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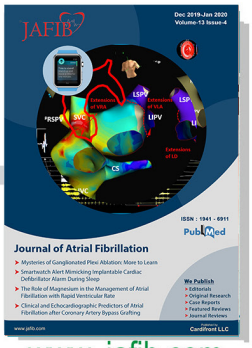

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Effect of Intensive Blood Pressure Lowering on Incident Atrial Fibrillation: A Systematic Review and Meta-Analysis

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Abstract

The effect of intensive versus standard blood pressure (BP) lowering on the risk of atrial fibrillation (AF) is uncertain. Intensive BP lowering is associated with a lower risk of AF among patients with hypertension. We searched PubMed, EMBASE, and CENTRAL (inception to June 5, 2020) for randomized controlled trials evaluating the effect of intensive versus standard (target systolic BP < 140 mmHg) BP lowering on incident AF. We assessed heterogeneity using the I2 statistic then usedfixed-effects meta-analysis models to report pooled treatment effects and 95% confidence intervals. We also tested for publication bias by three funnel plot-based methods. The quality of each study was assessed with the Cochrane Risk of Bias tool. We assessed 16 candidate studies for eligibility from 2,312 published articles, but only three randomized clinical trials were eligible for inclusion and included a combined 12,219 participants with hypertension: Cardio-Sis (Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica), ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial), and SPRINT (Systolic Blood Pressure Intervention Trial). The target systolic BP in the intensive BP arm was <120 mmHg for participants in SPRINT and ACCORD-BP, but <130 mmHg for participants in Cardio-Sis. Participants randomized to intensive BP lowering had significantly lower risk of incident AF compared with those randomized to standard BP lowering (AF incidence 2.2% vs. 3.0%, respectively; pooled hazard ratio (95% confidence interval): 0.74 (0.59 – 0.93)).Intensive BP lowering is associated with a significantly lower risk of incident AF in patients with hypertension. These findings add to the current evidence supporting the benefits of intensive BP control.

Introduction

Atrial fibrillation (AF) is the most common arrhythmia and is associated with a five-fold increased risk of ischemic stroke and a two-fold increased risk of death.[1-4]The prevalence of atrial fibrillation continues to increase and is projected to exceed 12 million in the US alone by 2030,[5,6] which has led to calls for additional research exploring primary prevention of AF.[7] In observational studies, there is a strong relationship between blood pressure and the risk of AF, with hypertension accounting for the largest population attributable fraction of risk of incident AF.[8] There is mounting evidence that intensive blood pressure lowering can decrease the risk of death, atherosclerotic cardiovascular disease, heart failure, and stroke.[9,10] However, the extent to which the risk of AF can be decreased by intensive blood pressure lowering remains uncertain.[11,12] Therefore, a systematic review and meta-analysis was performed to determine whether intensive blood pressure lowering is associated with a reduced risk of incident AF.

Key Words

Atrial Fibrillation, Blood Pressure, Hypertension, Intensive, Meta-Analysis

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Methods

We performed a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines.[13] We searched PubMed, EMBASE, and CENTRAL for articles published from inception to June 1st, 2020, without language or other restrictions. Search terms included: atrial fibrillation AND (blood pressure OR hypertens* OR antihy pertens* OR anti-hypertens*) AND (placebo OR control*) AND random. One author (MJS) screened titles and abstracts. For relevant articles, full texts were retrieved and reviewed. The reference lists from all included trials were also reviewed for relevant articles. Trials were eligible for inclusion in the meta-analysis if they were randomized clinical trials comparing two intensities of blood pressure management and included incident AF as a reported outcome in any analysis of the trial. Secondary prevention trials of blood pressure lowering for reducing the risk of recurrent AF after catheter ablation were excluded. Control was defined as the standard blood pressure lowering according to the blood pressure guidelines at the time of conducting the study.

Data were extracted by author MJS using a standardized data extraction form. All included studies and their extracted data were independently reviewed by JY and ES. The primary out come of this meta-analysis was incident AF. We utilized the Cochrane Risk of Bias tool version 2 to assess the quality of the included studies.[14] Domains of assessment included selection bias, performance bias, detection bias, attrition bias, and reporting bias. Hazard ratios (HRs) and 95% confidence intervals (95% CI) were taken from each trial. Chi-squared analysis was used to quantify the degree of heterogeneity between included studies, with a pre-specified p-value of 0.10 used to define significant heterogeneity. Variability and heterogeneity across studies was further assessed using a forest plot and I2 statistics. Weighted pooled treatment effects were calculated using a fixed-effects meta-analytic model given the low between-study heterogeneity.[15] Publication bias was assessed using Egger's funnel plot.[16] Pooled absolute and relative risk reductions were calculated. Statistical analysis was performed using RevMan 5.3.[17]

Results

The systematic search strategy of published articles yielded 3,142 articles for review (Figure 1). After excluding duplicates, 2,312 articles were considered for inclusion by reviewing their titles and abstracts. Full texts were retrieved for 16 candidate studies. Of these, one was excluded for being a secondary prevention trial, nine were excluded for not randomizing participants to antihypertensive therapies, and three were excluded for randomizing to a specific class of antihypertensive agent, rather than intensity of therapy, leaving three trials eligible for inclusion in the meta-analysis: Cardio-Sis (Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica),[18] ACCORD-BP (Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial),[19] and SPRINT (Systolic Blood Pressure Intervention Trial).[20]

A descriptive analysis of the participants eligible for this analysis who were initially free of AF from each of the included studies is provided in Table 1. All included studies were open-label randomized clinical trials comparing two intensities of blood pressure control. Two of three were conducted in the USA, while the third was conducted in Italy. Important differences include diabetes being one of the inclusion criteria in ACCORD-BP, but an exclusion in SPRINT and Cardio-Sis. Also, the target systolic blood pressure for the intensive arm was < 120 mmHg in SPRINT and ACCORD-BP, but < 130 mmHg in Cardio-Sis.

Between the three included trials, there were 12,219 participants. The mean age of trial participants was 66.1 ± 8.3 years and 41.0% were women. The mean baseline systolic and diastolic blood pressures were 141.4 ± 15.1 and 79.0 ± 10.9 mmHg, respectively (Table 2). The median duration of follow-up was 3.8 years. The publication year ranged from 2009 to 2020. Risk of bias was assessed in all included studies, with the overall risk being low in all three studies in all domains assessed (Figure 2). The funnel plot was not suggestive of publication bias, with relative symmetry about the cumulative effect size (Figure 3).

Participants assigned to intensive blood pressure lowering achieved lower systolic and diastolic blood pressures than those assigned to standard blood pressure lowering by 12.4 and 7.1 mmHg, respectively.

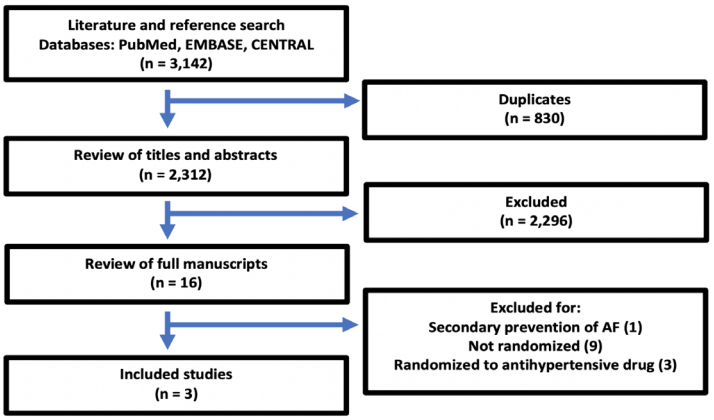

Figure 1: **Study flow for systematic review and meta-analysis.**

Of 2,312 unique articles found during the literature search, 16 full-texts were retrieved and 3 studies met criteria for inclusion in the meta-analysis.

Incident AF was diagnosed in 135 of 6,111 participants in the intensive blood pressure lowering group and 184 of 6,108 in the control group. The effect sizes as hazard ratios ranged from 0.46 to 0.87. In a fixed-effect meta-analytic model, intensive blood pressure lowering was associated with a decreased risk of incident AF (2.2% vs. 3.0%; hazard ratio 0.74, 95% confidence interval 0.59 – 0.93; absolute risk reduction 0.8%, relative risk reduction 27%; Figure 4). The effects were fairly

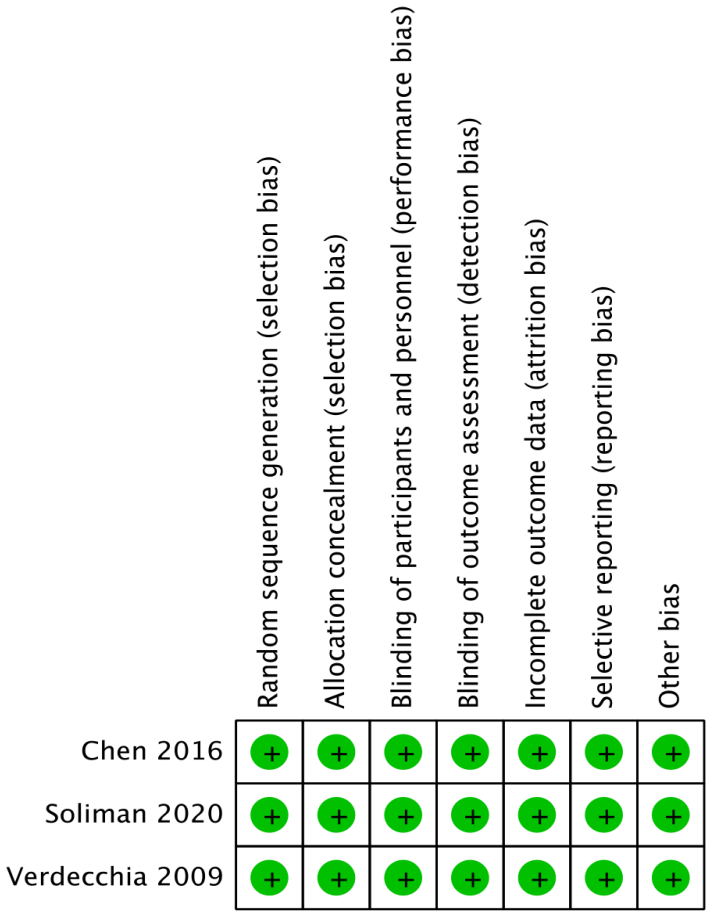

Figure 2: **Risk of bias of included studies.**

All included studies had a low risk of bias in all domains assessed.

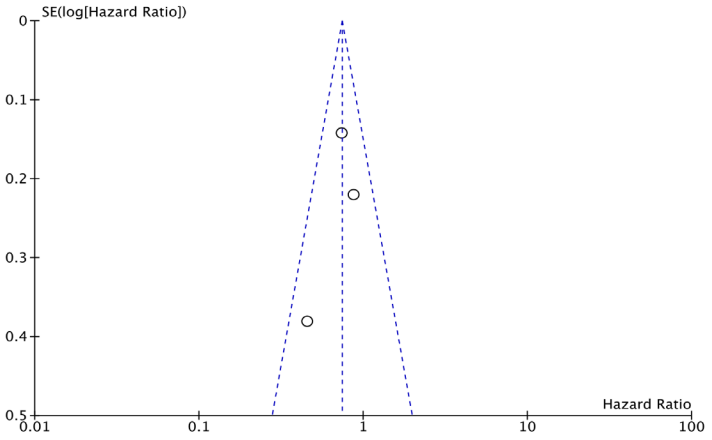

Figure 3: **Funnel plot of included studies.**

Funnel plot depicting the relationship between treatment effect and study precision is not suggestive of publication bias.

consistent across trials with low heterogeneity (I2 = 5%).

Discussion

Principal Findings

This systematic review and meta-analysis, which included three trials with 12,219 participants, found intensive blood pressure lowering compared with standard blood pressure control results in a 26% decreased risk of incident AF. The low degree of heterogeneity suggests that this effect is conserved across multiple patient populations. This meta-analysis adds to the known epidemiological association of blood pressure and AF risk in the literature by providing further evidence that intensive blood pressure lowering as a therapeutic strategy that may lower the risk of AF.

In aggregate, the evidence available from the epidemiological literature strongly supports the association between higher blood pressure and increased risk of incident AF. However, the question of whether intensive blood pressure lowering decreases the risk of incident AF, or if the propensity for AF might be irreversible such that intensive lowering of blood pressure might not have salutary benefits in prevention of AF, has been un answered.[11] Our findings of a consistent benefit of intensive blood pressure lowering in attenuating the risk of AF lends support to the idea that aggressive control of hypertension may decrease the societal burden of AF.

How Low Is Too Low?

Though intensive blood pressure lowering was found to decrease the risk of AF in our analysis, it remains unclear whether there is a lower limit of blood pressure below which there is no further reduction in AF risk, or even an increased risk. This is particularly important if intensive blood pressure lowering is to be considered as a tool for lowering the risk of AF, as the target blood pressure depends on the shape of the curve relating blood pressure to AF risk. One study found evidence of a J-shaped curve relating blood pressure to AF risk, such that patients receiving treatment for hypertension with achieved systolic blood pressure< 120 had double the risk of AF compared to those with achieved systolic blood pressure 120 – 129, though the case-control design may allow for residual confounding.[21] In contrast, in the Women's Health Study, a 10 mmHg increase in systolic blood pressure was associated with a 12% increase in risk of AF.[22] Importantly, this dose-risk relationship was conserved in all strata of blood pressures tested, with continuously-decreasing risk of AF with progressively decreasing blood pressures, including an systolic blood pressure< 120 mmHg stratum. Findings were similar in a study of Norwegian men, with those in the lowest quartile of systolic blood pressure (88 – 116 mmHg) having the lowest risk of AF.[23] An analysis from the ONTARGET/TRANSCEND trials found the group with systolic blood pressure< 120 had the lowest risk of AF.[24] Overall, the epidemiological literature suggests that there is no lower limit of blood pressure target below which the benefit in AF prevention is lost, and these findings are in agreement with the result of our meta-analysis.

Less Benefit In Diabetes?

Of the three trials included in this meta-analysis, only ACCORD-BP did not individually demonstrate a statistically-significant reduction in the risk of incident AF with intensive blood pressure control. This may be explained by ACCORD-BP being underpowered for incident AF, though it should be noted that there were more cases of incident AF in ACCORD-BP than Cardio-Sis. As an alternative explanation, since ACCORD-BP only included participants with diabetes and the other trials specifically excluded participants with diabetes, it is possible that the benefits of intensive blood pressure lowering in decreasing the risk of AF in those with diabetes are less than that seen in those without diabetes. The presence or absence of diabetes may influence the effects of intensive blood pressure lowering on the risk of AF, particularly in light of the fact that intensive blood pressure control has been shown to be beneficial in those without diabetes, but not in those with diabetes, when comparing the SPRINT and ACCORD-BP trials in their primary outcomes.[10,25] It should be noted, however, that although the ACCORD-BP study did not reach statistical significance for reduction in risk of AF, the direction of association still suggested a benefit of intensive blood pressure lowering and the magnitude of the

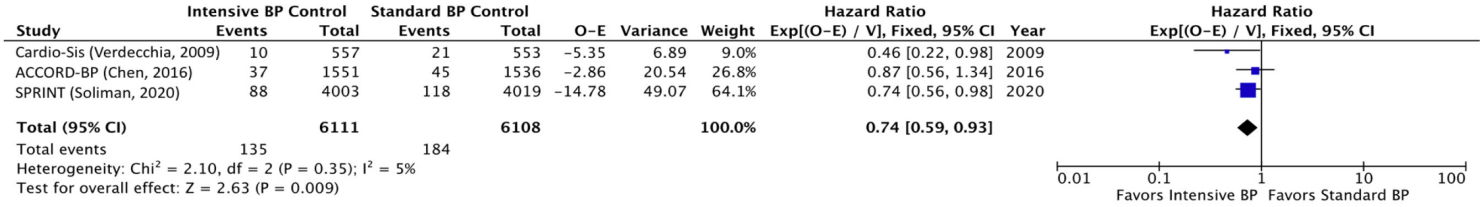

Figure 4: **Association of Intensive Blood Pressure Lowering with Incident Atrial Fibrillation**

The blue squares and bars represent the mean values and 95% confidence intervals of the effect sizes, with the area of the blue squares reflecting the weight of the studies. The black diamond represents the combined effect, with the vertical line representing no association.

Table 1: Participant Baseline Characteristics of Studies Included in Systematic Review and Meta-Analysis of the Association of Blood Pressure Lowering with Incident Atrial Fibrillation

Trial	Trial Design	Country	Study Population	Intervention	Control	Participants	Age mean, SD	Female
Cardio-Sis[18] (2009)	Open-label randomized clinical trial	Italy	Age ≥ 55, SBP ≥ 150 mmHg, no diabetes, no AF	Goal SBP < 130 mmHg	Goal SBP < 140 mmHg	1,111	67.0 (7.0)	59.0%
ACCORD-BP[19] (2016)	Open-label randomized clinical trial	USA	Diabetes, SBP 130 – 180 mmHg, high CVD risk	Goal SBP <120 mmHg	Goal SBP < 140 mmHg	3,087	62.2 (6.6)	48.2%
SPRINT[20] (2020)	Open-label randomized clinical trial	USA	No diabetes, no stroke, LVEF ≥ 35%, SBP 130 – 180, increased CVD risk	Goal SBP <120 mmHg	Goal SBP 135 – 139	8,022	67.7 (9.2)	35.5%

Cardio-Sis – Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica
ACCORD-BP – Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial
SPRINT – Systolic Blood Pressure Intervention Trial
SD – standard deviation; SBP – systolic blood pressure (mmHg); AF – atrial fibrillation; CVD – cardiovascular disease; LVEF – left ventricular ejection fraction

association was only slightly less than that seen in the meta-analysis as a whole.

Benefit In Diverse Populations

The fact that intensive blood pressure lowering appears to confer a lower risk of AF in each of the included trials, despite the differences in their inclusion criteria and participant characteristics, is noteworthy. While ACCORD-BP included 39.2% non-white and SPRINT included 31.6% black participants, Cardio-Sis was a study of nearly all white participants. Since the incidence of AF is approximately 50% higher in whites than blacks,[26] the larger magnitude of beneficial effects from intensive blood pressure lowering found in the Cardio-Sis trial may be explained by the predominantly white study population. The mean BMI was 27.8 in Cardio-Sis, 29.9 in SPRINT, and 32.1 in ACCORD. While we cannot exclude an interaction between BMI and intensive blood pressure lowering with regard to AF risk, prior studies have found that the benefits of intensive blood pressure lowering appear to be conserved across all tested BMI strata.[27] The proportion of participants with prevalent cardiovascular disease also differed between trials. Only 12% of Cardio-Sis participants had baseline cardiovascular disease, but 19.5% of SPRINT participants and 30.9% of ACCORD-BP participants had prevalent cardiovascular disease. Taken together, the overall consistency of the relationship between intensive blood pressure lowering and AF risk, despite the differences in study populations, is reassuring and increases the generalizability of this finding.

Mechanisms

The mechanisms of the observed benefits of intensive blood pressure lowering on reducing AF risk likely involve several pathophysiological pathways.[11] Animal studies of the effects of chronic hypertension and its treatment on atrial myocardium have demonstrated that spontaneously hypertensive rats have higher incidence and duration of pacing-induced atrial tachycarrhythmias, with associated deranged calcium handling and increased interstitial fibrosis.[28] In an experimental rat model of hypertension in which the atria from rats with surgically-induced partial aortic stenosis were compared with controls, increased after load led to atrial fibrosis, reduced vectorial conduction velocity, reduced calcium content in the cardiomyocyte sarcoplasmic reticulum, and heterogeneity of conduction velocity, as well as heightened susceptibility to pacing-induced AF and more persistence in AF.[29,30] It is likely that intensive blood pressure lowering either slows progression of these processes or even leads to partial reversal. While it remains unproven that treatment of hypertension can lead to reversal of atrial cardiopathy,[31] this is a plausible explanation as there are several studies describing how treatment of hypertension can lead to regression of electrical and structural remodeling in the ventricle, including regression of left ventricular hypertrophy, decreases

Table 2: Outcomes of Studies Included in Systematic Review and Meta-Analysis of the Association of Blood Pressure Lowering with Incident Atrial Fibrillation

Trial	Follow-up years, median	Intervention Group BP (mean, SD)			Control Group BP (mean, SD)			Difference in BP Difference	Cases Intensive vs. control	HR (95% CI, p-value)
		Baseline	Follow-Up	Difference	Baseline	Follow-Up	Difference			
Cardio-Sis[18] (2009)	2.0	Systolic: 163.3 (11.3) Diastolic: 89.6 (8.8)	Systolic: 136.0 Diastolic: 79.2	Systolic: 27.3 (11.0) Diastolic: 10.4 (7.5)	Systolic: 163.3 (11.1) Diastolic: 89.7 (8.8)	Systolic: 139.8 Diastolic: 80.0	Systolic: 23.5 (10.6) Diastolic: 8.9 (7.0)	Systolic: 3.8 Diastolic: 1.5	10 vs. 21	0.46 (0.22 – 0.98, 0.044)
ACCORD-BP[19] (2016)	4.4	Systolic: 139.0 (15.0) Diastolic: 77.5 (9.5)	Systolic: 119.3 Diastolic: 64.4	Systolic: 19.7 Diastolic: 13.1	Systolic: 139.4 (15.5) Diastolic: 76.0 (10.2)	Systolic: 133.5 Diastolic:70.5	Systolic: 5.9 Diastolic:5.5	Systolic: 13.8 Diastolic: 7.6	37 vs. 45	0.85 (0.55 – 1.32, 0.48)
SPRINT[20] (2020)	3.8	Systolic: 139.5 (15.7) Diastolic: 78.2 (11.8)	Systolic: 121.5 Diastolic: 68.7	Systolic: 18.0 Diastolic: 9.5	Systolic: 139.6 (15.3) Diastolic: 78.1 (11.8)	Systolic: 134.6 Diastolic: 76.3	Systolic: 5.0 Diastolic: 1.8	Systolic: 13.0 Diastolic: 7.7	88 vs. 118	0.74 (0.56 – 0.98, 0.037)

Cardio-Sis – Studio Italiano Sugli Effetti Cardiovascolari del Controllo della Pressione Arteriosa Sistolica
ACCORD-BP – Action to Control Cardiovascular Risk in Diabetes Blood Pressure trial
SPRINT – Systolic Blood Pressure Intervention Trial
BP – blood pressure (mmHg); SD – standard deviation; HR – hazard ratio; 95% CI – 95% confidence interval

in left ventricular mass, and improvement in diastolic function.[32,33]

Limitations And Strengths

Our findings should be interpreted in the context of their limitations. We cannot exclude the possibility that there may be additional studies of intensive blood pressure lowering that reported incident AF as an outcome that were not captured by our search strategy. In addition, despite querying PubMed, EMBASE, and CENTRAL, we found only three studies eligible for inclusion in our meta-analysis, providing us with limited ability to perform more detailed analysis and meta-regression. Surveillance for AF was limited to study electrocardiography in the included studies, so subclinical AF may have escaped detection, though we would not expect a differential effect by intensity of blood pressure lowering. Our data did not include further characterization of AF as paroxysmal or persistent, so any benefits of intensive blood pressure control on slowing progression from paroxysmal AF to persistent AF would not be appreciated in our study. The lack of sex-specific and race/ethnicity-specific event data precludes us from assessing for interaction between demographic characteristics and intensive blood pressure lowering. Since prevalent diabetes was an inclusion criteria for ACCORD and an exclusion criteria for Cardio-Sis and SPRINT, it is possible that the difference in effect size of intensive blood pressure control may be explained by prevalent diabetes serving as a residual confounder, and our meta-analytic methodology with the three included studies does not allow us to teasing out the differential effects in those with and without diabetes. Our study also does not address the effect of intensive blood pressure control on the risk of recurrent AF in patients who have had a prior episode of AF, as Cardio-Sis did not include any participants with prevalent AF and the analyses from ACCORD-BP and SPRINT specifically excluded participants with prevalent AF. Study strengths include the methodological rigor of the underlying randomized controlled trials, rigorous search strategy, inclusion of over 12,000 eligible participants, and the consistent direction of effect observed with low heterogeneity.

Conclusion

This systematic review and meta-analysis of randomized clinical trials published to date demonstrates that intensive blood pressure lowering compared with standard blood pressure control results in a 26% decreased risk of incident AF, and that this effect appears to be consistent in multiple patient populations. Further studies exploring the utility of intensive blood pressure lowering for primary prevention of AF are needed.

References

1. January CT, Wann LS, Calkins H, Chen LY, Cigarroa JE, Cleveland JC, Jr., Ellinor PT, Ezekowitz MD, Field ME, Furie KL, Heidenreich PA, Murray KT, Shea JB, Tracy CM and Yancy CW. 2019 AHA/ACC/HRS Focused Update of the 2014 AHA/ACC/HRS Guideline for the Management of Patients With Atrial Fibrillation. Circulation. 2019:Cir0000000000000665.
2. Ruddox V, Sandven I, Munkhaugen J, Skattebu J, Edvardsen T and Otterstad JE. Atrial fibrillation and the risk for myocardial infarction, all-cause mortality and heart failure: A systematic review and meta-analysis. Eur J Prev Cardiol. 2017;24:1555-1566.
3. Kannel WB, Wolf PA, Benjamin EJ and Levy D. Prevalence, incidence, prognosis, and predisposing conditions for atrial fibrillation: population-based estimates. Am J Cardiol. 1998;82:2N-9N.
4. Wolf PA, Dawber TR, Thomas HE and Kannel WB. Epidemiologic Assessment of Chronic Atrial-Fibrillation and Risk of Stroke - Framingham Study. Neurology. 1978;28:973-977.
5. Colilla S, Crow A, Petkun W, Singer DE, Simon T and Liu X. Estimates of current and future incidence and prevalence of atrial fibrillation in the US adult population. The American journal of cardiology. 2013;112:1142-1147.
6. Virani SS, Alonso A, Benjamin EJ, Bittencourt MS, Callaway CW, Carson AP, Chamberlain AM, Chang AR, Cheng S and Delling FN. Heart disease and stroke statistics—2020 update: a report from the American Heart Association. Circulation. 2020:E139-E596.
7. Zakeri R, Van Wagoner DR, Calkins H, Wong T, Ross HM, Heist EK, Meyer TE, Kowey PR, Mentz RJ, Cleland JG, Pitt B, Zannad F and Linde C. The burden of proof: The current state of atrial fibrillation prevention and treatment trials. Heart Rhythm. 2017;14:763-782.
8. Huxley RR, Lopez FL, Folsom AR, Agarwal SK, Loehr LR, Soliman EZ, Maclehose R, Konety S and Alonso A. Absolute and attributable risks of atrial fibrillation in relation to optimal and borderline risk factors: the Atherosclerosis Risk in Communities (ARIC) study. Circulation. 2011;123:1501-1508.
9. Verdecchia P, Angeli F, Gentile G and Reboldi G. More Versus Less Intensive Blood Pressure-Lowering Strategy: Cumulative Evidence and Trial Sequential Analysis. Hypertension. 2016;68:642-53.
10. Wright JT, Jr., Williamson JD, Whelton PK, Snyder JK, Sink KM, Rocco MV, Reboussin DM, Rahman M, Oparil S, Lewis CE, Kimmel PL, Johnson KC, Goff DC, Jr., Fine LJ, Cutler JA, Cushman WC, Cheung AK and Ambrosius WT. A Randomized Trial of Intensive versus Standard Blood-Pressure Control. N Engl J Med. 2015;373:2103-16.
11. Verdecchia P, Angeli F and Reboldi G. Hypertension and Atrial Fibrillation: Doubts and Certainties From Basic and Clinical Studies. Circulation research. 2018;122:352-368.
12. Lip GYH, Force ObotT, Coca A and Force ObotT. Hypertension and cardiac arrhythmias. Eur Heart J. 2017;38:223-225.
13. Liberati A, Altman DG, Tetzlaff J, Mulrow C, Gøtzsche PC, Ioannidis JP, Clarke M, Devereaux PJ, Kleijnen J and Moher D. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration. Bmj. 2009;339:b2700.
14. Sterne JA, Savović J, Page MJ, Elbers RG, Blencowe NS, Boutron I, Cates CJ, Cheng H-Y, Corbett MS and Eldridge SM. RoB 2: a revised tool for assessing risk of bias in randomised trials. bmj. 2019;366.
15. Higgins JP, Thomas J, Chandler J, Cumpston M, Li T, Page MJ and Welch VA. Cochrane handbook for systematic reviews of interventions: John Wiley & Sons; 2019.
16. Egger M, Smith GD, Schneider M and Minder C. Bias in meta-analysis detected by a simple, graphical test. Bmj. 1997;315:629-634.
17. Review Manager (RevMan) Version 5.3 [computer program]. Copenhagen, Denmark Copenhagen: The Nordic Cochrane Center; 2014
18. Verdecchia P, Staessen JA, Angeli F, de Simone G, Achilli A, Ganau A, Mureddu G, Pede S, Maggioni AP, Lucci D and Reboldi G. Usual versus tight control of systolic blood pressure in non-diabetic patients with hypertension (Cardio-Sis): an open-label randomised trial. Lancet. 2009;374:525-33.
19. Chen LY, Bigger JT, Hickey KT, Chen H, Lopez-Jimenez C, Banerji MA, Evans G, Fleg JL, Papademetriou V, Thomas A, Woo V, Seaquist ER and Soliman EZ. Effect of Intensive Blood Pressure Lowering on Incident Atrial Fibrillation and P-Wave Indices in the ACCORD Blood Pressure Trial. Am J Hypertens. 2016;29:1276-1282.
20. Soliman EZ, Rahman AF, Zhang ZM, Rodriguez CJ, Chang TI, Bates JT, Ghazi L, Blackshear JL, Chonchol M, Fine LJ, Ambrosius WT and Lewis CE. Effect of Intensive Blood Pressure Lowering on the Risk of Atrial Fibrillation. Hypertension. 2020;75:1491-1496.
21. Thomas MC, Dublin S, Kaplan RC, Glazer NL, Lumley T, Longstreth WT, Smith

NL, Psaty BM, Siscovick DS and Heckbert SR. Blood Pressure Control and Risk of Incident Atrial Fibrillation. American Journal of Hypertension. 2008;21:1111-1116.
22. Conen D, Tedrow UB, Koplan BA, Glynn RJ, Buring JE and Albert CM. Influence of systolic and diastolic blood pressure on the risk of incident atrial fibrillation in women. Circulation. 2009;119:2146-52.
23. Grundvold I, Skretteberg PT, Liestøl K, Erikssen G, Kjeldsen SE, Arnesen H, Erikssen J and Bodegard J. Upper Normal Blood Pressures Predict Incident Atrial Fibrillation in Healthy Middle-Aged Men. Hypertension. 2012;59:198-204.
24. Verdecchia P, Dagenais G, Healey J, Gao P, Dans AL, Chazova I, Binbrek AS, Iacobellis G, Ferreira R, Holwerda N and et al. Blood pressure and other determinants of new-onset atrial fibrillation in patients at high cardiovascular risk in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial/ Telmisartan Randomized AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease studies. Journal of hypertension. 2012;30:1004-1014.
25. Group AS, Cushman WC, Evans GW, Byington RP, Goff DC, Jr., Grimm RH, Jr., Cutler JA, Simons-Morton DG, Basile JN, Corson MA, Probstfield JL, Katz L, Peterson KA, Friedewald WT, Buse JB, Bigger JT, Gerstein HC and Ismail-Beigi F. Effects of intensive blood-pressure control in type 2 diabetes mellitus. N Engl J Med. 2010;362:1575-85.
26. Mou L, Norby FL, Chen LY, O'Neal WT, Lewis TT, Loehr LR, Soliman EZ and Alonso A. Lifetime Risk of Atrial Fibrillation by Race and Socioeconomic Status. Circulation: Arrhythmia and Electrophysiology. 2018;11:e006350.
27. Oxlund CS, Pareek M, Rasmussen BSB, Vaduganathan M, Biering-Sørensen T, Byrne C, Almarzooq Z, Olsen MH and Bhatt DL. Body Mass Index, Intensive Blood Pressure Management, and Cardiovascular Events in the SPRINT Trial. Am J Med. 2019;132:840-846.
28. Choisy SC, Arberry LA, Hancox JC and James AF. Increased susceptibility to atrial tachyarrhythmia in spontaneously hypertensive rat hearts. Hypertension. 2007;49:498-505.
29. Kim SJ, Choisy SC, Barman P, Zhang H, Hancox JC, Jones SA and James AF. Atrial remodeling and the substrate for atrial fibrillation in rat hearts with elevated afterload. Circ Arrhythm Electrophysiol. 2011;4:761-9.
30. Zhang H, Cannell MB, Kim SJ, Watson JJ, Norman R, Calaghan SC, Orchard CH and James AF. Cellular Hypertrophy and Increased Susceptibility to Spontaneous Calcium-Release of Rat Left Atrial Myocytes Due to Elevated Afterload. PLoS One. 2015;10:e0144309.
31. Kamel H, Okin PM, Longstreth WT, Jr., Elkind MS and Soliman EZ. Atrial cardiopathy: a broadened concept of left atrial thromboembolism beyond atrial fibrillation. Future Cardiol. 2015;11:323-31.
32. Soliman EZ, Ambrosius WT, Cushman WC, Zhang ZM, Bates JT, Neyra JA, Carson TY, Tamariz L, Ghazi L, Cho ME, Shapiro BP, He J, Fine LJ and Lewis CE. Effect of Intensive Blood Pressure Lowering on Left Ventricular Hypertrophy in Patients With Hypertension: SPRINT (Systolic Blood Pressure Intervention Trial). Circulation. 2017;136:440-450.
33. Wachtell K, Bella JN, Rokkedal J, Palmieri V, Papademetriou V, Dahlöf B, Aalto T, Gerdts E and Devereux RB. Change in diastolic left ventricular filling after one year of antihypertensive treatment: The Losartan Intervention For Endpoint Reduction in Hypertension (LIFE) Study. Circulation. 2002;105:1071-6.