**Beta-blockers in hypertension. Overview and meta-analysis of randomized outcome trials**

Authors: Costas Thomopoulosa, George Bazoukisb, Costas Tsioufisc, Giuseppe Manciad

**Affiliations**

a, Department of Cardiology, Helena Venizelou Hospital, Athens, Greece.

b, Department of Cardiology, Evangelismos General Hospital of Athens, Athens, Greece.

c, First Cardiology Clinic, Medical School, National and Kapodistrian University of Athens, Hippokration Hospital, Greece.

d, University Milano-Bicocca, Milan, Policlinico di Monza, Monza, Italy

**Supplementary Table S1**. Searching strategy in PubMed and Cochrane Collaboration Library

|  |  |
| --- | --- |
| Pubmed | "hypertension"[All Fields] OR "blood pressure"[All Fields]) AND "antihypertensive agents"[All Fields]) OR "adrenergic beta antagonists"[All Fields]) OR "atenolol"[All Fields]) OR "metoprolol"[All Fields]) OR "pindolol"[All Fields]) OR "timolol"[All Fields]) OR "oxprenolol"[All Fields]) OR "nadolol"[All Fields]) OR "labetalol"[All Fields]) OR "celiprolol"[All Fields]) OR "bisoprolol"[All Fields]) OR "acebutolol"[All Fields]) OR "propranolol"[All Fields]) OR "xamoterol"[All Fields]) OR "bucindolol"[All Fields]) OR "carvedilol"[All Fields]) OR "nebivolol"[All Fields]) OR "alprenolol"[All Fields]) OR "carteolol"[All Fields]) OR "practolol"[All Fields]) OR "sotalol"[All Fields]) AND "randomized controlled trial"[Filter]) NOT "animal"[Filter] **N=17,625 records** |
| Cochrane Collaboration Library | #1 hypertension; #2 blood pressure; #3 antihypertensive agents; #4 #1 or #2, #5 #3 and #4; #6 adrenergic beta blockers; #7 atenolol; #8 metoprolol; #9 pindolol; #10 timolol; #11 oxprenolol; #12 nadolol; #13 labetalol; #14 celiprolol; #15 nebivolol; #16 bisoprolol; #17 acebutolol; #18 propranolol; #19 xamoterol; #20 bucindolol; #21 carvedilol; #22 alprenolol; #23 carteolol; #24 practolol; #25 sotalol; #26 {OR #5-#25} in Trials Limits; #27 animal; #28 #26 NOT #27 in Trials Limits **N= 23,740 records** |

**Supplementary Table S2**. Excluded studies and reason for exclusion

|  |  |
| --- | --- |
| **Reason of exclusion** | **Excluded studies, First author or trial acronym (year)REF** |
| 1. number of total outcomes less than 5 or no events | Palazzuoli (2005)E68, EVIDENCE (2017)E69, Hansson (2017)E70, Broch et al (2016)E71, Sumbria (2014)E72, Guha (2013)E73, Lin (2013)E74, DETECT (2013)E75, CARDHIAC (2008)E76, COSMOS (2010)E77, Boissel (1995)E78, van der Does (1999)E79, REASON (2009)E80, ELIZA trial (2013)E81, SILVHIA study (2011)E82, Kim (2013)E83, Galzerano (2012)E85, Ozaydin (2016)E66, Yusuf (1979)E19, Takeda (2004)E130, ELANDD (2012)E129, SWEDIC (2004)E67  **[N=22]** |
| 2. follow-up (on-treatment) of less than 6 months | ISIS-1 (1986)E42, Evemy (1978)E23, Heber (1987)E34, Roberts (1984)E38, Thompson (1979)E13, Tonkin (1981) E15, Bristow (1994)E131, CHHIPS (2009)E86, Mittal (2017)E87, EARLY-BAMI (2016)E88, POISE (2008)E89, Woodley (1991)E90, Olsen (1995)E91, METOCARD-CNIC (2013)E92, Roque (1987)E93, BEAT-AMI (2016)E132, EXPLOR (2014)E94, Giles (2013)E95, Lewin (2013)E96, Dietz (2008)E133, Nilsson (2007)E134, IMAGE (1996)E135, Pehrsson (2000)E136, TIBBS (1995)E137, NEHIS (2017)E138, Weber (2012)E139, Balcon (1996)E1, Clausen (1966)E2, Multicentre (1966)E3, Barber (1967)E4, Norris (1968)E5, Kahler (1968)E6, Ledwich (1968)E7, Snow (1966)E8, Fuccella (1969)E9, Briant (1970)E10, Pitt (1976)E11, Lombardo (1979)E12, Hutton (1979)E14, Gupta (1982)E16, Roland (1980)E20, Wilcox (1979)E17, CPRG (1981)E18, Hjalmarson (1981)E101, Sloman (1967)E21, Waagstein (1975)E22, Peter (1978)E24, Norris (1978)E25, Mueller (1980)E26, McLeod (1980)E27, Lloyd (1988)E28, Azancot (1982)E29, von Essen (1982)E30, Yusuf (1983)E32, Nigam (1983)E31, Federman (1984)E33, AAMI (1984)E36, MILIS (1984)E38, MIAMIE39, Owensby (1984)E40, COMMIT (2005)E46, EMIT (2002)E47, Gardtman (1999)E48, PREMIS (1988)E49, ICSG (1984)E50, TIARA (1987)E51, Rossi (1983)E52, Galcerá-Tomás (2001)E41, Curtis (1991)E53, McMurray (1991)E54, Ranganathan (1988)E55, TIMI IIb (1989)E37, Van de Werf (1993)E56, Yang (1987)E57, Pollock (1990)E58, Woodley (1991)E59, Paolisso (1992)E60, Wisenbaugh (1993)E63, Eichhorn (1994)E64, Metra (1994)E65, Olsen (1995)E61, Krum (1995)E62 **[N=82]** |
| 3. no randomization | Mazur E45, Carvedilol or Metoprolol Evaluation Study (2015)E100, Studinger (2013)E97, Golikov (1983)E43, Johansson (1980)E44, ADaPT (2008)E145 **[N=6]** |
| 4. comparison between two different beta-blockers | COMET (2003)E102, Boberg (1992)E103, GEMINI (2004)E104, Jonsson (2005)E105, Kukin (1999)E106, BETACAR (2006)E107, Metra (2000)E108, Toyoda (2017)E109, CREATIVE (2017)E110, Oh et al (2016)E111, Hung et al (2016)E112, CIBIS-ELD (2016)E113, Erdil (2014)E114, Karabacak et al (2015)E84, Redon (2014)E115, EFFORT (2013)E116, MAIN-CHF II trial (2014)E99, CARNEBI (2013)E98, Park (2013)E117, Marrazzi (2011)E140 **[N=20]** |
| 5. cross-over studies | PATHWAY-2 (2015)E118, Findlay (1987)E119, Hopkinson (1991)E120  **[N=3]** |
| 6. same drug at two different periods or posology | Jiang (2017)E121, AF Carvedilol study (2017)E122, IMPACT-HF (2004)E123, J-CHF (2013)124 **[N=4]** |
| 7. unusual comparison or mixed drug comparison including a beta-blocker or overlapping population | MEMO (1999)E125, STOP (1991)E141, CAPPP (1999)E142, NORDIL (2000)E143, STOP-2 (1999)E144, MAPPHY (1998)E146 **[N=6]** |
| 8. Age <18 years | Forteza (2016)E126, Sandor (2015)E127, Lacro (2014)E128 **[N=3]** |

References of all excluded studies **(N=146)** are reported in the present supplemental material as Supplementary References.

**Supplementary Table S3.** Selected (included) trials of beta-blockers compared with placebo, no treatment or less intense treatment

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial, publication year** | **Clinical setting, randomization time** | **Hypertension prevalence, %** |  | **Drugs compared** | |  | **Patient number** | **Follow-up, years** |  | **Baseline BP, mmHg** | |  | **Achieved SBP,**  **mmHg** | |  | **Achieved DBP, mmHg** | |
|  | **Active** | **Control** |  |  | **SBP** | **DBP** |  | **Active** | **Control** |  | **Active** | **Control** |
| Ahlmark et al [34], 1974 | AMI (at 15 days after) | NR |  | Alprenolol | Untreated |  | 162 | 2 |  | NR | NR |  | NR | NR |  | NR | NR |
| Andersen et al [35],1979 | AMI  (at admission) | NR |  | Alprenolol | Placebo |  | 470 | 1 |  | NR | NR |  | NR | NR |  | NR | NR |
| Anderson et al [36], 1985 | HF | NR |  | Metoprolol | Untreated |  | 50 | 1.6 |  | 118 | 74 |  | NR | NR |  | NR | NR |
| ANZHF [37], 1997 | HF | NR |  | Carvedilol | Placebo |  | 415 | 1.6 |  | NR | NR |  | NR | NR |  | NR | NR |
| APSI [38], 1990 | AMI (3-31 days) | 33 |  | Acebutolol | Placebo |  | 607 | 1 |  | NR | NR |  | NR | NR |  | NR | NR |
| Aronow et al [39], 1997 | HF | 52 |  | Propranolol | Untreated |  | 158 | 2.7 |  | NR | NR |  | NR | NR |  | NR | NR |
| ASIST [40], 1994 | CHD | 30 |  | Atenolol | Placebo |  | 306 | 0.9 |  | 137.5 | 80 |  | NR | NR |  | NR | NR |
| ASPSG [41],1983 | AMI (1-21 days) | 70 |  | Pindolol | Placebo |  | 529 | 2 |  | 120.8 | 76.4 |  | NR | NR |  | NR | NR |
| Baber et al [42],1980 | AMI (2-14 days) | 14 |  | Propranolol | Placebo |  | 720 | 0.5 |  | 143.5 | 91.4 |  | NR | NR |  | NR | NR |
| Barber et al [43], 1976 | AMI  (at admission) | NR |  | Practolol | Placebo |  | 484 | 2 |  | 118 | NR |  | NR | NR |  | NR | NR |
| Basu et al [44], 1997 | AMI  (at first day) | NR |  | Carvedilol | Placebo |  | 146 | 0.5 |  | NR | NR |  | NR | NR |  | NR | NR |
| BCAPS [45], 2001 | Subclinical atherosclerosis | 22 |  | Metoprolol | Placebo |  | 398 | 3 |  | 138.5 | 85 |  | 137.5 | 141.6 |  | NR | NR |
| BEAT [46], 2002 | AMI  (in-hospital) and LVD | NR |  | Bucindolol | Placebo |  | 343 | 0.5 |  | 121 | 72.5 |  | 123 | 128 |  | 73 | 75 |
| BEST [47], 2004 | HF | 59 |  | Bucindolol | Placebo |  | 2708 | 2 |  | 117 | 71 |  | NR | NR |  | NR | NR |
| BHAT [48], 1982 | AMI (5-21 days) | 40.2 |  | Propranolol | Placebo |  | 3837 | 2.1 |  | 112 | 72.4 |  | 127 | 130 |  | 80 | 81 |
| Bristow et al [49], 1996 | HF | NR |  | Carvedilol | Placebo |  | 345 | 0.5 |  | 115 | 71 |  | 116 | 116 |  | 70.5 | 71 |
| CAPITAL-RCT [50], 2018 | AMI  (2 to 8 days) | 60 |  | Carvedilol | Untreated |  | 794 | 3.9 |  | 121 | 70.5 |  | NR | NR |  | NR | NR |
| Capricorn [51], 2001 | AMI (3-21 days) and LVD | 54 |  | Carvedilol | Placebo |  | 1959 | 1.3 |  | 121.2 | 73.1 |  | NR | NR |  | NR | NR |
| CARMEN [52], 2004 | HF | 33 |  | Carvedilol and enalapril | Enalapril |  | 381 | 1.5 |  | 131 | 80 |  | 131 | 132 |  | 77.8 | 80 |
| CELICARD [53], 2000 | HF | 57 |  | Celiprolol | Placebo |  | 124 | 1 |  | 128 | 78 |  | NR | NR |  | NR | NR |
| CHRISTMAS [54], 2003 | HF | NR |  | Carvedilol | Placebo |  | 387 | 0.5 |  | 127 | 77 |  | 116 | 125 |  | 71 | 78 |
| CIBIS II [55], 1999 | HF | NR |  | Bisoprolol | Placebo |  | 2647 | 1.3 |  | 129.6 | 79.7 |  | NR | NR |  | NR | NR |
| CIBIS [56], 1994 | HF | NR |  | Bisoprolol | Placebo |  | 641 | 1.9 |  | 126.5 | 78.5 |  | NR | NR |  | NR | NR |
| Cice et al [57], 2003 | HF, Dialysis | NR |  | Carvedilol | Placebo |  | 114 | 2 |  | 134.5 | 75 |  | 123 | 134 |  | 68 | 74 |
| Cohn et al [58], 1997 | HF | NR |  | Carvedilol | Placebo |  | 105 | 0.5 |  | 116 | 72.5 |  | 110.6 | 118.5 |  | 68.7 | 72.7 |
| Colucci et al [59],1996 | HF | NR |  | Carvedilol | Placebo |  | 366 | 0.6 |  | NR | NR |  | NR | NR |  | NR | NR |
| COPERNICUS [60], 2001 | HF | NR |  | Carvedilol | Placebo |  | 2289 | 0.9 |  | 123 | 76 |  | 120.6 | 121 |  | 73.3 | 74.2 |
| Darasz et al [61], 1995 | AMI  (up to 12 days) | NR |  | Xamoterol | Placebo |  | 47 | 0.5 |  | 124 | 76.5 |  | NR | NR |  | NR | NR |
| De Milliano [62], 2002 | HF | 65 |  | Metoprolol | Placebo |  | 54 | 0.5 |  | 131 | NR |  | 128 | 135 |  | NR | NR |
| Dutch-TIA [63], 1993 | Post-stroke | 65 |  | Atenolol | Placebo |  | 1473 | 2.6 |  | 157.5 | 91 |  | 147.5 | 152.8 |  | 85 | 87.9 |
| EIS [64], 1984 | AMI  (14-36 days) | 25 |  | Oxprenolol | Placebo |  | 1741 | 1 |  | 127.6 | 81.2 |  | NR | NR |  | NR | NR |
| ENECA [65], 2005 | HF | 57.3 |  | Nebivolol | Placebo |  | 240 | 0.7 |  | 135.5 | 80.5 |  | 136 | 136 |  | 80.5 | 80.5 |
| Engelmeier et al [66],1985 | HF | NR |  | Metoprolol | Placebo |  | 25 | 1 |  | 120.5 | 92 |  | NR | NR |  | NR | NR |
| Fisher et al [67], 1994 | HF | NR |  | Metoprolol | Placebo |  | 50 | 0.5 |  | 117 | 73.5 |  | NR | NR |  | NR | NR |
| Hansteen et al [68], 1982 | AMI (4-6 days) | 56 |  | Propranolol | Placebo |  | 560 | 1 |  | NR | NR |  | NR | NR |  | NR | NR |
| HEP [69], 1986 | Hypertension | 100 |  | Atenolol | Untreated |  | 884 | 4.4 |  | 196 | 98 |  | 162.1 | 180.1 |  | 77 | 88 |
| Hori et al [70], 2004 | HF | 24 |  | Carvedilol | Placebo |  | 173 | 0.8 |  | 118.5 | 72.3 |  | NR | NR |  | NR | NR |
| ISDPG [71], 1992 | AMI  (20-40 days) | NR |  | Oxprenolol | Placebo |  | 973 | 1.8 |  | NR | NR |  | NR | NR |  | NR | NR |
| J-DHF [72], 2013 | HF | 81 |  | Carvedilol | Untreated |  | 245 | 3.2 |  | 133.5 | 74.5 |  | NR | NR |  | NR | NR |
| Julian et al [73], 1982 | AMI (5-14 days) | 12 |  | Sotalol | Placebo |  | 1456 | 1 |  | 122.8 | NR |  | NR | NR |  | NR | NR |
| Kaul et al [74], 1988 | AMI (at admission) | 16 |  | Propranolol | Placebo |  | 50 | 0.5 |  | 140.9 | 87.5 |  | NR | NR |  | NR | NR |
| LIT [75], 1987 | AMI (6-16 days) | 36 |  | Metoprolol | Placebo |  | 2395 | 1 |  | 116 | 73 |  | NR | NR |  | NR | NR |
| MACB [76], 1995 | CHD | 31 |  | Metoprolol | Placebo |  | 967 | 2 |  | 120 | 70 |  | NR | NR |  | NR | NR |
| Manger Cats et al [77], 1985 | AMI  (21-42 days) | NR |  | Metoprolol | Placebo |  | 583 | 1 |  | NR | NR |  | NR | NR |  | NR | NR |
| MERIT-HF [78],2000 | HF | 44 |  | Metoprolol | Placebo |  | 3991 | 1 |  | 130 | 78.3 |  | NR | NR |  | NR | NR |
| MRC-mild [15], 1985 | Hypertension | 100 |  | Propranolol | Placebo |  | 13057 | 5 |  | 161 | 98 |  | 139.7 | 149.5 |  | 86.5 | 93 |
| MRC-old [79], 1992 | Hypertension | 100 |  | Atenolol | Placebo |  | 3315 | 5.8 |  | 185 | 91 |  | 154.5 | 167 |  | 77 | 86.5 |
| Multicentre Int [80],1975 | AMI (7-28 days) | NR |  | Practolol | Placebo |  | 3038 | 1.2 |  | 123.1 | 78 |  | 132 | 136 |  | 82 | 85 |
| Norwegian MSG [81], 1981 | AMI (7-28 days) | 20 |  | Timolol | Placebo |  | 1884 | 1.4 |  | NR | NR |  | NR | NR |  | NR | NR |
| Olsson et al [82], 1985 | AMI (7-14 days) | 25 |  | Metoprolol | Placebo |  | 301 | 3 |  | NR | NR |  | NR | NR |  | NR | NR |
| Packer et al [83], 1996 | HF | NR |  | Carvedilol | Placebo |  | 1094 | 0.5 |  | 115.5 | 72.5 |  | NR | NR |  | NR | NR |
| PRECISE [84], 1996 | HF | NR |  | Carvedilol | Placebo |  | 278 | 0.5 |  | 117 | 73 |  | 111.2 | 116.3 |  | 67.3 | 73.7 |
| Rehnqvist et al [85], 1980 | AMI  (at discharge) | NR |  | Metoprolol | Placebo |  | 111 | 1 |  | NR | NR |  | NR | NR |  | NR | NR |
| RESOLVD [86], 2000 | HF | 36 |  | Metoprolol | Placebo |  | 426 | 0.5 |  | NR | NR |  | NR | NR |  | NR | NR |
| Reynolds et al [87], 1972 | AMI  (at admission) | NR |  | Alprenonol | Placebo |  | 77 | 1 |  | 137.3 | NR |  | 133.8 | 136.8 |  | NR | NR |
| RIMA [88], 1999 | AMI  (at admission) | 38 |  | Metoprolol and captopril | Captopril |  | 166 | 0.5 |  | 119 | 73.5 |  | 122 | 123.5 |  | 77.5 | 80 |
| Salathia et al [89], 1985 | AMI  (at admission) | 47 |  | Metoprolol | Placebo |  | 400 | 0.8 |  | NR | NR |  | NR | NR |  | NR | NR |
| SENIORS [90], 2005 | HF | 62 |  | Nebivolol | Placebo |  | 2128 | 0.9 |  | 139 | 80.5 |  | 132.3 | 135.2 |  | 68.8 | 77.4 |
| SSSD [91], 1993 | AMI  (10-60 days) | 34 |  | Metoprolol | Untreated |  | 253 | 2.8 |  | 137.5 | NR |  | NR | NR |  | NR | NR |
| Sturm et al [92], 2000 | HF | 18 |  | Atenolol | Placebo |  | 100 | 1.1 |  | 116.5 | 78 |  | NR | NR |  | NR | NR |
| Taylor et al [93], 1982 | CHD | 0 |  | Oxprenolol | Placebo |  | 1103 | 4 |  | 134.5 | 83 |  | 127 | 132 |  | 77 | 82 |
| TEST [94], 1995 | Hypertension  Post-stroke | 100 |  | Atenolol | Placebo |  | 720 | 2.3 |  | 163 | 90 |  | 157 | 161 |  | 85 | 89 |
| TIBET [95], 1996 | CHD | 50 |  | Atenolol and nifedipine | Nifedipine |  | 456 | 2 |  | NR | NR |  | NR | NR |  | NR | NR |
| UKPDS [96], 1998 | Hypertension | 100 |  | Atenolol | Less active |  | 748 | 8.4 |  | 160 | 94 |  | 143 | 154 |  | 81 | 87 |
| Waagstein et al [97], 1993 | HF | NR |  | Metoprolol | Placebo |  | 383 | 1 |  | 118 | NR |  | 130 | 121 |  | NR | NR |
| Wilcox et al [98], 1980 | AMI  (at admission) | 12 |  | Propranolol or atenolol | Placebo |  | 388 | 1 |  | 146.8 | 91.5 |  | 125.5 | 136 |  | 77 | 86 |
| Wilhelmsson et al [99], 1974 | AMI  (at discharge) | NR |  | Alprenolol | Placebo |  | 230 | 2 |  | NR | NR |  | NR | NR |  | NR | NR |

AMI, acute myocardial infarction; LVD, left ventricular dysfunction; CHD, coronary heart disease; HF, heart failure; NR, not reported, SBP, systolic blood pressure; DBP, diastolic blood pressure. TIBET reports only the attained systolic/diastolic BP difference (-8.1/-4.3 mmHg, respectively).

**Supplementary Table S4.** Selected (included) trials of beta-blockers compared with other active drugs (comparison trials)

|  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
| **Trial** | **Clinical setting** | **Hypertension prevalence, %** |  | **Drugs compared** | | **Patient number** | **Follow-up, years** |  | **Baseline BP, mmHg** | |  | **Achieved SBP, mmHg** | |  | **Achieved DBP, mmHg** | |
|  | **Active** | **Control** |  | **SBP** | **DBP** |  | **Active** | **Control** |  | **Active** | **Control** |
| AASK [100], 2002 | Hypertension | 100 |  | Metoprolol  Metoprolol | Amlodipine  Ramipril | 1094 | 3  4 |  | 150  150.5 | 95.3  95.5 |  | 135  135 | 133  135 |  | 81  81 | 81  82 |
| APSIS [101], 1996 | CHD | 27 |  | Metoprolol | Verapamil | 809 | 3.4 |  | NR | NR |  | NR | NR |  | NR | NR |
| ASCOT [6], 2005 | Hypertension | 100 |  | Atenolol | Amlodipine | 19257 | 5.5 |  | 164 | 94.7 |  | 138.9 | 136.3 |  | 79.1 | 77.8 |
| Berglund et al [102], 1986 | Hypertension | 100 |  | Propranolol | Bendroflumethiazide | 106 | 10 |  | NR | NR |  | NR | NR |  | NR | NR |
| CARMEN [52], 1999 | HF | 33 |  | Carvedilol | Enalapril | 381 | 1.5 |  | 130.5 | 80 |  | 129 | 132 |  | 80 | 80 |
| CIBIS III [103], 2005 | HF | 66 |  | Bisoprolol | Enalapril | 1010 | 0.5 |  | 134 | 80.5 |  | 128.5 | 128.2 |  | 76.4 | 77 |
| CONVINCE [104], 2003 | Hypertension | 100 |  | Atenolol | Hydrochlorothiazide  or verapamil-COER | 16476 | 3 |  | 150.1 | 86.8 |  | 136.6 | 136.5 |  | 79.7 | 79 |
| COPE [105], 2011 | Hypertension | 100 |  | Any BB  Any BB | Any ARB  Any TZ | 3293 | 3.6  3.6 |  | 153.8  153.9 | 88.7  88.7 |  | 133.9  133.9 | 134.7  134 |  | 77  77 | 77.2  76.6 |
| Darasz et al [61], 1995 | AMI | NR |  | Xamoterol | Captopril | 46 | 0.5 |  | 126 | 77 |  | NR | NR |  | NR | NR |
| ELSA [106], 2002 | Hypertension | 100 |  | Atenolol | Lacidipine | 2334 | 3.8 |  | 163.5 | 101.4 |  | 141.5 | 142.1 |  | 85.7 | 85.9 |
| HAPPHY [14], 1987 | Hypertension | 100 |  | Atenolol  or  metoprolol | Bendroflumethiazide or hydrochlorothiazide | 6569 | 3.8 |  | 166 | 107 |  | 140 | 140.5 |  | 89 | 90 |
| HDPAL [107], 2014 | Hypertension,  dialysis | 100 |  | Atenolol | Lisinopril | 200 | 1 |  | 155.5 | 87.1 |  | 140.2 | 147 |  | 82.5 | 79.8 |
| INVEST [16], 2003 | Hypertension | 100 |  | Atenolol | Verapamil SR | 22576 | 2.7 |  | 149.5 | 86.3 |  | 130.5 | 130.8 |  | 76.1 | 76.3 |
| IPPPSH [13], 1985 | Hypertension | 100 |  | Oxprenolol | Any TZ | 6357 | 4 |  | 173 | 107.8 |  | 143.6 | 147.4 |  | 88.9 | 90.1 |
| JBCMI [108], 2004 | AMI | 52 |  | Any BB | Any CCB | 1090 | 1.3 |  | NR | NR |  | NR | NR |  | NR | NR |
| LIFE [7], 2002 | Hypertension | 100 |  | Atenolol | Losartan | 9193 | 4.8 |  | 174.4 | 97.8 |  | 145.4 | 144.1 |  | 80.9 | 81.3 |
| MRC-mild [15], 1985 | Hypertension | 100 |  | Propranolol | Bendroflumethiazide | 8700 | 5 |  | 161.4 | 98.5 |  | 138.9 | 135.2 |  | 86.5 | 85.3 |
| MRC-old [79],1992 | Hypertension | 100 |  | Atenolol | Hydrochlorothiazide and  amiloride | 2183 | 5.8 |  | 184.8 | 90.9 |  | 155.3 | 152 |  | 79 | 79 |
| Nakagomi et al [109], 2011 | AMI | 76 |  | Atenolol | Benidipine | 120 | 3.1 |  | 130.5 | 74.5 |  | 132.7 | 128 |  | 76.2 | 75.1 |
| RIMA [88], 1999 | AMI | 42 |  | Metoprolol | Captopril | 168 | 0.5 |  | 119 | 74 |  | 123.3 | 127.6 |  | 77 | 77.3 |
| TIBET [95], 1996 | CHD | 53 |  | Atenolol | Nifedipine | 458 | 2 |  | NR | NR |  | NR | NR |  | NR | NR |
| UKPDS [17], 1998 | Hypertension | 100 |  | Atenolol | Captopril | 758 | 8.4 |  | 159 | 93.5 |  | 143 | 144 |  | 81 | 83 |
| USSR [110],1992 | Hypertension | 100 |  | Propranolol | Diuretics | 304 | 4.1 |  | 168.5 | 105.9 |  | 152.4 | 152.7 |  | 98.8 | 98.7 |
| VA-COOP [111],1982 | Hypertension | 100 |  | Propranolol | Hydrochlorothiazide | 302 | 1 |  | 145.8 | 101.6 |  | 133.1 | 129.2 |  | 90.2 | 88.5 |

For abbreviations refer to footnote of Supplementary Table S3. Berglund et al and TIBET provide the attained systolic/diastolic blood pressure difference among arms (not reported/1 mmHg and 0.4/0.6 mmHg, respectively); in CONVINCE the entire trial BP values are reported; in HDPAL the BP values are from home measurements.

**Supplementary Table S5**. Risk of bias of the included trials and categorization of trials in larger or smaller than 2,000 patient-years.

|  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- |
| Study | Outcome | R | D | Mi | Me | S | O | Studies with at least 2,000 patient-years |
| MRC-mild | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| HEP | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Dutch-TIA | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| MRC-old | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Taylor | CHD |  |  |  |  |  |  | yes |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| TEST | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| TIBET | CHD |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| UKPDS | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| BCAPS | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Multicentre Int. | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Norwegian MSG | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| BHAT | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| EIS | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Capricorn | CHD |  |  |  |  |  |  | yes |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| ISDPG | CHD |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Hansteen | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Olsson | CHD |  |  |  |  |  |  | no |
| stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| ASPSG | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Julian | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Wilhelmsson | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Baber | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Barber | CHD |  |  |  |  |  |  | no |
| All-cause death |  |  |  |  |  |  |
| Manger Cats | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Andersen | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| LIT | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Ahlmark | CHD |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Salathia | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| BEAT | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| All-cause Death |  |  |  |  |  |  |
| APSI | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Basu | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| SSSD | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Reynolds | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Kaul | CHD |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| MACB | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| ASIST | CHD |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Wilcox | All-cause death |  |  |  |  |  |  | no |
| Rehnqvist | CHD |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| MERIT-HF | CHD |  |  |  |  |  |  | yes |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| BEST | CHD |  |  |  |  |  |  | yes |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| CIBIS II | CHD |  |  |  |  |  |  | yes |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| SENIORS | HF |  |  |  |  |  |  | yes |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| COPERNICUS | CHD |  |  |  |  |  |  | yes |
| HF |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| ANZHF | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Aronow | CHD |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Bristow | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Packer | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Colucci | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Cohn | HF |  |  |  |  |  |  | no |
| All-cause death |  |  |  |  |  |  |
| CIBIS | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Sturm | HF |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| CHRISTMAS | HF |  |  |  |  |  |  | no |
| All-cause death |  |  |  |  |  |  |
| Hori | HF |  |  |  |  |  |  | no |
| All-cause death |  |  |  |  |  |  |
| Cice | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Waagstein | Stroke |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| RESOLVD | HF |  |  |  |  |  |  | no |
| All-cause death |  |  |  |  |  |  |
| ENECA | HF |  |  |  |  |  |  | no |
| All-cause death |  |  |  |  |  |  |
| Darasz | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| CARMEN | HF |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| PRECISE | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Anderson | HF |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Engelmeier | HF |  |  |  |  |  |  | no |
| All-cause death |  |  |  |  |  |  |
| Fisher | HF |  |  |  |  |  |  | no |
| All-cause death |  |  |  |  |  |  |
| J-DHF | HF |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| RIMA | CHD |  |  |  |  |  |  | no |
| All-cause death |  |  |  |  |  |  |
| CAPITAL-RCT | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| CELICARD | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| De Milliano | CV Death |  |  |  |  |  |  | no |
| All-cause death |  |  |  |  |  |  |
| AASK | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| ASCOT | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Berglund | All-cause death |  |  |  |  |  |  | no |
| CONVINCE | Double |  |  |  |  |  |  | yes |
| COPE | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| ELSA | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| HAPPHY | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| INVEST | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| IPPPSH | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| LIFE | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| USSR | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| VA-COOP | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| JBCMI | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| Nakagomi | CHD |  |  |  |  |  |  | no |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| CIBIS III | HF |  |  |  |  |  |  | no |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| APSIS | CHD |  |  |  |  |  |  | yes |
| Stroke |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |
| HDPAL | CHD |  |  |  |  |  |  | no |
| Stroke |  |  |  |  |  |  |
| HF |  |  |  |  |  |  |
| Double |  |  |  |  |  |  |
| Triple |  |  |  |  |  |  |
| CV Death |  |  |  |  |  |  |
| All-cause death |  |  |  |  |  |  |

Abbreviations of the reported outcomes: CHD; coronary heart disease; HF, heart failure; Double, composite of coronary heart disease and stroke; Triple, composite of coronary heart disease, stroke, and heart failure; CV death, cardiovascular death. Risk of bias legend: R, bias arising from randomization process; D, bias due to deviations from intended interventions; Mi, bias due to missing outcome data; Me, bias in measurement of the outcome; S, bias in selection of the reported result; O, overall risk of bias.

, low risk of bias; , some concerns, , high risk of bias

**Supplementary Table S6.** Specific beta-blockers versus placebo or no treatment or less intense treatment without a beta-blocker

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
| Outcome | Type of BB | Trials (n) | Active  Events  n/patients | Control  Events  n/patients | RR (95% CI) \* | P-heterogeneity |
| CHD | Alprenolol  Atenolol  Bisoprolol  Bucindolol  Carvedilol  Metoprolol  Oxprenolol  Practolol  Propranolol | 4  7  2  2  10  10  3  2  6 | 49 / 459  248 / 3359  10 / 1647  51 / 1524  83 / 4187  181 / 4995  180 / 1975  118 / 1768  347 / 7056 | 71 / 490  368 / 4543  10 / 1641  102 / 1527  131 / 3613  271 / 4970  208 / 1842  136 / 1754  548 / 11326 | 0.75 (0.48-1.18)  0.89 (0.75-1.06)  0.99 (0.41-2.40)  0.48 (0.30-0.76)  0.63 (0.48-0.82)  0.66 (0.55-0.79)  0.71 (0.43-1.16)  1.04 (0.52-2.09)  0.81 (0.71-0.92) | 0.11 |
| Stroke | Atenolol  Carvedilol  Metoprolol  Propranolol | 5  2  5  2 | 226 / 2983  17 / 469  3 / 2222  71 / 6319 | 347 / 4157  12 / 471  15 / 2222  139 / 10575 | 0.79 (0.63-0.99)  1.44 (0.70-2.98)  0.27 (0.09-0.83)  0.82 (0.61-1.10) | 0.11 |
| HF | Alprenolol  Atenolol  Bisoprolol  Bucindolol  Carvedilol  Metoprolol  Nebivolol  Propranolol | 3  3  2  2  15  15  2  3 | 7 / 390  36 / 828  220 / 1647  485 / 1524  463 / 4885  294 / 5122  96 / 1201  173 / 2549 | 7 / 397  72 / 904  322 / 1641  573 / 1527  620 / 4206  350 / 5102  93 / 1187  166 / 2568 | 1.01 (0.36-2.88)  0.54 (0.37-0.80)  0.68 (0.58-0.80)  1.17 (0.46-2.95)  0.61 (0.48-0.77)  0.93 (0.65-1.32)  1.02 (0.77-1.34)  1.05 (0.85-1.29) | 0.001 |
| Stroke+CHD | Atenolol  Carvedilol  Metoprolol  Propranolol | 5  3  4  2 | 461 / 2983  43 / 527  46 / 2028  366 / 6319 | 691 / 4157  56 / 527  69 / 2033  622 / 10575 | 0.86 (0.74-0.99)  0.71 (0.40-1.28)  0.68 (0.39-1.17)  0.81 (0.71-0.92) | 0.78 |
| Stroke+CHD+HF | Atenolol  Carvedilol  Metoprolol  Propranolol | 3  2  3  3 | 300 / 1879  40 / 469  66 / 1829  530 / 6597 | 554 / 3068  46 / 471  67 / 1834  806 / 10857 | 0.77 (0.57-1.04)  0.86 (0.58-1.28)  1.01 (0.61-1.68)  0.84 (0.76-0.93) | 0.83 |
| CV death | Alprenolol  Atenolol  Bisoprolol  Carvedilol  Metoprolol  Oxprenolol  Propranolol | 3  8  2  9  11  3  6 | 7 / 221  243 / 3410  157 / 1647  184 / 2948321 / 4976  117 / 1975  274 / 7056 | 23 / 248  377 / 4592  220 / 1641  261 / 2566  391 / 4912  119 / 1842  413 / 11326 | 0.38 (0.13-1.08)  0.84 (0.66-1.07)  0.71 (0.59-0.86)  0.63 (0.46-0.86)  0.90 (0.71-1.14)  0.81 (0.45-1.46)  0.79 (0.69-0.90) | 0.41 |
| All-cause death | Alprenolol  Atenolol  Bisoprolol  Bucindolol  Carvedilol  Metoprolol  Nebivolol  Oxprenolol  Practolol  Propranolol | 4  8  2  2  15  16  2  3  2  7 | 76 / 459  411 / 3410  209 / 1647438 / 1524  407 / 4885  374 / 5505  176 / 1201  136 / 1975  93 / 1768  359 / 7315 | 92 / 490  603 / 4592  295 / 1641  479 / 1527  546 / 4206  460 / 5448  199 / 1187  134 / 1842  122 / 1754  562 / 11455 | 0.88 (0.67-1.16)  0.95 (0.83-1.08)  0.71 (0.60-0.83)  0.92 (0.82-1.02)  0.69 (0.70-0.98)  0.83 (0.70-0.98)  0.88 (0.73-1.06)  0.85 (0.50-1.44)  0.76 (0.59-0.98)  0.80 (0.71-0.91) | 0.044 |

Baseline systolic/diastolic blood pressure (mmHg): alprenolol, NA; atenolol, 173.5/91.3; bisoprolol, 129/79.5; bucindolol, 117/71.2; carvedilol, 121.7/74; metoprolol, 124.8/75.9; nebivolol, 138.6/80.5; oxprenolol, 130.3/81.9; practolol, 122.4/78; propranolol, 149.7/92.3. Agents represented in one only trial were excluded from the analysis. \* Mantel-Haenszel risk ratios under random effects model and 95% confidence interval. CHD, coronary heart disease; CV, cardiovascular HF, heart failure. Due to Bonferroni correction, statistical significance may be lower than 0.05 depending on the number of comparisons for each individual outcome.

**Supplementary Table S7.** Types of beta-blockers versus other active agents

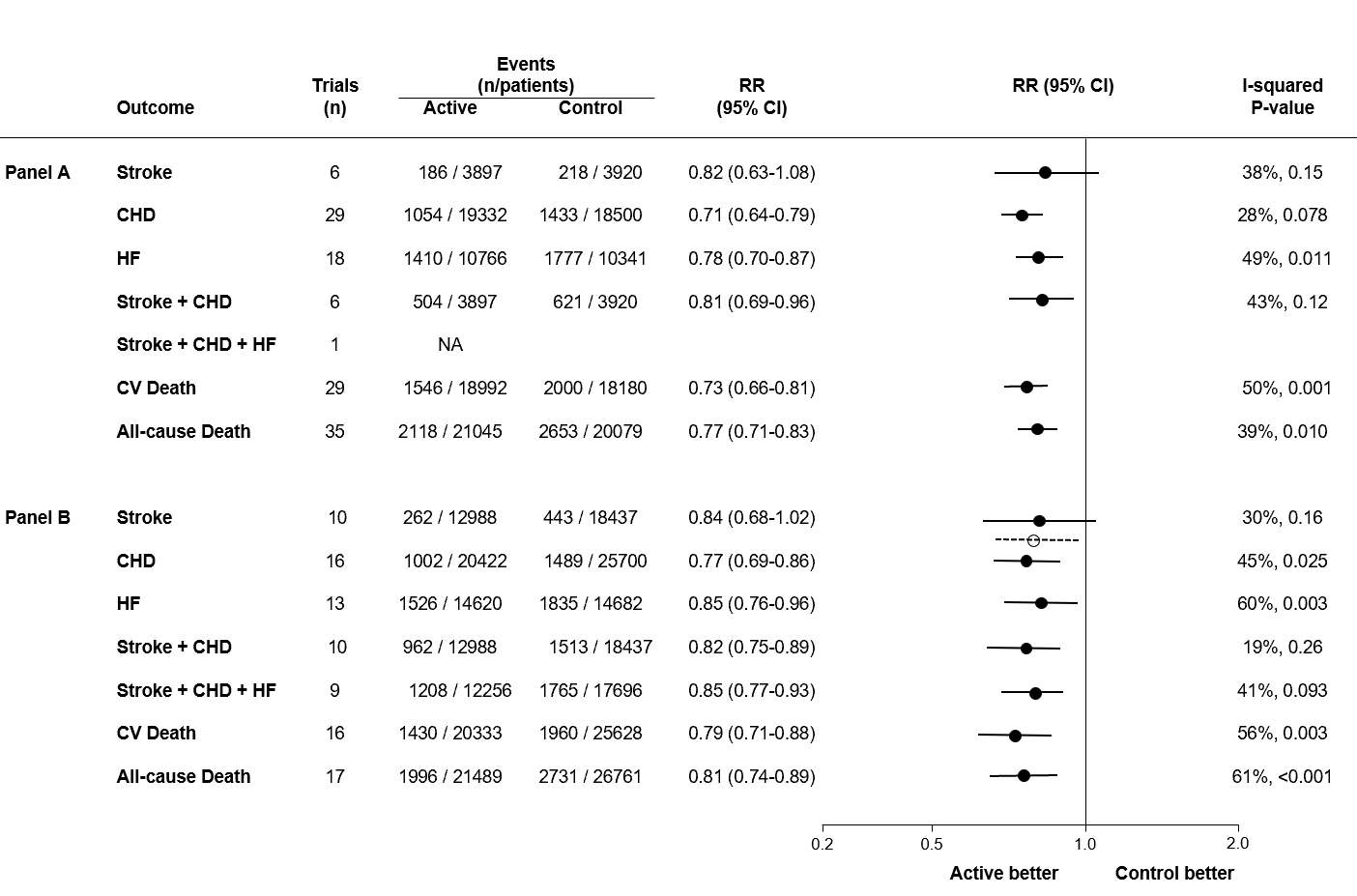
|  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- |
| Outcome | Type of BBs | Trials (n) | BP difference | Active  Events  n/patients | Control  Events  n/patients | RR (95% CI) \* | P-heterogeneity |
| CHD | Atenolol  Metoprolol  Propranolol | 10  3  3 | 0.99/0.44  1.1/0.1  3.6/1.19 | 1236 / 29607  51 / 931  112 / 4678 | 1195 / 30765  46 / 1140  127 / 4628 | 1.04 (0.93-1.17)  1.31 (0.88-1.94)  0.87 (0.68-1.12) | 0.20 |
| Stroke | Atenolol  Metoprolol  Propranolol | 8  2  3 | 1/0.44  1.57/0.1  3.6/1.19 | 1048 / 29321  35 / 847  48 / 4678 | 841 / 30473  47 / 1056  32 / 4628 | 1.28 (1.17-1.40)  0.97 (0.65-147)  0.93 (0.25-3.41) | 0.41 |
| HF | Atenolol  Metoprolol | 7  2 | 0.97/0.48  1.16/-0.47 | 512 / 27122  24 / 525 | 504 / 28275  29 / 737 | 1.03 (0.91-1.16)  1.20 (0.70-2.03) | 0.58 |
| Double | Atenolol  Metoprolol  Propranolol | 10  2  3 | 0.78/0.5  1.57/0.1  3.6/1.19 | 2470 / 33827  81 / 847  160 / 4678 | 2550 / 42543  89 / 1056  159 / 4628 | 1.13 (1.03-1.23)  1.13 (0.85-1.51)  0.99 (0.80-1.23) | 0.58 |
| Triple | Atenolol | 8 | 1.06/0.47 | 2767 / 28224 | 2514 / 29356 | 1.12 (0.99-1.25) | - |
| CV death | Atenolol  Metoprolol  Propranolol | 8  2  2 | 1.07/0.46  1.57/0.1  3.6/1.16 | 1144 / 28458  31 / 847  66 / 4553 | 1017 / 28501  38 / 1056  76 / 4451 | 1.14 (0.98-1.32)  0.97 (0.61-1.54)  0.49 (0.09-2.74) | 0.53 |
| All-cause death | Atenolol  Metoprolol  Propranolol | 10  3  3 | 0.99/0.44  1.1/0.1  3.5/1/16 | 2418 / 29607  75 / 931  126 / 4606 | 2275 / 30765  82 / 1140  139 / 4504 | 1.08 (1.02-1.14)  1.17 (0.79-1.73)  0.81 (0.39-1.68) | 0.69 |

Baseline systolic/diastolic blood pressure (mmHg): atenolol, 158/90.7; metoprolol, 146.1/92.6; propranolol, 161.1/98.8. Agents represented in one only trial were excluded from the analysis. Agents represented in one only trial were excluded from the analysis. \* Mantel-Haenszel risk ratios under random effects model and 95% confidence interval. BP, blood pressure; CHD, coronary heart disease; CV, cardiovascular HF, heart failure. Due to Bonferroni correction, statistical significance may be lower than 0.05 depending on the number of comparisons for each individual outcome.

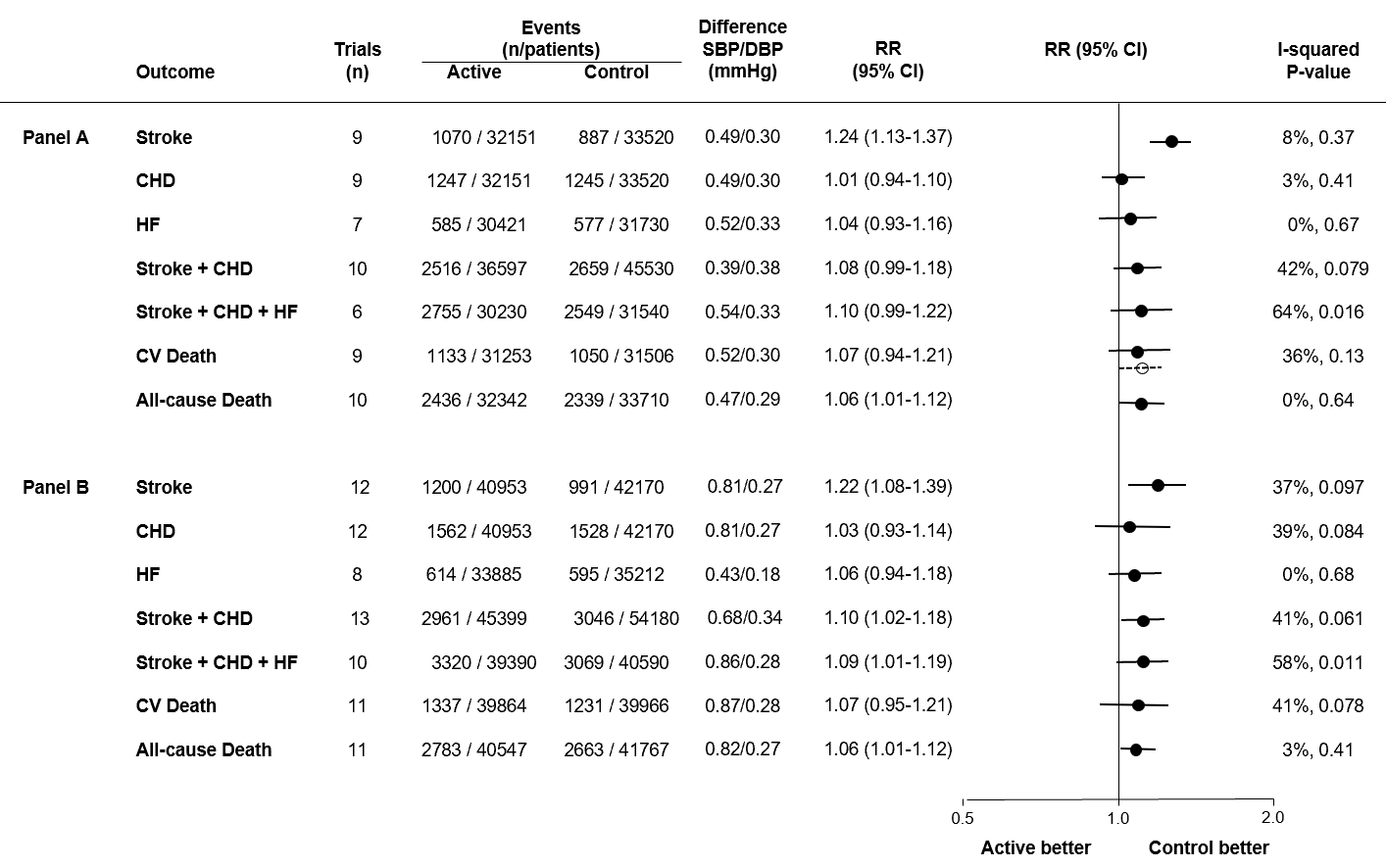
**Supplementary Table S8**. Publication bias (under random-effects model) for outcome assessment according to Duval and Tweedie trim-and-fill method and the Egger’s regression testing in beta-blocker BP lowering against placebo, no or less treatment (A) and comparison (B) trials. Abbreviations as in preceding Tables and Figures

|  |  |  |  |  |
| --- | --- | --- | --- | --- |
| **Outcomes of interest** | **Duval and Tweedie trim-and fill method (imputed studies)** | **Egger’s regression testing** | **Funnel plot inspection for evidence of bias** | **Overall Publication Bias Assessment** |
| **A. Blood pressure lowering trials** | | | | |
| CHD | Four studies to the right of the mean | P=0.49 | No evidence | No bias |
| Stroke | Three studies to the right of the mean | P=0.49 | Mild evidence | No bias |
| HF | Two studies to the right of the mean | P=0.73 | No evidence | No bias |
| CHD+Stroke | No imputed study | P=0.52 | No evidence | No bias |
| CHD+Stroke+HF | No imputed study | P=0.99 | No evidence | No bias |
| CV Death | Three studies to the right of the mean | P=0.26 | No evidence | No bias |
| All-cause death | Two studies to the right of the mean | P=0.33 | No evidence | No bias |
| **B. Blood pressure lowering trials** | | | | |
| CHD | No imputed study | P=0.99 | No evidence | No bias |
| Stroke | Two studies to the right of the mean | P=0.37 | Mild evidence | No bias |
| HF | Two studies to the left of the mean | P=0.46 | Mild evidence | No bias |
| CHD+Stroke | Three studies to the right of the mean | P=0.45 | Mild evidence | No bias |
| CHD+Stroke+HF | Two studies to the left of the mean | P=0.85 | No evidence | No bias |
| CV Death | Two studies to the right of the mean | P=0.25 | Mild evidence | No bias |
| All-cause death | One study to the right of the mean | P=0.57 | No evidence | No bias |

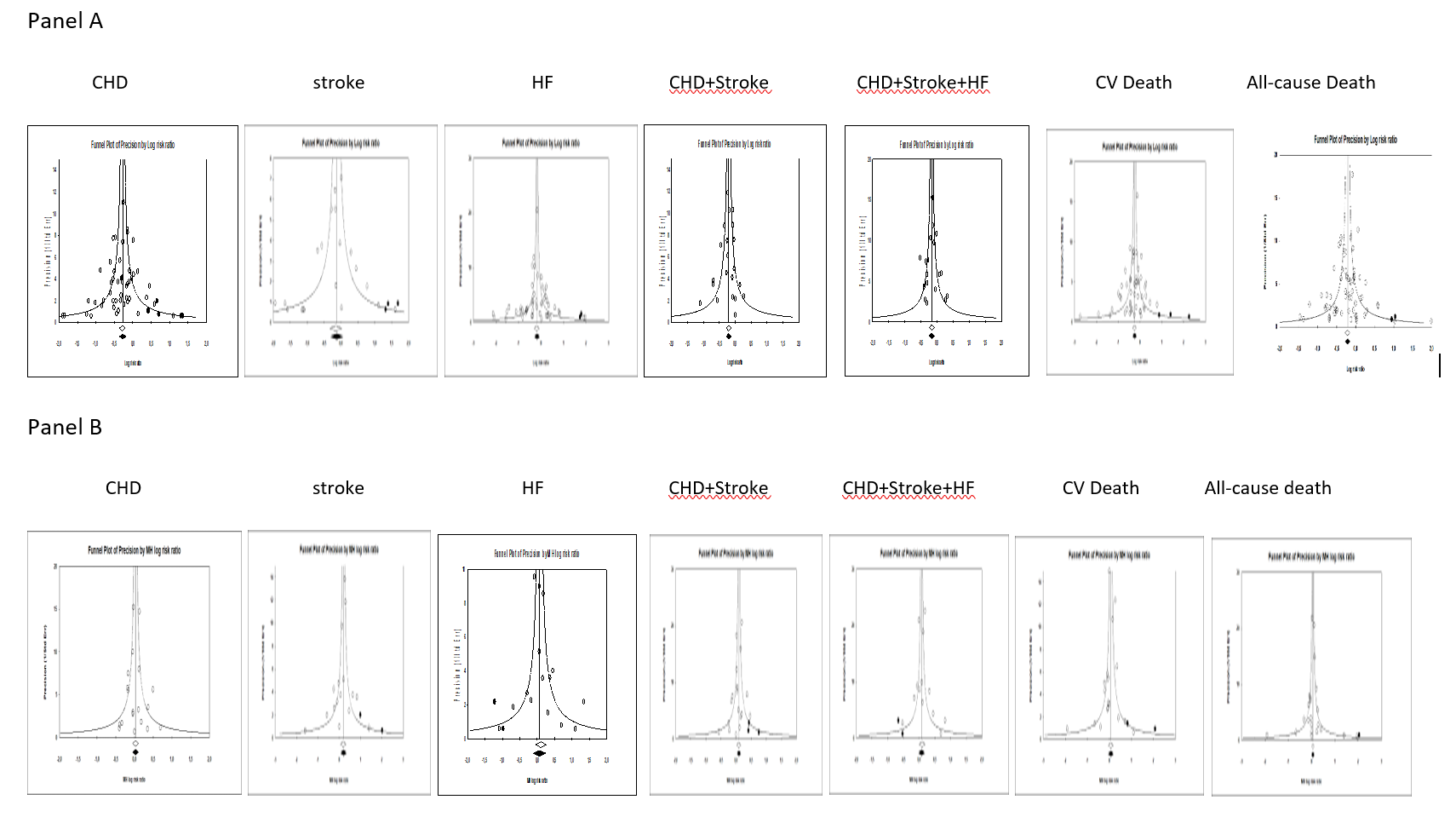
**Supplementary Figure S1.** Trials on Beta-Blockers versus placebo, no treatment or less intense treatment without beta-blockers. Sensitivity analysis based on quality (Panel A, only trials with low overall risk of bias) and magnitude of trial patient-year product (Panel B, only trials with 2,000 patient-years and over). Abbreviations and explanations as in preceding Figures and Supplementary Tables.



**Supplementary Figure S2**. Comparison trials of Beta-Blockers versus other drugs. Sensitivity analysis based on quality (Panel A, only trials with low overall risk of bias) and magnitude of trial patient-year product (Panel B, only trials with 2,000 patient-years and over). Abbreviations and explanations as in preceding Figures and Supplementary Tables.



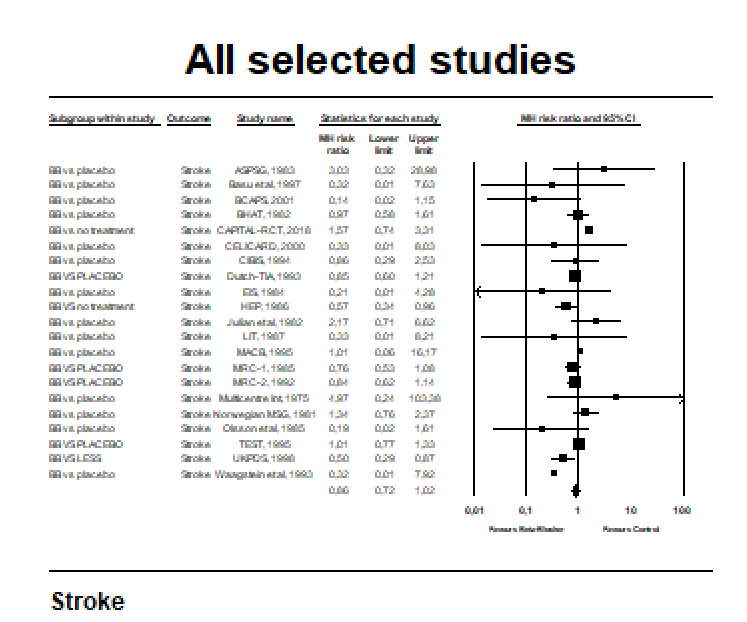
**Supplementary Figure S3**. Publication bias (under random-effects) funnel plots of the included trials. Trials on Beta-blockers versus placebo, no treatment or less intense treatment without beta-blockers are shown in Panel A. Comparison trials are shown in Panel B.



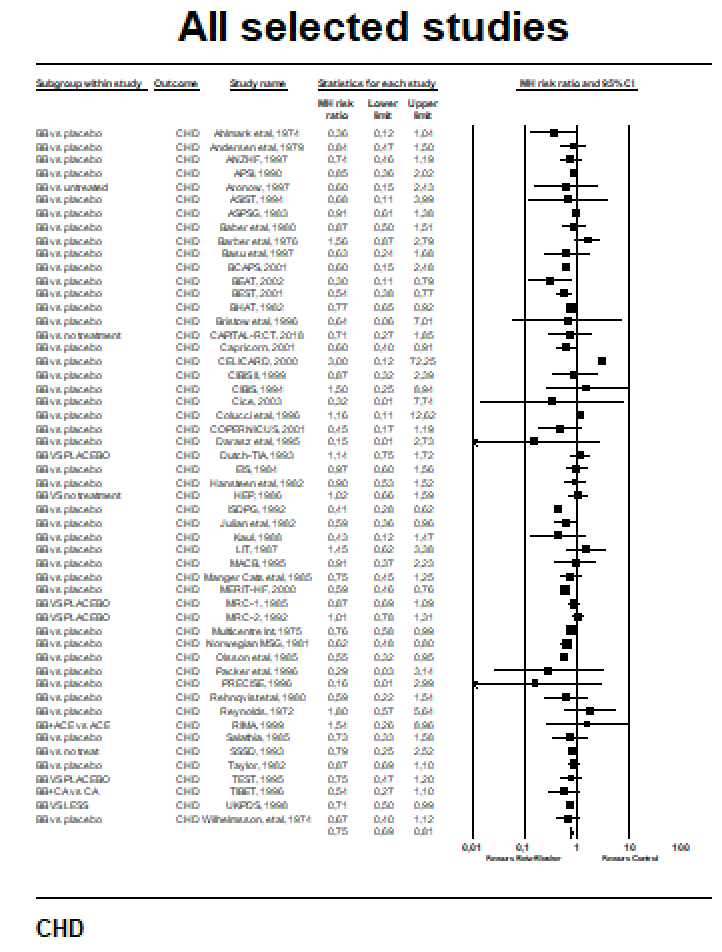
**Supplementary Figure S4.** Detailed results for the effect of beta-blockers vs controls (Panel A: placebo, no treatment or less intense treatment without beta-blockers; Panel B: other drugs) on stroke, CHD (coronary heart disease), HF (heart failure), CV (cardiovascular) death all-cause mortality. AMI, acute myocardial infarction.

**Panel A: BP-lowering trials**

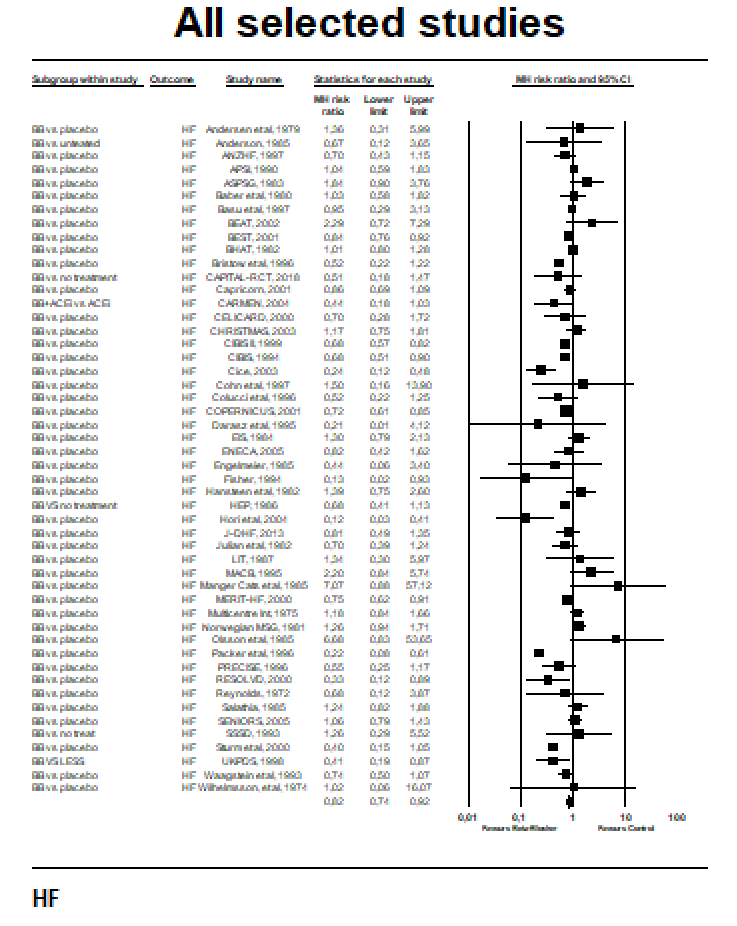
**1. All-selected studies, Stroke**



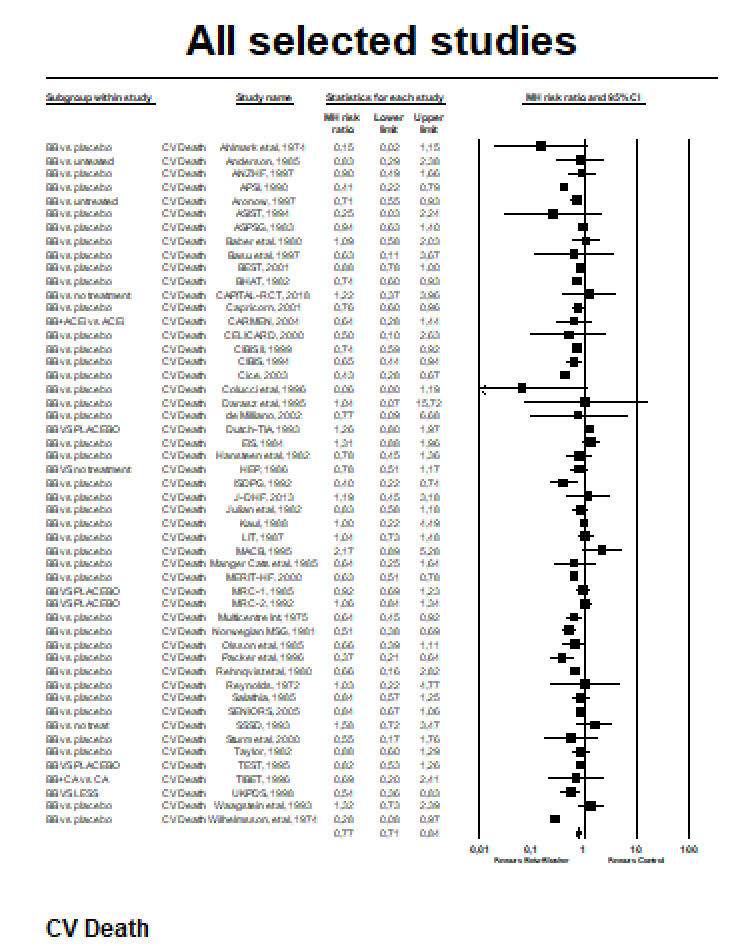
**2. All-selected studies, CHD**



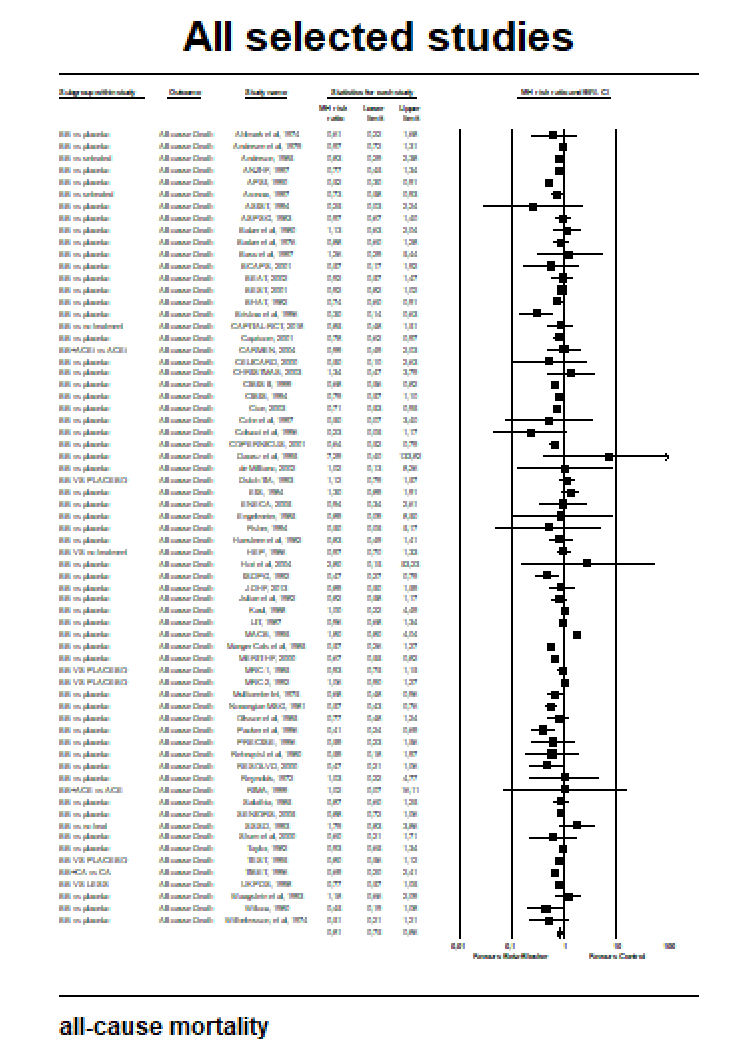
**3. All selected studies, HF**



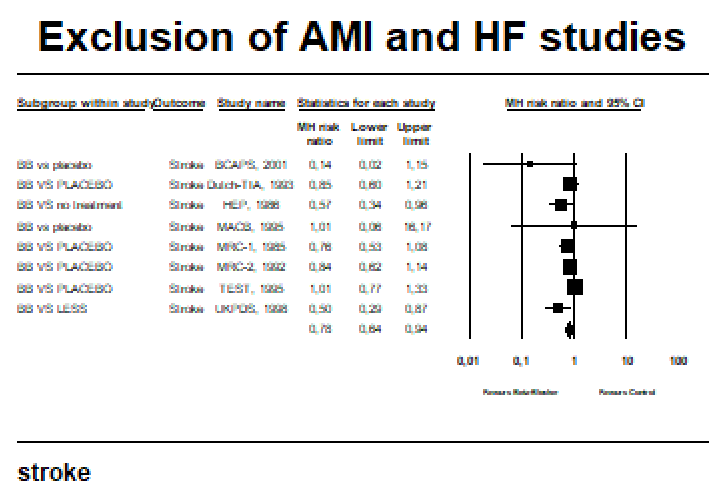
**4. All-selected studies, CV mortality**



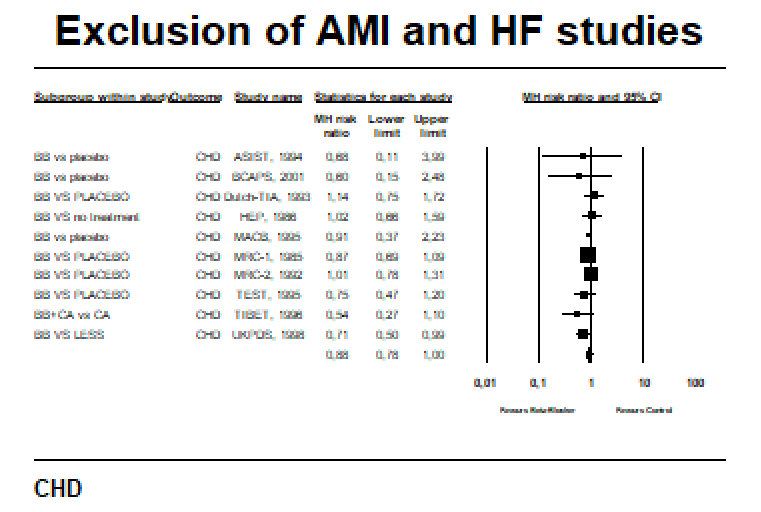
**5. All-selected studies, All-cause mortality**



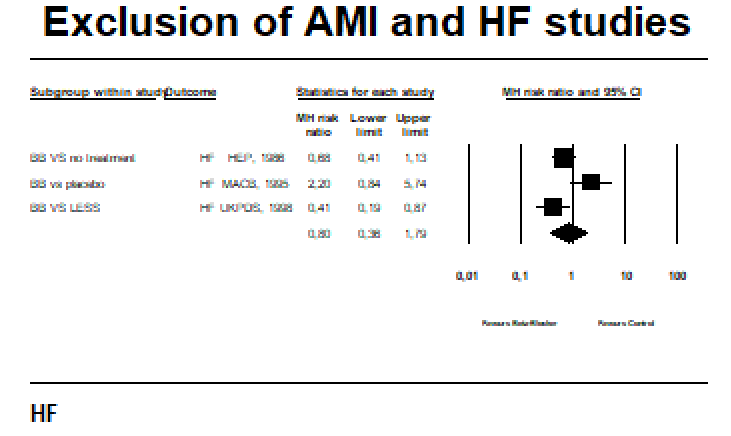
**6. Exclusion of AMI and HF studies, Stroke**



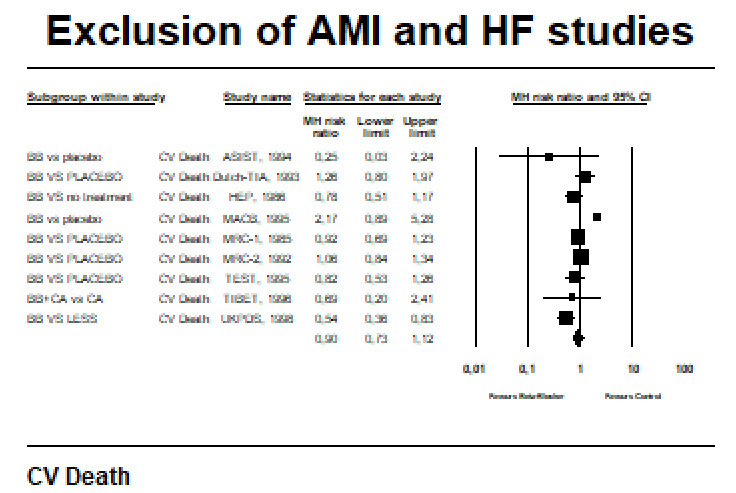
**7. Exclusion of AMI and HF studies, CHD**



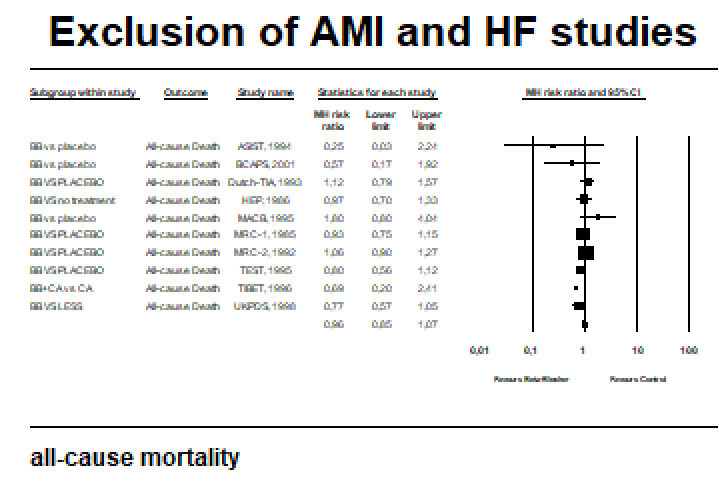
**8. Exclusion of AMI and HF studies, HF**



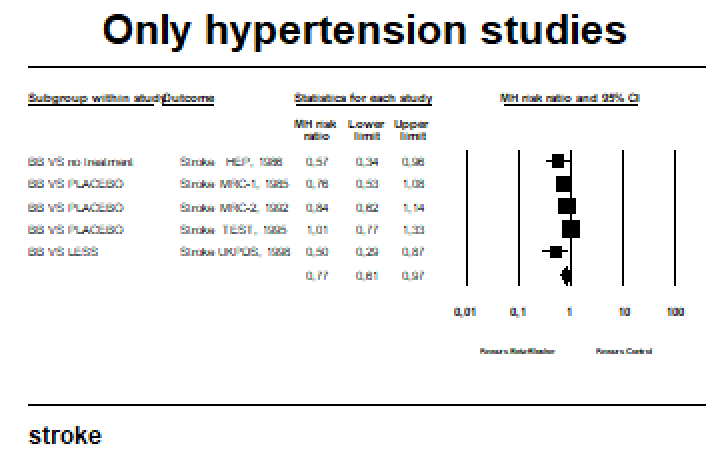
**9. Exclusion of AMI and HF studies, CV Death**



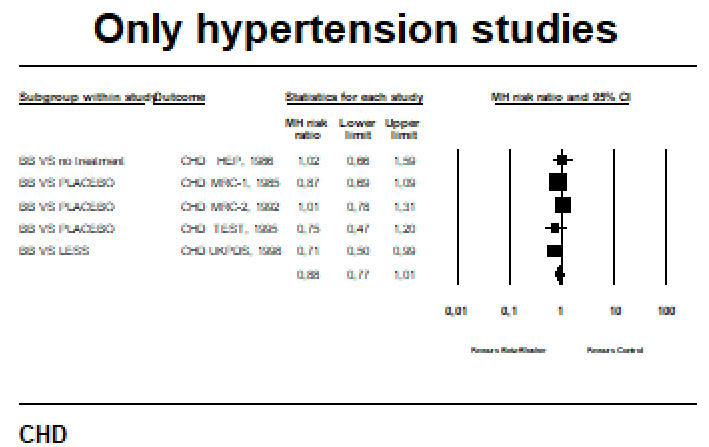
**10. Exclusion of AMI and HF studies, all-cause Death**



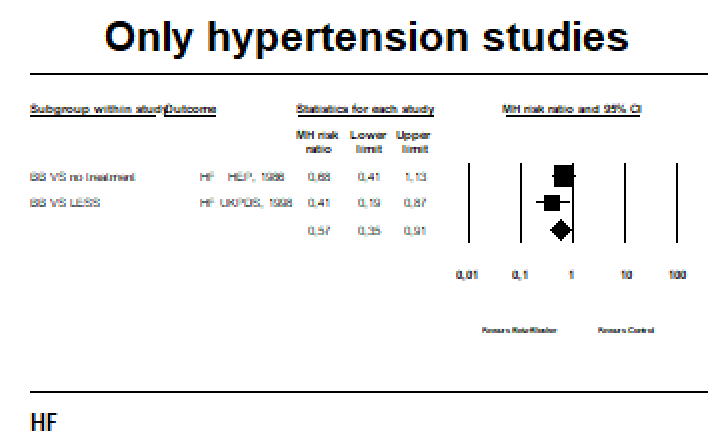
**11. only hypertension studies, stroke**



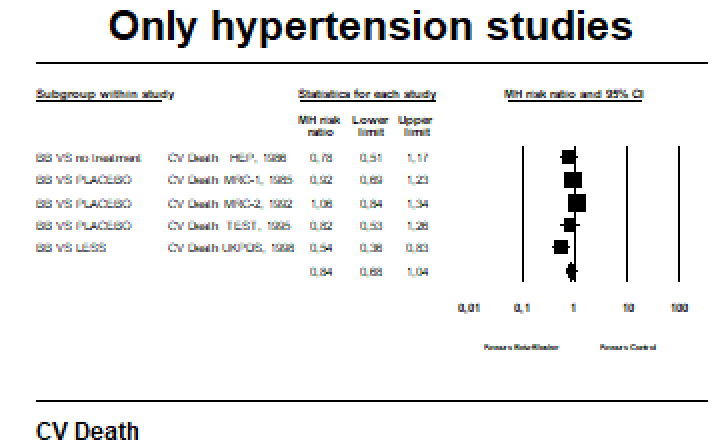
12. **only hypertension studies, CHD**



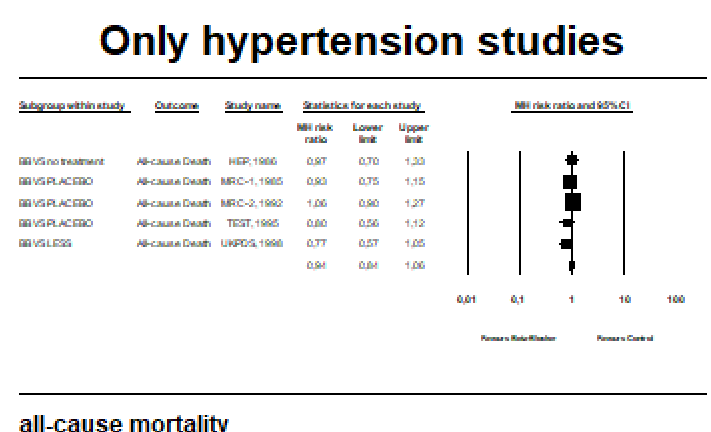
**13. only hypertension studies, HF**



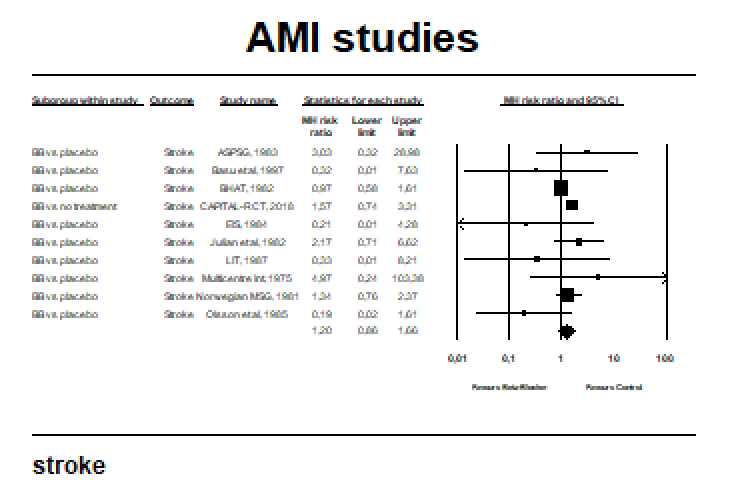
**14. only hypertension studies, CV death**



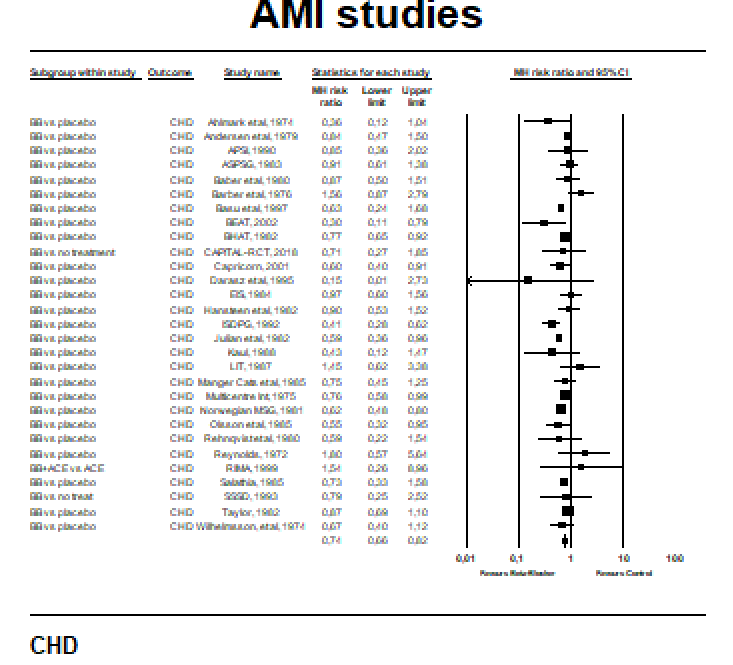
**15. only hypertension studies, all-cause death**



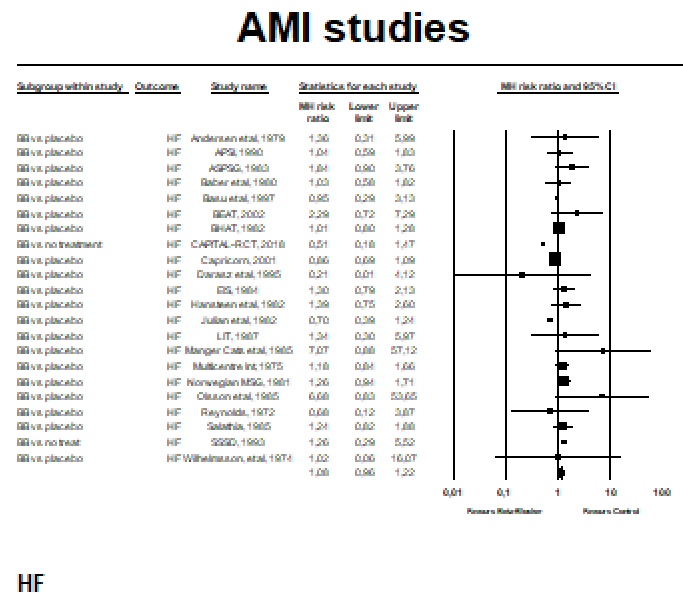
**16. AMI trials, stroke**



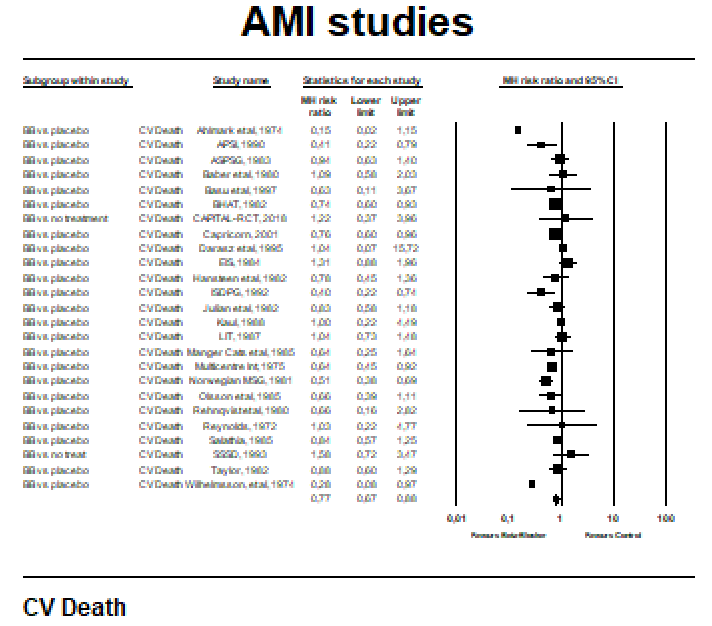
**17. AMI trials, CHD**



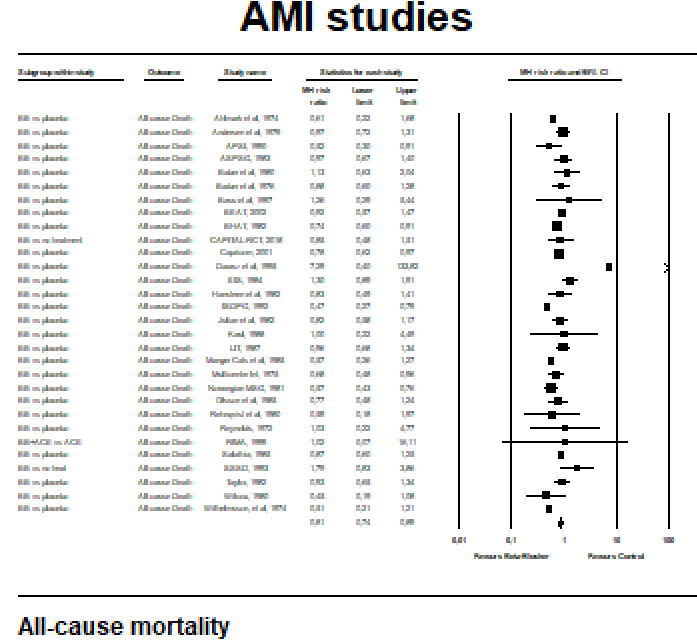
**18. AMI trials, HF**



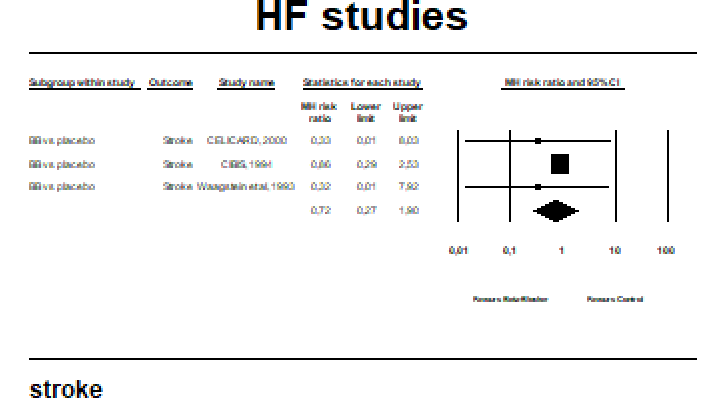
**19. AMI trials, CV Death**



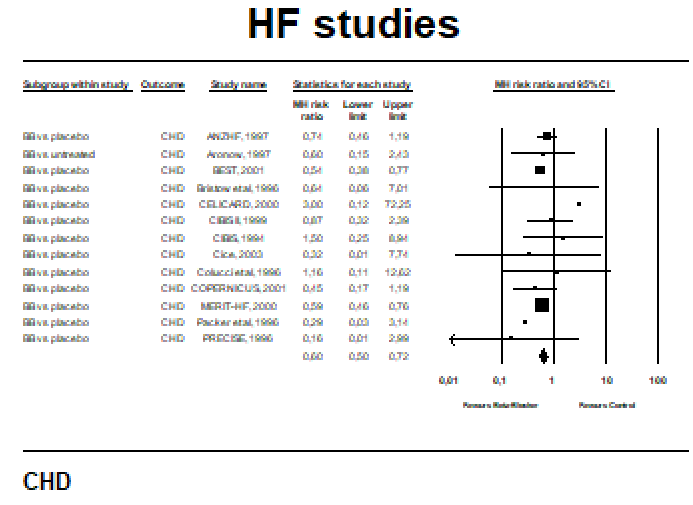
**20. AMI trials, all-cause mortality**



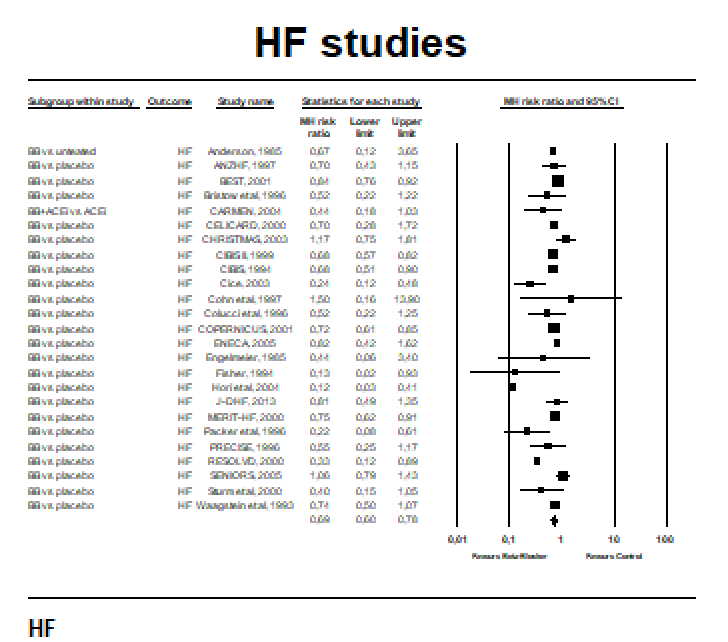
**21. HF trials, stroke**



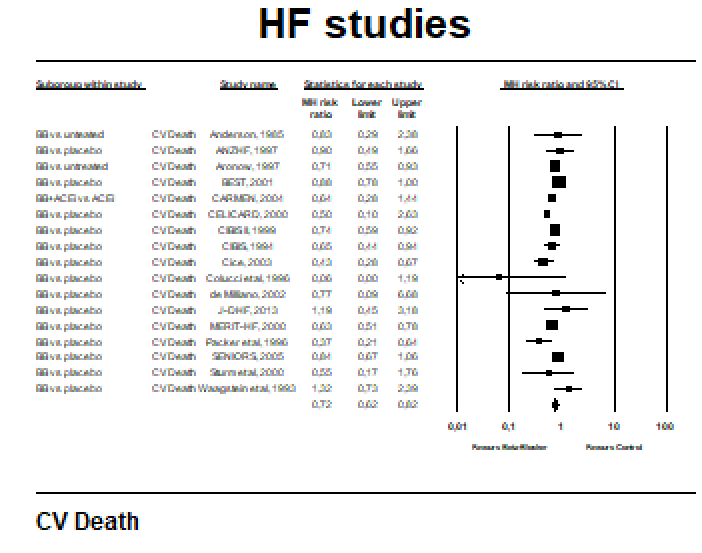
**22. HF trials, CHD**



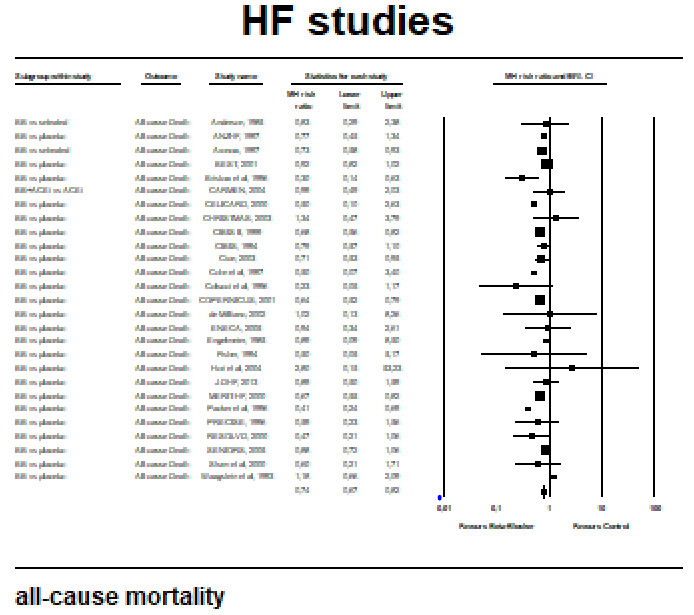
**23. HF trials, HF**



**24. HF trials, CV Death**

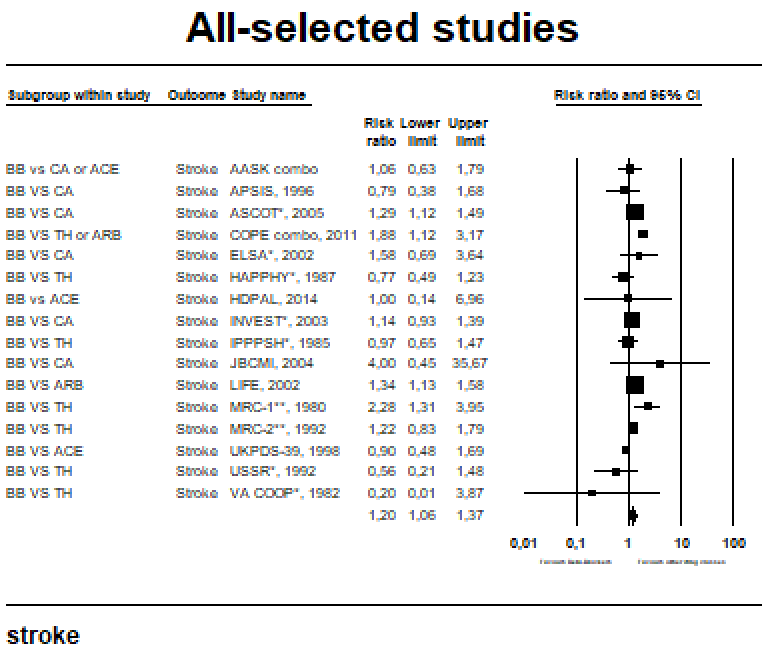


**25. HF trials, all-cause mortality**

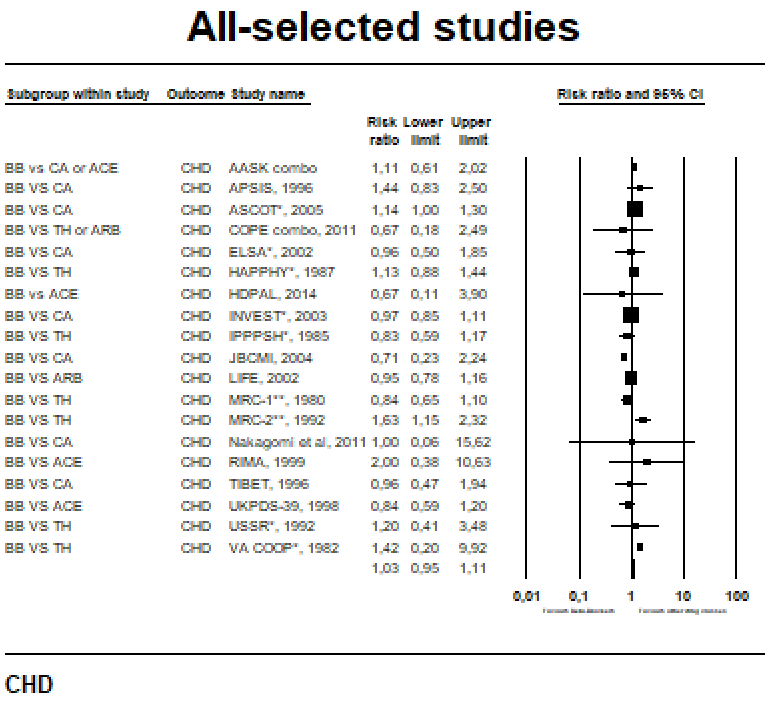


**Panel B: Comparison trials**

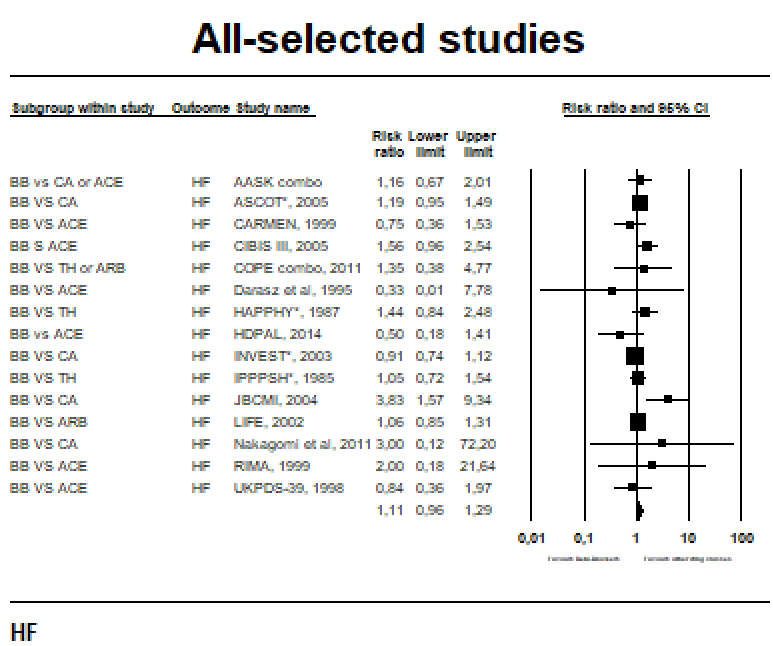
**1. all selected trials, stroke**



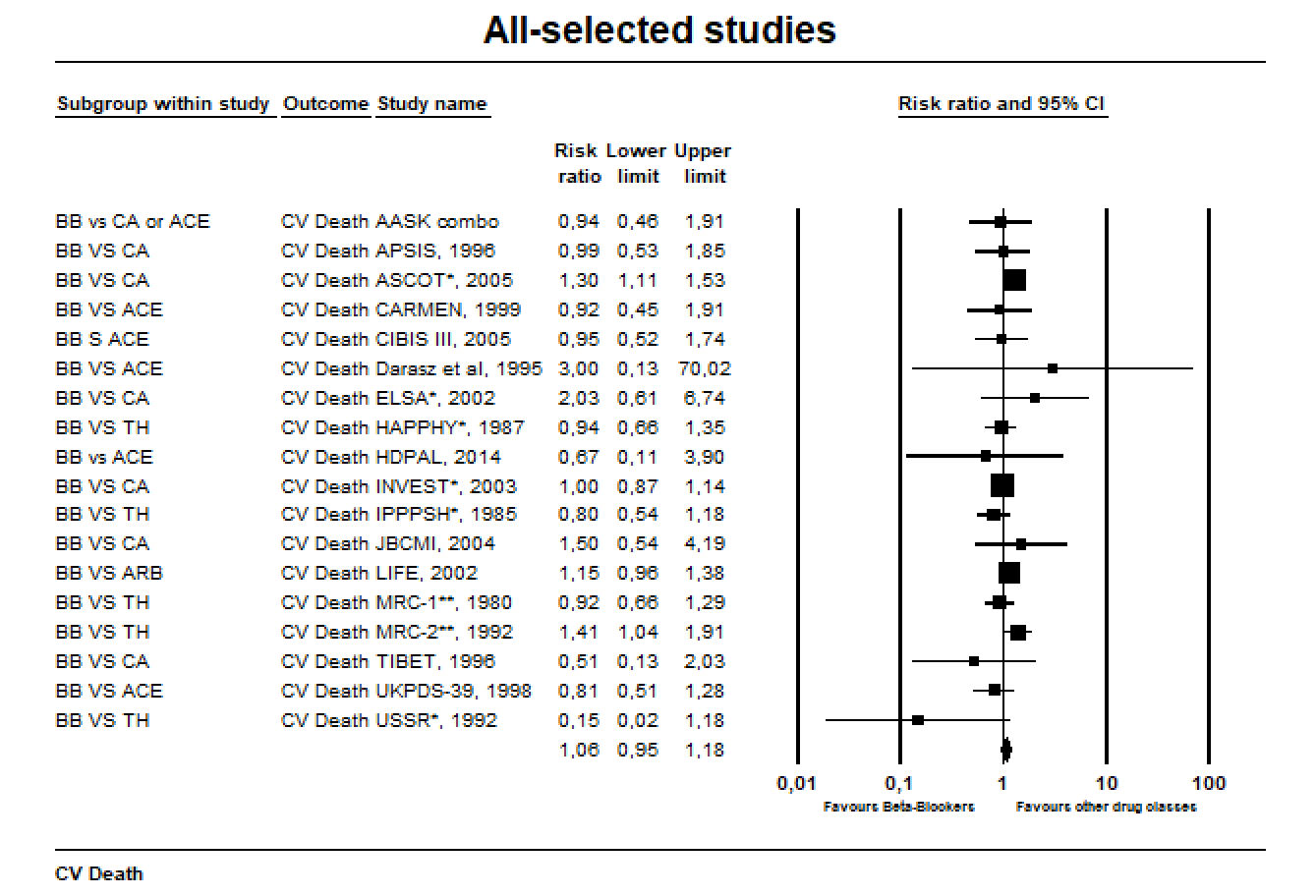
**2. all selected trials, CHD**



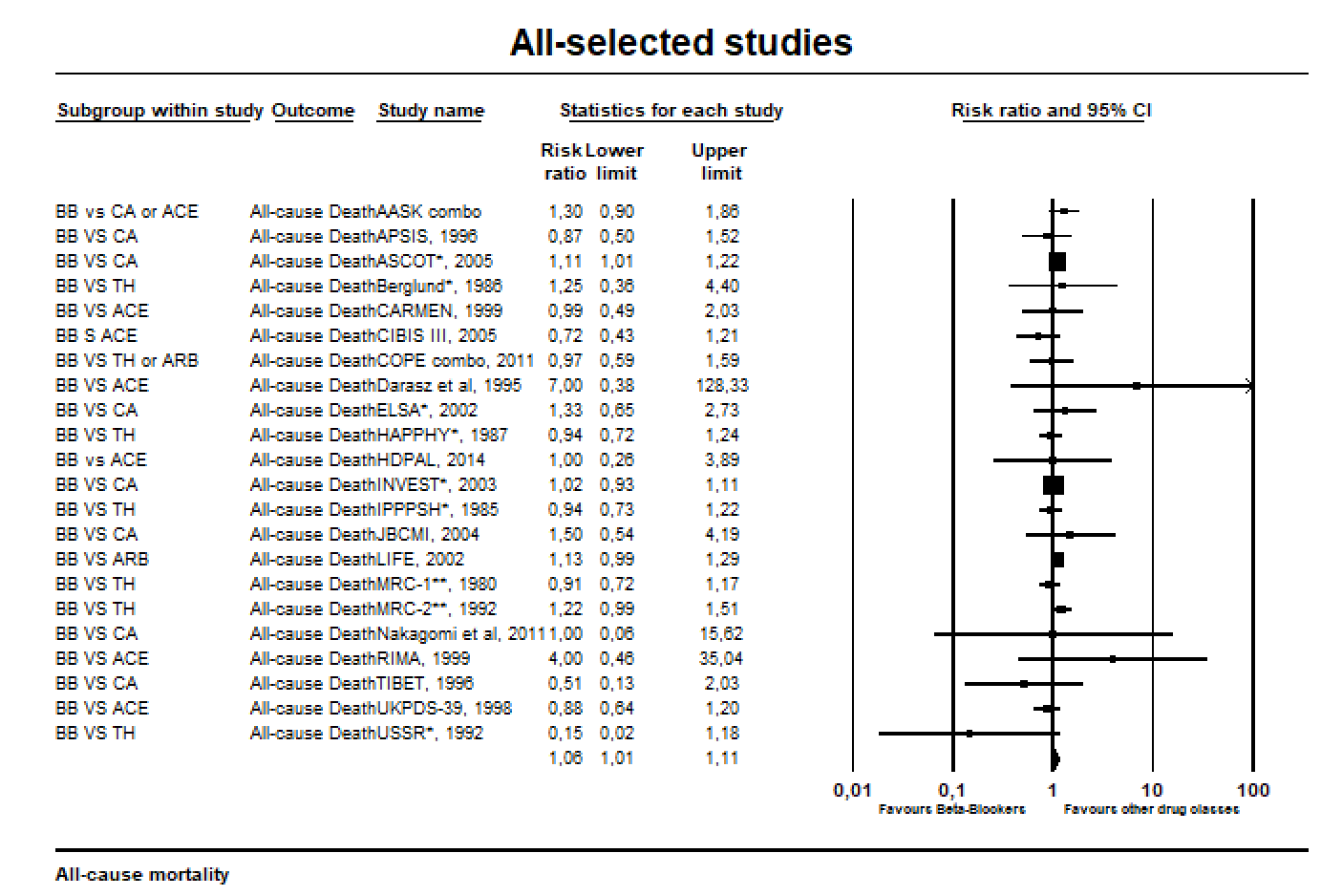
**3. all-selected studies, HF**



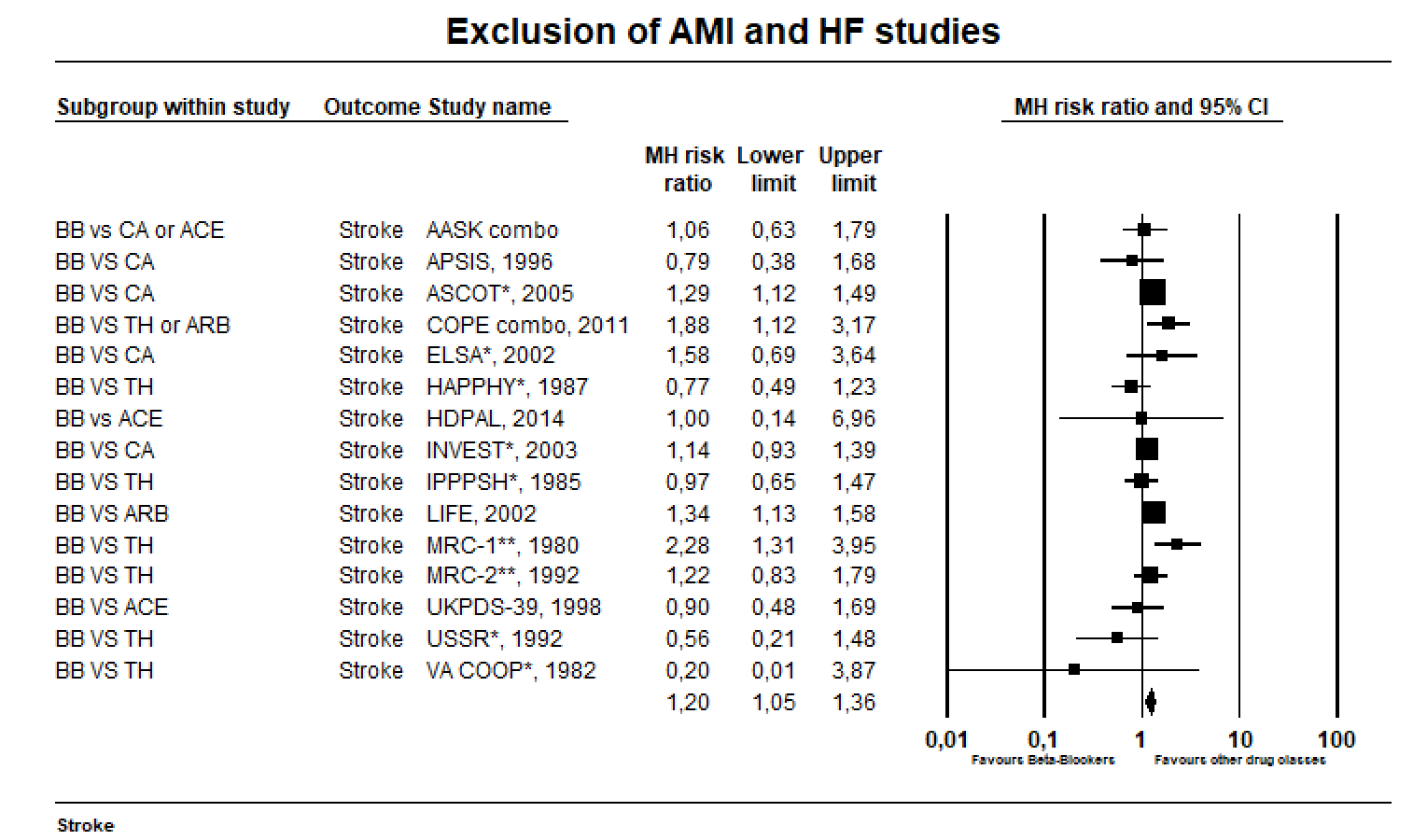
**4. All-selected studies, CV death**



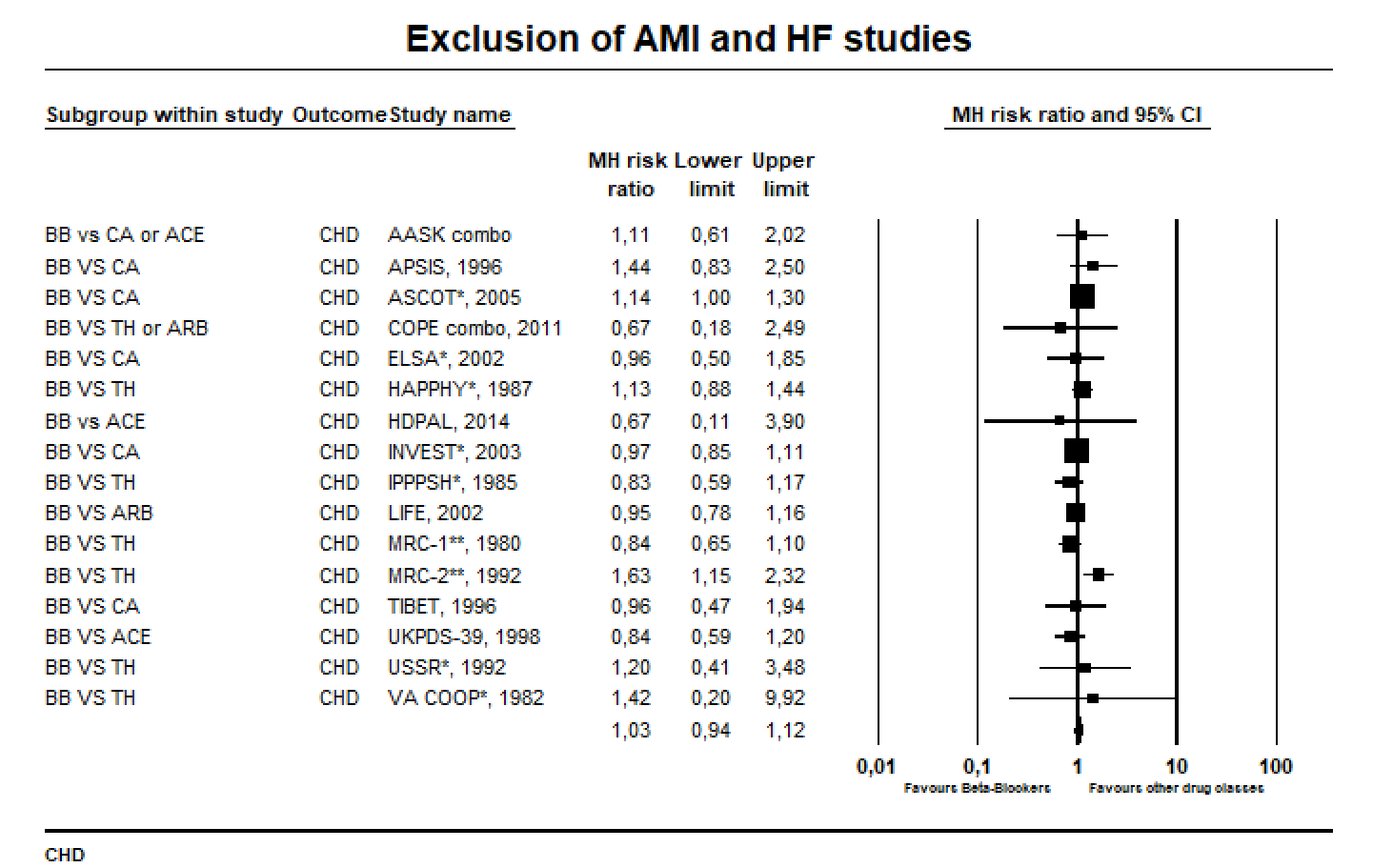
**5. All-selected studies, all-cause mortality**



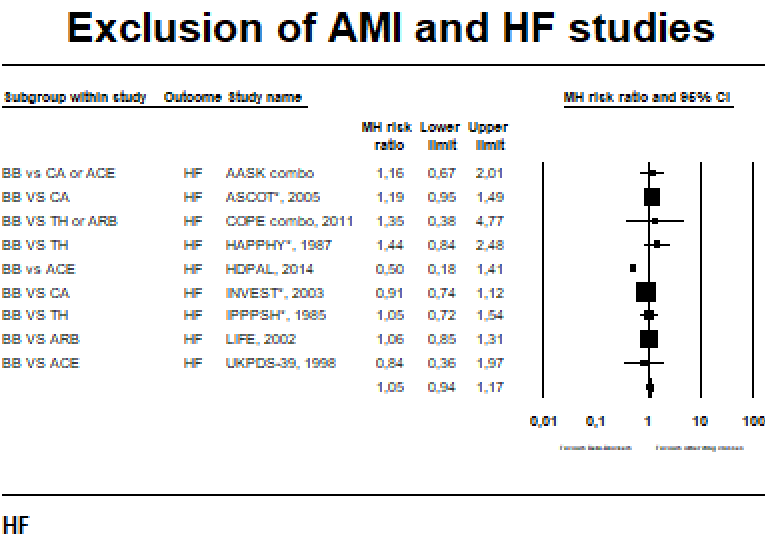
**6. Exclusion of AMI and HF trials, stroke**



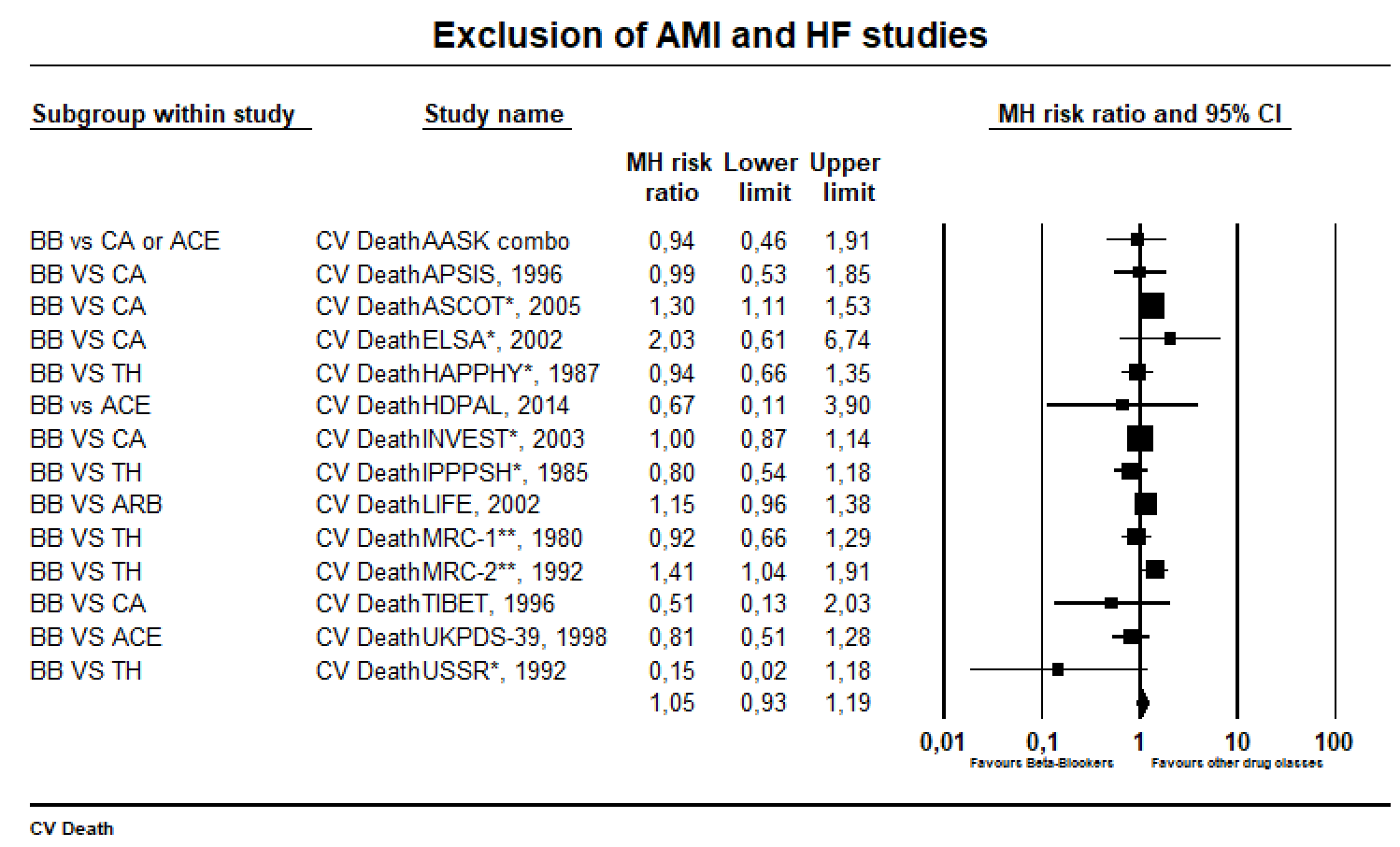
**7. Exclusion of AMI and HF trials, CHD**



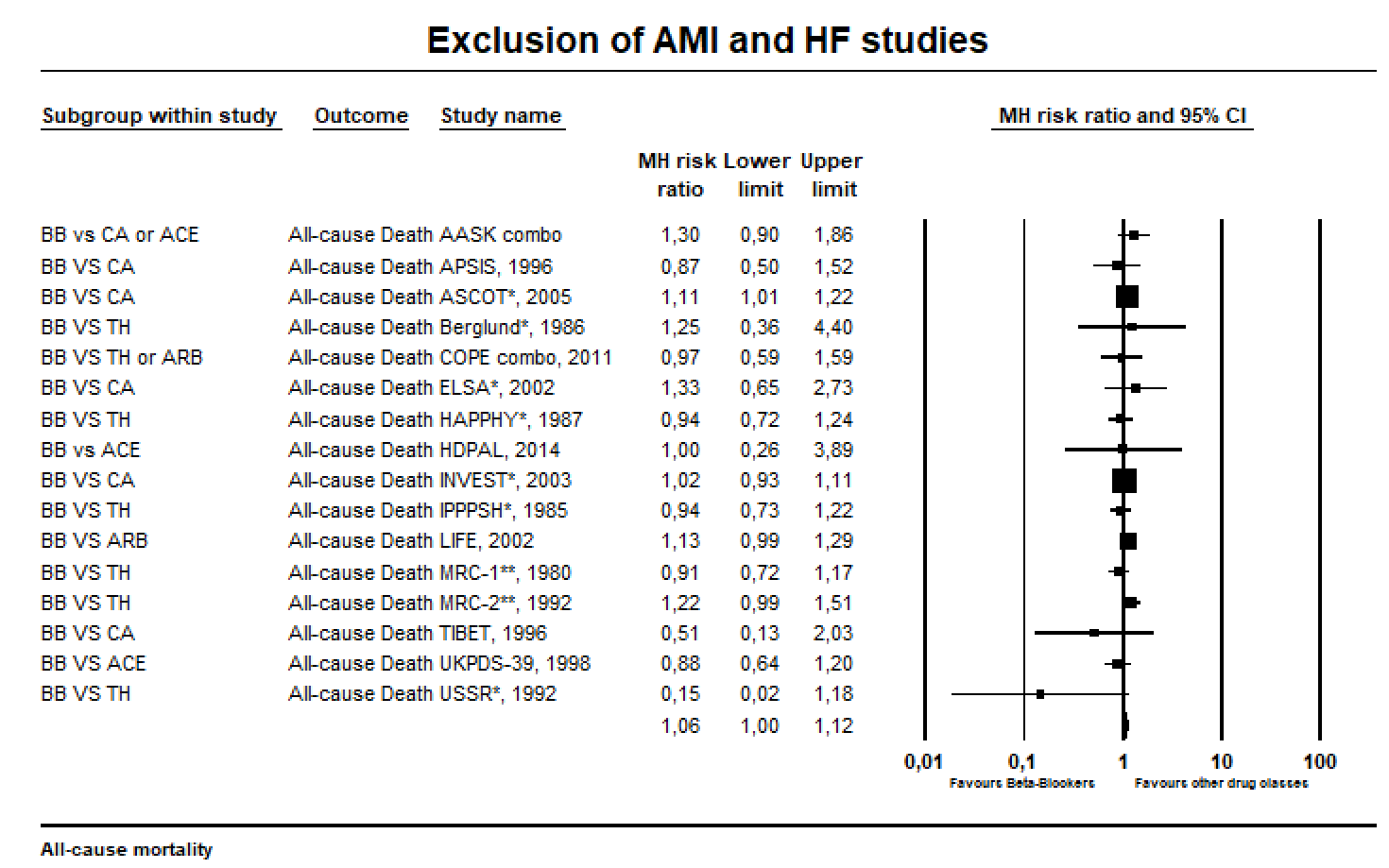
**8. Exclusion of AMI and HF trials, HF**



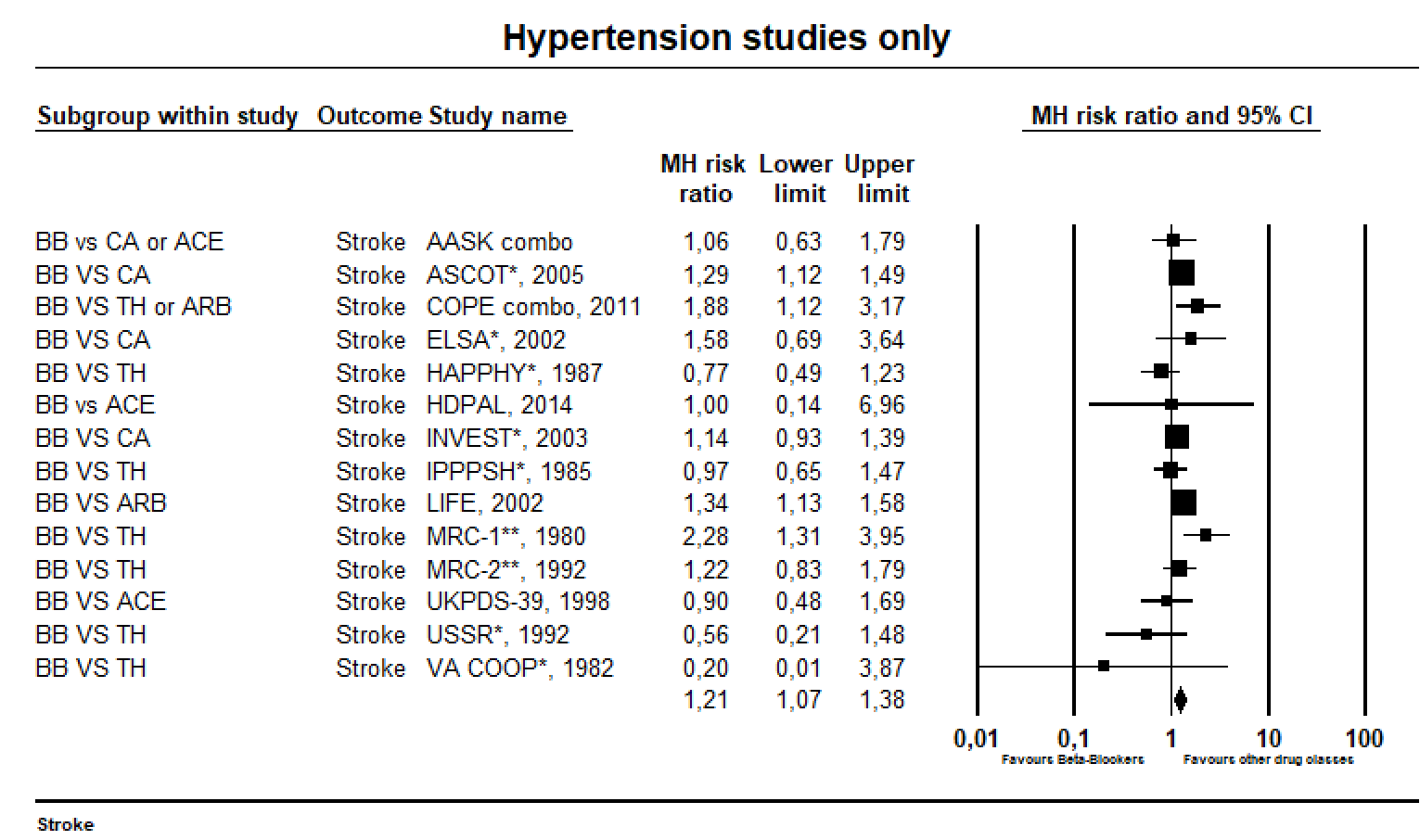
**9. Exclusion of AMI and HF trials, CV death**



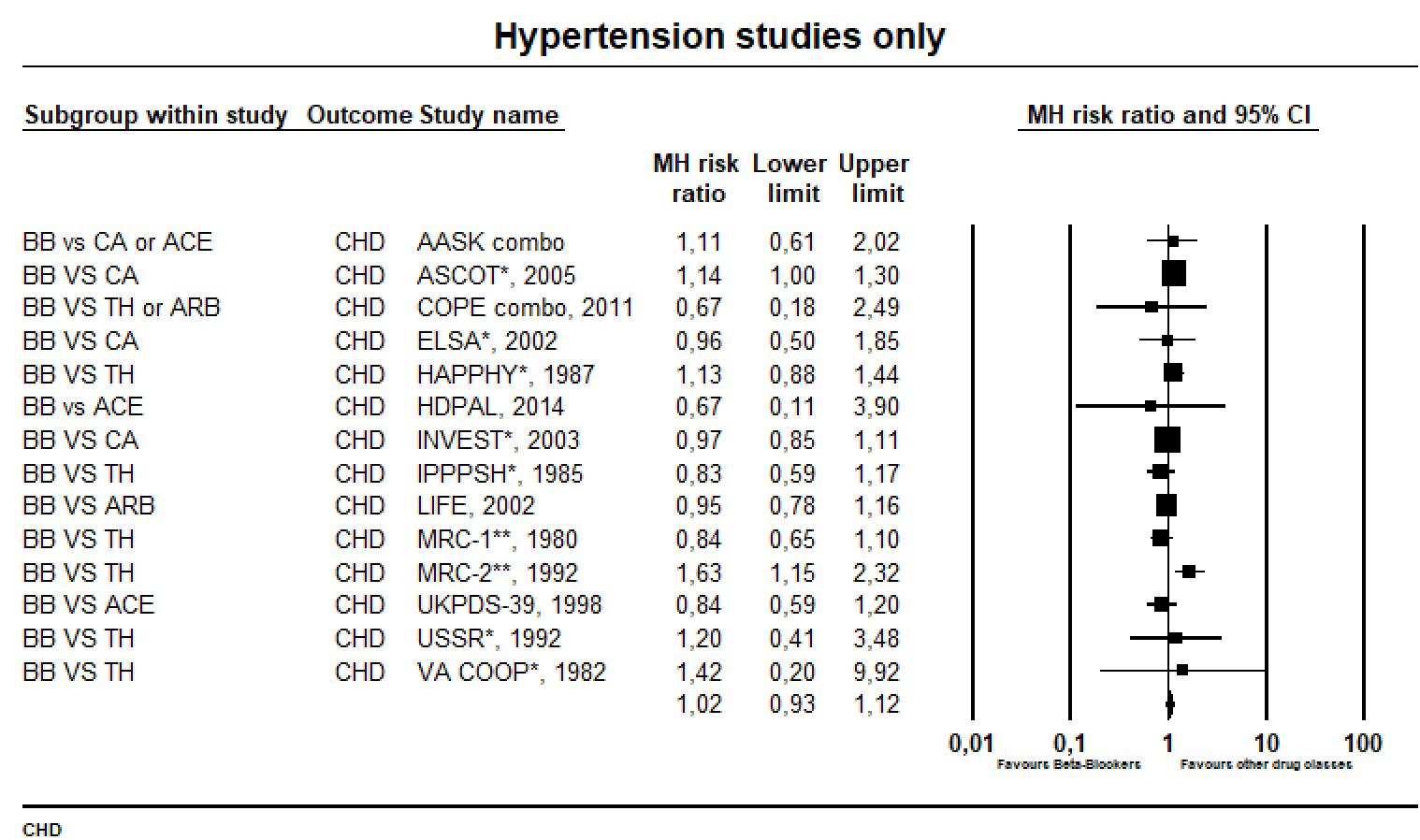
**10. Exclusion of AMI and HF trials, all-cause death**



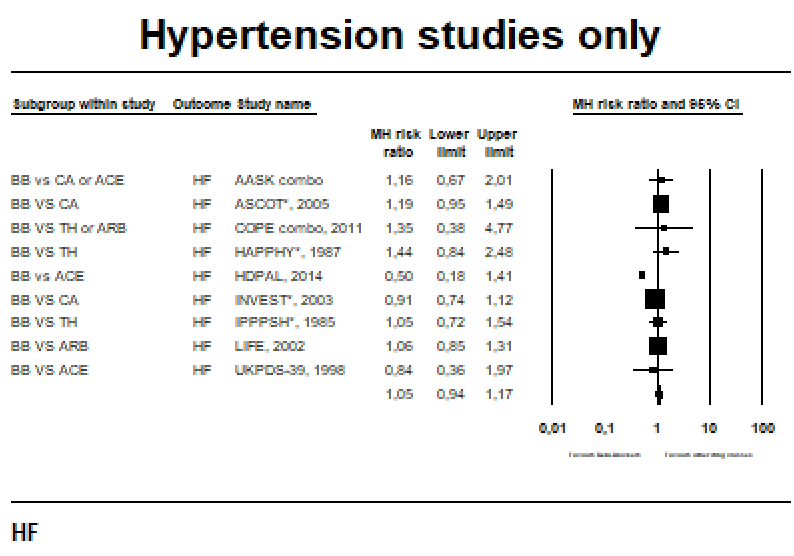
**11. Hypertension studies only, stroke**



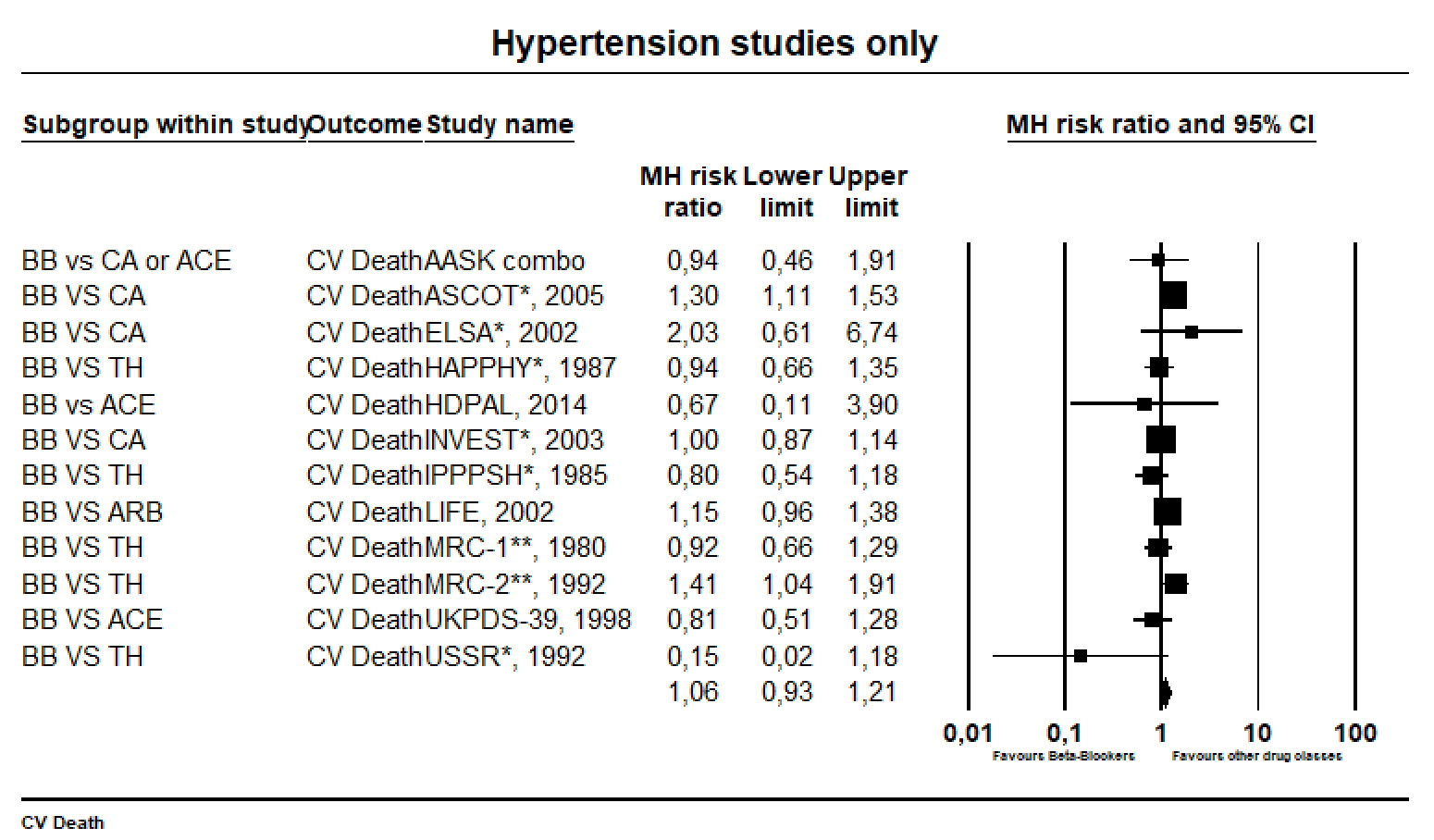
**12. Hypertension studies only, CHD**



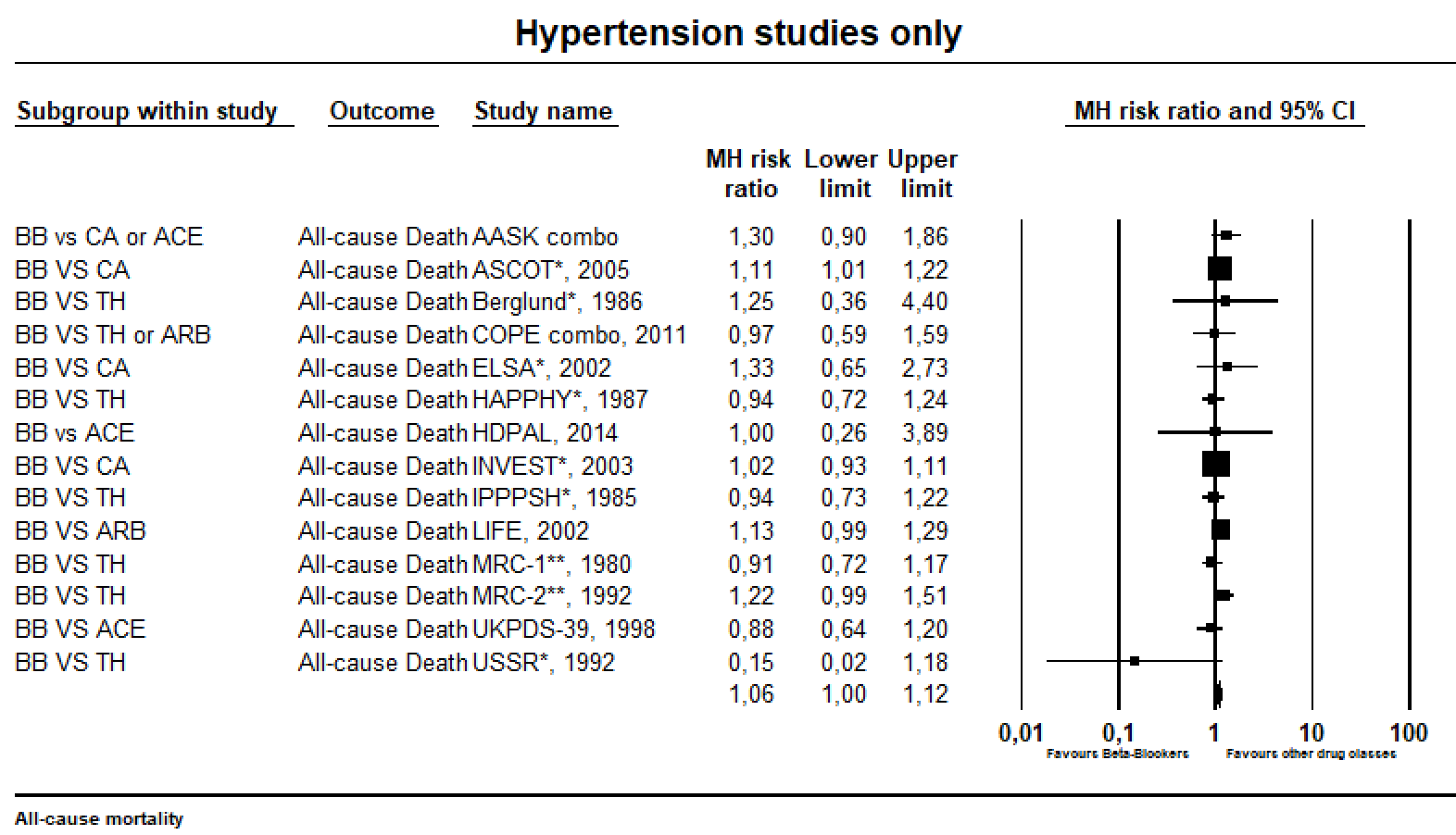
**13. Hypertension studies only, HF**



**14. Hypertension studies only, CV Death**



**15. Hypertension studies only, all-cause mortality**



**Supplementary References** (refer to Supplementary Table S2)

E1. Balcon R, Jewitt DE, Davies JPH, Oram S. A controlled trial of propranolol in acute myocardial infarction. Lancet 1996;ii:917-20.

E2. Clausen J, Felsby M, Jorgensen FS, Nielsen BL, Roin J, Strange B. Absence of prophylactic effect of propranolol in myocardial infarction. Lancet 1966;ii:920-4.

E3. Multicentre: Bath JCJL, Blake S, Bloom RA, Brown R, Fleming HA, Franklin AJ, et al. Propranolol in acute myocardial infarction: a multicentre trial. Lancet 1966;ii:1435-8.

E4. Barber JM, Murphy FM, Merrett JD. Clinical trial of propranolol in acute myocardial infarction. Ulster Med J. 1967;36:127-30

E5. Norris RM, Caughey DE, Scott PJ. Trial of propranolol in acute myocardial infarction. BMJ 1968;2:398-400.

E6. Kahler RL, Brill SJ, Perkins WE. The role of propranolol in the management of acute myocardial infarction. In: Kattus AA, Ross G, Hall YE, eds. Cardiovascular β adrenergic responses. Los Angeles, CA: California Press, 1968:213-22.

E7. Ledwich JR. A trial of propranolol in myocardial infarction. Can Med Assoc J 1968;98:988-94.

E8. Snow P. Treatment of acute myocardial infarction with propranolol. Am J Cardiol. 1966;18(3):458-462.

E9. Fuccella LM. Trasicor: review of the pharmacology and clinical results. S Afr Med J. 1969;Dec 6:Suppl:7-14.

E10. Briant RB, Norris RM. Alprenolol in acute myocardial infarction: double-blind trial. N Z Med J. 1970;71(454):135-138.

E11. Pitt B, Weiss JL, Schulze RA, Taylor DR, Kennedy HL, Caralis D. Reduction of myocardial infarct extension in man by propranolol. Circulation 1976;29(suppl 2):53-4.

E12. Lombardo M, Selvini A, Motolese M, et al., eds. Beta-blocking treatment in 440 cases of acute myocardial infarction: a study with oxprenolol. Proceedings of Florence International Meeting on Myocardial Infarction. Amsterdam: Excerpta Medica; 1979.

E13. Thompson PL, Jones AS, Noon D, Katavatis V. A randomised trial of oral β -blockade during myocardial infarction lack of effect on enzymatic indices of myocardial necrosis. Aust NZ J Med 1979;9:757

E14. Hutton I, Vallance BD, Beattie JM. A prospective randomized trial of propranolol in acute myocardial infarction. Excerta Med Inst Congr Ser 1979;2:824-6.

E15. Tonkin AM. β -blockade in acute myocardial infarction: inability of relatively late administration to influence infarct size and arrhythmias. Med J Aust 1981;2:145-6.

E16. Gupta RC, Sharma SK, Mittal SR. Effect of oral propranolol on the extent of acute anterior myocardial infarction. Abstracts of the ninth world congress on cardiology, Moscow. 1982;2:616.

E17. Wilcox RG, Rowley JM, Hampton JR, Mitchell JRA, Rolan JM, Banks DC. Randomised placebo-controlled trial comparing oxprenolol with diopryramide phosphate in immediate treatment of suspected myocardial infarction. Lancet 1980b;ii:765-769.

E18. Coronary Prevention Research Group (CPRG). An early intervention secondary prevention study with oxprenolol following myocardial infarction. Eur Heart J 1981;2:389-93.

E19. Yusuf S, Lopez R, Sleight P. Effect of atenolol on recovery of the electrocardiographic signs of myocardial infarction. Lancet 1979;ii:868-9.

E20. Roland JM, Wilcox RG, Banks DC, et al: Effect of beta-blockers on arrhythmias during six weeks after suspected myocardial infarction. Br Med J 1979; 2:518-521.

E21. Sloman G, Stannard M: Beta-adrenergic blockade and cardiac arrhythmias. Br Med J 1967;4:508-512.

E22. Waagstein F, Hjalmarson ÅC. Double blind study of the effect of cardioselective β -blockade on chest pain in acute myocardial infarction. Acta Med Scand 1975;587(suppl):201-11.

E23. Evemy KL, Pentecost BL: Intravenous and oral practolol in the acute stages of myocardial infarction. Eur J Cardiol 1978;7:391-398.

E24. Peter T, Norris RM, Clarke ED, et al: Reduction of enzyme levels by propranolol after acute myocardial infarction. Circulation 1978; 57:1091-1095.

E25. Norris RM, Clarke ED, Sammel NL, et al: Protective effect of propranolol in threatened myocardial infarction. Lancet 1978;2:907-909.

E26. Mueller HS, Ayres SM. Propranolol decreases sympathetic nervous activity reflected by plasma catecholamines during evolution of myocardial infarction in man. J Clin Invest 1980;65:338-46.

E27. Macleod A, Fananapazir L, Kitchin AH, Murray A, Neilson J.M. Prophylactic selective β -blockade in acute myocardial infarction. Abstracts of the VIII European Congress on Cardiology, Paris, 1980.

E28. Lloyd EA, Charles RG, Gordon GD, Adams CM, Mabin TA, Commerford PJ, et al. β -blockade by sotalol in early myocardial infarction decreases ventricular arrhythmias without increasing left ventricular volume. S Afr Med J1988;74:5-10.

E29. Azancot I, Lorente P, Georgiopoulos G, Beaufils P, Masquet C, Baudouy Y, et al. Effects of acebutolol on myocardial infarct extension: a randomized electrocardiographic enzymatic and angiographic study. Circulation 1982;66:986-94.

E30. Von Essen R, Merx W, Neis W, Ritz R. Wirkung von Metoprolol auf die Infarktröbe beim Akuten Myokardinfarkt: Doppelbindstudie. Deutsches Medizin Wochenschr 1982;107:1267-73.

E31. Nigam PD, Popli R, Charan S. Cardioprotection by β -blockade in acute myocardian infarction. Abstracts of the ninth world congress of cardiology, Moscow. 1983;2:616.

E32. Yusuf S, Sleight P, Rossi PRF, et al: Reduction in infarct size, arrhythmias, chest pain, and morbidity by early intravenous beta-blockade in suspected acute myocardial infarction. Circulation 1983;67 (pt 2):32-41.

E33. Federman J, Pitt A, Tonkin A, et al. Australian trial of intravenous and oral timolol in acute myocardial infarction. Circulation. 1984:70(Part 2):57th.

E34. Heber ME, Rosenthal E, Thomas N, Haskett VL, Burwood RD, Lutkin J, et al. Effect of labetalol on indices of myocardial necrosis in patients with suspected acute infarction. Eur Heart J 1987;8:11-18.

E35. Norris RM, Barnaby PF, Brown MA, Geary GG, Clarke ED, Logan RL, et al. Prevention of ventricular fibrillation during acute myocardial infarction by intravenous propranolol. Lancet 1984;ii:883-6.

E36. Gupta RC, Butaney B, Narang NK. Effect of iv propranolol on the extent of myocardial ischemic injury in patients of acute anterior myocardial infarction (AAMI). J Assoc Physicians India 1984;32:67-68.

E37. The TIMI Study Group. Comparison of invasive and conservative strategies after treatment with intravenous tissue plasminogen activator in acute myocardial infarction: results of the thrombolysis in myocardial infarction (TIMI) phase II trial. N Engl J Med 1989;320:618-27.

E38. Roberts R, Croft C, Gold HK, et al. Effect of propranolol on myocardial infarct size in a randomized blinded multicenter trial. N Engl J Med. 1984;311(4):218-225.

E39. Group MTR. Metoprolol in acute myocardial infarction (MIAMI). A randomised placebo-controlled international trial. Eur Heart J. 1985; 6(3):199-226.

E40. Owensby DA, O'Rourke MF. Failure of pindolol to alter determinants of myocardial oxygen requirements, enzyme release or clinical course in acute myocardial infarction. Circulation 1984;70(suppl II):156.

E41. Galcerá-Tomás J, Castillo-Soria FJ, Villegas-García M, et al. Effects of early use of atenolol or captopril on infarct size and ventricular volume A double-blind comparison in patients with anterior acute myocardial infarction. Circulation. 2001;103(6):813-819.

E42. First International Study of Infarct Survival Collaborative Group. Randomised trial of intravenous atenolol among 16<thin>027 cases of suspected acute myocardial infarction: ISIS1. Lancet 1986;ii:57-67.

E43. Golikov AP, Ryabinim VA, Yu V, et al: Propranolol treatment for myocardial infarction patients with the hyperdynamic syndrome. Kardiologia 1983;23:24-29.

E44. Johansson BW: A comparative study of cardioselectire beta-blockade and diazepam in patients with acute myocardial infarction and tachycardia. Acta Med Scand 1980;207:47.

E45. Mazur NA, Kulginskaya IV, Ivanova LA, Ostrovskaya TP, Smirnova TM, Svet EA, et al. Results of long term propranolol treatment in myocardial infarction survivors with advanced grades of ventricular extasystoles: randomized study. Cor Vasa 1984;26:241-7.

E46. Chen ZM, Pan HC, Chen YP, et al. Early intravenous then oral metoprolol in 45,852 patients with acute myocardial infarction: randomized placebo-controlled trial. Lancet. 2005;366(9497):1622-1632.

E47. Mitchell RG, Stoddard MF, Ben-Yehuda O, et al. Esmolol in acute ischemic syndromes. Am Heart J. 2002;144(5):E9.

E48. Gardtman M, Dellborg M, Brunnhage C, et al. Effect of intravenous metoprolol before hospital admission on chest pain in suspected acute myocardial infarction. Am Heart J. 1999;137(5):821-829.

E49. Herlitz J, Hjalmarson A, Swedberg K, et al. Effects on mortality during five years after early intervention with metoprolol in suspected acute myocardial infarction. Acta Med Scand. 1988;223(3):227-231.

E50. Reduction of infarct size by the early use of intravenous timolol in acute myocardial infarction. International Collaborative Study Group. Am J Cardiol. 1984;54(11):14E-15E.

E51. Roque F, Amuchastegui LM, Lopez Morillos MA, et al. Beneficial effects of timolol on infarct size and late ventricular tachycardia in patients with acute myocardial infarction. Circulation. 1987;76(3): 610-617.

E52. Rossi PR, Yusuf S, Ramsdale D, et al. Reduction of ventricular arrhythmias by early intravenous atenolol in suspected acute myocardial infarction. Br Med J (Clin Res Ed). 1983;286(6364):506-510.

E53. Curtis JL, Houghton JL, Patterson JH, Koch G, Bradley DA, Adams KF. Propranolol therapy alters estimation of potential cardiovascular risk derived from submaximal postinfarction exercise testing. Am Heart J 1991;121:1655.

E54. McMurray J, Lang CC, MacLean D, Struthers AD, McDevitt DG. Effects of xamaterol in acute myocardial infarction: blood pressure, heart rate, arrhythmias and early clinical course. Int J Cardiol 1991;31:295-304.

E55. Ranganathan N, Rautaharju PM, Jablonsky GC, Larochelle P, Lopez JF, Matangi MF. Prophylaxis of post myocardial infarction dysrhythmias by long term timolol therapy. Am Heart J 1988;115:340-50.

E56. Van de Werf F, Janssens L, Brzostek T, Mortelmans L, Wackers F, Willems GM, et al. Short term effects of early intravenous treatment with a β -adrenergic-blocking agent or a specific bradycardiac agent in patients with acute myocardial infarction receiving thrombolytic therapy. J Am Coll Cardiol 1993;22:407-16.

E57. Yang XS, Coupez R, Ector H, Kesteloot H, Geest HD. Effects of betaxolol on heart rate in patients with a recent transmural myocardial infarction. Acta Cardiol 1987;XLII:273-86.

E58. Pollock SG, Lystash J, Tedesco C, Craddock G, Smucker ML. Usefulness of bucindolol in congestive heart failure. Am J Cardiol. 1990;66:603-7.

E59. Woodley SL, Gilbert EM, Anderson JL, O’Connell JB, Deitchman D, Yanowitz FG, et al. Beta-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. Circulation. 1991;84:2426-41.

E60. Paolisso G, Gambardella A, Marrazzo G, Verza M, Teasuro P, Varricchio M, et al. Metabolic and cardiovascular benefits deriving from beta-adrenergic blockade in chronic congestive heart failure. Am Heart J. 1992;123:103-10.

E61. Olsen SL, Gilbert EM, Renlund DG, Taylor DO, Yanowitz FD, Bristow MR. Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. J Am Coll Cardiol. 1995;25:1225-31.

E62. Krum H, Sackner-Bernstein JD, Goldsmith RL, Kukin ML, Schwartz B, Penn J, et al. Double-blind, placebo-controlled study of the long-term efficacy of carvedilol in patients with severe chronic heart failure. Circulation. 1995;92:1499-506.

E63. Wisenbaugh T, Katz I, Davis J, Essop R, Skoularigis J, Middlemost S, et al. Long-term (3-month) effects of a new beta-blocker (nebivolol) on cardiac performance in dilated cardiomyopathy. J Am Coll Cardiol. 1993;21:1094-100.

E64. Eichhorn EJ, Heesch CM, Barnett JH, Alvarez LG, Fass SM, Grayburn PA, et al. Effect of metoprolol on myocardial function and energetics in patients with nonischemic dilated cardiomyopathy: a randomized, double-blind, placebo-controlled study. J Am Coll Cardiol. 1994;24:1310-20.

E65. Metra M, Nardi M, Giubbini R, Dei Cas L. Effects of short- and long-term carvedilol administration on rest and exercise hemodynamic variables, exercise capacity and clinical conditions in patients with idiopathic dilated cardiomyopathy. J Am Coll Cardiol. 1994;24:1678-87.

E66. Ozaydin M, Yucel H, Kocyigit S, et al. Nebivolol versus Carvedilol or Metoprolol in Patients Presenting with Acute Myocardial Infarction Complicated by Left Ventricular Dysfunction. Med Princ Pract. 2016;25:316-22.

E67. Bergström A, Andersson B, Edner M, et al. Effect of carvedilol on diastolic function in patients with diastolic heart failure and preserved systolic function. Results of the Swedish Doppler-echocardiographic study (SWEDIC). Eur J Heart Fail. 2004;6:453-61.

E68. Palazzuoli A, Quatrini I, Vecchiato L, Calabria P, Gennari L, Martini G, Nuti R. Left ventricular diastolic function improvement by carvedilol therapy in advanced heart failure. J Cardiovasc Pharmacol. 2005 Jun;45(6):563-8.

E69. Duprez DA, Florea N, Duval S, Koukol C, Cohn JN. Effect of nebivolol or atenolol vs. placebo on cardiovascular health in subjects with borderline blood pressure: the EVIDENCE study. J Hum Hypertens. 2017;32(1):20-25.

E70. Hansson NH, Sörensen J, Harms HJ et al. Metoprolol Reduces Hemodynamic and Metabolic Overload in Asymptomatic Aortic Valve Stenosis Patients: A Randomized Trial. Circ Cardiovasc Imaging. 2017 Oct;10(10). pii: e006557.

E71. Broch K, Urheim S, Lønnebakken MT, Stueflotten W, Massey R, Fosså K, Hopp E, Aakhus S, Gullestad L. Controlled release metoprolol for aortic regurgitation: a randomised clinical trial. Heart. 2016;102(3):191-7.

E72. Sumbria M, Negi PC, Sahai AK, Kaundal PK. To compare the effect of Telmisartan with Metoprolol on arterial stiffness in hypertension: prospective randomized parallel group trial. Indian Heart J. 2014;66(4):415-21.

E73. Guha S, Avasthi R, Narain VS, et al. A multicentric double blind randomised controlled trial of atenolol versus losartan as first line drug for mild to moderate essential hypertension. J Indian Med Assoc. 2013;111(12):821-825.

E74. Lin ZP, Dong M, Liu J. Bisoprolol improved endothelial function and myocardium survival of hypertension with stable angina: a randomized double-blinded trial. Eur Rev Med Pharmacol Sci. 2013;17(6):794-801.

E75. Saul SM, Duprez DA, Zhong W, Grandits GA, Cohn JN. Effect of carvedilol, lisinopril and their combination on vascular and cardiac health in patients with borderline blood pressure: the DETECT Study. J Hum Hypertens. 2013 Jun;27(6):362-7.

E76. Barrios V, Escobar C, Tomás JP, Calderon A, Echarri R. Comparison of the effects of doxazosin and atenolol on target organ damage in adults with type 2 diabetes mellitus and hypertension in the CARDHIAC study: a 9-month, prospective, randomized, open-label, blinded-evaluation trial. Clin Ther. 2008 Jan;30(1):98-107.

E77. Bakris GL, Iyengar M, Lukas MA, Ordronneau P, Weber MA. Effect of combining extended-release carvedilol and lisinopril in hypertension: results of the COSMOS study. Journal of Clinical Hypertension (Greenwich) 2010;12:678–86.

E78. Boissel JP, Collet JP, Lion L, Ducruet T, Moleur P, Luciani J, Milon H, Madonna O, Gillet J, Gerini P, et al. A randomized comparison of the effect of four antihypertensive monotherapies on the subjective quality of life in previously untreated asymptomatic patients: field trial in general practice. The OCAPI Study Group. Optimiser le Choix d'un Anti-hypertenseur de Première Intention. J Hypertens. 1995 Sep;13(9):1059-67.

E79. van der Does R, Hauf-Zachariou U, Pfarr E, Holtbrügge W, König S, Griffiths M, Lahiri A. Comparison of safety and efficacy of carvedilol and metoprolol in stable angina pectoris. Am J Cardiol. 1999 Mar 1;83(5):643-9.

E80. Protogerou A, Blacher J, Stergiou GS, Achimastos A, Safar ME. Blood pressure response under chronic antihypertensive drug therapy: the role of aortic stiffness in the REASON (Preterax in Regression of Arterial Stiffness in a Controlled Double-Blind) study. Journal of the American College of Cardiology 2009;53:445–51.

E81. Radchenko GD, Sirenko YM, Kushnir SM, Torbas OO, Dobrokhod AS. Comparative effectiveness of a fixed-dose combination of losartan + HCTZ versus bisoprolol + HCTZ in patients with moderate-to-severe hypertension: results of the 6-month ELIZA trial. Vasc Health Risk Manag. 2013;9:535-49.

E82. Malmqvist K, Kahan T, Edner M, Held C, Hägg A, Lind L, Müller-Brunotte R, Nyström F, Ohman KP, Osbakken MD, Ostergern J. Regression of left ventricular hypertrophy in human hypertension with irbesartan. J Hypertens. 2001 Jun;19(6):1167-76.

E83. Kim EJ, Song WH, Lee JU, Shin MS, Lee S, Kim BO, Hong KS, Han SW, Park CG, Seo HS. Efficacy of losartan and carvedilol on central hemodynamics in hypertensives: a prospective, randomized, open, blinded end point, multicenter study. Hypertens Res. 2014 Jan;37(1):50-6.

E84. Karabacak M, Doğan A, Tayyar Ş, Özaydın M, Erdoğan D. Carvedilol and nebivolol improve left ventricular systolic functions in patients with non-ischemic heart failure. Anatol J Cardiol. 2015 Apr;15(4):271-6.

E85. Galzerano D1, Di Michele S, Paolisso G, Tuccillo B, Lama D, Carbotta S, Cittadini A, Tedesco MA, Gaudio C. A multicentre, randomized study of telmisartan versus carvedilol for prevention of atrial fibrillation recurrence in hypertensive patients. J Renin Angiotensin Aldosterone Syst. 2012 Dec;13(4):496-503

E86. Potter JF, Robinson TG, Ford GA, Mistri A, James M, Chernova J, Jagger C. Controlling hypertension and hypotension immediately post-stroke (CHHIPS): a randomised, placebo-controlled, double-blind pilot trial. Lancet Neurol. 2009;8(1):48-56.

E87. Mittal N, Shafiq N, Reddy S, Malhotra S, Kumari S, Varma S. Evaluation of efficacy of metoprolol in patients having heart failure with preserved ejection fraction: A randomized, double-blind, placebo-controlled pilot trial. Perspect Clin Res. 2017 Jul-Sep;8(3):124-131

E88. Roolvink V, Ibáñez B, Ottervanger JP, et al. Early Intravenous Beta-Blockers in Patients With ST-Segment Elevation Myocardial Infarction Before Primary Percutaneous Coronary Intervention. J Am Coll Cardiol. 2016 Jun 14;67(23):2705-2715.

E89. POISE Study Group, Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P. Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): a randomised controlled trial. Lancet. 2008 May 31;371(9627):1839-47.

E90. Woodley SL, Gilbert EM, Anderson JL, O'Connell JB, Deitchman D, Yanowitz FG, Mealey PC, Volkman K, Renlund DG, Menlove R, et al. Beta-blockade with bucindolol in heart failure caused by ischemic versus idiopathic dilated cardiomyopathy. Circulation. 1991 Dec;84(6):2426-41.

E91. Olsen SL, Gilbert EM, Renlund DG, Taylor DO, Yanowitz FD, Bristow MR. Carvedilol improves left ventricular function and symptoms in chronic heart failure: a double-blind randomized study. J Am Coll Cardiol. 1995;25:1225-31.

E92. Ibanez B, Macaya C, Sánchez-Brunete V, et al. Effect of early metoprolol on infarct size in ST-segment-elevation myocardial infarction patients undergoing primary percutaneous coronary intervention: the Effect of Metoprolol in Cardioprotection During an Acute Myocardial Infarction (METOCARD-CNIC) trial. Circulation. 2013 Oct 1;128(14):1495-503.

E93. Roqué F, Amuchastegui LM, Lopez Morillos MA, Mon GA, Girotti AL, Drajer S, Fortunato M, Moreyra E, Tuero P, Solchaga JC, et al. Beneficial effects of timolol on infarct size and late ventricular tachycardia in patients with acute myocardial infarction. Circulation. 1987 Sep;76(3):610-7.

E94. Boutouyrie P, Beaussier H, Achouba A, Laurent S; EXPLOR trialists. Destiffening effect of valsartan and atenolol: influence of heart rate and blood pressure. J Hypertens. 2014 Jan;32(1):108-14.

E95. Giles TD, Khan BV, Lato J, Brener L, Ma Y, Lukic T. Nebivolol monotherapy in younger adults (younger than 55 years) with hypertension: a randomized, placebo-controlled trial. J Clin Hypertens (Greenwich). 2013 Sep;15(9):687-93.

E96. Lewin A, Punzi H, Luo X, Stapff M. Nebivolol monotherapy for patients with systolic stage II hypertension: results of a randomized, placebo-controlled trial. Clin Ther. 2013;35(2):142-52.

E97. Studinger P, Tabák ÁG, Chen CH, Salvi P, Othmane TE, Torzsa P, Kapocsi J, Fekete BC, Tislér A. The effect of low-dose carvedilol, nebivolol, and metoprolol on central arterial pressure and its determinants: a randomized clinical trial. J Clin Hypertens (Greenwich). 2013 Dec;15(12):910-7.

E98. Contini M, Apostolo A, Cattadori G, et al. Multiparametric comparison of CARvedilol, vs. NEbivolol, vs. BIsoprolol in moderate heart failure: the CARNEBI trial. Int J Cardiol. 2013 Oct 3;168(3):2134-40.

E99. Hori M, Nagai R, Izumi T, Matsuzaki M. Efficacy and safety of bisoprolol fumarate compared with carvedilol in Japanese patients with chronic heart failure: results of the randomized, controlled, double-blind, Multistep Administration of bisoprolol IN Chronic Heart Failure II (MAIN-CHF II) study. Heart Vessels. 2014 Mar;29(2):238-47.

E100. Fröhlich H, Zhao J, Täger T, Cebola R, Schellberg D, Katus HA, Grundtvig M, Hole T, Atar D, Agewall S, Frankenstein L. Carvedilol Compared With Metoprolol Succinate in the Treatment and Prognosis of Patients With Stable Chronic Heart Failure: Carvedilol or Metoprolol Evaluation Study. Circ Heart Fail. 2015 Sep;8(5):887-96.

E101. Hjalmarson A, Elmfeldt D, Herlitz J, et al: Effect on mortality of metoprolol in acute myocardial infarction: A double-blind randomised trial. Lancet 1981; 2:823-827.

E102. Poole-Wilson PA, Swedberg K, Cleland JG, Di Lenarda A, Hanrath P, Komajda M, Lubsen J, Lutiger B, Metra M, Remme WJ, Torp-Pedersen C, Scherhag A, Skene A; Carvedilol Or Metoprolol European Trial Investigators. Comparison of carvedilol and metoprolol on clinical outcomes in patients with chronic heart failure in the Carvedilol Or Metoprolol European Trial (COMET): randomised controlled trial. Lancet. 2003 Jul 5;362(9377):7-13.

E103. Boberg J, Larsen FF, Pehrsson SK. The effects of beta blockade with (epanolol) and without (atenolol) intrinsic sympathomimetic activity in stable angina pectoris. The Visacor Study Group. Clin Cardiol. 1992 Aug;15(8):591-5.

E104. Bakris GL, Fonseca V, Katholi RE, McGill JB, Messerli FH, Phillips RA, Raskin P, Wright JT Jr, Oakes R, Lukas MA, Anderson KM, Bell DS; GEMINI Investigators. Metabolic effects of carvedilol vs metoprolol in patients with type 2 diabetes mellitus and hypertension: a randomized controlled trial. JAMA. 2004 Nov 10;292(18):2227-36.

E105. Jonsson G, Abdelnoor M, Müller C, Kjeldsen SE, Os I, Westheim A. A comparison of the two beta-blockers carvedilol and atenolol on left ventricular ejection fraction and clinical endpoints after myocardial infarction. a single-centre, randomized study of 232 patients. Cardiology. 2005;103(3):148-55.

E106. Kukin ML, Kalman J, Charney RH, Levy DK, Buchholz-Varley C, Ocampo ON, Eng C. Prospective, randomized comparison of effect of long-term treatment with metoprolol or carvedilol on symptoms, exercise, ejection fraction, and oxidative stress in heart failure. Circulation. 1999 May 25;99(20):2645-51.

E107. Figulla HR, Krzeminska-Pakula M, Wrabec K, Chochola J, Kalmbach C, Fridl P. Betaxolol is equivalent to carvedilol in patients with heart failure NYHA II or III: result of a randomized multicenter trial (BETACAR Trial). Int J Cardiol. 2006 Nov 10;113(2):153-60.

E108. Metra M, Giubbini R, Nodari S, Boldi E, Modena MG, Dei Cas L. Differential effects of beta-blockers in patients with heart failure: A prospective, randomized, double-blind comparison of the long-term effects of metoprolol versus carvedilol. Circulation. 2000 Aug 1;102(5):546-51.

E109. Toyoda S, Haruyama A, Inami S, Amano H, Arikawa T, Sakuma M, Abe S, Tanaka A, Node K, Inoue T. Protective effects of bisoprolol against myocardial injury and pulmonary dysfunction in patients with chronic heart failure. Int J Cardiol. 2017 Jan 1;226:71-76.

E110. Yang T, Jiang Y, Hao Y, Zhou S, Xu X, Qu B, Lin X, Ma T. Comparison of bisoprolol to a metoprolol CR/ZOK tablet for control of heart rate and blood pressure in mild-to-moderate hypertensive patients: the CREATIVE study. Hypertens Res. 2017 Jan;40(1):79-86.

E111. Oh PC, Kang WC, Moon J, Park YM, Kim S, Kim MG, Lee K, Ahn T, Shin EK. Anti-Anginal and Metabolic Effects of Carvedilol and Atenolol in Patients with Stable Angina Pectoris: A Prospective, Randomized, Parallel, Open-Label Study. Am J Cardiovasc Drugs. 2016 Jun;16(3):221-8.

E112. Hung OY, Molony D, Corban MT, et al. Comprehensive Assessment of Coronary Plaque Progression With Advanced Intravascular Imaging, Physiological Measures, and Wall Shear Stress: A Pilot Double-Blinded Randomized Controlled Clinical Trial of Nebivolol Versus Atenolol in Nonobstructive Coronary Artery Disease. J Am Heart Assoc. 2016 Jan 25;5(1). pii: e002764.

E113. Gelbrich G, Edelmann F, Inkrot S, Lainscak M, Apostolovic S, Neskovic AN, Waagstein F, Loeffler M, Anker SD, Dietz R, Düngen HD; CIBIS-ELD investigators. Is target dose the treatment target? Uptitrating beta-blockers for heart failure in the elderly. Int J Cardiol. 2012 Feb 23;155(1):160-6.

E114. Erdil N, Kaynak M, Dönmez K, Disli OM, Battaloglu B. Nebivolol in preventing atrial fibrillation following coronary surgery in patients over 60 years of age. Rev Bras Cir Cardiovasc. 2014 Oct-Dec;29(4):581-7.

E115. Redón J, Pascual-Izuel JM, Rodilla E, Vicente A, Oliván J, Bonet J, Torguet JP, Calaforra O, Almirall J. Effects of nebivolol and atenolol on central aortic pressure in hypertensive patients: a multicenter, randomized, double-blind study. Blood Press. 2014 Jun;23(3):181-8.

E116. Briasoulis A, Oliva R, Kalaitzidis R, Flynn C, Lazich I, Schlaffer C, Bakris G. Effects of nebivolol on aortic compliance in patients with diabetes and maximal renin angiotensin system blockade: the EFFORT study. J Clin Hypertens (Greenwich). 2013 Jul;15(7):473-9.

E117. Park S, Rhee MY, Lee SY, Park SW, Jeon D, Kim BW, Kwan J, Choi D. A prospective, randomized, open-label, active-controlled, clinical trial to assess central haemodynamic effects of bisoprolol and atenolol in hypertensive patients. J Hypertens. 2013 Apr;31(4):813-9.

E118. Williams B, MacDonald TM, Morant S, Webb DJ, Sever P, McInnes G, Ford I, Cruickshank JK, Caulfield MJ, Salsbury J, Mackenzie I, Padmanabhan S, Brown MJ; British Hypertension Society's PATHWAY Studies Group. Spironolactone versus placebo, bisoprolol, and doxazosin to determine the optimal treatment for drug-resistant hypertension (PATHWAY-2): a randomised, double-blind, crossover trial. Lancet. 2015 Nov 21;386(10008):2059-2068.

E119. Findlay IN, MacLeod K, Gillen G, Elliott AT, Aitchison T, Dargie HJ. A double blind placebo controlled comparison of verapamil, atenolol, and their combination in patients with chronic stable angina pectoris. Br Heart J. 1987 Apr;57(4):336-43.

E120. Hopkinson ND, Hui KP, Smith MP, Hollinrake K. A comparison of sustained release verapamil versus atenolol for 24 h protection from exercise-induced angina pectoris. Eur Heart J. 1991 Dec;12(12):1273-7.

E121. Jiang J, Cong H, Zhang Y, Li Z, Tao G, Li X, Qing L, Tan N, Zhao Z, Dong Y, Ji Z, Chen Y, Ge J, He B, Sun Y, Cao K, Huo Y. Effect of Metoprolol Succinate in Patients with Stable Angina and Elevated Heart Rate Receiving Low-Dose β-Blocker Therapy. Int J Med Sci. 2017 Apr 9;14(5):477-483.

E122. Inoue H, Atarashi H, Okumura K, Yamashita T, Fukuzawa M, Shiosakai K, Kimura T. Heart rate control by carvedilol in Japanese patients with chronic atrial fibrillation: The AF Carvedilol study. J Cardiol. 2017 Jan;69(1):293-301.

E123. Gattis WA, O'Connor CM, Gallup DS, Hasselblad V, Gheorghiade M; IMPACT-HF Investigators and Coordinators. Predischarge initiation of carvedilol in patients hospitalized for decompensated heart failure: results of the Initiation Management Predischarge: Process for Assessment of Carvedilol Therapy in Heart Failure (IMPACT-HF) trial. J Am Coll Cardiol. 2004 May 5;43(9):1534-41.

E124 Okamoto H, Hori M, Matsuzaki M, Tsutsui H, Yamazaki T, Nagai R, Yoshikawa T, Fujio Y, Nonen S, Azuma J, Izumi T, Ohashi Y, Kitabatake A; J-CHF Investigators.Minimal dose for effective clinical outcome and predictive factors for responsiveness to carvedilol: Japanese chronic heart failure (J-CHF) study. Int J Cardiol. 2013 Apr 5;164(2):238-44.

E125. Everts B, Karlson B, Abdon NJ, et al. A comparison of metoprolol and morphine in the treatment of chest pain in patients with suspected acute myocardial infarctionethe MEMO study. J Intern Med. 1999;245(2):133-141.

E126. Forteza A, Evangelista A, Sánchez V, Teixidó-Turà G, Sanz P, Gutiérrez L, Gracia T, Centeno J, Rodríguez-Palomares J, Rufilanchas JJ, Cortina J, Ferreira-González I, García-Dorado D. Efficacy of losartan vs. atenolol for the prevention of aortic dilation in Marfan syndrome: a randomized clinical trial. Eur Heart J. 2016 Mar 21;37(12):978-85.

E127. Sandor GG, Alghamdi MH, Raffin LA, Potts MT, Williams LD, Potts JE, Kiess M, van Breemen C. A randomized, double blind pilot study to assess the effects of losartan vs. atenolol on the biophysical properties of the aorta in patients with Marfan and Loeys-Dietz syndromes. Int J Cardiol. 2015 Jan 20;179:470-5.

E128. Lacro RV, Dietz HC, Sleeper LA, Yetman AT, Bradley TJ, Colan SD, Pearson GD, Selamet Tierney ES, Levine JC, Atz AM, Benson DW, Braverman AC, Chen S, De Backer J, Gelb BD, Grossfeld PD, Klein GL, Lai WW, Liou A, Loeys BL, Markham LW, Olson AK, Paridon SM, Pemberton VL, Pierpont ME, Pyeritz RE, Radojewski E, Roman MJ, Sharkey AM, Stylianou MP, Wechsler SB, Young LT, Mahony L; Pediatric Heart Network Investigators. Atenolol versus losartan in children and young adults with Marfan's syndrome. N Engl J Med. 2014 Nov 27;371(22):2061-71.

E129. Conraads VM, Metra M, Kamp O, De Keulenaer GW, Pieske B, Zamorano J, Vardas PE, Böhm M, Dei Cas L: Effects of the long-term administration of nebivolol on the clinical symptoms, exercise capacity, and left ventricular function of patients with diastolic dysfunction: results of the ELANDD study. Eur J Heart Fail 2012, 14:219-225.

E130. Takeda Y, Fukutomi T, Suzuki S et al. Effects of carvedilol on plasma B-Type natriuretic peptide concentration and symptoms in patients with heart failure and preserved ejection fraction. Am J Cardiol 2004;94:448-453.

E131. Bristow MR, O'Connell JB, Gilbert EM, French WJ, Leatherman G, Kantrowitz NE, Orie J, Smucker ML, Marshall G, Kelly P, et al, Dose-response of chronic beta-blocker treatment in heart failure from either idiopathic dilated or ischemic cardiomyopathy. Bucindolol Investigators. Circulation 1994; 89:1632-1642.

E132. Er F, Dahlem KM, Nia AM, Erdmann E, Waltenberger J, Hellmich M, Kuhr K, Le MT, Herrfurth T, Taghiyev Z, Biesenbach E, Yüksel D, Eran-Ergöknil A, Vanezi M, Caglayan E, Gassanov N. Randomized Control of Sympathetic Drive With Continuous Intravenous Esmolol in Patients With Acute ST-Segment Elevation Myocardial Infarction: The BEtA-Blocker Therapy in Acute Myocardial Infarction (BEAT-AMI) Trial. JACC Cardiovasc Interv. 2016;9(3):231-240.

E133. Dietz R, Dechend R, Yu CM, Bheda M, Ford J, Prescott MF, Keefe DL. Effects of the direct renin inhibitor aliskiren and atenolol alone or in combination in patients with hypertension. J Renin Angiotensin Aldosterone Syst. 2008;9:163-175.

E134. Nilsson P. Antihypertensive efficacy of zofenopril compared with atenolol in patients with mild to moderate hypertension. Blood Press Suppl. 2007;2:25-30.

E135. Savonitto S, Ardissiono D, Egstrup K, Rasmussen K, Bae EA, Omland T, Schjelderup-Mathiesen PM, Marraccini P, Wahlqvist I, Merlini PA, Rehnqvist N. Combination therapy with metoprolol and nifedipine versus monotherapy in patients with stable angina pectoris. Results of the International Multicenter Angina Exercise (IMAGE) Study. J Am Coll Cardiol. 1996;27(2):311-6.

E136. Pehrsson SK, Ringqvist I, Ekdahl S, Karlson BW, Ulvenstam G, Persson S. Monotherapy with amlodipine or atenolol versus their combination in stable angina pectoris. Clin Cardiol. 2000;23(10):763-770.

E137. von Arnim T. Medical treatment to reduce total ischemic burden: total ischemic burden bisoprolol study (TIBBS), a multicenter trial comparing bisoprolol and nifedipine. The TIBBS Investigators. J Am Coll Cardiol. 1995;25(1):231-8.

E138. Grassi G, Seravalle G, Brambilla G, Dell'Oro R, Trevano FQ, Fici F, van Bortel L, Mancia G. Multicenter Randomized Double-Blind Comparison of Nebivolol plus HCTZ and Irbesartan plus HCTZ in the Treatment of Isolated Systolic Hypertension in Elderly Patients: Results of the NEHIS Study. Adv Ther. 2017;33(12):2173-2187.

E139. Weber MA, Basile J, Stapff M, Khan B, Zhou D. Blood pressure effects of combined β-blocker and angiotensin-converting enzyme inhibitor therapy compared with the individual agents: a placebo-controlled study with nebivolol and lisinopril. J Clin Hypertens (Greenwich). 2012;14(9):588-592.

E140. Marazzi G, Volterrani M, Caminiti G, Iaia L, Massaro R, Vitale C, Sposato B, Mercuro G, Rosano G. Comparative long term effects of nebivolol and carvedilol in hypertensive heart failure patients. J Card Fail. 2011 Sep;17:703-709.

E141. Dahlof B, Lindholm LH, Hansson L, Schersten B, Ekbom T, Wester PO. Morbidity and mortality in the Swedish Trial in Old Patients with Hypertension (STOP-Hypertension). Lancet 1991; 338:1281–1285.

E142. Hansson L, Lindholm LH, Niskanen L, Lanke J, Hedner T, Niklason A, et al. Effect of angiotensin-converting-enzyme inhibition compared with conventional therapy on cardiovascular morbidity and mortalityin hypertension: the Captopril Prevention Project (CAPPP) randomized trial. Lancet 1999; 353:611–616.

E143. Hansson L, Hedner T, Lund-Johansen P, Kjeldsen SE, Lindholm LH, Syvertsen JO, et al. Randomised trial of effects of calcium antagonists compared with diuretics and beta-blockers on cardiovascular morbidity and mortality in hypertension: the Nordic Diltiazem (NORDIL) study. Lancet 2000; 356:359-365.

E144. Hansson L, Lindholm LH, Ekbom T, Dahlof B, Lanke J, Scherste´n B, et al. Randomised trial of old and new antihypertensive drugs in elderly patients: cardiovascular mortality and morbidity. The Swedish Trial in Old Patients with Hypertension-2 study. Lancet 1999; 354:1751-1756.

E145. Zidek W, Schrader J, Lüders S, Matthaei S, Hasslacher C, Hoyer J, et al. First-line antihypertensive treatment in patients with pre-diabetes: rationale, design and baseline results of the ADaPT investigation. Cardiovascular Diabetology 2008;7:22.

E146. Wikstrand J, Warnold I, Olsson G, Tuomilehto J, Elmfeldt D, Berglund G. Primary prevention with metoprolol in patients with hypertension. Mortality results from the MAPHY study. JAMA. 1988;259(13):1976-82.