-fatal stroke	30	36

CHD mortality	124	115
Heart failure	17	2
Angina	817	646
Total mortality	260	265

* Data taken from MacMahon et al (89)

Quality assessment by the review group	Study quality rating (according to check list) High / ++	
Study description	Author, year, study name	Hanefeld, 1991, DIS (84)
	Setting	Specialised diabetes clinic/16 local clinics
	Country	Germany
	Aim (as described in the article)	Evaluate effect of IHE (intensified health education) on course of NIDDM and micro- and macro-angiopathy
	Study design	Randomised, controlled three-arm study – IHF vs conventional treatment, and clofibrate vs placebo in IHE group
	Inclusion period (year start-year end)	1977-1980
	Mean follow-up (year)	5 years
Intervention	Drug (pharmaceutical) in treatment arms	Clofibrate
	Initial drug dose	1.6 g
	Actual usage	
Population characteristics	Mean age	46
	Age range	30-55
	Sex	M+F
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	Hypertension (number at start) 109 IHE placebo 119 IHE clofibrate 127 control
	Concomittant medication	
	N intervention	382 (M/F 231/151) IHE placebo 379 (M/F 198/181) IHE clofibrate
	N control	378 (M/F 206/172) control
	N excluded	
	N lost to follow-up	

	Discontinuance (n, percent)	131
	Crossover (n, percent)	
Method	Criteria for inclusion	Fasting blood glucose > 7.21 mmol/L newly detected, and additional criteria
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Chi square test. Multivariate covariance. Kaplan-Meier.
	Power calculation description	
Results	Primary endpoint of study	Triglycerides lower with clofibrate. Lower incidence rate for MI in controls. Lower death rate in IHE groups than control group.
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	
	Adverse events	Clofibrate – placebo Gall stone 4.2 vs. 5.5%

Events	Control	Health education
	N= 366	N= 328
Total mortality	16	10
Fatal stroke	1	1
Myocardial infarction	10	17

Events	Control	Health education + clofibrate
	N= 366	N= 334
Total mortality	16	9
Fatal stroke	1	3
Myocardial infarction	10	18

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +

Study description	Author, year, study name	Gæde, 2003 Steno-2-study (85)
	Setting	Steno diabetes center
	Country	Denmark
	Aim (as described in the article)	Compare the effect of multifactorial intervention with conventional treatment on modifiable risk factors of CVD in patients with type 2 diabetes and micralbuminuria
	Study design	RCT
	Inclusion period (year start-year end)	
	Mean follow-up (year)	7.8y
Intervention	Drug (pharmaceutical) in treatment arms	Polypharmacological therapy and behaviour modification (diet + exercise) versus conventional intervention. All received hypertensives, vitamins, aspirin (after October 1999).
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	Intensive: 55.2y / standard 54.9y
	Age range	
	Sex	M/W: Intensive 56/25, Standard 63/17
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intensive	80
	N standard	80
	N excluded	
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Type 2 diabetes, microalbuminuria
	Criteria for exclusion	
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Kaplan Meier, Cox
	Power calculation description	Yes
Results	Primary endpoint of study	Composite of death from CVD-causes
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	Hazard ratio

Adverse events	At least on major hypoglycaemic event: 5 intensive gr/12 conventional gr. (p=0.12) Over 75% ov major events occurred in persons taking insulin. At least one minor hypoglycaemic event: 42 intensive gr. /39 conventional gr.

Events	Conventional	Intensive
	N= 80	N= 80
Total mortality	15	12
CVD deaths	7	7
Nonfatal MI	17	5
Nonfatal Stroke	20	3
Revascularization	15	5
All CVD events	85	33

Food supplements

PPP 2001 (5), JELIS 2007 (86)

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author	PPP group, 2001, PPP (5)
	Setting	General practice + hospital hypertension units (5.3%)
	Country	Italy
	Aim (as described in the article)	To investigate in general practice the effiCCBy of antiplatelets and antioxidants in primary prevention of cardiovascular events in people with one or more major cardiovascular risk factor
	Study design	Randomised, open, 2x2 factorial
	Inclusion period (year start-year end)	1994-98
	Mean follow-up (year)	3.6
Intervention	Drug (pharmaceutical) in treatment arms	Vitamin E [Aspirin (ASA) 100 mg]
	Initial drug dose	
	Actual usage	
Population characteristics	Mean age	65.4
	Age range	
	Sex	M 43%, F 57%
	Ethnicity (frequency)	
	Comorbidity (frequency CVD, diabetes)	
	Concomittant medication	
	N intervention	2226 (aspirin)
	N control	2269
	N excluded	
	N lost to follow-up	31
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Age equal or more than 65, one or more major risk factors (SBP >160, DBP > 95, total cholesterol >6.4, diabetes, obesity BMI>30kg/m2, family history of MI before 55 in at least one parent or sibling)

	Criteria for exclusion	Treatment with antiplatelet therapy, chronic use of anti-inflammatory agents or anticoagulants , contra indications to aspirin, poor short term prognosis, predictable psychological or logistical difficulties
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox
	Power calculation description	Alfa 0.05, 1-beta= 90%
Results	Primary endpoint of study	Combined: CVDeath, nonfatal MI, nonfatal stroke
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	RR
	Adverse events	Bleeding Vit E 16; no Vit E 14 GI disease exept bleeding Vit E 6; no Vit E 5 Other events Vit E 30; no Vit E 27 Total Vit E 138; no Vit E 126

Events	No vitamin E	Vitamin E
	N= 2264	N= 2231
Total mortality	68	72
Nonfatal MI	18	19
All MI	25	22
Nonfatal stroke	13	20
All stroke	18	22

Quality assessment by the review group	Study quality rating (according to check list) Moderate / +	
Study description	Author, year, study name	Yokoyama, 2007, JELIS (86)
	Setting	
	Country	Japan
	Aim (as described in the article)	To evaluate treatment with fish oil supplement eicosapentaenoic acid (EPA) in addition to statin therapy alone among patients with hypercholesterolemia.
	Study design	RCT, open-label
	Inclusion period (year start-year end)	November 1996- November 1999
	Mean follow-up (year)	4.6y
Intervention	Drug (pharmaceutical) in treatment arms	Statin and EPA versus statin

	Initial drug dose	Pravastatin 10mg/d or simvastatin 5mg/d. EPA 600 mg 3X / day. EPADEL capsule of 300mg of highly (>98%) purified EPA ethyl ester. EPA is purified from a long-chain polyunsaturated fatty acid present in fish oil.
	Actual usage	
Population characteristics	Mean age	61y
	Age range	
	Sex	69% women:
	Ethnicity (frequency)	Japanese
	Comorbidity (frequency CVD, diabetes)	20% had CHD, 16% diabetes. 14981 had no CHD.
	Concomittant medication	Other medication taken as needed, but not other antihyperlipidemic agents.
	N EPA + statin	9326
	N statin	9319
	N excluded	821
	N lost to follow-up	
	Discontinuance (n, percent)	
	Crossover (n, percent)	
Method	Criteria for inclusion	Age >40y for men, women postmenopausal, all ≤ 75y, total cholesterol > 250 mg/dl,
	Criteria for exclusion	MI, unstable angina, history of serious heart disease , or cerbrovascular disease within last 6 months, malignant tumour, uncontrolled diabetes, secondary hyperlipidemia, hypersensitivity to drug formulation.
	Main statistical analysis (Logistic regression, Cox, Kaplan Meier, other)	Cox, Kaplein Meier, log rank test
	Power calculation description	Yes
Results	Primary endpoint of study	MACE – major coronary event: sudden cardiac death, fatal and nonfatal MI, and unstable angina including hospitalization for documented ischaemic episodes, and events of angioplasty/stenting or coronary artery bypass grafting
	Endpoints and effect estimate (RR/OR/Rate ratio/Hazard ratio 95% CI)	HR
	Adverse events	Total no: EPA 25.3%, Control 21.7% (p<0.0001) Cancer: ns. Joint or muscle pain: EPA 1.6%, control 2.05 (p=0.04) GI disturbance EPA 3.8%, control 1.7% (p<0.0001) Skin abnormality EPA 1.7%, control 0.7% (p<0.0001) Haemorrhage EPA 1.1%, control 0.6% (p=0.0006)

Events	EPA + statin	Statin only
	N = 9326	N = 9319
All cause death	286	265
Coronary death or MI	88	113
Stroke	166	162

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Vedlegg 4

PRIMÆRFOREBYGGING AV HJERTE- OG KARSYKDOM (KUNNSKAPSSENTERETS RAPPORT NR 20-2008)

EKSKLUDERT LITTERATUR (TABLE OF EXCLUDED STUDIES)

Oversikt over ekskludert litteratur ved Trinn 3

Name of study or author (year of publication)	Cause(s) for exclusion
Wolff & Lindeman (1966)	Not primary endpoint: Study the feasibility and value of maintaining patients with essential hypertension on effective long-term hypotensive therapy. Low internal validity Small study and large proportion not followed up.
Barraclough (1973)	Not primary endpoint: Achieved blood pressure level /on treatment blood pressure level. A combination of drugs was used without dosage given.
Morisky (1983)	Intervention aimed at improving adherence to hypertension treatment.
Berglund (1986)	Small trial where only diabetogenic effects were evaluated.
Gøteborg-study (Wilhelmsen 1986)	The study was populationbased and not a sample of persons with increased risk of CVD.
WHO factory study (1986)	Population-based study, not targetting high-risk groups.
MAPPHY (1988)	MAPPHY-study included in HAPPHY-study.
STARS (Watts) (1992)	Secondary prevention; not our primary endpoint.
TOMHS (1993)	Not our primary endpoints.
SCRIP (1994)	Secondary prevention study.
GLANT (1995)	Not randomised controlled trial.
KAPS (1995)	Not our primary endpoints.
Physicians' Health Study (beta-carotene	Not high-risk population.

component) (1996)	
CAIUS (1996)	Not our primary endpoints.
STONE (1996)	Patients were not randomised, but allocated alternately to treatment groups.
VHAS (1997)	Not our primary endpoints.
VA-HIT (1999)	Secondary prevention.
SCAT (2000)	Not our primary endpoints.
Kyushu Lipid Intervention Study (2000)	Unsuccessful randomisation procedure.
SYST-CHINA (2000)	Patients were not randomised, but allocated alternately to treatment groups.
HOPE og Micro HOPE (2001)	80% MI.
Progress (2001)	Secondary prevention of stroke.
AASK (2001)	Not relevant endpoints.
IRMA (2001)	Our endpoints not reported.
ELSA (2002)	Regression study.
TRIPOD (2002)	Study population: women with previous getational diabetes; not our primary endpoints.
Diabetes Prevention Program (2002)	Not our primary endpoints.
INVEST (2003)	Secondary prevention.
JMIC-B (2004)	Secondary prevention.
PREVEND-IT (2004)	Not our primary endpoints. Also questionable whether the inclusions criteria (microablumiuria identified by population-based screening) is relevant to us.
XENDOS (2004)	Not our primary endpoints.
FEVER (2005)	All participants were started on low-dose diuretic medication, and later randomised to placebo or felodipine. This design does not answer questions of direct relevance to our review.
PIPOD (2006)	Follow-up study of TRIPOD-trial (which was excluded).
CHARISMA (2006)	More than three quarters of the participants had established cardiovascular disease.
Diabetes Prevention Study (2006)	Only results on incidence of Type 2 diabetes.
MARPLE (2006)	Not randomised controlled trial.

Vedlegg 5

PRIMÆRFOREBYGGING AV HJERTE- OG KARSYKDOM (KUNNSKAPSSENTERETS RAPPORT NR 20-2008)

GRADERING AV KVALITETEN PÅ DOKUMENTASJONEN ("GRADE" EVIDENCE-PROFILES)

Dette vedlegget inneholder 38 tabeller som oppsummerer kvalitetsvurderingen av den foreliggende dokumentasjonen. Nestsiste kolonne (nummer 2 fra høyre) angir kvalitetsgradering etter følgende system:

- Høy kvalitet: Det er lite sannsynlig at videre forskning kommer til å endre vår tillit til resultatene.
- Middels kvalitet: Det er sannsynlig at videre forskning kommer til å ha en viktig innflytelse på vår tillit til resultatene og kan endre dem.
- Lav kvalitet: Det er svært sannsynlig at videre forskning kommer til å ha en viktig innflytelse på vår tillit til resultatene og vil endre dem.
- Svært lav kvalitet: Alle resultater er veldig usikre.

Vurderingene er fortatt av Atle Fretheim og Gunn Vist (begge Kunnskapssenteret).

INNHOLD

Antithrombotics

Author(s): Atle Fretheim and Gunn E. Vist.
Date: 2008-06-08
Question: Should Aspirin be used for Risk of cardiovascular disease?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Aspirin	control	Relative (95% CI)	Absolute		
Mortality												
6	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1555/47293 (3.3%)	1514/45618 (3.3%)	RR 0.94 (0.87 to 1)	2 fewer per 1000 (from 4 fewer to 0 more)	⊕⊕⊕⊕ HIGH	
Myocardial infarction												
6	randomised trial	no serious limitations	serious[1]	no serious indirectness	serious[2]	none	713/47293 (1.5%)	787/45618 (1.7%)	RR 0.78 (0.62 to 0.97)	4 fewer per 1000 (from 1 fewer to 6 fewer)	⊕⊕OO LOW	
Stroke												
6	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	613/47293 (1.3%)	600/45618 (1.3%)	RR 0.96 (0.81 to 1.13)	1 fewer per 1000 (from 2 fewer to	⊕⊕⊕⊕ HIGH	

										2 more)		
Angina												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	serious[2]	none	54/2226 (2.4%)	67/2269 (3%)	RR 0.82 (0.58 to 1.17)	5 fewer per 1000 (from 13 fewer to 5 more)	⊕⊕OO LOW	

[1] High I-squared value.
[2] Wide 95% CI.
[3] Trial rated "Moderate" quality by expert group.

Author(s): Atle Fretheim and Gunn E. Vist.
Date: 2008-06-08
Question: Should Aspirin vs Warfarin be used for Risk of cardiovascular disease?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aspirin**	**Warfarin**	**Relative (95% CI)**	**Absolute**		
Mortality												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	113/1268 (8.9%)	95/1268 (7.5%)	RR 1.19 (0.92 to 1.54)	14 more per 1000 (from 6 fewer to 40 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	83/1268 (6.5%)	83/1268 (6.5%)	RR 1.00 (0.75 to 1.34)	0 fewer per 1000 (from 16	⊕⊕⊕O MODERATE	

										fewer to 22 more)		
Stroke												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	18/1268 (1.4%)	22/1268 (1.7%)	RR 0.82 (0.44 to 1.52)	3 fewer per 1000 (from 10 fewer to 9 more)	⊕⊕⊕O MODERATE	

[1] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist.
Date: 2008-06-08
Question: Should Aspirin and warfarin be used for Risk of cardiovascular disease?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Aspirin and warfarin**	**control**	**Relative (95% CI)**	**Absolute**		
Mortality												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	103/1277 (8.1%)	110/1272 (8.6%)	RR 0.92 (0.72 to 1.21)	7 fewer per 1000 (from 24 fewer to 18 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	71/1277 (5.6%)	107/1272 (8.4%)	RR 0.66 (0.49 to 0.88)	29 fewer per 1000 (from 10 fewer to	⊕⊕⊕O MODERATE	

										43 fewer)		
Stroke												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	29/1277 (2.3%)	26/1272 (2%)	RR 1.11 (0.66 to 1.88)	2 more per 1000 (from 7 fewer to 18 more)	⊕⊕⊕O MODERATE	

[1] Wide 95% CI.
[2] Only one trial.

Author(s): Atle Fretheim and Gunn E. Vist.
Date: 2008-06-08
Question: Should Warfarin be used for Risk of cardiovascular disease?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Warfarin**	**control**	**Relative (95% CI)**	**Absolute**		
Mortality												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	95/1268 (7.5%)	110/1272 (8.6%)	RR 0.87 (0.67 to 1.13)	11 fewer per 1000 (from 28 fewer to 11 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	83/1268 (6.5%)	107/1272 (8.4%)	RR 0.78 (0.59 to 1.03)	18 fewer per 1000 (from 34	⊕⊕⊕O MODERATE	

										fewer to 3 more)		
Stroke												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	22/1268 (1.7%)	26/1272 (2%)	RR 0.85 (0.48 to 1.49)	3 fewer per 1000 (from 10 fewer to 10 more)	⊕⊕⊕O MODERATE	

[1] Wide 95% CI.

Lipid-lowering drugs

Author(s): Atle Fretheim and Gunn E. Vist.
Date: 2008-06-08
Question: Should Statins be used for Hypercholesterolaemia?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Statins	control	Relative (95% CI)	Absolute		
Mortality												
7	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1416/25129 (5.6%)	1532/25205 (6.1%)	RR 0.93 (0.86 to	4 fewer per 1000	⊕⊕⊕⊕ HIGH	

									99)	(from 9 fewer to 1000 more)		
Myocardial infarction												
8	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1350/28107 (4.8%)	1761/28190 (6.2%)	RR 0.77 (0.72 to 0.82)	14 fewer per 1000 (from 11 fewer to 17 fewer)	⊕⊕⊕⊕ HIGH	
Stroke												
8	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	893/28107 (3.2%)	1083/28190 (3.8%)	RR 0.83 (0.76 to 0.9)	6 fewer per 1000 (from 4 fewer to 9 fewer)	⊕⊕⊕⊕ HIGH	
Angina												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	134/13766 (1%)	177/13814 (1.3%)	RR 0.76 (0.61 to 0.95)	3 fewer per 1000 (from 1 fewer to 5 fewer)	⊕⊕⊕O MODERATE	

[1] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist.
Date: 2008-06-08
Question: Should Non-statin lipid-lowering medication be used for Hypercholesterolaemia?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment	Summary of findings	Importance

							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Non-statin lipid-lowering medication**	**control**	**Relative (95% CI)**	**Absolute**		
Mortality												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	418/7584 (5.5%)	392/7476 (5.2%)	RR 1.05 (0.92 to 1.2)	3 more per 1000 (from 4 fewer to 10 more)	⊕⊕⊕⊕ HIGH	
Myocardial infarction												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	462/8942 (5.2%)	546/8830 (6.2%)	RR 0.84 (0.74 to 0.94)	10 fewer per 1000 (from 4 fewer to 16 fewer)	⊕⊕⊕⊕ HIGH	
Stroke												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	158/4985 (3.2%)	175/4900 (3.6%)	RR 0.89 (0.72 to 1.1)	4 fewer per 1000 (from 10 fewer to 4 more)	⊕⊕⊕O MODERATE	

[1] Wide 95% CI.

Antihypertensive medication

Drug vs placebo

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-11
Question: Should Antihypertensive medication be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Antihypertensive medication	control	Relative (95% CI)	Absolute	Quality	
Mortality												
17	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	1498/24653 (6.1%)	1627/23774 (6.8%)	RR 0.89 (0.84 to 0.95)	7 fewer per 1000 (from 3 fewer to 11 fewer)	⊕⊕⊕⊕ HIGH	
Myocardial infarction												
15	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	705/22756 (3.1%)	815/22308 (3.7%)	RR 0.85 (0.77 to 0.94)	6 fewer per 1000 (from 2 fewer to 9 fewer)	⊕⊕⊕⊕ HIGH	
Stroke												
17	randomised	no serious	no serious	no serious	no serious	none	521/24653 (2.1%)	834/23774	RR 0.60	14 fewer	⊕⊕⊕⊕	

	trial	limitations	inconsistency	indirectness	imprecision			(3.5%)	(0.54 to 0.67)	per 1000 (from 12 fewer to 16 fewer)	HIGH	
Angina												
2	randomised trial	serious[1]	no serious inconsistency	serious[2]	serious[3]	none	11/849 (1.3%)	5/487 (1%)	RR 0.88 (0.31 to 2.48)	1 fewer per 1000 (from 7 fewer to 15 more)	⊕OOO VERY LOW	
Heart failure												
11	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	165/10949 (1.5%)	311/10513 (3%)	RR 0.52 (0.43 to 0.63)	14 fewer per 1000 (from 11 fewer to 17 fewer)	⊕⊕⊕⊕ HIGH	

[1] Both trials rated "Moderate" quality by expert group.

[2] Both trials used high-dose diuretics.

[3] Wide 95% CI.

Drug vs drug

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-02
Question: Should Diuretic vs Beta-blocker be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Diuretic	Beta-blocker	Relative (95% CI)	Absolute		
Mortality												
3	randomised trial	serious[1]	serious[2]	serious[3]	no serious imprecision	none	363/8650 (4.2%)	383/8802 (4.4%)	RR 0.97 (0.8 to 1.18)	1 fewer per 1000 (from 9 fewer to 8 more)	⊕OOO VERY LOW	
Myocardial infarction												
3	randomised trial	serious[1]	serious[2]	serious[3]	serious[4]	none	283/8650 (3.3%)	315/8802 (3.6%)	RR 0.88 (0.62 to 1.24)	4 fewer per 1000 (from 14 fewer to 9 more)	⊕OOO VERY LOW	
Stroke												
3	randomised trial	serious[1]	serious[2]	serious[3]	serious[4]	none	104/8650 (1.2%)	130/8802 (1.5%)	RR 0.79 (0.45 to 1.37)	3 fewer per 1000 (from 8 fewer to 6 more)	⊕OOO VERY LOW	
Heart failure												
1	randomised trial	serious[1]	no serious inconsistency	serious[5]	serious[4]	none	22/3272 (0.7%)	32/3297 (1%)	RR 0.69 (0.4 to 1.19)	3 fewer per 1000 (from 6 fewer to 2 more)	⊕OOO VERY LOW	
Diabetes-incidence												
1	randomised trial	serious[1]	no serious inconsistency	serious[5]	serious[4]	none	75/3272 (2.3%)	86/3297 (2.6%)	RR 0.88 (0.65 to 1.19)	3 fewer per 1000 (from 9 fewer to 5 more)	⊕OOO VERY LOW	

[1] Rated "Moderate" by expert group.

[2] High I-squared value.

[3] High-dose diuretics used in 2 of 3 studies.

[4] Wide 95% CI.

[5] Used high-dose diuretic.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-02
Question: Should ACE-inhibitor vs Beta-blocker and/or diuretc be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-inhibitor	Beta-blocker and/or diuretc	Relative (95% CI)	Absolute		
Mortality												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	570/7697 (7.4%)	553/7706 (7.2%)	RR 1.03 (0.93 to 1.15)	2 more per 1000 (from 5 fewer to 11 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	570/7697 (7.4%)	553/7706 (7.2%)	RR 1.03 (0.93 to 1.15)	2 more per 1000 (from 5 fewer to 11 more)	⊕⊕⊕O MODERATE	
Stroke												
2	randomised trial	serious[1]	serious[2]	no serious indirectness	serious[3]	none	404/7697 (5.2%)	385/7706 (5%)	RR 1.07 (0.77 to	4 more per 1000 (from 12 fewer to	⊕OOO VERY LOW	

									1.49)	24 more)		
Angina												
1	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	258/5492 (4.7%)	251/5493 (4.6%)	RR 1.03 (0.87 to 1.22)	1 more per 1000 (from 6 fewer to 10 more)	⊕⊕⊕O MODERATE	
Heart failure												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[5]	none	224/7697 (2.9%)	243/7706 (3.2%)	RR 0.95 (0.72 to 1.27)	2 fewer per 1000 (from 9 fewer to 9 more)	⊕⊕OO LOW	
Diabetes-incidence												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	430/7697 (5.6%)	477/7706 (6.2%)	RR 0.90 (0.71 to 1.02)	6 fewer per 1000 (from 18 fewer to 1 more)	⊕⊕⊕O MODERATE	

[1] Both trials rated "Moderate" quality by expert group

[2] Point-estimates far apart, with 95% CIs barely overlapping.

[3] Wide 95% CI

[4] Trial rated "Moderate" quality by expert group.

[5] 95% CI includes appreciable benefit and appreciable harm.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-04
Question: Should CCB vs Beta-blocker and/or diuretic be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	CCB	Beta-blocker	Relative	Absolute		

studies						considerations		and/or diuretic	(95% CI)			
Mortality												
3	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	930/15785 (5.9%)	916/15981 (5.7%)	RR 1.02 (0.94 to 1.12)	1 more per 1000 (from 3 fewer to 7 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
3	randomised trial	serious[1]	serious[2]	no serious indirectness	serious[3]	none	537/15785 (3.4%)	522/15981 (3.3%)	RR 1.03 (0.83 to 1.28)	1 more per 1000 (from 6 fewer to 9 more)	⊕OOO VERY LOW	
Stroke												
3	randomised trial	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	499/15785 (3.2%)	551/15981 (3.4%)	RR 0.93 (0.77 to 1.11)	2 fewer per 1000 (from 8 fewer to 4 more)	⊕⊕OO LOW	
Angina												
1	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	serious[5]	none	202/8179 (2.5%)	190/8297 (2.3%)	RR 1.08 (0.89 to 1.31)	2 more per 1000 (from 3 fewer to 7 more)	⊕⊕OO LOW	
Heart failure												
3	randomised trial	serious[5]	no serious inconsistency	no serious indirectness	no serious imprecision	none	375/15785 (2.4%)	330/15981 (2.1%)	RR 1.14 (0.99 to 1.32)	3 more per 1000 (from 0 fewer to 7 more)	⊕⊕⊕O MODERATE	
Diabetes-incidence												
2	randomised trial	serious[6]	no serious inconsistency	no serious indirectness	no serious imprecision	none	311/7606 (4.1%)	348/7684 (4.5%)	RR 0.90 (0.78 to	5 fewer per 1000 (from 10 fewer to	⊕⊕⊕O MODERATE	

									1.05)	2 more)		

[1] 2 of 3 trials rated "Moderate" quality by expert group.

[2] High I-squared value.

[3] Wide 95% CI.

[4] Rated "Moderate" quality by expert group.

[5] No explanation was provided

[6] Both trials rated "Moderate" quality by expert group.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-04
Question: Should ACE-inhibitor vs CCB be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-inhibitor	CCB	Relative (95% CI)	Absolute		
Mortality												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1694/11259 (15%)	1618/11244 (14.4%)	RR 1.05 (0.98 to 1.11)	7 more per 1000 (from 3 fewer to 16 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
2	randomised trial	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	1699/11259 (15.1%)	1687/11244 (15%)	RR 0.97 (0.84 to 1.13)	4 fewer per 1000 (from 24 fewer to 20 more)	⊕⊕OO LOW	
Stroke												
2	randomised	serious[1]	no serious	no serious	serious[3]	none	672/11259	584/11244	RR 1.13	7 more per 1000	⊕⊕OO	

	trial		inconsistency	indirectness			(6%)	(5.2%)	(0.97 to 1.32)	(from 2 fewer to 17 more)	LOW	
Angina												
1	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1019/9054 (11.3%)	950/9048 (10.5%)	RR 1.07 (0.99 to 1.17)	7 more per 1000 (from 1 fewer to 18 more)	⊕⊕⊕O MODERATE	
Heart failure												
2	randomised trial	serious	no serious inconsistency	no serious indirectness	no serious imprecision	none	761/11259 (6.8%)	892/11244 (7.9%)	RR 0.85 (0.78 to 0.94)	12 fewer per 1000 (from 5 fewer to 17 fewer)	⊕⊕⊕O MODERATE	
Diabetes-incidence												
2	randomised trial	serious	no serious inconsistency	no serious indirectness	serious	none	336/11259 (3%)	394/11244 (3.5%)	RR 0.86 (0.73 to 1.01)	5 fewer per 1000 (from 9 fewer to 0 more)	⊕⊕OO LOW	

[1] Both trials rated "Moderate" quality by expert group.

[2] High I-squared value.

[3] Wide 95% CI.

[4] Trial rated "Moderate" quality by expert group.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-04
Question: Should Diuretic vs Alpha-blocker be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	Diuretic	Alpha-	Relative	Absolute		

studies						considerations		blocker	(95% CI)			
Mortality												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	851/15268 (5.6%)	514/9067 (0%)	RR 0.98 (0.88 to 1.09)	0 fewer per 1,000	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	608/15268 (4%)	365/9067 (4%)	RR 0.99 (0.87 to 1.12)	0 fewer per 1000 (from 5 fewer to 5 more)	⊕⊕⊕O MODERATE	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	351/15268 (2.3%)	244/9067 (2.7%)	RR 0.88 (0.75 to 1.03)	3 fewer per 1000 (from 7 fewer to 1 more)	⊕⊕OO LOW	
Angina												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1082/15268 (7.1%)	725/9067 (8%)	RR 0.89 (0.81 to 0.97)	9 fewer per 1000 (from 2 fewer to 15 fewer)	⊕⊕⊕O MODERATE	
Heart failure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	420/15268 (2.8%)	491/9067 (0%)	RR 0.51 (0.45 to 0.58)	0 fewer per 1,000	⊕⊕⊕O MODERATE	

[1] Trial rated "Moderate" quality by expert panel.

[2] Wide 95% CI.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-04
Question: Should Diuretic vs CCB be used for Hypertension?

Settings:
Bibliography: Primary Prevention of Cardiovascular disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Diuretic	CCB	Relative (95% CI)	Absolute		
Mortality												
3	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2477/19359 (12.8%)	1554/13147 (11.8%)	RR 0.99 (0.88 to 1.11)	1 fewer per 1000 (from 14 fewer to 13 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
3	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2562/19359 (13.2%)	1588/13147 (12.1%)	RR 0.99 (0.93 to 1.05)	1 fewer per 1000 (from 8 fewer to 6 more)	⊕⊕⊕O MODERATE	
Stroke												
3	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	787/19359 (4.1%)	481/13147 (3.7%)	RR 1.06 (0.95 to 1.19)	2 more per 1000 (from 2 fewer to 7 more)	⊕⊕⊕O MODERATE	
Angina												
2	randomised trial	serious[2]	serious[3]	no serious indirectness	serious[4]	none	1644/18419 (8.9%)	1007/12205 (8.3%)	RR 1.10 (0.81 to 1.49)	8 more per 1000 (from 16 fewer to 41 more)	⊕OOO VERY LOW	
Heart failure												
3	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	901/19359 (4.7%)	755/13147 (5.7%)	RR 0.73 (0.66 to	15 fewer per 1000 (from 11 fewer to	⊕⊕⊕O MODERATE	

									0.8)	19 fewer)		
Diabetes-incidence												
2	randomised trial	serious[2]	no serious inconsistency	no serious indirectness	no serious imprecision	none	812/18419 (4.4%)	435/12205 (3.6%)	RR 1.27 (1.13 to 1.42)	10 more per 1000 (from 5 more to 15 more)	⊕⊕⊕O MODERATE	

[1] 2 of 3 studies rated "Moderate" quality by expert group.

[2] One trial rated "Moderate" quality by expert panel.

[3] High I-squared value.

[4] Wide 95% CI.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-05
Question: Should Diuretic vs ACE-inhibitor be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Diuretic**	**ACE-inhibitor**	**Relative (95% CI)**	**Absolute**		
Mortality												
3	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	2443/18720 (13.1%)	1536/12529 (12.3%)	RR 1.00 (0.95 to 1.07)	0 fewer per 1000 (from 6 fewer to 9 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
2	randomised trial	serious[1]	serious[2]	no serious indirectness	no serious imprecision	none	2646/18294 (14.5%)	1678/12098 (13.9%)	RR 1.01 (0.88 to 1.17)	1 more per 1000 (from 17 fewer to 24 more)	⊕⊕OO LOW	

Stroke												
3	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	788/18720 (4.2%)	581/12529 (4.6%)	RR 0.88 (0.8 to 0.98)	6 fewer per 1000 (from 1 fewer to 9 fewer)	⊕⊕⊕O MODERATE	
Angina												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	1567/15255 (10.3%)	1019/9054 (11.3%)	RR 0.91 (0.85 to 0.98)	10 fewer per 1000 (from 2 fewer to 17 fewer)	⊕⊕⊕O MODERATE	
Heart failure												
2	randomised trial	serious[1]	serious[2]	no serious indirectness	serious[4]	none	948/18294 (5.2%)	681/12089 (5.6%)	RR 0.94 (0.71 to 1.24)	3 fewer per 1000 (from 16 fewer to 13 more)	⊕OOO VERY LOW	
Diabetes-incidence												
1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	no serious imprecision	none	636/15255 (4.2%)	243/9054 (2.7%)	RR 1.55 (1.34 to 1.8)	15 more per 1000 (from 9 more to 22 more)	⊕⊕⊕O MODERATE	

[1] All trials rated "Moderate" quality by expert group.

[2] High I-squared value.

[3] Trial rated "Moderate" quality by expert group.

[4] Wide 95% CI.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-05
Question: Should ARB vs Beta-blocker be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance

							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**ARB**	**Beta-blocker**	**Relative (95% CI)**	**Absolute**		
Mortality												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	383/4605 (8.3%)	431/4588 (9.4%)	RR 0.89 (0.78 to 1.01)	10 fewer per 1000 (from 21 fewer to 1 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	198/4605 (4.3%)	188/4588 (4.1%)	RR 1.05 (0.86 to 1.28)	2 more per 1000 (from 6 fewer to 11 more)	⊕⊕⊕O MODERATE	
Stroke												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none	232/4605 (5%)	309/4588 (6.7%)	RR 0.75 (0.63 to 0.88)	17 fewer per 1000 (from 8 fewer to 25 fewer)	⊕⊕OO LOW	
Angina												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	160/4605 (3.5%)	141/4588 (3.1%)	RR 1.13 (0.9 to 1.41)	4 more per 1000 (from 3 fewer to 13 more)	⊕⊕⊕O MODERATE	
Heart failure												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	153/4605 (3.3%)	161/4588 (3.5%)	RR 0.95 (0.76 to 1.18)	2 fewer per 1000 (from 8 fewer to 6 more)	⊕⊕⊕O MODERATE	
Diabetes-incidence												
1	randomised	no serious	no serious	no serious	serious[1]	none	241/4605	319/4588	RR 0.75	18 fewer per 1000	⊕⊕⊕O	

	trial	limitations	inconsistency	indirectness			(5.2%)	(7%)	(0.64 to 0.89)	(from 8 fewer to 25 fewer)	MODERATE	

[1] Only one trial.

[2] Wide 95% CI.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-05
Question: Should ARB vs CCB be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	CCB	Relative (95% CI)	Absolute		
Mortality												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	914/10003 (9.1%)	904/9945 (9.1%)	RR 0.99 (0.86 to 1.14)	1 fewer per 1000 (from 13 fewer to 13 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	397/10003 (4%)	346/9945 (3.5%)	RR 1.09 (0.84 to 1.42)	3 more per 1000 (from 6 fewer to 15 more)	⊕⊕OO LOW	
Stroke												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	382/10003 (3.8%)	328/9945 (3.3%)	RR 1.16 (1 to 1.34)	5 more per 1000 (from 0 more to 11 more)	⊕⊕OO LOW	
Angina												

1	randomised trial	serious[3]	no serious inconsistency	no serious indirectness	very serious[2]	none	8/2354 (0.3%)	14/2349 (0.6%)	RR 0.57 (0.24 to 1.36)	3 fewer per 1000 (from 5 fewer to 2 more)	⊕OOO VERY LOW	
Heart failure												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	374/10003 (3.7%)	416/9945 (4.2%)	RR 0.90 (0.76 to 1.07)	4 fewer per 1000 (from 10 fewer to 3 more)	⊕⊕⊕O MODERATE	
Diabetes-incidence												
2	randomised trial	serious[1]	serious[4]	no serious indirectness	no serious imprecision	none	756/10003 (7.6%)	949/9945 (9.5%)	RR 0.75 (0.6 to 0.94)	24 fewer per 1000 (from 6 fewer to 38 fewer)	⊕⊕OO LOW	

[1] One trial rated "Moderate" quality by expert group.

[2] Wide 95% CI.

[3] Trial rated "Moderate" quality by expert group.

[4] High I-squared value.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-05
Question: Should CCB (+ACE-inhibitor) vs Beta-blocker (+diuretic) be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CCB (+ACE-inhibitor)	Beta-blocker (+diuretic)	Relative (95% CI)	Absolute		
Mortality												
1	randomised	no serious	no serious	no serious	serious[1]	none	738/9639	820/9618	RR 0.90	9 fewer per 1000	⊕⊕⊕O	

	trial	limitations	inconsistency	indirectness			(7.7%)	(8.5%)	(0.82 to 0.99)	(from 1 fewer to 15 fewer)	MODERATE	
Myocardial infarction												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	753/9639 (7.8%)	852/9618 (8.9%)	RR 0.88 (0.8 to 0.97)	11 fewer per 1000 (from 3 fewer to 18 fewer)	⊕⊕⊕O MODERATE	
Stroke												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	327/9639 (3.4%)	422/9618 (4.4%)	RR 0.77 (0.67 to 0.89)	10 fewer per 1000 (from 5 fewer to 15 fewer)	⊕⊕⊕O MODERATE	
Angina												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	278/9639 (2.9%)	314/9618 (3.3%)	RR 0.88 (0.75 to 1.04)	4 fewer per 1000 (from 8 fewer to 1 more)	⊕⊕⊕O MODERATE	
Heart failure												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	134/9639 (1.4%)	159/9618 (1.7%)	RR 0.84 (0 to 0)	3 fewer per 1000 (from 17 fewer to 17 fewer)	⊕⊕⊕O MODERATE	

[1] Only one trial.

[2] Wide 95% CI.

Drug vs placebo in diabetics

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-05
Question: Should Antihypertensives be used for Diabetes (with or without hypetension)?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Antihypertensives	control	Relative (95% CI)	Absolute		
Mortality												
4	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	1070/9909 (10.8%)	1043/9371 (11.1%)	RR 0.95 (0.88 to 1.03)	6 fewer per 1000 (from 13 fewer to 3 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	397/9158 (4.3%)	418/8609 (4.9%)	RR 0.86 (0.75 to 0.99)	7 fewer per 1000 (from 0 fewer to 12 fewer)	⊕⊕⊕⊕ HIGH	
Stroke												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	376/9158 (4.1%)	360/8609 (4.2%)	RR 0.98 (0.85 to 1.13)	1 fewer per 1000 (from 6 fewer to 5 more)	⊕⊕⊕O MODERATE	
Heart failure												

2	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	238/3589 (6.6%)	174/3038 (5.7%)	RR 0.95 (0.78 to 1.15)	3 fewer per 1000 (from 13 fewer to 9 more)	⊕⊕⊕O MODERATE	
Renal failure												
3	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	no serious imprecision	none	344/4340 (7.9%)	307/3800 (8.1%)	RR 0.83 (0.72 to 0.96)	14 fewer per 1000 (from 3 fewer to 23 fewer)	⊕⊕⊕⊕ HIGH	

[1] 95% CI considered wide by expert group.

Drug vs drug in diabetics

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-05
Question: Should ACE-inhibitor vs CCB be used for Hypertension in diabetics?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-inhibitor	CCB	Relative (95% CI)	Absolute		
Mortality												

3	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	73/659 (11.1%)	72/657 (11%)	RR 1.02 (0.76 to 1.36)	2 more per 1000 (from 26 fewer to 40 more)	⊕⊕OO LOW	
Myocardial infarction												
3	randomised trial	serious[1]	serious[3]	no serious indirectness	serious[2]	none	32/659 (4.9%)	70/657 (10.7%)	RR 0.46 (0.23 to 0.9)	58 fewer per 1000 (from 11 fewer to 82 fewer)	⊕OOO VERY LOW	
Stroke												
3	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	45/659 (6.8%)	50/657 (7.6%)	RR 0.79 (0.43 to 1.46)	16 fewer per 1000 (from 43 fewer to 35 more)	⊕⊕OO LOW	
Angina												
1	randomised trial	serious[4]	no serious inconsistency	no serious indirectness	very serious[2]	none	0/189 (0%)	4/191 (2.1%)	RR 0.11 (0.01 to 2.07)	19 fewer per 1000 (from 21 fewer to 22 more)	⊕OOO VERY LOW	
Heart failure												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	28/470 (6%)	30/466 (6.4%)	RR 0.92 (0.56 to 1.51)	5 fewer per 1000 (from 28 fewer to 33 more)	⊕⊕OO LOW	

[1] All trials rated "Moderate" quality by expert group.
[2] Wide 95% CI.
[3] High I-squared value.
[4] Trial rated "Moderate" quality by expert group.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-05
Question: Should ACE-inhibitor vs Beta-blocker be used for Hypertension in diabetics?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-inhibitor	Beta-blocker	Relative (95% CI)	Absolute		
Mortality												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	75/400 (18.8%)	59/358 (16.5%)	RR 1.14 (0.83 to 1.55)	23 more per 1000 (from 28 fewer to 91 more)	⊕⊕OO LOW	
Myocardial infarction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	61/400 (15.3%)	46/358 (12.8%)	RR 1.19 (0.83 to 1.69)	24 more per 1000 (from 22 fewer to 88 more)	⊕⊕OO LOW	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/400 (5.3%)	17/358 (4.7%)	RR 1.11 (0.59 to 2.06)	5 more per 1000 (from 19	⊕⊕OO LOW	

										fewer to 50 more)		
Angina												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	20/400 (5%)	25/358 (7%)	RR 0.72 (0.4 to 1.27)	20 fewer per 1000 (from 42 fewer to 19 more)	⊕⊕OO LOW	
Heart failure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/400 (3%)	9/358 (2.5%)	RR 1.19 (0.51 to 2.8)	5 more per 1000 (from 12 fewer to 45 more)	⊕⊕OO LOW	
Renal failure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	4/400 (1%)	4/358 (1.1%)	RR 0.90 (0.23 to 3.55)	1 fewer per 1000 (from 8 fewer to 28 more)	⊕⊕OO LOW	

[1] Trial rated "Moderate" quality by expert group.
[2] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-05
Question: Should ARB vs CCB be used for Hypertension i diabetics?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other	ARB	CCB	Relative	Absolute		

studies						considerations			(95% CI)			
Mortalilty												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	87/579 (15%)	83/567 (14.6%)	RR 1.03 (0.78 to 1.35)	4 more per 1000 (from 32 fewer to 51 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	44/579 (7.6%)	27/567 (4.8%)	RR 1.60 (1 to 2.54)	29 more per 1000 (from 0 more to 74 more)	⊕⊕⊕O MODERATE	
Stroke												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	28/579 (4.8%)	15/567 (2.6%)	RR 1.83 (0.99 to 3.39)	22 more per 1000 (from 0 fewer to 62 more)	⊕⊕⊕O MODERATE	
Heart failure												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	60/579 (10.4%)	93/567 (16.4%)	RR 0.63 (0.47 to 0.86)	61 fewer per 1000 (from 23 fewer to 87 fewer)	⊕⊕⊕O MODERATE	
Renal failure												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	82/579 (14.2%)	104/567 (18.3%)	RR 0.77 (0.59 to 1.01)	42 fewer per 1000 (from 75	⊕⊕⊕O MODERATE	

										fewer to 2 more)		

[1] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-05
Question: Should ACE-inhibitor vs ARB be used for Hypertension in diabetics?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-inhibitor	ARB	Relative (95% CI)	Absolute		
Mortality												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/130 (4.6%)	6/120 (5%)	RR 0.92 (0.31 to 2.78)	4 fewer per 1000 (from 34 fewer to 89 more)	⊕OOO VERY LOW	
Myocardial infarction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/130 (4.6%)	9/120 (7.5%)	RR 0.62 (0.23 to 1.68)	29 fewer per 1000 (from 58 fewer to 51 more)	⊕OOO VERY LOW	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	6/130 (4.6%)	6/120 (5%)	RR 0.92 (0.31 to 2.78)	4 fewer per 1000 (from 34 fewer to	⊕OOO VERY LOW	

										89 more)		
Heart failure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	very serious[2]	none	7/130 (5.4%)	9/120 (7.5%)	RR 0.72 (0.28 to 1.87)	21 fewer per 1000 (from 54 fewer to 65 more)	⊕OOO VERY LOW	

[1] Trial rated "Moderate" quality by expert group.
[2] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-05
Question: Should ACE-inhibitor vs Diuretic and/or beta-blocker be used for Hyypertension in diabetics?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ACE-inhibitor	Diuretic and/or beta-blocker	Relative (95% CI)	Absolute	Quality	
Mortality												
2	randomised trial	serious[1]	serious[2]	no serious indirectness	serious[3]	none	76/544 (14%)	101/516 (19.6%)	RR 0.70 (0.39 to 1.24)	59 fewer per 1000 (from 120 fewer to 47 more)	⊕OOO VERY LOW	
Myocardial infarction												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	29/544 (5.3%)	53/516 (10.3%)	RR 0.53 (0.29 to	48 fewer per 1000	⊕⊕OO LOW	

									0.97)	(from 3 fewer to 73 fewer)		
Stroke												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	57/544 (10.5%)	58/516 (11.2%)	RR 0.97 (0.69 to 1.37)	3 fewer per 1000 (from 35 fewer to 41 more)	⊕⊕OO LOW	
Heart failure												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	33/544 (6.1%)	46/516 (8.9%)	RR 0.72 (0.47 to 1.1)	25 fewer per 1000 (from 47 fewer to 9 more)	⊕⊕OO LOW	

[1] Trials rated "Moderate" quality by expert group.
[2] High I-sqared value.
[3] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-05
Question: Should CCB vs Diuretic and/or beta-blocker be used for Hypertension in diabetics?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					
							No of patients		Effect		Quality	Importance
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	CCB	Diuretic and/or beta-blocker	Relative (95% CI)	Absolute		

Mortality												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	78/582 (13.4%)	93/629 (14.8%)	RR 0.91 (0.67 to 1.26)	13 fewer per 1000 (from 49 fewer to 38 more)	⊕⊕OO LOW	
Myocardial infarction												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/582 (8.4%)	44/629 (7%)	RR 1.22 (0.82 to 1.79)	15 more per 1000 (from 13 fewer to 55 more)	⊕⊕OO LOW	
Stroke												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	49/582 (8.4%)	59/629 (9.4%)	RR 0.90 (0.63 to 1.28)	9 fewer per 1000 (from 35 fewer to 26 more)	⊕⊕OO LOW	
Heart failure												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	37/582 (6.4%)	36/629 (5.7%)	RR 1.22 (0.58 to 2.59)	13 more per 1000 (from 24 fewer to 91 more)	⊕⊕OO LOW	

[1] Trials rated "Moderate" quality by expert group.
[2] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-06
Question: Should ARB vs Beta-blocker be used for Hypertension in diabetics?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	ARB	Beta-blocker	Relative (95% CI)	Absolute		
Mortality												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	63/586 (10.8%)	104/609 (17.1%)	RR 0.63 (0.47 to 0.84)	63 fewer per 1000 (from 27 fewer to 91 fewer)	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	41/586 (7%)	50/609 (8.2%)	RR 0.85 (0.57 to 1.27)	12 fewer per 1000 (from 35 fewer to 22 more)	⊕⊕⊕O MODERATE	
Stroke												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	51/586 (8.7%)	65/609 (10.7%)	RR 0.82 (0.58 to 1.16)	19 fewer per 1000 (from 45 fewer to 17 more)	⊕⊕⊕O MODERATE	
Angina												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	30/586 (5.1%)	30/609 (4.9%)	RR 1.04 (0.63 to 1.7)	2 more per 1000 (from 18 fewer to 34 more)	⊕⊕⊕O MODERATE	

Heart failure												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[2]	none	32/586 (5.5%)	55/609 (9%)	RR 0.60 (0.4 to 0.92)	36 fewer per 1000 (from 7 fewer to 54 fewer)	⊕⊕⊕O MODERATE	

[1] Only one trial.
[2] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-06
Question: Should Diurectic vs CCB be used for Hypertension in diabetics?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Diurectic	CCB	Relative (95% CI)	Absolute		
Mortality												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	59/653 (9%)	44/649 (6.8%)	RR 1.33 (0.92 to 1.94)	22 more per 1000 (from 5 fewer to 64 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	25/653 (3.8%)	28/649 (4.3%)	RR 0.89 (0.52 to 1.5)	5 fewer per 1000 (from 21 fewer to	⊕⊕⊕O MODERATE	

										22 more)		
Stroke												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	19/653 (2.9%)	17/649 (2.6%)	RR 1.11 (0.58 to 2.12)	3 more per 1000 (from 11 fewer to 29 more)	⊕⊕⊕O MODERATE	
Heart failure												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	6/653 (0.9%)	9/649 (1.4%)	RR 0.66 (0.24 to 1.85)	5 fewer per 1000 (from 11 fewer to 12 more)	⊕⊕⊕O MODERATE	

[1] Wide 95% CI.

Glucose-lowering drugs

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-06
Question: Should Sylphonylurea be used for Diabetes?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Sylphonylurea	control	Relative (95% CI)	Absolute		
Mortality												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	257/1234 (20.8%)	190/896 (21.2%)	RR 0.98 (0.83 to 1.16)	4 fewer per 1000 (from 36 fewer to 34 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	190/1234 (15.4%)	162/896 (18.1%)	RR 0.85 (0.7 to 1.03)	27 fewer per 1000 (from 54 fewer to 5 more)	⊕⊕OO LOW	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	78/1234 (6.3%)	47/896 (5.2%)	RR 1.21 (0.85 to 1.71)	11 more per 1000 (from 8 fewer to	⊕⊕OO LOW	

										37 more)		
Angina												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	92/1234 (7.5%)	58/896 (6.5%)	RR 1.15 (0.84 to 1.58)	10 more per 1000 (from 10 fewer to 38 more)	⊕⊕OO LOW	
Heart failure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	46/1234 (3.7%)	31/896 (3.5%)	RR 1.08 (0.69 to 1.69)	3 more per 1000 (from 11 fewer to 24 more)	⊕⊕OO LOW	

[1] Trial rated "Moderate" quality by expert group.
[2] Wide 95% CI.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-07
Question: Should Metformin be used for Diabetes?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	**Design**	**Limitations**	**Inconsistency**	**Indirectness**	**Imprecision**	**Other considerations**	**Metformin**	**control**	**Relative (95% CI)**	**Absolute**		
Mortality												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	50/342 (14.6%)	89/411 (21.7%)	RR 0.68 (0.49 to 0.93)	69 fewer per 1000 (from 15 fewer to		

										111 fewer)		
Myocardial infarction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	39/342 (11.4%)	73/411 (17.8%)	RR 0.64 (0.45 to 0.92)	64 fewer per 1000 (from 14 fewer to 98 fewer)	⊕⊕OO LOW	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/342 (3.5%)	23/411 (5.6%)	RR 0.63 (0.32 to 1.24)	21 fewer per 1000 (from 38 fewer to 13 more)	⊕⊕OO LOW	
Angina												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	21/342 (6.1%)	22/411 (5.4%)	RR 1.15 (0.64 to 2.05)	8 more per 1000 (from 19 fewer to 57 more)	⊕⊕OO LOW	
Heart failure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	11/342 (3.2%)	17/411 (4.1%)	RR 0.78 (0.37 to 1.64)	9 fewer per 1000 (from 26 fewer to 26 more)	⊕⊕OO LOW	

[1] Trial rated "Moderate" quality by expert group.
[2] Wide 95% CI.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-08
Question: Should Acarbose be used for Diabetes?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Acarbose	control	Relative (95% CI)	Absolute		
Myocardial infarction												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	1/628 (0.2%)	12/686 (1.7%)	RR 0.08 (0.01 to 0.64)	16 fewer per 1000 (from 6 fewer to 17 fewer)	⊕⊕⊕O MODERATE	
Stroke												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none	2/682 (0.3%)	4/686 (0.6%)	RR 0.50 (0.09 to 2.74)	3 fewer per 1000 (from 5 fewer to 10 more)	⊕⊕OO LOW	
Angina												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none	5/682 (0.7%)	12/686 (1.7%)	RR 0.42 (0.15 to 1.18)	10 fewer per 1000 (from 14 fewer to 3 more)	⊕⊕OO LOW	
Heart failure												

1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[1]	none	0/682 (0%)	2/686 (0.3%)	RR 0.20 (0.01 to 4.18)	2 fewer per 1000 (from 3 fewer to 10 more)	⊕⊕OO LOW	

[1] Wide 95% CI.

Author(s): Atle Fretheim Gunn E. Vist
Date: 2008-06-08
Question: Should Rosiglitazone be used for Diabetes?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Rosiglitazone	control	Relative (95% CI)	Absolute		
Mortality												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	104/4855 (2.1%)	113/4861 (2.3%)	RR 0.92 (0.71 to 1.2)	2 fewer per 1000 (from 7 fewer to 5 more)	⊕⊕OO LOW	
Myocardial infarction												
2	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	58/4855 (1.2%)	46/4861 (0.9%)	RR 1.26 (0.86 to 1.86)	2 more per 1000 (from 1 fewer to 8 more)	⊕⊕OO LOW	
Stroke												
1	randomised	no serious	no serious	no serious	very	none	7/2635	5/2634	RR 1.40	1 more	⊕⊕OO	

	trial	limitations	inconsistency	indirectness	serious[2]		(0.3%)	(0.2%)	(0.44 to 4.4)	per 1000 (from 1 fewer to 7 more)	LOW	
Angina												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	very serious[2]	none	24/2635 (0.9%)	20/2634 (0.8%)	RR 1.20 (0.66 to 2.17)	2 more per 1000 (from 3 fewer to 9 more)	⊕⊕OO LOW	
Heart failure												
2	randomised trial	serious[1]	serious[3]	no serious indirectness	serious[2]	none	52/4855 (1.1%)	19/4861 (0.4%)	RR 2.74 (1.63 to 4.63)	7 more per 1000 (from 3 more to 15 more)	⊕OOO VERY LOW	

[1] One trial rated "Moderate" quality by expert group.

[2] Wide 95% CI.

[3] High I-squared value.

Multifactorial interventions

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-08
Question: Should "Stepped care" antihypertensive treatment with free follow-up and advice on diet and smoking-cessation [HDFP] be used for Hypertension?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	"Stepped care" antihypertensive treatment with free follow-up and advice on diet and smoking-cessation [HDFP]	control	Relative (95% CI)	Absolute		
Mortality												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	349/5485 (6.4%)	419/5455 (7.7%)	RR 0.83 (0.72 to 0.95)	13 fewer per 1000 (from 4 fewer to 22 fewer)	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	558/5485 (10.2%)	669/5455 (12.3%)	RR 0.83 (0.75 to 0.92)	21 fewer per 1000 (from 10 fewer to 31 fewer)	⊕⊕⊕O MODERATE	
Stroke												

1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	102/5485 (1.9%)	158/5455 (2.9%)	RR 0.64 (0.5 to 0.82)	10 fewer per 1000 (from 5 fewer to 15 fewer)	⊕⊕⊕O MODERATE	
Angina												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	325/5485 (5.9%)	449/5455 (8.2%)	RR 0.72 (0.63 to 0.83)	23 fewer per 1000 (from 14 fewer to 30 fewer)	⊕⊕⊕O MODERATE	

[1] Trial rated "Moderate" quality by expert group.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-08
Question: Should Advice on low-fat diet and smoking cessation [Oslo-study] be used for Healthy men at increased risk of coronary heart disease?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Advice on low-fat diet and smoking cessation [Oslo-study]	control	Relative (95% CI)	Absolute		
Mortality												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	16/604 (2.6%)	24/628 (3.8%)	RR 0.69 (0.37 to 1.29)	12 fewer per 1000 (from 24 fewer to 11 more)	⊕⊕OO LOW	
Myocardial infarction												

1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/604 (3.1%)	36/628 (5.7%)	RR 0.55 (0.32 to 0.95)	26 fewer per 1000 (from 3 fewer to 39 fewer)	⊕⊕OO LOW	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/604 (0.5%)	3/628 (0.5%)	RR 1.04 (0.21 to 5.13)	0 more per 1000 (from 4 fewer to 21 more)	⊕⊕OO LOW	

[1] Trial rated "Moderate" quality by expert group.

[2] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-08
Question: Should Antihypertensive mediaction and councelling (individually and group-based) on diet and smoking cessation [MRFIT] be used for Healthy men at increased risk of coronary heart disease?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Antihypertensive mediaction and councelling (individually and group-based) on diet and smoking cessation [MRFIT]	control	Relative (95% CI)	Absolute		
Mortality												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	265/6428 (4.1%)	260/6438 (4%)	RR 1.02 (0.86 to 1.21)	1 more per 1000 (from 6 fewer to 8	⊕⊕⊕O MODERATE	

										more)		
Myocardial infarction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	115/6428 (1.8%)	124/6438 (1.9%)	RR 0.93 (0.72 to 1.19)	1 fewer per 1000 (from 5 fewer to 4 more)	⊕⊕OO LOW	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	36/6428 (0.6%)	30/6438 (0.5%)	RR 1.20 (0.74 to 1.95)	1 more per 1000 (from 1 fewer to 5 more)	⊕⊕OO LOW	
Angina												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	no serious imprecision	none	646/6428 (10%)	817/6438 (12.7%)	RR 0.79 (0.71 to 0.87)	27 fewer per 1000 (from 17 fewer to 37 fewer)	⊕⊕⊕O MODERATE	
Heart failure												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	2/6428 (0%)	17/6438 (0.3%)	RR 0.12 (0.03 to 0.51)	3 fewer per 1000 (from 1 fewer to 3 fewer)	⊕⊕OO LOW	

[1] Trial rated "Moderate" quality by expert group.

[2] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-08
Question: Should Written av oral dietary advice; exercise program and advice on smoking cessation, supplemented with antihypertensive and lipid-loweing medication [Finnish businessmen study] be used for Healthy men with at least one coronary risk factor.?

Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Written av oral dietary advice; exercise program and advice on smoking cessation, supplemented with antihypertensive and lipid-loweing medication [Finnish businessmen study]	control	Relative (95% CI)	Absolute	Quality	
Mortality												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	10/612 (1.6%)	5/610 (0.8%)	RR 1.99 (0.69 to 5.8)	8 more per 1000 (from 2 fewer to 38 more)	⊕⊕OO LOW	
Myocardial infarction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	19/612 (3.1%)	9/610 (1.5%)	RR 2.10 (0.96 to 4.61)	16 more per 1000 (from 1 fewer to 54 more)	⊕⊕OO LOW	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[3]	none	0/612 (0%)	8/610 (1.3%)	RR 0.06 (0 to 1.01)	12 fewer per 1000 (from 13 fewer to 0 more)	⊕⊕OO LOW	

[1] Trial rated "Moderate" quality by expert group.

[2] Wide 95% CI.

[3] No explanation was provided

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-08
Question: Should Written and oral advice on low-calory and low-fat diet, exercise, smoking cessation, with antihypertensive treatment [Diabetes Intervention Study] be used for Diabetes type 2?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Written and oral advice on low-calory and low-fat diet, exercise, smoking cessation, with antihypertensive treatment [Diabetes Intervention Study]	control	Relative (95% CI)	Absolute		
Mortality												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	19/662 (2.9%)	16/366 (4.4%)	RR 0.66 (0.34 to 1.26)	15 fewer per 1000 (from 29 fewer to 11 more)	⊕⊕⊕O MODERATE	
Myocardial infarction												
1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	35/662 (5.3%)	10/366 (2.7%)	RR 1.94 (0.97 to 3.86)	25 more per 1000 (from 1 fewer to 77 more)	⊕⊕⊕O MODERATE	
Stroke												

1	randomised trial	no serious limitations	no serious inconsistency	no serious indirectness	serious[1]	none	4/662 (0.6%)	1/366 (0.3%)	RR 2.21 (0.25 to 19.71)	4 more per 1000 (from 2 fewer to 56 more)	⊕⊕⊕O MODERATE	

[1] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist
Date: 2008-06-08
Question: Should Dietary advice and councelling on exercise and smoking cessation, with ACE-inhibitor, vfitamin and mineral supplements, ASA and glucose-loweing drugs as needed [Steno-2] be used for Diabetes type with microalbuminuria?
Settings:
Bibliography: Primary Prevention of Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					
							No of patients		Effect			
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Dietary advice and councelling on exercise and smoking cessation, with ACE-inhibitor, vfitamin and mineral supplements, ASA and glucose-loweing drugs as needed [Steno-2]	control	Relative (95% CI)	Absolute	Quality	Importance
Mortality												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	12/80 (15%)	15/80 (18.8%)	RR 00.80 (0.4 to 1.6)	38 fewer per 1000 (from 113 fewer to 113 more)	⊕⊕OO LOW	
Myocardial infarction												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	5/80 (6.3%)	17/80	RR 0.29	151 fewer per	⊕⊕OO	

	trial		inconsistency	indirectness				(21.3%)	(0.11 to 0.76)	1000 (from 51 fewer to 190 fewer)	LOW	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	3/80 (3.8%)	20/80 (25%)	RR 0.15 (0.05 to 0.48)	212 fewer per 1000 (from 130 fewer to 238 fewer)	⊕⊕OO LOW	

[1] Trial rated "Moderate" quality by expert group.

[2] Wide 95% CI.

Food supplements

Author(s): Atle Fretheim and Gunn E. Vist.
Date: 2008-06-08
Question: Should Omega-3-fatty acid be used for Hypercholesterolaemia?
Settings:
Bibliography: Primary Prevention for Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Omega-3-fatty acid	control	Relative (95% CI)	Absolute		
Mortality												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	286/9326	265/9319	RR 1.08	2 more	⊕⊕OO	

	trial		inconsistency	indirectness			(3.1%)	(2.8%)	(0.91 to 1.27)	per 1000 (from 3 fewer to 8 more)	LOW	
Myocardial infarction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	88/9326 (0.9%)	113/9319 (1.2%)	RR 0.78 (0.59 to 1.03)	3 fewer per 1000 (from 5 fewer to 0 more)	⊕⊕OO LOW	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	166/9326 (1.8%)	162/9319 (1.7%)	RR 1.02 (0.83 to 1.27)	0 more per 1000 (from 3 fewer to 5 more)	⊕⊕OO LOW	

[1] Trial rated "Moderate" quality by expert group.
[2] Wide 95% CI.

Author(s): Atle Fretheim and Gunn E. Vist.
Date: 2008-06-08
Question: Should Vitamin E be used for Persons with at least one coronary risk factor?
Settings:
Bibliography: Primary Prevention for Cardiovascular Disease, Norwegian Knowledge Centre for the Health Services, 2008

Quality assessment							Summary of findings					Importance
							No of patients		Effect		Quality	
No of studies	Design	Limitations	Inconsistency	Indirectness	Imprecision	Other considerations	Vitamin E	control	Relative (95% CI)	Absolute		
Mortality												
1	randomised	serious[1]	no serious	no serious	serious[2]	none	72/2231	68/2264	RR 1.07	2 more	⊕⊕OO	

	trial		inconsistency	indirectness			(3.2%)	(3%)	(0.78 to 1.49)	per 1000 (from 7 fewer to 15 more)	LOW	
Myocardial infarction												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/2231 (1%)	25/2264 (1.1%)	RR 0.89 (0.51 to 1.58)	1 fewer per 1000 (from 5 fewer to 6 more)	⊕⊕OO LOW	
Stroke												
1	randomised trial	serious[1]	no serious inconsistency	no serious indirectness	serious[2]	none	22/2231 (1%)	18/2264 (0.8%)	RR 1.24 (0.67 to 2.31)	2 more per 1000 (from 3 fewer to 10 more)	⊕⊕OO LOW	

[1] Trial rated "Moderate" quality by expert group.

[2] Wide 95% CI.

Vedlegg 6

PRIMÆRFOREBYGGING AV HJERTE- OG KARSYKDOM (KUNNSKAPSSENTERETS RAPPORT NR 20-2008)

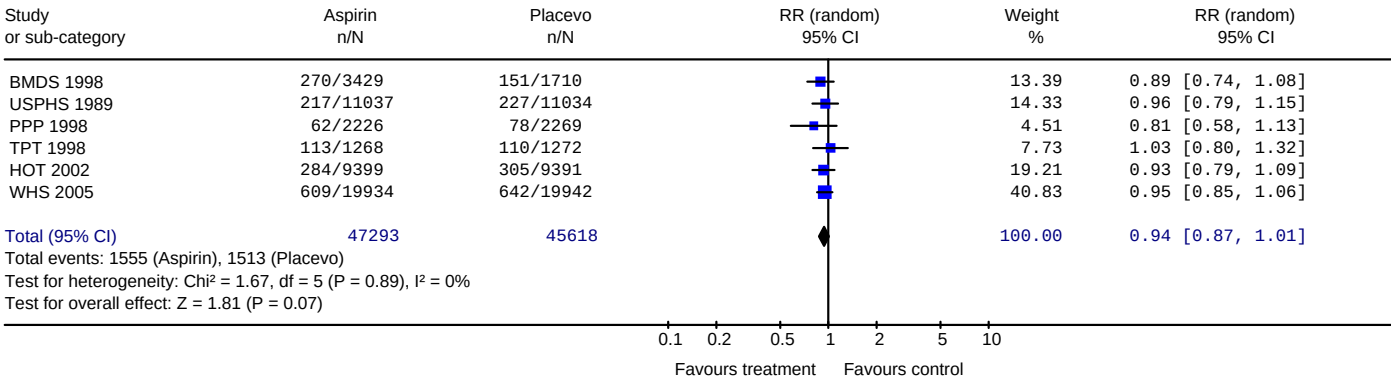
META-ANALYSER

I dette vedlegget presenterer vi hver enkelt av meta-analysene vi har utført.

INNHOLD

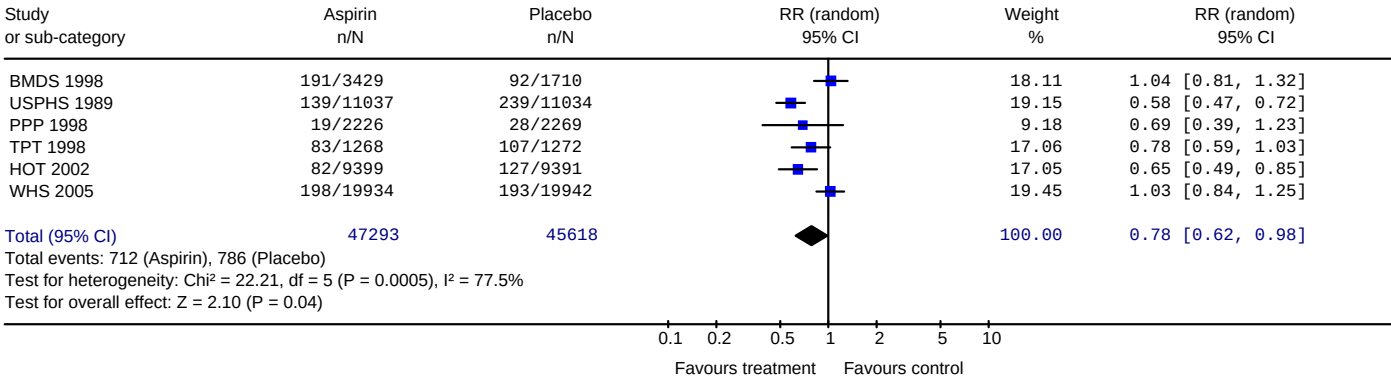
Antitrombotika

Review: Antithrombotic drugs
Comparison: 01 Aspirin versus placebo
Outcome: 01 All-cause mortality



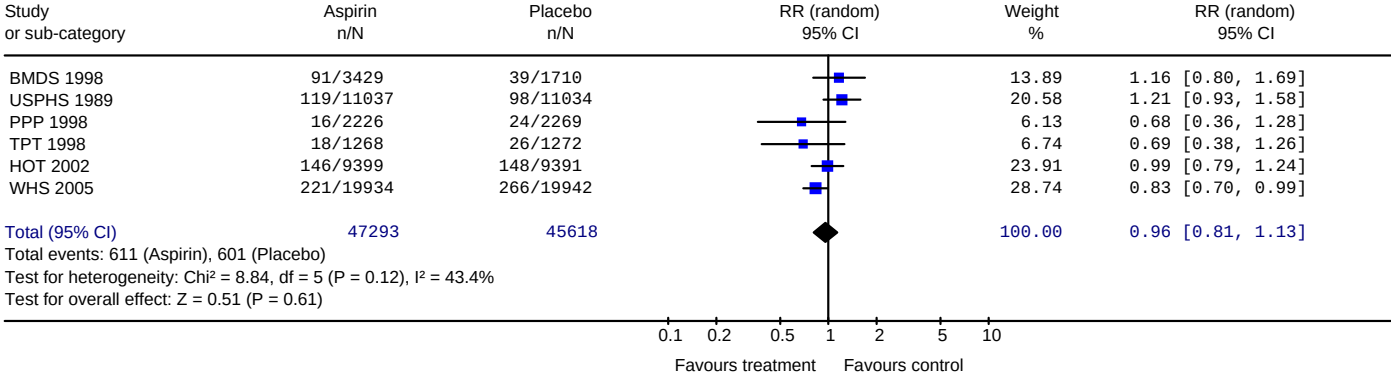
Total events: 1555 (Aspirin), 1513 (Placevo)
Test for heterogeneity: Chi² = 1.67, df = 5 (P = 0.89), I² = 0%
Test for overall effect: Z = 1.81 (P = 0.07)

Review: Antithrombotic drugs
Comparison: 01 Aspirin versus placebo
Outcome: 02 Myocardial infarction



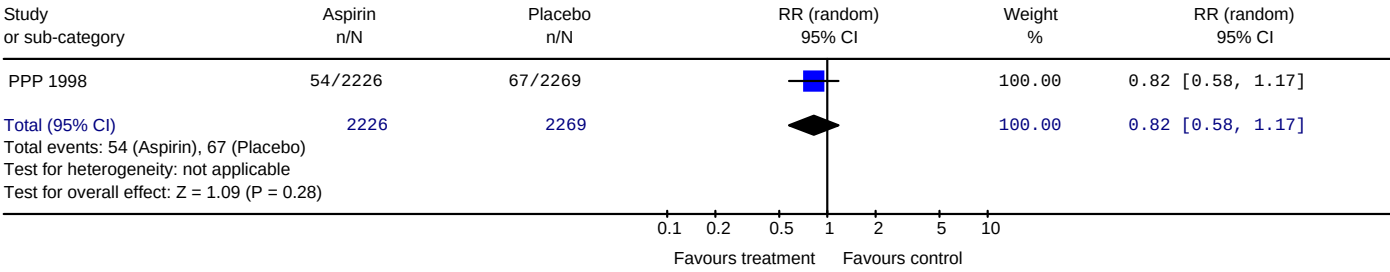
Total events: 712 (Aspirin), 786 (Placebo)
Test for heterogeneity: Chi² = 22.21, df = 5 (P = 0.0005), I² = 77.5%
Test for overall effect: Z = 2.10 (P = 0.04)

Review: Antithrombotic drugs
Comparison: 01 Aspirin versus placebo
Outcome: 03 Stroke

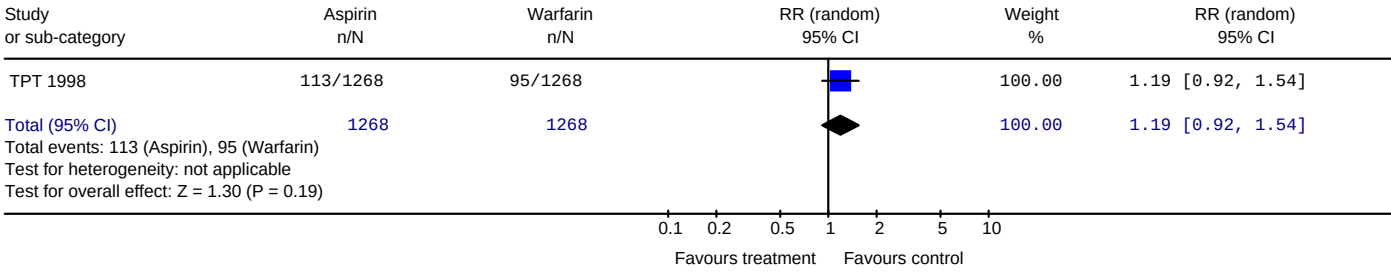


Total events: 611 (Aspirin), 601 (Placebo)
Test for heterogeneity: Chi² = 8.84, df = 5 (P = 0.12), I² = 43.4%
Test for overall effect: Z = 0.51 (P = 0.61)

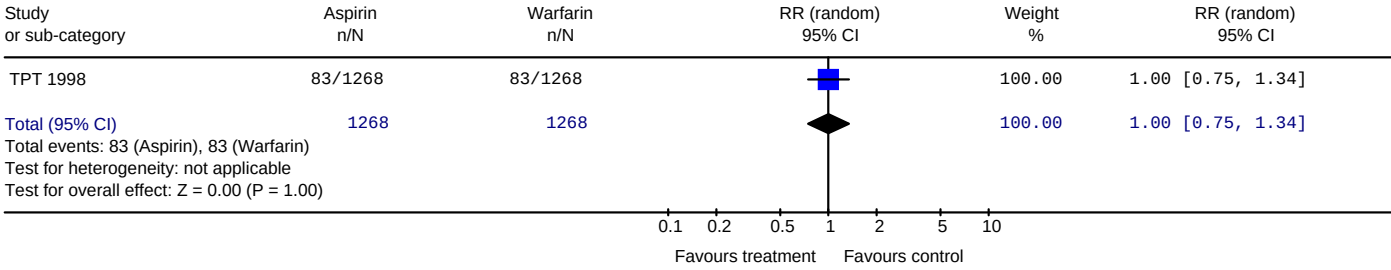
Review: Antithrombotic drugs
Comparison: 01 Aspirin versus placebo
Outcome: 04 Angina



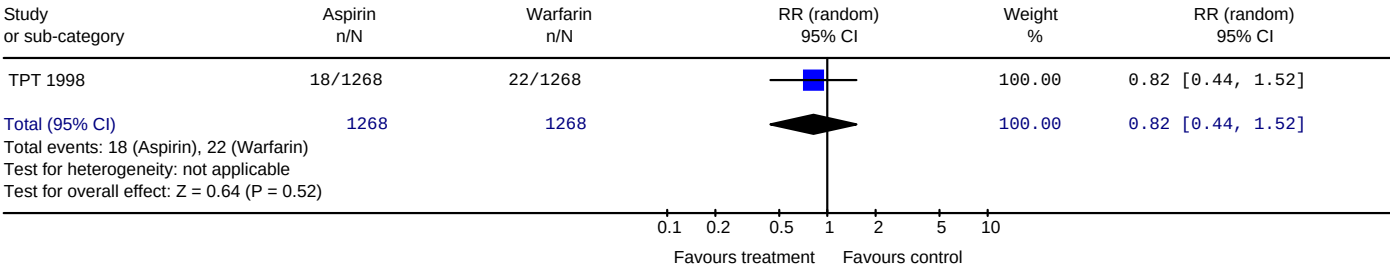
Review: Antithrombotic drugs
Comparison: 02 Aspirin versus Warfarin
Outcome: 01 All-cause mortality



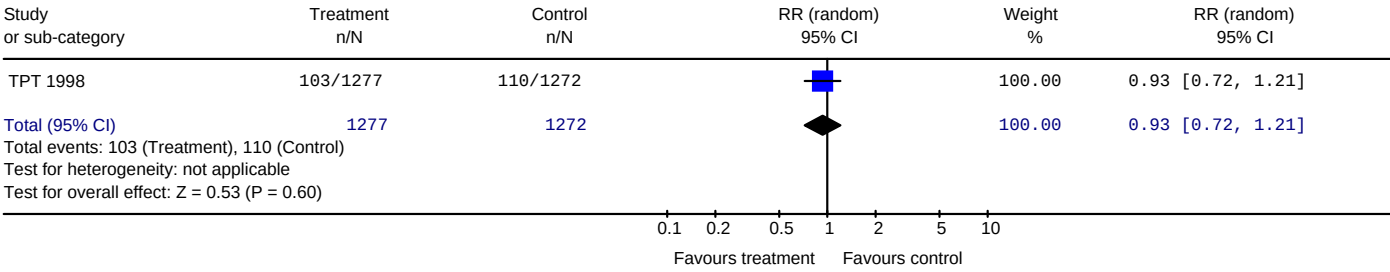
Review: Antithrombotic drugs
Comparison: 02 Aspirin versus Warfarin
Outcome: 02 Myocardial infarction



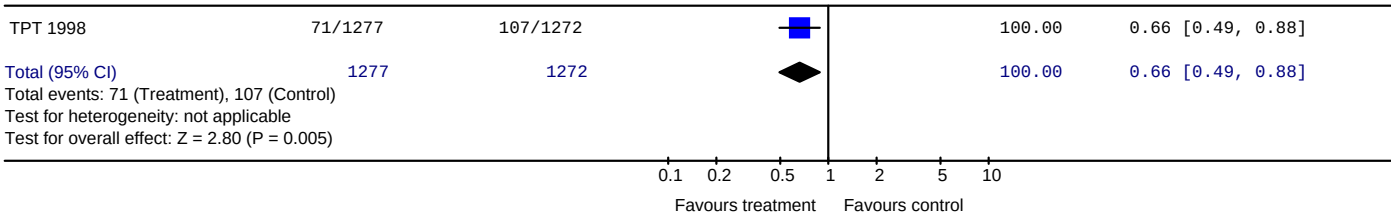
Review: Antithrombotic drugs
Comparison: 02 Aspirin versus Warfarin
Outcome: 03 Stroke



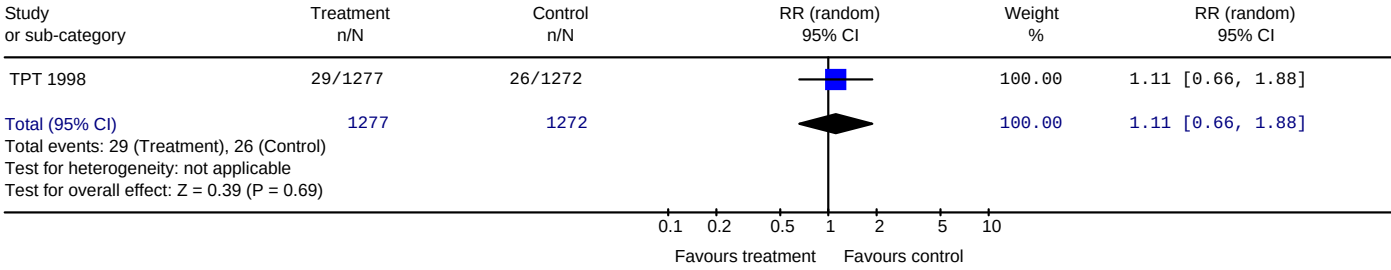
Review: Antithrombotic drugs
Comparison: 04 Aspirin and Warfarin versus placebo
Outcome: 01 All-cause mortality



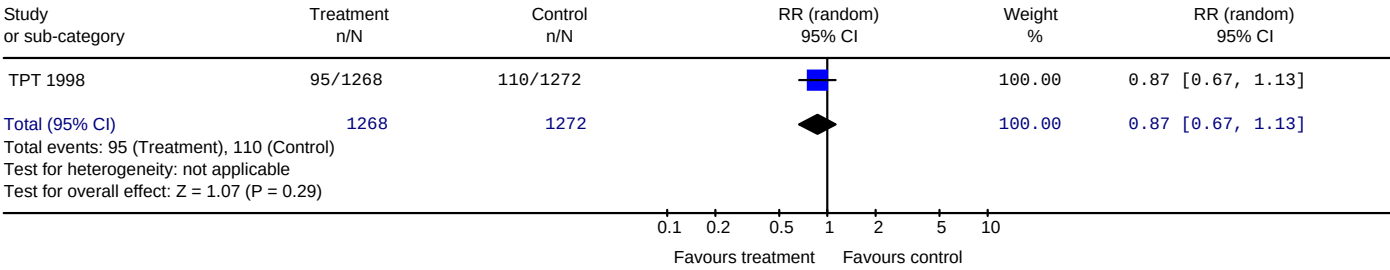
Review: Antithrombotic drugs
Comparison: 04 Aspirin and Warfarin versus placebo
Outcome: 02 Myocardial infarction



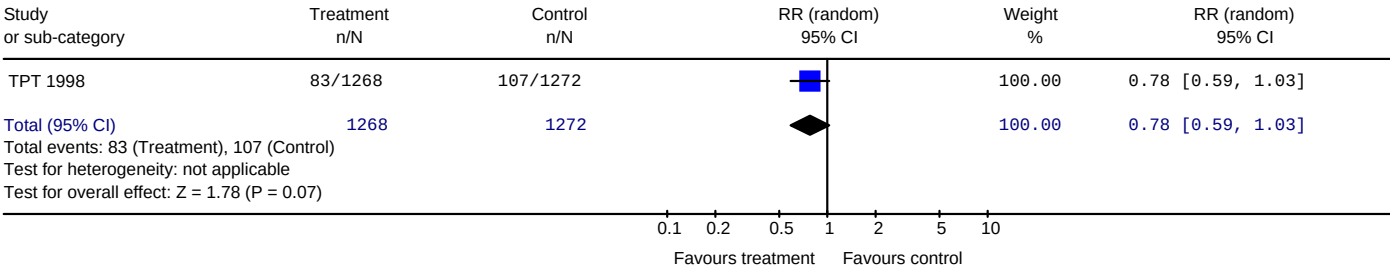
Review: Antithrombotic drugs
Comparison: 04 Aspirin and Warfarin versus placebo
Outcome: 03 Stroke



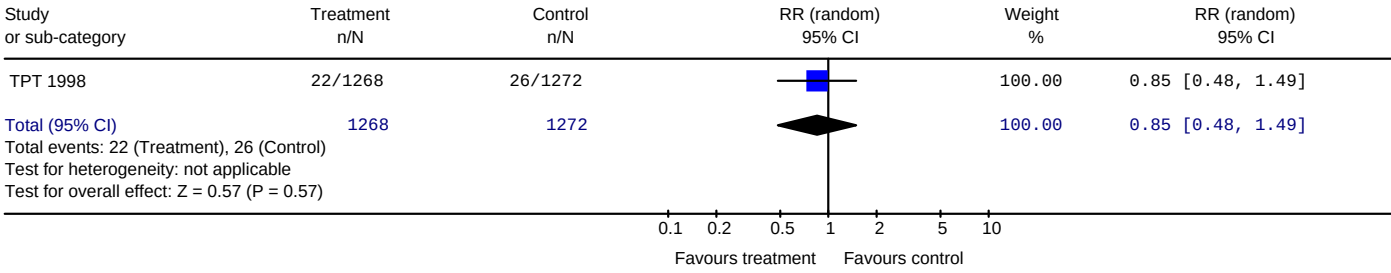
Review: Antithrombotic drugs
Comparison: 05 Warfarin versus placebo
Outcome: 01 All-cause mortality



Review: Antithrombotic drugs
Comparison: 05 Warfarin versus placebo
Outcome: 02 Myocardial infarction

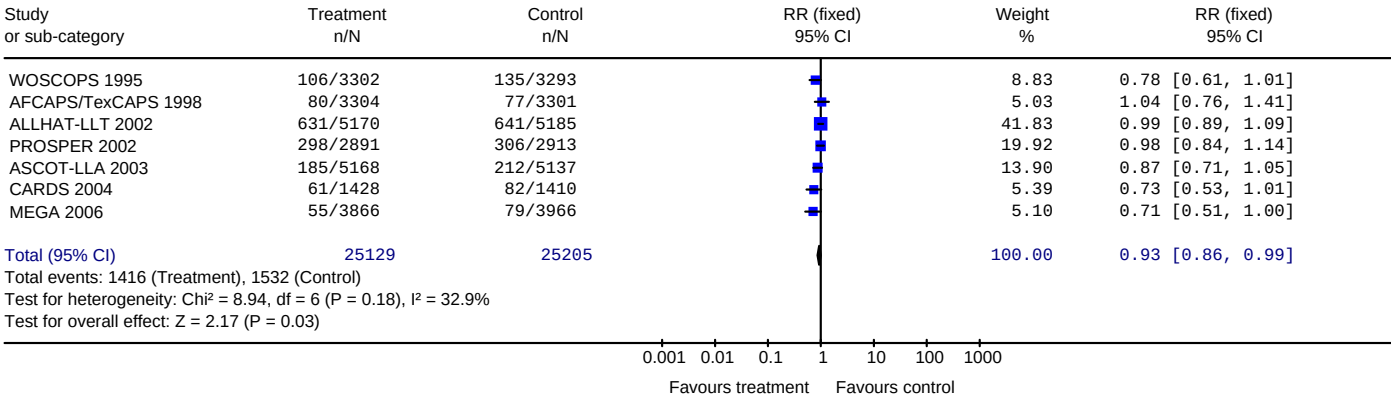


Review: Antithrombotic drugs
Comparison: 05 Warfarin versus placebo
Outcome: 03 Stroke



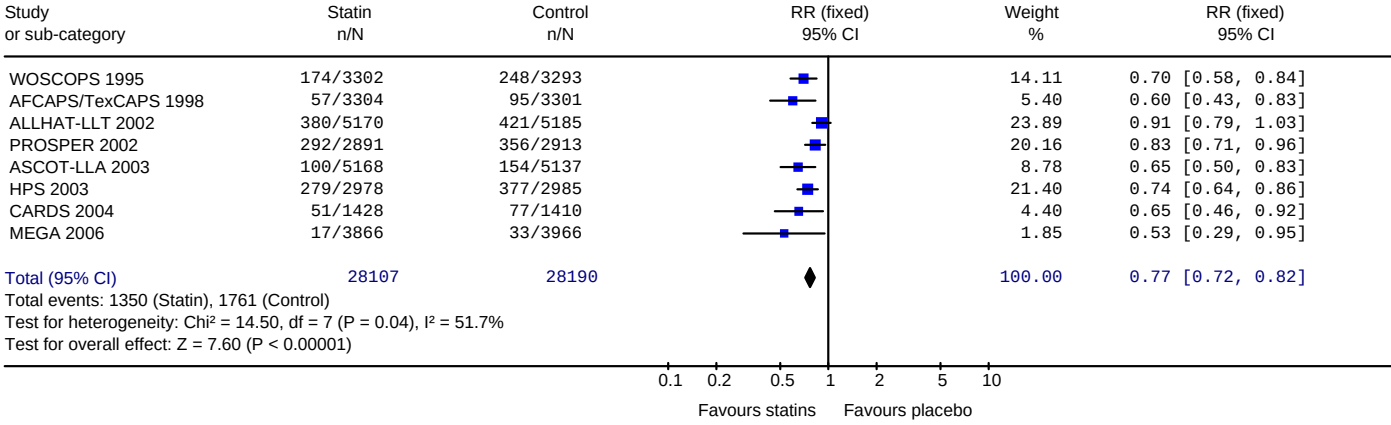
Lipidsenkende midler

Review: Cholesterol reducing drugs
Comparison: 01 Statins versus control
Outcome: 01 All-cause mortality



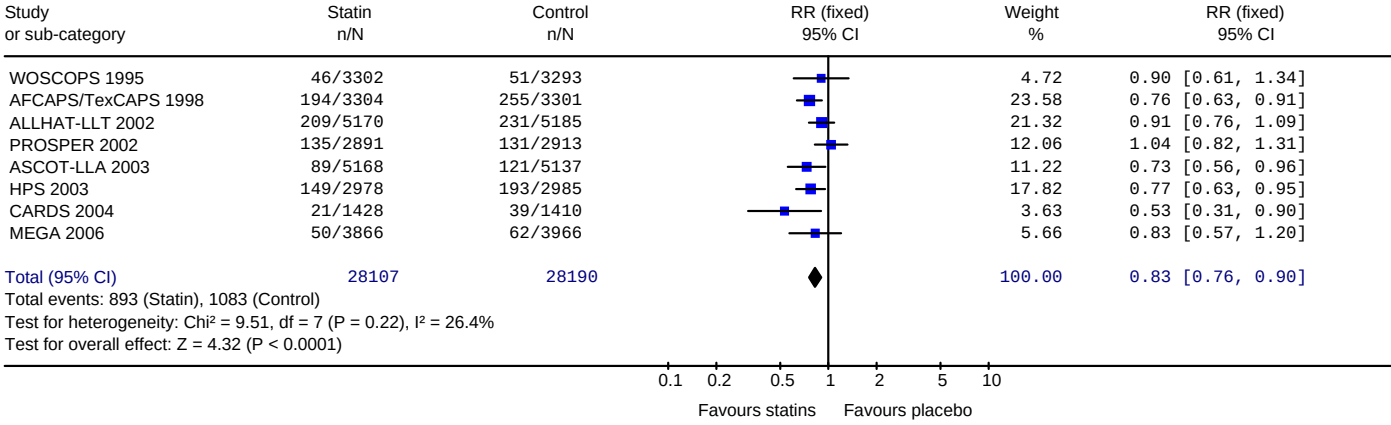
Total events: 1416 (Treatment), 1532 (Control)
Test for heterogeneity: Chi² = 8.94, df = 6 (P = 0.18), I² = 32.9%
Test for overall effect: Z = 2.17 (P = 0.03)

Review: Cholesterol reducing drugs
Comparison: 01 Statins versus control
Outcome: 02 Myocardial infarction



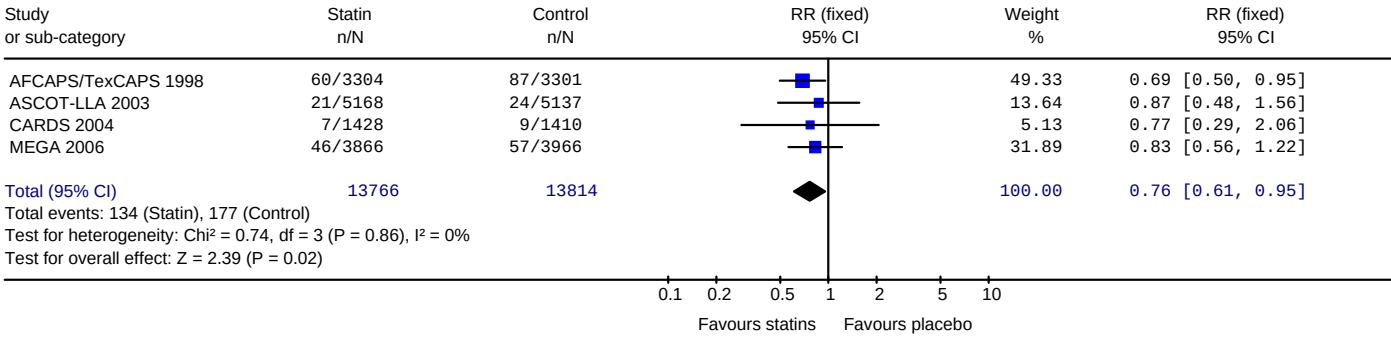
Total events: 1350 (Statin), 1761 (Control)
Test for heterogeneity: Chi² = 14.50, df = 7 (P = 0.04), I² = 51.7%
Test for overall effect: Z = 7.60 (P < 0.00001)

Review: Cholesterol reducing drugs
Comparison: 01 Statins versus control
Outcome: 03 Stroke

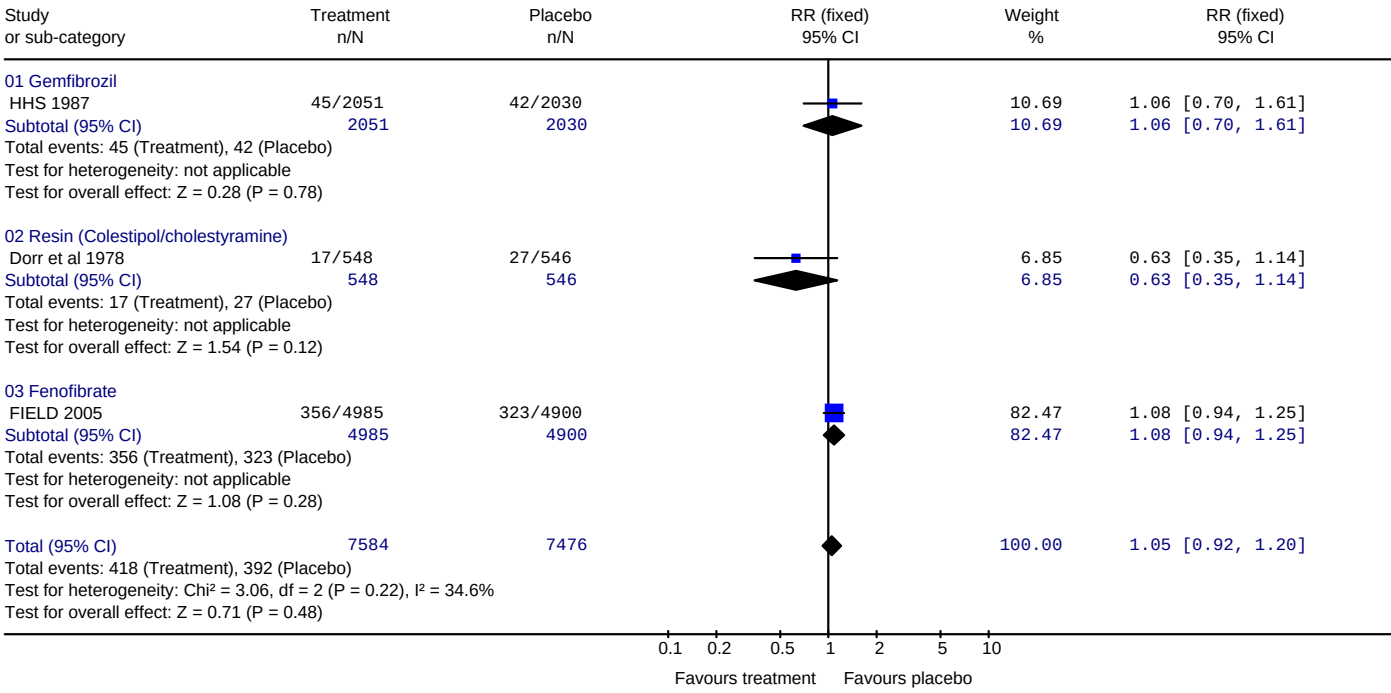


Total events: 893 (Statin), 1083 (Control)
Test for heterogeneity: Chi² = 9.51, df = 7 (P = 0.22), I² = 26.4%
Test for overall effect: Z = 4.32 (P < 0.0001)

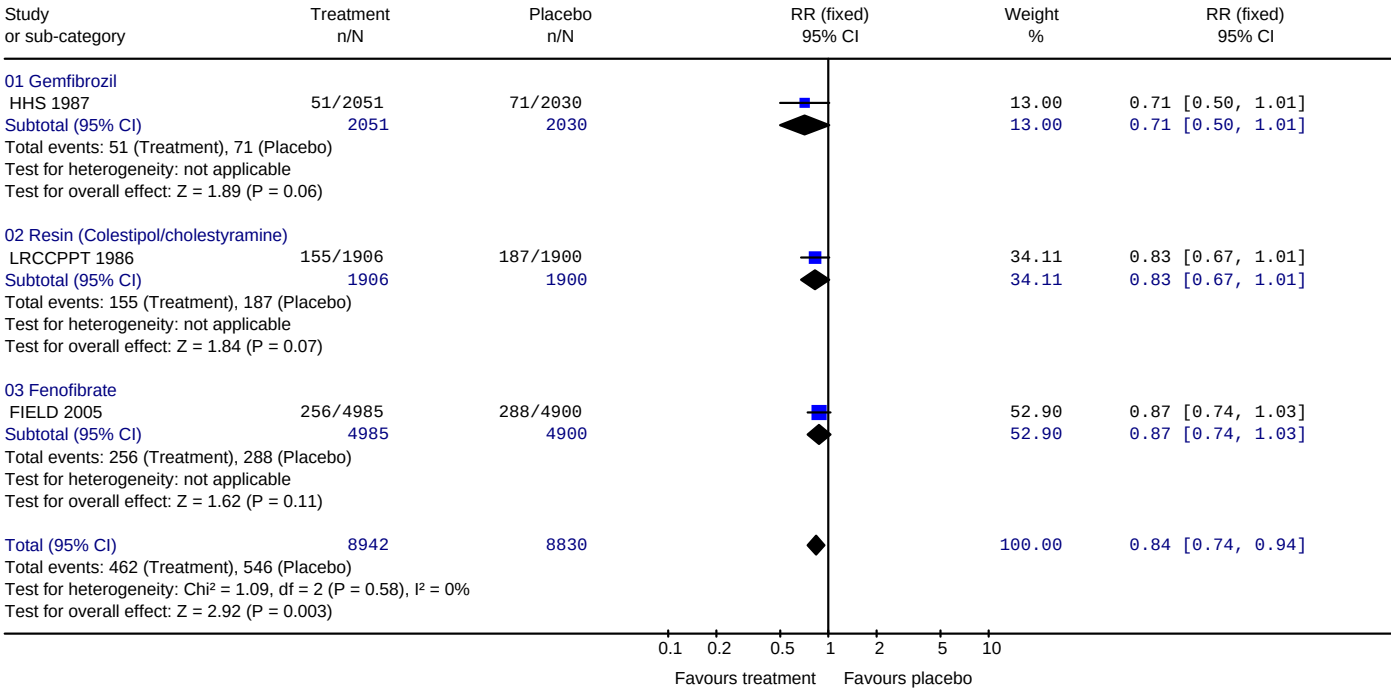
Review: Cholesterol reducing drugs
Comparison: 01 Statins versus control
Outcome: 05 Angina



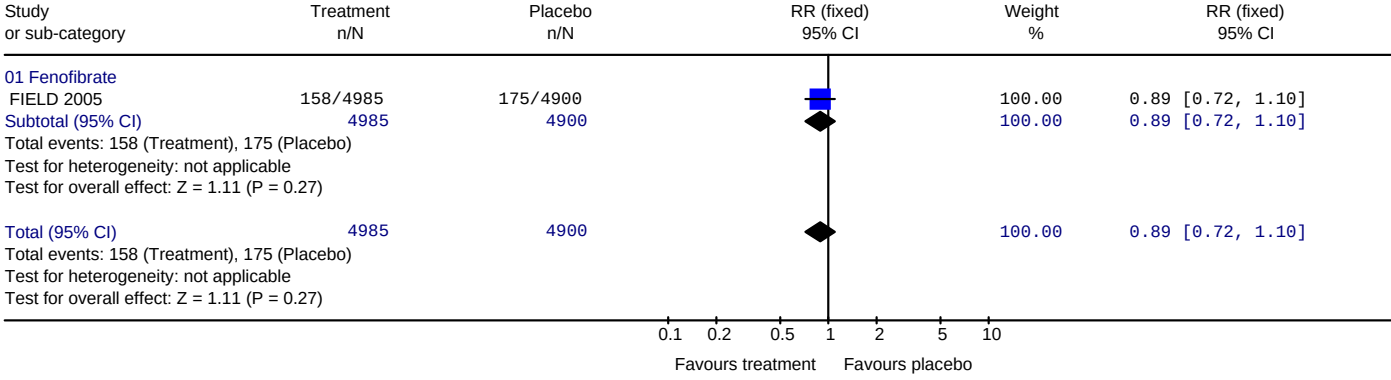
Review: Cholesterol reducing drugs
Comparison: 02 Non-statin lipid-lowering drugs vs. placebo
Outcome: 01 All-cause mortality



Review: Cholesterol reducing drugs
Comparison: 02 Non-statin lipid-lowering drugs vs. placebo
Outcome: 02 Myocardial infarction



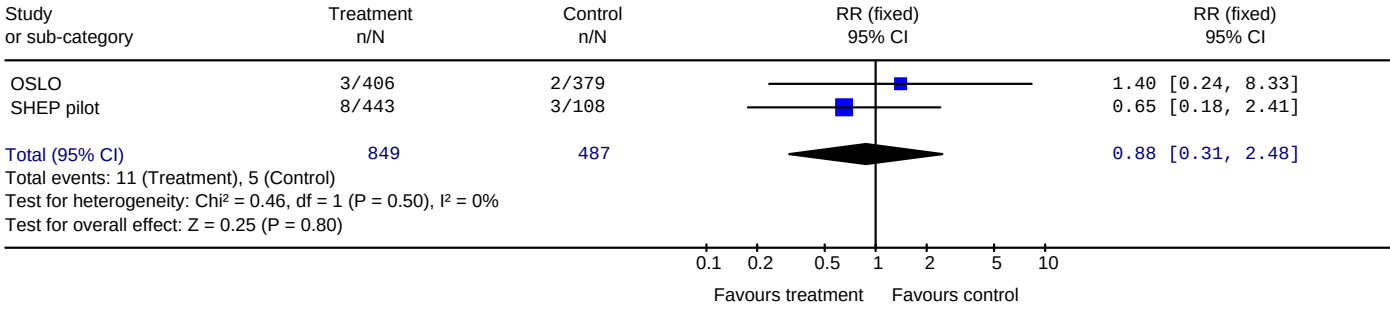
Review: Cholesterol reducing drugs
Comparison: 02 Non-statin lipid-lowering drugs vs. placebo
Outcome: 05 Stroke



Blodtrykkssenkende medikamenter

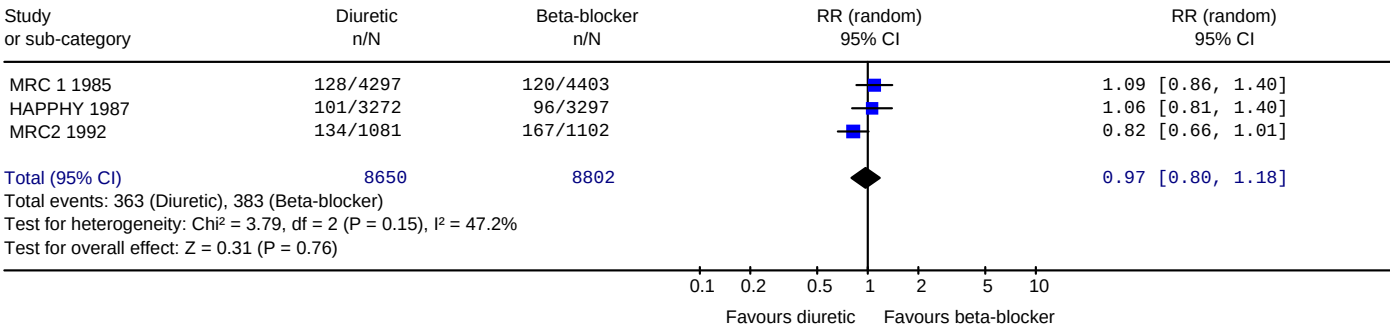
Medikament versus placebo

Review: Antihypertensive drug vs control
Comparison: 01 Drug vs placebo
Outcome: 04 Angina

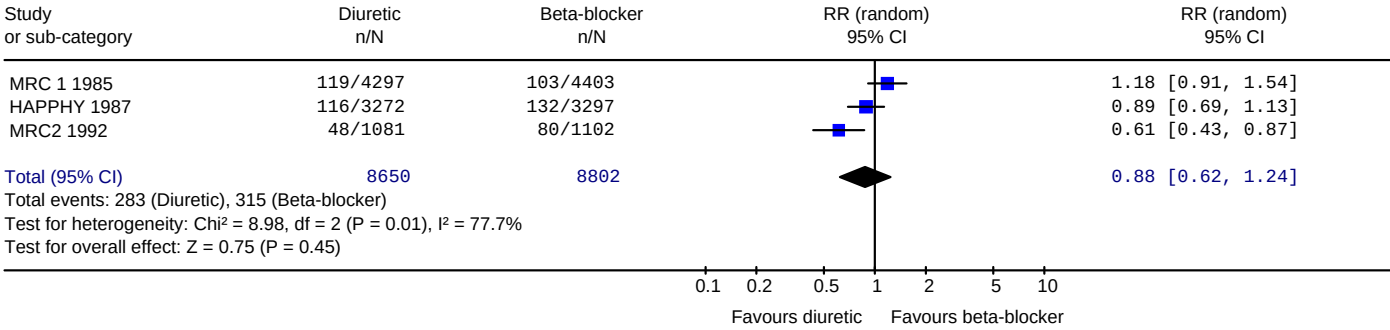


Medikament versus medikament

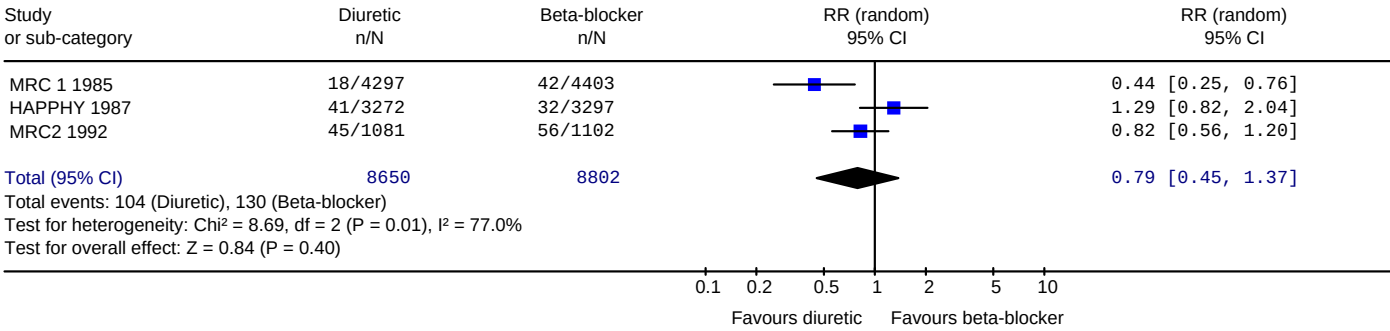
Review: Antihypertensive drug vs drug
Comparison: 01 Diuretic vs beta-blocker
Outcome: 01 All cause mortality



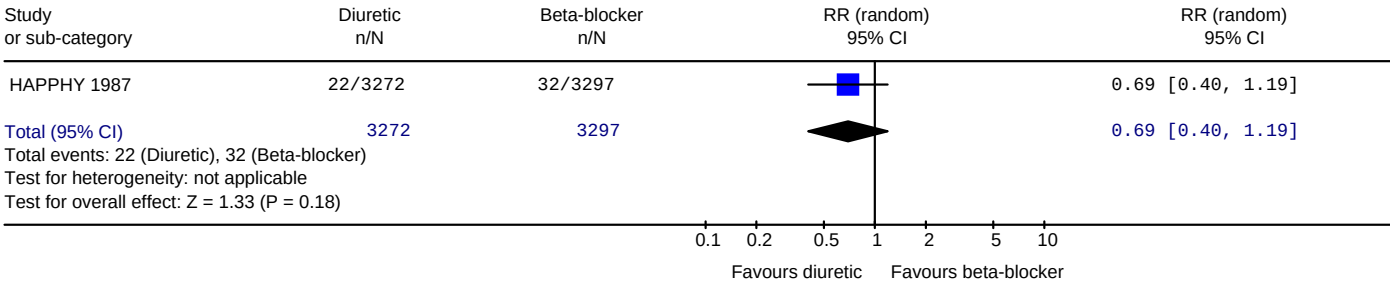
Review: Antihypertensive drug vs drug
Comparison: 01 Diuretic vs beta-blocker
Outcome: 02 Myocardial infarction



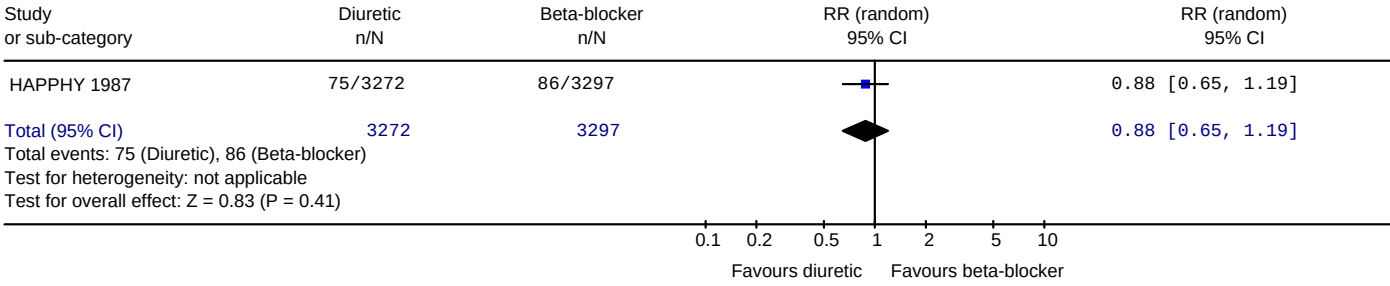
Review: Antihypertensive drug vs drug
Comparison: 01 Diuretic vs beta-blocker
Outcome: 03 Stroke



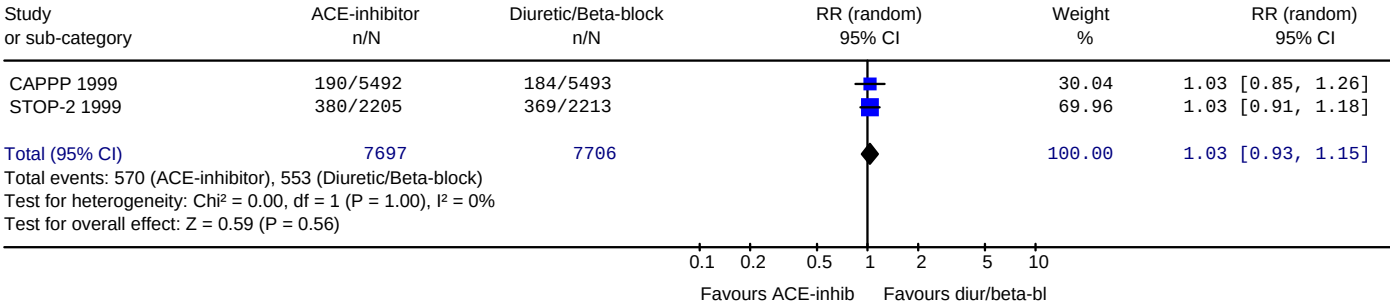
Review: Antihypertensive drug vs drug
Comparison: 01 Diuretic vs beta-blocker
Outcome: 05 Heart failure



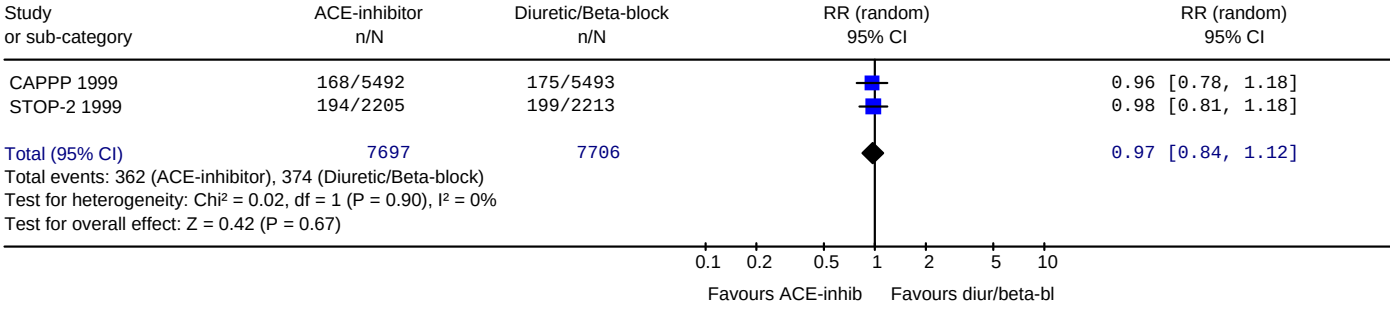
Review: Antihypertensive drug vs drug
Comparison: 01 Diuretic vs beta-blocker
Outcome: 06 Diabetes-incidence



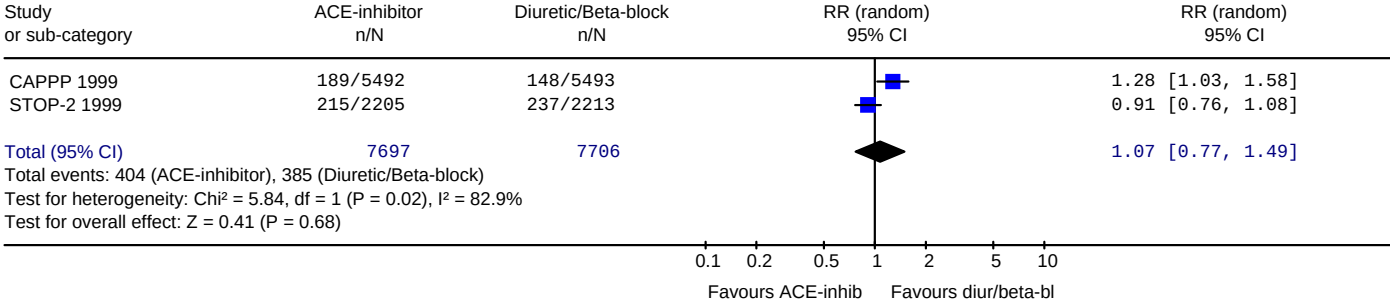
Review: Antihypertensive drug vs drug
Comparison: 02 ACE-inhibitor vs diuretic and/or beta-blocker
Outcome: 01 All cause mortality



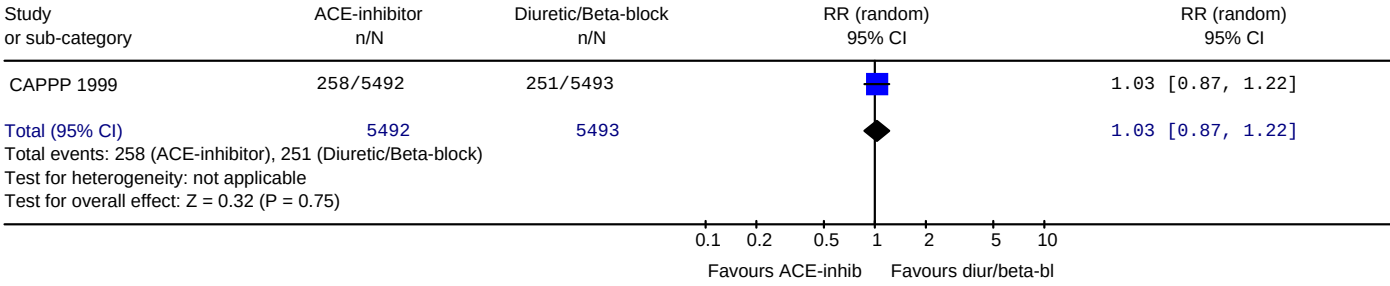
Review: Antihypertensive drug vs drug
Comparison: 02 ACE-inhibitor vs diuretic and/or beta-blocker
Outcome: 02 Myocardial infarction



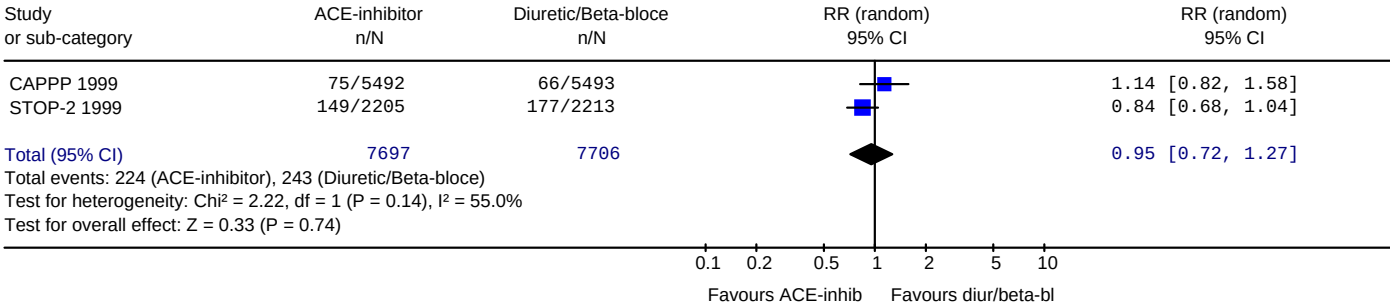
Review: Antihypertensive drug vs drug
Comparison: 02 ACE-inhibitor vs diuretic and/or beta-blocker
Outcome: 03 Stroke



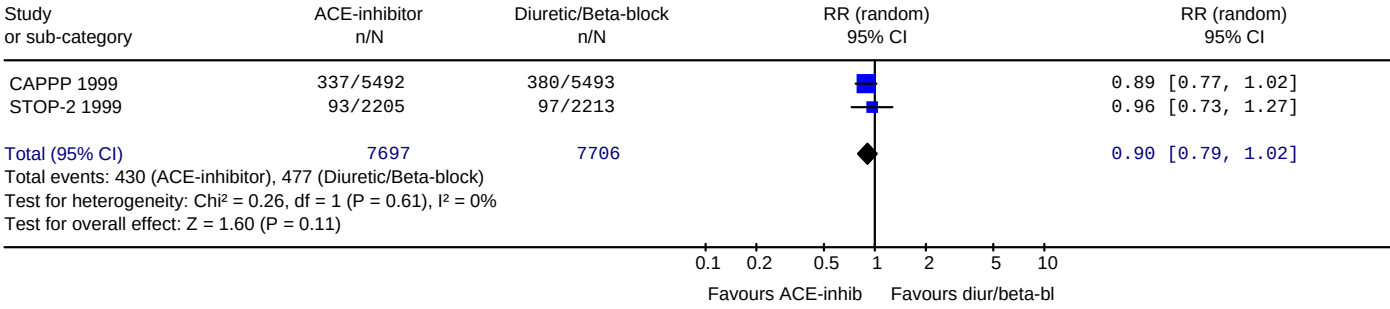
Review: Antihypertensive drug vs drug
Comparison: 02 ACE-inhibitor vs diuretic and/or beta-blocker
Outcome: 04 Angina



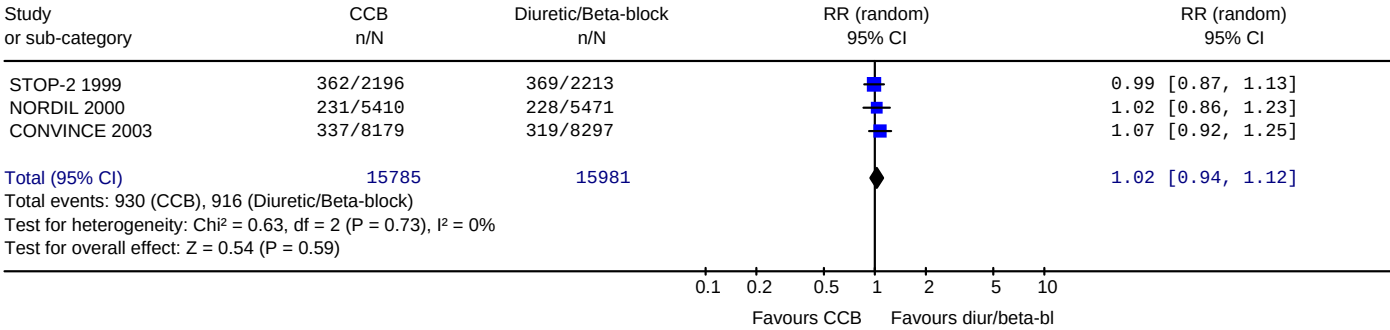
Review: Antihypertensive drug vs drug
Comparison: 02 ACE-inhibitor vs diuretic and/or beta-blocker
Outcome: 05 Heart failure



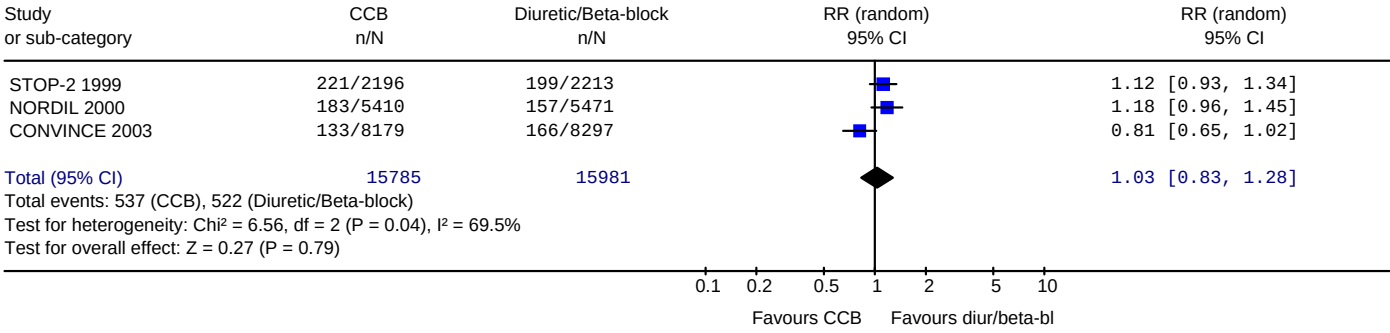
Review: Antihypertensive drug vs drug
Comparison: 02 ACE-inhibitor vs diuretic and/or beta-blocker
Outcome: 06 Diabetes-incidence



Review: Antihypertensive drug vs drug
Comparison: 03 CCB vs diuretic and/or beta-blocker
Outcome: 01 All cause mortality

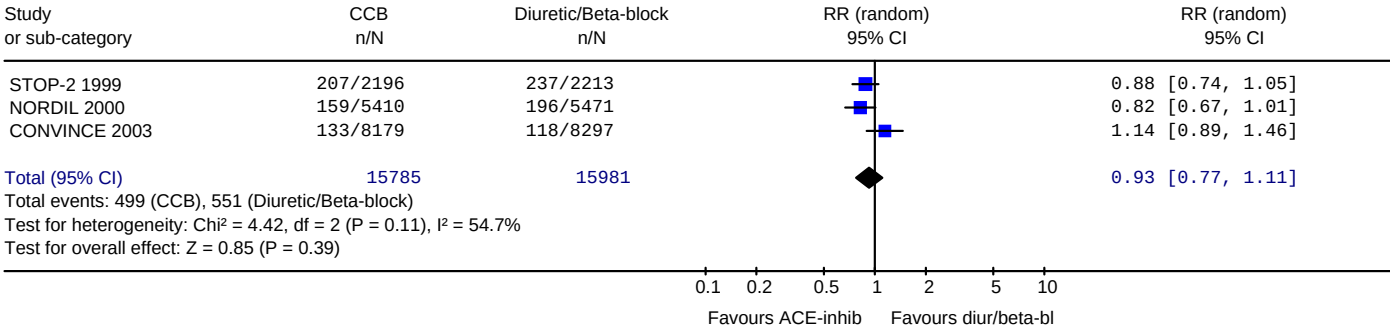


Review: Antihypertensive drug vs drug
Comparison: 03 CCB vs diuretic and/or beta-blocker
Outcome: 02 Myocardial infarction



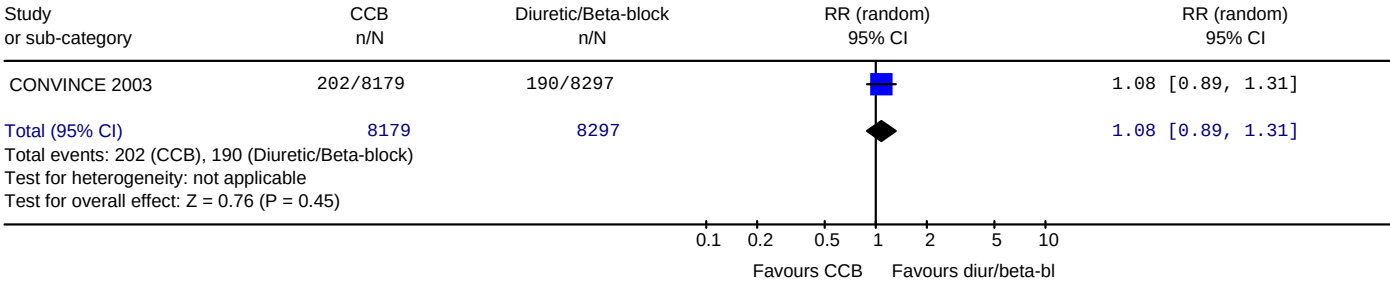
Total events: 537 (CCB), 522 (Diuretic/Beta-block)
Test for heterogeneity: Chi² = 6.56, df = 2 (P = 0.04), I² = 69.5%
Test for overall effect: Z = 0.27 (P = 0.79)

Review: Antihypertensive drug vs drug
Comparison: 03 CCB vs diuretic and/or beta-blocker
Outcome: 03 Stroke



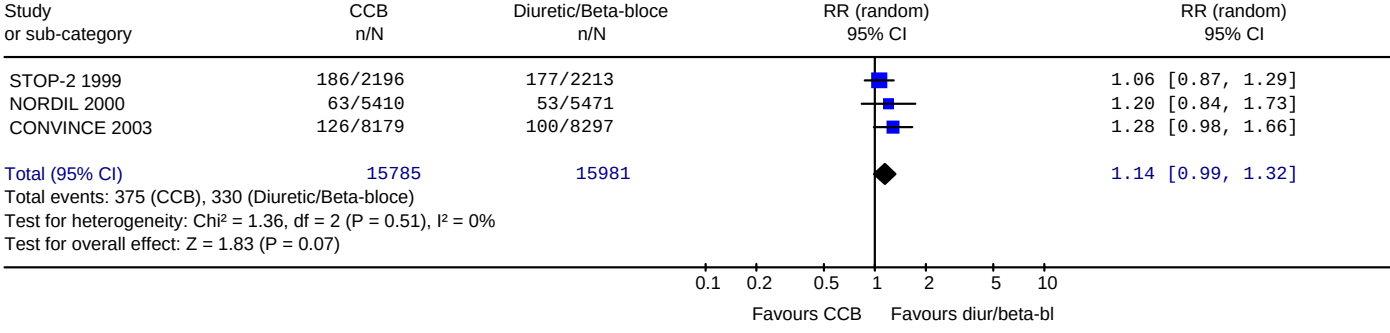
Total events: 499 (CCB), 551 (Diuretic/Beta-block)
Test for heterogeneity: Chi² = 4.42, df = 2 (P = 0.11), I² = 54.7%
Test for overall effect: Z = 0.85 (P = 0.39)

Review: Antihypertensive drug vs drug
Comparison: 03 CCB vs diuretic and/or beta-blocker
Outcome: 04 Angina



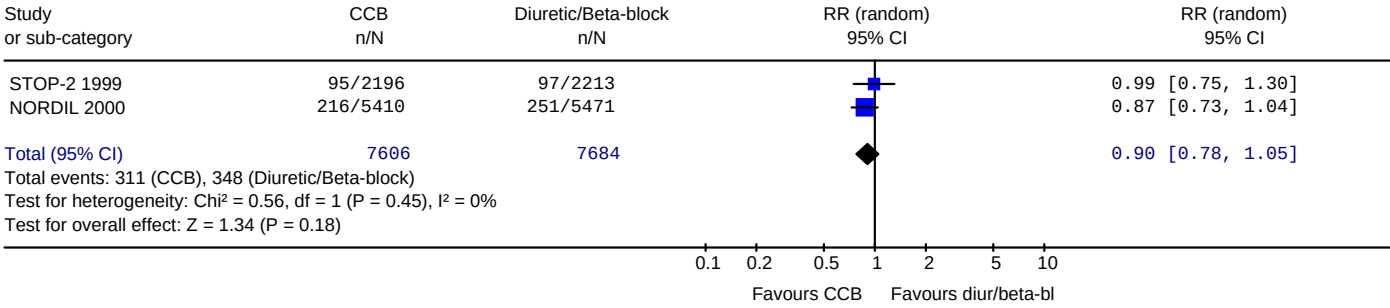
Total events: 202 (CCB), 190 (Diuretic/Beta-block)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.76 (P = 0.45)

Review: Antihypertensive drug vs drug
Comparison: 03 CCB vs diuretic and/or beta-blocker
Outcome: 05 Heart failure

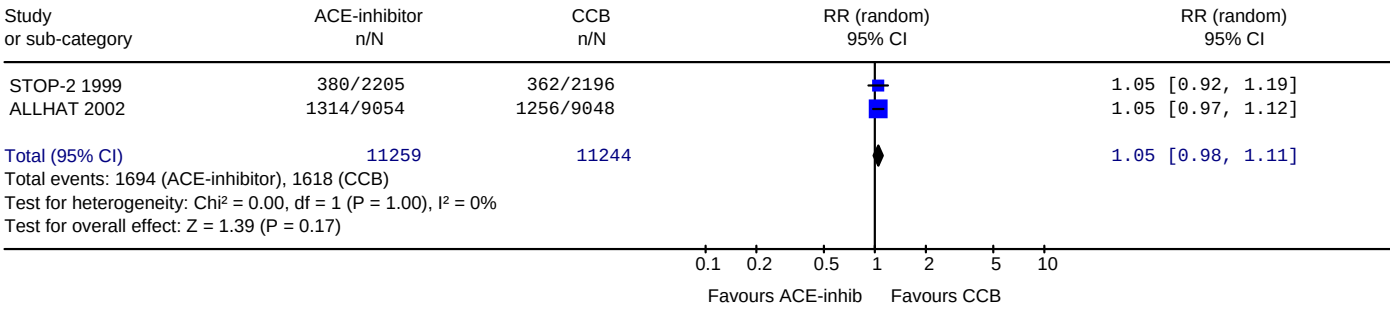


Total events: 375 (CCB), 330 (Diuretic/Beta-bloce)
Test for heterogeneity: Chi² = 1.36, df = 2 (P = 0.51), I² = 0%
Test for overall effect: Z = 1.83 (P = 0.07)

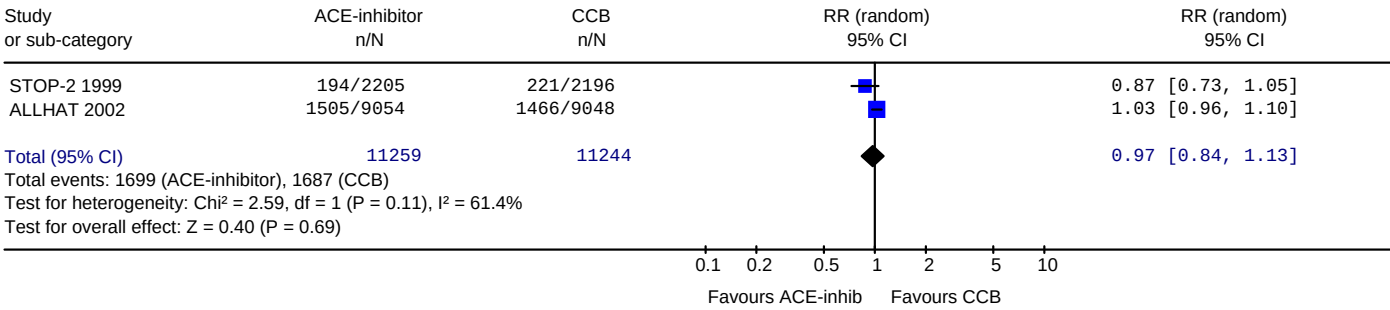
Review: Antihypertensive drug vs drug
Comparison: 03 CCB vs diuretic and/or beta-blocker
Outcome: 06 Diabetes-incidence



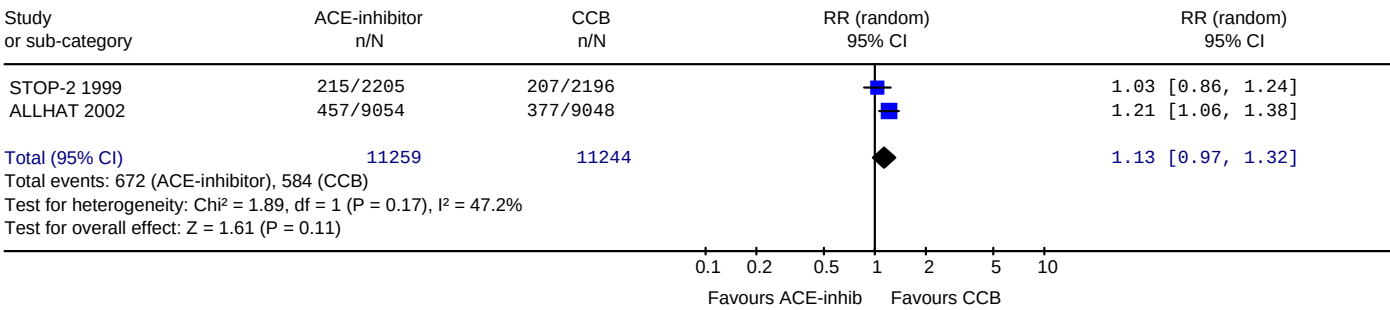
Review: Antihypertensive drug vs drug
Comparison: 04 ACE-inhibitor vs CCB
Outcome: 01 All cause mortality



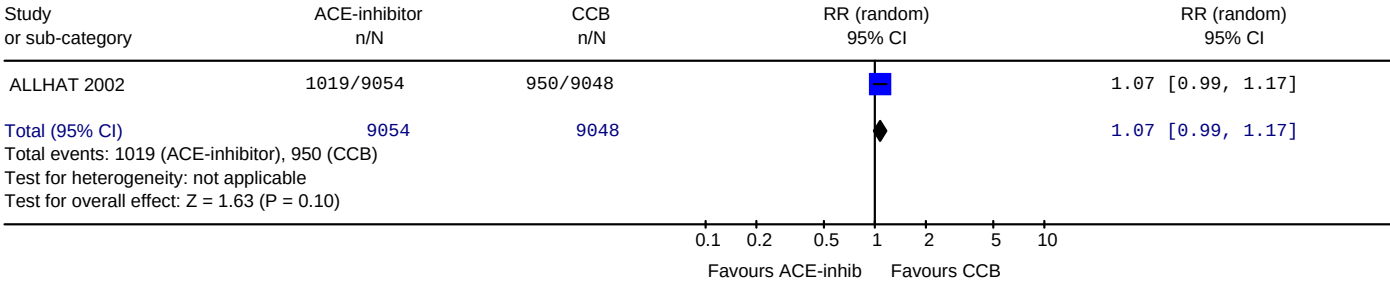
Review: Antihypertensive drug vs drug
Comparison: 04 ACE-inhibitor vs CCB
Outcome: 02 Myocardial infarction



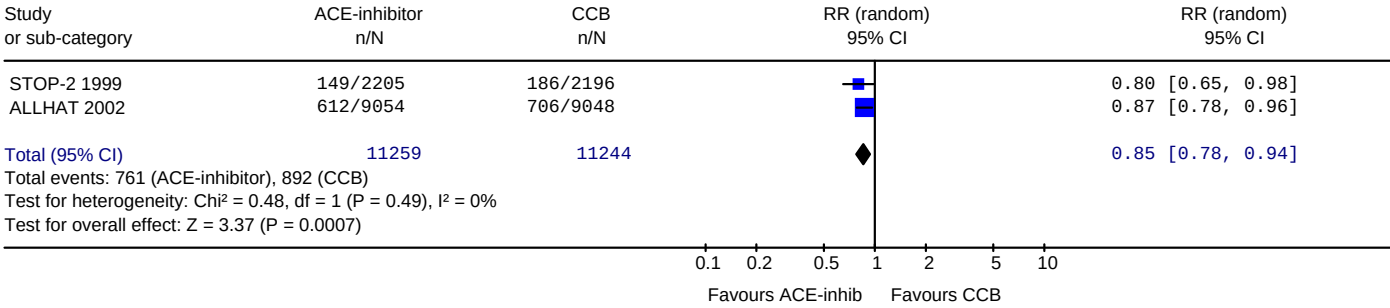
Review: Antihypertensive drug vs drug
Comparison: 04 ACE-inhibitor vs CCB
Outcome: 03 Stroke



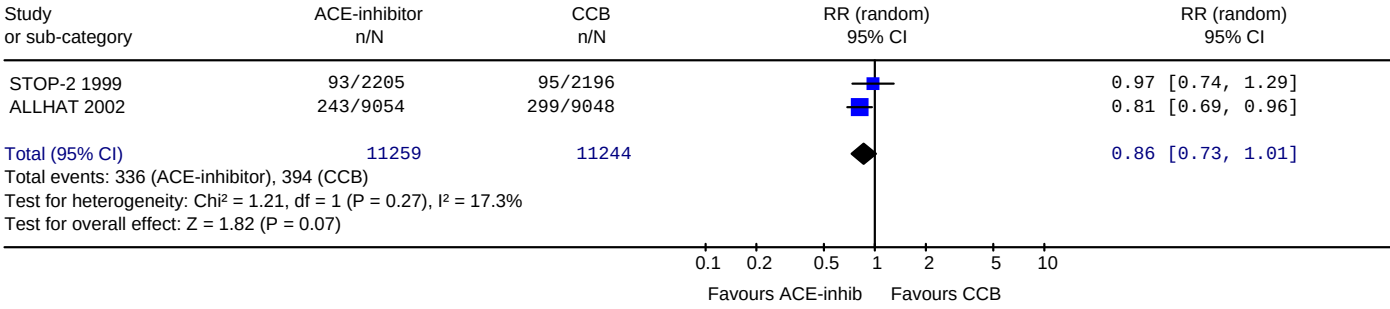
Review: Antihypertensive drug vs drug
Comparison: 04 ACE-inhibitor vs CCB
Outcome: 04 Angina



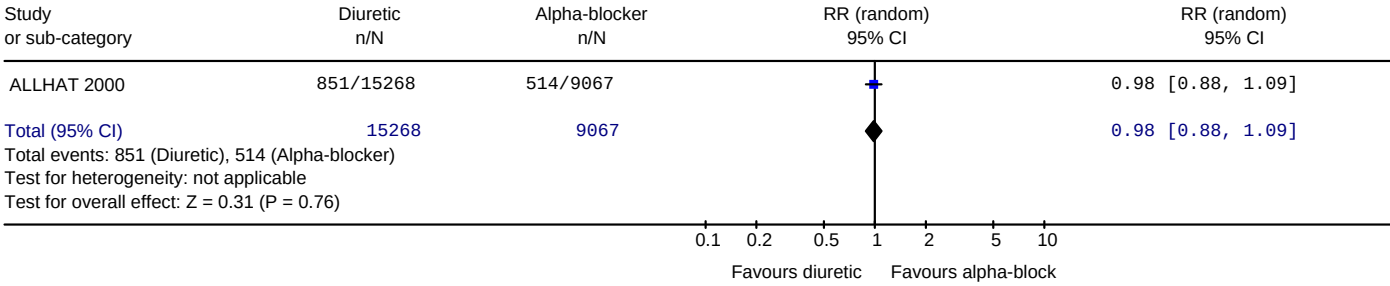
Review: Antihypertensive drug vs drug
Comparison: 04 ACE-inhibitor vs CCB
Outcome: 05 Heart failure



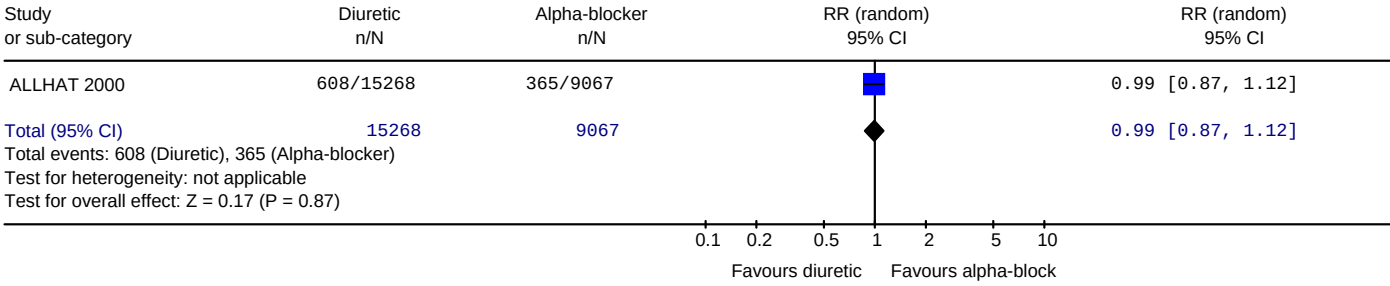
Review: Antihypertensive drug vs drug
Comparison: 04 ACE-inhibitor vs CCB
Outcome: 06 Diabetes-incidence



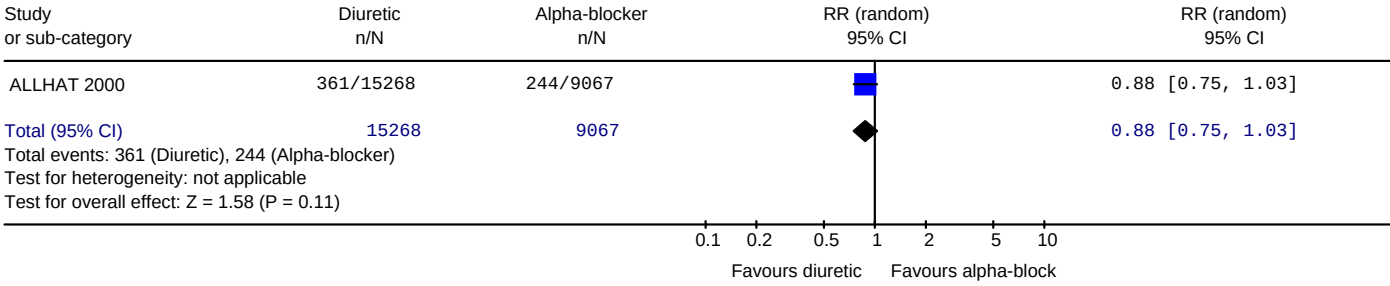
Review: Antihypertensive drug vs drug
Comparison: 05 Diuretic vs alpha-blocker
Outcome: 01 All cause mortality



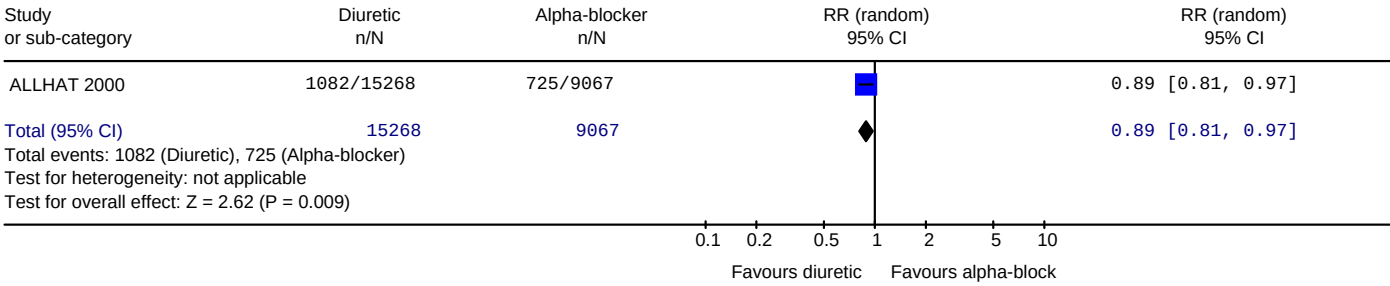
Review: Antihypertensive drug vs drug
Comparison: 05 Diuretic vs alpha-blocker
Outcome: 02 Myocardial infarction



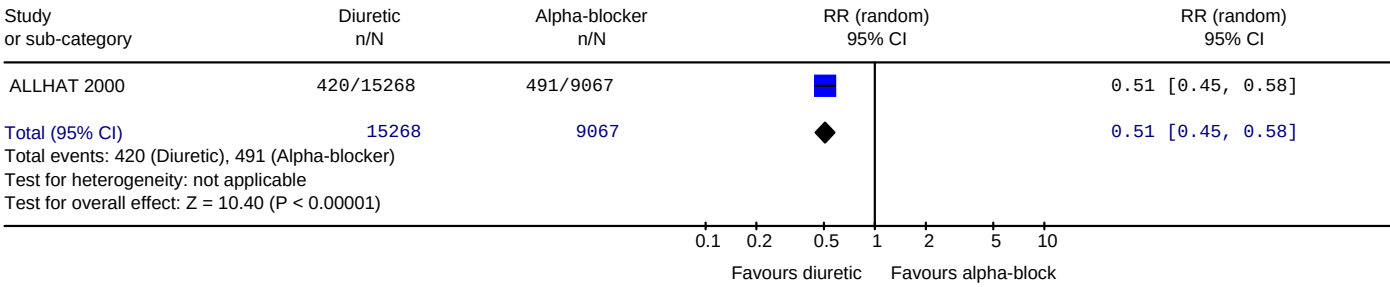
Review: Antihypertensive drug vs drug
Comparison: 05 Diuretic vs alpha-blocker
Outcome: 03 Stroke



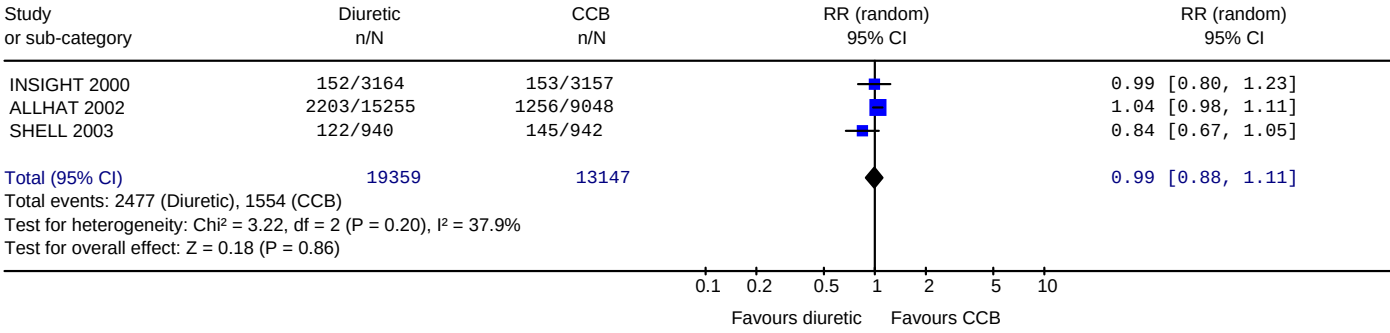
Review: Antihypertensive drug vs drug
Comparison: 05 Diuretic vs alpha-blocker
Outcome: 04 Angina



Review: Antihypertensive drug vs drug
Comparison: 05 Diuretic vs alpha-blocker
Outcome: 05 Heart failure

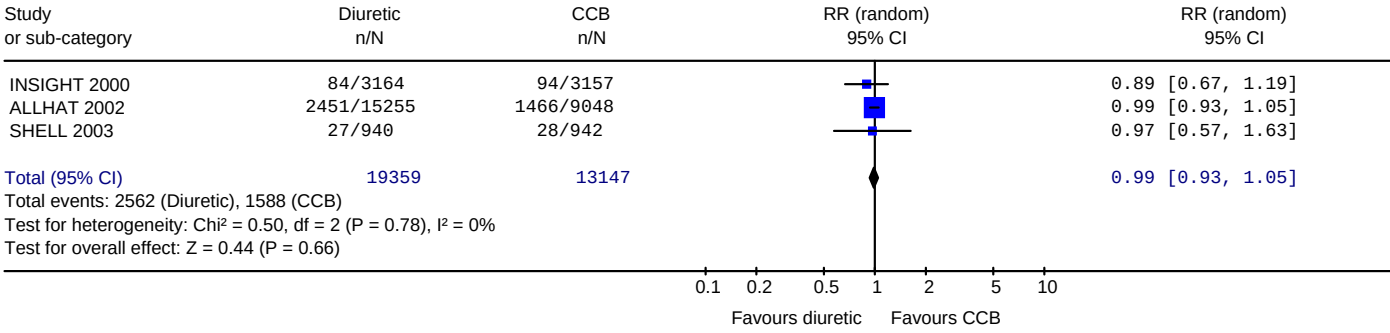


Review: Antihypertensive drug vs drug
Comparison: 06 Diuretic vs CCB
Outcome: 01 All cause mortality



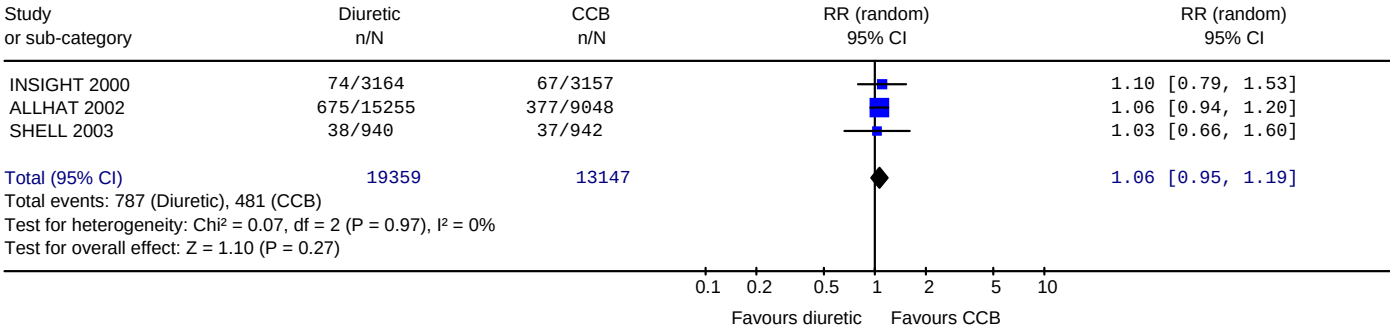
Total events: 2477 (Diuretic), 1554 (CCB)
Test for heterogeneity: Chi² = 3.22, df = 2 (P = 0.20), I² = 37.9%
Test for overall effect: Z = 0.18 (P = 0.86)

Review: Antihypertensive drug vs drug
Comparison: 06 Diuretic vs CCB
Outcome: 02 Myocardial infarction



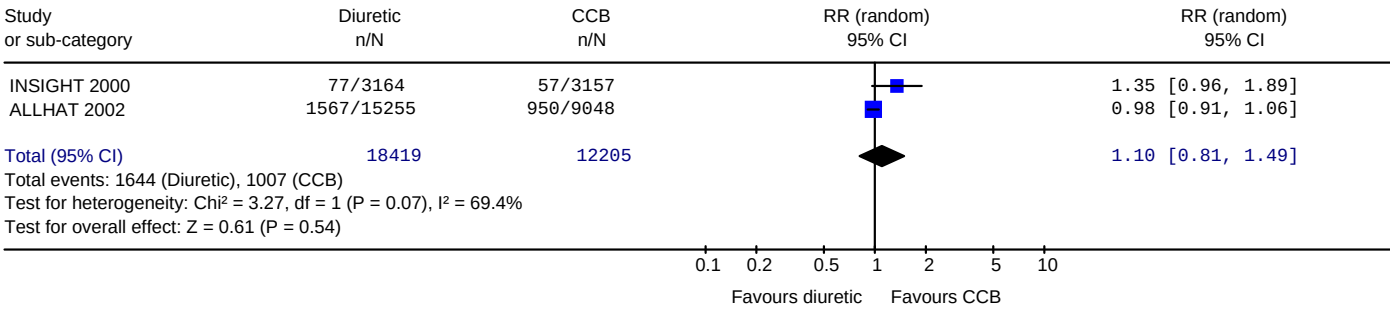
Total events: 2562 (Diuretic), 1588 (CCB)
Test for heterogeneity: Chi² = 0.50, df = 2 (P = 0.78), I² = 0%
Test for overall effect: Z = 0.44 (P = 0.66)

Review: Antihypertensive drug vs drug
Comparison: 06 Diuretic vs CCB
Outcome: 03 Stroke



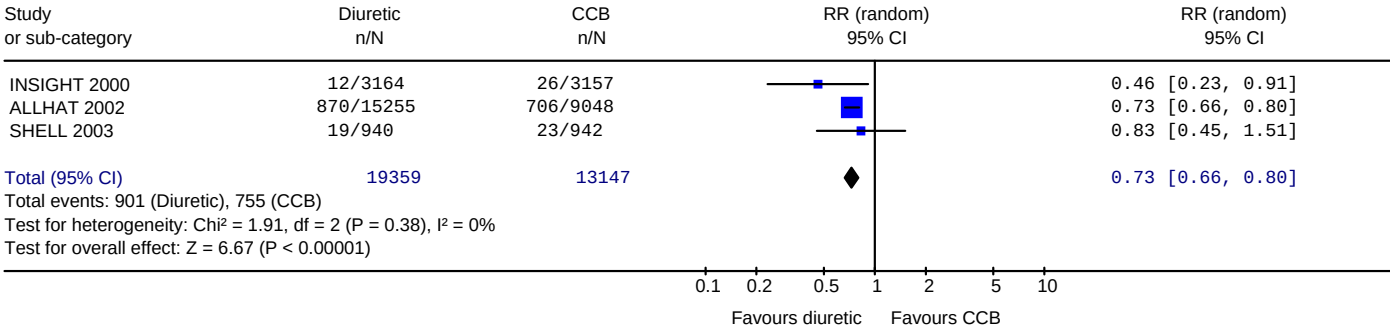
Total events: 787 (Diuretic), 481 (CCB)
Test for heterogeneity: Chi² = 0.07, df = 2 (P = 0.97), I² = 0%
Test for overall effect: Z = 1.10 (P = 0.27)

Review: Antihypertensive drug vs drug
Comparison: 06 Diuretic vs CCB
Outcome: 04 Angina



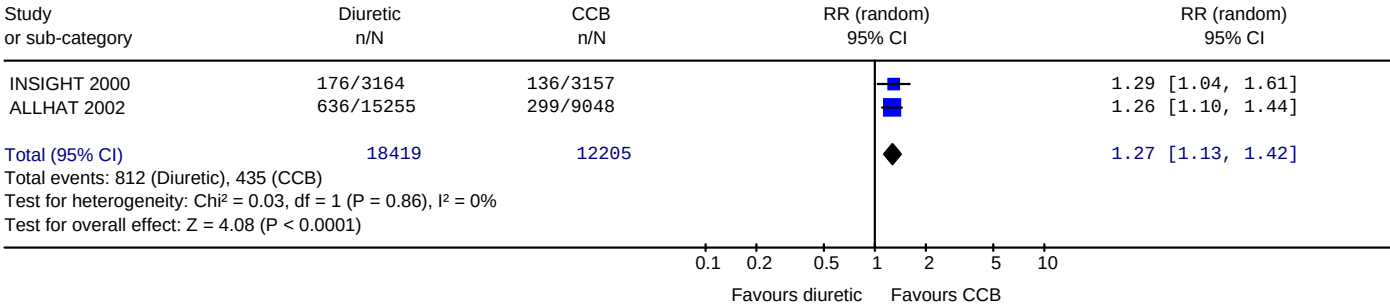
Total events: 1644 (Diuretic), 1007 (CCB)
Test for heterogeneity: Chi² = 3.27, df = 1 (P = 0.07), I² = 69.4%
Test for overall effect: Z = 0.61 (P = 0.54)

Review: Antihypertensive drug vs drug
Comparison: 06 Diuretic vs CCB
Outcome: 05 Heart failure



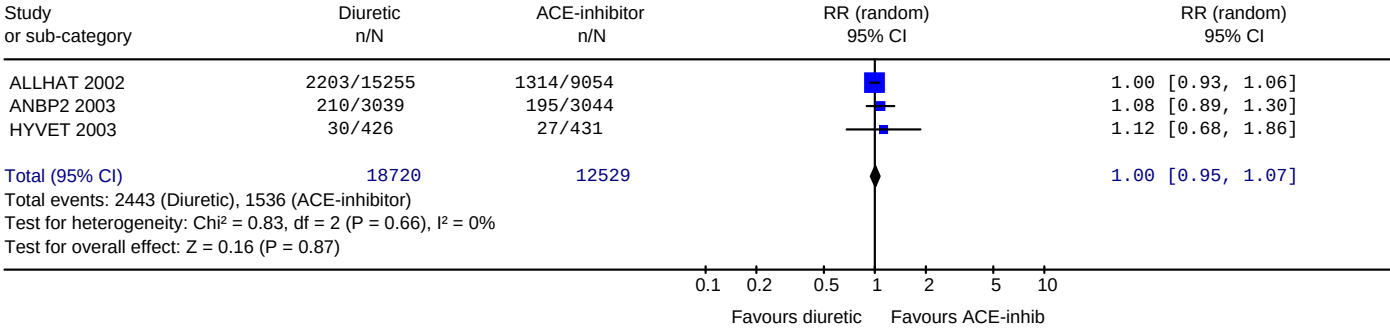
Total events: 901 (Diuretic), 755 (CCB)
Test for heterogeneity: Chi² = 1.91, df = 2 (P = 0.38), I² = 0%
Test for overall effect: Z = 6.67 (P < 0.00001)

Review: Antihypertensive drug vs drug
Comparison: 06 Diuretic vs CCB
Outcome: 06 Diabetes-incidence



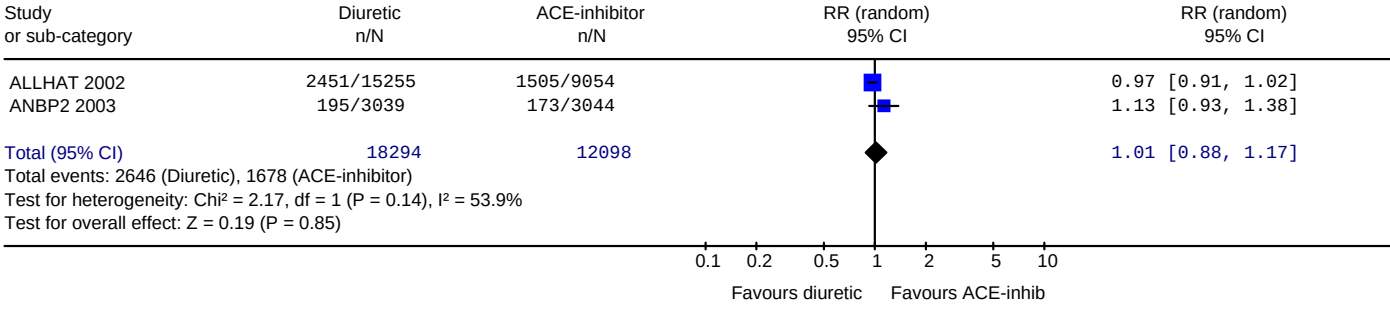
Total events: 812 (Diuretic), 435 (CCB)
Test for heterogeneity: Chi² = 0.03, df = 1 (P = 0.86), I² = 0%
Test for overall effect: Z = 4.08 (P < 0.0001)

Review: Antihypertensive drug vs drug
Comparison: 07 Diuretic vs ACE-inhibitor
Outcome: 01 All cause mortality



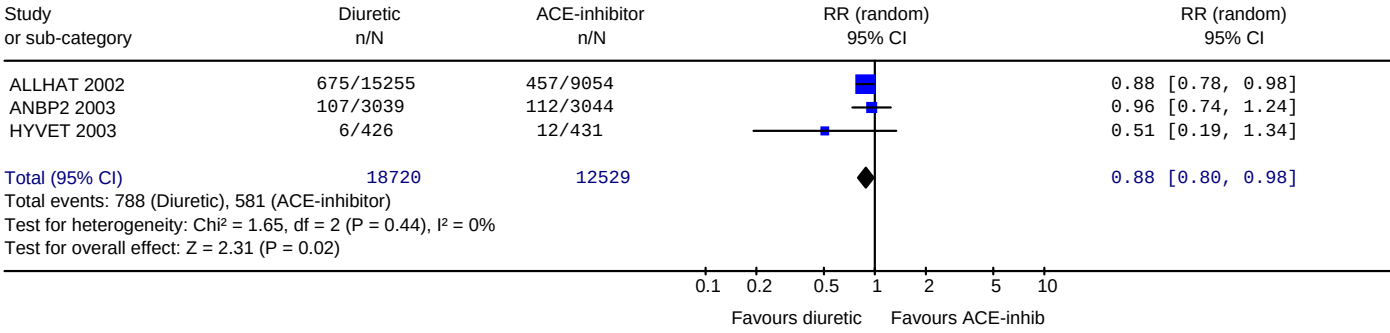
Total events: 2443 (Diuretic), 1536 (ACE-inhibitor)
Test for heterogeneity: Chi² = 0.83, df = 2 (P = 0.66), I² = 0%
Test for overall effect: Z = 0.16 (P = 0.87)

Review: Antihypertensive drug vs drug
Comparison: 07 Diuretic vs ACE-inhibitor
Outcome: 02 Myocardial infarction



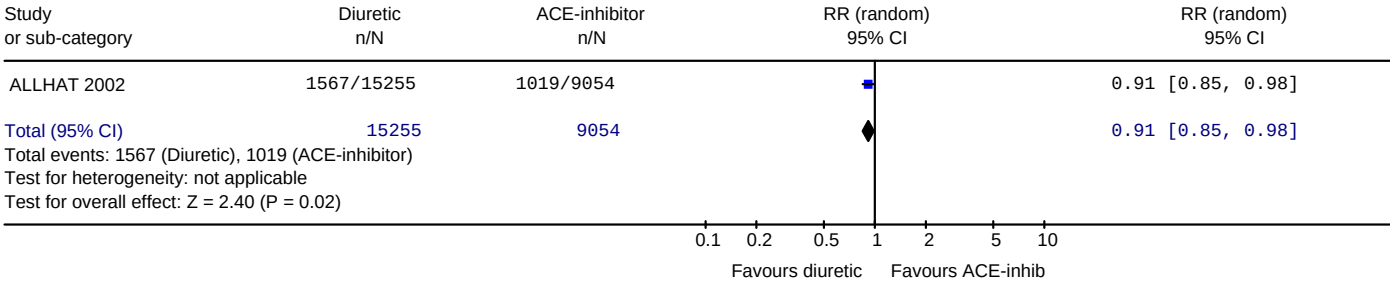
Total events: 2646 (Diuretic), 1678 (ACE-inhibitor)
Test for heterogeneity: Chi² = 2.17, df = 1 (P = 0.14), I² = 53.9%
Test for overall effect: Z = 0.19 (P = 0.85)

Review: Antihypertensive drug vs drug
Comparison: 07 Diuretic vs ACE-inhibitor
Outcome: 03 Stroke



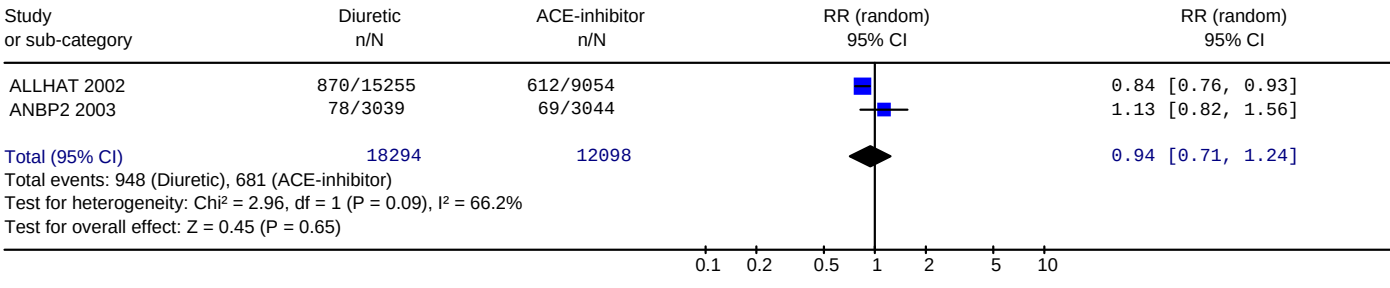
Total events: 788 (Diuretic), 581 (ACE-inhibitor)
Test for heterogeneity: Chi² = 1.65, df = 2 (P = 0.44), I² = 0%
Test for overall effect: Z = 2.31 (P = 0.02)

Review: Antihypertensive drug vs drug
Comparison: 07 Diuretic vs ACE-inhibitor
Outcome: 04 Angina



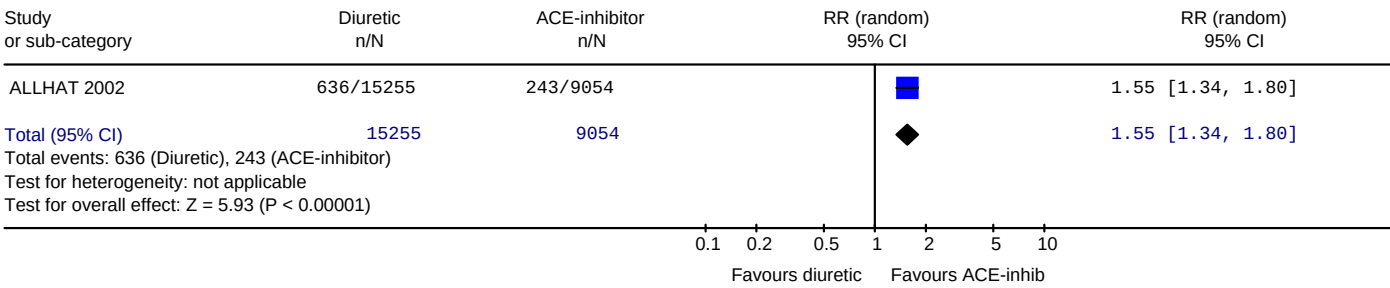
Total events: 1567 (Diuretic), 1019 (ACE-inhibitor)
Test for heterogeneity: not applicable
Test for overall effect: Z = 2.40 (P = 0.02)

Review: Antihypertensive drug vs drug
Comparison: 07 Diuretic vs ACE-inhibitor
Outcome: 05 Heart failure



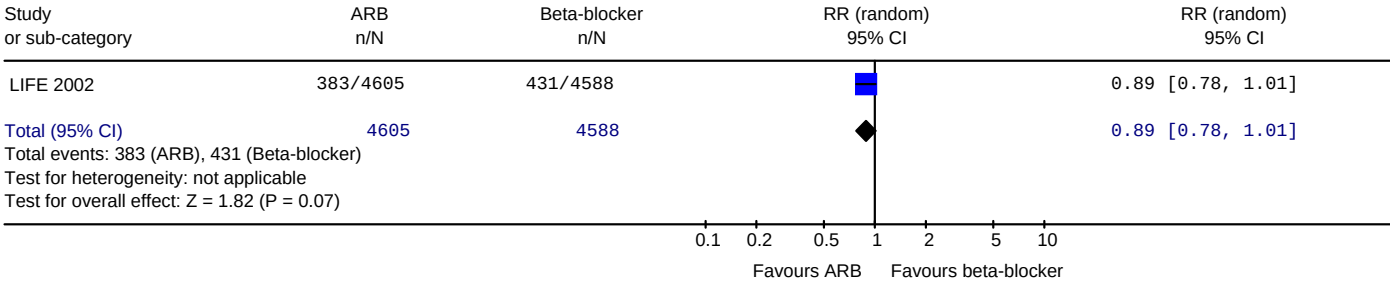
Total events: 948 (Diuretic), 681 (ACE-inhibitor)
Test for heterogeneity: Chi² = 2.96, df = 1 (P = 0.09), I² = 66.2%
Test for overall effect: Z = 0.45 (P = 0.65)

Review: Antihypertensive drug vs drug
Comparison: 07 Diuretic vs ACE-inhibitor
Outcome: 06 Diabetes-incidence

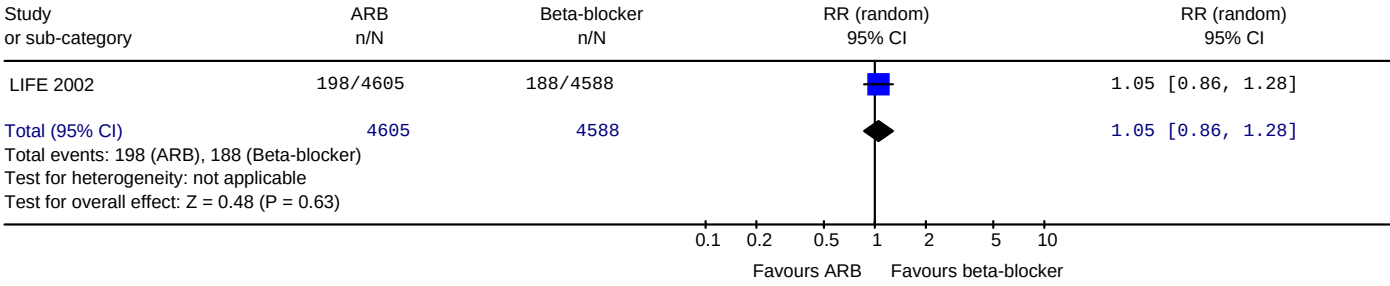


Total events: 636 (Diuretic), 243 (ACE-inhibitor)
Test for heterogeneity: not applicable
Test for overall effect: Z = 5.93 (P < 0.00001)

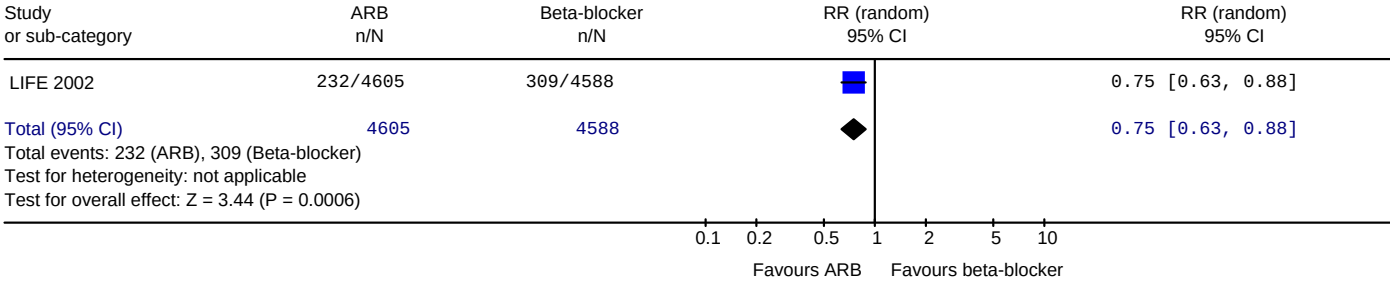
Review: Antihypertensive drug vs drug
Comparison: 08 ARB vs beta-blocker
Outcome: 01 All cause mortality



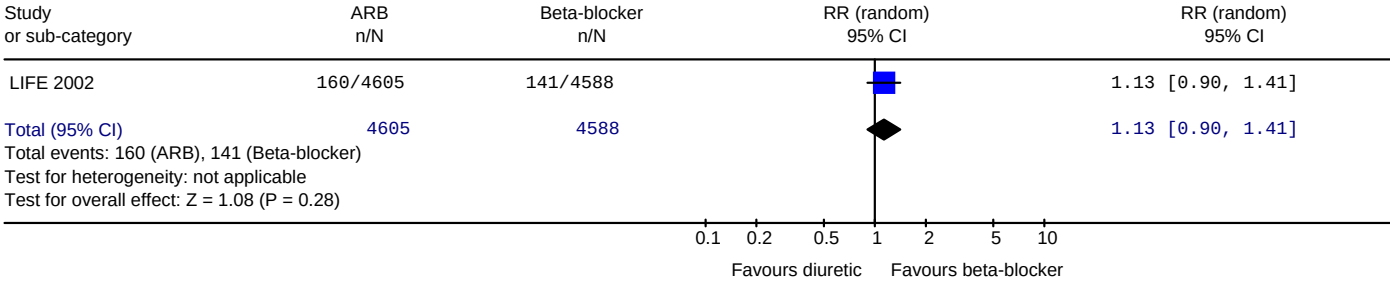
Review: Antihypertensive drug vs drug
Comparison: 08 ARB vs beta-blocker
Outcome: 02 Myocardial infarction



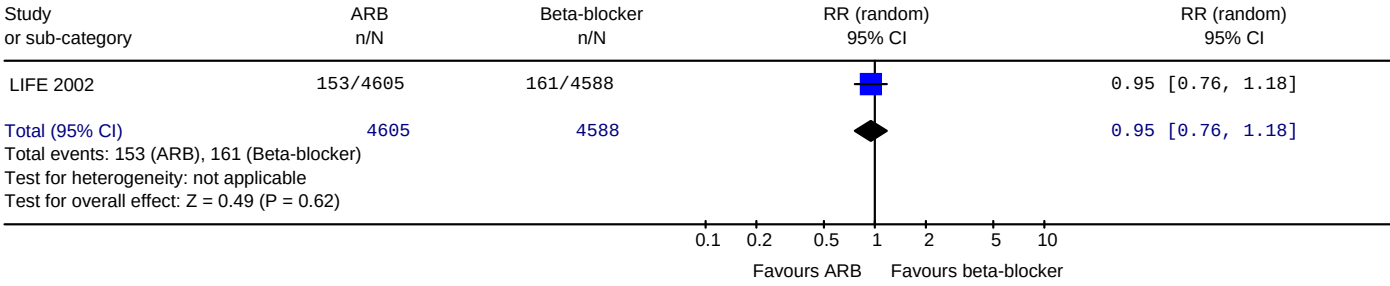
Review: Antihypertensive drug vs drug
Comparison: 08 ARB vs beta-blocker
Outcome: 03 Stroke



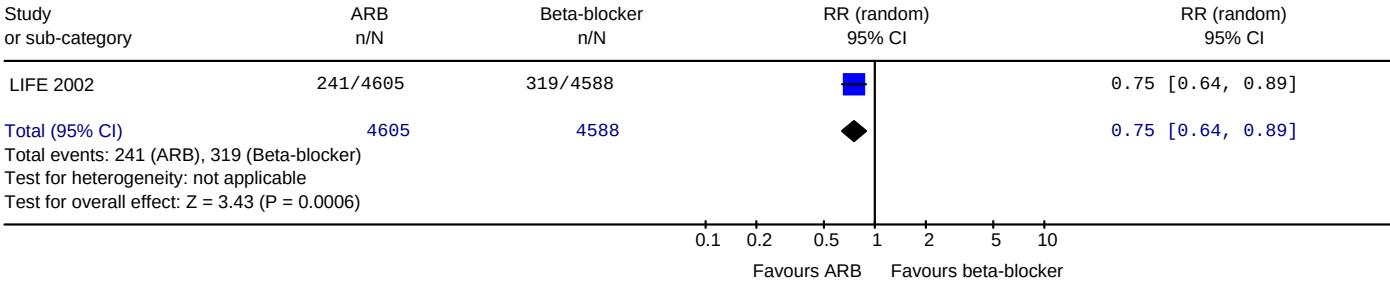
Review: Antihypertensive drug vs drug
Comparison: 08 ARB vs beta-blocker
Outcome: 04 Angina



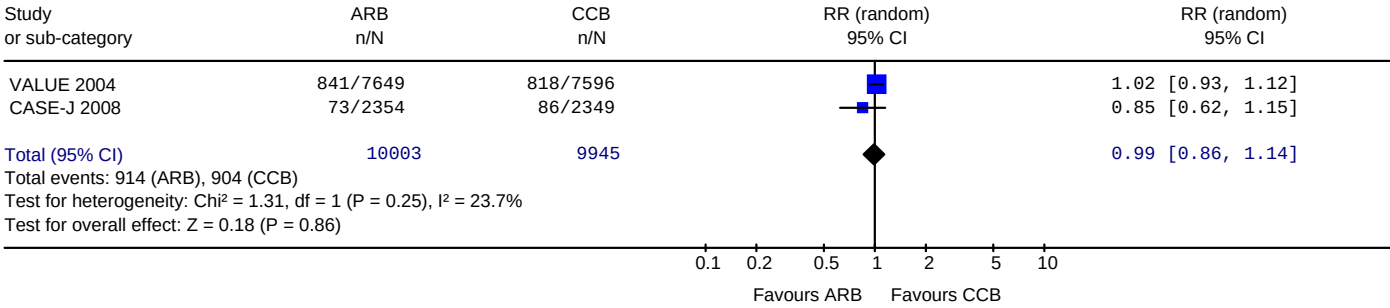
Review: Antihypertensive drug vs drug
Comparison: 08 ARB vs beta-blocker
Outcome: 05 Heart failure



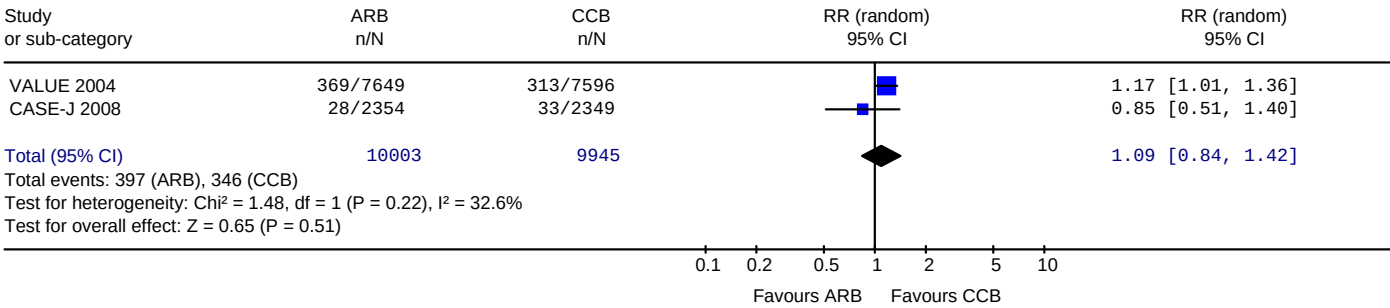
Review: Antihypertensive drug vs drug
Comparison: 08 ARB vs beta-blocker
Outcome: 06 Diabetes-incidence



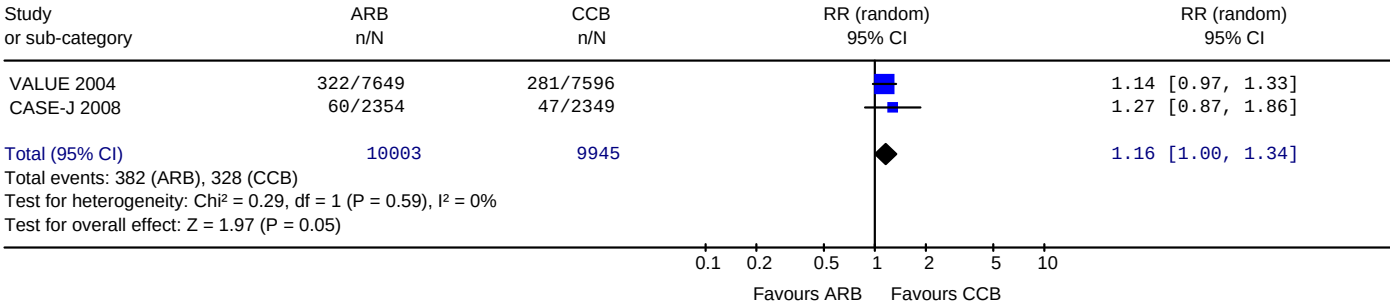
Review: Antihypertensive drug vs drug
Comparison: 09 ARB vs CCB
Outcome: 01 All cause mortality



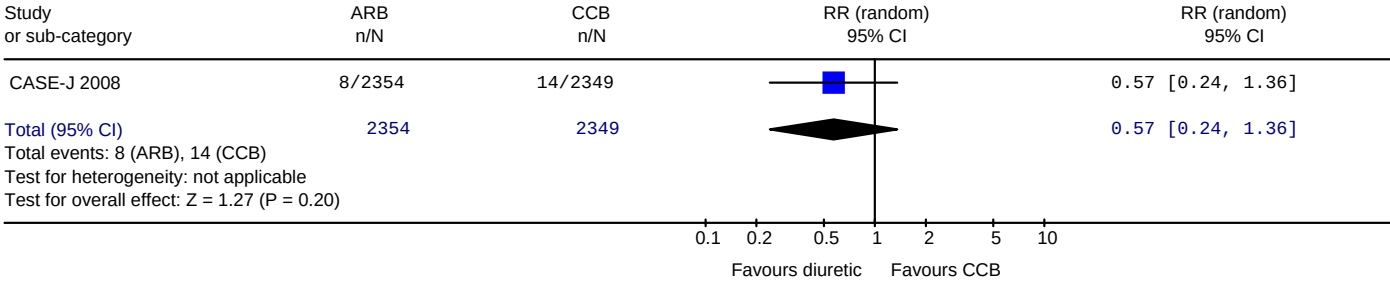
Review: Antihypertensive drug vs drug
Comparison: 09 ARB vs CCB
Outcome: 02 Myocardial infarction



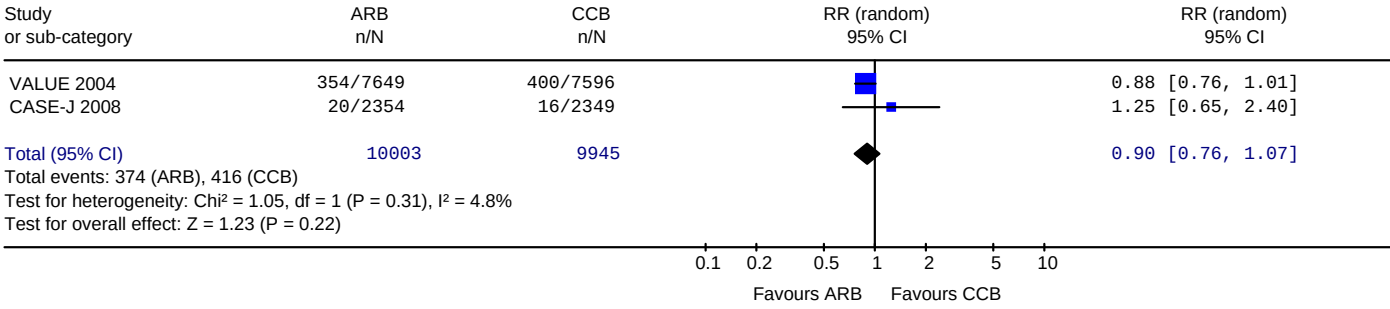
Review: Antihypertensive drug vs drug
Comparison: 09 ARB vs CCB
Outcome: 03 Stroke



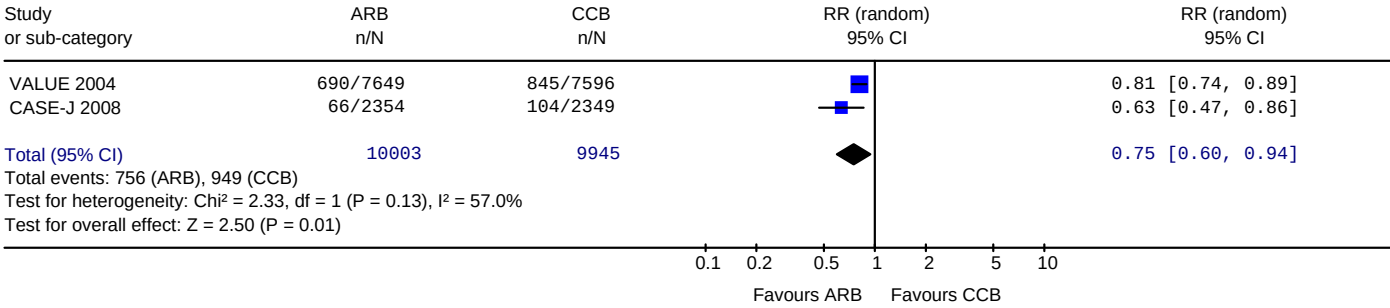
Review: Antihypertensive drug vs drug
Comparison: 09 ARB vs CCB
Outcome: 04 Angina



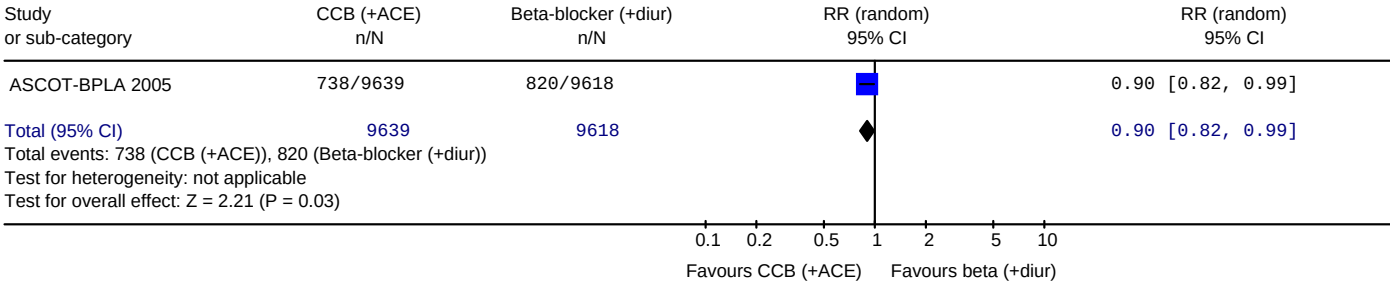
Review: Antihypertensive drug vs drug
Comparison: 09 ARB vs CCB
Outcome: 05 Heart failure



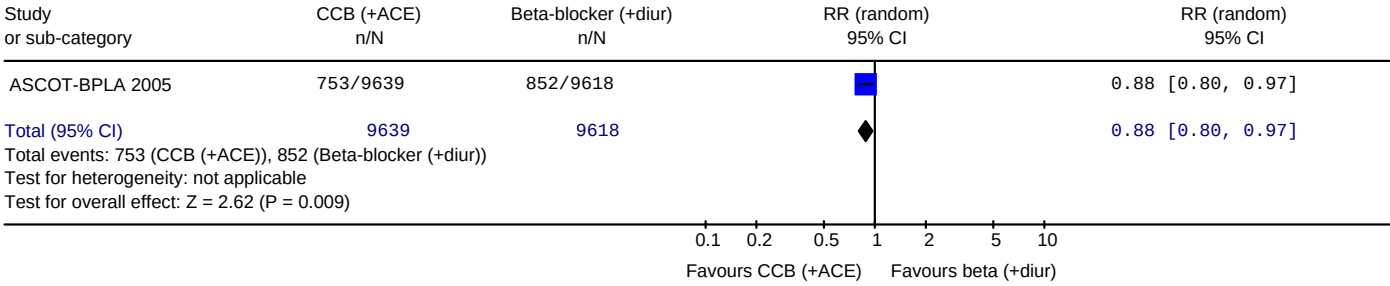
Review: Antihypertensive drug vs drug
Comparison: 09 ARB vs CCB
Outcome: 06 Diabetes-incidence



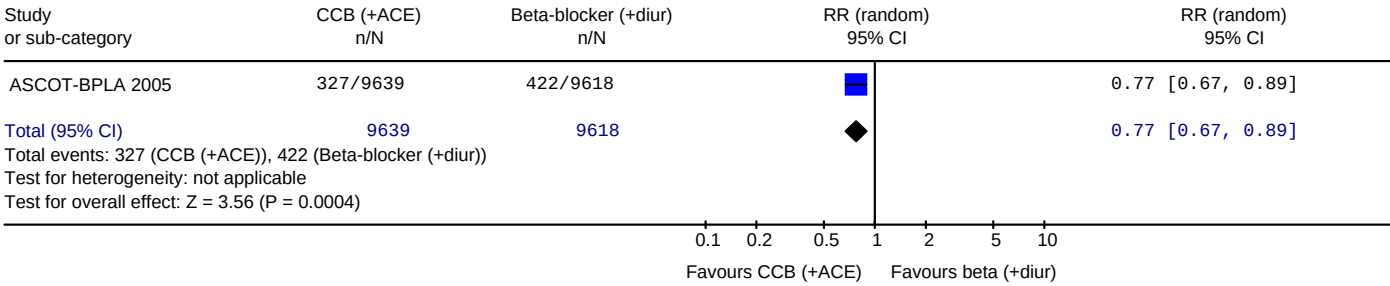
Review: Antihypertensive drug vs drug
Comparison: 10 CCB (+ACE) vs beta-blocker (+diuretic)
Outcome: 01 All cause mortality



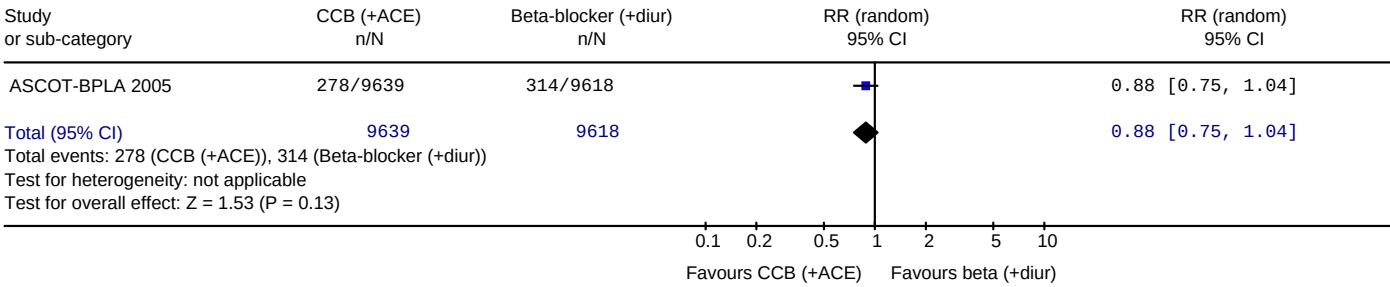
Review: Antihypertensive drug vs drug
Comparison: 10 CCB (+ACE) vs beta-blocker (+diuretic)
Outcome: 02 Myocardial infarction



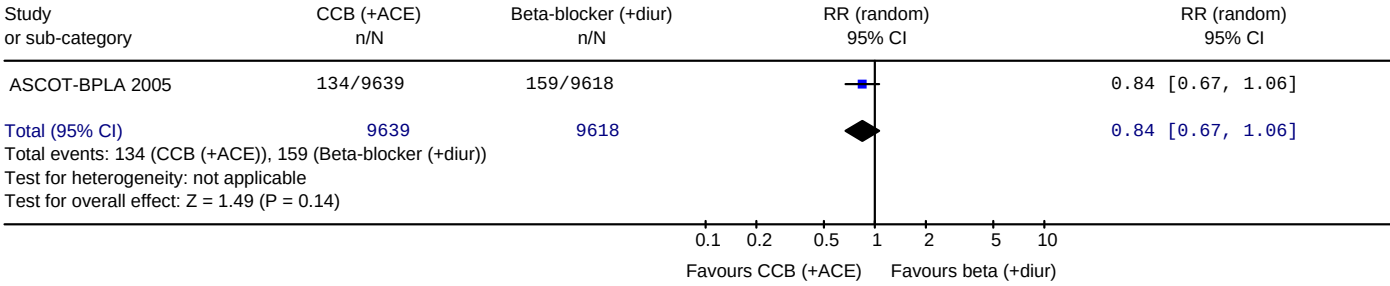
Review: Antihypertensive drug vs drug
Comparison: 10 CCB (+ACE) vs beta-blocker (+diuretic)
Outcome: 03 Stroke



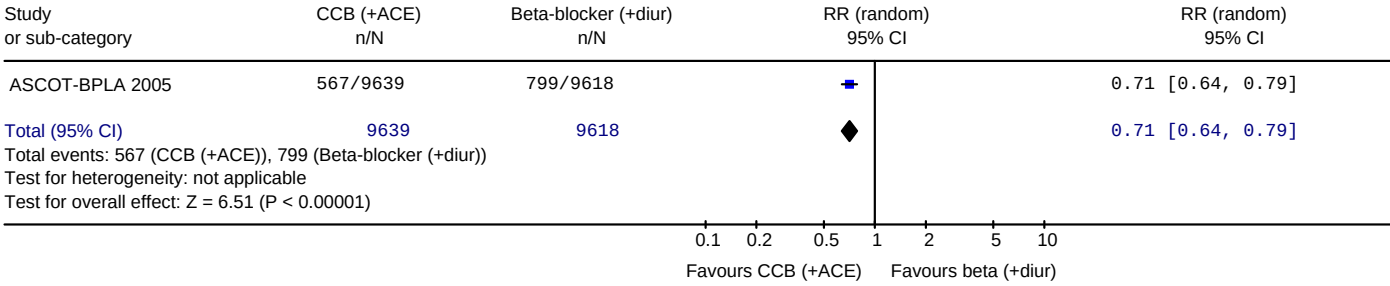
Review: Antihypertensive drug vs drug
Comparison: 10 CCB (+ACE) vs beta-blocker (+diuretic)
Outcome: 04 Angina



Review: Antihypertensive drug vs drug
Comparison: 10 CCB (+ACE) vs beta-blocker (+diuretic)
Outcome: 05 Heart failure

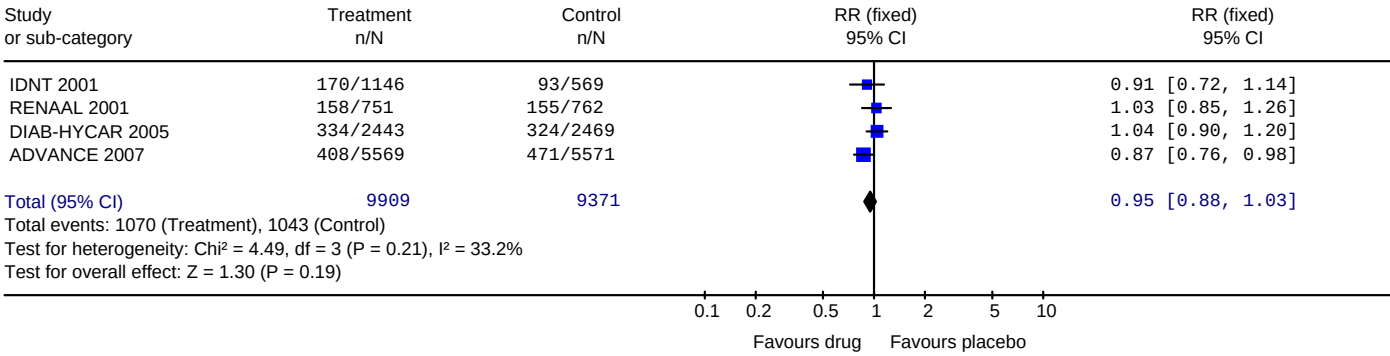


Review: Antihypertensive drug vs drug
Comparison: 10 CCB (+ACE) vs beta-blocker (+diuretic)
Outcome: 06 Diabetes-incidence

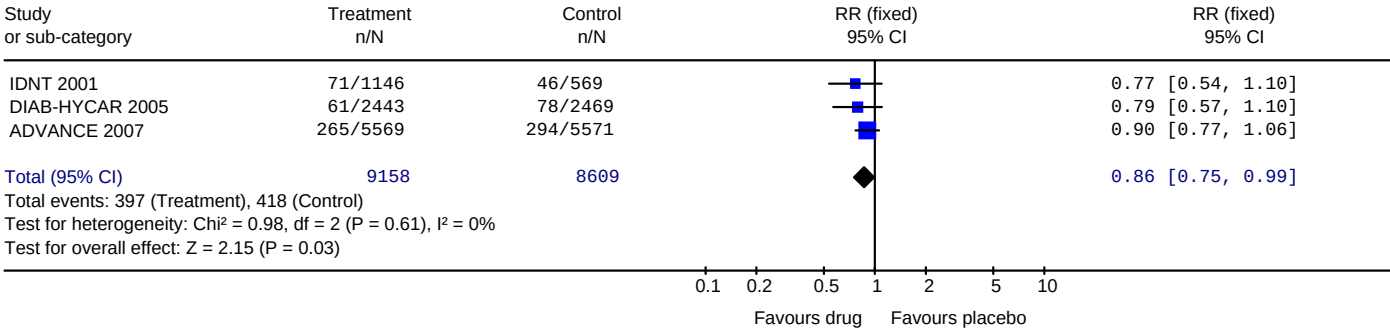


Medikament versus placebo, diabetikere

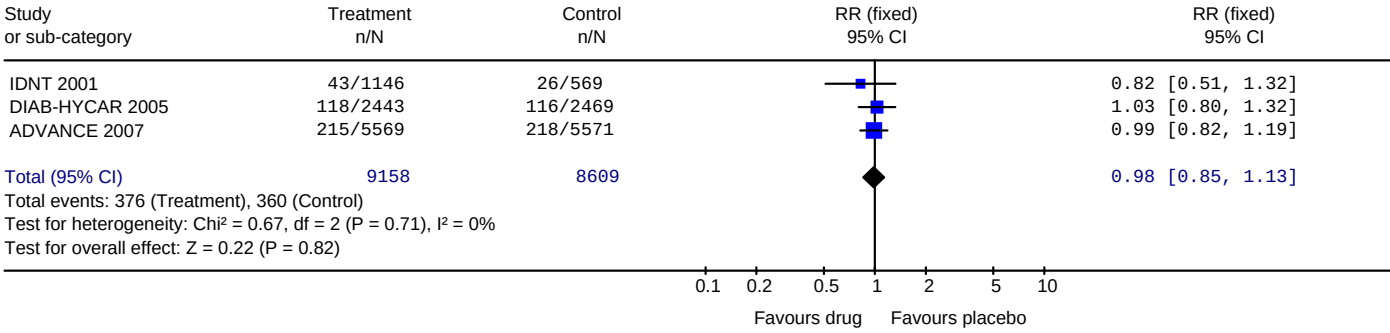
Review: Antihypertensives for diabetics, drug vs placebo
Comparison: 02 Drug vs placebo
Outcome: 01 All cause mortality



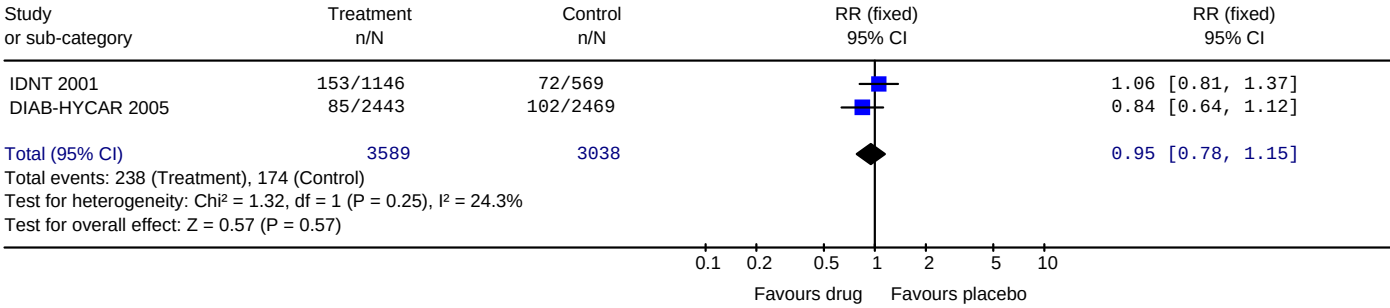
Review: Antihypertensives for diabetics, drug vs placebo
Comparison: 02 Drug vs placebo
Outcome: 02 Myocardial infarction



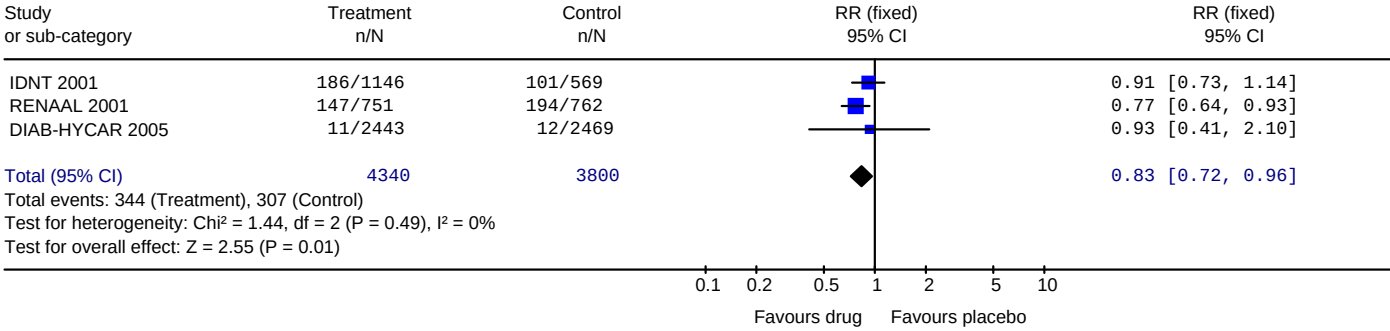
Review: Antihypertensives for diabetics, drug vs placebo
Comparison: 02 Drug vs placebo
Outcome: 03 Stroke



Review: Antihypertensives for diabetics, drug vs placebo
Comparison: 02 Drug vs placebo
Outcome: 05 Heart failure

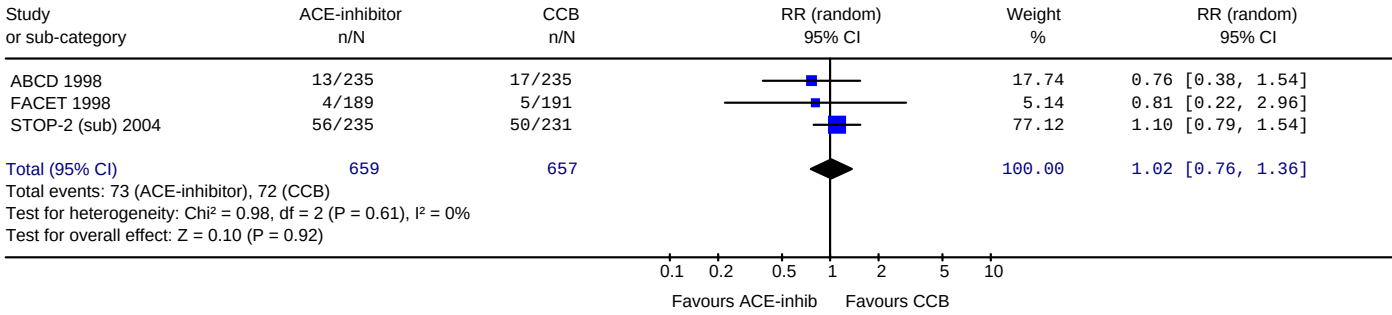


Review: Antihypertensives for diabetics, drug vs placebo
Comparison: 02 Drug vs placebo
Outcome: 06 Renal failure

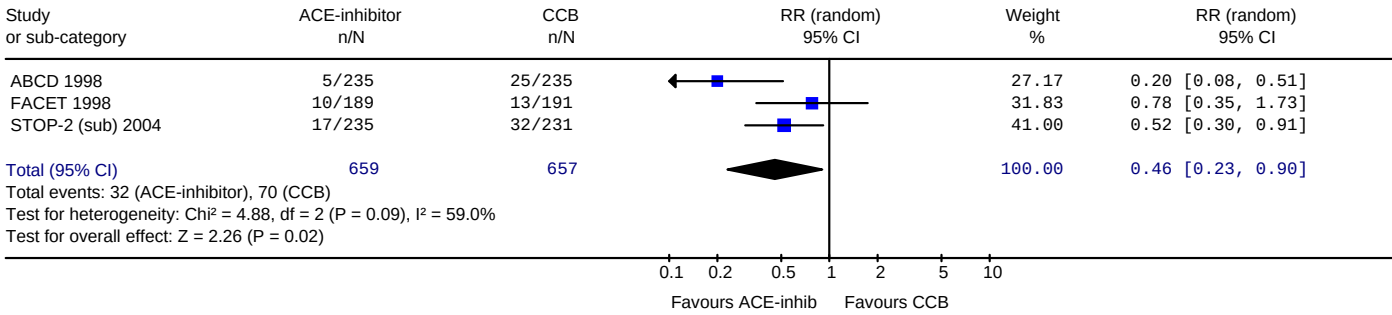


Medikament versus medikament, diabetikere

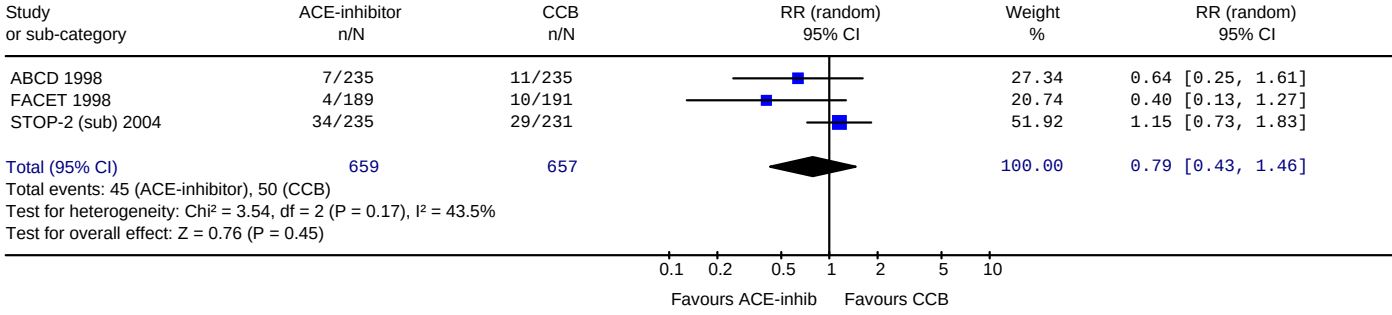
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 01 ACE-inhibitor vs CCB
Outcome: 01 All cause mortality



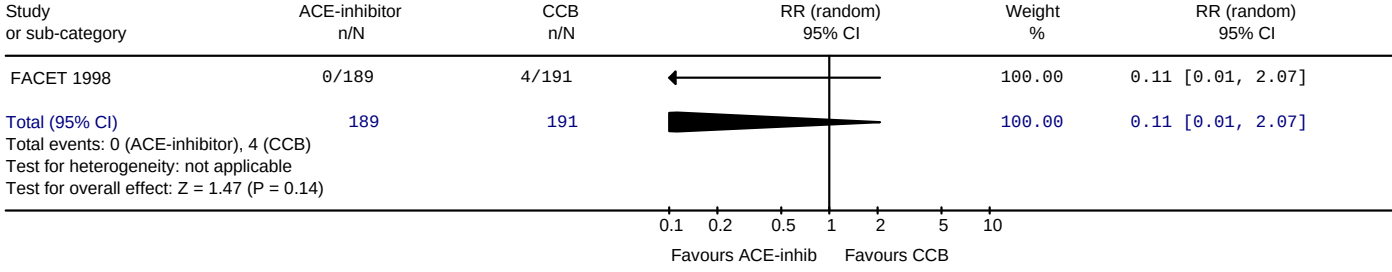
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 01 ACE-inhibitor vs CCB
Outcome: 02 Myocardial infarction



Review: Antihypertensives for diabetics, drug vs drug
Comparison: 01 ACE-inhibitor vs CCB
Outcome: 03 Stroke



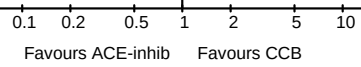
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 01 ACE-inhibitor vs CCB
Outcome: 04 Angina



Review: Antihypertensives for diabetics, drug vs drug
Comparison: 01 ACE-inhibitor vs CCB
Outcome: 05 Heart failure

Study or sub-category	ACE-inhibitor n/N	CCB n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
ABCD 1998	6/235	6/235		19.47	1.00 [0.33, 3.06]
STOP-2 (sub) 2004	22/235	24/231		80.53	0.90 [0.52, 1.56]
Total (95% CI)	470	466		100.00	0.92 [0.56, 1.51]

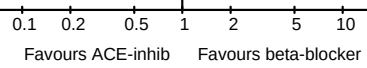
Total events: 28 (ACE-inhibitor), 30 (CCB)
Test for heterogeneity: Chi² = 0.03, df = 1 (P = 0.87), I² = 0%
Test for overall effect: Z = 0.33 (P = 0.74)



Review: Antihypertensives for diabetics, drug vs drug
Comparison: 02 ACE-inhibitor vs beta-blocker
Outcome: 01 All cause mortality

Study or sub-category	ACE-inhibitor n/N	Beta-blocker n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
UKPDS 39 1998	75/400	59/358		100.00	1.14 [0.83, 1.55]
Total (95% CI)	400	358		100.00	1.14 [0.83, 1.55]

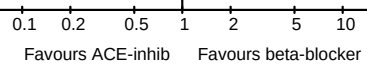
Total events: 75 (ACE-inhibitor), 59 (Beta-blocker)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.82 (P = 0.41)



Review: Antihypertensives for diabetics, drug vs drug
Comparison: 02 ACE-inhibitor vs beta-blocker
Outcome: 02 Myocardial infarction

Study or sub-category	ACE-inhibitor n/N	Beta-blocker n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
UKPDS 39 1998	61/400	46/358		100.00	1.19 [0.83, 1.69]
Total (95% CI)	400	358		100.00	1.19 [0.83, 1.69]

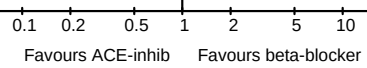
Total events: 61 (ACE-inhibitor), 46 (Beta-blocker)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.95 (P = 0.34)



Review: Antihypertensives for diabetics, drug vs drug
Comparison: 02 ACE-inhibitor vs beta-blocker
Outcome: 03 Stroke

Study or sub-category	ACE-inhibitor n/N	Beta-blocker n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
UKPDS 39 1998	21/400	17/358		100.00	1.11 [0.59, 2.06]
Total (95% CI)	400	358		100.00	1.11 [0.59, 2.06]

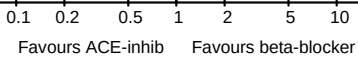
Total events: 21 (ACE-inhibitor), 17 (Beta-blocker)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.32 (P = 0.75)



Review: Antihypertensives for diabetics, drug vs drug
Comparison: 02 ACE-inhibitor vs beta-blocker
Outcome: 04 Angina

Study or sub-category	ACE-inhibitor n/N	Beta-blocker n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
UKPDS 39 1998	20/400	25/358		100.00	0.72 [0.40, 1.27]
Total (95% CI)	400	358		100.00	0.72 [0.40, 1.27]

Total events: 20 (ACE-inhibitor), 25 (Beta-blocker)
Test for heterogeneity: not applicable
Test for overall effect: Z = 1.15 (P = 0.25)

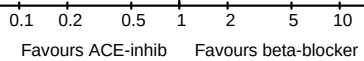


Favours ACE-inhib Favours beta-blocker

Review: Antihypertensives for diabetics, drug vs drug
Comparison: 02 ACE-inhibitor vs beta-blocker
Outcome: 05 Heart failure

Study or sub-category	ACE-inhibitor n/N	Beta-blocker n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
UKPDS 39 1998	12/400	9/358		100.00	1.19 [0.51, 2.80]
Total (95% CI)	400	358		100.00	1.19 [0.51, 2.80]

Total events: 12 (ACE-inhibitor), 9 (Beta-blocker)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.41 (P = 0.68)

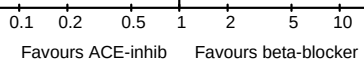


Favours ACE-inhib Favours beta-blocker

Review: Antihypertensives for diabetics, drug vs drug
Comparison: 02 ACE-inhibitor vs beta-blocker
Outcome: 06 Renal failure

Study or sub-category	ACE-inhibitor n/N	Beta-blocker n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
UKPDS 39 1998	4/400	4/358		100.00	0.90 [0.23, 3.55]
Total (95% CI)	400	358		100.00	0.90 [0.23, 3.55]

Total events: 4 (ACE-inhibitor), 4 (Beta-blocker)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.16 (P = 0.87)

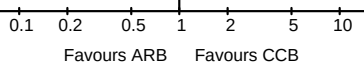


Favours ACE-inhib Favours beta-blocker

Review: Antihypertensives for diabetics, drug vs drug
Comparison: 03 ARB vs CCB
Outcome: 01 All cause mortality

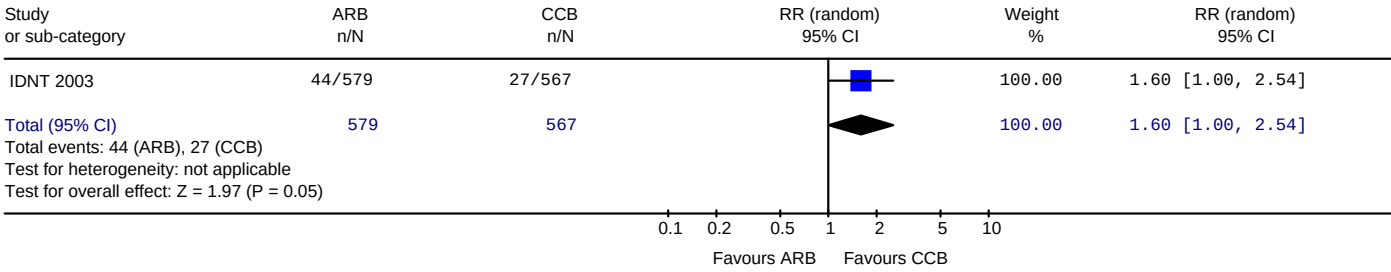
Study or sub-category	ARB n/N	CCB n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
IDNT 2003	87/579	83/567		100.00	1.03 [0.78, 1.35]
Total (95% CI)	579	567		100.00	1.03 [0.78, 1.35]

Total events: 87 (ARB), 83 (CCB)
Test for heterogeneity: not applicable
Test for overall effect: Z = 0.18 (P = 0.85)

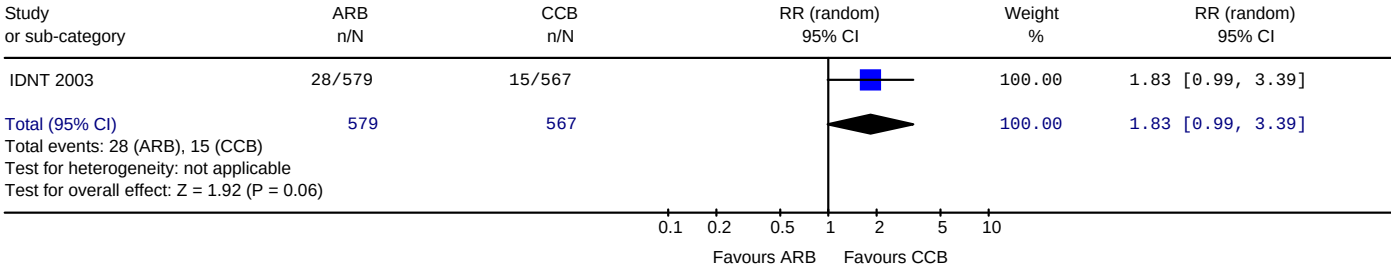


Favours ARB Favours CCB

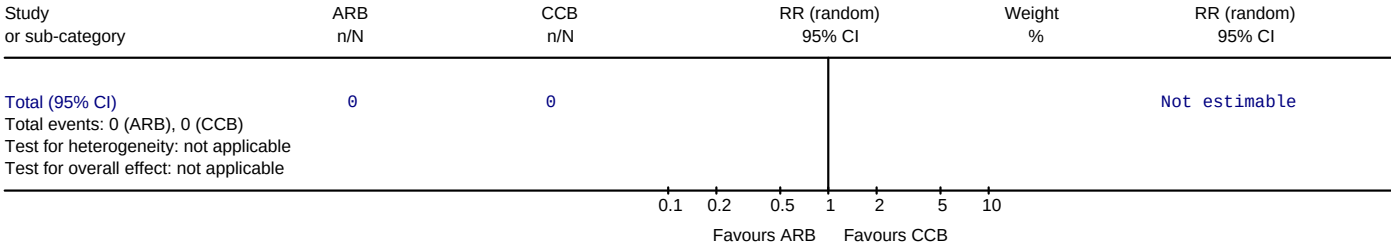
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 03 ARB vs CCB
Outcome: 02 Myocardial infarction



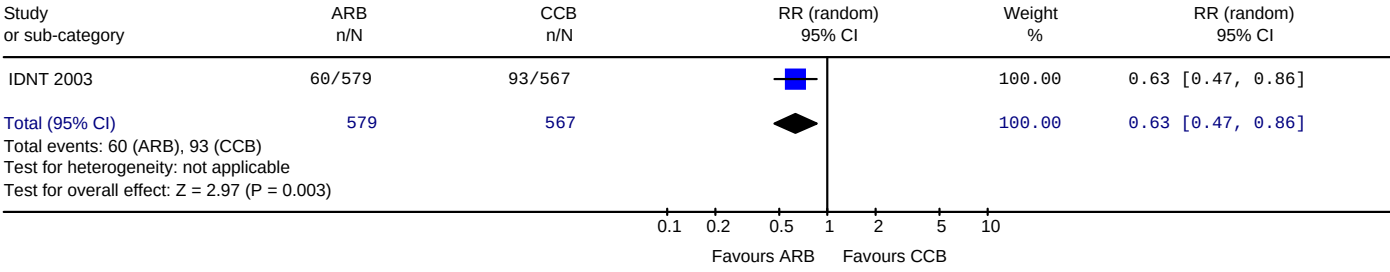
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 03 ARB vs CCB
Outcome: 03 Stroke



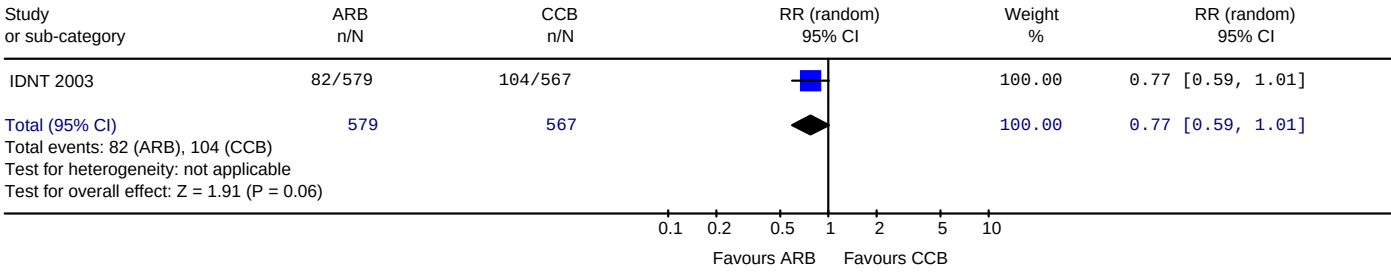
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 03 ARB vs CCB
Outcome: 04 Angina



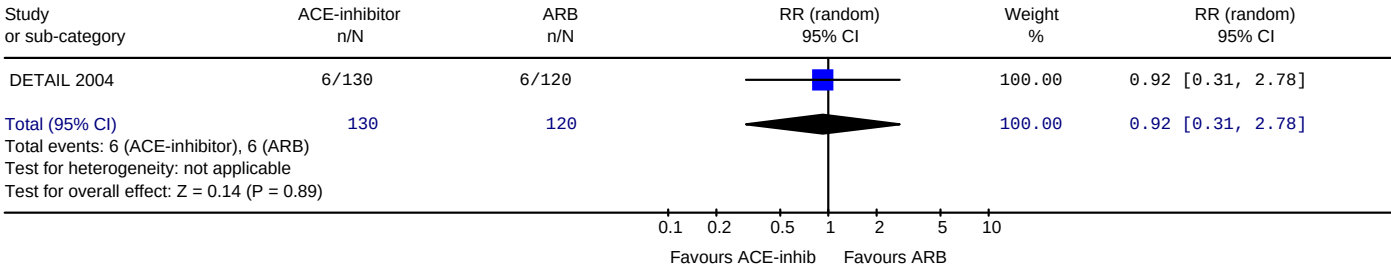
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 03 ARB vs CCB
Outcome: 05 Heart failure



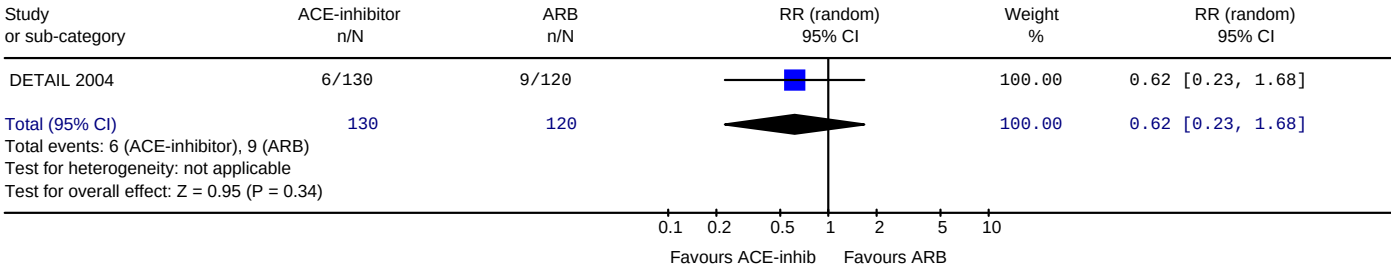
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 03 ARB vs CCB
Outcome: 06 Renal failure



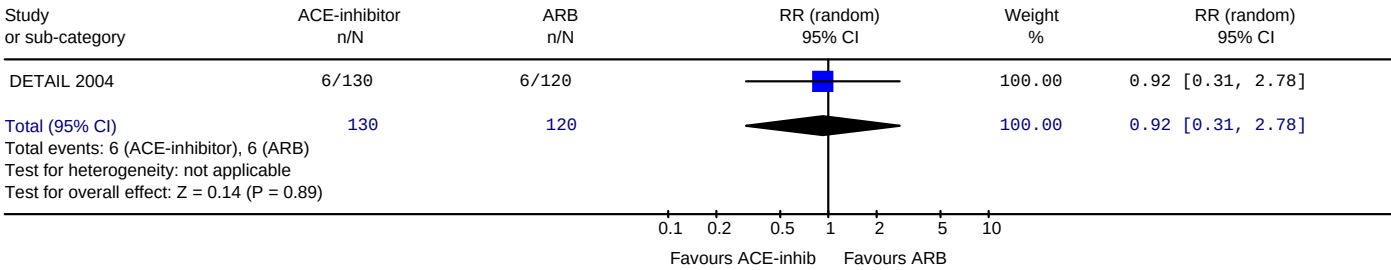
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 04 ACE-inhibitor vs ARB
Outcome: 01 All cause mortality



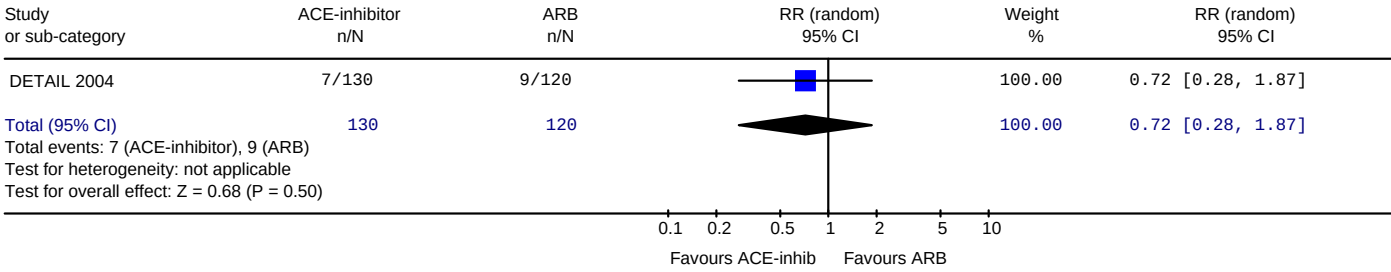
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 04 ACE-inhibitor vs ARB
Outcome: 02 Myocardial infarction



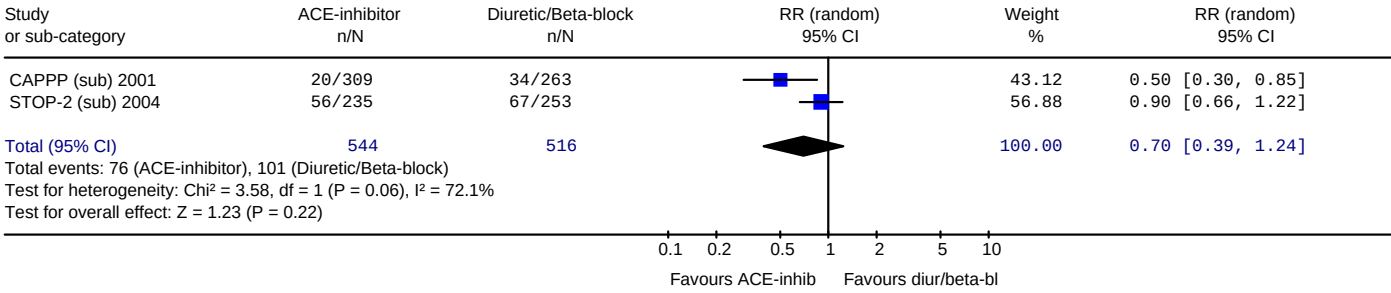
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 04 ACE-inhibitor vs ARB
Outcome: 03 Stroke



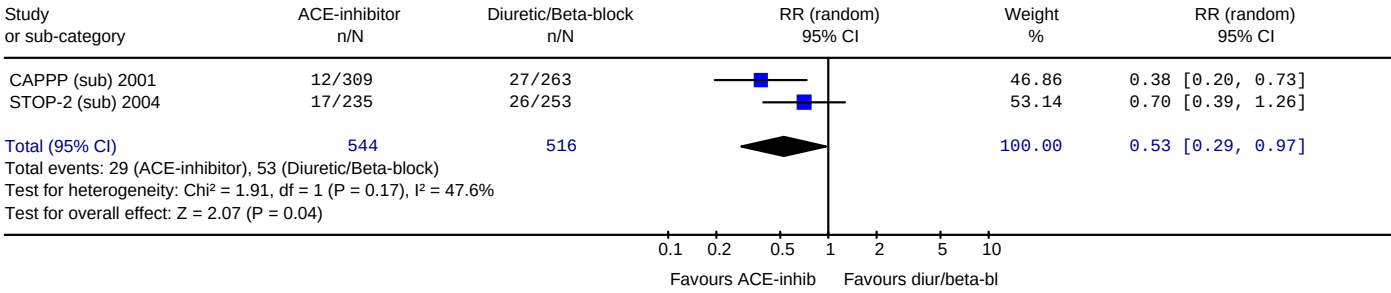
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 04 ACE-inhibitor vs ARB
Outcome: 05 Heart failure



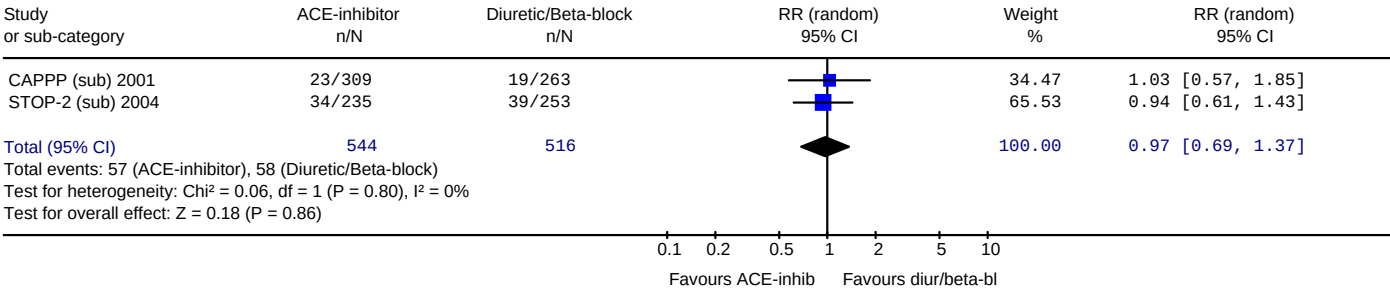
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 05 ACE-inhibitor vs diuretic and/or beta-blocker
Outcome: 01 All cause mortality



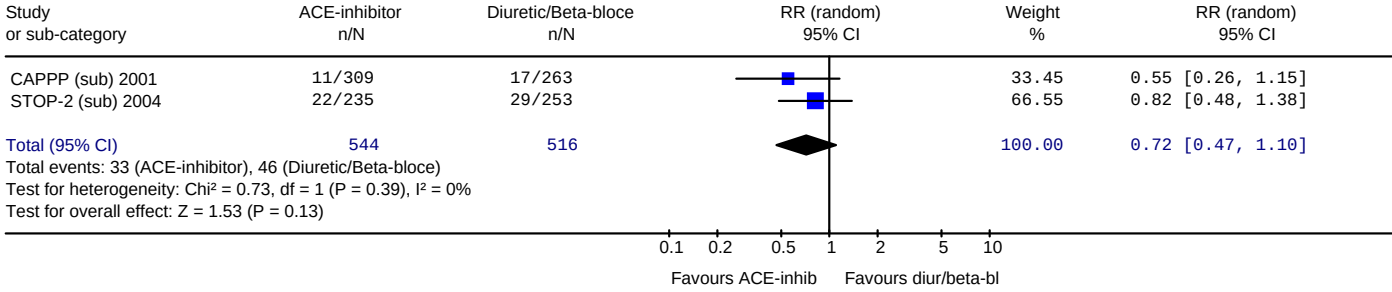
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 05 ACE-inhibitor vs diuretic and/or beta-blocker
Outcome: 02 Myocardial infarction



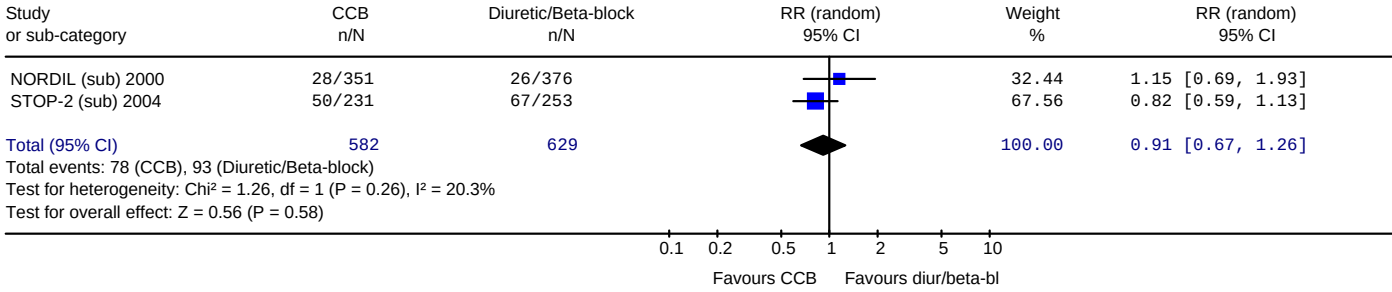
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 05 ACE-inhibitor vs diuretic and/or beta-blocker
Outcome: 03 Stroke



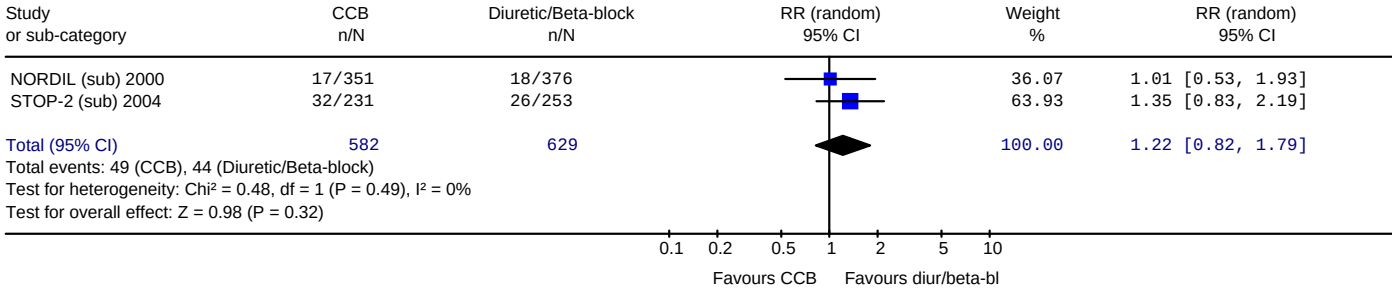
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 05 ACE-inhibitor vs diuretic and/or beta-blocker
Outcome: 05 Heart failure



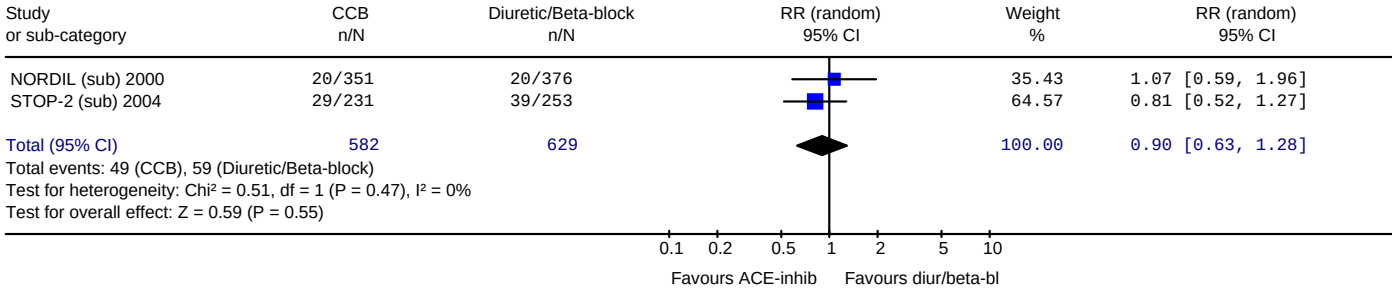
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 06 CCB vs diuretic and/or beta-blocker
Outcome: 01 All cause mortality



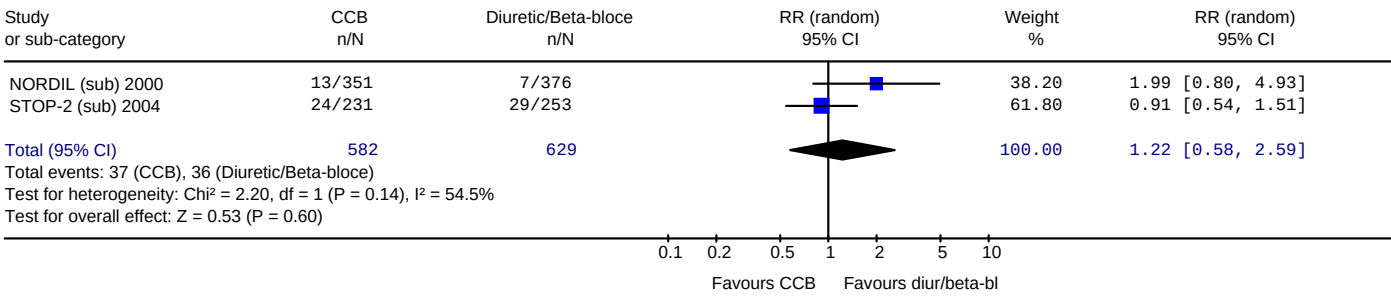
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 06 CCB vs diuretic and/or beta-blocker
Outcome: 02 Myocardial infarction



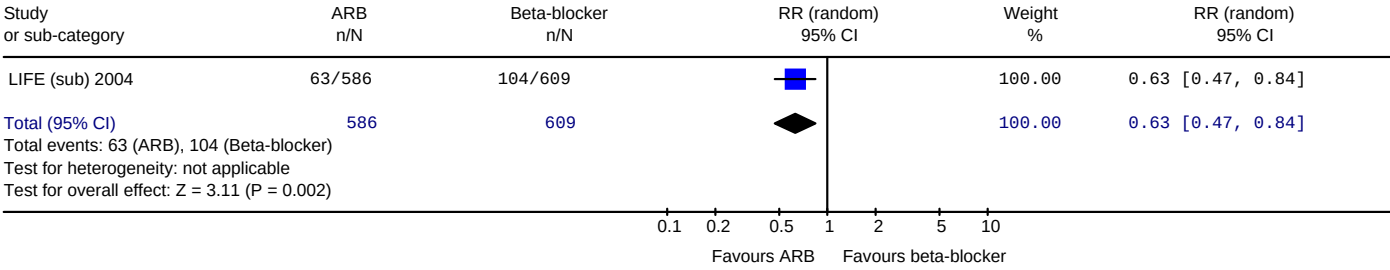
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 06 CCB vs diuretic and/or beta-blocker
Outcome: 03 Stroke



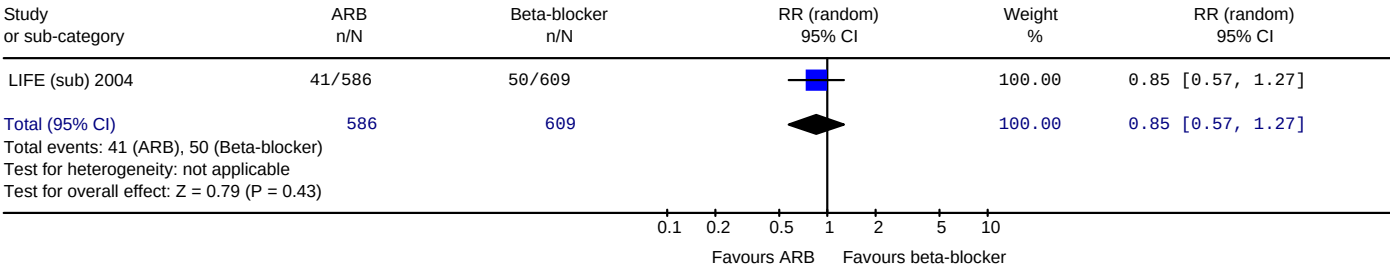
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 06 CCB vs diuretic and/or beta-blocker
Outcome: 05 Heart failure



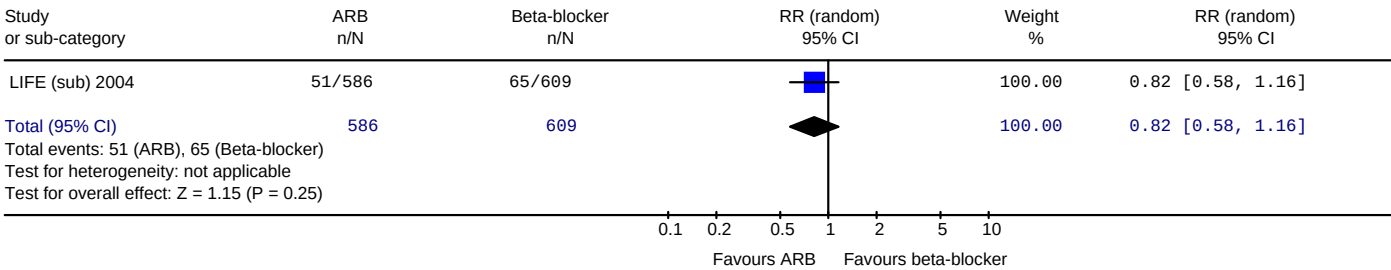
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 07 ARB vs beta-blocker
Outcome: 01 All cause mortality



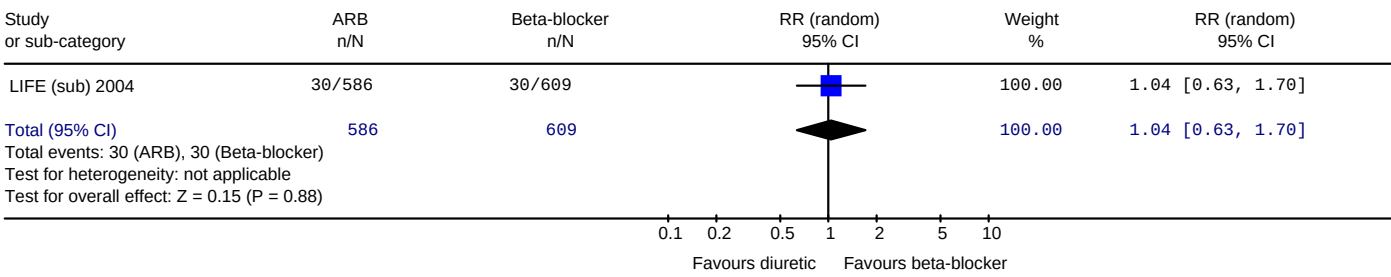
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 07 ARB vs beta-blocker
Outcome: 02 Myocardial infarction



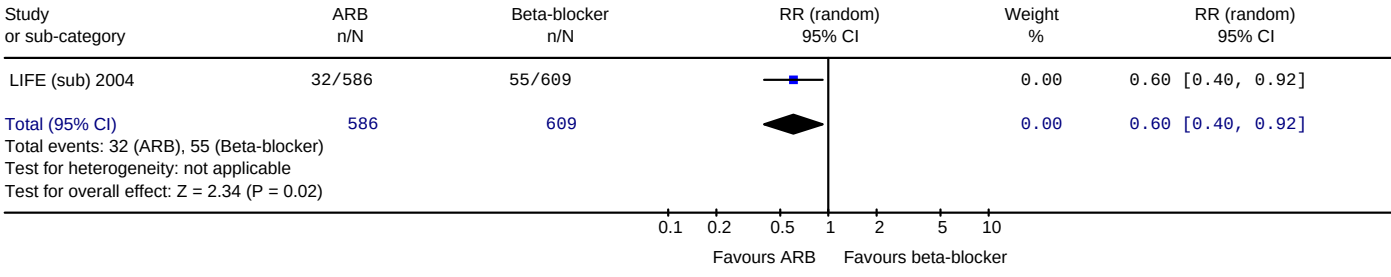
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 07 ARB vs beta-blocker
Outcome: 03 Stroke



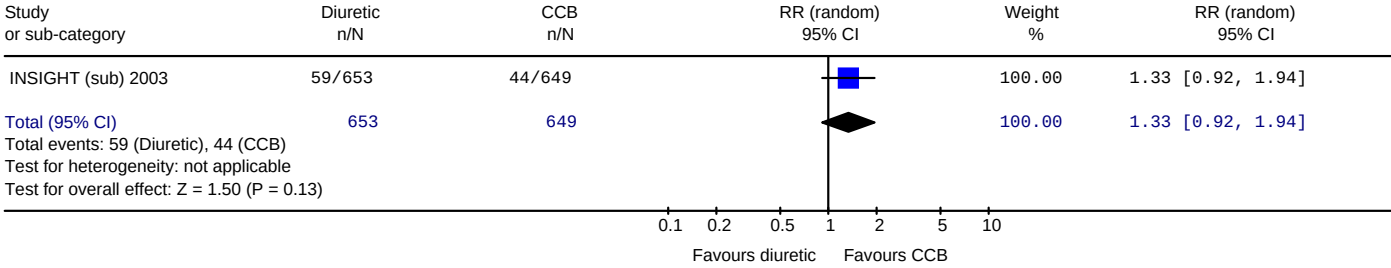
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 07 ARB vs beta-blocker
Outcome: 04 Angina



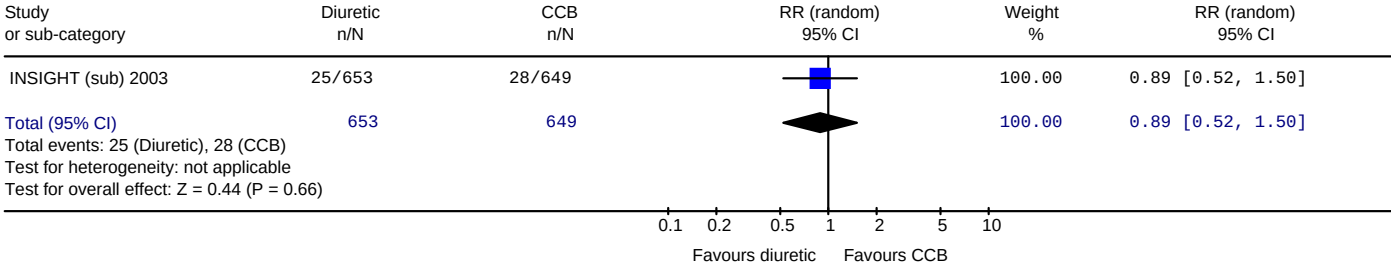
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 07 ARB vs beta-blocker
Outcome: 05 Heart failure



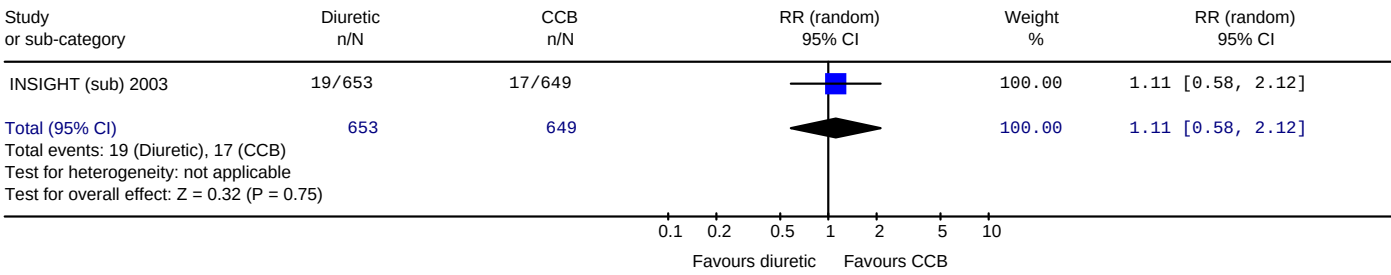
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 08 Diuretic vs CCB
Outcome: 01 All cause mortality



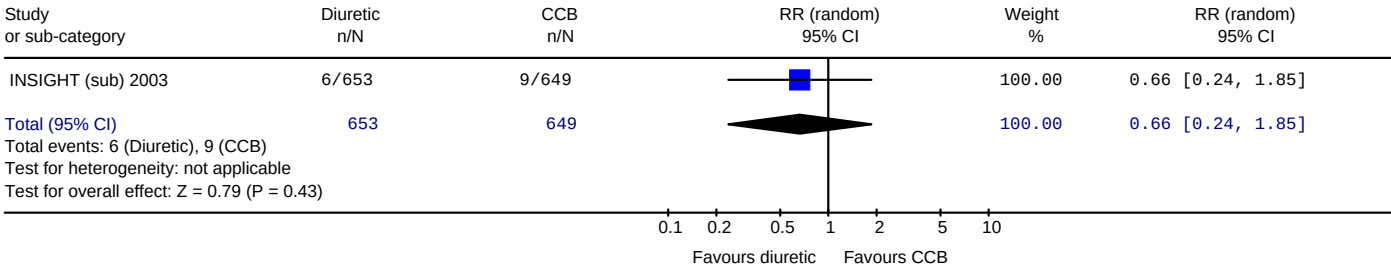
Review: Antihypertensives for diabetics, drug vs drug
Comparison: 08 Diuretic vs CCB
Outcome: 02 Myocardial infarction



Review: Antihypertensives for diabetics, drug vs drug
Comparison: 08 Diuretic vs CCB
Outcome: 03 Stroke

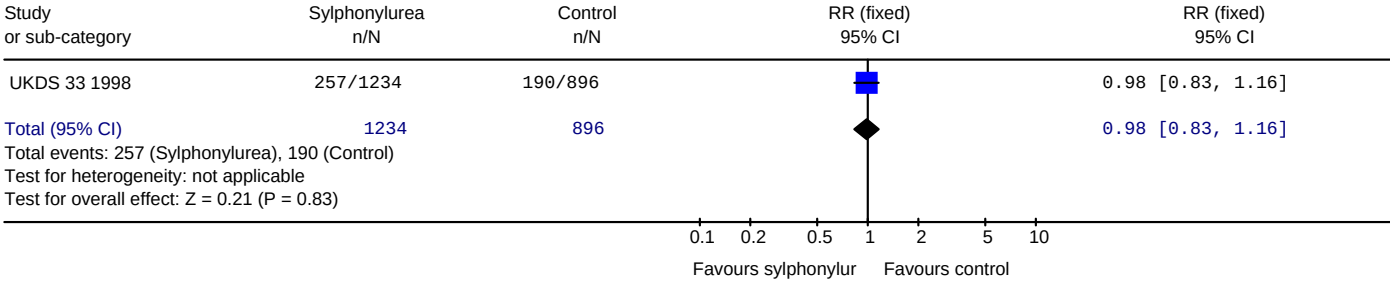


Review: Antihypertensives for diabetics, drug vs drug
Comparison: 08 Diuretic vs CCB
Outcome: 05 Heart failure

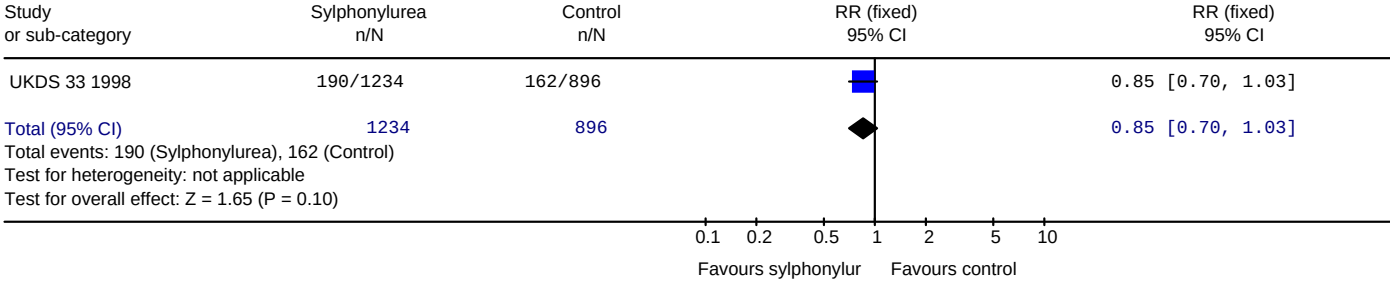


Blodglukosesenkende midler

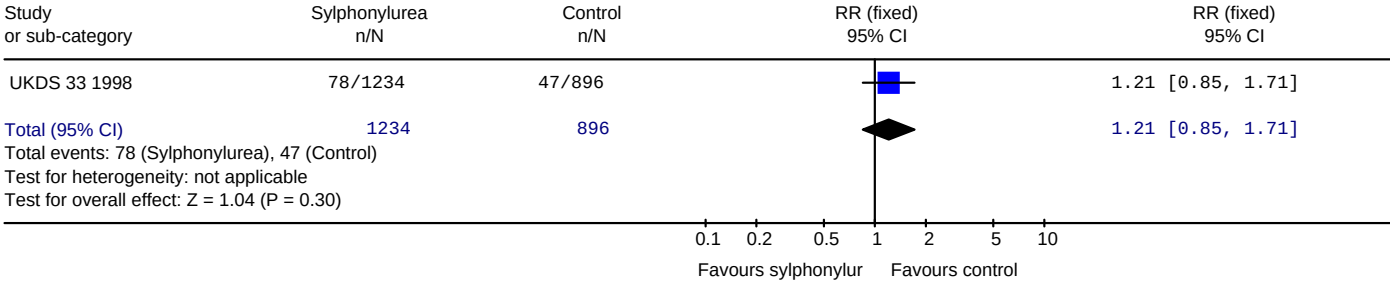
Review: Glucose-lowering drug vs control
Comparison: 01 Sylphonyurea vs control
Outcome: 01 All-cause mortality



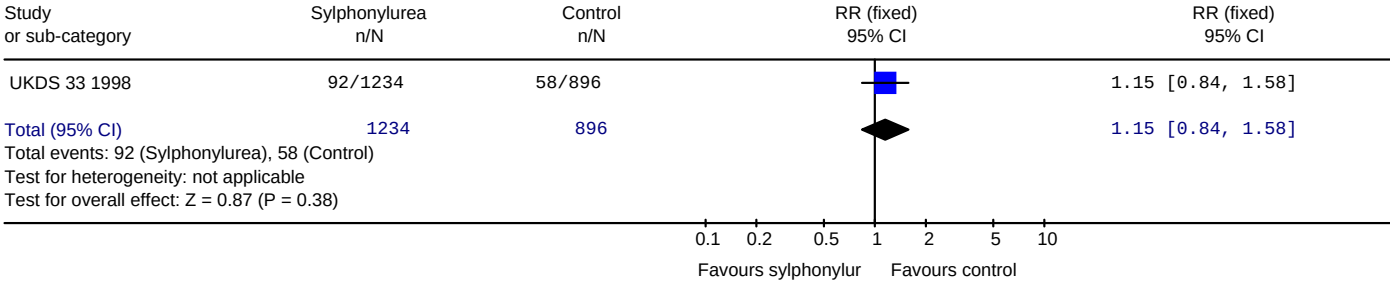
Review: Glucose-lowering drug vs control
Comparison: 01 Sylphonyurea vs control
Outcome: 02 Myocardial infarction



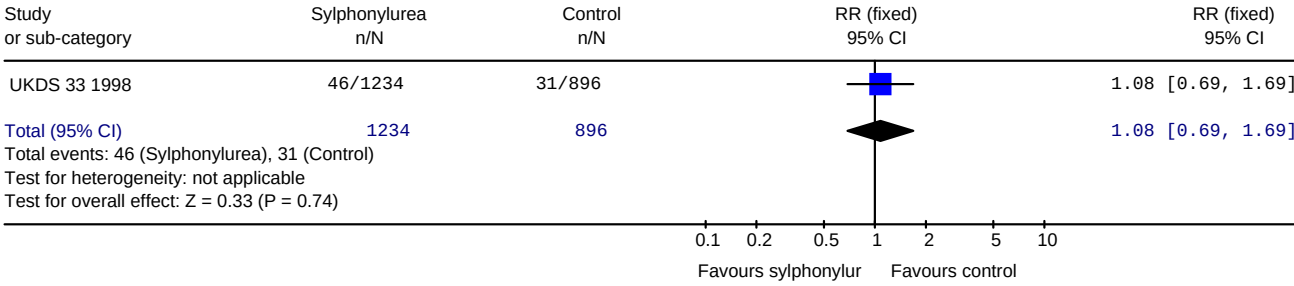
Review: Glucose-lowering drug vs control
Comparison: 01 Sylphonyurea vs control
Outcome: 03 Stroke



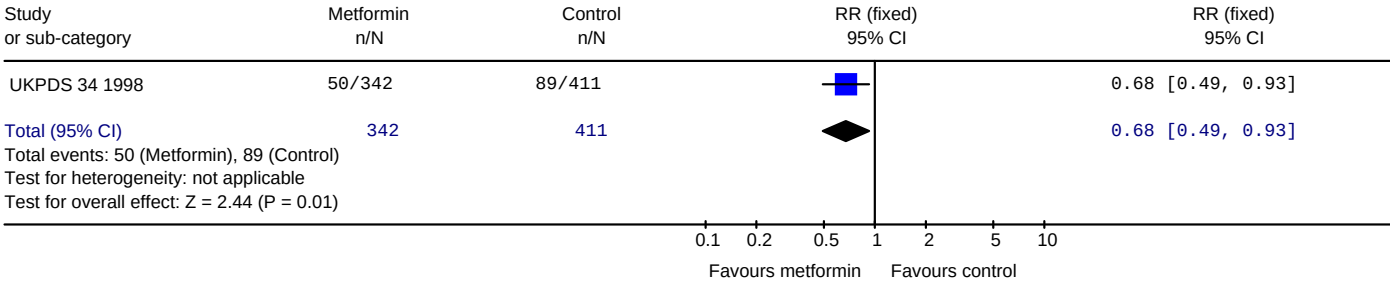
Review: Glucose-lowering drug vs control
Comparison: 01 Sylphonyurea vs control
Outcome: 04 Angina



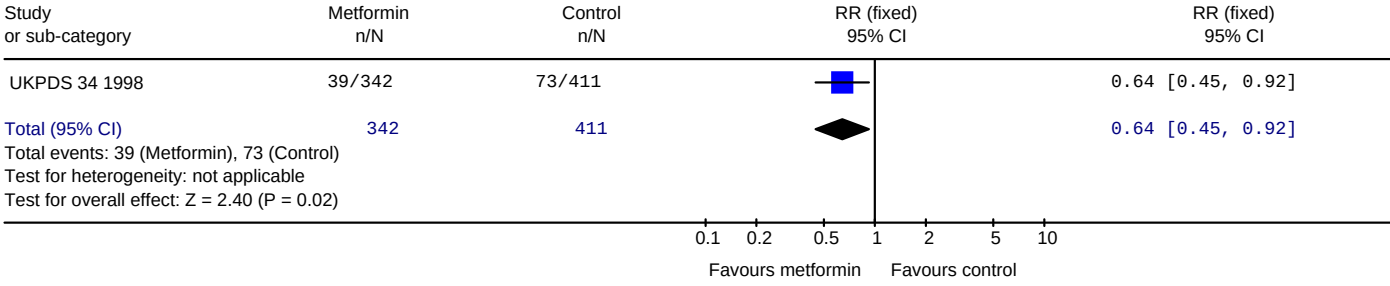
Review: Glucose-lowering drug vs control
Comparison: 01 Sylphonyurea vs control
Outcome: 05 Heart failure



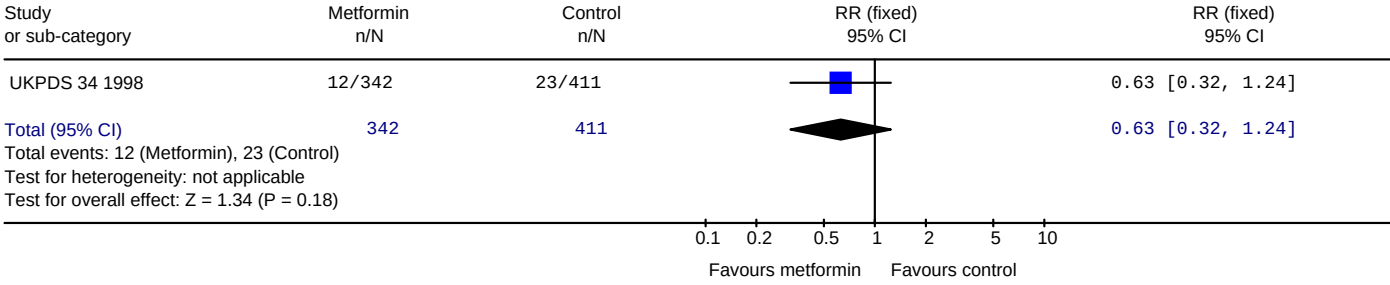
Review: Glucose-lowering drug vs control
Comparison: 02 Metformin vs control
Outcome: 01 All-cause mortality



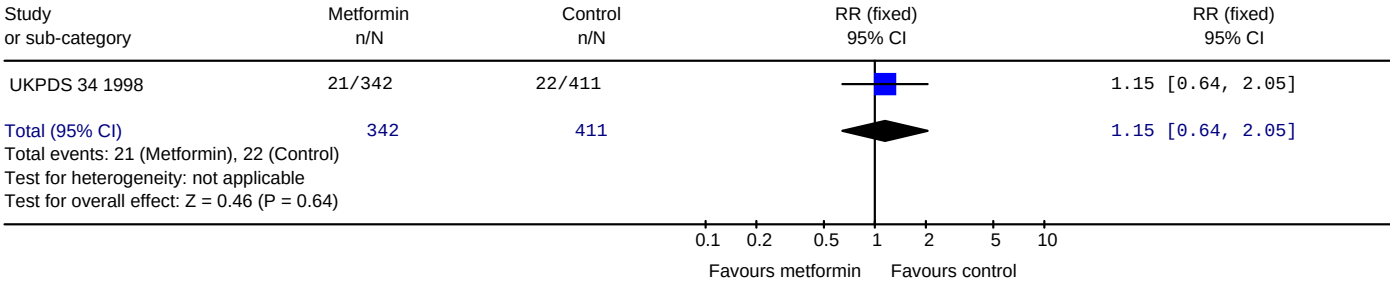
Review: Glucose-lowering drug vs control
Comparison: 02 Metformin vs control
Outcome: 02 Myocardial infarction



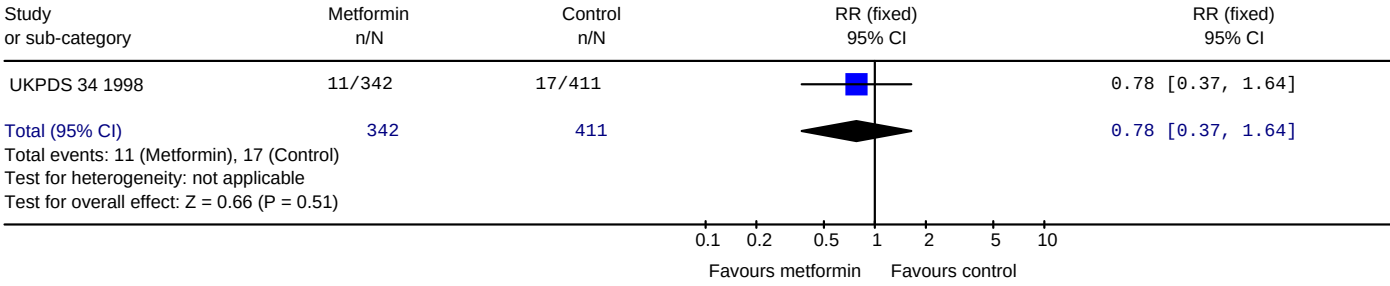
Review: Glucose-lowering drug vs control
Comparison: 02 Metformin vs control
Outcome: 03 Stroke



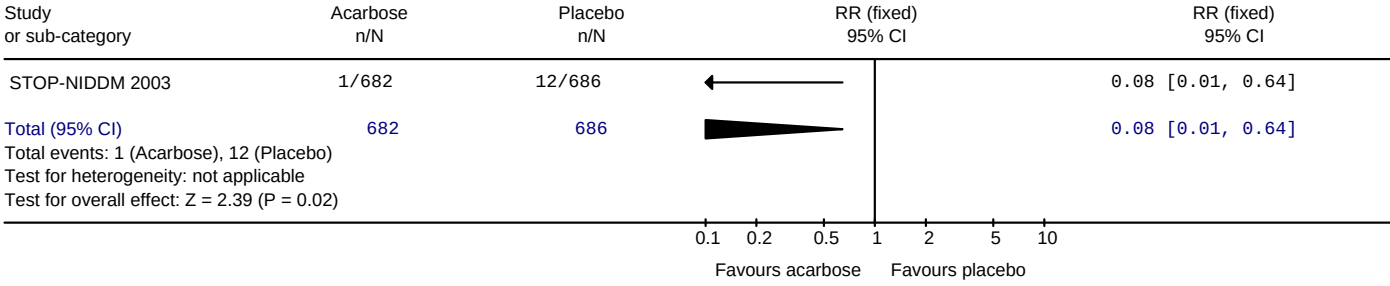
Review: Glucose-lowering drug vs control
Comparison: 02 Metformin vs control
Outcome: 04 Angina



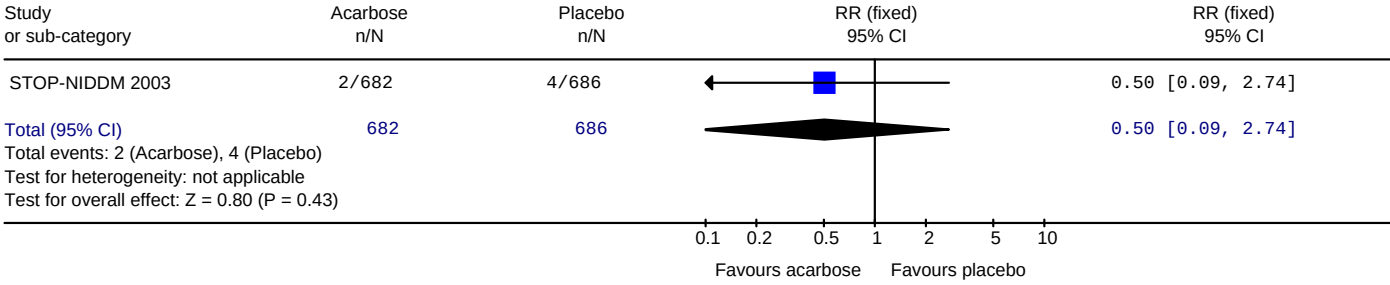
Review: Glucose-lowering drug vs control
Comparison: 02 Metformin vs control
Outcome: 05 Heart failure



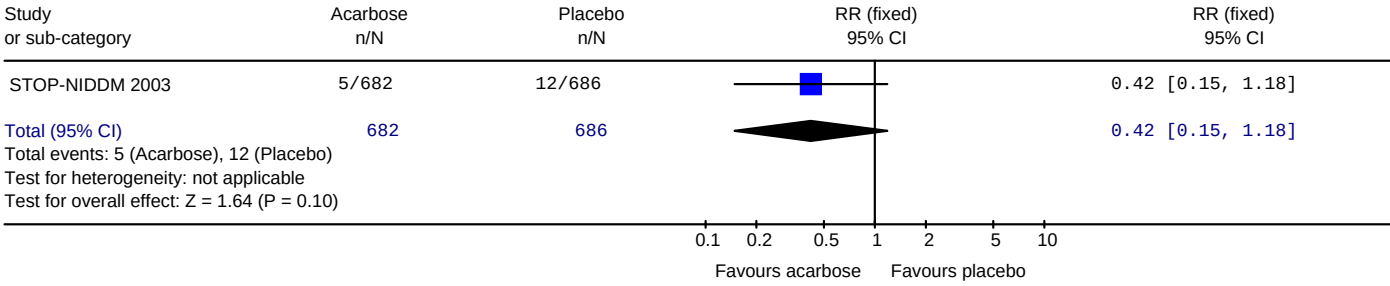
Review: Glucose-lowering drug vs control
Comparison: 03 Acarbose vs placebo
Outcome: 01 Myocardial infarction



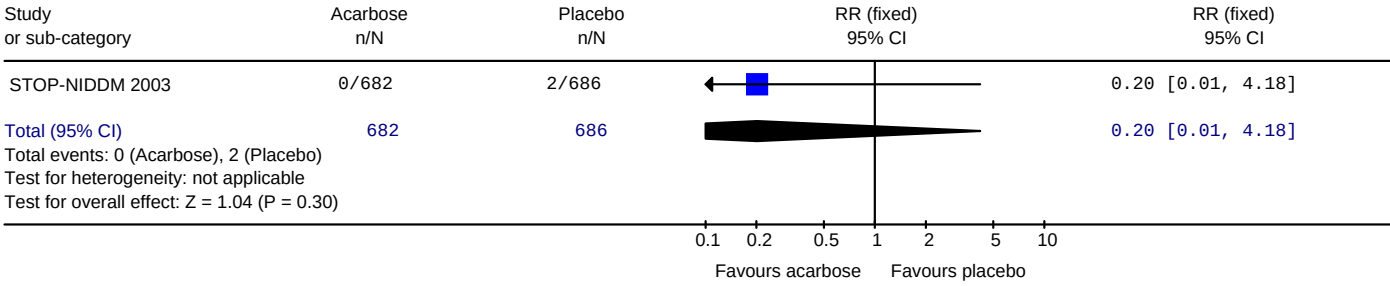
Review: Glucose-lowering drug vs control
Comparison: 03 Acarbose vs placebo
Outcome: 02 Stroke



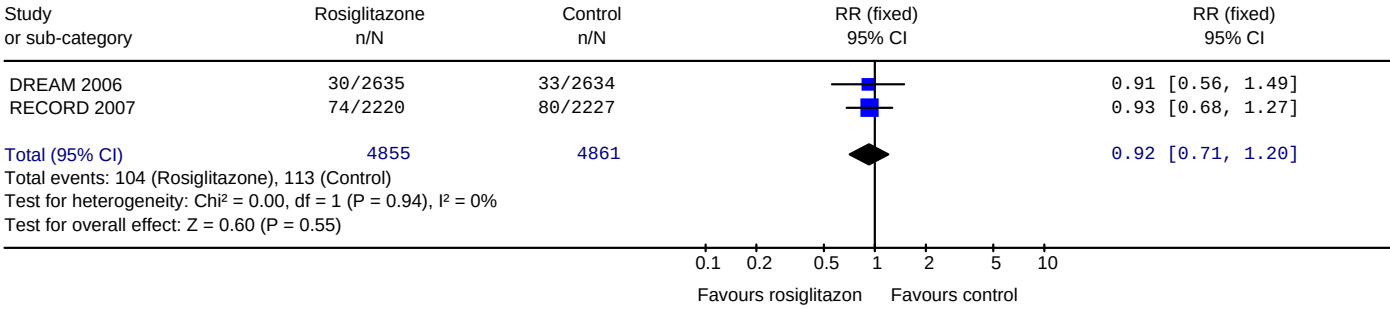
Review: Glucose-lowering drug vs control
Comparison: 03 Acarbose vs placebo
Outcome: 03 Angina



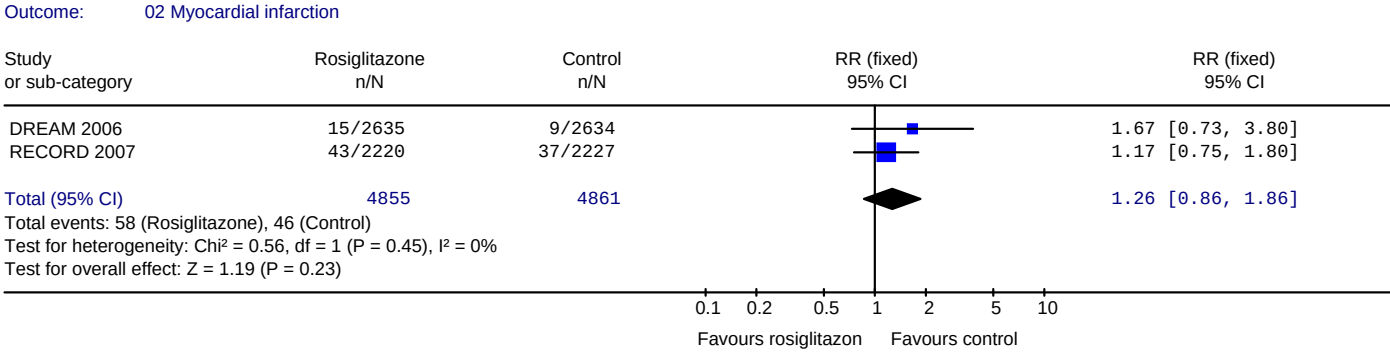
Review: Glucose-lowering drug vs control
Comparison: 03 Acarbose vs placebo
Outcome: 04 Heart failure



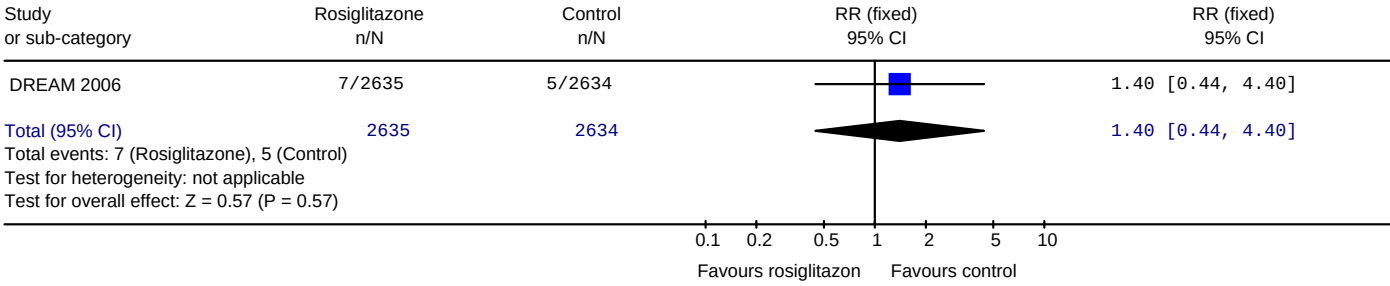
Review: Glucose-lowering drug vs control
Comparison: 04 Rosiglitazone vs control
Outcome: 01 All-cause mortality



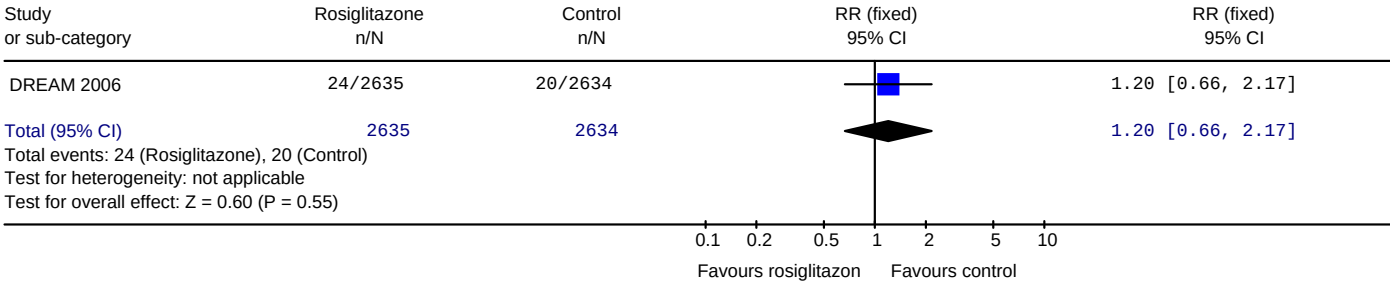
Review: Glucose-lowering drug vs control
Comparison: 04 Rosiglitazone vs control
Outcome: 02 Myocardial infarction



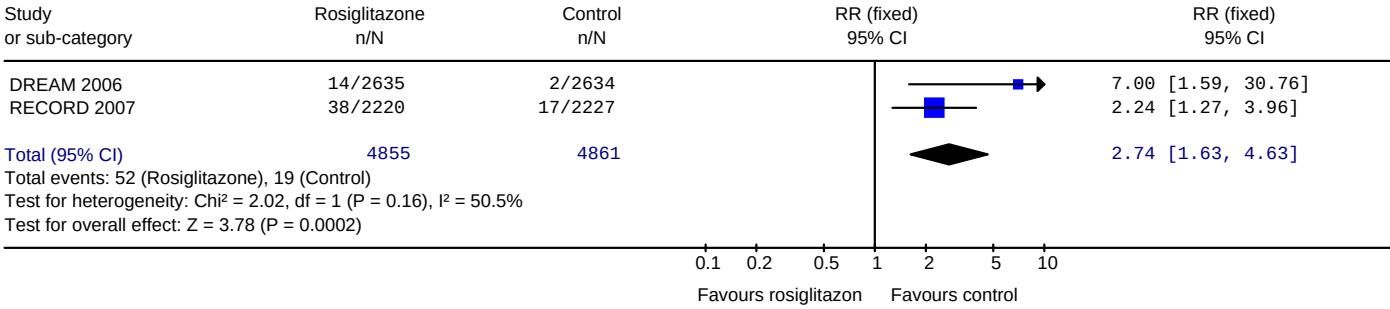
Review: Glucose-lowering drug vs control
Comparison: 04 Rosiglitazone vs control
Outcome: 03 Stroke



Review: Glucose-lowering drug vs control
Comparison: 04 Rosiglitazone vs control
Outcome: 04 Angina

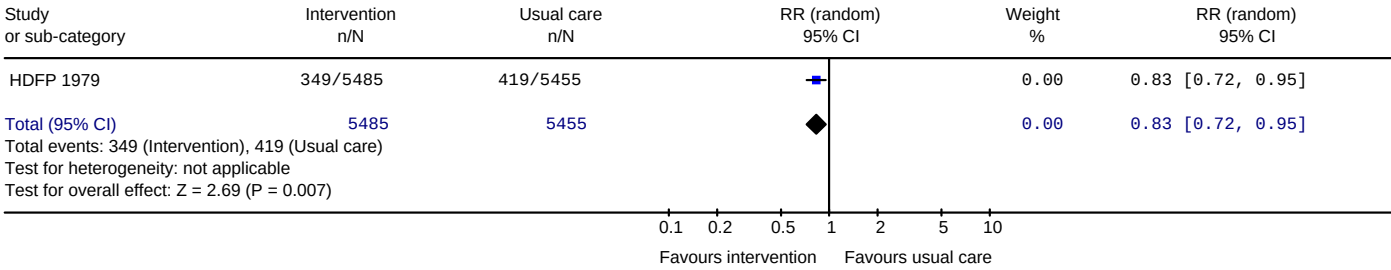


Review: Glucose-lowering drug vs control
Comparison: 04 Rosiglitazone vs control
Outcome: 05 Heart failure

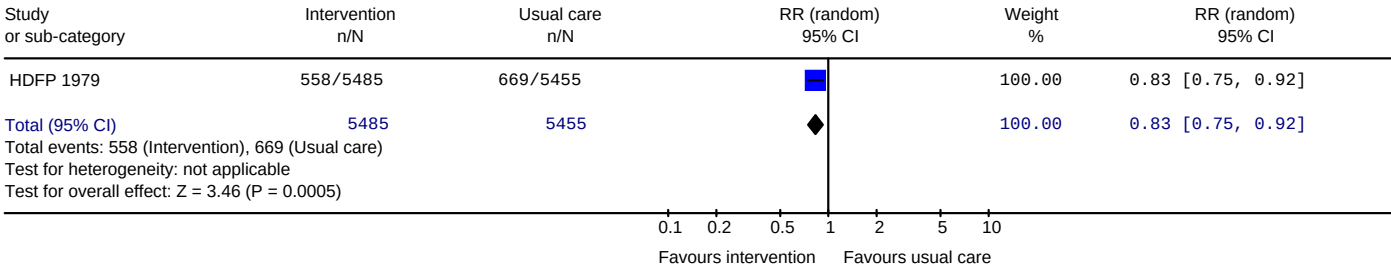


Sammensatte tiltak

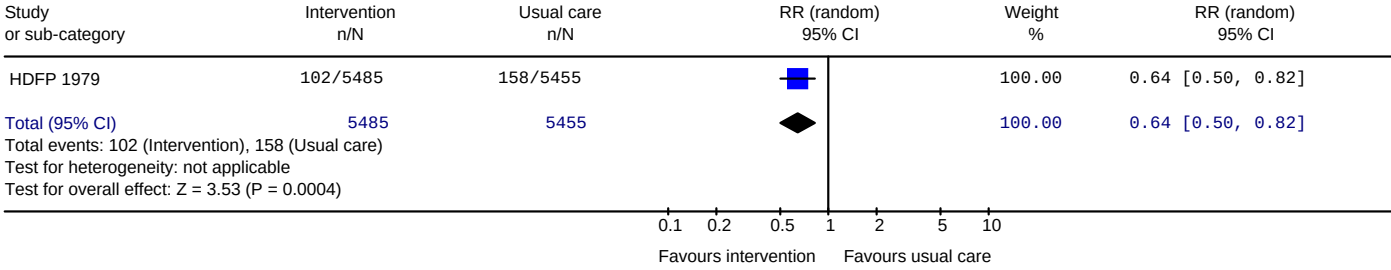
Review: Multifactorial interventions
Comparison: 01 HDFP
Outcome: 01 All cause mortality



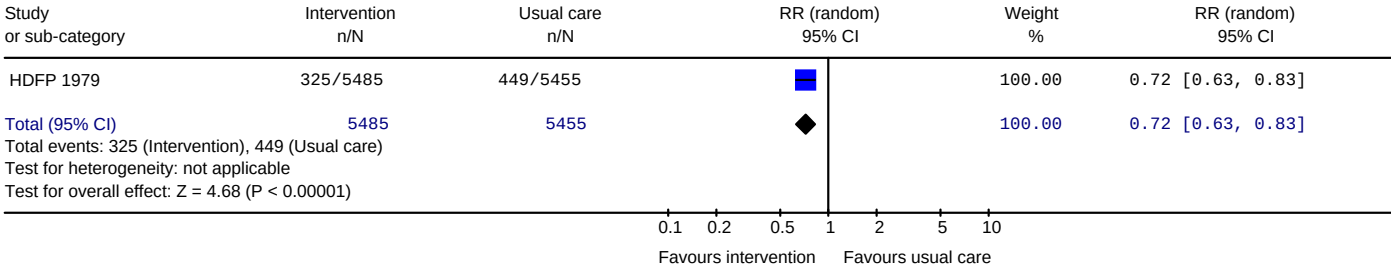
Review: Multifactorial interventions
Comparison: 01 HDFP
Outcome: 02 Myocardial infarction



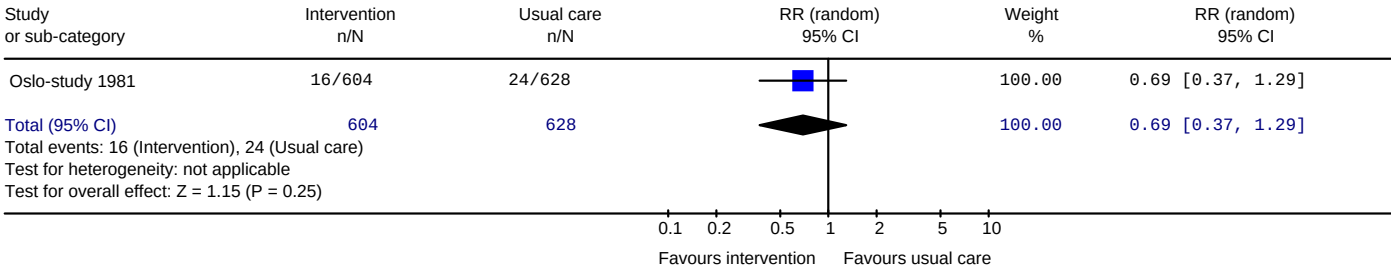
Review: Multifactorial interventions
Comparison: 01 HDFP
Outcome: 03 Stroke



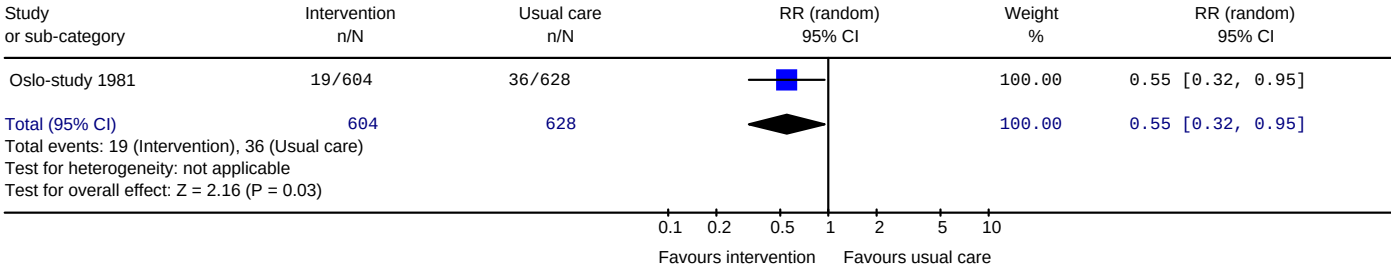
Review: Multifactorial interventions
Comparison: 01 HDFP
Outcome: 04 Angina



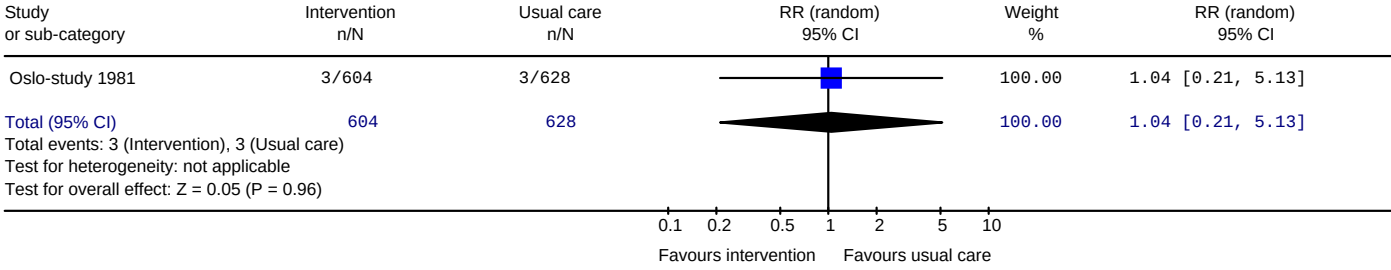
Review: Multifactorial interventions
Comparison: 02 Oslo study
Outcome: 01 All cause mortality



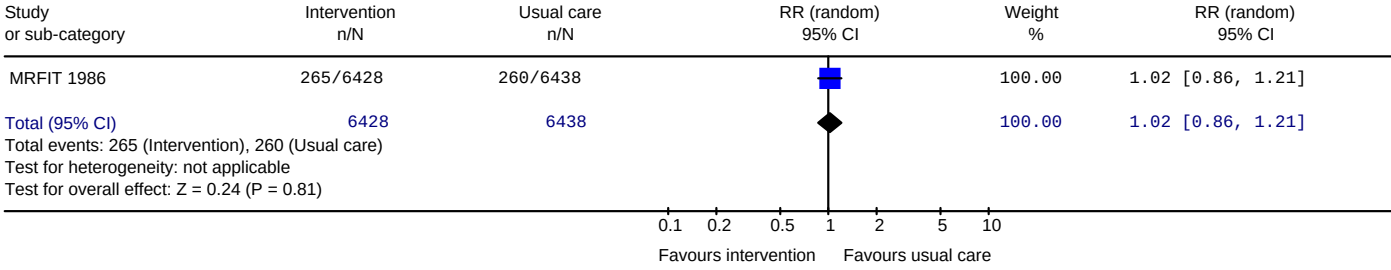
Review: Multifactorial interventions
Comparison: 02 Oslo study
Outcome: 02 Myocardial infarction



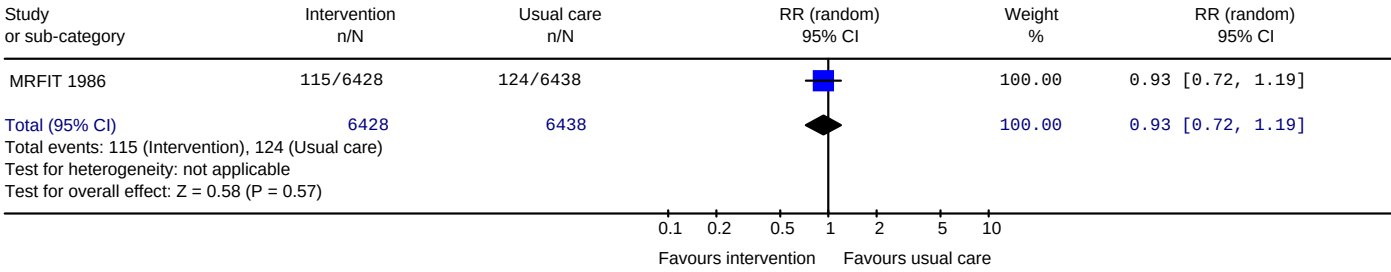
Review: Multifactorial interventions
Comparison: 02 Oslo study
Outcome: 03 Stroke



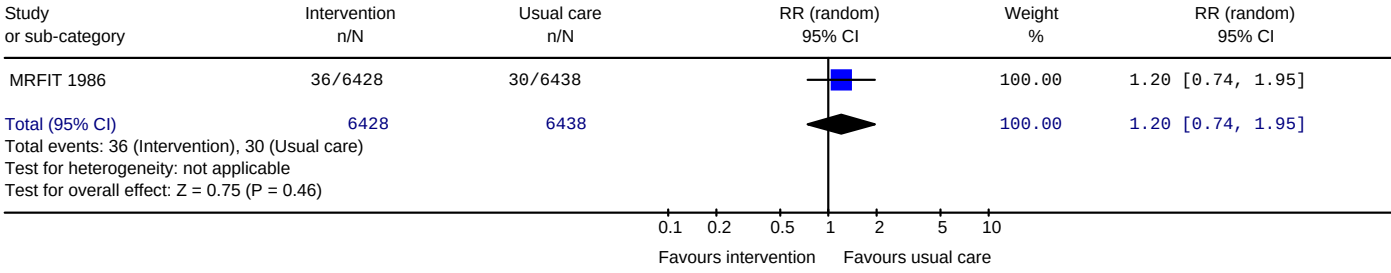
Review: Multifactorial interventions
Comparison: 03 MRFIT
Outcome: 01 All cause mortality



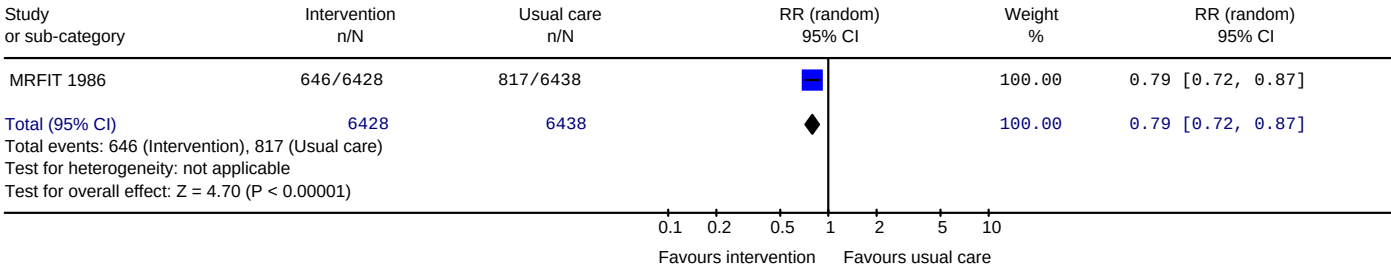
Review: Multifactorial interventions
Comparison: 03 MRFIT
Outcome: 02 Myocardial infarction



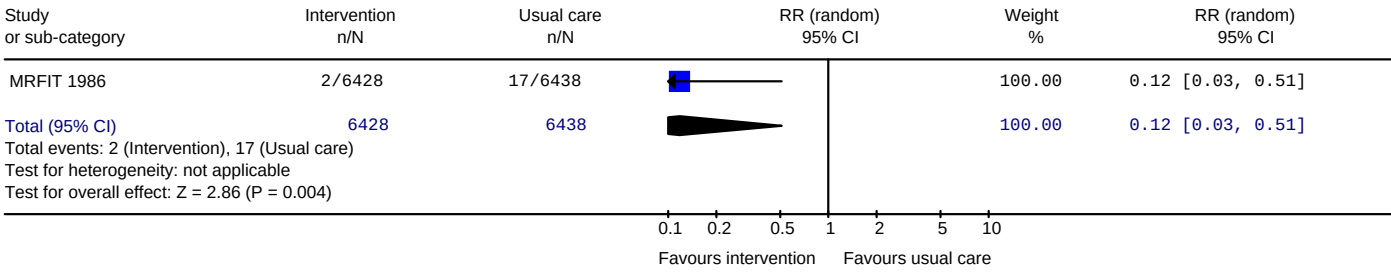
Review: Multifactorial interventions
Comparison: 03 MRFIT
Outcome: 03 Stroke



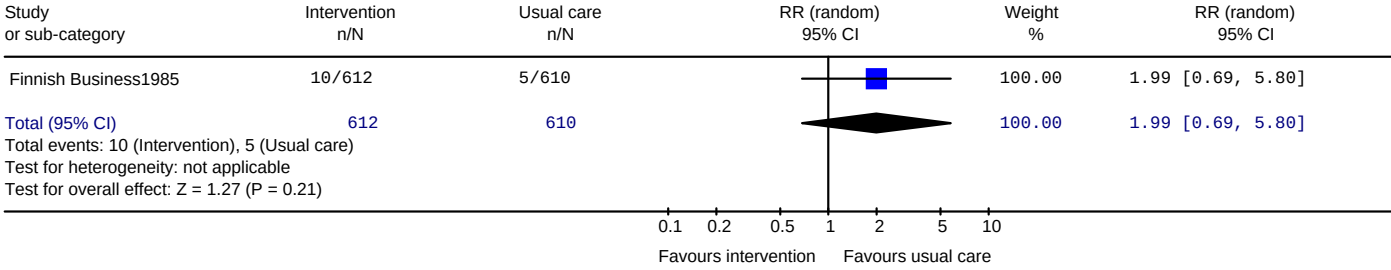
Review: Multifactorial interventions
Comparison: 03 MRFIT
Outcome: 04 Angina



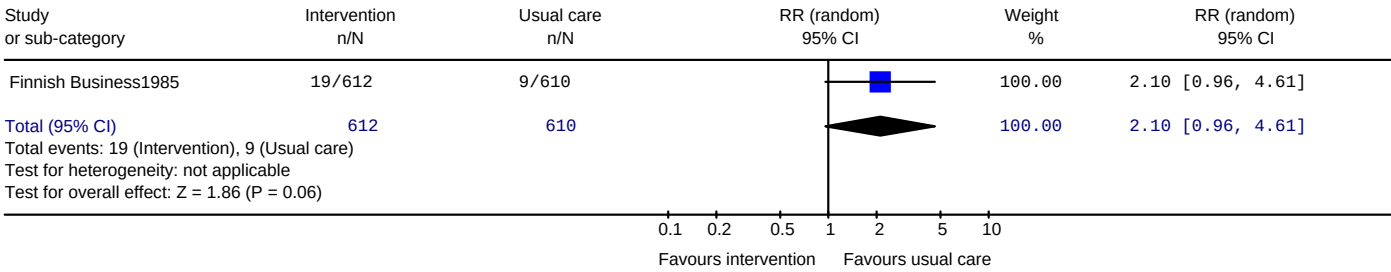
Review: Multifactorial interventions
Comparison: 03 MRFIT
Outcome: 05 Heart failure



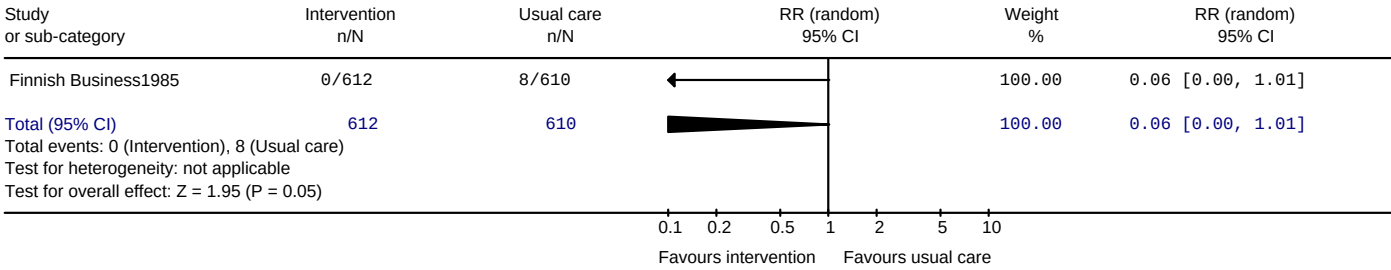
Review: Multifactorial interventions
Comparison: 04 Finnish Businessmen
Outcome: 01 All cause mortality



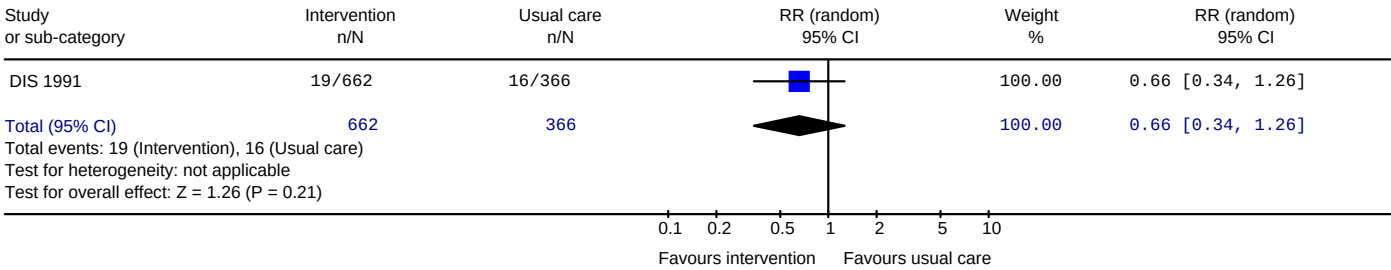
Review: Multifactorial interventions
Comparison: 04 Finnish Businessmen
Outcome: 02 Myocardial infarction



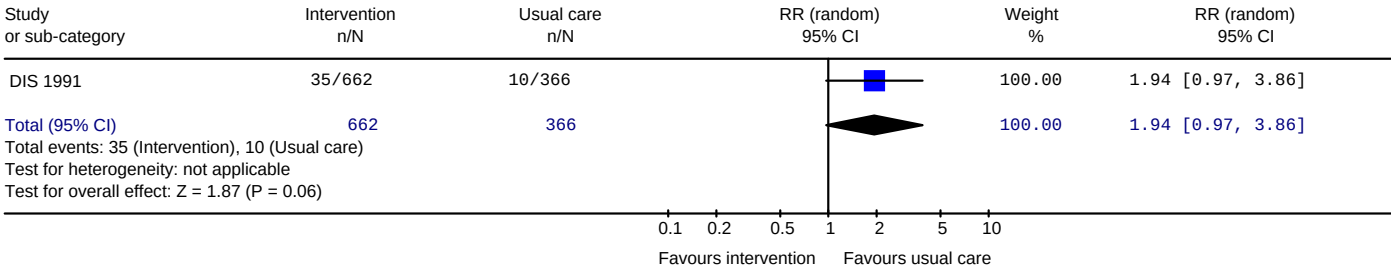
Review: Multifactorial interventions
Comparison: 04 Finnish Businessmen
Outcome: 03 Stroke



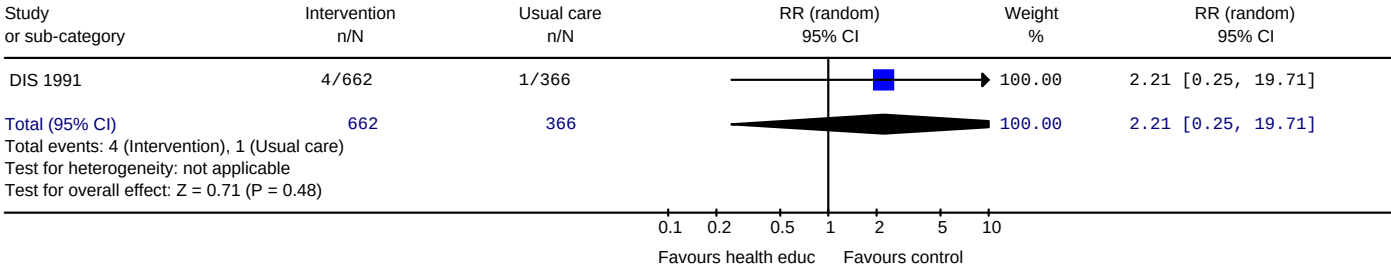
Review: Multifactorial interventions
Comparison: 05 Diabetes Intervention Study
Outcome: 01 All cause mortality



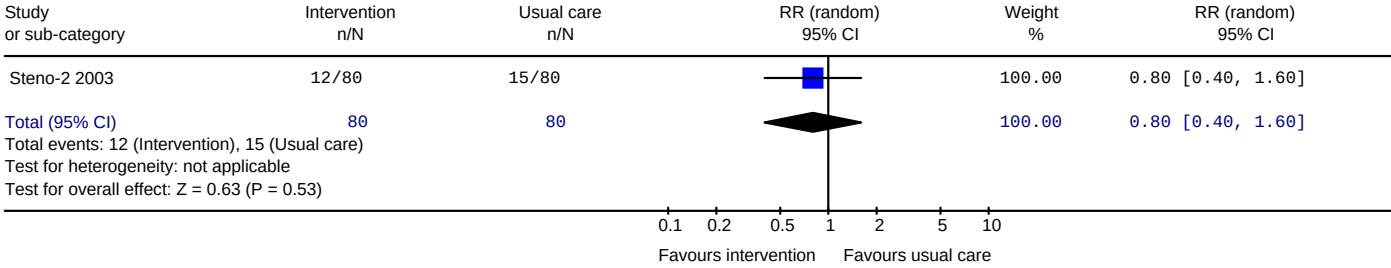
Review: Multifactorial interventions
Comparison: 05 Diabetes Intervention Study
Outcome: 02 Myocardial infarction



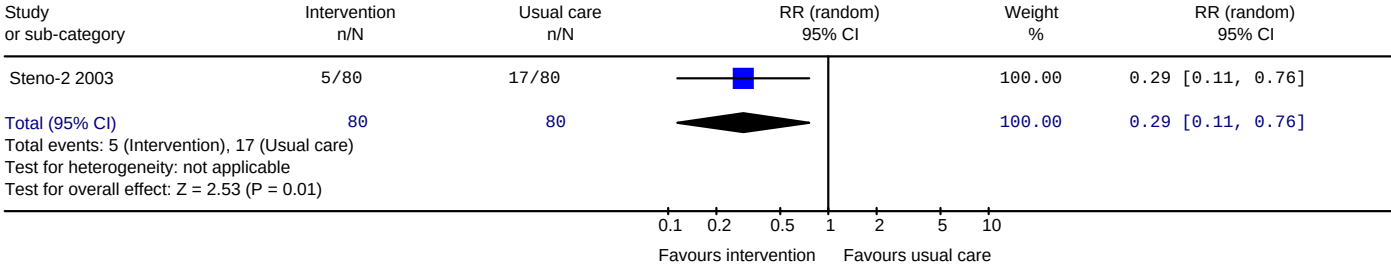
Review: Multifactorial interventions
Comparison: 05 Diabetes Intervention Study
Outcome: 03 Stroke



Review: Multifactorial interventions
Comparison: 06 Steno-2
Outcome: 01 All cause mortality



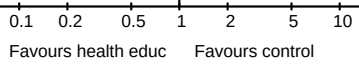
Review: Multifactorial interventions
Comparison: 06 Steno-2
Outcome: 02 Myocardial infarction



Review: Multifactorial interventions
Comparison: 06 Steno-2
Outcome: 03 Stroke

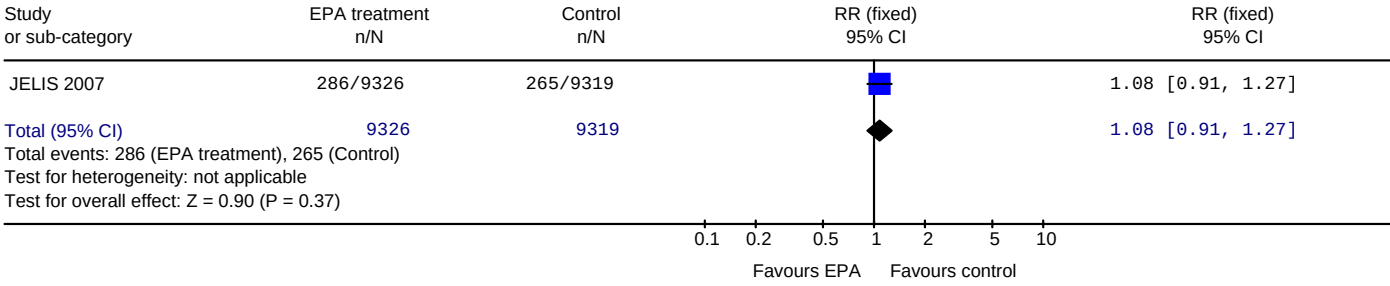
Study or sub-category	Intervention n/N	Usual care n/N	RR (random) 95% CI	Weight %	RR (random) 95% CI
Steno-2 2003	3/80	20/80		100.00	0.15 [0.05, 0.48]
Total (95% CI)	80	80		100.00	0.15 [0.05, 0.48]

Total events: 3 (Intervention), 20 (Usual care)
Test for heterogeneity: not applicable
Test for overall effect: Z = 3.17 (P = 0.002)

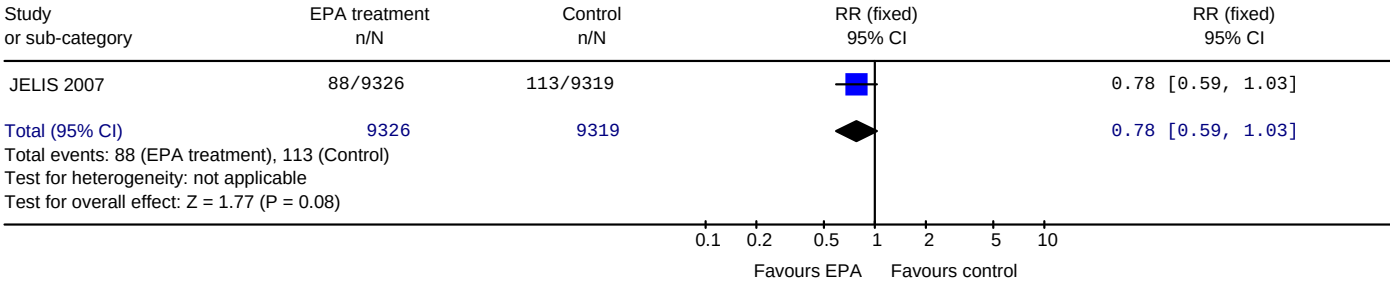


Kosttilskudd

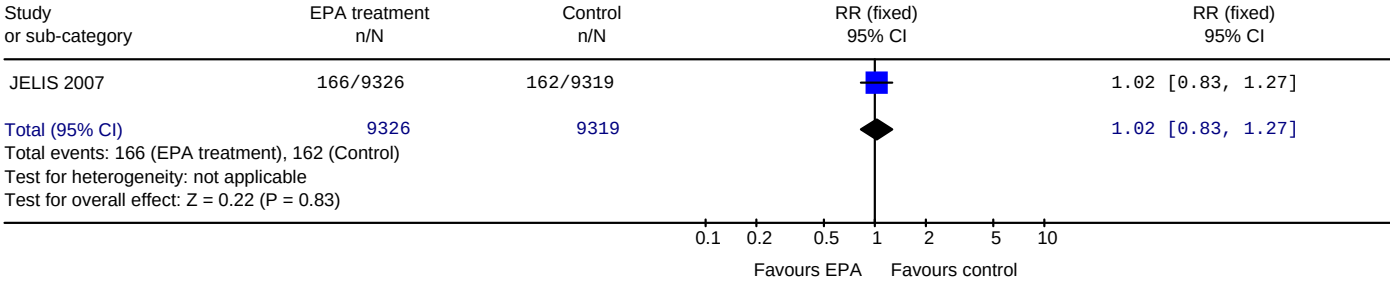
Review: Food supplements
Comparison: 01 JELIS-study
Outcome: 01 All cause mortality



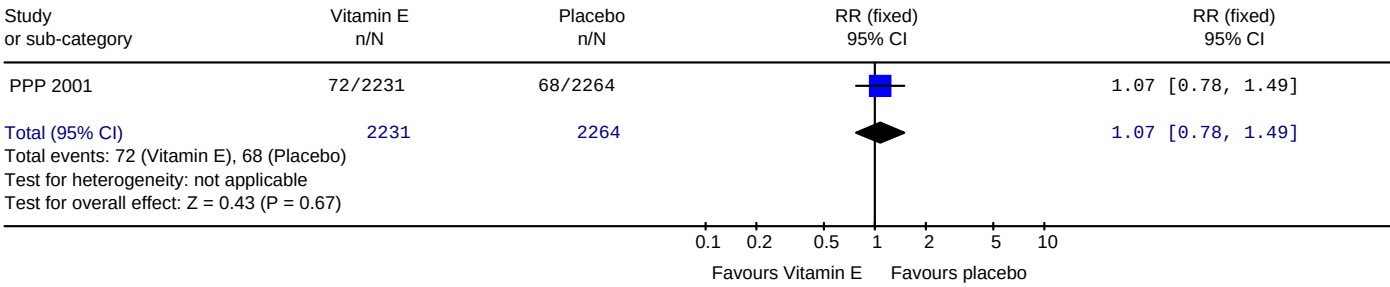
Review: Food supplements
Comparison: 01 JELIS-study
Outcome: 02 Myocardial infarction



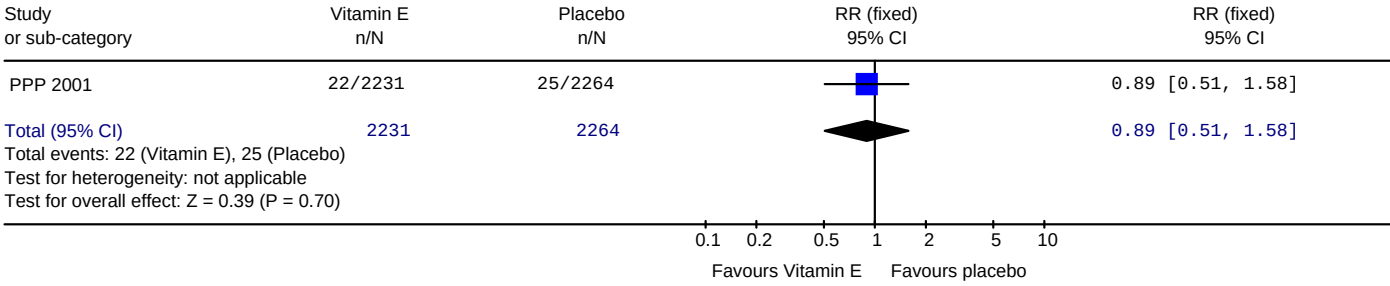
Review: Food supplements
Comparison: 01 JELIS-study
Outcome: 03 Stroke



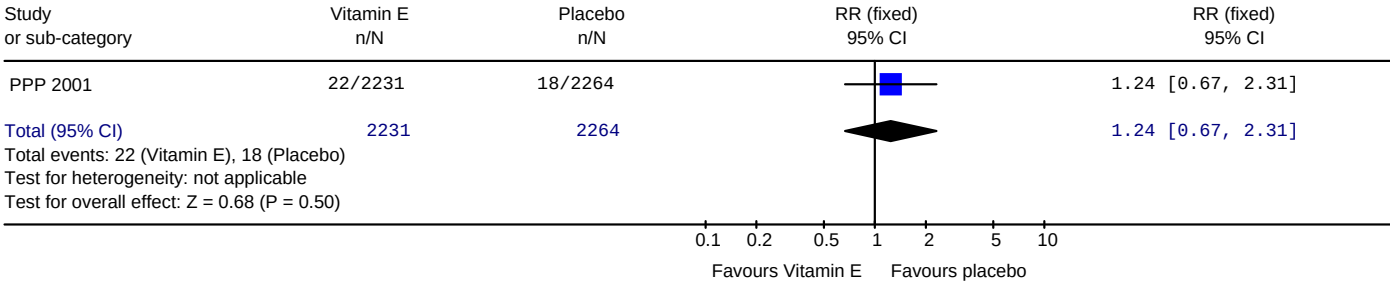
Review: Food supplements
Comparison: 02 Primary Prevention Project
Outcome: 01 All cause mortality



Review: Food supplements
Comparison: 02 Primary Prevention Project
Outcome: 02 Myocardial infarction



Review: Food supplements
Comparison: 02 Primary Prevention Project
Outcome: 03 Stroke



Vedlegg 7

PRIMÆRFOREBYGGING AV HJERTE- OG KARSYKDOM (KUNNSKAPSSENTERETS RAPPORT NR 20-2008)

OVERSIKT OVER DOSERING AV DIURETIKA I HYPERTENSJONSSTUDIER

STUDIENAVN	DIURETIKA OG DOSE	DOSENIVÅ
VA I 1967	50 mg klortal. (16 %) 100 mg (31 %) 100 mg + 0,25 mg res. (44 %)	Høydose
USPHS 1977	1000 mg klortiazid (+ 200 mg rauw.serp.)	Høydose
Oslo Study 1980	50 mg HCTZ	Høydose
EWPHE 1985	25 mg HCTZ+50 mg triamteren (51 %) 50 mg HCTZ+100 mg triamteren, eventuelt høyere (45 %)	Lavdose / Høydose (50:50)
ANBP I 1980	Klorotiazid 500 mg x 1 (økt til 500 mg x 2 eller "2nd order drug, i.e. metyldopa, propranolol eller pindolol)	Høydose
IPPPSH 1985	Uspesifisert diuretikum og dose med tillegg av kaliumsparende diuretikum som amilorid, spironolacton eller triamteren hos 42-43 % av pasientene i gruppene	Ikke klassifiserbar mht dosenivå. (67 % i oxprenolol- og 82 % i non-beta-blokkergruppen brukte diuretikum, og sammenlikningen sier derfor ingenting om diuretikaeffekter)
Coope 1986	5 mg Bendroflumetiazid (60 %)	Høydose
HAPPHY 1987	Bendroflumetiazid 5 mg eller HCTZ 50 mg	Høydose
MRC 1 1988	Bendroflumetiazid 10 mg	Høydose
STOP I 1991	HCTZ 25 mg + amiloride 2.5 mg eller atenolol 50 mg / metoprolol 100 mg / pindolol 5 mg	Lavdose
SHEP 1991	12,5 mg klortalidon (41 %) 25 mg klortalidon (28 %)	Høydose

	21 % annen aktiv beh. 9 % ingen medikamenter	
MRC 2 1992	HCTZ 25 mg + amilorid 2,5 mg, eller HCTZ 50 mg + amilorid 5 mg	Lavdose (alle satt på laveste dose i 1985)
Syst-Eur1997	12,5-25 mg HCTZ	Lavdose
CAPPP 1999	HCTZ 25 mg, bendroflumetiazid 2,5 mg (– men kunne titreres opp)	Lavdose? (an optimum dose was used)
INSIGHT 2000	HCTZ 25 mg + amillorid 2,5 mg, ev. dobling av dosen	Høydose (ordeling mellom dosenivåer ikke angitt)
ALLHAT 2000	Klortalidon 12,5 eller 25 mg	Høydose (etter 1 år tok 40 % 25 mg pr. dag, etter 2 år 53 %, etter 3 år 57 %)
NORDIL 2000	Ikke spesifisert dose; fordeling mellom diuretikar og slynge-diuretika i diltiazemgruppen var 222/369 pasienter og i diuretika og beta-blokkergruppen 726/458 pasienter (også andre diuretika-kombinasjoner ble brukt)	Ikke klarifiserbar i høy- eller lavdose
SHELL 2003	Klortalidon 12,5-25 mg	Høydose
ANBP 2 2003	HCTZ (blodtrykksfall i diuretikagruppen 24/10 mm Hg etter 2 år og 26/12 mm Hg etter 5 år)	Ukjent dose (choice of diuretic and dose free)
HYVET 2003	Bendroflumetiazid 2,5 mg eller 5 mg (51 %), klor talidon (34 %) og hydroklor tiacid (13 %)	Høydose (60 % høydose, 36 % lavdose - 28,8 % brukte 2,5 mg bendro fluemetiacid og 21 % brukte 5 mg, 0,3 % brukte over 5 mg). 8 % brukte hydroklortiazid i dose 12,5 eller 25 mg og 5,1 % i dose 50 mg eller mer). 29,3 % brukte klor talidon og 4,4 % i dose 50mg)
SCOPE 2003	HCTZ 12,5 mg	Lavdose – nokså likt i begge grupper; ikke studiemedikament
CONVINCE 2003	HCTZ 12,5 - 25 mg.	Lavdose
LIFE 2003	HCTZ 12,5 – 25 mg	Lavdose (>55 % i atenololgruppen og >58 % i losartangruppen brukte diuretika, og sammenlikningen sier derfor ingenting om diuretikaeffekter)
STOP II 2004	HCTZ 25 mg + amilorid 2,5 mg	Lavdose
ASCOT 2005	Bendroflumetiazid 1,25-2,5 mg	Lavdose