

1 **DATA SUPPLEMENT**

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4 **adults**

5 **A systematic review and meta-analysis**

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PubMed	Embase	Cochrane Library	Web of science
<p><b>Concept 1: antihypertensive drugs/lowering blood pressure</b>  <u>MeSH</u>            Adrenergic alpha-antagonists [MeSH] OR Adrenergic beta-antagonists [MeSH] OR Angiotensin-converting enzyme inhibitors [MeSH] OR Antihypertensive agents [MeSH] OR Antihypertensive agents [pharmacological action] OR Diuretics [MeSH] OR Ganglionic blockers [MeSH] OR Vasodilator agents [MeSH] OR adrenergic beta-antagonists [Pharmacological action] OR Adrenergic alpha-antagonists [Pharmacological action] OR Angiotensin-Converting Enzyme Inhibitors [Pharmacological action] OR Diuretics [Pharmacological action] OR Ganglionic Blockers [Pharmacological action] OR Vasodilator agents [Pharmacological action] OR Calcium channel blockers [MeSH] OR Calcium channel blockers [Pharmacological action]</p> <p><b>OR</b>  <u>Tiab</u>            Adrenergic alpha-antagonist* [tiab] OR Adrenergic beta-antagonist* [tiab] OR Angiotensin-converting enzyme inhibitor* [tiab] OR Anti-hypertensive* [tiab] OR Antihypertensive* [tiab] OR Blood pressure lowering [tiab] OR</p>	<p><b>Concept 1: antihypertensive drugs/lowering blood pressure</b>            Emtree            Exp Antihypertensive agent/ OR Exp Alpha adrenergic receptor blocking agent/ OR Exp Beta adrenergic receptor blocking agent/ OR Exp Dipeptidyl carboxypeptidase inhibitor/ OR Exp Diuretic agent/ OR Exp Ganglion blocking agent/ OR Exp Vasodilator agent/  <b>OR</b>  <u>Tiab</u>            (Adrenergic alpha-antagonist* OR Adrenergic beta-antagonist* OR Angiotensin-converting enzyme inhibitor* OR Antihypertensive* OR Blood pressure lowering OR Calcium channel blocker* OR Diuretic* OR Ganglionic block* OR Vasodilat*).ti,ab,kw.  <b>OR</b>  <i>Diuretics</i>            (Diuretic* or Bumetanide or Furosemide or Lasix or Chlorthalidone or Hydrochlorothiazide or Amiloride or Acetazolamide or anaritide or azosemide or Bendroflumethiazide or bumepamine or buthiazide or canrenoic acid or canrenone or chlorothiazide or cicletanine or clopamide or</p>	<p><b>Concept 1: antihypertensive drugs/lowering blood pressure</b>            (Adrenergic alpha-antagonist* OR Adrenergic beta-antagonist* OR Angiotensin-converting enzyme inhibitor* OR Antihypertensive* OR Blood pressure lowering OR Calcium channel blocker* OR Diuretic* OR Ganglionic block* OR Vasodilat*):ti,ab,kw  <b>OR</b>            (Diuretic* or Bumetanide or Furosemide or Lasix or Chlorthalidone or Hydrochlorothiazide or Amiloride or Acetazolamide or anaritide or azosemide or Bendroflumethiazide or bumepamine or buthiazide or canrenoic acid or canrenone or chlorothiazide or cicletanine or clopamide or cyclopenthiazide or drospirenone or eplerenone or Ethacrynic Acid or ethoxzolamide or ethylisopropylamiloride or etozolin or fenquizone or hydroflumethiazide or ibopamine or indacrinone or indapamide or isosorbide or mannitol or mefruside or methazolamide or methyclothiazide or metolazone or muzolimine or ozolinone or piretanide or polythiazide or quinethazone or rolofylline or spiradoline or</p>	<p><b>Concept 1: antihypertensive drugs/lowering blood pressure</b>            TS=(“Adrenergic alpha-antagonist*” OR “Adrenergic beta-antagonist*” OR “Angiotensin-converting enzyme inhibitor*” OR Antihypertensive* OR “Blood pressure lowering” OR “Calcium channel blocker*” OR Diuretic* OR “Ganglionic block*” OR “Vasodilat*”)  <b>OR</b>            TS=(Diuretic* or Bumetanide or Furosemide or Lasix or Chlorthalidone or Hydrochlorothiazide or Amiloride or Acetazolamide or anaritide or azosemide or Bendroflumethiazide or bumepamine or buthiazide or canrenoic acid or canrenone or chlorothiazide or cicletanine or clopamide or cyclopenthiazide or drospirenone or eplerenone or Ethacrynic Acid or ethoxzolamide or ethylisopropylamiloride or etozolin or fenquizone or hydroflumethiazide or ibopamine or indacrinone or indapamide or isosorbide or mannitol or mefruside or methazolamide or methyclothiazide or metolazone or muzolimine or ozolinone or piretanide or polythiazide or quinethazone or rolofylline or spiradoline or spironolactone or telmisartan or</p>

<p>Calcium channel blocker* [tiab] OR Diuretic* [tiab] OR Ganglionic block* [tiab] OR Vasodilat* [tiab]</p> <p><b>OR</b></p> <p><i>Diuretics</i></p> <p>Diuretic* [tiab] OR Bumetanide[tiab] OR Furosemide[tiab] OR Lasix[tiab] OR Chlorthalidone[tiab] OR Hydrochlorothiazide[tiab] OR Amiloride[tiab] OR Acetazolamide [tiab] OR anaritide [tiab] OR azosemide [tiab] OR Bendroflumethiazide [tiab] OR bumepamine[tiab] OR buthiazide [tiab] OR “canrenoic acid” [tiab] OR canrenone [tiab] OR chlorothiazide [tiab] OR cicletanine [tiab] OR clopamide [tiab] OR cyclopenthiiazide [tiab] OR drospirenone[tiab] OR eplerenone [tiab] OR “ Ethacrynic Acid” [tiab] OR ethoxzolamide [tiab] OR ethylisopropylamiloride [tiab] OR etozolin [tiab] OR fenquizone [tiab] OR hydroflumethiazide [tiab] OR ibopamine [tiab] OR indacrinone[tiab] OR indapamide [tiab] OR isosorbide [tiab] OR mannitol[tiab] OR mefruside [tiab] OR methazolamide [tiab] OR methyclothiazide [tiab] OR metolazone [tiab] OR muzolimine [tiab] OR ozolinone [tiab] OR piretanide [tiab] OR polythiazide [tiab] OR quinethazone [tiab] OR rolofylline[tiab] OR spiradoline[tiab] OR spironolactone [tiab] OR telmisartan [tiab] OR ticrynafen [tiab] OR tifuladom [tiab] OR torsemide [tiab] OR traxanox [tiab] OR triamterene [tiab] OR</p>	<p>cyclopenthiiazide or drospirenone or eplerenone or Ethacrynic Acid or ethoxzolamide or ethylisopropylamiloride or etozolin or fenquizone or hydroflumethiazide or ibopamine or indacrinone or indapamide or isosorbide or mannitol or mefruside or methazolamide or methyclothiazide or metolazone or muzolimine or ozolinone or piretanide or polythiazide or quinethazone or rolofylline or spiradoline or spironolactone or telmisartan or ticrynafen or tifuladom or torsemide or traxanox or triamterene or trichlormethiazide or tripamide or xipamide or ularitide).ti,ab,kw.</p> <p><b>OR</b></p> <p><i>Beta blockers</i></p> <p>(Beta-block* or Beta-adrenergic antagonist* or Beta-adrenergic receptor antagonist* or Beta-adrenergic block* or Beta-adrenergic receptor block* or Beta-adrenoreceptor antagonist* or Adrenergic beta-Antagonist* or Adrenergic beta-1 Receptor Antagonist* or Adrenergic beta-block* or Adrenergic beta-receptor block* or Acebutolol or Alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or Brimonidine Tartrate or bromoacetylalprenololmenthane or bucindolol or bufetolol or bufuralol or bunolol or bupranolol or butofilolol or butoxamin* or carazolol or carteolol or carvedilol or celiprolol or cyanopindolol</p>	<p>spironolactone or telmisartan or ticrynafen or tifuladom or torsemide or traxanox or triamterene or trichlormethiazide or tripamide or xipamide or ularitide):ti,ab,kw</p> <p><b>OR</b></p> <p>(Beta-block* or Beta-adrenergic antagonist* or Beta-adrenergic receptor antagonist* or Beta-adrenergic block* or Beta-adrenergic receptor block* or Beta-adrenoreceptor antagonist* or Adrenergic beta-Antagonist* or Adrenergic beta-1 Receptor Antagonist* or Adrenergic beta-block* or Adrenergic beta-receptor block* or Acebutolol or Alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or Brimonidine Tartrate or bromoacetylalprenololmenthane or bucindolol or bufetolol or bufuralol or bunolol or bupranolol or butofilolol or butoxamin* or carazolol or carteolol or carvedilol or celiprolol or cyanopindolol or dihydroalprenolol or epanolol or esmolol or exaprolol or fleistolol or indenolol or lodocyanopindolol or labetalol or levobunolol or medroxalol or mepindolol or metipranolol or oxprenolol or penbutolol or pindolol or practolol or prizidilol or propranolol or sotalol or talinolol or tertatolol or tilisolol or timolol or tobanum):ti,ab,kw</p> <p><b>OR</b></p> <p>(Calcium Channel Block* or Calcium channel antagonist* or Amlodipin* or</p>	<p>ticrynafen or tifuladom or torsemide or traxanox or triamterene or trichlormethiazide or tripamide or xipamide or ularitide)</p> <p><b>OR</b></p> <p>TS=(“Beta-block*” or “Beta-adrenergic antagonist*” or “Beta-adrenergic receptor antagonist*” or “Beta-adrenergic block*” or “Beta-adrenergic receptor block*” or “Beta-adrenoreceptor antagonist*” or “Adrenergic beta-Antagonist*” or “Adrenergic beta-1 Receptor Antagonist*” or “Adrenergic beta-block*” or “Adrenergic beta-receptor block*” or Acebutolol or Alprenolol or amosulalol or arotinolol or atenolol or befunolol or betaxolol or bevantolol or bisoprolol or bopindolol or Brimonidine Tartrate or bromoacetylalprenololmenthane or bucindolol or bufetolol or bufuralol or bunolol or bupranolol or butofilolol or butoxamin* or carazolol or carteolol or carvedilol or celiprolol or cyanopindolol or dihydroalprenolol or epanolol or esmolol or exaprolol or fleistolol or indenolol or lodocyanopindolol or labetalol or levobunolol or medroxalol or mepindolol or metipranolol or oxprenolol or penbutolol or pindolol or practolol or prizidilol or propranolol or sotalol or talinolol or tertatolol or tilisolol or timolol or tobanum)</p> <p><b>OR</b></p>
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<p>trichlormethiazide [tiab] OR tripamide [tiab] OR xipamide [tiab] OR ularitide [tiab]</p> <p><b>OR</b></p> <p><i>Beta blockers</i></p> <p>Beta-block*[tiab] OR Beta-adrenergic antagonist*[tiab] OR Beta-adrenergic receptor antagonist*[tiab] OR Beta-adrenergic block*[tiab] OR Beta-adrenergic receptor block*[tiab] OR Beta-adrenoreceptor antagonist*[tiab] OR Adrenergic beta-Antagonist*[tiab] OR Adrenergic beta-1 Receptor Antagonist* [tiab] OR Adrenergic beta-block* [tiab] OR Adrenergic beta-receptor block* [tiab] OR Acebutolol [tiab] OR Alprenolol [tiab] OR amosulalol [tiab] OR arotinolol [tiab] OR atenolol [tiab] OR befunolol [tiab] OR betaxolol [tiab] OR bevantolol [tiab] OR bisoprolol [tiab] OR bopindolol [tiab] OR Brimonidine Tartrate [tiab] OR bromoacetylalprenololmenthane [tiab] OR bucindolol [tiab] OR bufetolol [tiab] OR bufuralol [tiab] OR bunolol [tiab] OR bupranolol [tiab] OR butofilolol [tiab] OR butoxamin* [tiab] OR carazolol [tiab] OR carteolol [tiab] OR carvedilol [tiab] OR celiprolol [tiab] OR cyanopindolol [tiab] OR dihydroalprenolol [tiab] OR epanolol [tiab] OR esmolol [tiab] OR exaprolol [tiab] OR flestolol [tiab] OR indenolol [tiab] OR Iodocyanopindolol [tiab] OR labetalol [tiab] OR levobunolol [tiab] OR medroxalol [tiab] OR mepindolol [tiab] OR metipranolol [tiab] OR metoprolol [tiab] OR nadolol [tiab]</p>	<p>or dihydroalprenolol or epanolol or esmolol or exaprolol or flestolol or indenolol or Iodocyanopindolol or labetalol or levobunolol or medroxalol or mepindolol or metipranolol or metoprolol or nadolol or nipradilol or oxprenolol or penbutolol or pindolol or practolol or prizidilol or propranolol or sotalol or talinolol or tertatolol or tilisolol or timolol or tobanum).ti,ab,kw.</p> <p><b>OR</b></p> <p><i>Calcium channel blockers</i></p> <p>(Calcium Channel Block* or Calcium channel antagonist* or Amlodipin* or Nifedipin* or Verapamil or Diltiazem or Nilvadipin* or Felodipin* or Isradipin* or Nicardipin* or Nimodipin* or Nisoldipin* or Nitrendipin* or Efonidipin*).ti,ab,kw.</p> <p><b>OR</b></p> <p><i>ACE inhibitors</i></p> <p>(Angiotensin-Converting Enzyme Inhibitor* or Angiotensin I-Converting Enzyme Inhibitor* or Angiotensin Converting Enzyme Antagonist* or ACE inhibitor* or Kininase II Inhibitor* or Captopril or Enalapril* or Lisinopril or Ramipril* or Alacepril or Benazepril* or ceronapril or cilazapril* or delapril or fosinopril* or gemopatrilat or imidapril* or libenzapril or moexipril or omapatrilat or perindopril* or quinapril* or rentiapril or spirapril or temocapril or teprotide or trandolapril or zofenopril or angiotensin I-converting enzyme antagonist*).ti,ab,kw.</p>	<p>Nifedipin* or Verapamil or Diltiazem or Nilvadipin* or Felodipin* or Isradipin* or Nicardipin* or Nimodipin* or Nisoldipin* or Nitrendipin* or Efonidipin*):ti,ab,kw</p> <p><b>OR</b></p> <p>(Angiotensin-Converting Enzyme Inhibitor* or Angiotensin I-Converting Enzyme Inhibitor* or Angiotensin Converting Enzyme Antagonist* or ACE inhibitor* or Kininase II Inhibitor* or Captopril or Enalapril* or Lisinopril or Ramipril* or Alacepril or Benazepril* or ceronapril or cilazapril* or delapril or fosinopril* or gemopatrilat or imidapril* or libenzapril or moexipril or omapatrilat or perindopril* or quinapril* or rentiapril or spirapril or temocapril or teprotide or trandolapril or zofenopril or angiotensin I-converting enzyme antagonist*):ti,ab,kw</p> <p><b>OR</b></p> <p>(Angiotensin-receptor blocker* or Angiotensin receptor antagonist* Angiotensin II Type 2 Receptor Blocker* or angiotensin II type 2 receptor blocker* or angiotensin II type 2 receptor blocker* or Angiotensin II Receptor Antagonist* or Angiotensin II Receptor Blocker* or Losartan or Valsartan or Candesartan or eprosartan or telmisartan or Olmesartan or azilsartan or Irbesartan or angiotensin II type 2 receptor antagonist*):ti,ab,kw</p> <p><b>AND</b></p>	<p>TS=(“Calcium Channel Block*” or “Calcium channel antagonist*” or Amlodipin* or Nifedipin* or Verapamil or Diltiazem or Nilvadipin* or Felodipin* or Isradipin* or Nicardipin* or Nimodipin* or Nisoldipin* or Nitrendipin* or Efonidipin*)</p> <p><b>OR</b></p> <p>TS=(“Angiotensin-Converting Enzyme Inhibitor*” or “Angiotensin I-Converting Enzyme Inhibitor*” or “Angiotensin Converting Enzyme Antagonist*” or “ACE inhibitor*” or “Kininase II Inhibitor*” or Captopril or Enalapril* or Lisinopril or Ramipril* or Alacepril or Benazepril* or ceronapril or cilazapril* or delapril or fosinopril* or gemopatrilat or imidapril* or libenzapril or moexipril or omapatrilat or perindopril* or quinapril* or rentiapril or spirapril or temocapril or teprotide or trandolapril or zofenopril or “angiotensin I-converting enzyme antagonist”)</p> <p><b>OR</b></p> <p>TS=(“Angiotensin-receptor blocker*” or “Angiotensin receptor antagonist*” “Angiotensin II Type 2 Receptor Blocker*” or “angiotensin II type 2 receptor blocker*” or “angiotensin II type 2 receptor blocker*” or “Angiotensin II Receptor Antagonist*” or “Angiotensin II Receptor Blocker*” or Losartan or Valsartan or Candesartan or eprosartan or telmisartan or Olmesartan or azilsartan or Irbesartan</p>
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<p>OR nipradilol [tiab] OR oxprenolol [tiab] OR penbutolol [tiab] OR pindolol [tiab] OR practolol [tiab] OR prizidilol [tiab] OR propranolol [tiab] OR sotalol [tiab] OR talinalol [tiab] OR tertatolol [tiab] OR tilisolol [tiab] OR timolol [tiab] OR tobanum [tiab]</p> <p><b>OR</b> <i>Calcium channel blockers</i> Calcium Channel Block* [tiab] OR Calcium channel antagonist* [tiab] OR Amlodipin* [tiab] OR Nifedipin* [tiab] OR Verapamil [tiab] OR Diltiazem [tiab] OR Nilvadipin* [tiab] OR Felodipin* [tiab] OR Isradipin* [tiab] OR Nicardipin* [tiab] OR Nimodipin* [tiab] OR Nisoldipin* [tiab] OR Nitrendipin* [tiab] OR Efonidipin* [tiab]</p> <p><b>OR</b> <i>ACE inhibitors</i> “Angiotensin-Converting Enzyme Inhibitor*” [tiab] OR “Angiotensin I- Converting Enzyme Inhibitor*” [tiab] OR “Angiotensin Converting Enzyme Antagonist*” [tiab] OR ACE inhibitor* [tiab] OR “Kininase II Inhibitor*” [tiab] OR Captopril [tiab] OR Enalapril* [tiab] OR Lisinopril [tiab] OR Ramipril* [tiab] OR Alacepril [tiab] OR Benazepril* [tiab] OR ceronapril [tiab] OR cilazapril* [tiab] OR delapril [tiab] OR fosinopril* [tiab] OR gemopatrilat [tiab] OR imidapril* [tiab] OR libenzapril [tiab] OR moexipril [tiab] OR omapatrilat [tiab] OR perindopril* [tiab] OR quinapril* [tiab] OR rentiapril [tiab] OR spirapril [tiab] OR temocapril [tiab] OR</p>	<p><b>OR</b> <i>ARBs</i> (Angiotensin-receptor blocker* or Angiotensin receptor antagonist* Angiotensin II Type 2 Receptor Blocker* or angiotensin II type 2 receptor blocker* or angiotensin II type 2 receptor blocker* or Angiotensin II Receptor Antagonist* or Angiotensin II Receptor Blocker* or Losartan or Valsartan or Candesartan or eprosartan or telmisartan or Olmesartan or azilsartan or Irbesartan or angiotensin II type 2 receptor antagonist*).ti,ab,kw.</p> <p><b>AND</b></p> <p><b><u>Concept 2: cerebral blood flow</u></b> Emtree Exp Brain circulation/ OR Transcranial doppler/ OR Exp brain blood flow</p> <p><b>OR</b> <b><u>Tiab</u></b> (Cerebral blood flow* OR Cerebral circulation* OR Cerebral perfusion* OR Cerebrovascular circulation OR Transcranial doppler OR cerebral hemodynamics OR cerebral autoregulation OR cerebral pressure- flow OR cerebrovascular effect* or brain circulation or brain blood flow or transcranial ultrasonograph*).ti,ab,kw.</p> <p><b>AND</b></p> <p><b><u>Concept 3: elderly OR cognitive impairment</u></b> <i>Cognitive disorders</i> Exp Cognitive defect/</p>	<p><b><u>Concept 2: cerebral blood flow</u></b> (Cerebral blood flow* OR Cerebral circulation* OR Cerebral perfusion* OR Cerebrovascular circulation OR Transcranial doppler OR cerebral hemodynamics OR cerebral autoregulation OR cerebral pressure- flow OR cerebrovascular effect* or brain circulation or brain blood flow or transcranial ultrasonograph*).ti,ab,kw</p> <p><b>AND</b></p> <p><b><u>Concept 3: elderly OR cognitive impairment</u></b> <i>Cognitive disorders</i> (Alzheimer* OR Amentia* OR Cognition disorder* OR Cognitive decline* OR Cognitive dysfunction* OR Cognitive impairment* OR Dementia* OR Familial dementia* OR Mental deterioration* OR Mild cognitive impairment* OR Mild neurocognitive disorder* OR Presenile dementia OR Senile dementia OR cognitive disorder* OR neurocognitive disorder*).ti,ab,kw</p> <p><b>OR</b> <i>Elderly</i> (Elde* OR Supercentenarian* OR Centenarian* OR Septuagenarian* OR Octagenarian* OR Nonagenarian* OR Oldest old* OR Very old* OR Older people OR Old people OR Older subject* OR Old subject* OR Older patient* OR Old patient* OR (Older age* NOT older agent*) OR (Old age* NOT Old agent*) OR Older man OR Old man OR Older men OR Old men OR</p>	<p>or “angiotensin II type 2 receptor antagonist*”)</p> <p><b>AND</b></p> <p><b><u>Concept 2: cerebral blood flow</u></b> TS=(“Cerebral blood flow*” OR “Cerebral circulation*” OR “Cerebral perfusion*” OR “Cerebrovascular circulation” OR “Transcranial doppler” OR “cerebral hemodynamic*” OR “cerebral autoregulation” OR “cerebral pressure-flow” OR “cerebrovascular effect*” or “brain circulation” or “brain blood flow” or “transcranial ultrasonograph”)</p> <p><b>AND</b></p> <p><b><u>Concept 3: elderly OR cognitive impairment</u></b> TS=(Alzheimer* OR Amentia* OR “Cognition disorder*” OR “Cognitive decline*” OR “Cognitive dysfunction*” OR “Cognitive impairment*” OR Dementia* OR “Familial dementia*” OR “Mental deterioration*” OR “Mild cognitive impairment*” OR “Mild neurocognitive disorder*” OR “Presenile dementia” OR “Senile dementia” OR “cognitive disorder*” OR “neurocognitive disorder”)</p> <p><b>OR</b> TS= (Elde* OR Supercentenarian* OR Centenarian* OR Septuagenarian* OR Octagenarian* OR Nonagenarian* OR “Oldest old*” OR “Very old*” OR “Older people” OR “Old people” OR “Older subject*” OR “Old subject*” OR “Older</p>
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<p>teprotide [tiab] OR trandolapril [tiab] OR zofenopril[tiab] OR angiotensin I-converting enzyme antagonist* [tiab]</p> <p><b>OR</b></p> <p><i>ARBs</i></p> <p>Angiotensin-receptor block* [tiab] OR Angiotensin receptor antagonist*[tiab] Angiotensin II Type 2 Receptor Block*[tiab] OR Angiotensin II Receptor Antagonist* [tiab] OR Angiotensin II Receptor Block* [tiab] OR Losartan[tiab] OR Valsartan[tiab] OR Candesartan[tiab] OR eprosartan [tiab] OR telmisartan [tiab] OR Olmesartan [tiab] OR azilsartan [tiab] OR Irbesartan[tiab] OR angiotensin II type 2 receptor antagonist* [tiab]</p> <p><b>AND</b></p> <p><b><u>Concept 2: cerebral blood flow</u></b></p> <p><u>MeSH</u></p> <p>Cerebrovascular circulation [MeSH] OR Transcranial Doppler Sonography [MeSH]</p> <p><b>OR</b></p> <p><u>Tiab</u></p> <p>Cerebral blood flow* [tiab] OR Cerebral circulation* [tiab] OR Cerebral perfusion [tiab] OR Cerebrovascular circulation [tiab] OR Transcranial doppler [tiab] OR cerebral hemodynamic* [tiab] OR cerebral autoregulation [tiab] OR cerebral pressure-flow [tiab] OR cerebrovascular effect* [tiab] OR transcranial ultrasonograph* [tiab] OR brain circulation [tiab] OR brain blood flow [tiab]</p>	<p><b>OR</b></p> <p>(Alzheimer* OR Amentia* OR Cognition disorder* OR Cognitive decline* OR Cognitive dysfunction* OR Cognitive impairment* OR Dementia* OR Familial dementia* OR Mental deterioration* OR Mild cognitive impairment* OR Mild neurocognitive disorder* OR Presenile dementia OR Senile dementia OR cognitive disorder* OR neurocognitive disorder*) .ti,ab,kw.</p> <p><b>OR</b></p> <p><i>Elderly</i></p> <p>(Elde* OR Supercentenarian* OR Centenarian* OR Septuagenarian* OR Octagenarian* OR Nonagenarian* OR Oldest old* OR Very old* OR Older people OR Old people OR Older subject* OR Old subject* OR Older patient* OR Old patient* OR (Older age* NOT older agent*) OR (Old age* NOT Old agent*) OR Older man OR Old man OR Older men OR Old men OR Older male* OR Old male* OR Older woman OR Old woman OR Older women OR Old women OR Older female* OR Old female* OR Older adult* OR Old adult* OR Older person* OR Old person* OR Older individual* OR Old individual* OR Older population* OR Old population* OR Old one* OR Older one* OR Older care OR Old care OR Aging population* OR Ageing population* OR Senior* OR Senium OR Geriatri* OR Gerontol* OR Homes for the Aged OR Home for the Aged OR Pension* OR Retirement OR Housing for the Elderly OR "60 and over" or "60 and older" or "65 and over" or "65 and older" or "70 and over" or "70 and older" or "75 and over" or "75 and older" or "80 and over" or "80 and older" or "85 and over" or "85 and older" or "90 and over" or "90 and older"):ti,ab,kw</p>	<p>Older male* OR Old male* OR Older woman OR Old woman OR Older women OR Old women OR Older female* OR Old female* OR Older adult* OR Old adult* OR Older person* OR Old person* OR Older individual* OR Old individual* OR Older population* OR Old population* OR Old one* OR Older one* OR Old care OR Older care OR Aging population* OR Ageing population* OR Senior* OR Senium OR Geriatri* OR Gerontol* OR Homes for the Aged OR Home for the Aged OR Pension* OR Retirement OR Housing for the Elderly OR "60 and over" or "60 and older" or "65 and over" or "65 and older" or "70 and over" or "70 and older" or "75 and over" or "75 and older" or "80 and over" or "80 and older" or "85 and over" or "85 and older" or "90 and over" or "90 and older"):ti,ab,kw</p>	<p>patient*" OR "Old patient*" OR ("Older age*" NOT "older agent*") OR ("Old age*" NOT "Old agent*") OR "Older man" OR "Old man" OR "Older men" OR "Old men" OR "Older male*" OR "Old male*" OR "Older woman" OR "Old woman" OR "Older women" OR "Old women" OR "Older female*" OR "Old female*" OR "Older adult*" OR "Old adult*" OR "Older person*" OR "Old person*" OR "Older individual*" OR "Old individual*" OR "Older population*" OR "Old population*" OR "Old one*" OR "Older one*" OR "Old care" OR "Older care" OR "Aging population*" OR "Ageing population*" OR Senior* OR Senium OR Geriatri* OR Gerontol* OR "Homes for the Aged" OR "Home for the Aged" OR Pension* OR Retirement OR "Housing for the Elderly" OR "60 and over" or "60 and older" or "65 and over" or "65 and older" or "70 and over" or "70 and older" or "75 and over" or "75 and older" or "80 and over" or "80 and older" or "85 and over" or "85 and older" or "90 and over" or "90 and older")</p>
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<p><b>AND</b></p> <p><b><u>Concept 3: elderly OR cognitive impairment</u></b></p> <p><i>Cognitive disorders</i>  Cognition disorders [MeSH] OR  Dementia [MeSH] OR Alzheimer* [tiab]  OR Amentia* [tiab] OR Cognition  disorder* [tiab] OR Cognitive decline*  [tiab] OR Cognitive dysfunction* [tiab]  OR Cognitive impairment* [tiab] OR  Dementia* [tiab] OR Familial dementia*  [tiab] OR Mental deterioration* [tiab]  OR Mild cognitive impairment* [tiab]  OR Mild neurocognitive disorder* [tiab]  OR Presenile dementia [tiab] OR Senile  dementia [tiab] OR Cognitive disorder  disorder* [tiab] OR Neurocognitive  disorder [tiab]</p> <p><b>OR</b></p> <p><i>Elderly</i>  Elde* [tiab] OR Supercentenarian*[tiab]  OR Centenarian*[tiab] OR  Septuagenarian*[tiab] OR  Octagenarian*[tiab] OR  Nonagenarian*[tiab] OR Oldest  old*[tiab] OR Very old*[tiab] OR Older  people[tiab] OR Old people[tiab] OR  Older subject*[tiab] OR Old  subject*[tiab] OR Older patient*[tiab]  OR Old patient*[tiab] OR (Older  age*[tiab] NOT older agent*[tiab]) OR  (Old age* [tiab] NOT old agent*[tiab])  OR Older man[tiab] OR Old man[tiab]  OR Older men[tiab] OR Old men[tiab]  OR Older male*[tiab] OR Old  male*[tiab] OR Older woman[tiab] OR</p>	<p>the Elderly OR "60 and over" or "60 and  older" or "65 and over" or "65 and  older" or "70 and over" or "70 and  older" or "75 and over" or "75 and  older" or "80 and over" or "80 and  older" or "85 and over" or "85 and  older" or "90 and over" or "90 and  older").ti,ab,kw.</p> <p><b>OR</b></p> <p>Aged/ or Aged Hospital Patient/ or Frail  Elderly/ or Institutionalized elderly/ or  Very elderly/ or Home for the aged/ or  Senior center/ or Aging/ or exp Elderly  care/</p> <p><b><u>Concept 4: human studies</u></b>  Limits → additional limits → special  ovid filters for embase → humans only</p>		
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<p>Old woman[tiab] OR Older women[tiab]  OR Old women[tiab] OR Older  female*[tiab] OR Old female*[tiab] OR  Older adult*[tiab] OR Old adult*[tiab]  OR Older person*[tiab] OR Old  person*[tiab] OR Older individual*[tiab]  OR Old individual*[tiab] OR Older  population*[tiab] OR Old  population*[tiab] OR Old one*[tiab] OR  Older one*[tiab] OR Old care[tiab] OR  Older care[tiab] OR Aging  population*[tiab] OR Ageing  population*[tiab] OR Senior*[tiab] OR  Senium[tiab] OR Geriatri*[tiab] OR  Gerontol*[tiab] OR "60 and over" [tiab]  OR "60 and older" [tiab] OR "65 and  over" [tiab] OR "65 and older" [tiab] OR  "70 and over" [tiab] OR "70 and older"  [tiab] OR "75 and over" [tiab] OR "75  and older" [tiab] OR "80 and over"  [tiab] OR "80 and older" [tiab] OR "85  and over" [tiab] OR "85 and older"  [tiab] OR "90 and over" [tiab] OR "90  and older" [tiab] OR Homes for the  Aged[tiab] OR Home for the Aged[tiab]  OR Pension*[tiab] OR Retirement[tiab]  OR Housing for the Elderly[tiab] OR  elderly [tiab] OR elderly subject* OR  Health Services for the Aged [MeSH] OR  Aged[MeSH] OR Aging[MeSH] OR Senior  Centers[MeSH] OR Homes for the Aged  [MeSH] OR Housing for the Elderly  [MeSh]</p> <p><b>NOT</b>  <u>Concept 4: human studies</u>  (Animals [MeSH] NOT Humans [MeSH])</p>			
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## 27 Supplemental methods 2. Data extraction

28 First, the study characteristics were extracted. These included study design, median/mean  
29 age, number of participants, study population, antihypertensive drug class, acute (<24 hours)  
30 or chronic (>2 weeks) assessment of the effect, method measuring CBF, units in which CBF  
31 was expressed, and follow-up time. Follow-up means the time between the measurement of  
32 CBF before and after AHT.

33

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Table S1. Reason for exclusion after full-text review

First Author	Reason for exclusion
Akopov, S. <sup>1</sup>	Full text not found
Bertel, O. <sup>2</sup>	Hypertensive emergency
Brown, F. <sup>3</sup>	Various neurological disorders, sodium nitroprusside
Canova, D. <sup>4</sup>	Mean age
Chrysant, S. <sup>5</sup>	Full text not found (but we suspect this is a review /opinion paper, not an original study)
Claassen, J. <sup>6</sup>	Mean age
Croall, I. <sup>7</sup>	Small vessel disease
De Bray, J. <sup>8</sup>	Did not report CBFV before and/or after AHT, mean age
Fagan, S. <sup>9</sup>	Suspicion of including the same data as Fagan 1995
Ferrarini, F. <sup>10</sup>	Full text not found
Fu, C. <sup>11</sup>	Did not report CBFV before and/or after AHT
Fu, C. <sup>12</sup>	Did not report CBFV before and/or after AHT
Gifford, R. <sup>13</sup>	Did not report CBF before and/or after AHT
Glodzik, L. <sup>14</sup>	Did not report CBF before and/or after AHT
Guell, A. <sup>15</sup>	Full text not found
Hajjar, I. <sup>16</sup>	Focus on aldosterone
James, I. <sup>17</sup>	Mean age
Jennings, J. <sup>18</sup>	Did not report CBF before and/or after AHT
Jennings, J. <sup>19</sup>	Did not report CBF before and/or after AHT
Joshi, S. <sup>20</sup>	vessel malformations, mean age, intracarotid verapamil
Kimura, Y. <sup>21</sup>	Ischemic white matter lesions
Kimura, Y. <sup>22</sup>	Small vessel disease
Lahiri, S. <sup>23</sup>	Case series, subarachnoid hemorrhage
Lawlor, B. <sup>24</sup>	Did not report CBF before and/or after AHT
Lemkuil, B. <sup>25</sup>	Mean age
Lipsitz, L. <sup>26</sup>	Did not report CBF before and/or after AHT
Liu, J. <sup>27</sup>	Normotensives
Markus, H. <sup>28</sup>	Meeting abstract
Meyer, J. <sup>29</sup>	Mean age
Minematsu, K. <sup>30</sup>	Mean age
Muller, M. <sup>31</sup>	Manifest coronary heart disease, cerebrovascular disease, peripheral arterial disease or abdominal aortic aneurysm
Muller, M. <sup>32</sup>	Comorbidity (stroke)
Olesen, J. <sup>33</sup>	No AHT
Ostroumova, T. <sup>34</sup>	Mean age
Périard, D. <sup>35</sup>	Did not report CBF before and/or after AHT
Schmidt, J. <sup>36</sup>	Mean age
Siegelova, J. <sup>37</sup>	Mean age
Sijbesma, J. <sup>38</sup>	Full text not found (Solely an abstract of a poster, the study presented was never conducted)
Simard, D. <sup>39</sup>	No AHT
Strandgaard, S. <sup>40</sup>	Full text not found (but we suspect this is a short survey)

Tzeng, Y. <sup>41</sup>	Did not report CBF before and/or after AHT, mean age
Van Dalen, J. <sup>42</sup>	No AHT
Weyl, A. <sup>43</sup>	Surgery, comorbidity
Yagi, S. <sup>44</sup>	Did not report CBF before and/or after AHT
Yamono, S. <sup>45</sup>	Did not report CBF before and/or after AHT
Zhang, L. <sup>46</sup>	No AHT
Zhang, P. <sup>47</sup>	Did not report CBF before and/or after AHT
Zhang, R. <sup>48</sup>	Mean age

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CBF, cerebral blood flow; AHT antihypertensive therapy

248 Table S2. GRADE assessment

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<b>GRADE item</b>	<b>Outcome of assessment</b>	<b>Remarks</b>
Number of studies	32	
Study design	Observational studies	Data from RCTs is also considered as observational data in this pre-post analysis
Risk of Bias	Very serious	Most studies were assessed as having a high risk of bias.
Inconsistency	Serious	$I^2$ is >60% (substantial – considerable).
Indirectness	Not serious	
Imprecision	Serious	Very large confidence intervals, many studies with small sample sizes.
Publication bias	Strongly suspected	Funnel plot could indicate missing smaller studies, with large positive effects on CBF.
Certainty	Very low	

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In this table we present the GRADE assessment (quality of evidence assessment) of our systematic review and meta-analysis. The GRADE assessment focusses on the quality of evidence for the main outcomes of the review based on certain domains (e.g. study design, risk of bias etc.), as opposed to quality at the individual study level. This facilitates the reader's interpretation of the quality of the findings of the review rather than study level quality. Framing the results of a meta-analysis using GRADE is considered best practice in evidence synthesis <sup>49</sup>.

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Table S3. Blood pressure and cerebral blood flow results chronic treatment

Study	Treatment	SBP/MAP* baseline (mmHg)	BP change (%)	Global CBF baseline (SD)	Global CBF follow-up (SD)
Conen 1988 <sup>50</sup>	Nitrendipine/verapamil	168	-11.3	74	75
	Chlorthalidone	163	-10.4	74	74
Cutler 1996 <sup>51</sup>	Ceronapril	120*	-10	44 (14)	35 (5)
De Jong 2019 <sup>52</sup>	Nilvadipine	138.7	-7.6	82.6 (23.3)	91.2 (24.1)
	Placebo	137.4	+1.0	90.1 (18.9)	90.7 (16.2)
Efimova 2008 <sup>53</sup>	Enalapril/idapamide retard	151.6	-21.1	44.9 (3.95)	48.2 (3.98)
Globus 1983 <sup>54</sup>	Propranolol	180	-1.9	48.5	59.3
Griffith 1979 <sup>55</sup>	Labetalol	137*	-20.4	45.1 (1.1)	47.1 (1.2)
	Metoprolol	138*	-18.1	45.4 (1.0)	44.6 (0.8)
	Oxprenol	139*	-16.5	45.4 (1.2)	46.7 (1.3)
	Sotalol	137*	-16.8	45.6 (1.0)	46.4 (1.2)
Hajjar 2013 <sup>56</sup>	Lisinopril	153	-17.6	28.00 (1.49)	25.89 (1.80)
	Candesartan	150	-17.3	29.12 (1.57)	30.13 (2.02)
	Hydrochlorothiazide	156	-16.0	29.52 (2.79)	27.12 (2.10)
Hamdy 1984 <sup>57</sup>	Propranolol	216.07	-9.0	49.3 (16.81)	49.45 (14.88)
	Dyazide	213.22	-11.9	48.4	51.6
Hanyu 2007 <sup>58</sup>	Nilvadipine	159	-13.2	0.92	0.94
	Amlodipine	156	-11.5	0.89	0.97
James 1988 <sup>59</sup>	Captopril	176.4	-12.3	36.8 (2.6)	39.8 (3.8)
Jennings 2008 <sup>60</sup>	Lisinopril	148.7	-14.7	48.0 (9.3)	47.2 (9)
	Atenolol	147.7	-16.0	44.2 (7.2)	39.9 (6.8)
Kashiwagi 1998 <sup>61</sup>	Nitrendipine	166	-15.1	37 (3.46)	36 (6.93)
Kume 2012 <sup>62</sup>	Telmisartan	150	-9.3	0.94	0.89
	Amlodipine	153	-12.4	0.80	0.86
Landmark 1995 <sup>63</sup>	Nitrendipine	178	-9.9	36 (6.4)	35.8 (6.3)
	Mefruside	183	-14.4	36 (6.4)	36.7 (5.9)
Miyamori 1987 <sup>64</sup>	Nifedipine	172	-13.2	15 (1)	16(2)
Nagata 2010 <sup>65</sup>	Olmesartan	156.2	-16.5	37.9 (3.8)	43.8 (4.2)
Nasrallah 2021 <sup>66</sup>	Intensive	Unknown	Unknown	52.59 (5.24)	51.27 (5.11)
	Standard	Unknown	Unknown	49.58 (5.14)	48.72 (5.29)



Oku 2005 <sup>67</sup>	Losartan	153.8	-13.3	38.4 (6.9)	38.2 (8.2)
Pandita-Gunawardena 1999 <sup>68</sup>	Amlodipine	185	-5.7	93	93
	Placebo	189	-1.1	94.4	94.5
Pandita-Gunawardena 1989 <sup>69</sup>	Nitrendipine	186	-8.1	54.2 (14.43)	51.5 (13.77)
Ram 1987 <sup>70</sup>	Prozasin/hydrochlorothiazide	166	-12.7	72 (10)	70 (11)
Shimamoto 1995 <sup>71</sup>	Nilvadipine	120.2*	-12.8	608 (178) carotid	766 (223) carotid
				378 (232) carotid	495 (170) carotid
	Nifedipine	119.7*	-13.4	629 (207) vertebral	688 (237) vertebral
				395 (202) vertebral	422 (184) vertebral
Thulin 1993 <sup>72</sup>	Felodipine	214	-23.4	40 (8.43)	39.75 (8.01)
Traub 1982 <sup>73</sup>	Hydrochlorothiazide	184	-11.11	38 (7.75)	37 (11.61)
Tryambake 2013 <sup>74</sup>	Intensive	149	-17.4	74 (14)	81 (11)
	Usual	155	-9.7	76 (15)	73 (9)
Waldemar 1990 <sup>75</sup>	Fosinopril	161	-9.9	55 (9)	53 (10)
Weiner 1992 <sup>76</sup>	Ceronapril	Unknown	Unknown	Unknown	Unknown

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SBP indicates systolic blood pressure; MAP, mean arterial pressure; BP, blood pressure; CBF, cerebral blood flow; SD, standard deviation. Most studies expressed CBF in ml/100g/min, except for Hajjar 2013 (cm/s), Hanyu 2007 (Z-score), Kume 2012 (Z-score), Miyamori 1987 (cm/s) and Shimamoto 1995 (ml/min).

262 Table S4. Blood pressure and cerebral blood flow results acute treatment

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Study	Treatment	SBP/MAP* baseline (mmHg)	BP change (%)	Global CBF baseline (SD)	Global CBF follow-up (SD)
Conen 1988 <sup>50</sup>	Nitrendipine	160	-15.6	38	38
Fagan 1992 <sup>77</sup>	Nifedipine	Unknown	Unknown	45.7	44.7
Fagan 1995 <sup>78</sup>	Enalapril/lisinopril/diltiazem/nifedipine/verapamil	Unknown	Unknown	45	45
Kamlow 1990 <sup>79</sup>	Atenolol	158	-13.9	Unknown	Unknown
	Enalapril	160	-13.1	Unknown	Unknown
Miller 2018 <sup>80</sup>	Hydrazilline/labetalol/nicardipine/clonidine	210	-18.0	49 (11)	44
Miyamori 1987 <sup>64</sup>	Nifedipine	172	-20.3	15.0 (0.8)	17.5 (0.9)
Pandita-Gunawardena 1989 <sup>69</sup>	Nitrendipine	Unknown	Unknown	54.2 (14.43)	51.23 (12.76)
Thulin 1993 <sup>72</sup>	Felodipine	214	-21.5	40 (8.43)	42.75 (10.87)
Zazulia 2010 <sup>81</sup>	Nicardipine	107*	-13.5	43.5 (11.1)	42.5 (9.7)

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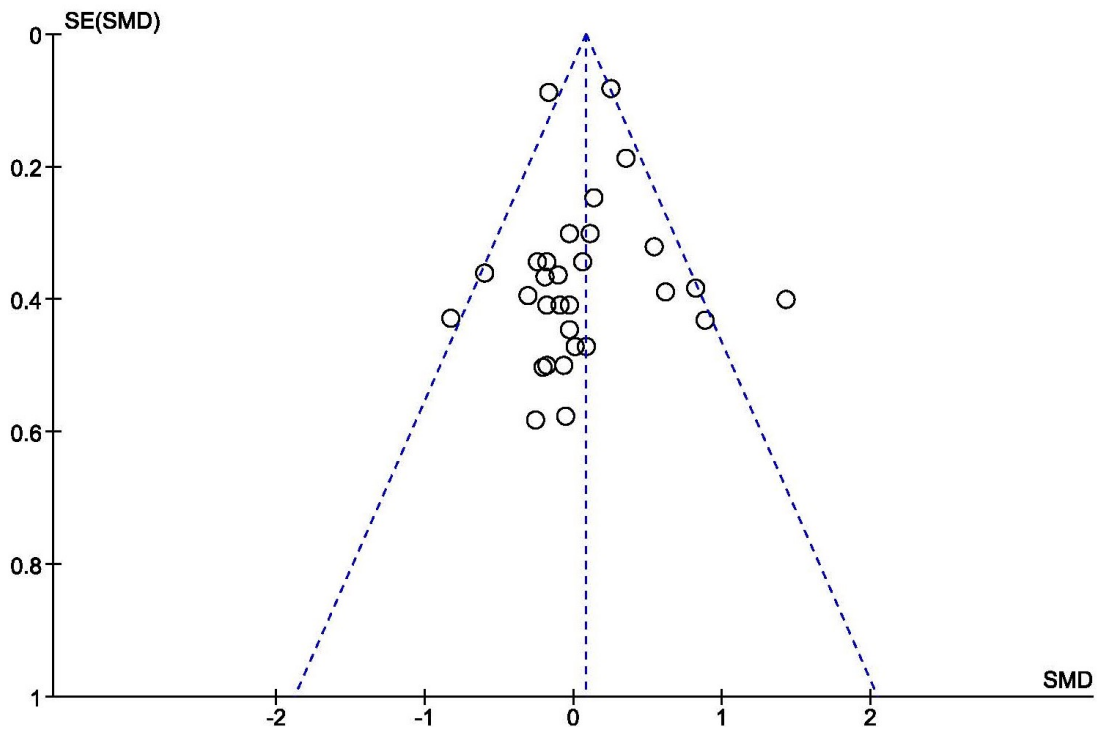
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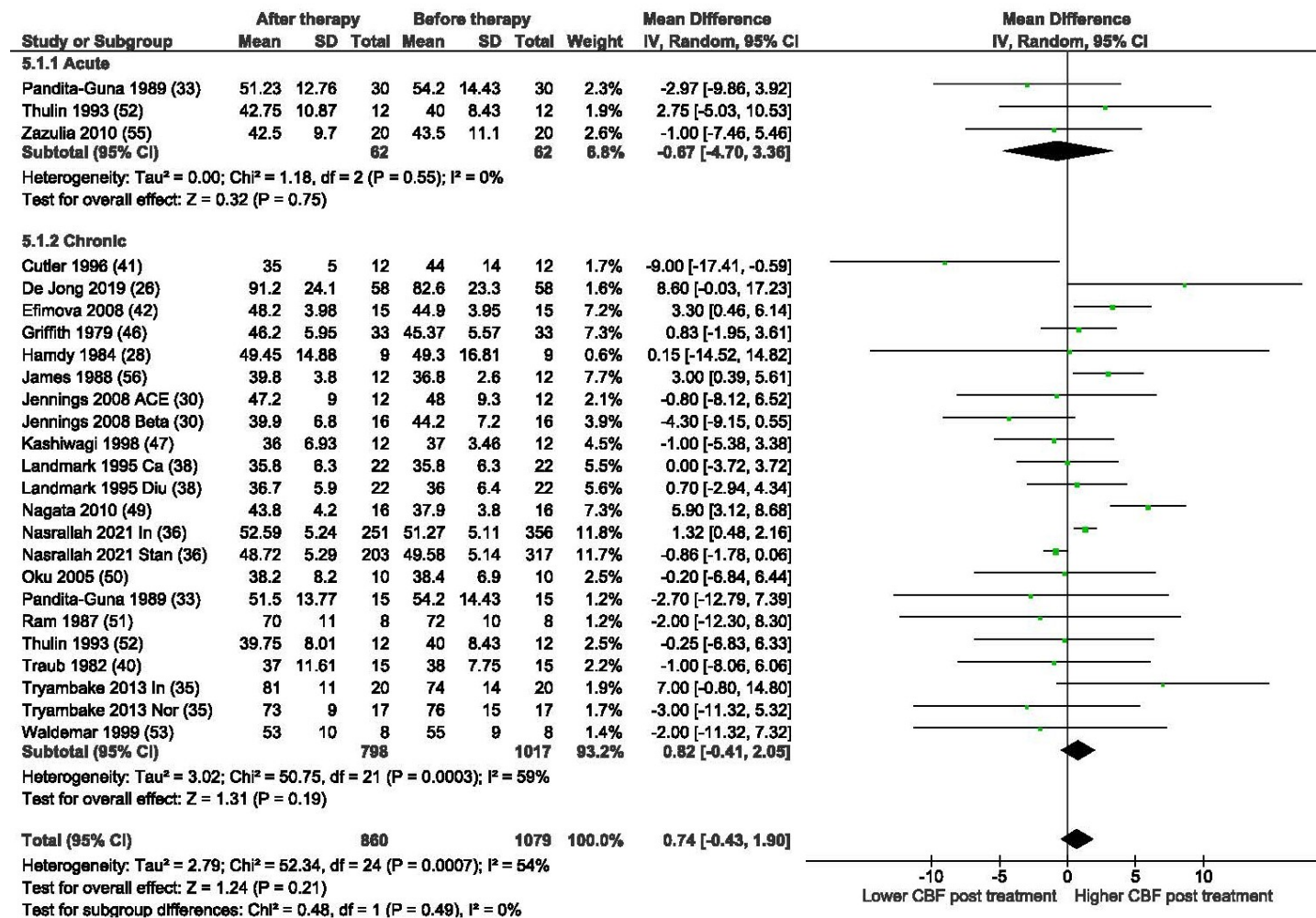
SBP indicates systolic blood pressure; MAP, mean arterial pressure; BP, blood pressure; CBF, cerebral blood flow; SD, standard deviation. Most studies expressed CBF in ml/100g/min, except for Fagan 1992 (cm/s), Miller 2019 (cm/s) and Miyamori 1987 (cm/s).

269 Figure S1. Funnel plot standardized mean difference (SMD) in cerebral blood flow before and  
270 after chronic antihypertensive treatment  
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274 The dotted perpendicular line displays the estimated overall effect and the two dotted oblique lines signify the  
275 95% confidence interval. The y-axis represents study precision, x-axis displays the result of the quantitative  
276 analysis. Asymmetry suggests the possibility of publication bias. SE indicates standard error; SMD, standardized  
277 mean difference.

278 Figure S2. Mean difference in cerebral blood flow before and after acute and chronic antihypertensive treatment



279 Total indicates number of participants. Some randomized controlled trials investigated the effect of two different therapies. SD indicates standard deviation; IV, inverse variance;  
 280 CI, confidence interval; CBF, cerebral blood flow; ACE, angiotensin-converting enzyme. CBF is expressed in ml/100g/min.  
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283 [Figure S3. Funnel plot mean difference \(MD\) of cerebral blood flow before and after acute](#)  
284 [and chronic antihypertensive treatment](#)

285 The dotted perpendicular line displays the estimated overall effect and the two dotted  
286 oblique lines signify the 95% confidence interval. The y-axis represents study precision, x-axis  
287 displays the result of the quantitative analysis. Asymmetry suggests the possibility of  
288 publication bias. SE indicates standard error; MD, mean difference. The diamonds indicate  
289 studies that investigated cerebral blood flow before and after chronic antihypertensive  
290 treatment. The circles indicate studies that investigated cerebral blood flow before and after  
291 acute antihypertensive treatment.

292 [Figure S4. Subgroup analysis antihypertensive class](#)

293 Total indicates number of participants. Some randomized controlled trials investigated the  
294 effect of two different therapies. SD indicates standard deviation; IV, inverse variance; CI,  
295 confidence interval; CBF, cerebral blood flow; ACE, angiotensin-converting enzyme; ARB,  
296 angiotensin receptor blocker. CBF is expressed in ml/100g/min.

297 [Figure S5. Subgroup analysis method measuring cerebral blood flow](#)

298 Total indicates number of participants. Some randomized controlled trials investigated the  
299 effect of two different therapies. SD indicates standard deviation; IV, inverse variance; CI,  
300 confidence interval; CBF, cerebral blood flow; ASL, arterial spin labeling; MRI, magnetic  
301 resonance imaging; Xe, xenon; SPECT, single photon emission computed tomography. CBF is  
302 expressed in ml/100g/min.

303 [Figure S6. Subgroup analysis study design](#)

304 Total indicates number of participants. Some randomized controlled trials investigated the  
305 effect of two different therapies. SD indicates standard deviation; IV, inverse variance; CI,  
306 confidence interval; CBF, cerebral blood flow; ACE, angiotensin-converting enzyme; RCT,  
307 randomized controlled trial. CBF is expressed in ml/100g/min.