Published in final edited form as:
Am J Cardiol. 2011 April 15; 107(8): 1208–1214. doi:10.1016/j.amjcard.2010.12.020.

Relation of Baseline Systolic Blood Pressure and Long-Term Outcomes in Ambulatory Patients with Chronic Mild to Moderate Heart Failure

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Abstract

We studied the impact of baseline systolic blood pressure (SBP) on outcomes in mild to moderate chronic systolic and diastolic heart failure (HF) patients in the Digitalis Investigation Group trial using propensity-matched design. Of the 7788 patients, 7785 had baseline SBP data and 3538 had SBP ≤120 mm Hg. Propensity scores for SBP ≤120 mm Hg, calculated for each of the 7785 patients, were used to assemble a matched cohort of 3738 patients with SBP ≤120 and >120 mm Hg who were well-balanced on 32 baseline characteristics. All-cause mortality occurred in 35% and 32% of matched patients with SBP ≤120 and >120 mm Hg respectively during 5 years of follow-up (hazard ratio {HR} when SBP ≤120 was compared with >120 mm Hg, 1.10; 95% confidence interval {CI}, 0.99–1.23; p=0.088). HRs (95% CIs) for cardiovascular and HF mortality associated with SBP ≤120 mm Hg were 1.15 (1.01–1.30; p=0.031) and 1.30 (1.08–1.57; p=0.006). Cardiovascular hospitalization occurred in 53% and 49% of matched patients with SBP ≤120 and >120 mm Hg respectively (HR for SBP ≤120 was compared with >120 mm Hg, 1.13; 95% CI, 1.03–1.24; P=0.008). HRs (95% CIs) for all-cause and HF hospitalization associated with SBP ≤120 mm Hg were 1.10 (1.02–1.194; p=0.017) and 1.21 (1.07–1.36; p=0.002). In conclusion, in patients with mild to moderate chronic systolic and diastolic HF, baseline SBP ≤120 mm Hg was associated with increased cardiovascular and HF mortality and all-cause, cardiovascular and HF hospitalization that was independent of other baseline characteristics.

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Conflict of Interest Disclosures: None

Keywords

heart failure; systolic blood pressure; mortality; hospitalization

Hypertension is a known risk factor for incident heart failure (HF).[1, 2] However, several studies have demonstrated that in patients with acute decompensated HF, a low systolic blood pressure (SBP) is associated with poor outcomes.[3–8] We have recently demonstrated similar associations between low SBP and poor outcomes in a propensity-matched cohort of chronic advanced systolic HF patients.[9] However, the role of baseline SBP on outcomes in patients with chronic mild to moderate systolic and diastolic HF is relatively less known and has not been investigated using propensity-matched design. The purpose of the current study was to examine the association between baseline SBP and outcomes in a propensity-matched cohort of mild to moderate chronic systolic and diastolic HF patients.

Methods

A public-use copy of the Digitalis Investigation Group (DIG) data set was used for the current analysis. DIG was a multicenter randomized placebo-controlled clinical trial of digoxin in patients with HF.[10] Briefly, 7788 patients with advanced chronic systolic HF were enrolled from 302 different sites across the United States and Canada between February 1991 and August 1993. At baseline, patients had a mean duration of 17 months of HF and had a mean left ventricular ejection fraction (LVEF) of 29%. Most patients had New York Heart Association (NYHA) class I-III symptoms and over 80% of all patients were receiving angiotensin-converting enzyme (ACE) inhibitors and diuretics.

Data on baseline SBP was available from 7785 patients and were documented by study investigators. Of these, 3538 (45%) had SBP ≤120 mm Hg (median, 110 mm Hg, interquartile range, 8 mm Hg), and 4247 (54%) had SBP >120 mm Hg (median, 140 mm Hg, interquartile range, 20 mm Hg). We chose SBP of 120 mm Hg as our cutoff as it is often considered the upper limit of normal range. Taking into account the significant imbalances in baseline characteristics between the two groups (Table 1), we used propensity scores to assemble a matched cohort of 1869 pairs of patients who were well-balanced on 32 baseline characteristics.[11, 12] We began by estimating propensity scores for SBP ≤120 mmHg for each of the 7785 patients using a non-parsimonious multivariable logistic regression model and then assembled a cohort of 1869 pairs (n=3838) of propensity-matched patients with SBP ≤120 and >120 mm Hg who were well-balanced on 32 baseline characteristics.[13–21] Absolute standardized differences were estimated to evaluate the pre-match imbalance and post-match balance, and presented as a Love plot.[13–21] An absolute standardized difference of 0% indicates no residual bias and differences <10% are considered inconsequential.

The primary outcome for the current analysis was all-cause mortality during 5 years of follow-up. The secondary outcomes included various cause-specific mortalities and hospitalizations. Kaplan-Meier and Cox regression analyses were used to determine associations between SBP ≤120 mm Hg and outcomes during 5 years of follow-up. Subgroup analyses were conducted to determine the homogeneity of association between SBP≤120 mm Hg and all-cause mortality. Formal sensitivity analyses were conducted to determine the impact of an unmeasured confounder. All statistical tests were two-tailed with a p-value <0.05 considered significant. All data analyses were performed using SPSS for Windows version 18 (SPSS Inc., Chicago, IL).

Results

Matched patients had a mean age of 64 (±10) years with 23% women and 14% non-whites. Matched patients with SBP ≤120 mm Hg had a median SBP of 114 mm Hg (interquartile range, 10 mm Hg) and those with SBP >120 mm Hg had a median SBP of 134 mm Hg (interquartile range, 10 mm Hg). Over 90% of the matched patients with SBP ≤120 mm Hg had their SBP between 110 and 120 mm Hg. Before matching, patients with SBP ≤120 mm Hg were younger (by a mean age of 3 years) and had a lower prevalence of hypertension, diabetes, chronic kidney disease (Table 1). They were also more likely to be male, have higher prevalence of ischemic cardiomyopathy, higher symptom burden and a lower mean LVEF. These and other pre-match imbalances in baseline covariates were balanced after matching (Table 1). Post-match standardized differences for all measured covariates were <10% (most were <5%), suggesting substantial covariate balance across the groups (Figure 1).

All-cause mortality occurred in 35% and 32% of matched patients with SBP ≤120 and >120 mm Hg respectively during 5 years of follow-up (hazard ratio {HR} when SBP ≤120 was compared with SBP >120 mm Hg, 1.10; 95% confidence interval {CI}, 0.99–1.23; p=0.088; Table 2 and Figure 2). This association was homogeneous across various subgroups of patients except that it was only observed among those receiving diuretics (Figure 3). In the absence of a hidden bias, a sign-score test for matched data with censoring provides evidence (p=0.0147) that patients with SBP ≤120 mm Hg clearly had higher mortality than those with SBP >120 mm Hg. A hidden covariate that is a near-perfect predictor of mortality could explain away this association if it also increased the odds of having SBP≤120 by only 3.13%. Associations of SBP ≤120 mm Hg with other cause-specific mortalities before and after matching are displayed in Table 2.

Cardiovascular hospitalization occurred in 53% and 49% of matched patients with SBP ≤120 and >120 mm Hg respectively (HR for SBP ≤120, 1.13; 95% CI, 1.03–1.24; P=0.008; Table 3 and Figure 2). Associations of SBP ≤120 mm Hg with all-cause and other cause-specific hospitalizations before and after matching are displayed in Table 3.

Discussion

The result of the current analysis demonstrate that in patients with mild to moderate HF, baseline SBP≤120 was associated with increased long-term mortality and hospitalization, which remained significant for all outcome except all-cause mortality in a well-balanced propensity-matched cohort. These findings suggest that baseline SBP ≤120 mm Hg is a powerful predictor of poor outcomes even among ambulatory patients with mild to moderate chronic HF and that these associations were at least part intrinsic in nature. These findings are important as over 90% of the patients in the group with SBP ≤120 mm Hg had their SBP between 110 and 120 mm Hg, a range often considered optimal. And, yet these patients consistently had poor outcomes from all-cause, cardiovascular and HF mortalities and hospitalizations.

Significant unadjusted associations are often in part confounded by covariates that maybe imbalanced at baseline. However, potential confounding covariates were equally distributed between patients with SBP ≤120 and >120 mm Hg. While patients with SBP ≤120 mm Hg were younger with a lower prevalence of hypertension, diabetes and chronic kidney disease, they were also more likely to be male with a higher prevalence of ischemic cardiomyopathy, a higher symptom burden and a lower mean LVEF. It appears that imbalances in these latter characteristics may have at least in part confounded the unadjusted associations between SBP ≤120 mm Hg and poor outcomes. This is also supported by the substantial attenuation

of the magnitude of these associations after propensity matching. However, the persistence of significant associations of SBP ≤120 mm Hg with poor outcomes among matched cohort suggest that these associations were also independent of those measured baseline covariates.

The intrinsic association between SBP ≤120 mm Hg and poor outcomes is unlikely to be solely or primarily due to hypoperfusion as the vast majority of these patients had their SBP between 110 and 120 mm Hg. It is therefore possible that SBP ≤120 mm Hg was rather a marker than cause of poor outcomes. HF patients SBP ≤120 mm Hg were more likely to have ischemic cardiomyopathy at baseline. Although the prevalence of ischemic heart disease between the two SBP groups were balanced after matching, it is possible that HF patients with SBP ≤120 mm Hg had more severe ischemia, the continuation of which during follow-up may have resulted in further lowering of SBP and hypoperfusion. This notion is also supported by our findings of an association between SBP ≤120 mm Hg and increased risk of hospitalizations due to unstable angina. However, the interaction between ischemic heart disease, SBP ≤120 mm Hg and all-cause mortality in mild to moderate HF may be more complex. While it is possible that myocardial ischemia may contribute to low SBP, and yet findings from our subgroup analysis suggest that in these patients, baseline SBP ≤120 mm Hg had no association with all-cause mortality. This is important as over 70% of matched patients in our study had ischemic cardiomyopathy at baseline and findings from our study suggest that baseline SBP had no association with outcomes in these patients.

As the cardiac performance deteriorates with advancing HF, a drop in SBP may be part of the natural history of HF. However, therapy with neurohormonal blockade and diuretics may also contribute to that process. Interestingly, even before matching, patients in both SBP groups in our study had similar duration of HF and over 90% were receiving angiotensin-converting enzyme inhibitors. Although little is known about the benefits of treating hypertension in patients with HF, the American College of Cardiology/American Heart Association guideline for management of chronic HF recommends that it is prudent to manage hypertension in patients with HF as if they did not have HF.[22] HF patients with a history of hypertension may be less likely to have low SBP and yet findings from our subgroup analysis suggest that in those with hypertension, baseline SBP ≤120 mm Hg was associated with increased mortality. This is in contrast to patients with hypertension but without HF in whom a lower SBP has been shown to be associated with improved outcomes.[23] However, intensive lowering of SBP has not been shown to be beneficial in patients with hypertension and other morbidities such as diabetes and coronary artery disease.[24–26]

Several studies have examined the association between SBP and outcomes in chronic HF.[5, 7–9, 27, 28] One of these studies has examined the association of SBP and mortality among DIG participants with low LVEF and NYHA class I–III.[28] Our study is distinguished by the inclusion of DIG participants with normal LVEF and other outcomes, the use of SBP 120 as a cutoff, a often-used goal for SBP in HF, and insightful subgroup analyses. Further, our study is distinguished by the use of propensity-matched design which allowed us to assemble a balanced cohort. Although traditional regression-based multivariable models are useful for risk adjustment, they may be limited by strong untenable model assumptions, and concerns for residual bias and procedural transparency.[12, 29]

Several limitations of the current study must be acknowledged. Although propensity score technique accounts for imbalances in all of the measured covariates, it may or may not balance unmeasured covariates. Despite a relatively modest sensitivity of our findings to an unmeasured covariate, for such a covariate to become a confounder, in addition to be a near-perfect predictor of HF hospitalization plus all-cause mortality it must also be associated with SBP and should not be strongly correlated with any of the 32 baseline characteristics.

Considering the strong correlation between various clinical covariates, it seems unlikely. Finally, the findings of this study need to be replicated in more contemporary HF patients. In conclusion, in patients with mild to moderate chronic systolic and diastolic HF, baseline SBP ≤120 mm Hg is associated with poor clinical outcomes.

Acknowledgments

"The Digitalis Investigation Group (DIG) study was conducted and supported by the NHLBI in collaboration with the DIG Investigators. This manuscript was prepared using a limited access dataset obtained by the NHLBI and does not necessarily reflect the opinions or views of the DIG Study or the NHLBI."

Funding/Support: Dr. Ahmed is supported by the National Institutes of Health through grants (R01-HL085561 and R01-HL097047) from the National Heart, Lung, and Blood Institute and a generous gift from Ms. Jean B. Morris of Birmingham, Alabama

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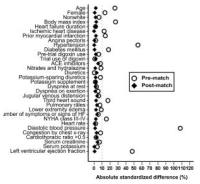

Figure 1.
Love plot for pre-and post-match absolute standardized differences for baseline covariates for patients with systolic blood pressure ≤120 and >120 mm Hg (ACE=angiotensin converting enzyme; HF=heart failure; NYHA=New York Heart Association)

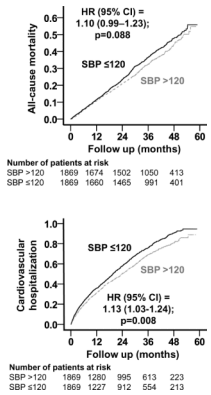

Figure 2.

Kaplan-Meier plots for all-cause mortality (top panel) and cardiovascular hospitalization (bottom panel) by systolic blood pressure (SBP) (CI=confidence interval; HR=hazard ratio)

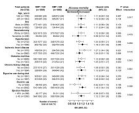

Figure 3.
Hazard ratio and 95% confidence interval (CI) for all-cause mortality associated with systolic blood pressure (SBP) ≤ 120 mm Hg in subgroups of matched patients with heart failure

Table 1

Baseline characteristics of heart failure patient, by systolic blood pressure (BP), pre and post–propensity score matching

	Pre-match			Post-match		
	Systolic BP (mm Hg)			Systolic BP (mm Hg)		
	>120 (n = 4247)	≤120 (n = 3538)	P Value	>120 (n = 1869)	≤120 (n = 1869)	P Value
Age (years)	65 ± 10	62 ± 11	<0.001	64 ± 10	64 ± 11	0.511
Female	1163 (27%)	762 (22%)	<0.001	438 (23%)	444 (24%)	0.847
Non-white	657 (16%)	470 (13%)	0.006	254 (14%)	242 (13%)	0.595
Body mass index (kg/m^2)	28 ± 6	27 ± 5	<0.001	27 ±5	27 ±6	0.410
Duration of heart failure (months)	30 ±37	29 ±35	0.434	30 ±37	30 ±36	0.565
Primary cause of heart failure						
Ischemic	2811 (66%)	2548 (72%)	<0.001	1330 (71%)	1330 (71%)	0.223
Hypertensive	622 (15%)	182 (5%)		150 (8%)	133 (7%)	
Idiopathic	545 (13%)	565 (16%)		261 (14%)	293 (15%)	
Others	269 (6%)	243 (7%)		128 (7%)	113 (6%)	
Prior myocardial infarction	2546 (60%)	2361 (67%)	<0.001	1237 (66%)	1217 (65%)	0.507
Current angina pectoris	1170 (28%)	944 (27%)	0.392	520 (28%)	524 (28%)	0.913
Hypertension	1159 (59%)	2514 (33%)	<0.001	792 (42%)	794 (43%)	0.972
Diabetes mellitus	1366 (32%)	852 (24%)	<0.001	519 (28%)	524 (28%)	0.883
Chronic kidney disease	2017 (48%)	1508 (43%)	<0.001	854 (46%)	840 (45%)	0.646
Medications						
Pre–trial digoxin use	1780 (42%)	1584 (45%)	0.011	811 (43%)	831 (45%)	0.529
Trial use of digoxin	2131 (50%)	1757 (50%)	0.650	938 (50%)	919 (50%)	0.554
ACE inhibitors	3929 (93%)	3343 (95%)	<0.001	1740 (93%)	1745 (93%)	0.793
Nitroglycerine and hydralazine	80 (2%)	31 (1%)	<0.001	20 (1%)	23 (1%)	0.761
Diuretics	3311 (78%)	2762 (78%)	0.911	1464 (78%)	1438 (77%)	0.338
Potassium-sparing diuretics	284 (7%)	312 (9%)	<0.001	146 (8%)	156 (8%)	0.581
Potassium supplement	1185 (28%)	1013 (29%)	0.476	545 (29%)	529 (28%)	0.595
Symptoms and signs of heart failure						
Dyspnea at rest	922 (22%)	782 (22%)	0.676	395 (21%)	381 (20%)	0.602
Dyspnea on exertion	3155 (74%)	2705 (77%)	0.027	1422 (76%)	1410 (75%)	0.673

Am J Cardiol. Author manuscript; available in PMC 2012 April 15.

	Pre-match			Post-match		
	Systolic BP (mm Hg)			Systolic BP (mm Hg)		
	>120 (n = 4247)	≤120 (n = 3538)	P Value	>120 (n = 1869)	≤120 (n = 1869)	P Value
Jugular venous distension	519 (12%)	501 (14%)	0.012	251 (13%)	227 (12%)	0.249
Third heart sound	864 (20%)	981 (28%)	<0.001	455 (24%)	435 (23%)	0.471
Pulmonary rales	657 (16%)	644 (18%)	<0.001	314 (17%)	289 (16%)	0.272
Lower extremity edema	961 (23%)	672 (19%)	<0.001	393 (21%)	375 (20%)	0.489
Number of symptom/signs	5.4 ±2.0	5.5 ±2.0	0.021	5.5 ±2.0	5.5 ±2.0	0.251
New York Heart Association						
Class I	650 (15%)	453 (13%)		254 (14%)	267 (14%)	
Class II	2404 (57%)	1838 (52%)		1026 (55%)	1038 (56%)	
Class III	1127 (27%)	1159 (33%)		557 (30%)	538 (29%)	
Class IV	66 (2%)	88 (3%)		32 (2%)	26 (1%)	
Heart rate (beats /minute)	78 ±12	79 ±13	0.393	78 ±12	78 ±13	0.819
Diastolic blood pressure (mm Hg)	80 ±11	69 ±9	<0.001	74 ±9	74 ±8	0.578
Chest radiograph findings						
Pulmonary congestion	550 (13%)	559 (16%)	<0.001	276 (15%)	256 (14%)	0.365
Cardiothoracic ratio >0.5	2541 (60%)	2148 (61%)	0.429	1115 (60%)	1086 (58%)	0.349
Serum creatinine (mg/dL)	1.29 ±0.38	1.27±0.36	0.004	1.29±0.38	1.27 ±0.36	0.208
Serum potassium (mEq/L)	4.33 ±0.44	4.34 ±0.44	0.078	4.35 ±0.44	4.35 ±0.45	0.923
LV ejection fraction (%)	35 ±13	29 ±11	<0.001	31 ±11	31 ±12	0.834
LV ejection fraction >45%	725 (17%)	263 (7%)	<0.001	177 (10%)	211 (11%)	0.068

ACE =angiotensin-converting enzyme; HF=; LV=left ventricular

Table 2

Baseline systolic blood pressure (SBP) and mortality

Events, n (%)	Systolic blood pressure (mm Hg)		Absolute risk increase*	Hazard ratio† (95% CI)	p value
	>120	≤120			
Pre-match	(n=4247)	(n=3538)			
All-cause	1289 (30%)	1316 (37%)	7%	1.31 (1.21–1.41)	<0.001
Cardiovascular	987 (23%)	1064 (30%)	7%	1.38 (1.27–1.51)	<0.001
Heart failure	396 (9%)	511 (14%)	5%	1.66 (1.45–1.89)	<0.001
Other cardiovascular	591 (14%)	553 (16%)	2%	1.20 (1.06–1.34)	0.003
Non-cardiovascular	232 (6%)	178 (5%)	−1%	0.99 (0.81–1.20)	0.894
Unknown	70 (2%)	74 (2%)	0%	1.36 (0.98–1.88)	0.068
Post-match	(n=1869)	(n=1869)			
All-cause	606 (32%)	650 (35%)	3%	1.10 (0.99–1.23)	0.088
Cardiovascular	459 (25%)	514 (28%)	3%	1.15 (1.01–1.30)	0.031
Heart failure	194 (10%)	246 (13%)	3%	1.30 (1.08–1.57)	0.006
Other cardiovascular	265 (14%)	268 (14%)	0%	1.04 (0.87–1.23)	0.682
Non-cardiovascular	110 (6%)	99 (5%)	−1%	0.93 (0.71–1.22)	0.581
Unknown	37 (2%)	37 (2%)	0%	1.03 (0.65–1.62)	0.907

*Absolute risk increase was calculated by subtracting events in the ≤120 SBP group from those in the >120 SBP group.

†Hazard ratios and confidence intervals (CI) when SBP≤120 was compared with SBP>120 mm Hg

Am J Cardiol. Author manuscript; available in PMC 2012 April 15.

Table 3

Baseline systolic blood pressure (SBP) and hospitalization

Events, n (%)	Systolic blood pressure (mm Hg)		Absolute risk increase*	Hazard ratio† (95% CI)	p value
	>120	≤120			
Pre-match	(n=4247)	(n=3538)			
All-cause	2779 (65%)	2347 (66%)	1%	1.08 (1.03–1.15)	0.004
Cardiovascular	2129 (50%)	1880 (53%)	3%	1.15 (1.08–1.22)	<0.001
Heart failure	1136 (27%)	1150 (33%)	6%	1.33 (1.22–1.44)	<0.001
Myocardial infarction	266 (6%)	184 (5%)	1%	0.88 (0.73–1.06)	0.177
Unstable angina pectoris	504 (12%)	437 (12%)	0%	1.11 (0.98–1.26)	0.112
Post-match	(n=1869)	(n=1869)			
All-cause	1203 (64%)	1255 (67%)	3%	1.10 (1.02–1.19)	0.017
Cardiovascular	918 (49%)	985 (53%)	4%	1.13 (1.03–1.24)	0.008
Heart failure	496 (27%)	576 (31%)	4%	1.21 (1.07–1.36)	0.002
Myocardial infarction	117 (6%)	106 (6%)	0%	0.92 (0.71–1.20)	0.549
Unstable angina pectors	216 (12%)	255 (14%)	2%	1.23 (1.02–1.47)	0.028

*Absolute risk increase was calculated by subtracting events in the ≤120 SBP group from those in the >120 SBP group.

†Hazard ratios and confidence intervals (CI) when SBP ≤120 was compared with SBP>120 mm Hg