Systolic Blood Pressure and Risk for Ventricular Arrhythmia in Patients With an Implantable Cardioverter Defibrillator

Roy Beinart, MD[a], Ilan Goldenberg, MD[b], Arwa Younis, MD[b], Scott McNitt, MS[b], David Huang, MD[b], Mehmet K. Aktas, MD[b], Rosero Spencer, MD[b], Valentina Kutyifa, MD[b], and Eyal Nof, MD[a,*]

Low systolic blood pressure (SBP) was previously suggested to be a marker for heart failure and mortality in patients with low left ventricular ejection fraction. We aimed to explore the association of SBP on risk of ventricular tachyarrhythmias (VTA) and atrial arrhythmias as well as appropriate and inappropriate Implantable Cardioverter Defibrillator (ICD) therapy. The study population comprised 1,481 of 1,500 (99%) patients enrolled in the Multicenter Automatic Defibrillator Implantation Trial − Reduce Inappropriate Therapy trial. Multivariate Cox proportional hazards regression modeling was used to identify the association of baseline SBP (recorded prior to ICD implantation) with the risk of VTA > 170 beats/min during follow-up (primary end point) and atrial arrhythmia, appropriate and inappropriate ICD therapy, hospitalization and death (secondary end points). SBP was dichotomized at 120 mm Hg (approximate mean and median) and was also assessed as a continuous measure. Multivariate analysis showed that each 10 mm Hg decrement in SBP was associated with corresponding 11% increased risk for VTA (p = 0.008). Low SBP (≤120 mm Hg) was associated with a significant 58% (p = 0.002) increased risk for VTA ≥170 beats/min; 53% (p = 0.019) increased risk for VTA ≥200 beats/min; and 65% (p = 0.001) increased risk for appropriate ICD therapy, as compared with SBP >120 mm Hg. Low SBP was not associated with increased risk of atrial arrhythmias, and inappropriate ICD therapy. In conclusion, in MADIT-RIT, SBP (≤120 mm Hg) predicted higher rates of VTA. These findings suggest that SBP may be utilized for VTA risk stratification in candidates for primary ICD therapy. **(Am J Cardiol 2021;143:74−79)**

Blood pressure (BP) is an established risk factor for cardiovascular disease.[1,2] In most studies systolic BP (SBP), mean BP but not diastolic (DBP) was shown to directly correlate with the risk of cardiovascular disease.[3] Our group showed previously an inverse relation between BP and clinical events in heart failure patients. Specifically, low SBP was shown to be associated with higher risk of mortality, heart failure (HF)[4,5] and sudden cardiac death in patients with low left ventricular ejection fraction (LVEF).[5] However, data on the association of SBP and the risk of ventricular tachyarrhythmias (VTA) or Implantable Cardioverter Defibrillator (ICD) shocks in low LVEF patients are limited. The Multicenter Automatic Defibrillator Implantation Trial − Reduce Inappropriate Therapy (MADIT-RIT) trial was a randomized study designed to evaluate the role of various programming features to reduce inappropriate therapy in patients with primary prevention ICD or Cardiac resynchronisation therapy (CRT) indications. It compared standard programming parameters to either high-rate therapy (≥200 beats/min) or long delays before therapy delivery.[6] All arrhythmic events (both treated and monitored) in the trial were evaluated by an independent adjudication committee. Thus, MADIT-RIT provides a unique opportunity to evaluate the association of SBP with cardiac arrhythmias in patient with low LVEF.

Methods

MADIT-RIT was a multicenter, randomized, prospective, controlled clinical trial evaluating patients with approved indications for primary prevention ICD or CRT therapy. The trial design and results have been published elsewhere.[6] Briefly, patients were randomized to standard ICD programming (arm A), a high-rate therapy cutoff (≥200 beats/min) programming strategy (arm B), or a prolonged detection duration (60-second delay for ventricular tachycardia [VT] zone 170−199 beats/min, 12-second delay for VT 200 to 249 beats/min, and 2.5-second delay for VF zone ≥250 beats/min) strategy (arm C) after successful implantation of a dual-chamber ICD or CRT device. The protocol was approved by the institutional review board at each of the participating centers. All patients provided written informed consent.

The MADIT-RIT trial enrolled 1,500 patients aged ≥21 years with ischemic or non-ischemic systolic heart

[a]Leviev Heart Institute and Sackler School of Medicine Tel Aviv University, Israel; and [b]Heart Research Follow-up Program, University of Rochester Medical Center, Rochester NY. Manuscript received September 18, 2020; revised manuscript received and accepted December 1, 2020.

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*Corresponding author: Tel: 9723 5302608.

E-mail address: eyalnof.dr@gmail.com (E. Nof).

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failure. All patients met the guideline criteria for primary prevention implantation of an ICD or CRT-D.[7] Patients were excluded from the trial for various reasons described elsewhere.[8] The analysis was performed on an efficacy basis; patients were censored at the time of device reprogramming, and therefore, patients who had programming deviations during the follow-up are not represented in this analysis. The present study population comprised 1,481 (99%) MADIT-RIT patients for whom baseline SBP was recorded prior to device implantation.

Patients had follow-up visits every 3 months during the first year and every 6 months thereafter. During each visit, an interim history was taken and a physical examination and ICD interrogation were performed. Data were transmitted to the study Coordination and Data Center at the University of Rochester, Rochester, New York.

During the duration of the study and for all patients, episodes with available intra-cardiac electrograms were collected from the device interrogations and adjudicated by an independent panel on the basis of prespecified criteria. Episodes were classified as appropriate and inappropriate therapies. Inappropriate therapy was defined as any therapy (ATP or shock) delivered for supraventricular rhythms (sinus tachycardia, atrial fibrillation, atrial flutter, regular supraventricular tachycardia including atrial tachycardia, atrioventricular reentry tachycardia, and atrioventricular tachycardia) or non-arrhythmic events such as electromechanical interference, oversensing, ICD lead noise, or myo-potentials. Notably, given the memory limitations of all ICDs, the arrhythmic events were stored chronologically in such a way that the electrograms of prior events could sometimes be erased from the device memory to allow the display of the most recent events. For those patients who had recurrent therapies that exceeded the memory capabilities of the device, only those that could be adjudicated were included for analysis.

Patients were divided into 2 SBP categories based upon approximate median SBP: lower SBP (≤120 mm Hg) and higher BP (>120 mm Hg). In addition, SBP was also assessed as a continuous measure. In a secondary analysis the >120 mmHg subgroup was further dichotomized at the approximate upper quartile (134 mm Hg) to assess the consistency of our findings within the higher SBP subset.

The primary end point of the current study was the first occurrence of ventricular tachyarrhythmia (VTA) ≥170 beats/min (treated or monitored) during the follow-up. Secondary end points were VTA≥200 beats/min, the composite end point of VTA or death, atrial arrhythmia, appropriate, inappropriate therapy.

Continuous variables are expressed as mean ± standard deviation. Categorical data are summarized as frequencies and percentages. Baseline clinical characteristics were compared between patients with SBP≤120 mm Hg and with SBP>120 mmHg using the Wilcoxon rank-sum test for continuous variables and Chi-square test or Fisher's exact test for dichotomous variables. The cumulative probability of a first event was displayed according to the Kaplan-Meier method, with statistical comparisons of cumulative event rates by the log-rank test.

Multivariate Cox proportional hazards regression analysis was used to identify and evaluate independent predictors of a first event and separate models were developed for arrhythmic and non-arrhythmic end points. The best subsets procedure was used to determine models of varying sizes and all variables needed to be significant at $p < 0.10$ to remain in each model. For the primary arrhythmic end point a violation of the proportional hazards assumption was detected and was remedied by estimating hazard ratios related to high versus low SBP during and after the first 6 months of follow-up. For the arrhythmic end points, the Cox model was adjusted for treatment arm, gender, history of atrial arrhythmias, heart rate, and race. For the end point of VT and/or VF or death, the model was further adjusted for LVEF, heart rate, ischemic status, and NYHA. To evaluate the consistency of our findings by medical therapy, we performed a secondary analysis in which all models were further adjusted for pharmacologic therapy consisting of angiotensin converting enzyme inhibitors (ACE-i), angiotensin receptor blockers (ARB) and beta-blockers.

All statistical tests were 2-sided, and $p < 0.05$ was considered statistically significant. The analyses were performed with SAS software (version 9.4, SAS Institute, Cary, North Carolina).

Results

The distribution of SBP in study patients is presented in Figure 1, showing a normal distribution with a mean SBP of 123 ± 19 mm Hg and a median of 121 mm Hg (IQ range 96 to 146). Among 1481 study patients, 727 (49%) patients had lower SBP and 754 (51%) had higher SBP. Relevant baseline clinical characteristics of patients with SBP≤120 mm Hg and SBP >120 mm Hg are shown in Table 1. Patients with SBP≤120 mm Hg were younger, were less likely to have diabetes mellitus and had a lower LVEF. They were also less likely to be treated with antihypertensive drugs, but were more likely to be treated with aldosterone blockers and digitalis. Notably, they had higher rates of past episodes of ventricular arrhythmias.

Kaplan−Meier survival analysis showed that the cumulative probability of the primary end point was significantly higher in patients who had lower SBP at baseline than in those who had higher SBP: at 2-years of follow-up the rate of VTA > 170 beats/min was 21% in patients with low SBP as compared with 13% in those with SBP > 120 mm Hg (log-rank $p < 0.001$ for the overall difference during follow-up; Figure 2]). Similar findings were shown for the composite end point of VTA > 170 beats/min or death, demonstrating a significantly higher event rate at 2 years in patients with baseline SBP ≤ 120 mm Hg (25%) as compared with those with baseline SBP > 120 mm Hg (19%, log-rank $p = 0.004$ for the overall difference during follow-up; Figure 2). In addition, lower SBP was associated with increased rate of VTA ≥200 beats/min and appropriate ICD therapy (Figure 3, respectively).

Furthermore, a secondary analysis consistency showed that SBP > 120 mm Hg subgroups were associated with a significantly lower rate of VTA events compared with SBP ≤ 120 mm Hg (Figure 4). However, SBP ≤ 120 mmHg was not associated with increased mortality (Figure 5).

Multivariate Cox proportional hazards regression analysis, showed that low SBP (≤120 mm Hg) was associated with a significant 58% ($p = 0.002$) increased risk for VTA

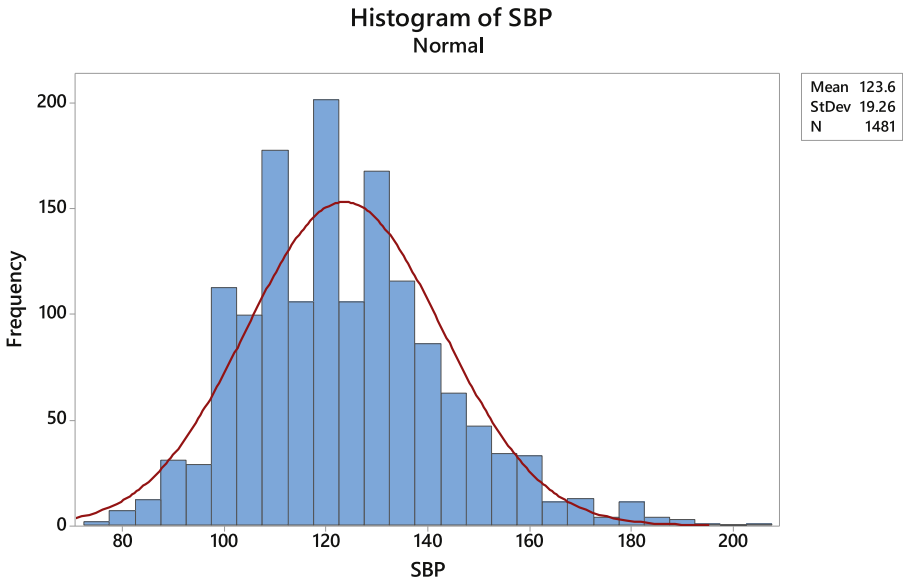

Figure 1. The frequency of systolic blood pressure (SBP) distribution in MADIT-RIT patient population.

Table 1
Clinical characteristics of the patients stratified by baseline systolic blood pressure groups

Variable	Systolic Blood Pressure (mmHg) ≤ 120 (n=727)	>120 (n=754)	p-value
Age (years mean ± SD)	61±12	65±11	**<0.001**
Women	213 (29%)	215 (29%)	0.739
QRS(ms, mean ± SD)	153±23	154±20	0.183
EF (%, mean ± SD)	25±7	27±6	**<.001**
Ischemic	376 (52%)	408 (54%)	0.342
Diabetes Mellitus	204 (28%)	277 (37%)	**<0.001**
Anti-Hypertensive Drugs	425 (59%)	594 (79%)	**<0.001**
Currently Smoker	135 (19%)	109 (15%)	**0.040**
Ventricular Arrhythmias at baseline	33 (5%)	15 (2%)	**0.006**
Atrial Arrhythmias at baseline	97(13%)	105(14%)	0.753
Prior CABG	157 (22%)	210 (28%)	**0.005**
Prior Myocardial Infarction	313 (44%)	319 (44%)	0.864
White	543 (75%)	563 (76%)	0.872
Body Mass Index (kg/m^2 ± SD)	28.8±6.8	29.7±6.8	**0.004**
Systolic Blood Pressure (mmHg, mean ± SD)	108.2±9.2	138.4±14.1	N/A
Diastolic Blood Pressure (mmHg, mean ± SD)	67.3±9.0	78.3±11.6	**<.001**
Resting Heart Rate (bpm, mean ± SD)	73.2±12.3	71.0±12.6	**<.001**
Anti-Arrhythmic (Class I)	11 (2%)	3 (0%)	**0.027**
Amiodarone	51 (7%)	45 (6%)	0.413
Sotalol	4 (1%)	9 (1%)	0.184
ACE Inhibitor	500 (69%)	501 (66%)	0.338
Angiotensin Receptor Blocker	144 (20%)	169 (22%)	0.219
Beta-blockers	680 (94%)	709 (94%)	0.692
Digitalis	107 (15%)	84 (11%)	**0.040**
Aldosterone Blockers	310 (43%)	228 (30%)	**<0.001**
Diuretic	503 (69%)	496 (66%)	0.162
Calcium Channel Blocker	39 (5%)	80 (11%)	**<.001**
Statins	404 (56%)	465 (62%)	**0.017**
Lipid Lowering Agents (not Statins)	58 (8%)	70 (9%)	0.371

* N/A = Not Applicable.

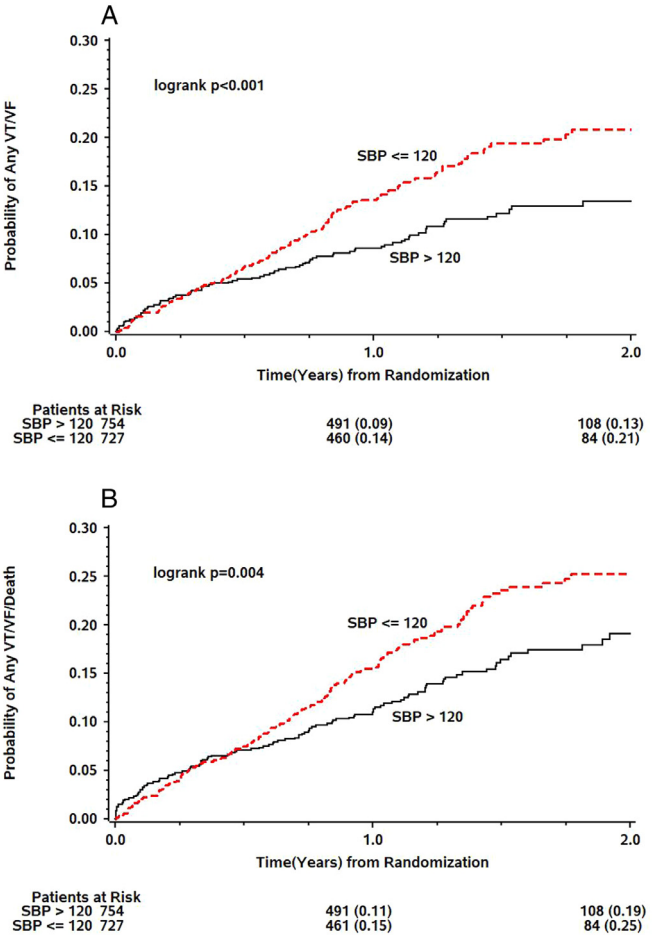

Figure 2. (A) Cumulative incidence of ventricular tachycardia ≥170 beats/min in patients with SBP≤120 mm Hg versus SBP>120 mm Hg. (B) Cumulative incidence of ventricular tachycardia ≥170 beats/min or death in patients with SBP≤120 mm Hg versus SBP>120 mm Hg.

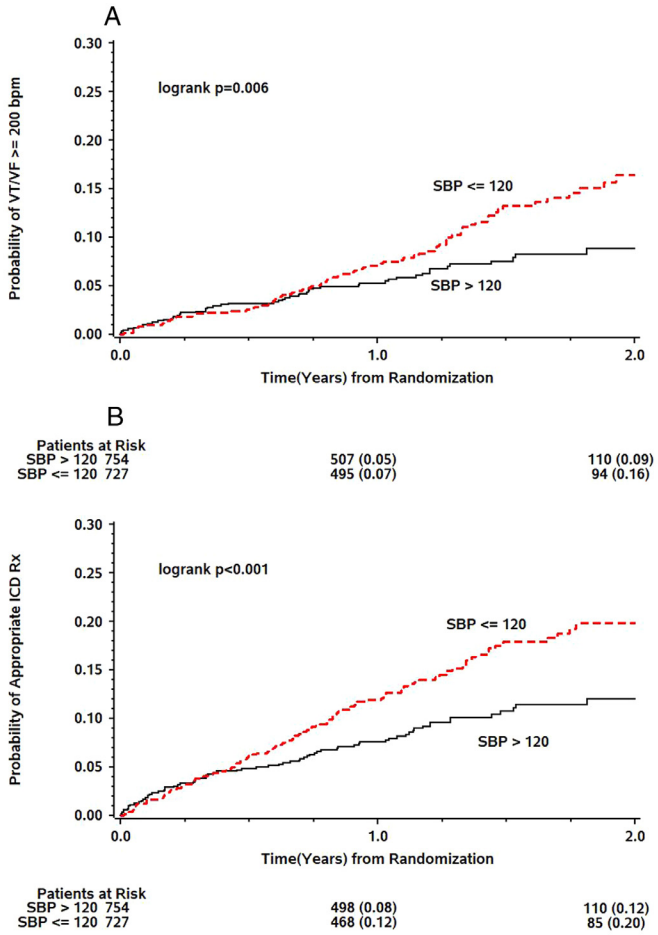

Figure 3. (A) Cumulative incidence of ventricular tachycardia ≥200 beats/min in patients with SBP≤120 mm Hg versus SBP>120 mm Hg. (B) Cumulative incidence of appropriate ICD therapy in patients with SBP≤120 mm Hg versus SBP>120 mm Hg.

≥170 beats/min; 53% (p = 0.019) increased risk for VTA ≥200 beats/min; and 65% (p = 0.001) increased risk for appropriate ICD therapy, as compared with SBP >120 mm Hg. Assessment of SBP as a continuous measure showed that each 10 mm Hg decrement in SBP was associated with corresponding 11% increased risk for primary end point (HR, 1.10; 95% CI, 1.02 to1.20; p = 0.008).

Consistent with the univariate Kaplan-Meier findings showing that risk for VTA became significant only at 6 months follow up and thereafter, multivariate Cox proportional hazards regression analysis showed that low SBP was associated with a significant 97% increased risk for the primary end point of VTA > 170 beats/min at 6 months [hazard ratio (HR), 1.97; 95% confidence interval (CI), 1.35 to 2.88; p = 0.001] when compared with SBP > 120 beats/min (Table 2). Similarly, lower SBP at was associated with a 78% (p = 0.001), increased risk for the composite end point of VTA >170 beats/min or death; a 118% (p = 0.001) increased risk for VT≥200 beats/min; and a significant 104% (p=0.001) increased risk for appropriate ICD therapy. All at 6 months follow up (Table 2). All findings were consistent after further adjustment for treatment with ACEi, ARBs and beta-blockers.

Kaplan-Meier survival analysis showed that at 2 years of follow-up the cumulative probability of inappropriate ICD therapy was similarly between patient with SBP ≤ 120 mm Hg as compared with those with SBP > 120 mm Hg (12% vs 13%, respectively; log-rank p value = 0.89 for the overall difference during follow-up). Similarly, multivariate analysis showed that low SBP was not associated with a significant increase in the risk of inappropriate ICD therapy (HR=1.02 [95% CI 0.73 to 0.41] p = 0.92) and of atrial arrhythmias (HR=1.13 [95% CI 0.89 to 1.44; p = 0.322).

Discussion

The main finding of this study is that patients with indication for ICD or CRT-D implantation and with lower SBP at baseline (≤120 mm Hg) are at greater risk for ventricular tachyarrhythmia compared with those with higher baseline SBP.

Elevated SBP has been described a surrogate marker for VTA events in large population studies[1,3,9] and in patients with HF, albeit with preserved ejection fraction (EF).[10] There are many mechanistic explanations for these finding. A possible common pathway in patients with preserved LVEF is mechanical-electrical association leading to left ventricular (LV) stress and hypertrophy, resulting in arrhythmic events. However, our patient population had different characteristics: all MADIT-RIT patients, by definition, had HF with low EF. In contrast to patients with preserved cardiac function, in patients with HF and a low LVEF, previous studies have shown that an inverse correlation between SBP and the risk of adverse events.[4,5,11]

Our study is in agreement with the previous ones. We found an association between lower SBP and life threatening VTA including appropriate ICD shocks. These finding remain valid even after adjusting for anti- hypertensive medication including ACEi and/or ARBs and beta-blockers. Hence, rates of VTA were not related to over- or under treatment of medications. Interestingly, there was no association with nonlife threatening arrhythmias, such as atrial fibrillation, atrial flutter, and supra-ventricular tachycardia. Our hypothesis is that in large and failing ventricles elevated SBP has less effect on the ventricle in terms of shear stress and overload and therefore is not associated with VTA. In contrast, the relatively low SBP despite increased sympathetic activity in low EF patients plays a significant role in electrical and contractile functions of the heart. This imbalance could lead to the generation of ventricular arrhythmia.[12] The ability to maintain elevated SBP in those with SBP > 120 mm Hg despite low EF may indicate better myocardial reserve. This translates into less VTA.

The MADIT-RIT enrolled only patients with primary prevention ICD indication. Although ICDs have been shown to increase survival in patients with cardiomyopathy and severe LV dysfunction,[13] most patients will not use it and/or receive an ICD therapy throughout their life time.[14,15] Thus, there is a need for improved risk stratification to identify those who would eventually benefit from ICD implantation. Our finding may suggest that a simple non-invasive measure such as SBP should be taken in account, as patients with SBP>120 mm Hg are at

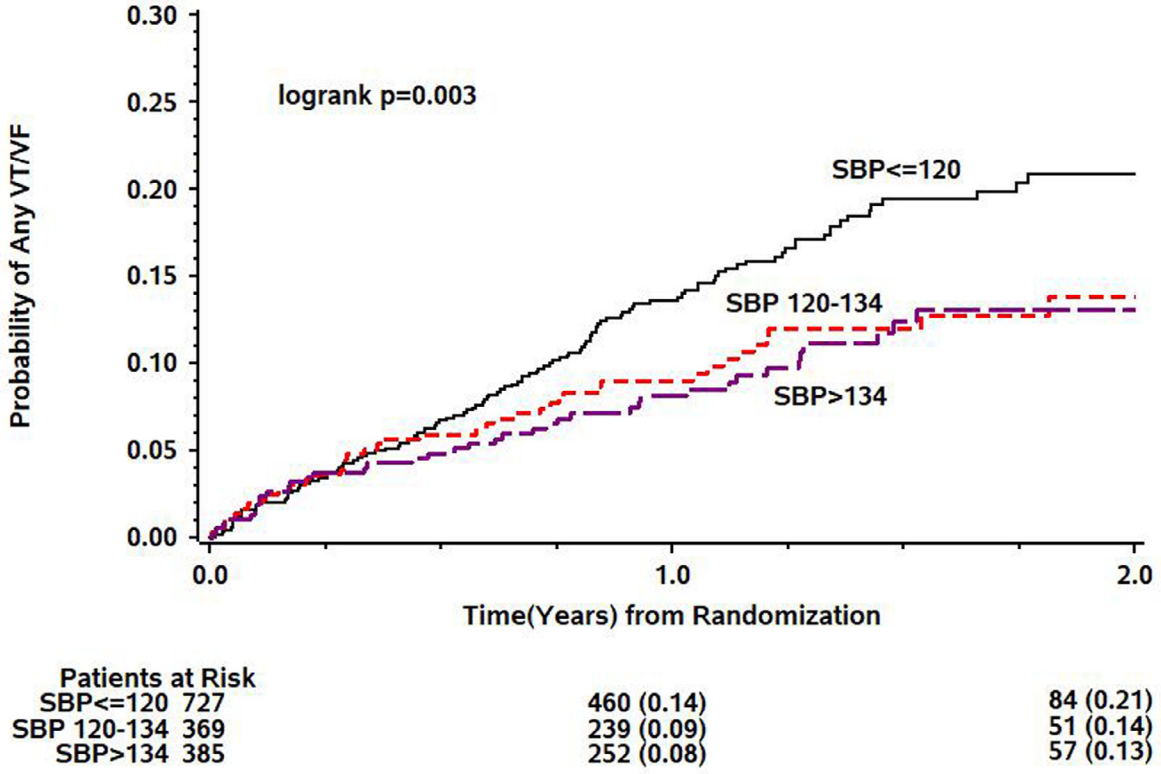

Figure 4. Secondary analysis of the >120 mm Hg subgroup further dichotomized at the approximate upper quartile (134 mm Hg) showing the consistency of the fact that higher SBP was associated with a significantly lower rate of VTA events compared with SBP≤120 mm Hg.

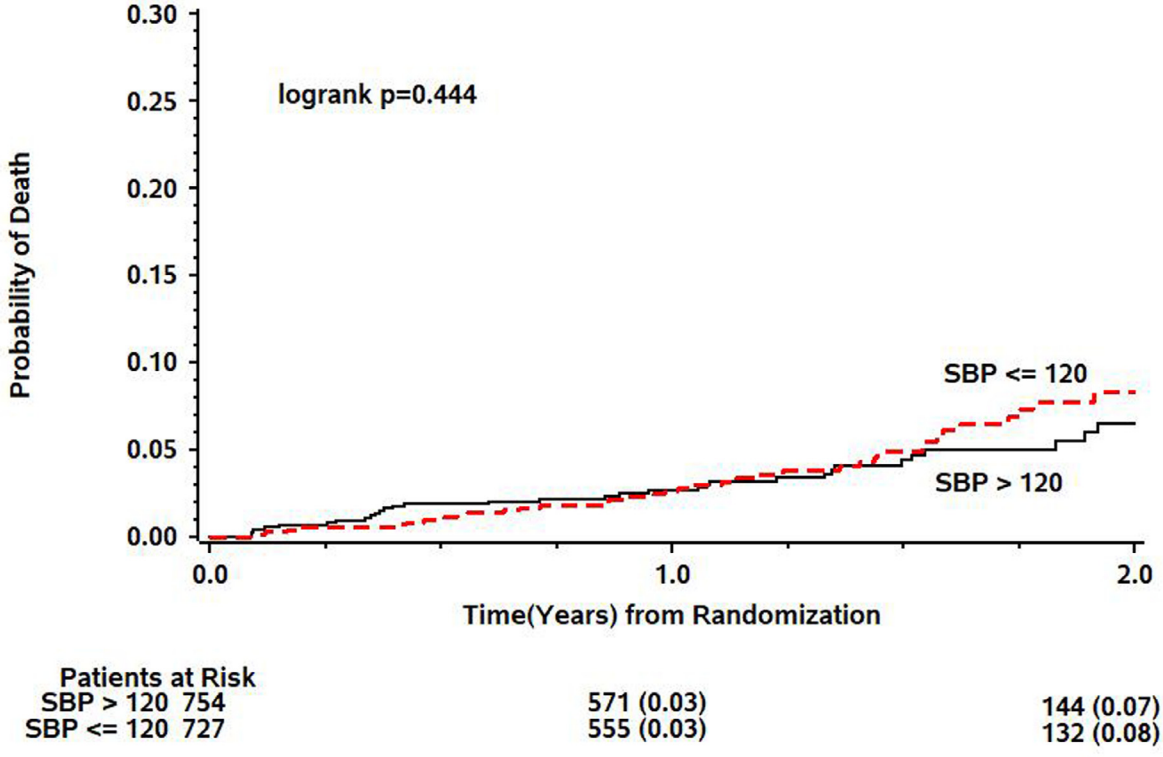

Figure 5. Secondary analysis showing the cumulative incidence of death in patients with SBP≤120 mm Hg versus SBP>120 mm Hg.

Table 2
Multivariate analysis: association of SBP≤120 mm Hg with ventricular arrhythmias

Endpoint	Time Period (months)	Hazard ratio	95% CI	p-value
Any VT/VF	<= 6	1.17	0.75 − 1.8	**0.4903**
	> 6	1.97	1.35-2.88	**0.001**
VT ≥200	<= 6	0.75	0.41-1.40	**0.369**
	> 6	2.18	1.39-3.4	**0.001**
Appropriate ICD therapy	<= 6	1.26	0.8 -1.98	**0.328**
	> 6	2.04	1.36-3.06	**0.001**
VT>170 or Death	<= 6	1.01	0.69-1.45	**0.945**
	> 6	1.78	1.27-2.48	**0.001**

The models are adjusted for age at enrollment, prior atrial arrhythmia before enrollment, type of cardiomyopathy (ischemic vs nonischemic), type of device (ICD vs CRT-D), gender and EF at enrollment.

* VT = Ventricular Tachycardia; VF = Ventricular fibrillation; EF = Ejection fraction.

significantly lower risk for VTA. Perhaps in those, the benefit of primary defibrillator implantation is more limited.

There are several limitations to this study. First, this is a nonrandomized post hoc study. Second, there are several clinical differences between the 2 groups. However, the analysis was adjusted for these differences. BP lowering medications such as Beta-blockers and ACE inhibitors have been shown to prolong life in this high-risk population, and should be administered to every patient with advanced LV dysfunction. Although there were no differences between groups in number of patients on the above mentioned medications, it is possible that those with lower SBP were on higher dosages. Whether, decreasing the dosages and improving SBP, would lead to a decrease in arrhythmic events is not known as dosages of medications were not collected in the MADIT- RIT study.

In conclusion, patients who are candidate for ICD or CRT-D, low SBP is associated with higher risk of VTA and appropriate ICD therapy, but not atrial arrhythmia. Hence, our data suggest that SBP may be used for VTA risk stratification in ICD candidates for primary prevention of sudden cardiac death.

Credit Author Statement

Eyal Nof, Roy Beinart, Ilan Goldenberg:Conceptualization, Methodology, Writing- Original draft preparation; Arwa Younis, David Huang, Mehmet K. Aktas , Rosero Spencer and Valentina Kutyifa: Methodology , Visualization, Investigation. Scott McNitt: Statistical Ananlysis

Disclosures

The authors declare that they have no known competing financial interests or personal relations that could have appeared to influence the work reported in this study.

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