**SUPPLEMENTAL DATA**

**Effects of vasodilating medications on cerebral hemodynamics in health and disease: systematic review and meta-analysis**

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**Supplemental Figure 1. PRISMA flowchart of identification, screening and inclusion of studies.**

**Abstracts screened**
(n = 478 )

**Records after duplicates removed**
(n = 10342 )

## Identification

## Eligibility

## Included

## Screening

**Comparisons of Reactivity to CO2**
(n = 14)

**Comparisons of CBF**

 (n = 20)

**Comparisons of TCD Measures (MFV or PI)**
(n = 32)

**Records excluded**
(n = 373)

**Full-text articles excluded**:

Unobtainable / only abctract published 6

Duplicate Population 6

Not Primary Data 5

No Control Group 22

Wrong patient group 4

No useable data 27

**Full-text articles assessed**
(n = 105)

**Studies included in quantitative synthesis** (meta-analysis)
(n = 35)

**Additional records identified through other sources**
(n = 14 )

**Records identified through database searching**
(n = 14,171)

**Supplemental Figure 2. Assessment of quality of included studies.** A) Assessment of study quality according to Cochrane Manual criteria, assessing each study for a low, unclear or high risk of bias; B – D) funnels plots of the effect size of each comparison against the standard error with 95% confidence limits for change in cerebral blood flow (CBF), change in mean flow velocity (MFV) or change in cerebrovascular reactivity (CVR). SMD – standardised mean difference. SE – standard error

**A)**

**B)**

**C)**

**D)**

**Supplemental Figure 3. Forest plot of difference in MFV between groups randomised to a vasodilating medication versus placebo or no change in treatment.**  Effect sizes are combined by both fixed effects and random effects meta-analysis weighted by the inverse variance. ∆MFV- change in mean flow velocity; Cilow- confidence interval lower limit; Cihigh confidence interval upper limit; p-het – p value for heterogeneity; N – number of subjects; GTN – glyceryl trinitrate;



**Supplemental Figure 4. Forest plots of difference in mean flow velocity between groups randomised to a vasodilating medication versus a non-vasodilating control group, stratified for Healthy Individuals (A), patients treated within 7 days of a stroke or TIA (B) or patients with chronic conditions (C).**  Control groups included patients treated with either placebo, a non-vasodilating medication or no change in treatment, with effect sizes combined by both fixed effects and random effects meta-analysis weighted by the inverse variance. Chronic conditions include previous stroke, cognitive impairment, hypertension or migraine. ∆MFV- change in mean flow velocity; Cilow- confidence interval lower limit; Cihigh confidence interval upper limit; p-het – p value for heterogeneity; N – number of subjects; GTN – glyceryl trinitrate; HCTZ – hydrochlorothiazide;

**A) Healthy Individuals**



**B) Acute cerebrovascular events**



**C) Chronic underlying conditions**



**Supplemental Figure 5. Forest plots of difference in mean flow velocity between groups randomised to a vasodilating medication versus a non-vasodilating control group, stratified by vasodilator drug class.**  Control groups included patients treated with either placebo, a non-vasodilating medication or no change in treatment, with effect sizes combined by both fixed effects and random effects meta-analysis weighted by the inverse variance. Chronic conditions include previous stroke, cognitive impairment, hypertension or migraine. ∆MFV- change in mean flow velocity; Cilow- confidence interval lower limit; Cihigh confidence interval upper limit; p-het – p value for heterogeneity; N – number of subjects; GTN – glyceryl trinitrate; HCTZ – hydrochlorothiazide;

1. **Phosphodiesterase inhibitors**



1. **Calcium Channel Blockers**



1. **Renin-angiotensin system inhibitors**



1. **Nitric Oxide donors**



**Supplemental Figure 6. Forest plot of difference on peak systolic (A) or end diastolic (B)** **velocity between groups randomised to a vasodilating medication versus a non-vasodilating control group.**  Control groups included patients treated with either placebo, a non-vasodilating medication or no change in treatment, with effect sizes combined by both fixed effects and random effects meta-analysis weighted by the inverse variance. ∆MFV- change in mean flow velocity; Cilow- confidence interval lower limit; Cihigh confidence interval upper limit; p-het – p value for heterogeneity; N – number of subjects;

**A) Peak Systolic Velocity**



**B) End Diastolic Velocity**



**Supplemental Figure 7. Forest plot of difference in cerebral arterial pulsatility index between groups randomised to a vasodilating medication versus a non-vasodilating control group, stratified by study design.**  Comparisons are stratified by comparisons with placebo or no change in treatment only (A), healthy participants (B), within 7 days of a stroke or TIA (C), chronic conditions (D), or whether medication was only given once (E) or for multiple days (F). Effect sizes are combined by both fixed effects and random effects meta-analysis weighted by the inverse variance. ∆PI- change in mean flow velocity; Cilow- confidence interval lower limit; Cihigh confidence interval upper limit; p-het – p value for heterogeneity; N – number of subjects; GTN – glyceryl trinitrate;

**A) No active control groups**

**B) Healthy participants**



**C) Acute cerebrovascular events**

**D) Chronic treatment in underlying conditions**

1. **Single dose studies**



**F) Prolonged treatment**

**Supplemental Figure 8. Forest plot of difference in cerebral blood flow between groups randomised to a vasodilating medication versus a non-vasodilating control group, stratified by study design.**  Comparisons are stratified by comparisons with placebo or no change in treatment only (A), whether medications were only given as a single dose (B), for healthy participants (C), within 7 days of a stroke or TIA (D) or in the context of chronic conditions (E). Effect sizes are combined by both fixed effects and random effects meta-analysis weighted by the inverse variance. ∆CBF- change in cerebral blood flow; Cilow- confidence interval lower limit; Cihigh confidence interval upper limit; p-het – p value for heterogeneity; N – number of subjects; GTN – glyceryl trinitrate; SMD – standardised mean difference.

1. **No active control groups**



1. **Single dose studies**
2. **Healthy participants**



1. **Acute treatment after cerebrovascular events**



1. **Chronic treatment in underlying conditions**



**Supplemental Figure 9. Forest plot of difference in grouped mean pulse pressure, between groups randomised to a vasodilating medication versus a non-vasodilating control group.**  Control groups included patients treated with either placebo, a non-vasodilating medication or no change in treatment, with effect sizes combined by both fixed effects and random effects meta-analysis weighted by the inverse variance, estimating the study specific pulse pressure from the group mean SBP and DBP. Cilow- confidence interval lower limit; Cihigh confidence interval upper limit; p-het – p value for heterogeneity; N – number of subjects; GTN – glyceryl trinitrate; HCTZ – hydrochlorothiazide;



**Supplemental Figure 10. Forest plot of difference in systolic blood pressure (SBP), diastolic blood pressure (DBP), cerebral mean flow velocity (MFV) or cerebral arterial pulsatility index (PI) between groups randomised to a vasodilating medication versus a non-vasodilating control group, limited to studies reporting both BP changes and ultrasound indices.**  Control groups included patients treated with either placebo, a non-vasodilating medication or no change in treatment, with effect sizes combined by both fixed effects and random effects meta-analysis weighted by the inverse variance. Cilow- confidence interval lower limit; Cihigh confidence interval upper limit; p-het – p value for heterogeneity; N – number of subjects; GTN – glyceryl trinitrate; HCTZ – hydrochlorothiazide;

1. SBP



1. DBP



1. Mean flow velocity



1. Pulsatility Index



**Supplemental Figure 11. Meta-regression of change in standardised mean differences in mean flow velocity (SMD-MFV), systolic blood (SMD-SBP), diastolic blood pressure (SMD-DBP) and cerebral arterial pulsatility index (SMD-PI).** Regressions are weighted by the inverse variance calculated for the meta-analyses.



**Supplemental Table 1. Characteristics of Included Studies**

|  |  |  |  |  |  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- | --- |
|  | 1st Author | Year | N | Age | Randomised | Blinding | Design | Placebo | Dosing | Population | Comparison |
| 1 | Schulz JM | 2018 | 10 | 22 | No | Single | Crossover | Placebo | Single | Healthy | Placebo vs Nitroglycerin |
| 2 | Choi MH | 2018 | 95 | 61 | Randomised | Double | Parallel | No Placebo | Prolonged | Stroke | Atenolol vs Valsartan vs Fimasartan |
| 3 | Lindberg U | 2017 | 17 | 35 | Randomised | Double | Crossover | Placebo | Prolonged | Becker MD | Placebo vs Sildenafil |
| 4 | Zhang W | 2016 | 610 | 62 | Randomised | Open | Parallel | No Placebo | Prolonged | Stroke | Control (no tx) vs Vinpocetine |
| 5 | Wong RH | 2016 | 36 | 69 | Randomised | Double | Crossover | Placebo | Single | T2DM | Placebo vs Resveratol vs Resveratol |
| 6 | Han SW | 2014 | 203 | 65 | Randomised | Double | Parallel | Placebo | Prolonged | Stroke | Placebo vs Cilostazol |
| 7 | Tzeng YC | 2013 | 23 | 26 | Randomised | Open | Parallel | Placebo | Single | Healthy | Placebo vs Nimodipine |
| 8 | Sakurai H | 2013 | 20 | 79 | Randomised | Open | Parallel | No Placebo | Prolonged | Dementia | Control (ASA or Clopidogrel) vs Cilostazol |
| 9 | Beer C | 2012 | 52 | 69 | Randomised | Double | Parallel | Placebo | Prolonged | Stroke | Placebo vs Irbesartan |
| 10 | Kume K | 2012 | 20 | 79 | Randomised | Open | Parallel | No Placebo | Prolonged | Dementia | Amlodipine vs Telmisartan |
| 11 | Kennedy DO | 2010 | 24 | 20 | Randomised | Single | Crossover | Placebo | Single | Healthy | Placebo vs trans-resveratol vs trans-resveratol |
| 12 | Hong KS | 2010 | 196 | 62 | Randomised | Double | Parallel | No Placebo | Prolonged | Stroke | Cilnidipine vs Losartan |
| 13 | Matsumoto S | 2009 | 35 | 61 | Randomised | Double | Parallel | No Placebo | Prolonged | Stroke | Amlodipine vs Olmesartan |
| 14 | Rashid P | 2003 | 90 | 71 | Randomised | Open | Parallel | No Placebo | Single | Stroke | No tx vs GTN vs GTN |
| 15 | Rosengarten  | 2006 | 11 | 49 | No | Open | Crossover | No Placebo | Single | PAH | Iloprost vs Sildenafil |
| 16 | Fu CH | 2005 | 90 | 60 | No | Open | Parallel | No Placebo | Prolonged | HTN | Control vs Nifedipine SR vs Atenolol |
| 17 | Diomedi M | 2005 | 28 | 57 | Randomised | Double | Parallel | Placebo | Single | Healthy | Placebo vs Sildenafil |
| 18 | Koksal M | 2005 | 30 | 46 | No | Double | Parallel | Placebo | Single | Healthy | Placebo vs Sildenafil |
| 19 | Birk S | 2004 | 12 | 26 | Randomised | Double | Crossover | Placebo | Single | Healthy | Placebo vs Cilostazol |
| 20 | Nazir FS | 2005 | 25 | 68 | Randomised | Double | Parallel | Placebo | Single | Stroke | Placebo vs Perindopril  |
| 21 | Hatazawa J | 2004 | 19 | 65 | Randomised | Single | Parallel | Placebo | Prolonged | Stroke | Placebo vs Perindopril |
| 22 | Walters M | 2004 | 12 | 63 | Randomised | Double | Crossover | Placebo | Prolonged | Stroke | Placebo vs Perindopril |
| 23 | Arnavaz A | 2003 | 6 | 26 | Randomised | Double | Crossover | Placebo | Single | Healthy | Placebo vs Sildenafil |
| 24 | Pieniazek W | 2001 | 30 | 47 | Randomised | Double | Crossover | No Placebo | Prolonged | Hypertension | Acebutolol vs Perindopril |
| 25 | Semplicini A | 2000 | 15 | ~50 | Randomised | Double | Parallel | Placebo | Prolonged | Hypertension  | HCTZ vs Lacidipne |
| 26 | Kruuse C | 2000 | 10 | 25 | Randomised | Double | Crossover | Placebo | Single | Healthy | PlAcebo vs Pentoxifylline |
| 27 | Belfort MA | 1999 | 21 | 27 | Randomised | Open | Parallel | No Placebo | Single | PET | MgSO4 vs Nimodipine |
| 28 | Semplicini A | 1993 | 14 | 61 | Randomised | Double | Parallel | No Placebo | Prolonged | HTN | HCTZ vs Fosinopril |
| 29 | Traub YM | 1991 | 20 | 67 | Randomised | Single | Crossover | No Placebo | Prolonged | Hypertension | Enalapril vs Nifedipine l |
| 30 | Kraaier V | 1991 | 24 | 23 | Randomised | Double | Crossover | Placebo | Prolonged | ischaemia) | Placebo vs Nimodipine |
| 31 | James IM | 1978 | 10 | 70 | No | Double | Parallel | Placebo | Prolonged | Dementia | Placebo vs Naftidofuryl |
| 32 | Hajjar I | 2014 | 47 | 72 | Randomised | Double | Parallel | No Placebo | Prolonged | MCI | HCTZ vs Candesartan vs Lisinopril |
| 33 | Webb AJS | 2016 | 10 | 29 | Randomised | Single | Crossover | No Placebo | Prolonged | Healthy | Propranolol LA vs Amlodipine |
| 34 | Han SW | 2013 | 203 | 65 | Randomised | Double | Parallel | Placebo | Prolonged | Stroke | Placebo vs Cilostazol |
| 35 | Willmot M | 2006 | 18 | 70 | Randomised | Single | Parallel | Placebo | Prolonged | Stroke | Placebo vs GTN |
| 36 | Guo JJ | 2009 | 68 | 60 | Randomised | Open | Parallel | No Placebo | Prolonged | Stroke | Aspirin vs Cilostazol |

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**Search Strategy (Pubmed)**

("transcranial ultrasound"[Title/Abstract] OR "transcranial doppler"[Title/Abstract] OR "transcranial ultrasonography"[Title/Abstract] OR "Gosling's pulsatility index"[Title/Abstract] OR "pulsatility index"[Title/Abstract] OR "peak systolic velocity"[Title/Abstract] OR "end diastolic velocity"[Title/Abstract] OR "mean flow velocity"[Title/Abstract] OR "cerebral blood flow"[Title/Abstract] OR "cerebral perfusion"[Title/Abstract] OR "ASL"[Title/Abstract] OR "CT perfusion"[Title/Abstract] OR "MRI perfusion"[Title/Abstract] OR "MR perfusion"[Title/Abstract] OR "cerebrovascular reactivity"[Title/Abstract] OR "breath holding index"[Title/Abstract] OR "hyperventilation"[Title/Abstract] OR "cerebral perfusion"[Title/Abstract]) AND (vasodilator[Title/Abstract] OR vasodilation[Title/Abstract] OR vasodilating[Title/Abstract] OR endothelin[Title/Abstract] OR phosphodiesterase[Title/Abstract] OR "calcium channel blocker"[Title/Abstract] OR angiotensin[Title/Abstract] OR "nitric oxide"[Title/Abstract] OR "nitrous oxide"[Title/Abstract] OR "amlodipine"[Title/Abstract] OR "felodipine"[Title/Abstract] OR "nimodipine"[Title/Abstract] OR "nitrendipine"[Title/Abstract] OR "isradipine"[Title/Abstract] OR "lacidipine"[Title/Abstract] OR "lercanidipine"[Title/Abstract] OR "nicardipine"[Title/Abstract] OR "nifedipine"[Title/Abstract] OR "nitrendipine"[Title/Abstract] OR "sildenafil"[Title/Abstract] OR "tadalafil"[Title/Abstract] OR "vardenafil"[Title/Abstract] OR "cilostazol"[Title/Abstract] OR "amrinone"[Title/Abstract] OR "candesartan"[Title/Abstract] OR eprosartan[Title/Abstract] OR irbesartan[Title/Abstract] OR losartan[Title/Abstract] OR olmesartan[Title/Abstract] OR telmisartan[Title/Abstract] OR valsartan[Title/Abstract] OR captopril[Title/Abstract] OR cilazapril[Title/Abstract] OR enalapril[Title/Abstract] OR fosinopril[Title/Abstract] OR imidapril[Title/Abstract] OR lisinopril[Title/Abstract] OR moexipril[Title/Abstract] OR perindopril[Title/Abstract] OR quinapril[Title/Abstract] OR ramipril[Title/Abstract] OR ambrisentan[Title/Abstract] OR bosentan[Title/Abstract] OR diazoxide[Title/Abstract] OR hydralazine[Title/Abstract] OR vinpocetine[Title/Abstract] OR sitaxsentan[Title/Abstract] OR iloprost[Title/Abstract] OR minoxidil[Title/Abstract] OR naftidrofuryl[Title/Abstract] OR nebivolol[Title/Abstract] OR nicorandil[Title/Abstract])

**Inclusion Criteria**

1. Controlled comparison
2. Compares groups of similar individuals
3. Control groups include placebo, no treatment or a non-vasodilating medication
4. Experimental group uses an accepted vasodilators:
	1. Phosphodiesterase inhibitors (specifically 3 or 5)
	2. Calcium channel blockers
	3. Renin-angiotensin system inhibitors (ACEI, ARBs etc)
	4. Endothelin receptor antagonists
	5. Nitric oxide donrs
	6. Direct vasodilators (ie hydralazine)
	7. Alpha-blockers
	8. Nebivolol, nicorandil
	9. Agents with a likely vasodilator effect: Resveratrol, vinpocetine
5. Acute treatment (within 7 days of an event) or chronic treatment (> 7 days after an acute event, or use in a chronic condition)
6. In any patient group (healthy individuals, stroke patients, small vessel disease or cognitive disorders…)
7. Reports effects on cerebral haemodynamics or reactivity to carbon dioxide using either:
	1. Transcranial Doppler ultrasound
	2. MRI sequences sensitive to blood flow or blood volume (BOLD, ASL, contrast based perfusion, phase contrast)
	3. CT perfusion
	4. Near infrared spectroscopy
	5. Any direct measure of cerebral blood flow (PET, SPECT etc)
8. Reports numerical effect size

**Exclusion Criteria**

1. Post-SAH vasospasm
2. Moderate to Severe head injury
3. Underlying genetic disorder (ie CADASIL)
4. Sequential study design with consistent treatment order (crossover trials with randomised order of interventions allowed)