

**The association between antihypertensive treatment and adverse events: a systematic review and meta-analysis of 58 randomised controlled trials including 280,638 patients with hypertension**

**Supplementary material**

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**Supplementary table 1.** Medline search strategy

| # ▲ | Search terms                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
|-----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 1   | hypertension/ or hypertension, malignant/ or hypertension, renal/ or hypertension, renovascular/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 2   | (hypertens* or antihypertens* or anti-hypertens* or blood pressure).ti.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 3   | *Blood Pressure/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 4   | *diastole/ or *systole/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 5   | (BP or DBP or SBP).ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 6   | ((diastol* or systol* or arterial) adj3 (pressure* or bp or mmHg or mmHg)).ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                |
| 7   | 1 or 2 or 3 or 4 or 5 or 6                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 8   | antihypertensive agents/ or acebutolol/ or alprenolol/ or amlodipine/ or atenolol/ or bendroflumethiazide/ or bepridil/ or betaxolol/ or bethanidine/ or bisoprolol/ or bupranolol/ or captopril/ or carteolol/ or celiprolol/ or chlorisondamine/ or chlorothiazide/ or chlorthalidone/ or cilazapril/ or clonidine/ or cyclopenthiazide/ or diazoxide/ or dihydralazine/ or diltiazem/ or doxazosin/ or enalapril/ or enalaprilat/ or felodipine/ or fosinopril/ or guanabenz/ or hydralazine/ or hydrochlorothiazide/ or hydroflumethiazide/ or indapamide/ or indoramin/ or isradipine/ or labetalol/ or lisinopril/ or losartan/ or methyldopa/ or metipranolol/ or metolazone/ or metoprolol/ or mibefradil/ or minoxidil/ or nadolol/ or nicardipine/ or nimodipine/ or nisoldipine/ or nitrendipine/ or oxprenolol/ or pempidine/ or penbutolol/ or perindopril/ or pinacidil/ or pindolol/ or polythiazide/ or prazosin/ or propranolol/ or ramipril/ or timolol/ or todralazine/ or trichlormethiazide/ or xipamide/ or (antihypertensive or anti-hypertensive).ti,ab. |
| 9   | adrenergic alpha-antagonists/ or adrenergic alpha-1 receptor antagonists/ or doxazosin/ or indoramin/ or labetalol/ or prazosin/ or adrenergic alpha-2 receptor antagonists/ or adrenergic beta-antagonists/ or alprenolol/ or bupranolol/ or carteolol/ or dihydroalprenolol/ or metipranolol/ or nadolol/ or oxprenolol/ or penbutolol/ or pindolol/ or propranolol/ or sotalol/ or timolol/ or adrenergic beta-1 receptor antagonists/ or acebutolol/ or atenolol/ or betaxolol/ or bisoprolol/ or celiprolol/ or metoprolol/ or adrenergic beta-2 receptor antagonists/ or adrenergic beta-3 receptor antagonists/ or (adrenergic alpha-antagonist* or adrenergic alphaantagonist*).ti,ab.                                                                                                                                                                                                                                                                                                                                                                                   |
| 10  | angiotensin-converting enzyme inhibitors/ or captopril/ or cilazapril/ or enalapril/ or enalaprilat/ or fosinopril/ or lisinopril/ or perindopril/ or ramipril/ or angiotensin-converting enzyme inhibitor*.ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 11  | angiotensin receptor antagonists/ or angiotensin ii type 1 receptor blockers/ or losartan/ or saralasin/ or angiotensin ii type 2 receptor blockers/ or angiotensin receptor antagonist*.ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 12  | calcium channel blockers/ or amlodipine/ or amrinone/ or bencyclane/ or bepridil/ or diltiazem/ or felodipine/ or fendiline/ or flunarizine/ or gallopamil/ or isradipine/ or lidoflazine/ or mibefradil/ or nicardipine/ or nifedipine/ or nimodipine/ or nisoldipine/ or nitrendipine/ or tiapamil hydrochloride/ or verapamil/ or calcium channel blocker*.ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 13  | diuretics/ or amiloride/ or bendroflumethiazide/ or chlorthalidone/ or cyclopenthiazide/ or furosemide/ or hydrochlorothiazide/ or hydroflumethiazide/ or indapamide/ or mefruside/ or methazolamide/ or methyclothiazide/ or metolazone/ or polythiazide/ or spironolactone/ or ticrynafen/ or triamterene/ or trichlormethiazide/ or xipamide/ or diuretics, osmotic/ or diuretics, potassium sparing/ or epithelial sodium channel blockers/ or mineralocorticoid receptor antagonists/ or sodium chloride symporter inhibitors/ or sodium potassium chloride symporter inhibitors/ or diuretic*.ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
|----|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| 14 | vasodilator agents/ or bencyclane/ or bepridil/ or celiprolol/ or chromonar/ or colforsin/ or cromakalim/ or cyclandelate/ or diazoxide/ or dilazep/ or diltiazem/ or enoximone/ or ergoloid mesylates/ or erythritol/ or flunarizine/ or iloprost/ or isradipine/ or lidoflazine/ or minoxidil/ or molsidomine/ or nicardipine/ or nicergoline/ or nifedipine/ or nimodipine/ or nisoldipine/ or nitrendipine/ or nylidrin/ or oxprenolol/ or oxyfedrine/ or perhexiline/ or phenoxybenzamine/ or pinacidil/ or pindolol/ or prenylamine/ or s-nitrosoglutathione/ or suloctidil/ or trapidil/ or trimetazidine/ or verapamil/ or vasodilator*.ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 15 | Aldosterone/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 16 | Chlorisondamine/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 17 | Mineralocorticoids/ or Desoxycorticosterone/ or Desoxycorticosterone Acetate/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                 |
| 18 | Pempidine/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 19 | Renin-Angiotensin System/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 20 | (accupro or accuretic or acebutolol or acepril or acezide or adalat or adanif or adcirca or adipine or adizem or aldomet or aliskiren or alphavase or ambrisentan or amias or amiloride or amlodipine or amlostin or angilol or angiopine or angiozem or angitol or antipressan or apresoline or aprinox or aprovel or apsolox or atenamin or atenix or atenolol or baratol or baycaron or bedranol or bendroflumethiazide or benthiazide or berkatens or berkolol or berkozide or beta-adalat or beta-cardone or betadur or betaloc or beta-progane or bi-carzem or bipranix or bisoprolol or blocadren or bosentan or brevibloc or britazim or cabren or calanif or calazem or calchan or calcicard or calcilat or candesartan or capoten or capozide or capto-co or captomex or captopril or captopril or caracace or carace or cardene or cardicor or cardide or cardilate or cardioplen or cardozin or cardura or carvedilol or cascor or catapres or celectol or celiprolol or centyl or chlorothaizide or chlortalidone or cilazapril or ciolixil or clonidine or clopamide or co-amilozone or coaprovel or co-betaloc or co-diovan or congescor or co-prenozide or coracten or cordilox or corgard or corgaretic or coroday or co-tenidone or co-tenidone or coversyl or cozaar or co-zidocapt or cyclopenthiazide or cyclopenthiazide or delvas or diazoxide or dibenylamine or dilcardia or diltiazem or dilzem or diovan or disogram or diurexan or diuril or dopamet or doxadura or doxazosin or ecopace or ednyt or emcor or enalapril or enalapril or enduron or eprosartan or esidrex or esmolol or ethibide or ethimil or eucardic or exforge or felendil or felodipine or felogen or felotens or fortipine or fosinopril or genalat or gopten or horizem or hydralazine or hydrenox or hydrochlorothiazide or hydroflumethiazide or hydromet or hygroton or hypertene or hypolar or hypovase or hytrin or iloprost or imidapril or indapamide or inderal or indipam or indoramin or innovace or innozone or irbesartan or isradipine or istin or kalspare or kalten or kaplon or keloc or kenzem or labetalol or labrocol or lacidipine or larbex or lercanidipine or lisinopril or lisopress or loniten or lopace or lopranol or lopresor or lopresoretic or lopresoretic or losartan or mapamid or mefruside or mepranix or meprobamate or metalpha or metenix or methyclothiazide or methyldopa or metolazone or metoprolol or metoros or metoprolol or micardis or minoxidil or moducron or moduretic or moexipril or monocor or motens or moxonidine or nadolol or natramid or natrilix or navidrex or nebivolol or neo-bendromax or neofel or neo-naclex or neozipine or nephril or nicardipine or nifedipine or nifedipress or nifelease or nimodrel or nimotop or nindaxa or nivaten or normetic or noyada or odrik or olmesartan or olmetec or optil or opumide or oxprenolol or parmid or perdix or perindopril or perindopril or phenoxybenzamine or phentolamine or physiotens or pindolol or pinodolod or plendil or pralenal or prazosin or prescal or prestim or probeta or propanix or propranolol or quinapril or quinil or ramipril or ranvera or raptorsin or rapranol or rasilez or rawel or retalzem or revatio or rogatine or saluric or secadrex or sectral or securon or sevika or sildenafil or slocinx or slofedipine or slo-pro or slopronol or slow-pren or slozem or sodium nitroprusside or sotacor or sotalol |

|    |                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
|----|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
|    | or spiro-co spironolactone or spiroprop or staril or syprol or tadalafil or tanatril or tarka or telmisartan or tenavoid or tenben or tenchlor or tenif or tenoret or tenoretic or tenormin or tensaid or tensipine or tensopril or terazosin or teveten or tildiem or timolol or tolerzide or totamol or totaretic or tracleer or trandate or trandolapril or trasicor or trasidrex or triamterene or triapin or tritace or uard or unipine or univer or valasartan or valni or varbim or vasaten or vascace or vascalpha or ventavis or verapamil or verapress or vera-til or vertab or viazem or visken or vivacor or xipamide or xuret or zanidip or zaroxolyn or zemret or zemtard or zestoretic or zestril or zida-co zildil or zolvera).mp. |
| 21 | 8 or 9 or 10 or 11 or 12 or 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 22 | exp Kidney Diseases/ or exp Kidney Failure, Chronic/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 23 | hypotension/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 24 | syncope/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 25 | electrolyte abnormalities/ or hypercalcemia/ or hypomagnesemia/ or hypophosphatemia/ or hyperkalemia/ or hypokalemia/ or hyponatremia/ or hyperglycemia/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 26 | gout/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                              |
| 27 | accidental falls/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 28 | exp fractures, bone/                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 29 | ((((kidney or renal) adj2 (injur* or failure or insufficienc*)) or aki).ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 30 | (falls or fracture? or syncope).ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 31 | (electrolyte? or hypercalc* or hypomagnes* or hypophosphat* or hyperkal* or hypokal* or hyponatr* or hypoglyc*).ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                             |
| 32 | hypotensi*.ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                  |
| 33 | gout.ti,ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 34 | 22 or 23 or 24 or 25 or 26 or 27 or 28 or 29 or 30 or 31 or 32 or 33                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                               |
| 35 | 7 and 21 and 34                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 36 | randomized controlled trial.pt.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                    |
| 37 | controlled clinical trial.pt.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                      |
| 38 | randomized.ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                     |
| 39 | placebo.ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 40 | drug therapy.fs.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                   |
| 41 | randomly.ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 42 | trial.ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 43 | groups.ab.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                         |
| 44 | 36 or 37 or 38 or 39 or 40 or 41 or 42 or 43                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                       |
| 45 | exp animals/ not humans.sh.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                        |
| 46 | 44 not 45                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 47 | 35 and 46                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |
| 48 | (case reports or comment or editorial or letter or news or "review").pt.                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                           |
| 49 | 47 not 48                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                                          |

**Supplementary table 2.** Risk of bias assessment for included trials

| Study                                           | Randomization process | Deviations from intended interventions | Missing outcome data | Measurement of the outcome | Selection of the reported result | Overall Bias |
|-------------------------------------------------|-----------------------|----------------------------------------|----------------------|----------------------------|----------------------------------|--------------|
| AASK 2002                                       | +                     | +                                      | +                    | +                          | +                                | +            |
| ACCORD 2010                                     | +                     | +                                      | +                    | +                          | +                                | +            |
| ACEi progressive renal insufficiency study 1996 | +                     | —                                      | +                    | +                          | +                                | —            |
| ADVANCE 2014                                    | ?                     | +                                      | +                    | +                          | +                                | ?            |
| AIRE 1993                                       | +                     | +                                      | +                    | +                          | +                                | +            |
| ALTITUDE 2012                                   | +                     | +                                      | +                    | ?                          | +                                | +            |
| ASPIRE 2011                                     | +                     | +                                      | +                    | +                          | +                                | +            |
| BEST 2001                                       | +                     | +                                      | +                    | +                          | +                                | +            |
| BHAT 1982                                       | —                     | ?                                      | +                    | —                          | +                                | —            |
| CARDIO-SIS 2009                                 | +                     | +                                      | +                    | +                          | ?                                | ?            |
| CCS-I 1997                                      | +                     | +                                      | +                    | +                          | +                                | +            |
| CHARM-ADDED 2003                                | +                     | +                                      | ?                    | +                          | +                                | ?            |
| CHARM-ALTERNATIVE 2003                          | +                     | +                                      | +                    | +                          | +                                | +            |
| CHARM-PRESERVED 2003                            | +                     | +                                      | +                    | +                          | +                                | +            |
| Collaborative Study group 2001                  | +                     | +                                      | ?                    | +                          | ?                                | ?            |
| CONSENSUS II 1992                               | +                     | +                                      | +                    | +                          | ?                                | +            |
| DIME 2014                                       | —                     | ?                                      | +                    | —                          | +                                | —            |
| Dutch TIA trial 1993                            | +                     | +                                      | +                    | +                          | ?                                | +            |
| EMPHASIS-HF 2011                                | +                     | +                                      | +                    | +                          | +                                | +            |
| EUROPA 2003                                     | +                     | +                                      | +                    | +                          | +                                | +            |



|                                                       |   |   |   |   |   |   |
|-------------------------------------------------------|---|---|---|---|---|---|
| EWPHE 1991                                            | + | + | + | — | ? | — |
| GISSI-3 1994                                          | + | + | + | + | + | + |
| GISSI-AF 2009                                         | ? | + | + | + | + | ? |
| HOPE 2007                                             | + | + | + | + | + | + |
| HOPE-3 2016                                           | + | + | + | + | + | + |
| Hypertension in Diabetes Study IV 1996                | + | + | + | + | + | + |
| HYVET 2010                                            | + | + | + | + | + | + |
| INFINITY 2019                                         | + | + | + | + | + | + |
| Intensive Antihypertensive Treatment for Elderly 2013 | ? | + | + | ? | + | ? |
| I-PRESERVE 2008                                       | + | + | + | + | + | + |
| MACB 1995                                             | + | + | ? | + | + | ? |
| MERIT-HF 2000                                         | + | ? | — | + | + | ? |
| MRC 1982                                              | + | + | + | + | + | + |
| Multicenter Diltiazem Postinfarction Trial 1988       | + | + | + | + | + | + |
| NAVIGATOR 2010                                        | ? | + | + | ? | + | ? |
| NICOLE 2003                                           | + | + | + | + | + | + |
| NILVAD 2018                                           | ? | ? | + | ? | + | ? |
| The Norwegian Multicenter Study 1981                  | + | + | + | + | + | + |
| ONTARGET 2008                                         | + | + | + | + | + | + |
| ORIENT 2011                                           | + | + | + | + | + | + |
| PEACE 2004                                            | + | + | + | + | + | + |
| PRoFESS 2008                                          | ? | + | + | + | + | ? |
| PROGRESS 2001                                         | ? | — | — | + | ? | — |
| ROADMAP 2011/12                                       | + | + | + | + | + | + |
| SANDS 2009                                            | — | ? | + | — | + | — |
| SENIORS 2005                                          | ? | ? | + | + | + | ? |

|                                           |  |  |  |  |  |  |
|-------------------------------------------|--|--|--|--|--|--|
| SHEP 1991                                 |  |  |  |  |  |  |
| SHEP 2000                                 |  |  |  |  |  |  |
| SOLVD 1992                                |  |  |  |  |  |  |
| Spironolactone in mild heart failure 2016 |  |  |  |  |  |  |
| SPRINT 2015                               |  |  |  |  |  |  |
| SPS3 2013                                 |  |  |  |  |  |  |
| TRACE 1995                                |  |  |  |  |  |  |
| TRANSCEND 2008                            |  |  |  |  |  |  |
| TROPHY 2006                               |  |  |  |  |  |  |
| VA NEPHRON-D 2013                         |  |  |  |  |  |  |
| Val-HeFT 2001                             |  |  |  |  |  |  |
| VALIANT 2003                              |  |  |  |  |  |  |
| VA-NHLBI 1978                             |  |  |  |  |  |  |



= Low risk

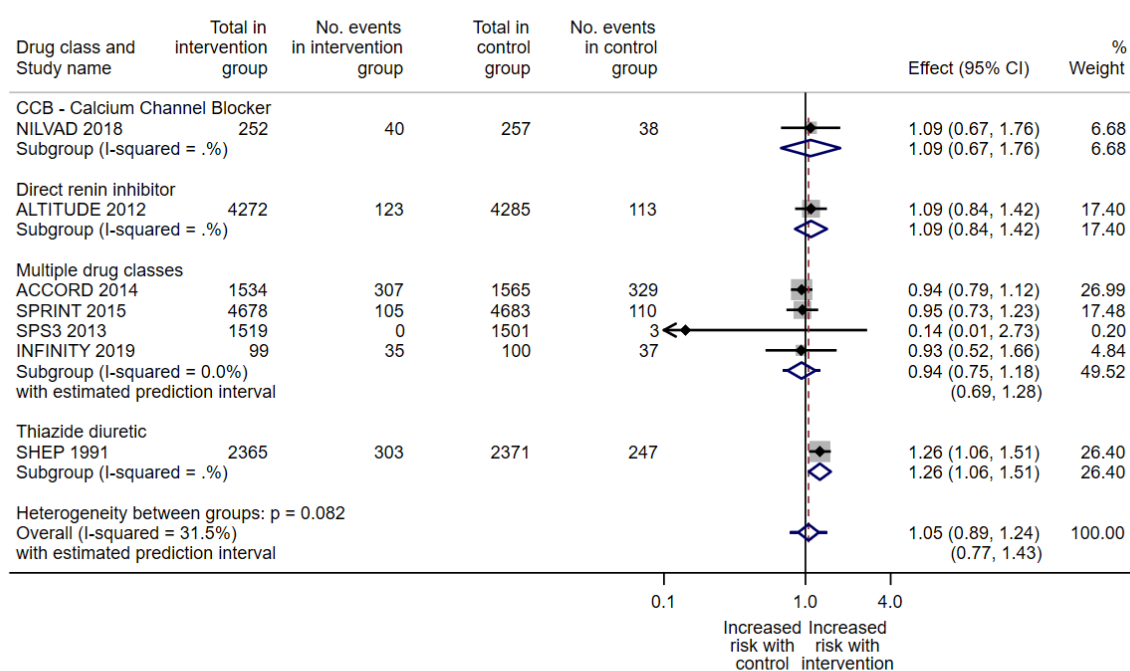


= Some concerns



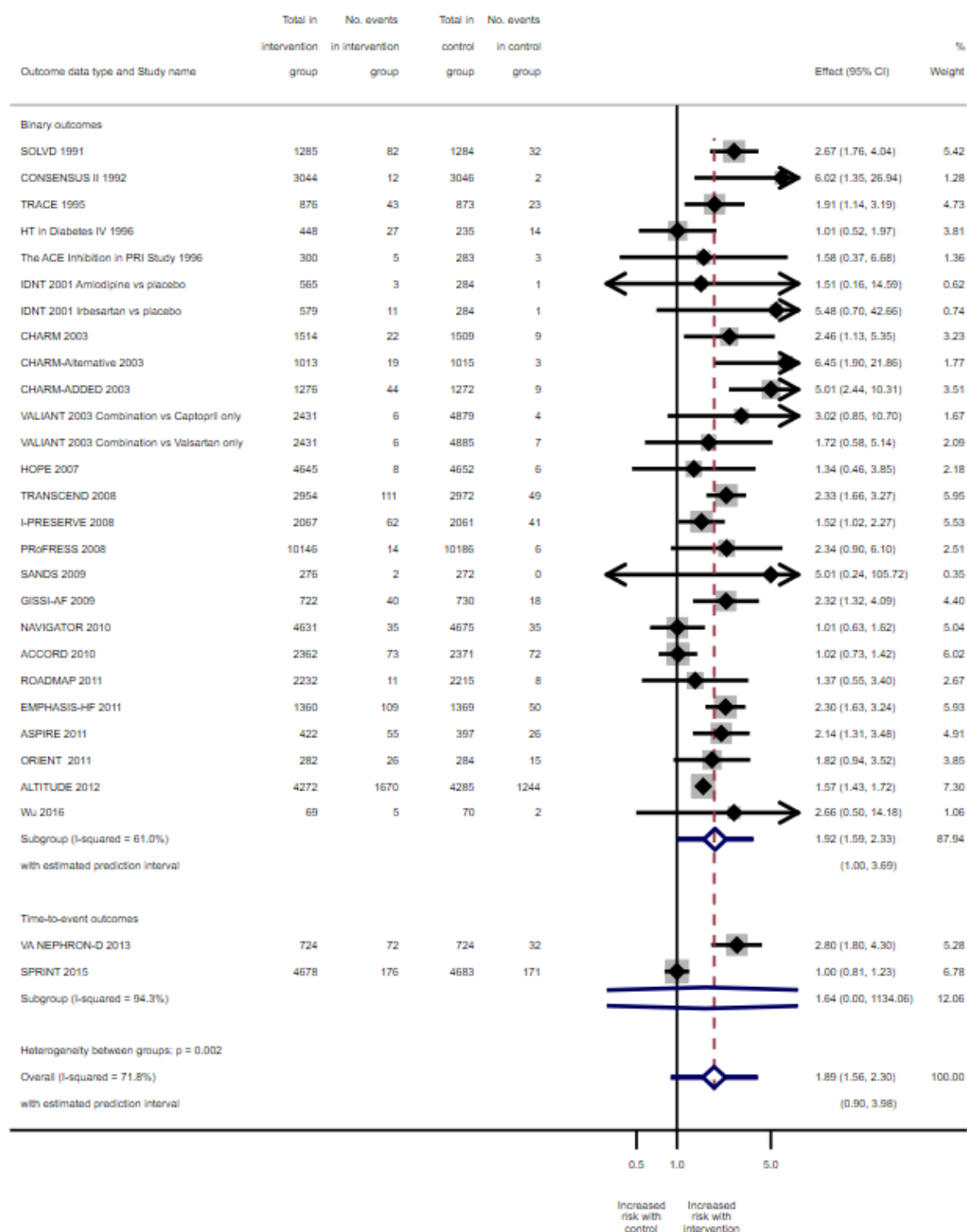
= High risk

**Supplementary figure 1.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and falls by drug class

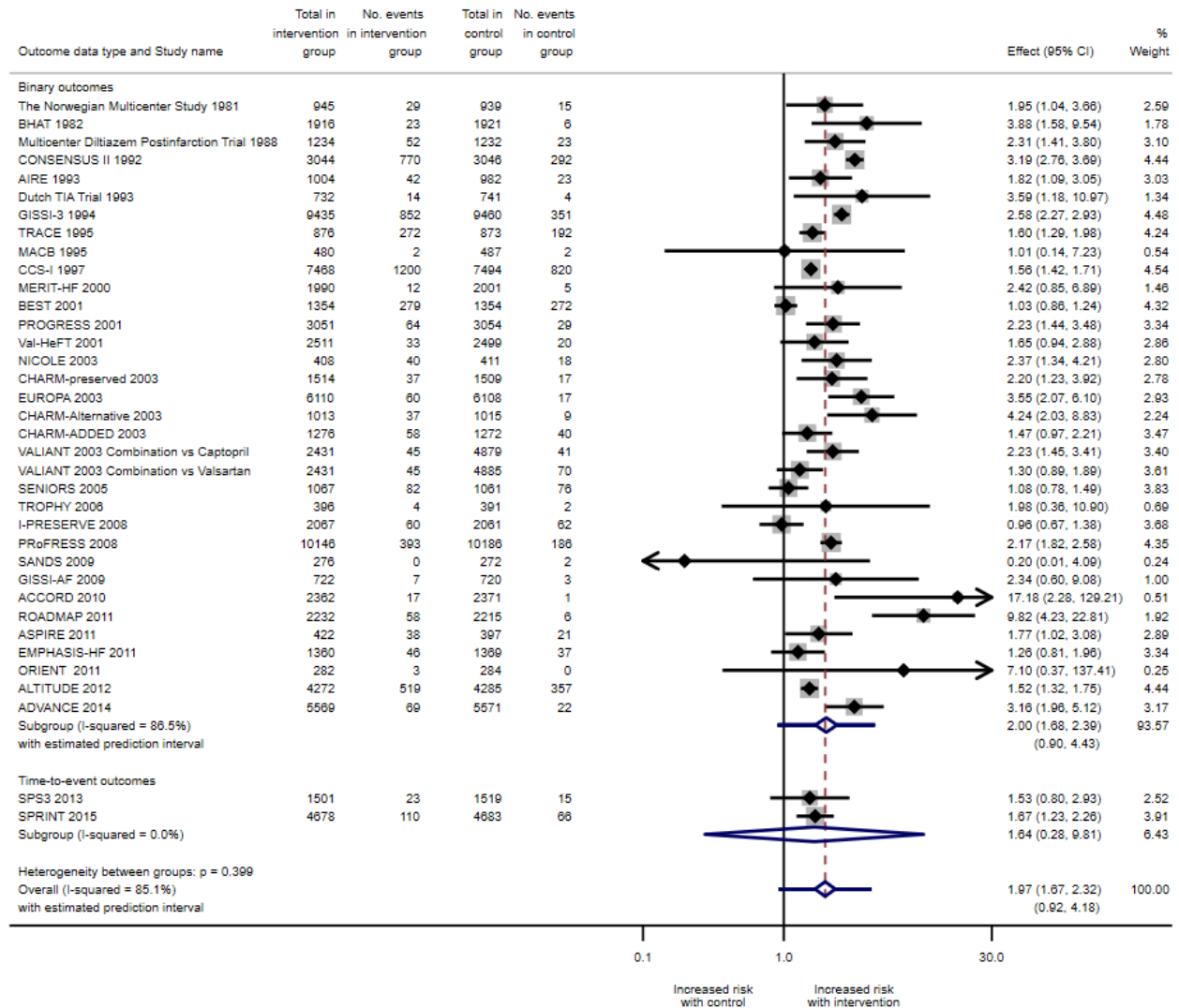


NOTE: Weights are from random-effects model

**Supplementary figure 2.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and hyperkalaemia

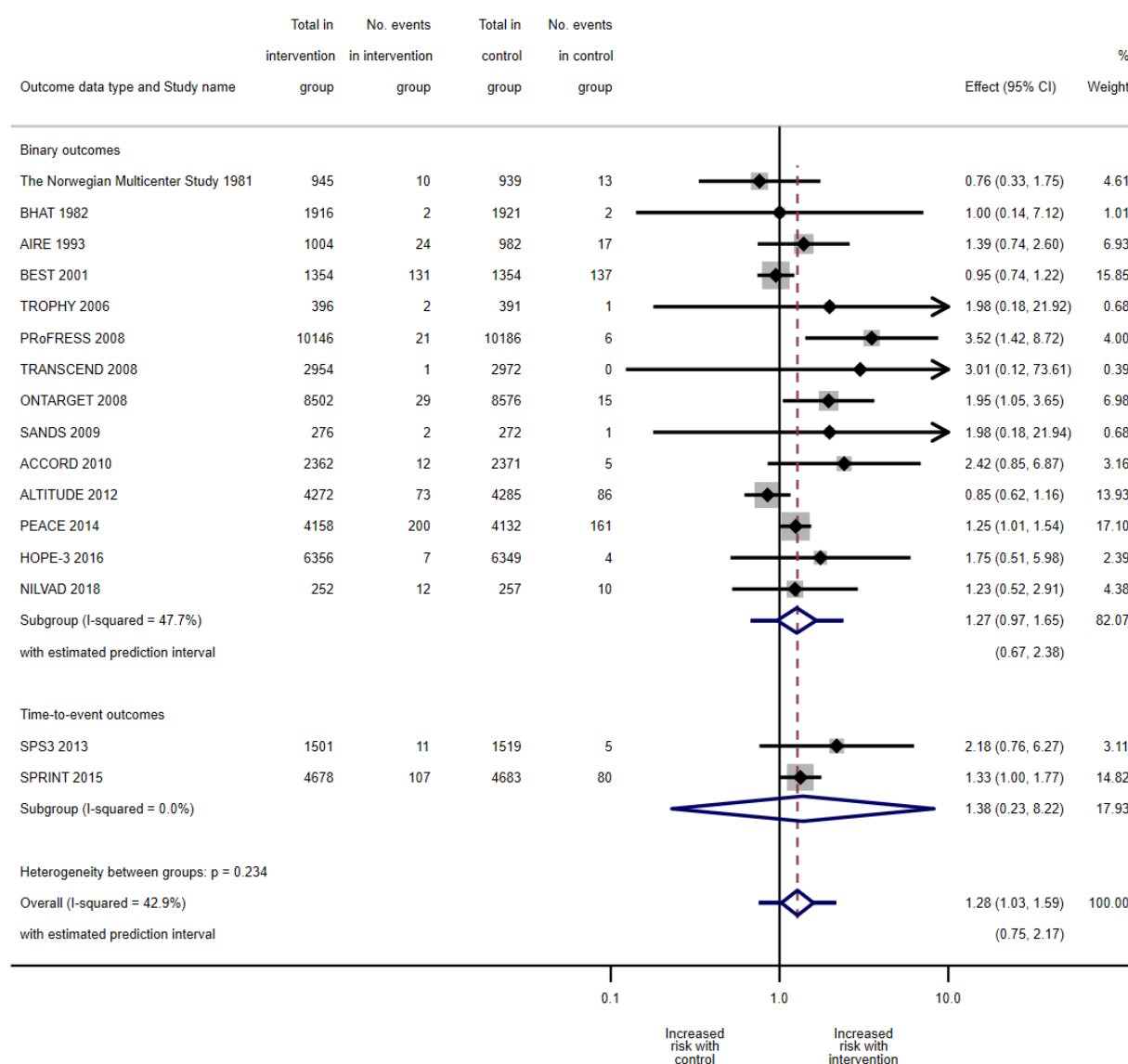


**Supplementary figure 3.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and hypotension

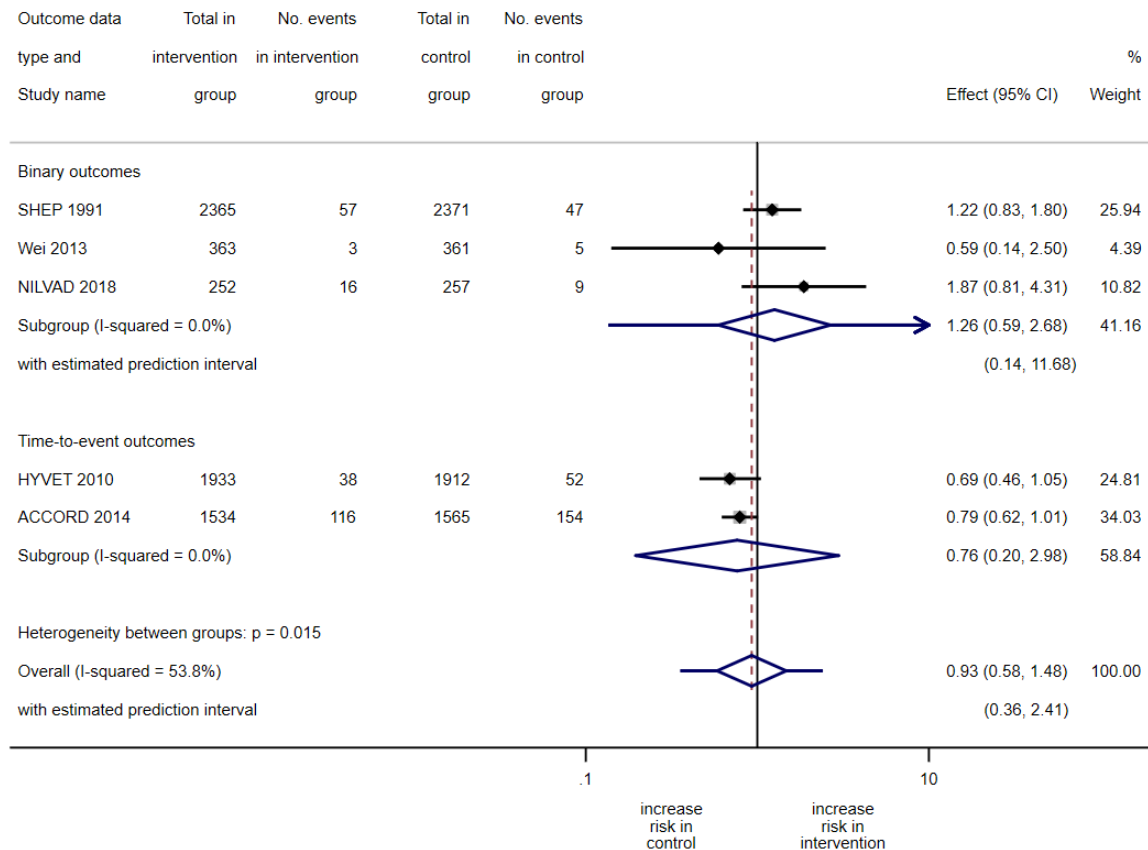


NOTE: Weights are from random-effects model

**Supplementary figure 4.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and syncope

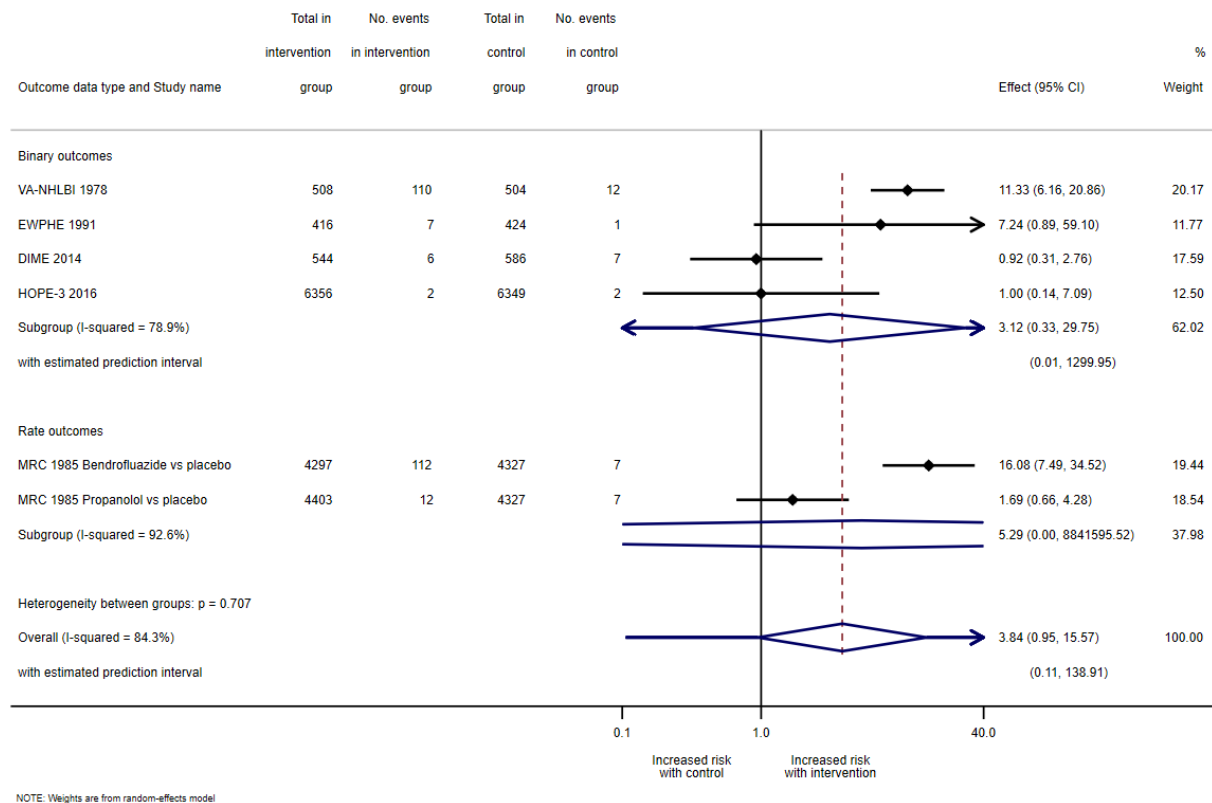


**Supplementary figure 5.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and fractures



NOTE: Weights are from random-effects model

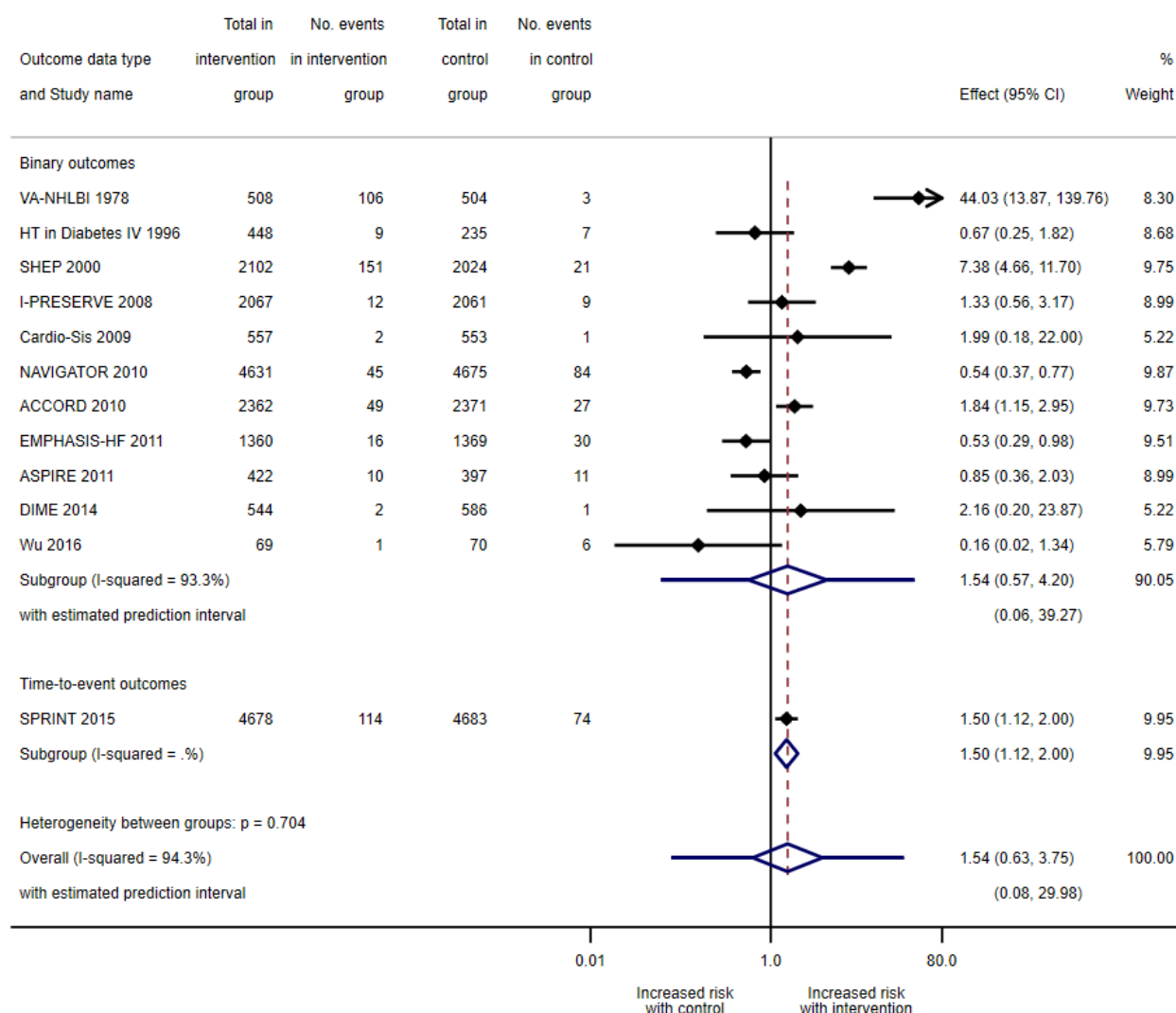
**Supplementary figure 6.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and gout



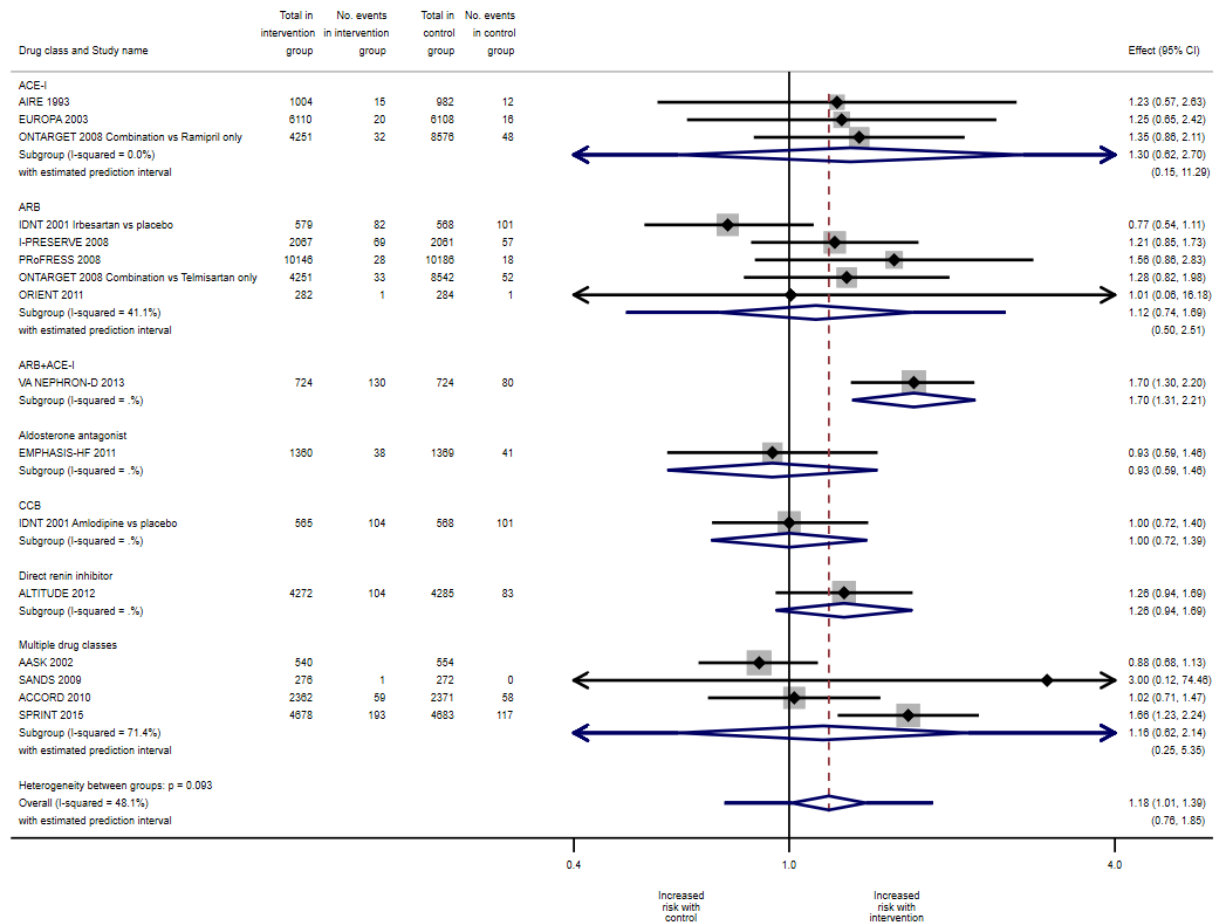
NOTE: Weights are from random-effects model



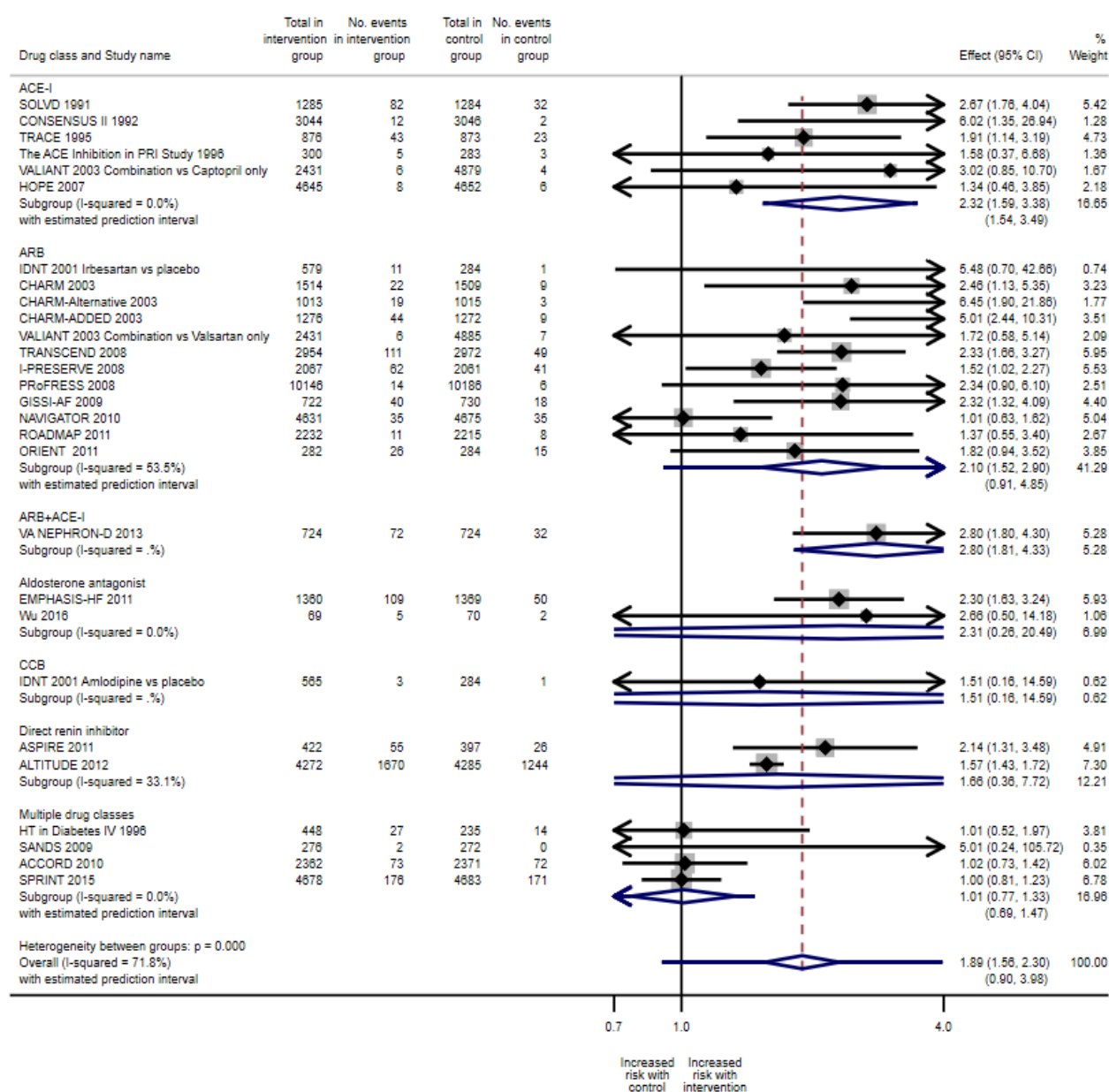
**Supplementary figure 7.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and hypokalaemia



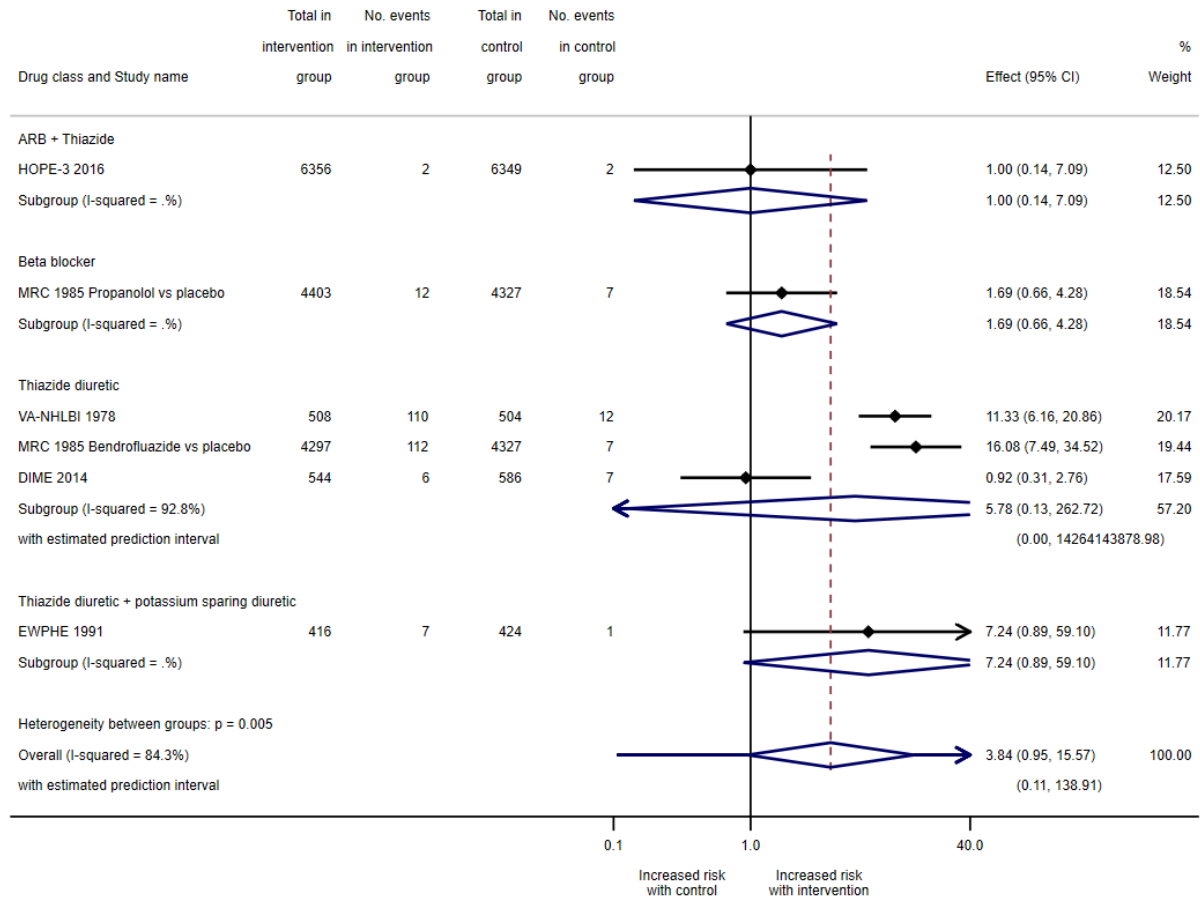
**Supplementary figure 8.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and acute kidney injury by drug class



**Supplementary figure 9.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and hyperkalaemia by drug class

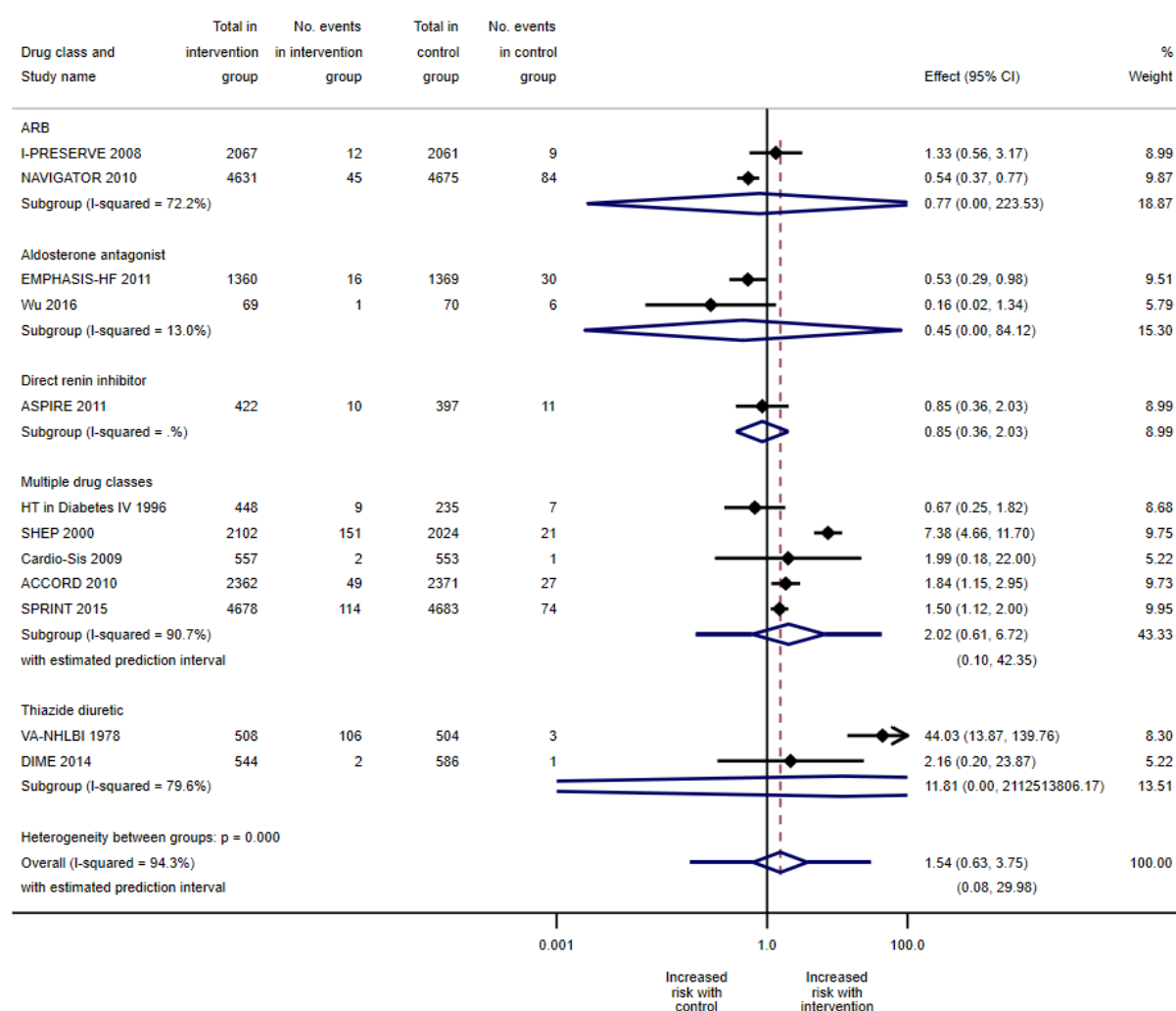


**Supplementary figure 10.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and gout by drug class



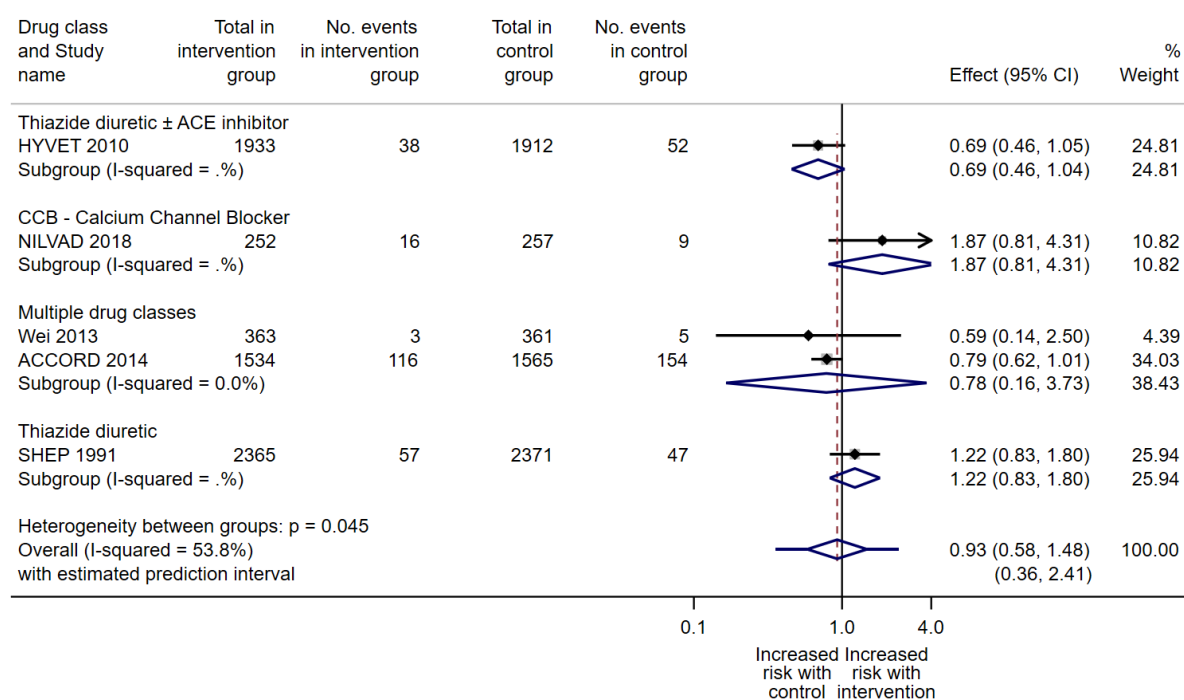
NOTE: Weights are from random-effects model

**Supplementary figure 11.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and hypokalaemia by drug class



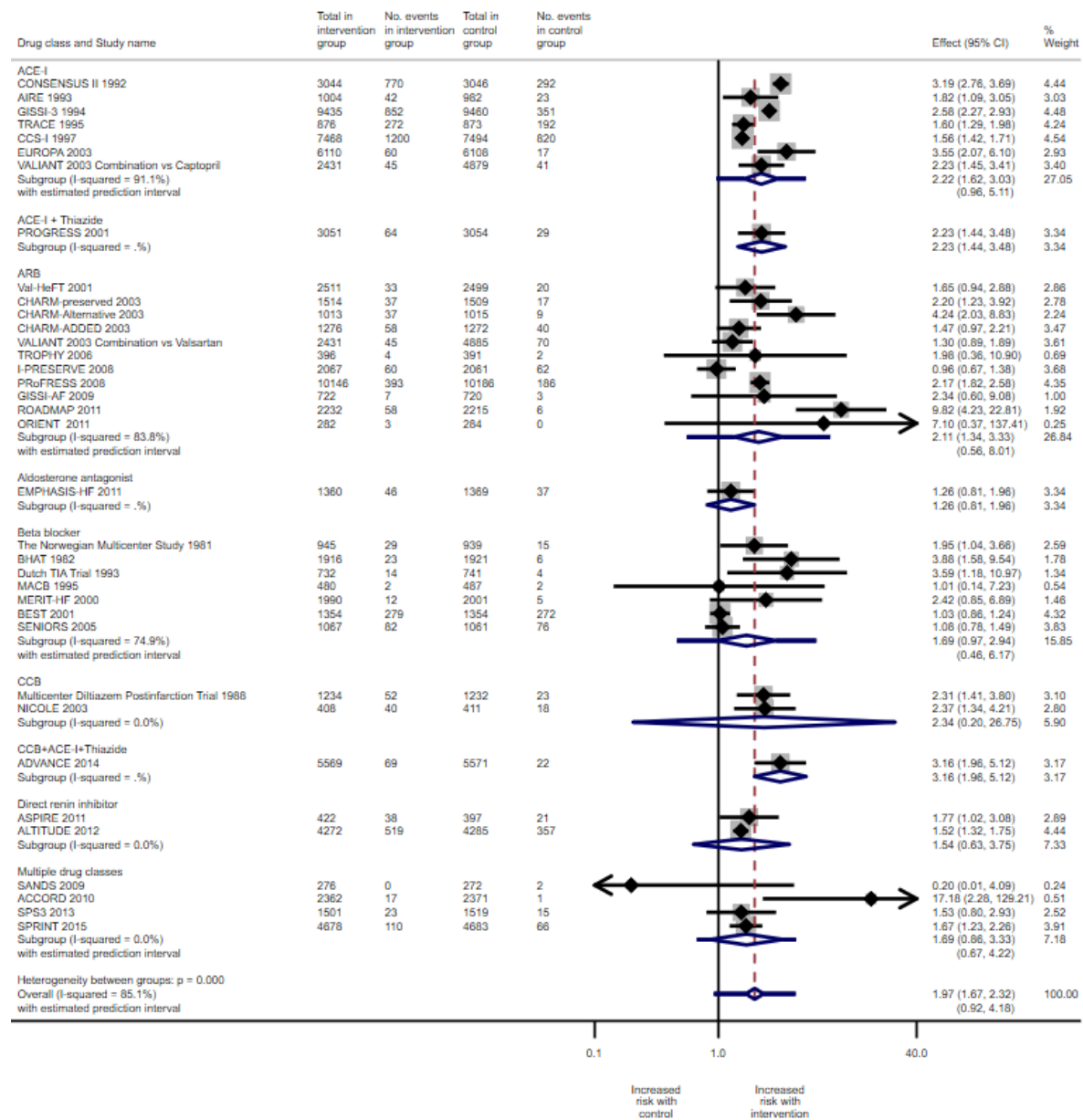
NOTE: Weights are from random-effects model

**Supplementary figure 12.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and fracture by drug class



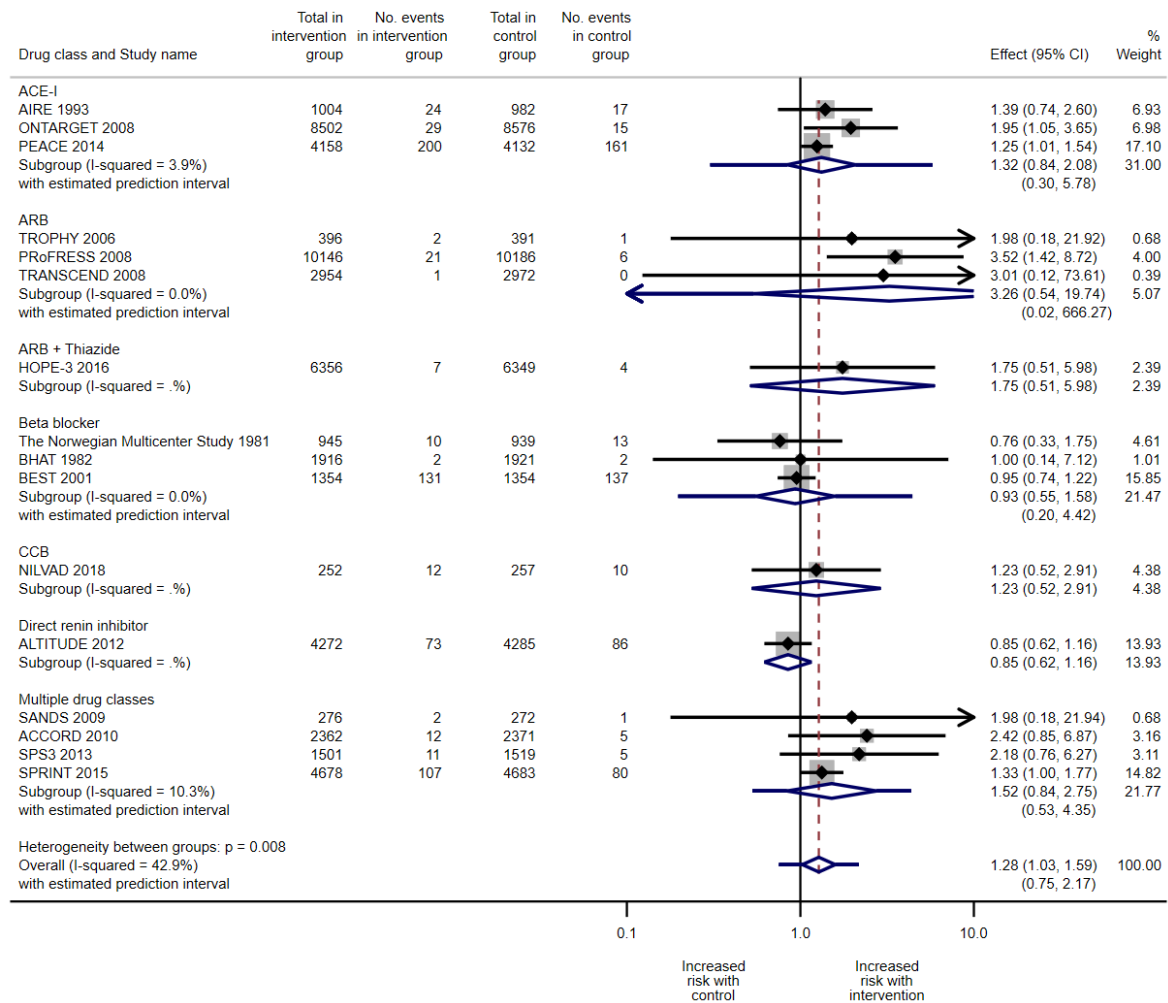
NOTE: Weights are from random-effects model

**Supplementary figure 13.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and hypotension by drug class



NOTE: Weights are from random-effects model

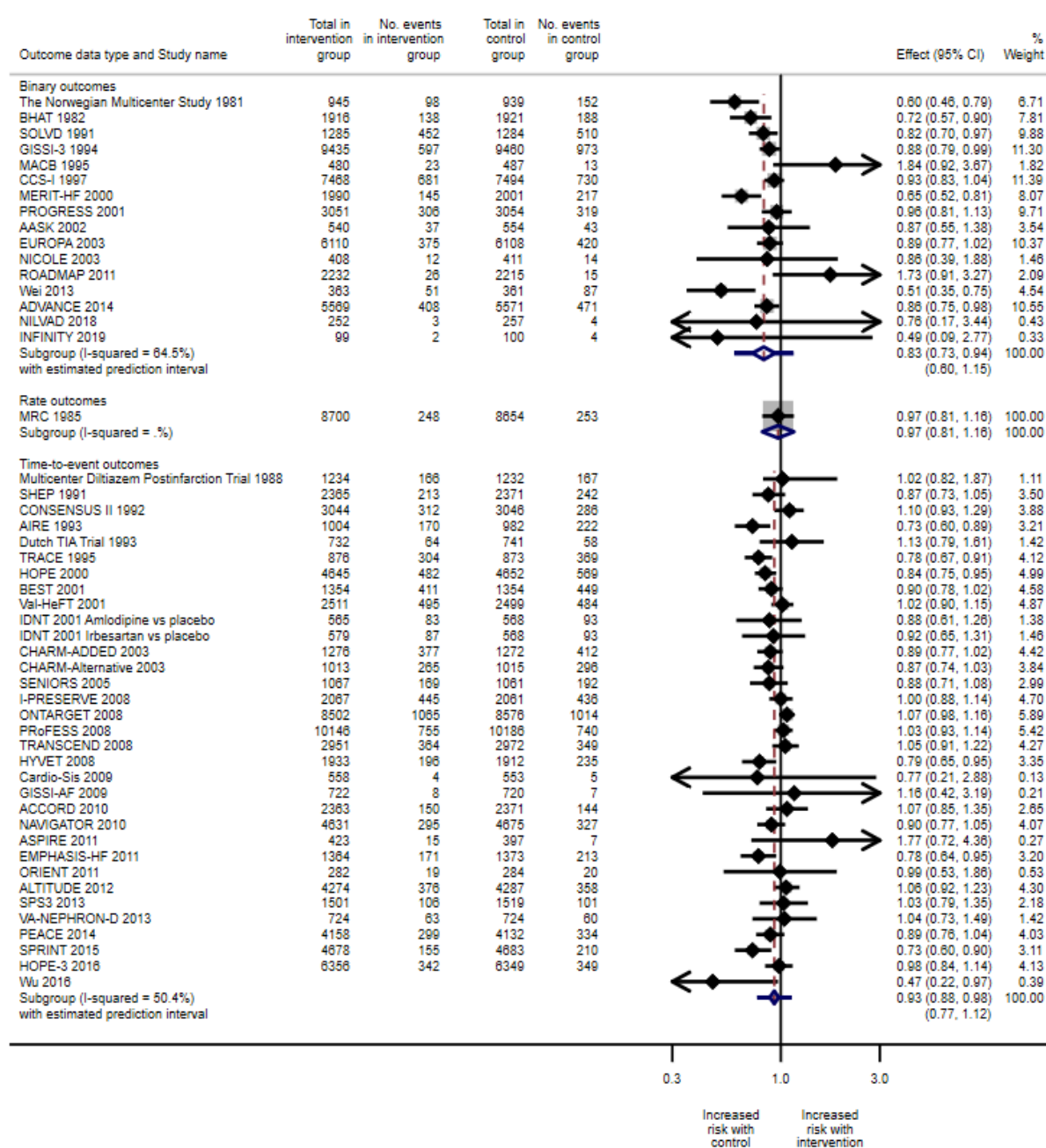
**Supplementary figure 14.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and syncope by drug class



NOTE: Weights are from random-effects model

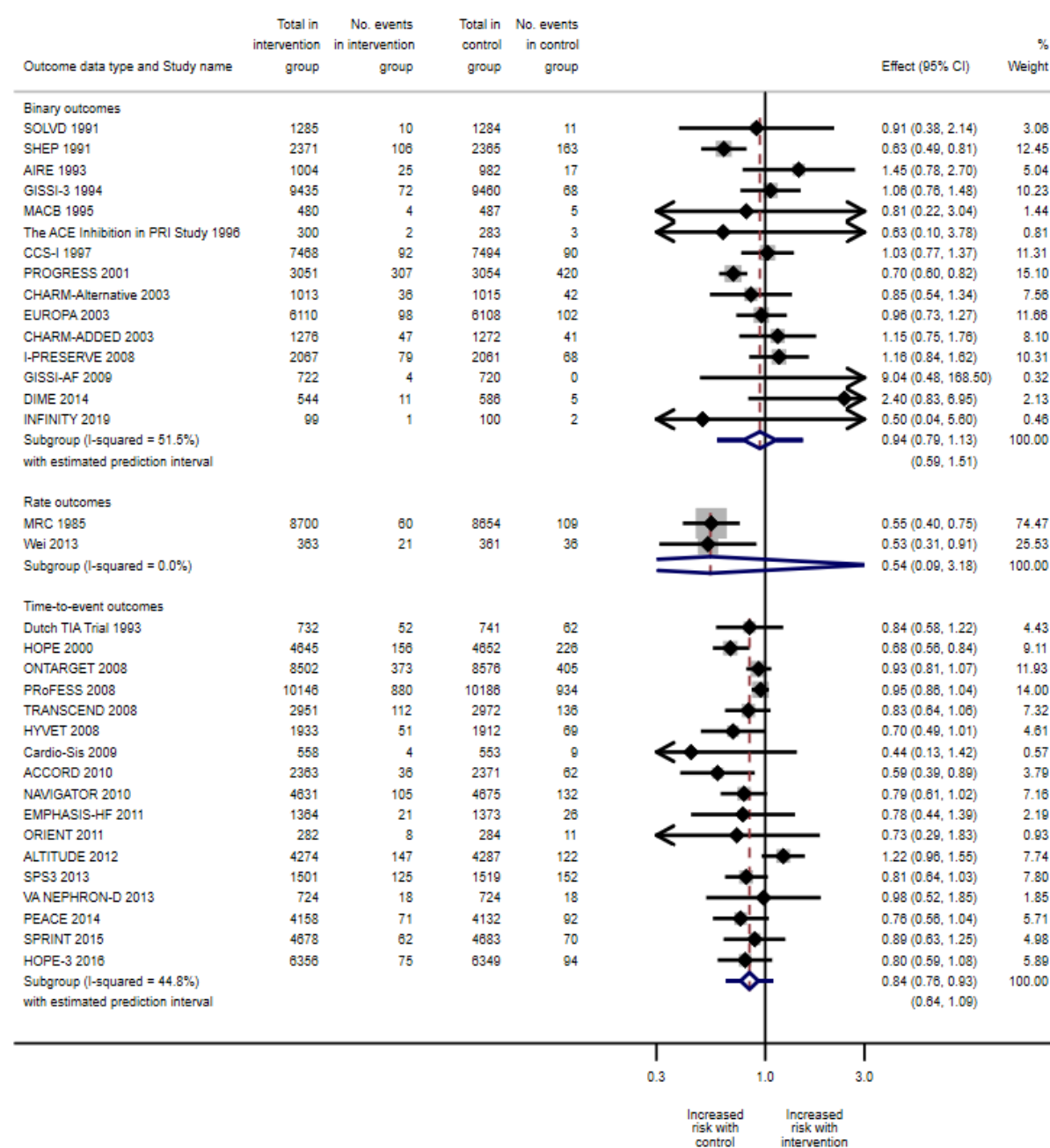


**Supplementary figure 15.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and all-cause mortality



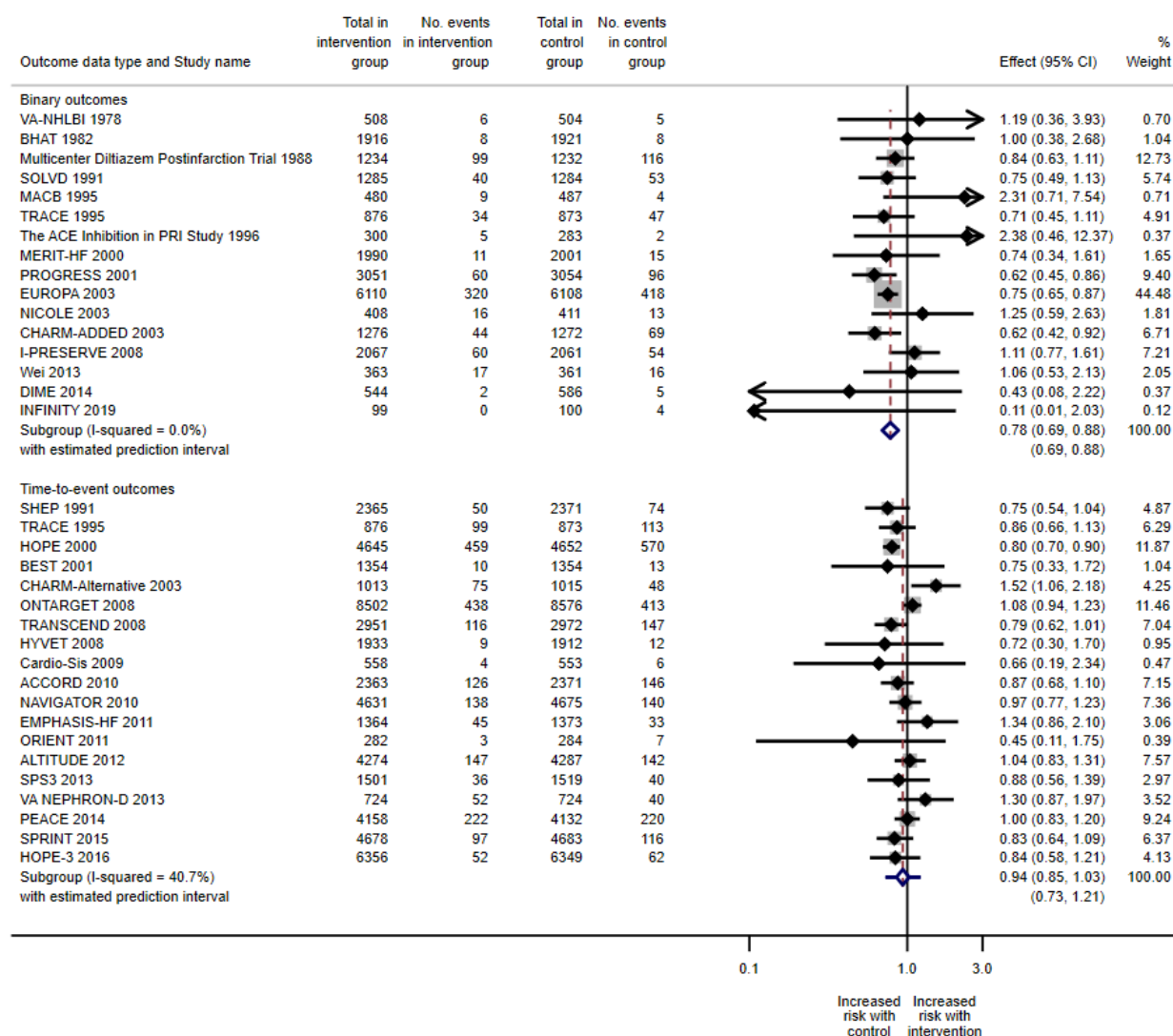
NOTE: Weights are from random-effects model

**Supplementary figure 16.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and stroke



NOTE: Weights are from random-effects model

**Supplementary figure 17.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and myocardial infarction



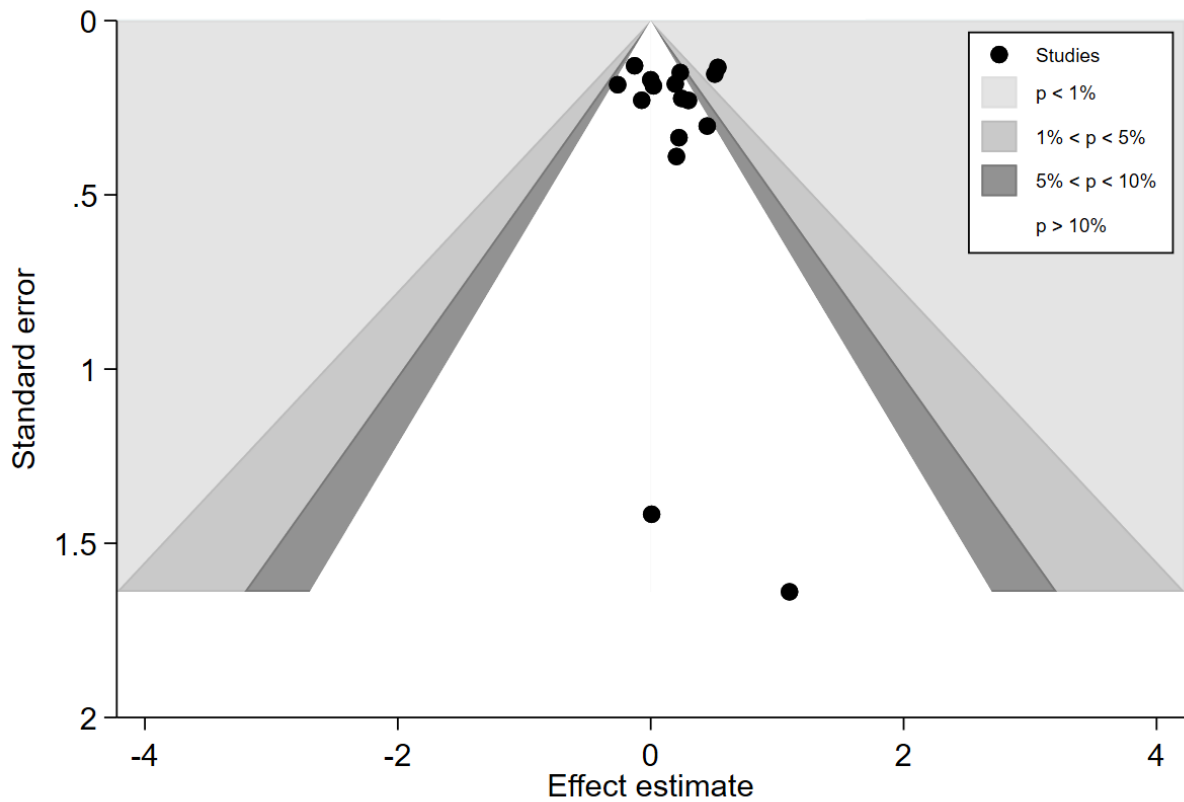
NOTE: Weights are from random-effects model

**Supplementary table 3.** Meta-regression examining the relationship between the observed treatment effects for each adverse event outcome and study quality

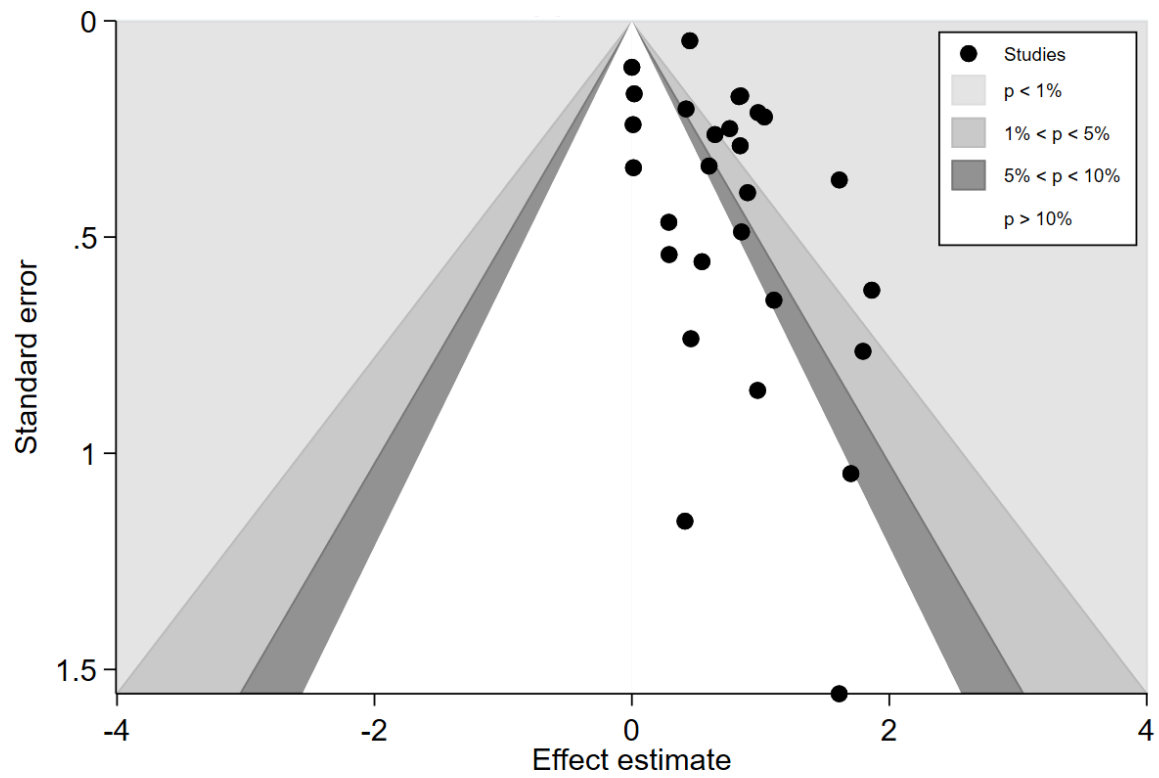
| Outcome             | Some concerns* |                 | High risk of bias* |                  |
|---------------------|----------------|-----------------|--------------------|------------------|
|                     | Coefficient    | 95% CI          | Coefficient        | 95% CI           |
| Falls               | -0.21          | (-0.65 to 0.23) | -0.26              | (-0.63 to 0.11)  |
| Acute kidney injury | 0.38           | (0.10 to 0.65)  | -0.04              | (-0.53 to 0.45)  |
| Fracture            | 0.75           | (-1.75 to 3.24) | -0.11              | (-1.87 to 1.66)  |
| Gout                | 1.96           | (-2.77 to 6.68) | -0.08              | (-5.71 to 5.54)  |
| Hyperkalaemia       | -0.32          | (-0.88 to 0.24) | -0.67              | (-1.17 to -0.18) |
| Hypokalaemia        | 1.13           | (-1.07 to 3.32) | -0.30              | (-2.56 to 1.95)  |
| Hypotension         | -0.20          | (-0.66 to 0.26) | -0.14              | (-0.65 to 0.38)  |
| Syncope             | -0.03          | (-0.65 to 0.58) | 0.00               | (-0.11 to 0.70)  |

\*Reference category – low risk of bias

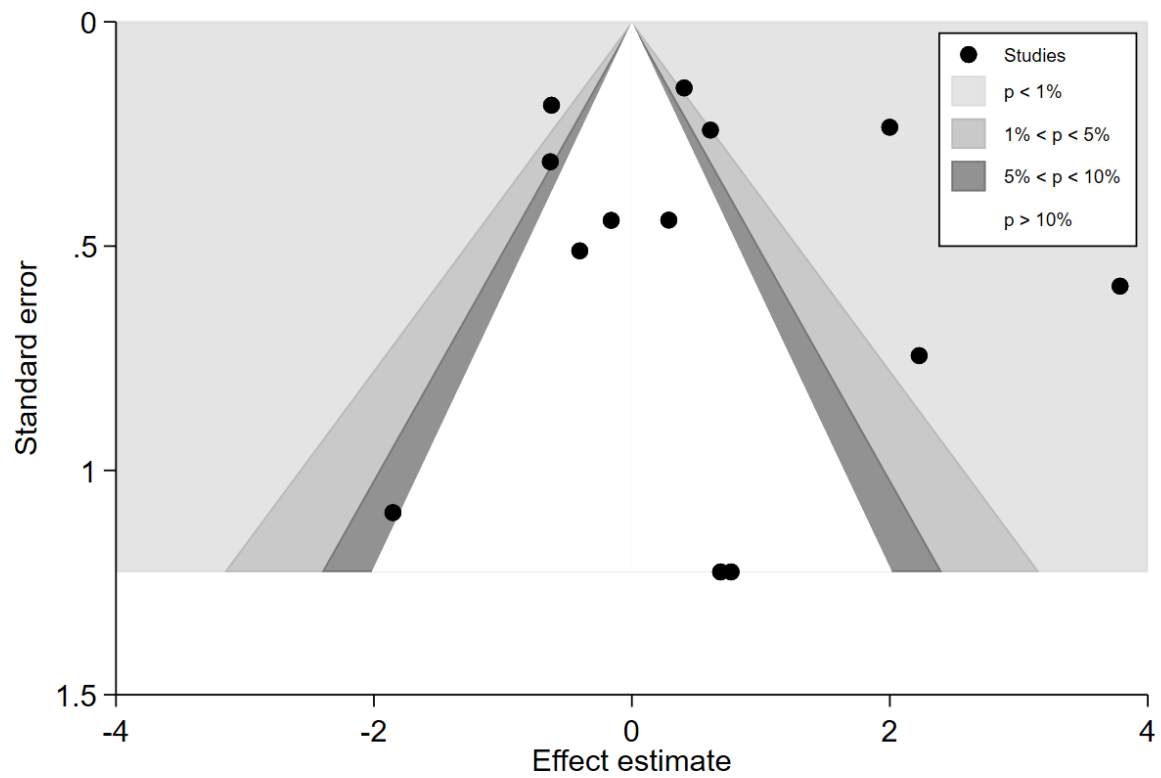
**Supplementary figure 18.** Funnel plots showing publication bias in studies reporting acute kidney injury outcomes



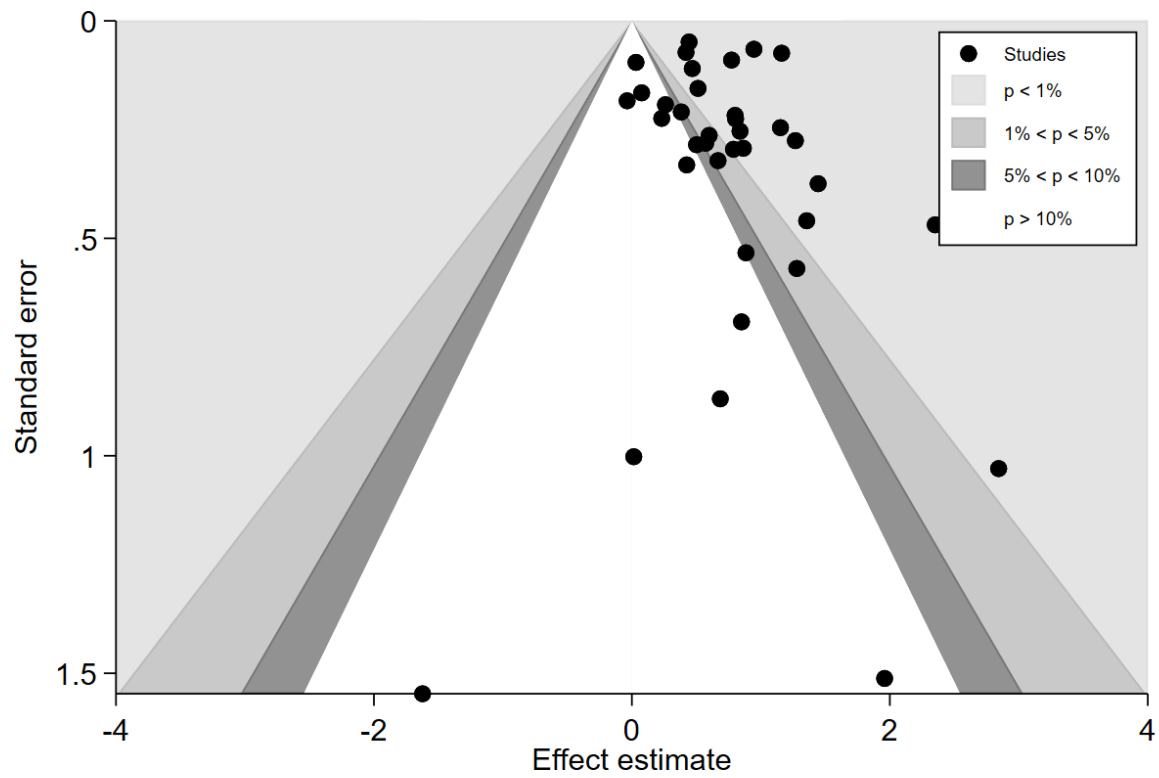
**Supplementary figure 19.** Funnel plots showing publication bias in studies reporting hyperkalaemia outcomes



**Supplementary figure 20.** Funnel plots showing publication bias in studies reporting hypokalaemia outcomes

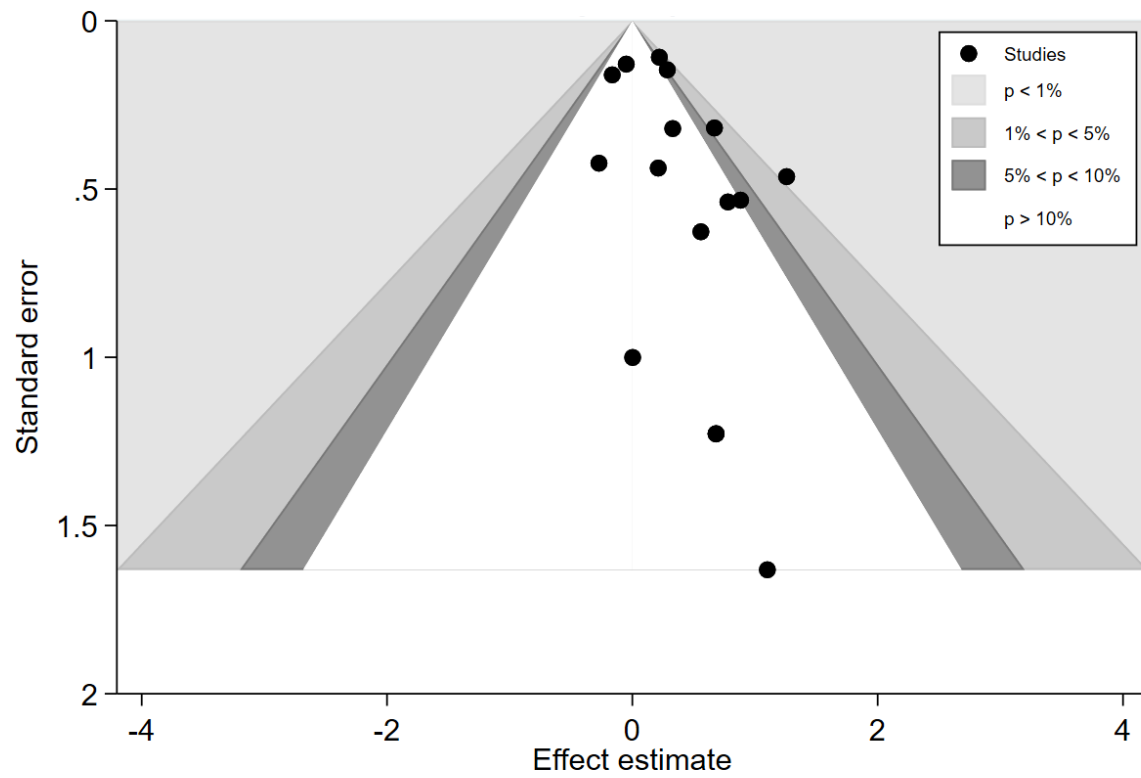


**Supplementary figure 21.** Funnel plots showing publication bias in studies reporting hypotension outcomes

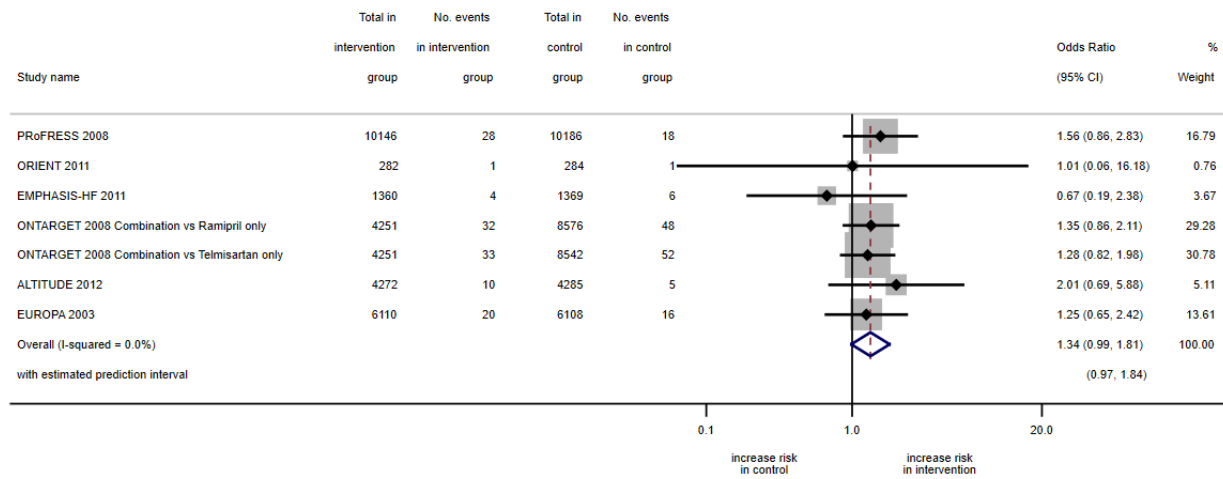




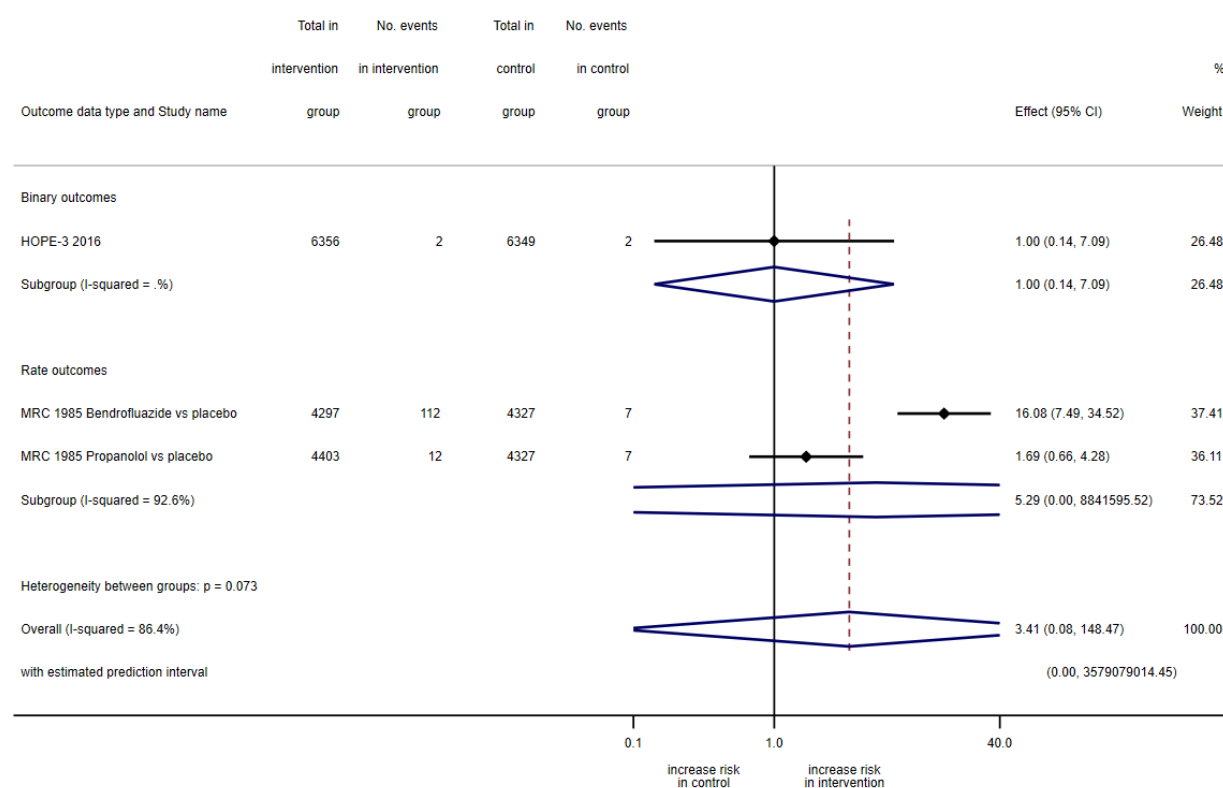
**Supplementary figure 22.** Funnel plots showing publication bias in studies reporting syncope outcomes



**Supplementary figure 23.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and acute kidney injury leading to permanent withdrawal from each trial

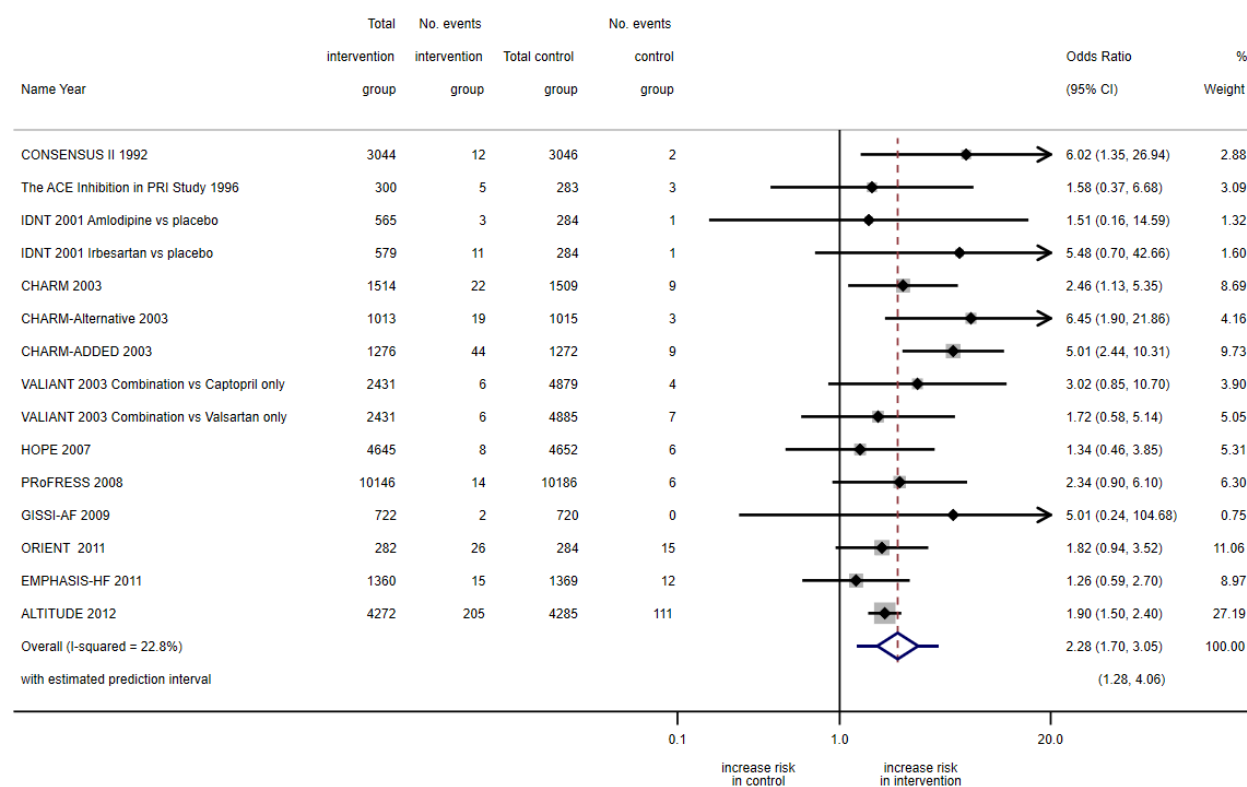


**Supplementary figure 24.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and gout leading to permanent withdrawal from each trial



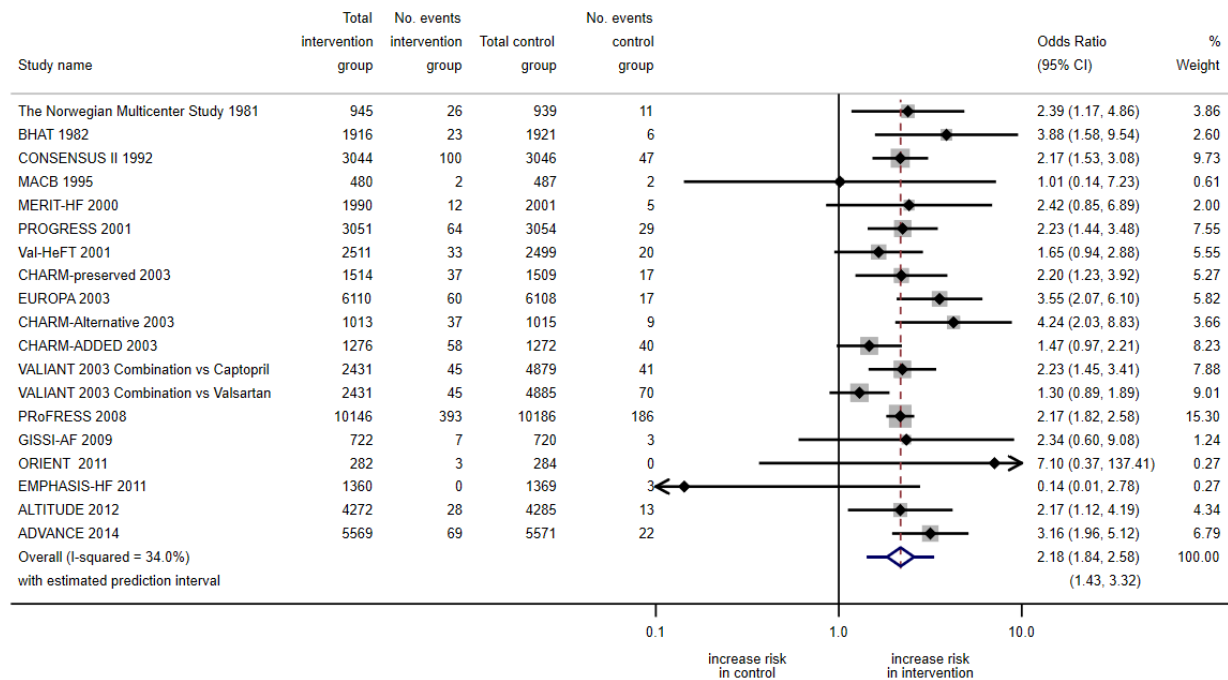
NOTE: Weights are from random-effects model

**Supplementary figure 25.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and hyperkalaemia leading to permanent withdrawal from each trial



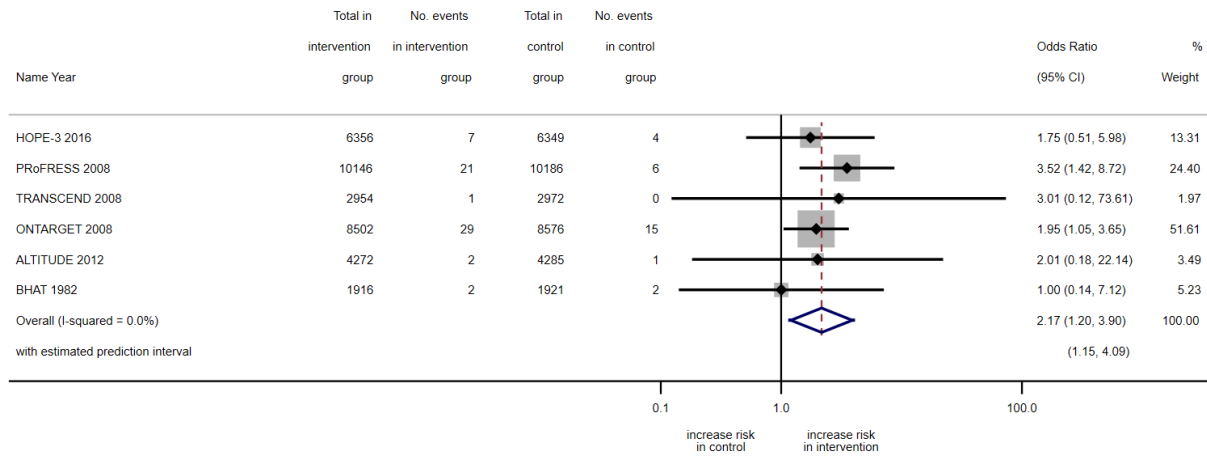
NOTE: Weights are from random-effects model; continuity correction applied to studies with zero cells

**Supplementary figure 26.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and hypotension leading to permanent withdrawal from each trial



NOTE: Weights are from random-effects model; continuity correction applied to studies with zero cells

**Supplementary figure 27.** Random effects meta-analysis of randomised controlled trials examining the association between antihypertensive treatment and syncope leading to permanent withdrawal from each trial



NOTE: Weights are from random-effects model; continuity correction applied to studies with zero cells