Pharmacological Treatment of Post-Prandial Reductions in Blood Pressure: a systematic review

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Key Words

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Key Points

Whilst post-prandial hypotension is not uncommon in older people and is of clinical significance, there are only a few studies which have focused on the pharmacological management of symptomatic patients.

Although drugs can attenuate the post-meal fall in BP, evidence is lacking with regard to their effect on those with symptomatic post-prandial hypotension.

These studies highlight the need of rigorous clinical trials in the treatment of this clinically important condition.

Abstract

Background: A fall in blood pressure (BP) after meals (postprandial hypotension [PPH]), is common in older adults and associated with significant morbidity and mortality.

Objectives: Our aim was to systematically review the current literature on the pharmacological treatment of post-meal reductions in BP.

Design: A systematic literature search and standardised data collection of randomised controlled studies on the pharmacological prevention of postprandial falls in BP in adults using MEDLINE (1950-), EMBASE (1980-) and CINAHL databases was conducted up to July 2013. Hand-searching of bibliographies of relevant reports was also carried out to identify all potentially eligible studies.

Setting: Systematic Review of RCTs using PRISMA guidelines

Measurements: Papers were assessed using CASP (Critical Appraisal Skills Programme) for randomised controlled trials.

Results: Thirteen papers reporting twelve studies (one study was reported in two papers) demonstrated that caffeine (five studies), acarbose, 3, 4-DL-threodihydroxyphenylserine (DL-DOPS), guar gum (three studies) and octreotide (two studies) statistically attenuated the postprandial BP fall. One caffeine study did not show this. However most studies did not include patients with symptomatic PPH and therefore interpretation and application of these findings to this patient group should be made with caution. For symptomatic participants there was improvement with acarbose but none with caffeine. Differences in the way the data were presented in the studies did not allow for quantification of treatment effects by meta-analysis.

Conclusion: Drug interventions can attenuate postprandial BP falls, but they may not necessarily be effective in people with symptomatic PPH.

Background

Postprandial hypotension (PPH) can be defined as a reduction in the systolic BP (SBP) of ≥20mmHg within 2 hours of the start of a meal or if SBP falls to ≤90mmHg within this period where the pre-prandial SBP was ≥100mmHg. [1] Post-prandial falls in BP are much more common in older people, with prevalence rates up to 36% of those residing in care homes [2,3] and as high as 67% in the older hospital population [4].

Symptomatic PPH can result in dizziness, falls, confusion, visual disturbances, nausea, tiredness and syncope as well as resulting in a poor quality of life. [1,4,5] While PPH may not always be associated with symptoms, the clinical impact can be substantial; being present in half of those with "unexplained" syncope [1], as well as being associated with an increased incidence of acute vascular events such as stroke or angina and increased mortality.[2]

The largest post-prandial reductions in BP are seen in those aged over 65 years and usually occur within 60-120 minutes of ingestion of an energy source (whether liquid or solid). This is particularly the case where there is a high simple carbohydrate substrate content e.g. glucose (but not with fructose). [6, 7, 8] Furthermore the post-prandial fall in BP is independent of the presence or absence of systemic hypertension [6, 7, 8] even when anti-hypertensive medication is withdrawn. [9] This post-prandial BP decrease reflects the failure of the normal homeostatic mechanisms to maintain BP levels in the face of a fall in systemic vascular resistance due to splanchnic and peripheral vasodilation not being compensated for by an increase in cardiac output. [1, 10]

Evidence suggests caffeine (an adenosine antagonist which blocks splanchnic methlyxanthine sensitive adenosine receptors) when given after meals can reduce post-prandial symptoms and BP reduction [10, 11, 12] indicating adenosine may have an underlying pathophysiological role for inducing this splanchnic vasodilatation. Other studies have shown that in addition there is an impairment of cardiac baroreflex sensitivity in older people resulting in impaired heart rate (HR) and stroke volume responses leading to the failure to increase cardiac output to compensate for the fall in systemic vascular resistance.[9]

In addition to some lifestyle measures [1], several other agents have also been tried in the treatment of PPH by addressing possible underlying pathophysiological mechanisms. For example acarbose, reduces complex carbohydrate breakdown thereby delaying gut glucose absorption [13, 14]. Whereas 3,4-DL-threodihydroxyphenylserine DL-DOPS, is a norepinephrine precursor converts to norepinephrine in the peripheral and central nervous system to replace levels of norepinephrine in autonomic failure [15]. Guar gum reduces postprandial falls in BP by delaying gastric emptying and glucose absorption in the small intestine [16]. Other agents such as octreotide (which inhibits the vasodilation of the splanchnic vasculature by inhibiting vasoactive peptides) given before a meal has been also been shown to have some benefit in preventing PPH in older adults with hypertension [17], as has midodrine (an α1-adrenergic agonist) administered concomitantly with denopamine (a selective β1-adrenergic agonist). [18]

However although there is some evidence of positive effects these various agents being useful in this setting, the magnitude of the effects of these therapeutic agents in a randomised controlled trial setting has not been examined systematically. Here we report a systematic review of randomised controlled studies involving the pharmacological management of post-prandial hypotension and post-prandial falls in BP, using PRISMA guidelines [19].

Methods

Eligibility criteria

Studies which specifically investigated the effect of the drug intervention on post-prandial change in BP were selected. They had to be controlled, randomised, studies which reported either supine and/or erect BP, and include administration of a standardised meal or glucose (oral/intraduodenal). Due to the nature of some treatments both open and blinded studies were included. Both patients and normal volunteers were included in the analysis if they were over 18 years of age as long as the aim of the study was to assess the effects of treatment on postprandial BP changes.

Information sources

A search of MEDLINE (1950-), EMBASE (1980-) and CINAHL (1937-) was carried out on the 16th of July 2013, limited to the English language and human subjects, and was followed by hand-searching of the bibliography of the full-text articles to identify potentially relevant

studies. Titles were screened by ACLO, whilst abstracts and papers were independently screened by ACLO and JFP, and discrepancies resolved by PKM.

Search terms

Search terms included “post-prandial hypotension.mp.” or “hypotension.mp.” or “Hypotension/or Hypotension, Orthostatic/” and “eating/ or meals.mp.” or “Food/ or prandial.mp. or Postprandial Period/”. Individual drugs were searched including “octreotide.mp. or Octreotide/”, caffeine.mp. or Caffeine/”, “NSAIDS.mp. or Anti-Inflammatory Agents, Non-Steroidal/”, “indomethacin.mp. or Indomethacin/”, “fludrocortisone.mp. or Fludrocortisone/”, “midodrine.mp. or Midodrine/”, “acarbose.mp. or Acarbose/”, “somatostatin.mp. or Somatostatin/”, in addition to more generic terms including “drug treatment.mp. or Adult/”, “drug therapy.mp. or Drug Therapy/”, Autonomic Nervous System Diseases/co, et, pp, th [Complications, Etiology, Physiopathology, Therapy]”

Data collection

Papers were assessed using the CASP (Critical Appraisal Skills Programme) approach for randomised controlled trials and are shown in the supplementary information, Table A. (Accessed 7th September 2012, http://www.casp-uk.net/find-appraise-act/). Data parameters were originally extracted by ACLO using a standardised form to assess paper suitability for meta-analysis. The form was developed specifically for the review after piloting with three randomly selected papers in the first instance to ensure all relevant data were captured. ACLO and JFP independently reviewed papers for systematic review, and discrepancies resolved by PKM.

Data items

Information on study participant characteristics (age, sex, and diagnosis), trial inclusion/exclusion criteria and drug intervention including dose and duration of treatment were extracted. The outcome measures of systolic and diastolic blood pressure or mean arterial pressure at baseline and with treatment for all arms of the study had to be available either as individual components of BP, MAP or as a change in these parameters. Results are given as mean ±SD mmHg unless otherwise stated.

Risk of bias in individual studies

Risk of bias for studies included was assessed including adequacy of sequence generation (presence of random component and method), allocation concealment (i.e. pre-assignment), whether missing data was accounted for and if there was evidence of within study selective reporting or other bias.

Summary measures

Due to the inconsistencies in outcome measurements and reporting, it was not possible to synthesise summary statistics using a formal meta-analysis approach.

Results

Fourteen randomised studies were included in the final selection for systematic review (Figure 1). The characteristics of the studies (including population and meal type) are shown in Table 1. Overall the studies were of good quality and the risks of bias within these studies are shown in Table 2. The timing of the intervention depended on the nature of the agent

being studied; in the majority of the studies the drug treatment was given before or with the meal or glucose load; and in the remainder it was immediately after the meal or glucose load. BP in all but two studies [10, 11] was not explicitly measured on more than one occasion at each time point. The majority of studies used an automated oscillometric BP monitor, others used an arteriosonde [20] or a Hawksley sphygmomanometer [10,11]. Only two studies [13, 22] were carried out in participants with a formal diagnosis of PPH using the defined criteria [1]. The hemodynamic responses but not the symptomatic relief of PPH were reported by the trials. Shorter-term studies were those which investigated the effects of a single dose of treatment within a 24 hour period. Longer-term studies include those where the intervention was continued for more than a 24 hour period.

Shorter-term studies

Caffeine

There were six randomised controlled studies [10,11,20,22-24] involving caffeine administered in various doses and forms: as tea or coffee or as pure caffeine in capsule form (e.g. 60mg five times a day, 250mg capsule single intervention), four of these studies were double-blind [10,11,20,22]. Only one study by Lipsitz et al enrolled participants with confirmed PPH (defined as a fall in the supine or seated systolic BP (SBP) of at least 20mmHg within 60 minutes of the meal), with symptoms of weakness or dizziness. [22] Most participants in these trials were regular caffeine consumers and no adverse effects were reported with caffeine consumption.

Onrot and colleagues [23] demonstrated in six participants with primary or secondary autonomic failure who were regular caffeine consumers but who had no history of PPH, that

a single 250mg dose of caffeine before a standardised meal (see Table 1) resulted in a significantly smaller post-prandial fall in SBP and DBP by 60 minutes ($p<0.05$) than without caffeine . As seen previously there was no significant difference in HR changes between placebo and caffeine phases in the studies. As no participants had a history of PPH, symptomatic differences with treatment were not recorded.

Lenders et al [20] studying fifteen healthy participants who regularly consumed caffeine, showed no fall in mean arterial pressure (MAP) from baseline after a single 250mg dose of caffeine given one hour before a standardised meal, compared to placebo, HR was also unchanged compared to baseline between placebo and caffeine phases.

Heseltine and colleagues [10] showed a significant reduction in post-prandial standing and supine SBP fall with caffeine (200mg coffee) compared to placebo in seven healthy older adults who were regular caffeine consumers. Symptoms of PPH were not relevant to these two studies. [10, 20]

In 20 regular caffeine drinking older adults with various co-morbidities, of whom four had symptoms suggestive of orthostatic or post-prandial hypotension, 100 mg of caffeine (given as coffee) resulted in a significant overall reduction in the sitting post-prandial fall in SBP compared to placebo (decaffeinated coffee).[11] No significant difference between placebo and caffeine phases was noted in DBP, or in standing SBP between placebo and caffeine. Three participants were noted to have a fall in SBP consistent with PPH. Symptoms of PPH were alleviated by caffeine in two participants and not by placebo.[11]

Lipsitz et al showed that caffeine (250mg) did not attenuate the decline in SBP, DBP or MAP associated with ingestion of a meal in nine patients with autonomic failure who experienced

symptomatic post-prandial hypotension.[22] Although this study included those with symptomatic PPH, there was no reporting of the effect of caffeine on symptoms.

Acarbose

In thirteen participants with autonomic failure and PPH, randomised to acarbose (100mg capsule) or placebo, given 20 minutes before a mixed meal, acarbose reduced the postprandial fall in supine SBP and DBP with no effect on HR and no adverse effects reported.[13] There was no specific reporting on the effects of treatment on symptoms. In another study, eight healthy older participants, randomised in a double-blind order to receive 100mg acarbose with an intraduodenal sucrose infusion (6kcal/min) or sucrose alone on two separate days, showed a similar attenuation in both the SBP and DBP, but this was accompanied by a rise in HR ($p<0.05$).[14]

DL-DOPS

The effect of DL-DOPS (1000mg) given three hours pre-meal, on post-prandial BP was assessed in a cross-over study in eleven participants with autonomic failure.[15] The greatest BP fall occurred 30 minutes after the mixed meal and SBP ($p=0.01$) and DBP ($p<0.01$) falls were significantly greater after placebo than with DL-DOPS. There were no significant differences in HR between placebo or DL-DOPS and no effect on symptoms reported.

Guar Gum

Three studies assessed the effect of guar gum against a placebo/control phase on post-prandial BP in older adults after either a 50g glucose drink or intraduodenal glucose.[16,25,26] Jones and colleagues carried out a randomised cross-over trial in ten healthy adults and demonstrated that 9g of guar gum (compared to control) significantly reduced the fall in SBP ($p=0.02$), DBP ($p<0.05$) and MAP ($p=0.05$) 30 minutes post-prandially with no HR changes.[16] Russo et al, in a randomised cross-over, studied eleven participants with type 2 diabetes mellitus, showed that 9g guar gum significantly ($p<0.05$) reduced the post-prandial fall in BP in response to a 50g oral glucose load.[25]

The use of intraduodenal, rather than an oral, glucose load allows the observation of the changes in BP independent of any effects of the intervention on gastric emptying, the rate of gastric emptying influencing the fall in postprandial BP. [26] O'Donovan et al [27] demonstrated a significantly smaller fall in SBP, but not DBP, with 4g of guar gum after a 50g intraduodenal glucose infusion in eight healthy adults compared to the glucose only infusion[27].

<u>Octreotide</u>

Three papers reporting the effect of subcutaneous octreotide on post-prandial BP did not include symptomatic PPH and symptoms of PPH were not considered.[17, 21, 28] However the data presented in two of these papers may report the same participant group.[17, 21]

Jansen and colleagues [17, 21] included ten hypertensive and ten normotensive adults, who received either a single dose of subcutaneous octreotide (50µg) or placebo (saline) in a double blind randomised fashion together with a 75g glucose drink. Both the normotensive and hypertensive groups showed significant falls in MAP at 30 and 60 minutes with placebo

but showed no significant fall after octreotide.[21] A significant difference between placebo and octreotide was shown for the SBP ($p=0.008$), DBP ($p<0.001$) and MAP ($p<0.001$) in the hypertensive group and for diastolic ($p=0.005$) and MAP ($p=0.007$) in the normotensive group.[17] Alam et al [28] demonstrated in eighteen participants with autonomic failure and symptomatic orthostatic hypotension, that octreotide (1µg/kg body weight) compared to no treatment, reduced the post-prandial BP fall from 10 minutes up to 120 minutes, with octreotide reducing the fall in SBP ($p<0.01$) and DBP ($p<0.05$). There were no significant differences in HR and no adverse effects were reported. [28]

Longer-term studies

Caffeine

Rakic et al enrolled 171 participants (98% regular caffeine drinkers), which included normotensives and treated or untreated hypertensives, who were randomised to a two week period of regular caffeine consumption (60mg five times daily) or no caffeine.[24] It was noted that the baseline post-prandial supine SBP falls were greater in those with untreated and treated hypertension compared to normotensives, with similar changes seen in standing SBP. Coffee significantly reduced the post-prandial fall in supine and standing SBP in regular coffee drinking normotensives and also in tea drinkers with treated hypertension. The effects on HR were not reported. Amongst those with untreated hypertension, the two week caffeine abstainers also had a significant reduction in the post-prandial fall of supine SBP. The effect of treatment on symptoms was not reported.

Onrot et al considered the longer-term effects of caffeine, with five participants being administered caffeine as a 250mg capsule daily for seven days. Participants were then

randomised to receive placebo or caffeine as a single dose. Despite longer-term caffeine, the post-prandial BP still remained higher after caffeine ($p<0.05$) compared with the placebo following a standardised meal.[23]

Results summary

Table 3 shows a summary of the various drug effects on the post-prandial falls in BP. However it should be noted that the majority of studies were carried out in participants who did not specifically have either a diagnosis of post-prandial hypotension with a proven minimal fall in post-prandial BP, or whom had symptoms suggestive of post-prandial hypotension. [1]

Discussion

Despite PPH being associated with significant morbidity and mortality in older people, the evidence for the benefits of pharmacological intervention in reducing these BP falls is limited. The studies included in this systematic review had great heterogeneity in terms of intervention drug type, dose, frequency and time of intervention relative to type and size of energy load. Another important influencing factor on effect is the heterogeneity in the population studied e.g. healthy adults as oppose to those with hypertension and diabetes, those with autonomic dysfunction with only one study specifically investigated the effect on those with symptomatic post-prandial hypotension. Thus caution is needed in the interpretation, and the use of, any therapeutic interventions based on the findings of this systematic review especially in older patients with symptomatic PPH.

This systematic review confirms that certain drug interventions may attenuate the post-prandial fall in BP both when given as a once only intervention as well as following chronic use and is summarised in Table 3. However most notably the majority of studies do not specifically include participants with PPH symptoms or who had a confirmed diagnosis of post-prandial hypotension.[1] Some studies tried to overcome this by including those with a history of orthostatic hypotension (OH), but the underlying pathophysiology of OH and PPH probably differs, albeit both conditions can exist in the same patient. It is therefore difficult to conclusively state which drug is the best for post-prandial hypotension, particularly as adverse effects need to be considered, such as supine hypertension with DL-DOPs.[15]

Post-prandial hypotension reflects the failure to maintain systemic blood pressure levels which fall as a result of a decrease in systemic resistance with blood being diverted into the splanchnic circulation.[1] Thus potential methods of decreasing PPH might focus on delaying the rate of food absorption from the gut or reducing local splanchnic bed vasodilation. However the drugs used to attenuate post-prandial falls in BP in this review have many differing mechanisms of action and the effects are likely to be variable, even more so between population groups.

Caffeine, an adenosine blocker, has some supportive evidence of having a positive effect on reducing a post-prandial blood pressure fall in both infrequent and regular users, although only one small study looked specifically at patients with symptomatic post-prandial hypotension. [22] Furthermore when used in participants with autonomic failure caffeine reduced the post-prandial fall in the group mean SBP. [23] Caffeine increased MAP in the study by Lenders et al [20] when given an hour before the meal, however its maximal

potential effect on reducing PPH may have been negated by the time elapsed between treatment administration and likely maximum post-prandial BP fall. The lack of effect on the erect SBP in the second study by Heseltine and colleagues [11] may have been due to the smaller dose of caffeine administered. Given that caffeine is readily available in the form of tea and coffee, its use in PPH could be simply part of a lifestyle change, though it would appear that a pre-prandial dose of at least 200 mg is needed.

DL-DOPS by increasing noradrenaline [15] and acarbose by delaying gut glucose absorption [13, 14] were shown to attenuate the postprandial fall in BP. Furthermore acarbose was shown to attenuate PPH in those with severe autonomic failure [13]. One study [29] of acarbose in PPH patients did not randomise the order which participants the control and acarbose (50mg) and was therefore excluded from this systematic review, however it is worth noting it showed a statistically significant reduction in the post-meal fall in SBP (at 60 minutes: 17.8±11.7mmHg to -4.2±13.1mmHg, $p<0.001$), DBP (-7.6±8.5mmHg to -3.9±6.9mmHg, $p<0.05$) and MAP (-10.3±8.4mmHg to -3.3±8.1mmHg, $p<0.05$). Guar gum also by presumably delaying absorption attenuated the post-prandial BP declines, however in some instances the BP changes were small (<5mmHg) and of doubtful clinical significance. Octreotide subcutaneously attenuates the postprandial fall in BP amongst those with orthostatic hypotension and hypertension, as well as those who are classified as normotensive.

The variability of timing of drug administration relative to the energy load (either a glucose drink, liquid meal or standardised mixed meal), as well as which BP parameters were recorded made it difficult to compare studies and include in a meta-analysis. Whilst some reported all BP parameters and HR changes others only reported MAP values, some only the

maximal post-prandial BP changes. For a “positive” treatment effect the majority of studies used the lack of a statistically significant fall in BP from baseline with the drug intervention, rather than a change that might be clinically significant. Furthermore the majority of studies (with the exception of two [10, 11]) did not explicitly measure BP on more than one occasion at each time point, although single measurements were carried out using validated methods. Also of importance and not reported in the studies is the effect of treatment on symptoms in those with symptomatic PPH.

The limitations of this systematic review include the fact that only studies reported in English were included and there were only a few studies available for each intervention. Furthermore we only included studies which were randomised and controlled in some way, but we did not require them to be blinded as this was difficult for the original investigators with some of the interventions. However this may be a potential source of bias from included studies. Furthermore the heterogeneity of study design and parameters assessed within the studies included in this systematic review prohibited meta-analysis.

Overall the pharmacological agents included have been shown to have some effect on the attenuation of post-prandial falls in BP. However only two studies [13,22] examined the effect of a drug intervention (caffeine and acarbose) on post-prandial hypotension, where caffeine was found to be ineffective. Thus future studies should be directed at measuring the effect of these drug interventions on post-prandial hypotension compared to lifestyle changes including regular caffeine consumption in the form of tea or coffee. Consideration should be given to other methods of reducing the post-prandial fall in BP such as altering meal composition in terms of energy load and carbohydrate type, paying particular

attention to their influence on PPH symptoms. The effects of PPH and its treatment on other important vascular beds, e.g. cerebral blood flow control which may account for some of the symptoms, also justifies further research. The variable nature of the BP parameters measured in the current studies and the heterogeneity of the populations studied make it difficult to accurately project the results of this systematic review to our older patients with symptomatic post-prandial hypotension. The studies reviewed suggest that caffeine may be helpful in reducing post-prandial falls in BP, but may not be useful in those with PPH. The evidence also suggests that acarbose may similarly be of some benefit amongst those suffering from PPH.

For the clinician managing older patients with symptomatic PPH, the most pragmatic approach appears to be give advice in: 1) avoiding large, simple carbohydrate meals; 2) to consume small frequent meals instead and 3) avoid alcohol (and other vasodilator agents) with meals. In some patients, having regular caffeinated beverages post-prandially may be of benefit in terms of PPH symptom reduction.

Conclusion

This systematic review highlights the limited data on the pharmacological treatment of PPH both in terms of reducing the postprandial BP fall and symptom improvement. Future studies should investigate the effectiveness of drug treatment and lifestyle changes in symptomatic postprandial hypotension. In the meantime best pragmatic advice would be to

avoid large simple carbohydrate meals, alcohol and vasodilators and in some cases caffeine may also reduce PPH symptoms.

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Conflict of interest

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Conflict of Interest Checklist:

Elements of Financial/Personal Conflicts	Alice C. L. Ong		Phyo K. Myint		John F. Potter	
	Yes	No	Yes	No	Yes	No
Employment or Affiliation		x		x		x
Grants/Funds	x			x		x
Honoraria		x		x		x
Speaker Forum		x		x		x
Consultant		x		x		x
Stocks		x		x		x
Royalties		x		x		x
Expert Testimony		x		x		x
Board Member		x		x		x
Patents		x		x		x
Personal Relationship		x		x		x

406 *Authors can be listed by abbreviations of their names

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410 **Author Contributions**:

411 study concept and design - Ong, Myint, Potter,

412 acquisition of subjects and/or data - Ong,

413 analysis and interpretation of data - Ong, Myint, Potter,

414 preparation of manuscript - Ong, Myint, Potter.

415

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417

418 **Supplementary Information**

419 Please note that supplementary information is available for this paper online and indicated

420 where appropriate.

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Figure 1: Flow chart

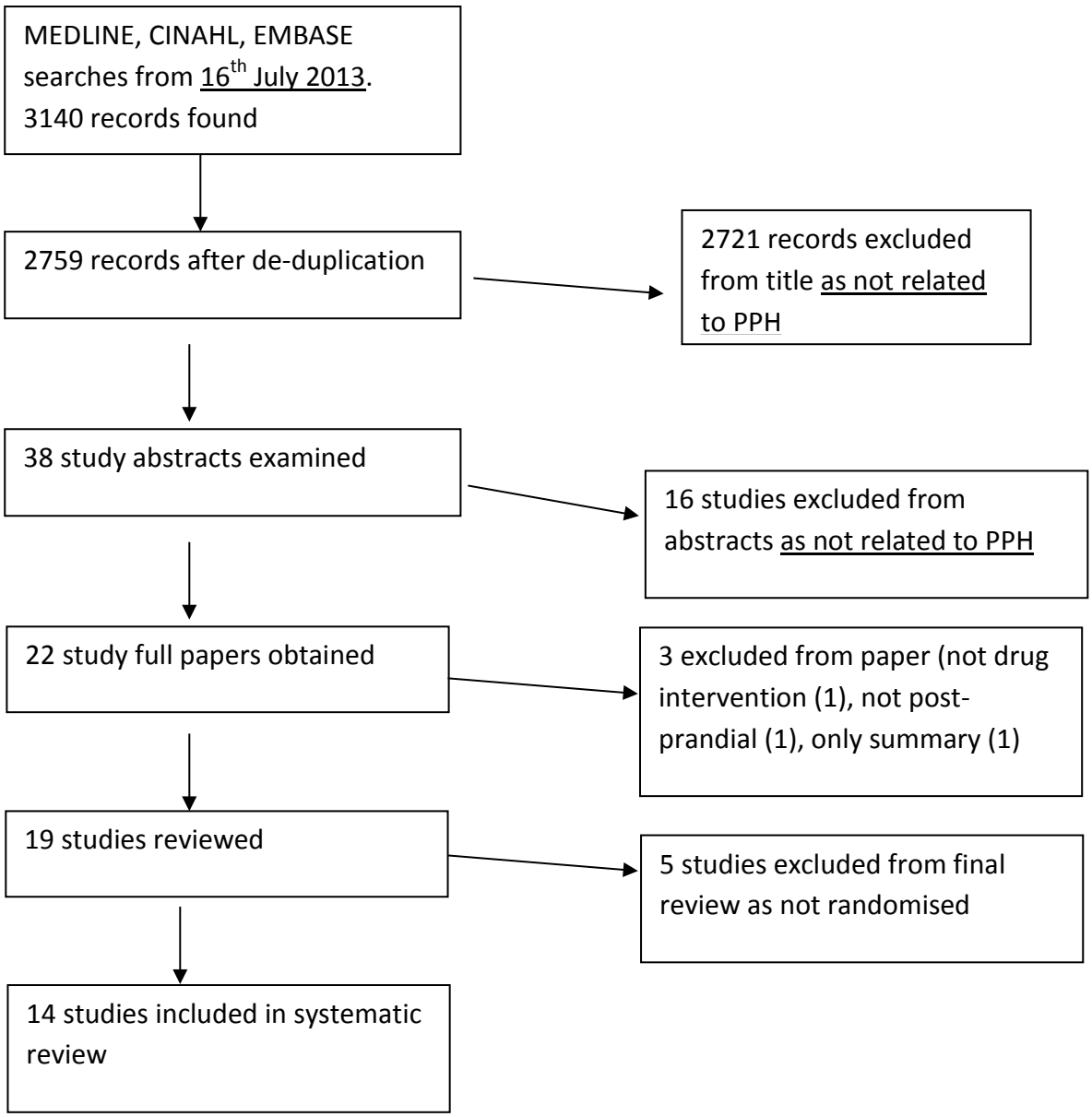

Table 1: Study Characteristics

Study Author (Year) [Reference]	**Drug/ Intervention**	**Design/ duration**	**Meal/Glucose**	**Study Population**	**Known PPH**	**PPH defined in study**	**Age (years)**	**Number of participants**	**Gender**	**Groups**
Shorter-term studies(<24hours)										
Onrot et al. (1985) [23]	Caffeine 250mg capsule	Study days randomised, consecutive participants, not blind (<24hrs & >24hrs)	Standard mixed meal *(kcal not given)*	Autonomic failure (primary – 11, secondary -1)	No	N/A	63.6 (SD ± 5.9)	12	6M:6F	Meal(12)/ Caffeine(12)/ Meal & Caffeine (6)
Lenders et al. (1988) [20]	Caffeine 250mg capsule	Randomised, double blind, controlled, cross-over (<24hrs)	Standard mixed meal *(405kcal)*	Healthy	No	N/A	75.4 (SD ± 6.6)	15	8M:7F	Placebo(15)/ Caffeine(15)
Heseltine et al. (1991) [10]	Caffeine 200mg coffee	Randomised, double blind, controlled, cross-over (<24hrs)	Standard mixed meal *(585kcal)*	Healthy	No	N/A	67.4 (range 64-72)	7	2M:5F	Placebo(7)/ Caffeine(7)
Heseltine et al. (1991) [11]	Caffeine 100mg coffee	Randomised, double blind, controlled, cross-over (<24hrs)	Glucose drink *(400kcal)*	Post-acute admission (CVD, IHD, CCF, PVD, DM, COPD, PD)	No	N/A	84 (SD ± 5)	20	10M:10F	Decaffeinated (20)/ Caffeine(20)
Lipsitz et al. (1994) [22]	Caffeine 250mg capsule	Randomised, double blind, controlled, cross-over (<24hrs)	Liquid mixed meal *(1674kJ)*	Pure autonomic failure, Shy-Drager, PD, unknown	Yes	≥20mmHg fall supine/seated SBP ≤60mins of meal	79 (SD ± 9)	9	2M:7F	Placebo (9)/ Caffeine (9)
Shibao et al. (2007) [13]	Acarbose 100mg	Randomised, single & double blind, controlled,	standard mixed meal *(414kcal)*	Pure autonomic failure (12), PD (1) [secondary cause excluded]	Yes	≥20mmHg fall in SBP ≤120mins	65 (SD ± 2.64)	13	5M:8F	Placebo (13)/ Acarbose (13)

		cross-over (<24hrs)								
Gentilcore et al. (2011) [14]	Acarbose 100mg	Randomised, double blind, controlled, cross-over (<24hrs)	Intraduodenal sucrose *(100g in 300ml 0.9% NaCl, 5ml/min, 6kcal/min)*	Healthy	No	N/A	Median 70 (range 66-77)	8	4M:4F	No acarbose/ Acarbose
Freeman et al. (1996) [15]	DL-DOPS 1000mg	Randomised, double blind, controlled, cross-over (<24hrs)	standard mixed meal *(400kcal)*	All Orthostatic hypotension (undefined by BP); mix of MSA, PD, PAF	No	N/A	54 (SD ± 13)	11	7M:4F	Placebo (11)/ DL-DOPS (11)
Jones et al. (2001) [16]	Guar gum 9g	Randomised, not blind, controlled, cross-over (<24hrs)	50g glucose drink	Healthy	No	30 min sustained fall SBP ≥20mmHg	median 70 (range 67-78)	10	5M:5F	Guar gum/ No guar gum
Russo et al. (2003) [25]	Guar gum 9g	Randomised, not blind, controlled, cross-over (<24hrs)	50g glucose drink	Type 2 DM	No	30 min sustained fall SBP ≥20mmHg	median 61 (range 57-69)	11	8M:3F	Guar gum/ No guar gum
O'Donovan et al. (2005) [27]	Guar gum 4g	Randomised, double blind, controlled, cross-over (<24hrs)	Intraduodenal glucose infusion *(50g in 300ml water, 5ml/min, 3kcal/min)*	Healthy	No	N/A	70.3 (SD ± 3.4)	8	4M:4F	Guar gum/ No guar gum
Jansen et al. (1988) [21]	Octreotide 50µg SC	Randomised, double blind, controlled, cross-over (<24hrs)	75g glucose drink	Normotensive, HTN	No	No	74 (SD ± 4)	20	unknown	Placebo/ octreotide
Jansen et al. (1989) [17]	Octreotide 50µg SC	Randomised, double blind, controlled, cross-over (<24hrs)	75g glucose drink	Normotensive, HTN	No	No	74 (SD ± 4)	20	7M:13F	Placebo/ octreotide
Alam et al. (1995) [28]	Octreotide 1µg/kg SC bd	Randomised, not blind,	Meal *(unspecified)*	Symptomatic OH (fall ≥30mmHg	No	No	range 44-73	18	11M:7F	Octreotide/ No octreotide

	(8am,6pm)	controlled, cross-over (<24hrs)		SBP); PAF, Shy-Drager. [Secondary causes excluded]						
Longer-term studies (>24 hours)										
Rakic et al. (1996) [24]	Caffeine 60mg 5 times/day as tea/ coffee	Randomised, not blind, controlled, cross-over (>24hrs)	High carbohydrate meal *(unspecified)*	Normotensive (62)/treated HTN (46)/untreated HTN (63)	No	N/A	75.2 (SD ± 0.7)	171	41M:127F	Decaffeinated/ Caffeine
Onrot et al. (1985) [23]	Caffeine 250mg capsule	Study days randomised, consecutive participants, not blind (<24hrs & >24hrs)	Standard mixed meal *(kcal not given)*	Autonomic failure (primary – 11, secondary -1)	No	N/A	63.6 (SD ± 5.9)	12	6M:6F	Meal(12)/ Caffeine(12)/ Meal & Caffeine (6)

Key: DM=diabetes mellitus; HTN=hypertension; OH=orthostatic hypotension; PAF=pure autonomic failure; MSA=multi-system atrophy; PD=Parkinson disease; CVD=cerebrovascular disease; PVD=peripheral vascular disease; IHD=ischemic heart disease; CCF=congestive cardiac failure; COPD=chronic obstructive pulmonary disease

Table 2: Assessment of Risk of Bias

Study (Author, Year, Reference)	**Adequate sequence generation**	**Allocation concealment**	**Incomplete outcome data addressed**	**Free of selective reporting**	**Free of other bias**
Shorter-term studies (<24 hours)					
Onrot et al. (1985) [23]	Study days randomised (unclear method), consecutive patients	Not blinded, controlled Unclear concealment	Yes	Yes	Yes
Lenders et al. (1988) [20]	Study days randomised (unclear method), cross-over	Double blind, controlled Unclear concealment	Yes	Yes	Yes
Heseltine et al. (1991) [10]	Randomised (unclear method), cross-over	Double blind, controlled Unclear concealment	Yes	Yes	Yes

Heseltine et al. (1991) [11]	Randomised (unclear method), cross-over	Double blind, controlled Unclear concealment	Yes	Yes	Yes
Lipsitz et al. (1994) [22]	Randomised (unclear method), cross-over	Double blind, controlled Unclear concealment	Yes	Yes	Yes
Shibao et al. (2007) [13]	Randomised (unclear method used, but different department), cross-over	Single & Double blind, controlled Identical color capsules used to maintain concealment	Yes	Yes	Yes
Gentilcore et al. (2011) [14]	Randomised (unclear method), cross-over	Double blind, controlled Unclear concealment	Yes	Yes	Yes
Freeman et al.	Randomised (unclear	Double blind, controlled	Yes	Yes	Yes

(1996) [15]	method used, but different department), cross-over	Identical color capsules used to maintain concealment			
Jones et al. (2001) [16]	Randomised (unclear method), cross-over	Not blinded (due to viscosity of drink), controlled	Yes	Yes	Yes
Russo et al. (2003) [25]	Randomised (unclear method), cross-over	Not blinded (due to viscosity of drink), controlled	Yes	Yes	Yes
O'Donovan et al. (2005) [27]	Randomised (unclear method), cross-over	Single blind, controlled Unclear concealment	Yes	Yes	Yes
Jansen et al. (1988) [21]	Randomised (unclear method), cross-over	Double blind, controlled Placebo injection used to maintain concealment	Yes	Yes	Unclear. It appears the same study data was published in two journals.

Jansen et al. (1989) [17]	Randomised (unclear method), cross-over	Double blind, controlled Placebo injection used to maintain concealment	Yes	Yes	Unclear. It appears the same study data was published in two journals.
Alam et al. (1995) [28]	Randomised (unclear method), cross-over	Not blinded, controlled Unclear concealment	Yes	Yes	Yes
Longer term studies(>24 hours)					
Onrot et al. (1985) [23]	Study days randomised (unclear method), consecutive patients	Not blinded, controlled Unclear concealment	Yes	Yes	Yes
Rakic et al. (1996) [24]	Randomised (unclear method), cross-over	Not blinded, controlled Unclear concealment	Yes	Yes	Yes

Table 3: Overall Study Conclusion for Alleviating Post-Prandial Falls in BP or PPH

Study (Author, Year, Reference)	**Participant Group**	**Drug**	**Approximate Maximal Mean Change in BP Compared to Baseline (mmHg) ***	**Maximal BP change at time from baseline (minutes)**	**Difference between Control and Intervention Arm in Approximate Maximal Mean Change in BP (mmHg)**	**Adverse events**
Shorter-term studies (<24 hours)						
Onrot et al. (1985) [23]	Autonomic Failure	Caffeine (250mg capsule)	SBP: -3 DBP: -6	60	SBP: 20 DBP: 8	None reported

		Control	SBP: -23 DBP: -14	60		
Lenders et al. (1988) [20]	Healthy participants	Caffeine (250mg capsule)	MAP: 0% (maximal increase of 12.5%)	30-60	MAP: 6.1%	None reported
		Control	MAP: -6.1%	30-60		
Heseltine et al. (JAGS, 1991) [10]	Healthy participants	Caffeine (200mg coffee)	SBP: 12	90	SBP: 29	None reported
		Control	SBP: -17	60		
Heseltine et al. (PMJ, 1991) [11]	Multiple comorbidities (4 of 20 had symptoms suggestive of PPH or OH)	Caffeine (100mg coffee)	Sitting SBP: 2	60	SBP: 10	Symptomatic postural hypotension with placebo
		Control	Sitting SBP: -8	60		

Lipsitz et al. (1994) [22]	Autonomic Failure	Caffeine (250mg capsule)	MAP: -31	30	MAP: 12	None reported
		Control	MAP: -19	30		
Rakic et al. (1996) [24]	Normotensive/Hypertension/Untreated Hypertension	Caffeine (60mg tea/coffee)	Standing SBP: -8 (UHTN), -9 (HTN), -3 (NTN)	60	SBP: 2 (UHTN), 3 (HTN), 5 (NTN)	None reported
		Control	Standing SBP: -10 (UHTN), -12 (HTN), -8 (NTN)	60		
Shibao et al. (2007) [13]	Autonomic failure	Acarbose	SBP: -17	60	SBP: 23	None reported
		Control	SBP: -40	60		
Gentilcore et al. (2011) [14]	Healthy	Acarbose	SBP: -1 DBP: -3	15-30 15-30	SBP: 7 DBP: 6	Flatulence, loose stools

		Control	SBP: -8 DBP: -9	15-30 15-30		
Freeman et al. (1996) [15]	Autonomic failure	DL-DOPS	MBP: -13 SBP: -34 DBP: -16	30 30 30	MBP: 17 SBP: 8 DBP: 6	Pattern of supine hypertension (not statistically significant)
		Control	MBP: -30 SBP: -42 DBP: -22	30 30 30		
Jones et al. (2001) [16]	Healthy	Guar gum	SBP: -4 DBP: -6 MBP: -4	15-30 15-30 15-30	SBP:3 DBP: 1 MBP: 4	"well tolerated", mild dizziness and faintness with glucose
		Control	SBP: -7	15-30		

			DBP: -7 MBP: -8	15-30 15-30		
Russo et al. (2003) [25]	Type 2 diabetes mellitus	Guar gum	SBP: -2.5 DBP: -2.9 MAP: -6.8	30 30 30	SBP: 2.4 DBP: 2.6 MAP: 3.4	None reported "well tolerated"
		Control	SBP: -4.9 DBP: -5.5 MAP: -10.2	30 30 30		
O'Donovan et al. (2005) [27]	Healthy	Guar gum	SBP: -2.5 DBP: -4	15-30	SBP: 8.5 DBP: 1	None reported "well tolerated"
		Control	SBP: -11 DBP: -5	15-30		

Jansen et al. (1988) [21]	Hypertension and Normotensive	Octreotide	MAP: 0 (NTN), -2 (HTN)	60	MAP: 7 (NTN), 12 (HTN)	None reported
		Control	MAP: -7 (NTN), -14 (HTN)	60		
Jansen et al. (1989) [17]	Hypertension and Normtensive	Octreotide	SBP: 1 (NTN), -1 (HTN) DBP: 0 (NTN), 0 (HTN)	60 60	SBP: 6 (NTN), 11 (HTN) DBP: 9 (NTN), 15 (HTN)	injections uncomfortable, "some" increased defaecation, slight abdominal pain
		Control	SBP: -5 (NTN), -12 (HTN) DBP: -9 (NTN), -15 (HTN)	60 60		
Alam et al. (1995)	Autonomic failure	Octreotide	SBP: 0	10	SBP: 3	None reported

[28]			DBP: -2	10	DBP: 3	
		Control	SBP: -3 DBP: -5	10 10		
Longer-term studies (>24 hours)						
Onrot et al. (1985) [23]	Autonomic Failure	Caffeine (250mg capsule)	SBP: -3 DBP: -6	60	SBP: 20 DBP: 8	None reported
		Control	SBP: -23 DBP: -14	60		
Rakic et al. (1996) [24]	Normotensive/Hypertension/Untreated Hypertension	Caffeine (60mg tea/coffee)	Standing SBP: -8 (UHTN), -9 (HTN), -3 (NTN)	60	SBP: 2 (UHTN), 3 (HTN), 5 (NTN)	None reported
		Control	Standing SBP: -10 (UHTN), -12 (HTN), -8	60		

			(NTN)			

Key: * Note that many values are estimated from graphs depicted by original authors. UHTN= Untreated Hypertension, HTN = Hypertension, NTN = Normotensive. A negative (-) sign indicates a fall in BP.

Supplementary Information

Table A: Critical Appraisal of Studies using CASP

Study	Focused issue	Randomised	Participants accounted for	"Blind" to treatment	Groups similar	Groups treated equally	Treatment effect & Precision of effect (mmHg)	Application of results	Important outcomes considered	Benefits outweigh harms/costs
Onrot et al. (1985) [23]	Yes	Study days only	Yes	No	Yes	Yes	SBP: 132±34 (baseline) to 129±31 (caffeine) DBP: 75±16 (baseline) to 69±13 (caffeine) SBP from 131±34 to 108±21 (control) DBP from 76±16 to	Autonomic failure, not proven PPH	No measure of symptom improvement	Yes

							62±14 (control)			
Lenders et al. (1988) [20]	Yes	Yes	Yes	Yes	Yes	Yes	MAP: 12.5% increase (caffeine), no change (control)	Healthy	No measure of symptom improvement	Yes
Heseltine et al. (JAGS, 1991) [10]	Yes	Yes	Yes	Yes	Yes	Yes	SBP: 12, 95% CI: 4 to 20 (caffeine) vs -17, 95% CI: -5 to -20 (control)	Healthy	No measure of symptom improvement	Yes
Heseltine et al. (PMJ, 1991) [11]	Yes	Yes	Yes	Yes	Yes	Yes	SBP: 2, 95% CI: 0 to 4 (caffeine) vs -8, 95% CI: -10 to -6 (control)	Hospital patients	No measure of symptom improvement	Yes
Lipsitz et al. (1994) [22]	Yes	Yes	Yes	Yes	Yes	Yes	MAP: -31±SEM 7 (caffeine) vs -19 ±SEM 6 (control) [between group	PPH	No measure of symptom improvement	Yes

							difference not significant]			
Rakic et al. (1996) [24]	Yes	Yes	Yes	Yes	Yes	Yes	Figures given, estimated values. NTN: -7, UHTN: 15, HTN: -15 (caffeine, supine) NTN: -11, UHTN: -17.5, HTN: -14 (control, supine)	NTN, HTN, Untreated HTN	No measure of symptom improvement	Yes
Shibao et al. (2007) [13]	Yes	Yes	Yes	Yes	Yes	Yes	increased SBP: 17, 95% CI: 7 to 28 (acarbose) increased DBP: 9, 95% CI: 5 to 14	PPH	No measure of symptom improvement	Yes

							(acarbose)			
Gentilcore et al. (2011) [14]	Yes	Yes	Yes	Yes	Yes	Yes	SBP: no fall (acarbose) vs -11.2±2 (control) DBP: -8.1±1.5 (acarbose) vs -10.9±0.9 (control)	Healthy	No measure of symptom improvement	Yes
Freeman et al. (1996) [15]	Yes	Yes	Yes	Yes	Yes	Yes	SBP: 147.8± SD 12.9 (DL-DOPS) vs 127± SD 11.4 (control) DBP: 81.7± SD 18.6 (DL-DOPS) vs 69.5± SD 12.6 (control)	OH	No measure of symptom improvement	Unclear
Jones et al. (2001) [16]	Yes	Yes	Yes	No	Yes	Yes	Figures used, estimated values.	Healthy	No measure of symptom	Yes

							SBP: 119±SEM 4 (baseline) to 115±5 (guar) vs 117±5 to 110±5 (control) DBP: 63.5±3 (baseline) to 61.5±4 (guar) vs 64.5±3 to 56.6±4 (control) MBP: -4 (guar) vs -8 (control)		improvement	
Russo et al. (2003) [25]	Yes	Yes	Yes	No	Yes	Yes	SBP: 145.1±4.8 (baseline) 142.6±4.5 (glucose) [guar gum] vs 143.9±4.7	Type 2 DM	No measure of symptom improvement	For SBP

							(baseline) to 139.0±4.2 (glucose) [control]			
O'Donovan et al. (2005) [27]	Yes	Yes	Yes	Yes	Yes	Yes	Figures used, estimated post-prandial values: SBP: -2.5±2.5 (guar) vs -11±2.5 (control) DBP: -5±3 (guar) vs -4±2 (control)	Healthy	No measure of symptom improvement	For SBP
Jansen et al. (1988) [21]	Yes	Yes	Yes	Yes	Yes	Yes	NTN: MAP 94±2 (baseline) to 87±2 (control) vs 95±2 (baseline) to 95±2	NTN, HTN	No measure of symptom improvement	Unclear as no comment on adverse

							(octreotide) HTN: MAP 123±3 (baseline) to 109±3 (control) vs 122±3 (baseline) to 120±3 (octreotide)			events
Jansen et al. (1989) [17]	Yes	Yes	Yes	Yes	Yes	Yes	Figures presented. HTN: control vs octreotide SBP p=0.008, DBP p<0.001, MAP p<0.001 NTN: control vs octreotide DBP p=0.005, MAP p=0.007	NTN, HTN	No measure of symptom improvement	Unclear

Alam et al. (1995) [28]	Yes	Yes	Yes	No	Yes	Yes	Post-prandial SBP: 122±5 (octreotide) vs 107±3 (control) DBP: 75±4 (octreotide) vs 65±2 (control)	OH	No measure of symptom improvement	No comment on adverse events

Key: NTN = normotension, UHTN = untreated hypertension, HTN = hypertension, SBP = systolic BP, DBP = diastolic BP, MAP = mean arterial pressure, PPH = post-prandial hypotension, OH = orthostatic hypotension, DM = diabetes mellitus