Low exercise blood pressure and risk of cardiovascular events and all-cause mortality: Systematic review and meta-analysis

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ABSTRACT

Objective: The independent prognostic significance of abnormally low systolic blood pressure (SBP) during exercise stress testing (LowExBP) across different clinical and exercise conditions is unknown. We sought by systematic review and meta-analysis to determine the association between cardiovascular/all-cause outcomes and LowExBP across different patient clinical presentations, exercise modes, exercise intensities and categories of LowExBP.

Methods: Seven online databases were searched for longitudinal studies reporting the association of LowExBP with risk of fatal and non-fatal cardiovascular events and/or all-cause mortality. LowExBP was defined as either: SBP drop below baseline; failure to increase >10 mmHg from baseline or; lowest SBP quantile among reporting studies.

Results: After review of 13,257 studies, 19 that adjusted for resting SBP were included in the meta-analysis, with a total of 45,895 participants (average follow-up, 4.4±3.0 years). For the whole population, LowExBP was associated with increased risk for fatal and non-fatal cardiovascular events and all-cause mortality (hazard ratio [HR]: 2.01, 95% confidence interval [CI]: 1.59–2.53, p < 0.001). In continuous analyses, a 10 mmHg decrease in exercise SBP was associated with higher risk (n = 9 HR: 1.13, 95% CI: 1.06–1.20, p < 0.001). LowExBP was associated with increased risk regardless of clinical presentation (coronary artery disease, heart failure, hypertrophic cardiomyopathy or peripheral artery disease), exercise mode (treadmill or bike), exercise intensity (moderate or maximal), or LowExBP category (all p < 0.05). However, bias toward positive results was apparent (Eggers test p < 0.001 and p = 0.005).

Conclusion: Our data show that irrespective of clinical or exercise conditions, LowExBP independently predicts fatal and non-fatal cardiovascular events and all-cause mortality.

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1. Introduction

Exercise stress testing is commonly used to identify ischemia in patients with known or suspected coronary artery disease (CAD), and blood pressure (BP) is a mandatory measurement during the test. Under normal conditions, systolic BP (SBP) increases with workload intensity, while diastolic BP remains relatively stable or decreases slightly. An excessive rise in SBP during moderate grade exercise is associated with increased cardiovascular (CV) mortality in people without CAD [1]. On the other hand, an abnormally low SBP during exercise stress testing (LowExBP) is thought to be an ominous sign because it reflects severe cardiac dysfunction [2].

LowExBP is defined as a drop in exercise SBP below the pre-test value or an initial increase followed by a decrease in SBP > 10 mm Hg despite an increase in workload [3], and has ~6% prevalence among patients referred for exercise stress testing [4]. Several studies have shown LowExBP to predict CV events and mortality [4–12]. However, others have failed to identify significant differences in survival rates between patients with LowExBP and those with normal SBP responses [13–15].

The above discrepancies may be explained by the lack of consistency in patient presentation (e.g. those with or without CAD/ ischemia, presence or severity of valvular disease, congenital heart disease, or other presentations of CV disease), exercise mode/intensity (e.g. treadmill vs. bike mode or moderate vs. maximal intensity) or categories/definitions of LowExBP used in analyses (e.g. exercise SBP drop below baseline vs. maximal exercise SBP < 150 mm Hg). The absence of taking these study differences into
account renders the prognostic significance of LowExBP somewhat unclear. To our knowledge, a systematic review and meta-analysis has never been completed to assess the prognostic importance of LowExBP independent of resting BP. This study aimed to conduct such an analysis whilst taking into account whether the prognostic risk varied among patients with different clinical presentations, exercise modes, exercise intensities or categories of LowExBP. We hypothesised that LowExBP would be independently associated with adverse outcomes regardless of these different conditions.

2. Methods

This systematic review and meta-analysis followed the reporting guidelines set by PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) [16] and MOOSE (Meta-analyses of Observational Studies in Epidemiology) [17] statements.

2.1. Literature search

Two reviewers (MGS and PAB) searched seven electronic databases (CINAHL, Cochrane, EMBASE, PubMed, Scopus, SPORTDiscus and Web of Science) including all studies through to April 2013. The search string included the following terms: ‘(exercise’ or ‘exer-
tional’ or ‘stress test’) and ‘(blood pressure’ or ‘hypotension’ or ‘BP’ or ‘arterial’ or ‘systolic’ or ‘haemodynamic’ or ‘hemodynamic’ or ‘pressure’) and ‘(mortality’ or ‘death’ or ‘event’ or ‘prognosis’ or ‘survival’ or ‘cox’ or ‘incident’ or ‘predict’) and ‘(coronary’ or ‘cardiovascular’ or ‘vascular’ or ‘chronic’ or ‘heart failure’ or ‘3-vessel disease’ or ‘left main trunk stenosis’ or ‘myocardial infarction’ or ‘ischaemia’ or ‘angina’ or ‘left-ventricular dysfunction’ or ‘hyper-
trophic’ or ‘cardiomyopathy’ or ‘stroke’ or ‘pulmonary embolism’ or ‘valvular’ or ‘revascularisation’ or ‘restenosis’ or ‘cardiac’ or ‘percutaneous’), and when possible a human limit search filter was applied. The reference lists of original and review articles were also searched.

2.2. Study eligibility

Studies were accepted for the systematic review if they met the following criteria: (1) full-length English publications, (2) longitudinal study design, (3) reported CV events and/or all-cause mortality, and (4) exercise BP reported in multivariate model with risk estimate (hazard ratio [HR], odds ratio, relative risk) and associated 95% CI. The inclusion for the meta-analysis required the risk estimate to be adjusted for resting SBP at a minimum. Additionally, studies were included if they did not specifically adjust for resting SBP, but instead reported their results as an SBP difference model (e.g. change in SBP from rest to maximal exercise, failure to increase SBP by >10 mm Hg from rest; 2) a measure based on change from resting SBP, as either a drop in exercise SBP below resting values or a failure to increase SBP by >10 mm Hg from rest; (3) a measure based on the level of SBP during exercise adjusted for resting SBP, defined as the lowest category of exercise SBP (Table 1 column headed “Definition of LowExBP for categorical SBP (prevalence)” shows details of the exposure for each study). The reference SBP group in each study was identified as either of the following: (1) an increase from resting SBP >10 mm Hg in SBP; (2) the highest category of SBP response to exercise adjusted for resting SBP. Continuous risk estimates were reported as per unit or standard deviation increase in either: (1) the exercise SBP change (peak exercise SBP minus rest SBP) or; (2) the peak exercise SBP. Continuous HRs were rescaled to represent per 10 mm Hg decrease in both types of continuous risk estimates. In addition, using the method outlined by Shi and Copas [18], we were able to estimate HR for continuous risk for two studies [19,20] that reported only categorical risk. For these studies we extracted the HR, associated 95% CI, participants, outcomes/ events, and the lowest and highest SBP values for each reported category of exercise SBP. Weighted regression through the exercise SBP categories was used to estimate an HR and standard error for a per unit increase in exercise SBP. Other studies did not supply sufficient information to perform this estimation. For studies reporting separate risk estimates for fatal and non-fatal CV events and all-cause mortality [7,11,21–24], analyses of the risk estimates for fatal and non-fatal CV events were chosen in preference to all-cause mortality. Two studies [4,25] did not report 95% CIs, standard errors were thus estimated from the associated p-value, in one study the p-value was reported as p < 0.005 [4], resulting in a conservative estimation of the standard error. All meta-analyses used random effects models with inverse variance weighting to compensate for expected heterogeneity among studies. Q and I² statistics were also calculated to test for heterogeneity.

To explore the prognostic risk of LowExBP between differences in study designs we conducted several pre-defined sub-group analyses, which included: (1) patient clinical presentation (suspected/known CAD vs. other clinical presentations of CV disease); (2) exercise mode (treadmill vs. cycling); and; (3) exercise intensity (moderate vs. maximal; where the intensity was defined in each individual study as described in Table 1). Further, we examined
Table 1
Characteristics of studies included in systematic review and meta-analysis.

<table>
<thead>
<tr>
<th>Study</th>
<th>Population</th>
<th>Sample size</th>
<th>Mean Age (± SD)</th>
<th>Male (%)</th>
<th>Follow-upa (Mean ± SD)</th>
<th>Outcome</th>
<th>Exercise mode/ intensity</th>
<th>Exercise SBP modelled</th>
<th>Definition of LowExSBP for categorical SBP (prevalence)</th>
<th>Variables adjusted for in multivariate model</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Al-Khalili et al., 2007 [21]</td>
<td>Survivors of MI and unstable angina</td>
<td>292</td>
<td>56.4 ± 7</td>
<td>0</td>
<td>9°</td>
<td>40 deaths (23 CV)</td>
<td>Cycle (10 W/min)/maximal</td>
<td>Continuous</td>
<td>Continuously (NA)</td>
<td>Age, sex, BMI, index event, LV function, diabetes, smoking, total cholesterol, β-blockers</td>
<td>8/9</td>
</tr>
<tr>
<td>Arnold et al., 1993 [9]</td>
<td>Post thrombolysis for MI</td>
<td>1043</td>
<td>NR</td>
<td>NR</td>
<td>1.47</td>
<td>42 Deaths</td>
<td>Cycle (10 W/mm or usual treadmill)/moderate</td>
<td>Dichotomous</td>
<td>Decrease in exercise SBP below baseline (&lt;20%)</td>
<td>Age, sex, ST-elevation, previous MI, Killip class, anterior infarct, angina, HF, atrial fibrillation, pericarditis, medications, SBP increase, max HR, exertional anemia, ST-segment, max workload, 3 predicted workload achieved, inability to exercise, exertional infarct, LV ejection fraction, angiography</td>
<td>5/9</td>
</tr>
<tr>
<td>Corra et al., 2009</td>
<td>HF treated with carvedilol</td>
<td>631</td>
<td>56 ± 10</td>
<td>90</td>
<td>3.8 ± 14</td>
<td>79 deaths</td>
<td>Cycle (10 W/min)/maximal</td>
<td>Continuous</td>
<td>Continuously only (NA)</td>
<td>Sex, LV-ejection fraction, NYHA class, atrial fibrillation, diuretics, exercise test parameters</td>
<td>N/A</td>
</tr>
<tr>
<td>Corra et al., 2012</td>
<td>HF</td>
<td>749</td>
<td>59 ± 10</td>
<td>88</td>
<td>2.65</td>
<td>119 Major CV events</td>
<td>Cycle (10 W/min)/maximal</td>
<td>Continuous</td>
<td>Continuously only (NA)</td>
<td>Peak VO2, slope of minute ventilation/adenosine production, exertional oscillatory ventilation</td>
<td>N/A</td>
</tr>
<tr>
<td>de Liefde et al., 2008 [22]</td>
<td>Suspected and known PAD</td>
<td>2022</td>
<td>62 ± 12</td>
<td>67</td>
<td>5</td>
<td>540 Deaths (264 CV)</td>
<td>Treadmill (4 km/h)/moderate</td>
<td>Dichotomous</td>
<td>Decrease in exercise SBP below baseline (&lt;20%)</td>
<td>Age, sex, smoking, HTN, COPD, hypercholesterolemia, diabetes, history of HF, previous CV disease, renal failure, rest SBP, rest ABI, time between exercise test and surgery, older age (&gt;66 years), LV ejection fraction &lt;55%, HR increase from entry to end rehab &lt;40 bpm</td>
<td>7/9</td>
</tr>
<tr>
<td>de Liefde et al., 2011 [5]</td>
<td>PAD &amp; major vascular surgery</td>
<td>665</td>
<td>64 ± 10</td>
<td>75</td>
<td>0.083</td>
<td>22 CV deaths and 73 non-fatal CV events</td>
<td>Treadmill (4 km/h)/moderate</td>
<td>Dichotomous</td>
<td>Decrease in exercise SBP below baseline (&lt;20%)</td>
<td>Age, sex, smoking, HTN, COPD, hypercholesterolemia, diabetes, history of HF, history of CV disease, renal failure, rest SBP, exercise ABI, time between exercise test and surgery, older age (&gt;66 years), LV ejection fraction &lt;55%, HR increase from entry to end rehab &lt;40 bpm</td>
<td>8/9</td>
</tr>
<tr>
<td>Di Valentine et al., 2010 [19]</td>
<td>Cardiac rehabilitation (50± CAD)</td>
<td>1853</td>
<td>60 ± 84</td>
<td>2.75°</td>
<td>51 deaths</td>
<td>Cycle/maximal</td>
<td>Dichotomous</td>
<td>&lt;54 mm Hg change in SBP from rest to peak exercise (50%)</td>
<td>Age, sex, BMI, index event, LV function, diabetes, smoking, total cholesterol, β-blockers</td>
<td>8/9</td>
<td></td>
</tr>
<tr>
<td>Dubach et al., 1988 [4]</td>
<td>Referred for clinical reasons (105 patients prior MI)</td>
<td>2022</td>
<td>58 ± 100</td>
<td>2.1</td>
<td>96 deaths</td>
<td>Treadmill (continuous)/maximal</td>
<td>Dichotomous</td>
<td>Decrease in exercise SBP below baseline (&lt;10%)</td>
<td>Age, max LV wall thickness, non-sustained ventricular tachycardia, family history of sudden death AND OR syncope</td>
<td>8/9</td>
<td></td>
</tr>
<tr>
<td>Elliott et al., 2000 [8]</td>
<td>Clinically determined HCM</td>
<td>368</td>
<td>37 ± 13</td>
<td>65</td>
<td>3.6 ± 2.5</td>
<td>36 deaths (22 sudden CV)</td>
<td>Bruce treadmill OR cycle/maximal</td>
<td>Dichotomous</td>
<td>Decrease in exercise SBP below baseline OR SBP unable to rise during exercise</td>
<td>Age, sex, BMI, rest SBP, peak VO2</td>
<td>8/9</td>
</tr>
<tr>
<td>Fagard et al., 1989 [21]</td>
<td>Severe HF (candidates for heart transplant)</td>
<td>274</td>
<td>515 ± 11</td>
<td>80</td>
<td>1.4°</td>
<td>55 Deaths. 145 CV deaths and 73 non-fatal events</td>
<td>Cycle (10 W/min)/moderate</td>
<td>Continuous</td>
<td>Continuously only (NA)</td>
<td>Age, sex, smoking, HTN, COPD, hypercholesterolemia, diabetes, history of HF, history of CV disease, renal failure, rest SBP, exercise ABI, time between exercise test and surgery, older age (&gt;66 years), LV ejection fraction &lt;55%, HR increase from entry to end rehab &lt;40 bpm</td>
<td>8/9</td>
</tr>
<tr>
<td>Froelicher 1994 [10]</td>
<td>Survivors of first MI</td>
<td>258</td>
<td>56 ± 85</td>
<td>7.9 ± 2.6</td>
<td>71 deaths (56 CV)</td>
<td>Treadmill/moderate</td>
<td>Dichotomous</td>
<td>Decrease in exercise SBP below baseline OR SBP unable to rise &gt;10 mm Hg (6%)</td>
<td>Age, sex, echocardiograms, ST-segment depression and elevation, exercise capacity, stress, angina, systemic HTN, previous MI, Killip class, digoxin</td>
<td>7/9</td>
<td></td>
</tr>
<tr>
<td>Gupta et al., 2007 [20]</td>
<td></td>
<td>64/5</td>
<td>59 ± 11</td>
<td>100</td>
<td>6.6 ± 3.7</td>
<td>676 CV deaths</td>
<td>Treadmill/moderate</td>
<td>Dichotomous</td>
<td></td>
<td></td>
<td>8/9</td>
</tr>
</tbody>
</table>

(continued on next page)
### Table 1 (continued)

<table>
<thead>
<tr>
<th>Study/randomized trial</th>
<th>Population</th>
<th>n</th>
<th>Age (Mean ± SD)</th>
<th>Male (%)</th>
<th>Follow-up (Mean ± SD)</th>
<th>Outcome</th>
<th>Exercise mode/ intensity</th>
<th>Exercise SBP modelled</th>
<th>Definition of LowExBP for categorical SBP (prevalence)</th>
<th>Variables adjusted for in multivariate model</th>
<th>NOS score</th>
</tr>
</thead>
<tbody>
<tr>
<td>Habibzadeh et al., 2013 [11]</td>
<td>Referred for clinical evaluation (&gt;173 patients with CAD)</td>
<td>908</td>
<td>66.6 ± 10</td>
<td>81.50</td>
<td>5</td>
<td>303 CV fatal and non-fatal events</td>
<td>Bruce treadmill/ maximal</td>
<td>Continuous; Quartiles</td>
<td>0–22 mm Hg change in SBP from rest to peak exercise (50%)</td>
<td>Age, exercise capacity, ST abnormalities, history of MI or HF, HTN, β-blockers</td>
<td>9/0</td>
</tr>
<tr>
<td>Hedberg et al., 2009 [24]</td>
<td>Confirmed CAD</td>
<td>382</td>
<td>75</td>
<td>50</td>
<td>10.6</td>
<td>140 Deaths (64.4 CV)</td>
<td>Cycle (30 W/min)/ maximal</td>
<td>Continuous; Tertiles</td>
<td>&lt;30 mm Hg change in SBP from rest to peak exercise (13%)</td>
<td>Age, sex, hypertension, diabetes, history of MI or HF, age, CAD, HTN, smoking, lipid level</td>
<td>9/0</td>
</tr>
<tr>
<td>Kallistratos et al., 2012 [30]</td>
<td>Elderly population (confirmed and suspected CAD)</td>
<td>160</td>
<td>58 ± 13</td>
<td>81</td>
<td>2.5 ± 0.8</td>
<td>22 Deaths and 5 heart transplantations</td>
<td>Bruce treadmill/ maximal</td>
<td>Continuous</td>
<td>Decrease in SBP &lt;10 mm Hg from baseline OR failure to rise &gt;10 mm Hg (27%)</td>
<td>Age, BMI, peak VO2, smoking, diabetes, β-blockers, platelet inhibitors, headache, antiarrhythmic, HTN medication, vasodilators, angina, ST-segment depression</td>
<td>N/A</td>
</tr>
<tr>
<td>Kato et al., 1990 [37]</td>
<td>Survivors of MI</td>
<td>217</td>
<td>56 ± 10</td>
<td>86</td>
<td>4</td>
<td>34 CV Fatal and non-fatal events</td>
<td>Modified Bruce treadmill/maximal</td>
<td>Dichotomous</td>
<td>Decrease in SBP before baseline OR SBP unable to rise &gt;10 mm Hg (2.7%)</td>
<td>Age, BMI, peak VO2, smoking, diabetes, β-blockers, platelet inhibitors, headache, antiarrhythmic, HTN medication, vasodilators, angina, ST-segment depression</td>
<td>7/0</td>
</tr>
<tr>
<td>Kavanagh et al., 2002 [39]</td>
<td>Referred for cardiac rehabilitation</td>
<td>12,169</td>
<td>55 ± 9</td>
<td>100</td>
<td>7.9</td>
<td>2512 Deaths (1,136 CV)</td>
<td>Cycle (16.7 W/min)/ maximal</td>
<td>Dichotomous</td>
<td>Decrease in SBP before baseline OR SBP unable to rise &gt;10 mm Hg (2.7%)</td>
<td>Age, BMI, peak VO2, smoking, diabetes, β-blockers, platelet inhibitors, headache, antiarrhythmic, HTN medication, vasodilators, angina, ST-segment depression</td>
<td>N/A</td>
</tr>
<tr>
<td>Krone et al., 1985 [38]</td>
<td>Survivors of MI</td>
<td>667</td>
<td>77.6</td>
<td>1</td>
<td>31 CV Deaths. 57 new MI and 75 CAD/CABG</td>
<td>Treadmill (1.7 miles)</td>
<td>Continuous</td>
<td>Peak SBP &lt;110 mm Hg (8.5%)</td>
<td>Age, NTHA class, pulmonary congestion, degree of saphenous stenosis</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Lauer et al., 1995 [40]</td>
<td>Suspected &amp; confirmed CAD</td>
<td>9608</td>
<td>53.6 ± 12</td>
<td>70</td>
<td>2</td>
<td>129 Deaths</td>
<td>Bruce treadmill/ maximal</td>
<td>Continuous</td>
<td>Continuous only (NA)</td>
<td>Age, sex, smoking, HTN, diabetes, lipid medication, angina, HF, rest MI, exercise fraction &lt;50%</td>
<td>N/A</td>
</tr>
<tr>
<td>Morris et al., 1993 [37]</td>
<td>Clinically referred for exercise test with chest pain symptoms (&lt;3 MI)</td>
<td>588</td>
<td>59 ± 9</td>
<td>100</td>
<td>2.5</td>
<td>61 Deaths (39 CV deaths). 43 Non-fatal MI 37 Deaths (31 CV)</td>
<td>Bruce treadmill/ maximal</td>
<td>Continuous</td>
<td>Continuous only (NA)</td>
<td>Age, sex, smoking, HTN, diabetes, lipid medication, smoking, diabetes, HTN, exercise fraction &lt;50%</td>
<td>N/A</td>
</tr>
<tr>
<td>Naughton et al., 2000 [12]</td>
<td>Referred for exercise test</td>
<td>641</td>
<td>51.8 ± 7.3</td>
<td>100</td>
<td>3</td>
<td>122 Deaths (58 CV)</td>
<td>Cycle (30–30 W/min)/ maximal</td>
<td>Continuous</td>
<td>Continuous only (NA)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Nienaber et al., 2009 [40]</td>
<td>Referred for exercise test</td>
<td>2029</td>
<td>57 ± 13</td>
<td>73.50</td>
<td>3.0 ± 1</td>
<td>122 Deaths (58 CV)</td>
<td>Cycle (30–30 W/min)/ maximal</td>
<td>Continuous</td>
<td>Continuous only (NA)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Nishiyama et al., 2010 [41]</td>
<td>HF (NTHA class 2 or 3)</td>
<td>136</td>
<td>62.5 ± 12</td>
<td>75.74</td>
<td>6.2 ± 2.5</td>
<td>34 Deaths</td>
<td>Bruce OR Sheffield treadmill/maximal</td>
<td>Continuous</td>
<td>Continuous only (NA)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Gluotz et al., 1999 [42]</td>
<td>Clinically determined HCM</td>
<td>126</td>
<td>42 ± 14</td>
<td>71</td>
<td>4.7 ± 3.7</td>
<td>9 Deaths</td>
<td>Cycle (25 W/3 min)/ maximal</td>
<td>Continuous</td>
<td>Continuous only (NA)</td>
<td>N/A</td>
<td></td>
</tr>
<tr>
<td>Waters et al., 1985 [29]</td>
<td>Survivors of MI</td>
<td>225</td>
<td>52 ± 9</td>
<td>87</td>
<td>6</td>
<td>58 Deaths</td>
<td>Naughton treadmill/ moderate</td>
<td>Continuous</td>
<td>Continuous only (NA)</td>
<td>Age, history of syncope, arrhythmia, atrial fibrillation</td>
<td>7/0</td>
</tr>
<tr>
<td>Williams et al., 2005 [34]</td>
<td>Stable HF</td>
<td>85</td>
<td>55.7 ± 12</td>
<td>84</td>
<td>5.08</td>
<td>16 Deaths</td>
<td>Bruce treadmill/ maximal</td>
<td>Continuous</td>
<td>Continuous only (NA)</td>
<td>Age, LV ejection fraction, NTHA class, B-Type natriuretic peptide level, peak circulatory power, peak mean arterial</td>
<td>N/A</td>
</tr>
</tbody>
</table>
differences for studies reporting fatal and non-fatal CV events (including mortality) vs. all-cause mortality, as well as differences for studies reporting adjustment for antihypertensive medications vs. those that did not adjust for antihypertensive medications, and also for differences in SBP measurement: for categorical BP analyses we compared the category of LowExBP (exercise SBP drop below baseline or failure to increase >10 mm Hg vs. lowest quantile exercise SBP value) and for continuous BP analyses we compared change from baseline vs. peak SBP. Univariable random effects meta-regression analyses were conducted to compare whether a difference existed in risk estimates between each of the sub-group analyses and to determine if study quality was related to effect size. Publication bias was assessed with funnel plots and Egger’s test and Duval and Tweedie’s trim and fill method [26] was used as a sensitivity analysis, which assesses the possible influence of missing studies. A p-value <0.05 was considered to be significant. All statistical calculations were made with STATA (version 12.1).

3. Results

3.1. Literature search and systematic review

As shown in Fig. 1, the literature search returned 21,033 studies. After exclusion of duplicates and primary review of title or abstract, 195 studies remained to be reviewed by full text. Twenty-seven full-length English publications were deemed eligible for the systematic review. Eight studies were excluded from the meta-analysis as they failed to adjust for resting SBP (Fig. 1). Searching the reference lists of review and original articles did not produce any additional studies. Key information from each of the studies included in the systematic review and meta-analysis is available in Table 1. The meta-analysis included a total of 45,895 patients that were followed for an average of 4.4 ± 3.0 years. 87% of the population were males with an average age of 57 ± 8 years. Participants came from a range of clinical presentations including suspected or known CAD (angina, myocardial infarction, ischemic heart disease or post-coronary bypass surgery/angioplasty), peripheral artery disease, heart failure and hypertrophic cardiomyopathy. Five studies reported the number of patients who experienced a drop in exercise SBP below baseline (prevalence 5.3%; 298 of 5625 patients). Eleven studies used a treadmill exercise mode compared with five studies that used a cycling mode and three with a mixture of both. In addition, 13 studies used a maximal intensity protocol compared to six studies that used a moderate intensity. In regards to the covariates corrected for in the risk analyses, 12 studies adjusted for both age and sex, while 13 studies additionally adjusted for one or more other CV risk factors (e.g. smoking, diabetes, hypertension). Table 1.

3.2. Categorical exercise BP and outcomes

When compared to the reference exercise SBP response, a LowExBP increased the risk for fatal and non-fatal CV events and all-cause mortality (n = 15, HR: 2.01, 95% CI: 1.59—2.53, p < 0.001) after adjustment for resting SBP (Fig. 2). A significant risk remained when comparing sub-groups of patient clinical presentation, exercise modes, exercise intensities and categories of LowExBP or type of outcome events (Table 2). Meta-regression analyses failed to identify any statistical difference in risk estimates when comparing patient clinical presentation, exercise modes, exercise intensities, categories of LowExBP, or type of outcome events. However, studies that did not adjust for antihypertensive medications had higher pooled HRs compared to those that adjusted for antihypertensive medications (Table 2). A slight but non-significant decrease in
A 10 mm Hg decrease in exercise SBP was associated with 13% increased risk for fatal and non-fatal CV events and all-cause mortality (n = 9, HR 1.13, 95% CI: 1.06–1.20, p < 0.001) (Fig. 3). When these data were analysed separately based on SBP change or peak SBP, increased prognostic risk was shown for a 10 mm Hg decrease in both exercise SBP change (n = 7, HR: 1.15, 95% CI: 1.03–1.28, p = 0.018) as well as peak exercise SBP after adjustment for resting SBP (n = 2, HR: 1.12, 95% CI: 0.95–1.33, p = 0.153). The prognostic risk remained for the sub-groups of patient clinical presentation and exercise modes (Table 3). Only one study reported a risk estimate for moderate intensity exercise and as a result the analyses comparing the risk estimate between moderate and maximal intensity exercise was unable to be completed. It was shown by meta-regression analyses that there was no statistical difference in risk estimates between the different patient clinical presentation, whether adjustment was made for antihypertensive medications, type of SBP measure, or type of outcome events, however, a significant difference was shown between a cycling and treadmill mode of exercise, with higher risk associated with cycling mode. A slight but non-significant decrease in hazard ratio with increasing study quality (as per the Newcastle–Ottawa Scale) was observed (p = 0.451).

3.3 Continuous exercise BP and outcomes

Asymmetry in the funnel plots and Eggers test (Fig. 4) indicates that there is evidence to support the presence of publication bias for both categorical and combined continuous BP data. The trim & fill method added an additional eight and four theoretically missing
SBP, systolic blood pressure. Hypertrophic cardiomyopathy; LowExBP, low systolic blood pressure during exercise. Separate analyses were performed on the eight studies that were excluded because they did not adjust for resting SBP (as indicated in Table 1, “N/A” far right column). The pooled HR was 3.00 \( (n = 3, 95\% CI: 1.22–7.36, p^2 = 36.5\% \) for those studies requiring LowExBP (categorical) and 1.21 \( (n = 5, 95\% CI: 1.15–1.26, p^2 = 0.0\% \) per 10 mm Hg in peak SBP. These HRs are inflated compared to studies that adjusted for resting SBP. A meta-regression was performed to determine the influence of sex on the heterogeneity of risk estimates. No association was found with male proportion for those studies reporting categorical risk estimates. However, there was a trend for an association between study heterogeneity and male proportion for studies reporting continuous estimates \( (p = 0.036; \) higher risk in women). This finding should be treated with caution as it appears to be partly driven by the only study that was exclusively in women \( [21] \). There was insufficient data provided to enable separate analysis of fatal from non-fatal events. Similarly, there was too much heterogeneity among variables included in multivariate models to enable separate analysis based on the level of adjustment across studies (Table 1).

4. Discussion

This systematic review and meta-analysis has shown that after adjustment for resting SBP, LowExBP was associated with increased risk for fatal and non-fatal CV events and all-cause mortality in patients undergoing exercise stress testing for clinical reasons. Moreover, the independent risk remained regardless of the patient clinical presentation, exercise mode, exercise intensity (categorical BP data only) or category used to define LowExBP. These results support the expected relevance of measuring BP during exercise stress testing for identifying higher risk patients potentially amenable to further medical investigation, but should also be considered in light of publication bias.

4.1. Prognostic significance of LowExBP

The association between LowExBP and adverse prognosis in patients with suspected or known CAD has long been suspected. Froelicher et al. \( [27] \) published a crude meta-analysis 27 years ago, which tentatively concluded that an “abnormal SBP response” to exercise was associated with poorer survival in patients recovering from myocardial infarction. However, confidence limits were not able to be provided and the analysis did not take into account whether studies included LowExBP in a multivariate model, or accounted for resting BP and other CV risk factors. Because of these omissions none of the 15 studies from the work of Froelicher et al. \( [27] \) were suitable for inclusion in this current analysis. A major strength of our work was inclusion of studies that reported risk estimates and associated 95% CIs from multivariate models adjusted for resting SBP (as a minimum), in addition to age, sex and other CV risk factors, which most studies corrected for. Additionally, our data show that the pooled independent prognostic risk for LowExBP remained irrespective of existing clinical conditions including heart failure, hypertrophic cardiomyopathy or peripheral artery disease. It should be noted, however, that the number of studies included in analyses for these conditions were low \( (n = 5) \) in comparison to the number of studies including patients with known or suspected CAD \( (n = 14) \).

To our knowledge, the prognostic risk of LowExBP recorded during treadmill compared with cycling mode has never been assessed and is a relevant consideration given that physiological responses to these modalities differ considerably. Indeed, maximal exercise is not always achievable using cycling protocols \( [3] \) and the SBP achieved during cycling has been reported as systematically higher than those attained during treadmill exercise in patients with documented CAD \( [28] \). Regardless of these differences, our analyses show that risk of adverse prognosis is increased whether the LowExBP occurred during treadmill or cycle testing. Increased prognostic risk was also noted for data analyzed from either moderate or maximal intensity stress testing. In the analyses of categorical data, LowExBP measured during a moderate intensity of exercise had higher pooled HR than LowExBP during a maximal intensity test. It was previously shown by Watson et al. \( [29] \) that LowExBP occurring within 5 min of test was indicative of severe CAD, whereas a late response (initial increase in SBP and subsequent drop with continued exercise after 5 min) was six times more likely to occur, and only 50% of those patients had significant CAD. Having regard to this, the higher risk for patients experiencing LowExBP at a moderate intensity may be explained by greater severity of CAD and cardiac dysfunction. However, further research is required to confirm this hypothesis.

Current thought suggests that greater severity of LowExBP signifies greater CV dysfunction and consequent expectation for worse prognosis. Slightly higher HR for fatal and non-fatal CV events and all-cause mortality were observed in studies that defined LowExBP
as an exercise SBP drop below baseline, or failure to increase
>10 mm Hg from baseline (4.2% prevalence: 766 of 18,317 patients),
when compared to studies that defined LowExBP as the lowest
quantile SBP value (35% prevalence: 6036 of 17,268 patients).
However, the difference in risk estimates between the two cate-
gories of LowExBP was not statistically significant. This may have
due to grouping the low quantile exercise SBP values together,
which varied greatly among studies (e.g. maximal SBP <140 mm Hg
vs. SBP increase <54 mm Hg from baseline).

4.2. Physiological mechanisms of LowExBP

A commonly proposed mechanism of LowExBP is severe left-
ventricular dysfunction and reduced cardiac output due to exer-
tional myocardial ischemia. This often occurs in conjunction with
other clinical signs (e.g. ST depression, angina) and has been
associated as a marker of severe CAD, such as left main or three-
vessel disease [2]. Return to a normal exercise SBP response oc-
curs following coronary artery bypass surgery, which tends to
support ischemia as contributor towards LowExBP in these patients
[30]. Additional causes of blunted exercise SBP may arise from
exercise-induced left-ventricular outflow tract obstruction, or
aortic or mitral valve stenoses which prevent appropriate increases
in cardiac output. Alternatively, LowExBP may be due to abnor-
manly pronounced vasodilation of the arterial vessels supplying
non-working muscles during exercise. The mechanism of this
abnormal response is unclear, although, has been proposed to be
due to over-activation of left-ventricular baroreceptors, causing
vasorelaxation through reduced sympathetic tone [31].

4.3. Limitations

For all studies included in the meta-analysis, only cumulative,
rather than individual patient, data were available and, thus, we
were unable to derive an exercise SBP cut point indicative of
increased risk. Studies varied with respect to the covariates
adjusted for in the final statistical model and as such we were
unable to account for all CV risk factors in the meta-analyses, but
also cannot discount the possibility of some studies being over-
adjusted. Restriction of only including studies reported in English
may have missed relevant work resulting in different conclusions,
although the chance of this is not high (about 1 in 36 meta-
analyses) [32]. Additionally, we cannot ignore the chance that

### Table 3

<table>
<thead>
<tr>
<th>Sub-groups</th>
<th>Studies (n)</th>
<th>Pooled hazard ratio</th>
<th>95% CI</th>
<th>p-Value for difference</th>
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<tbody>
<tr>
<td>Patient clinical presentation</td>
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<td></td>
<td></td>
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<td>Suspected/known CAD</td>
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<td>1.02–1.24</td>
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<tr>
<td>Heart failure</td>
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<td>1.16</td>
<td>0.97–1.39</td>
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<tr>
<td>Exercise mode</td>
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<td></td>
<td></td>
</tr>
<tr>
<td>Treadmill</td>
<td>5</td>
<td>1.08</td>
<td>1.01–1.16</td>
<td>0.046</td>
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<tr>
<td>Cycling</td>
<td>4</td>
<td>1.26</td>
<td>1.10–1.44</td>
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<tr>
<td>Antihypertensive medications</td>
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<td>Adjusted</td>
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<td>1.01–1.19</td>
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<tr>
<td>Not adjusted</td>
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<td>1.19</td>
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<td>Type of SBP</td>
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<tr>
<td>Change from baseline</td>
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<td>1.03–1.28</td>
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<td>0.95–1.33</td>
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<td>Outcome events</td>
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<tr>
<td>Fatal and non-fatal cardiovascular events</td>
<td>5</td>
<td>1.19</td>
<td>1.05–1.35</td>
<td>0.301</td>
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<tr>
<td>All-cause mortality</td>
<td>4</td>
<td>1.10</td>
<td>0.98–1.23</td>
<td></td>
</tr>
</tbody>
</table>

BP, blood pressure; CAD, coronary artery disease; CI, confidence interval; SBP, systolic blood pressure.

*Medications termed “cardiovascular” within individual studies. Only one study reported the hazard ratios for moderate intensity exercise and as such there is no sub-group analysis of different intensities.

**Fig. 3.** Continuous BP and risk for adverse events – forest plot representing the individual and pooled risk of fatal and non-fatal cardiovascular events and/or all-cause mortality for:
(1) per 10 mm Hg decrease in exercise SBP change (difference between rest and peak exercise) and; (2) per 10 mm Hg decrease in peak exercise SBP. $I^2 = 58.5\% (Q = 19.3, p = 0.013)$. BP, blood pressure; CI, confidence interval; mm Hg, millimetres mercury; SBP, systolic blood pressure.
some studies included in the meta-analysis could have recorded inaccurate exercise BP data due to incorrect measurement techniques or movement artefact [33]. Furthermore, our work included a high percentage of male patients (87%) and this limits the generalizability of findings to females. The under-representation of women is unusual because the proportion of males to females undergoing exercise testing should approximate 1:1. A possible explanation for this may be that LowExBP was not significantly associated with adverse outcome in studies of female patients (as shown in a cohort of 2380 females with known CAD) [15], and these negative findings may have been a contributory factor towards the observed publication bias in our current analysis (i.e. due to selective reporting of positive studies or other causes). In addition, we identified several studies [13–15] that found no statistically significant association between LowExBP and adverse outcomes in univariate analysis. Subsequently, these studies did not include LowExBP in a multivariate model or report associated risk estimates, thus not being eligible for the current meta-analysis. The trim and fill method was used to account for these missing studies, which suggested that an overestimation of the pooled HR had occurred for both categorical and continuous BP in the initial analyses. Nonetheless, even after taking this overestimation into consideration, LowExBP remained significantly associated with adverse outcomes. Finally, some of the sub-group analyses were performed with only two or three studies and caution should be applied to these conclusions.

4.4. Conclusions

This study found that LowExBP was associated with an increased risk of fatal and non-fatal CV events and all-cause mortality, even after adjustment for resting SBP, and other CV risk factors (in most cases). Furthermore, the significant risk associated with LowExBP remained among sub-groups of patients with differing clinical presentations, different exercise conditions and categories to define LowExBP. Publication bias had some influence on the analyses, but nevertheless, the findings support the importance of monitoring BP during exercise testing and providing optimal care to patients with abnormally low exercise BP.

Conflict of interest

PAB was supported by a Heart Foundation, Menzies and Human Life Sciences Scholarship for Medical Research. None of the authors declare a conflict of interest.

References