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Review Article

Risk of fatal and nonfatal coronary heart disease and stroke events among adult patients with hypertension: basic Markov model inputs for evaluating cost-effectiveness of hypertension treatment: systematic review of cohort studies

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Abstract

Objectives Hypertension is a risk factor for a number of vascular and cardiac complications. A Markov like simulation based on cardiovascular disease (CVD) policy model is being used for evaluating cost-effectiveness of hypertension treatment. Stroke, angina, myocardial infarction (MI), cardiac arrest and all-cause mortality were only included CVD outcome variables in the model. Therefore this systematic review was conducted to evaluate completeness of CVD policy model for evaluation of cost-effectiveness across different regions.

Key findings Fourteen cohort studies involving a total of 1 674 773 hypertensive adult population and 499 226 adults with treatment resistant hypertension were included in this systematic review. Hypertension is clearly associated with coronary heart disease (CHD) and stroke mortality, unstable angina, stable angina, MI, heart failure (HF), sudden cardiac death, transient ischemic attack, ischemic stroke, sub-arachnoid hemorrhage, intracranial hemorrhage, peripheral arterial disease (PAD), and abdominal aortic aneurism (AAA). Lifetime risk of developing HF is higher among hypertensives across all ages, with slight variation among regions. Treatment resistant hypertension is associated with higher relative risk of developing major CVD events and mortality when compared with the non-resistant hypertension.

Summary The CVD policy model can be used in most of the regions for evaluation of cost-effectiveness of hypertension treatment. However, hypertension is highly associated with HF in Latin America, Eastern Europe, and Sub-Saharan Africa. Therefore, it is important to consider HF in CVD policy model for evaluating cost-effectiveness of hypertension treatment in these regions. We do not suggest the inclusion of PAD and AAA in CVD policy model for evaluating cost-effectiveness of hypertension treatment due to lack of sufficient evidence. Researchers should consider the effect

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of treatment resistant hypertension either through including in the basic model or during setting the model assumptions.

Keywords: cardiovascular disease policy model; twelve major cardiovascular events; hypertension; cost-effectiveness analysis; systematic review

Background

Hypertension is a leading risk factor for all-cause mortality and the largest contributor to global disability-adjusted life years (DALYs). Of 56.9 million global deaths in 2016, 40.5 million were due to non-communicable diseases (NCDs). Hypertension was responsible for 7.5 million deaths (i.e. about 19.3% of all NCD deaths or 42% of all cardiovascular disease related deaths).[1] Hypertension-related adverse outcomes were mostly secondary to its complications such as stroke, ischemic heart disease, heart failure, renal disease, and other vascular and non-vascular comorbidities.[2, 3]

A study conducted to examine the global disparities of hypertension prevalence, awareness, treatment and control by world regions showed that the estimated global age-standardized prevalence of hypertension in adults aged ≥20 years in 2010 was 31.1%. The age-standardized prevalence of hypertension was 28.5% in high-income countries and 31.5% in low- and middle-income countries (P = 0.001).[4] The disparity is not only with prevalence but also with the level of blood pressure (BP) control. Globally less than 20% of people with hypertension have controlled their blood pressure.[5] This figure is less than 10% (5–10.3%) in Sub-Saharan Africa (SSA).[6–8] Hypertension is responsible for at least 45% and 51% of deaths due to heart disease and stroke, respectively.[9] In reality, it could be possible to achieve effective BP targets in about 70–80.5% of patients by improving adherence and/or intensifying therapy.[10, 11]

Controlling BP is one of seven key cardiovascular health metrics (i.e. smoking status, body mass index, physical activity, healthy diet, total cholesterol, BP and fasting plasma glucose) believed to reduce the risk of all-cause mortality, cardiovascular mortality, coronary heart disease (16%), stroke (38%) and vascular death (21%).[12–15] An annual cost directly attributable to hypertension is projected to increase by $130.4 billion in 2030.[16] The cost of hypertension exceeded the total health expenditure per capita in most low- and middle-income countries (LMICs).[17] Therefore, it is essential to conduct economic evaluation to determine whether the resources to evaluate the value for money being spent on hypertension treatment. The treatment cost-effectiveness of hypertension treatment is influenced by both the absolute initial cardiovascular risk, the relative risk reduction, and[18] clinical guidelines frequently updated upon arrival of new evidence.[19–26]

A cohort-based Markov-like cardiovascular disease (CVD) policy models have been the most commonly used methods in assessing the cost-effectiveness of hypertension treatment, as they are relatively simple to develop, debug, analyze and communicate.[27] Hypertension is a risk factor for several vascular and cardiac complications. The model should be comprehensive enough to include important variables (clinical states, secondary outcomes, treatment effects and costs).[28, 29] In addition to this, the cost-effectiveness model should be simple enough to be understood by decision-makers.[30, 31] The recent CVD modeling studies on the cost-effectiveness of hypertension treatment included stroke, angina, myocardial infarction (MI), cardiac arrest and all-cause mortality outcomes.[32]

However, hypertension is a risk factor for coronary heart disease (CHD) and stroke-related deaths, nonfatal stable angina, nonfatal unstable angina, heart failure, nonfatal MI, nonfatal ischemic stroke, subarachnoid hemorrhage, intracranial hemorrhage, transient ischemic attack, peripheral arterial disease (PAD) and abdominal aortic aneurysm (AAA).[33–35] Knowing the probabilities of these events among patients with hypertension (treated, untreated) is critical for researchers who want to conduct the cost-effectiveness of hypertension treatment based on standard treatment guidelines. This systematic review was conducted to provide a clear picture on the prevalence of fatal and nonfatal CHD and stroke events among patients with treated (controlled, uncontrolled and treatment-resistant) and untreated hypertension. In addition to this, the exclusion of cardiovascular events like heart failure, peripheral artery disease and AAA in previous cardiovascular disease policy model was explored.

Methods

Data sources and search strategy

We searched articles written in the English language from January 2000 to January 2020 from the following databases: PubMed/Medline, Ovid/Medline, Embase, Scopus, Web of Science and Google Scholar with a systematic search query (available in Supplementary file).

Review target and questions

This review is designed to answer the following three questions among adult hypertensive patients aged ≥18 years. The described relationship between hypertension with fatal and nonfatal CHD and stroke events was based on the CVD policy model (Figure 1).[27]

1. What is the risk of developing fatal (acute) and nonfatal (chronic) CHD among patients with hypertension?
2. What is the risk of developing fatal (acute) and nonfatal (chronic) CHD among patients with treatment-resistant hypertension?
3. How comprehensive is the CVD policy model being utilized for the evaluation of the cost-effectiveness of hypertension treatment in addressing most relevant events?

Study types

Cohort studies addressing fatal and nonfatal CHD and stroke events (CHD death, stroke death, nonfatal stable angina, nonfatal unstable angina, nonfatal myocardial infarction, nonfatal stroke and nonfatal transient ischemic attack) among adults with hypertension.

Inclusion and exclusion criteria

Cohort studies comparing fatal and nonfatal CHD and stroke events among adult patients with hypertension (treated controlled, treated uncontrolled and treatment-resistant hypertension) are included. Studies conducted before January 2000, systematic reviews, guidelines, short communications, conference proceedings and articles that do not meet quality evaluation criteria are excluded.

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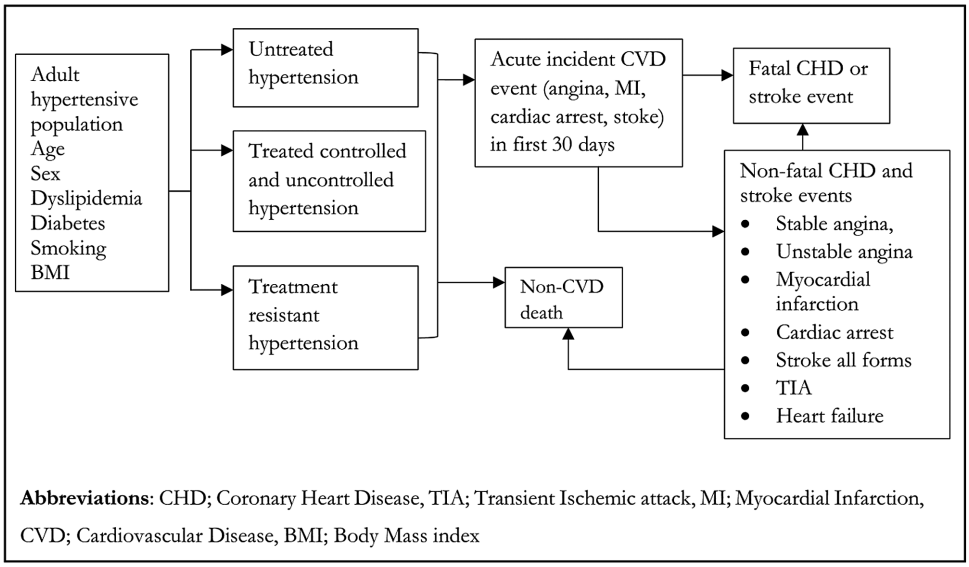

Figure 1 Cardiovascular disease policy model structure presenting the relationship between fatal and nonfatal CHD and stroke events in hypertensive adults. Adapted from: Moran *et al.*[27]
Abbreviations: BMI, body mass index; CHS, coronary heart disease; CVD, cardiovascular disease; MI, myocardial infarction; TIA, transient Ischemic attack.

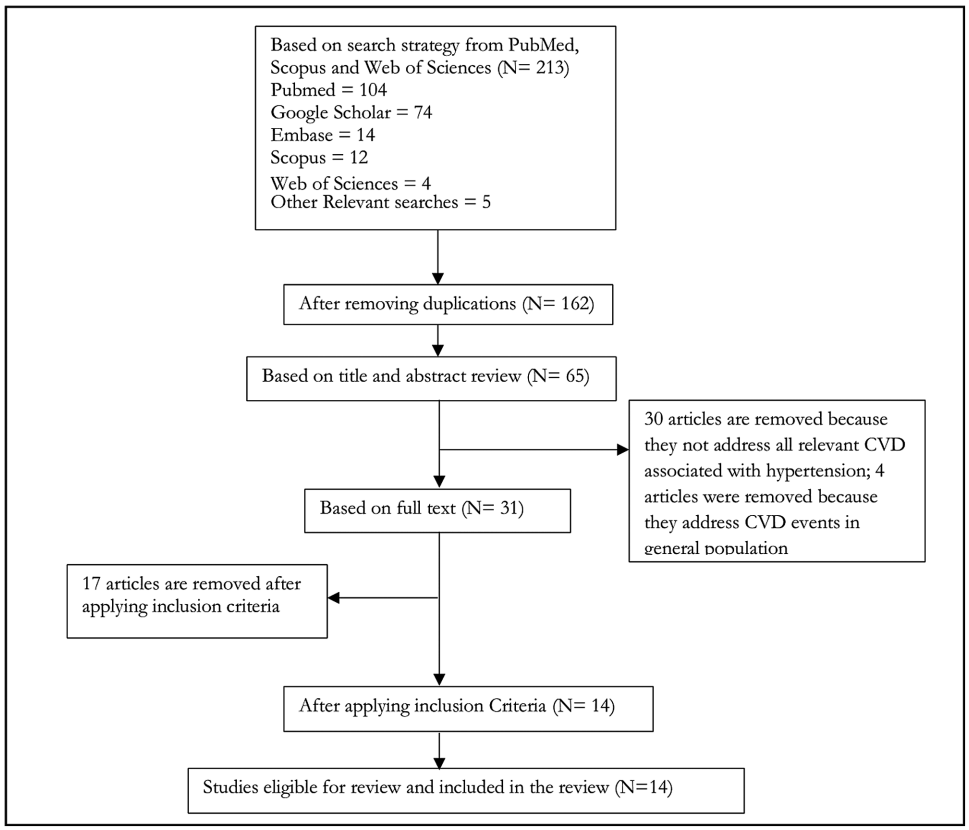

Figure 2 PRISMA flowchart representing the result of search and the number of articles excluded and eligible for review.

Study selection and data abstraction

From a total of 213 articles identified by literature search 35, potentially relevant articles were selected. After applying the inclusion–exclusion criteria listed above, only 14 articles were found to be relevant. These fourteen articles were included in the final review[36] (Figure 2).

Risk of bias assessment

Studies fulfilling our eligibility criteria were assessed for internal validity at the study level by two reviewers independently. The risk of bias of cohort studies was evaluated using the risk of bias assessment tool for cohort studies.[37] The tool contains eight questions with four

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ratings for each question. These questions address; selecting exposed and unexposed from the same population; certainty in the assessment of exposure; confidence that the outcome of the study is not present at the start of the study; matching exposed and unexposed for all variables; confidence in the assessment of presence or absence of prognostic factors; confident on the assessment of the outcome; adequacy of the follow-up; and similarity of co-interventions between groups. Definitely yes (low risk), probably yes, probably no, and definitely no (high risk).[37] All authors evaluated the risk of bias independently and rated the risk bias as high, intermediate or low. The overall risk of bias of included cohort studies was low (Table 1).

Quality assessment and data abstraction

Two investigators independently rated each study's quality as 'good', or 'poor' by using JBI Critical Appraisal Checklist for Cohort Studies (Table 2).[38] The checklist addresses the following 11 issues: recruiting cohort groups from a similar population; similarity in exposures measurement to assign people to both exposed and unexposed groups; validity and reliability exposure measurement methods; identification of confounding factors; setting strategies to deal with confounding factors stated; absence of the outcome in the groups/participants at the start of the study; validity and reliability of outcomes measurement; sufficiency of follow-up time for outcome occurrence; follow up completeness; strategies to address an incomplete follow up and appropriateness of statistical analysis being used.[38] We excluded poor-quality cohort studies. In general, good-quality studies did not meet at most one pre-specified criteria. A poor-quality study did not meet at least two criteria and had a fatal limitation. Disagreements among us are managed through discussion in the presence of other authors. Two investigators abstracted study design information, baseline population characteristics, intervention details, BP control and clinical outcomes from all included studies into an evidence table (Table 3). A third investigator checked these data for accuracy.

Data synthesis and analysis

We qualitatively described and summarized the evidence on the prevalence of fatal and nonfatal CHD and stroke events among adults with controlled and uncontrolled hypertension. We stratified results by prevalence of CHD and stroke mortality, prevalence of stable angina, prevalence of stable angina, prevalence of myocardial infarction, prevalence of stroke and transient ischemic attack, cardiovascular disease risk difference and transitional probabilities between events. Finally, appropriate conclusions and recommendations will be made based on the results of the included studies.

Results

Description of included studies

Fourteen cohort studies involving 1 674 773 hypertensive adult population and 499 226 adults with treatment-resistant hypertension were included in this systematic review. Seven studies were from the USA,[39–45] two were from China[46, 50] and one study from each of the following countries; Japan,[48] UK,[33] Spain,[47] Korea[49] and Sweden.[51] The duration of follow-up of included cohort studies ranged from 5 years to 29 years. The following twelve vascular, cerebral, and peripheral complications, along with fatal CHD and stroke events were included. The included events were CHD and stroke mortality, unstable angina, stable angina, myocardial infarction, heart failure (HF), cardiac arrest, transient ischemic attack, ischemic stroke, subarachnoid hemorrhage, intracranial hemorrhage, PAD and AAA.[33, 39–51]

Association between hypertension and all-cause, coronary heart disease and cardiovascular disease mortality

A cohort study conducted in the UK among 1.2 million adults showed that the relative risk of developing CHD death among hypertensive adults was 1.26 (95% CI, 1.19–1.34).[33] A cohort study conducted in the USA to evaluate the impact of sustained BP control showed that the relative risk of fatal CHD and composite outcomes (fatal CHD, stroke, and HF, and mortality) were 1.16 (95% CI, 0.93–1.44) and 1.14 (95% CI, 0.99–1.44), respectively.[41] A cohort study conducted in the UK showed that the relative risk of developing cardiac arrest among hypertensive adults was 1.19 (95% CI, 1.10–1.29).[33] A cohort study conducted to identify the relationship of SBP with all-cause mortality among 121 082 Chinese adults aged 18 or older showed higher mortality rate in men with SBP < 100 mmHg, SBP 120–139 mmHg, SBP 140–159 mmHg, SBP 160–179 mmHg and SBP ≥ 180 mmHg were 1.46 (95% CI, 1.14–1.86), 1.14 (95% CI, 1.04–1.26), 1.29 (95% CI, 1.16–1.44), 1.57 (95% CI, 1.38–1.79) and 2.07 (95% CI, 1.76–2.43, $P < 0.0001$), respectively.[50]

Another cohort study conducted among 97 013 Chinese adults to examine the impact of different levels of SBP on the incidence of cardiovascular and cerebrovascular events and all-cause mortality showed that the risk of all-cause mortality and cardiovascular and cerebrovascular events below 50 years was 1.20 (95% CI, 1.13–1.28) and 1.27 (95% CI, 1.20–1.34), respectively. Similarly, all-cause mortality and cardiovascular and cerebrovascular events at ≥50 years were 1.08 (95% CI, 1.05–1.10) and 1.17 (95% CI, 1.14–1.19), respectively at $P < 0.01$).[46]

A cohort study conducted in Spain among 52 007 adults aged ≥30 years to estimate the attributable risk associated with hypertension for all-cause mortality and cardiovascular hospitalization showed that avoidable deaths attributed by hypertension were (PAR) 41.8% (95% CI, 28–53.24) and 37.84% (95% CI, 5.74–61.5) in men and women, respectively. The risk of hypertension attributed to total mortality was 38.6 (95% CI, 24.1–53.0) and 13.4 (95% CI, 5.1–21.8) in men and women, respectively. The risk of hypertension attributed CHD in-hospital admission was 61.1 (95% CI, 43.8–78.3) and 14.7 (2.4–27.0) in men and women, respectively. Similarly, the risk of HTN attributed in-hospital stroke admission was 40.0 (95% CI, 24.1–55.8) and 14.7 (95% CI, 2.3–27.0) in men and women, respectively.[47]

A cohort study conducted in Japan to clarify the relationship between BP and mortality from stroke, heart disease, CVD and all causes of death showed higher risk all-cause mortality 1.01 (95% CI, 0.66–1.53, $P < 0.001$), and 1.33 (95% CI, 0.92–1.93, $P = 0.076$) among men and women respectively at BP 120–129/80–84 mmHg when compared with BP < 120/80 mmHg. A relative risk of CVD case mortality was also higher 1.28 (95% CI, 0.87–9.05, $P < 0.001$), and 1.73 (95% CI, 0.91–3.29, $P = 0.005$) among men and women respectively at BP 120–129/80–84 mmHg when compared with BP < 120/80 mmHg. Similarly, relative risk of CHD case mortality 5.25 (95% CI, 0.83–33.01, $P < 0.024$), and 1.62 (95% CI, 0.70–3.72, $P = 0.24$) among men and women respectively at BP 120–129/80–84 mmHg when compared with BP < 120/80 mmHg.[48] A cohort study conducted in Korea to estimate the proportion of hypertensive adults who would meet BP goals under SPRINT criteria and under

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Table 1 Rating risk bias of cohort studies included for estimating of lifetime risks of CVD associated with hypertension at different index ages, for potential consideration in basic Markov model as inputs for evaluating cost-effectiveness of hypertension treatment based on treatment guidelines based on tools for assessment of risk of bias in cohort studies

Tool question number	Rapsomanik E. *et al.* 2014		Huffman MD. *et al.* 2013		Lloyd-Jones DM. *et al.* 2002		Bowling CB. *et al.* 2019		Rodriguez CJ. *et al.* 2014		Bangalore S. *et al.* 2014		Irvin MR. *et al.* 2014		Sim JJ. *et al.* 2015)		Song Y. *et al.* 2016		Redon J. *et al.* 2016		Lida M. *et al.* 2003		Ko MJ. *et al.* 2016		Li C. *et al.* 2018		Holmqvist L. *et al.* 2018	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
1	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
2	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
3	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
4	√			√		√	√			√	√			√			√		√		√		√		√		√	
5	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
6	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
7	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
8	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
Over all bias	Low		Low		Low		Low		Low		Low		Low		Low		Low		Low		Low		Low		Low		Low	

Table 2 Critical appraisal of cohort studies included for estimating of lifetime risks of CVD associated with hypertension at different index ages, for potential consideration in basic Markov model as inputs for evaluating cost-effectiveness of hypertension treatment based on treatment guidelines based on JBI Critical Appraisal Checklist for Cohort Studies

Checklist Question number	Rapsomanik E. *et al.* 2014		Huffman MD. *et al.* 2013		Lloyd-Jones DM. *et al.* 2002		Bowling CB. *et al.* 2019		Rodriguez CJ. *et al.* 2014		Bangalore S. *et al.* 2014		Irvin MR. *et al.* 2014		Sim JJ. *et al.* 2015		Song Y. *et al.* 2016		Redon J. *et al.* 2016		Lida M. *et al.* 2003		Ko MJ. *et al.* 2016		Li C. *et al.* 2018		Holmqvist L. *et al.* 2018	
	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No	Yes	No
1	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
2	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
3	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
4	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
5	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
6	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
7	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
8	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
9	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
10	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
11	√		√		√		√		√		√		√		√		√		√		√		√		√		√	
Over all	100%		100%		100%		100%		100%		100%		100%		100%		100%		100%		100%		100%		100%		100%	

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Table 3 Cohort studies included for estimating of lifetime risks of CVD associated with hypertension at different index ages, for potential consideration in basic Markov model as inputs for evaluating cost-effectiveness of hypertension treatment based on treatment guidelines

S. No	Reference	Study type	Country	Study objective	Sample size	Events/Outcomes	Life time risk		
							Normotensives	Hypertensives	Lifetime risk difference
1	Rapsomanik E. *et al.* 2014[33]					**Index age 30**			
						Stable angina	4.9 (4.7–5.2)	8.9 (8.7–9.2)	4.0 (3.7, 4.3)
						Unstable angina	6.7 (6.4–7.0)	10.1 (9.8–10.3)	3.4 (3.0, 3.7)
						Myocardial infarction	5.5 (5.3–5.8)	8.0 (7.8–8.3)	2.5 (2.2, 2.8)
						Unheralded CHD death	1.9 (1.8–2.1)	2.5 (2.4–2.6)	0.6 (0.3, 0.8)
						Heart failure	5.2 (4.9–5.6)	7.8 (7.6–8.1)	2.6 (2.2, 3.0)
						Cardiac arrest/SCD	1.8 (1.7–2.0)	2.3 (2.2–2.4)	0.5 (0.3, 0.7)
						Transient ischemic attack	5.9 (5.6–6.2)	6.5 (6.3–6.7)	0.6 (0.3, 1.0)
						Ischemic stroke	6.5 (6.2–6.9)	7.6 (7.3–7.8)	1.0 (0.7, 1.4)
						Subarachnoid hemorrhage	0.6 (0.5–0.7)	0.9 (0.7–1.0)	0.3 (0.2, 0.4)
						Intracerebral hemorrhage	0.9 (0.8–1.0)	1.3 (1.2–1.4)	0.4 (0.2, 0.5)
						Peripheral arterial disease	4.5 (4.2–4.7)	5.8 (5.6–6.0)	1.3 (1.0, 1.6)
						Abdominal aortic aneurysm	1.5 (1.4–1.7)	1.6 (1.5–1.7)	0.1 (–0.1, 0.3)
						Index age 60			
						Stable angina	4.5 (4.3–4.7)	8.1 (7.9–8.4)	3.6 (3.3, 3.9)
						Unstable angina	5.9 (5.6–6.2)	8.6 (8.3–8.9)	2.7 (2.4, 3.0)
						Myocardial infarction	5.0 (4.8–5.2)	7.1 (6.9–7.4)	2.1 (1.8, 2.4)
						Unheralded CHD death	1.9 (1.8–2.1)	2.4 (2.3–2.6)	0.5 (0.3, 0.7)
						Heart failure	5.5 (5.2–5.9)	8.0 (7.7–8.3)	2.5 (2.1, 2.9)
						Cardiac arrest/SCD	1.7 (1.6–1.9)	2.0 (1.9–2.2)	0.3 (0.1, 0.5)
						Transient ischemic attack	5.9 (5.6–6.3)	6.6 (6.4–6.8)	0.6 (0.3, 1.0)
						Ischemic stroke	6.6 (6.3–7.0)	7.7 (7.5–8.0)	1.1 (0.7, 1.5)
						Subarachnoid hemorrhage	0.5 (0.4–0.6)	0.7 (0.6–0.9)	0.3 (0.1, 0.4)
						Intracerebral hemorrhage	0.9 (0.8–1.0)	1.3 (1.2–1.4)	0.4 (0.2, 0.5)
						Peripheral arterial disease	4.4 (4.1–4.6)	5.9 (5.7–6.1)	1.5 (1.2, 1.8)
						Abdominal aortic aneurysm	1.7 (1.5–1.9)	1.7 (1.5–1.8)	0.0 (–0.2, 0.2)
						Index age 80			
						Stable angina	3.6 (3.4–3.8)	6.6 (6.3–6.8)	3 (2.7, 3.2)
						Unstable angina	4.7 (4.5–5.0)	6.9 (6.6–7.2)	2.2 (1.9, 2.5)
						Myocardial infarction	4.0 (3.8–4.2)	5.9 (5.6–6.1)	1.8 (1.6, 2.1)
						Unheralded CHD death	1.8 (1.6–2.0)	2.3 (2.1–2.5)	0.5 (0.4, 0.7)
2	Huffman MD. *et al.* 2013[39]	Cohort	USA	To estimate lifetime risk of HF by race and sex	37, 572	HF risk among hypertensives at age 45 (%)			
						BP ≤ 120/80 mmHg white men	9.8 (5.8–13.9)	12.1(10.3–14.0)	2.3%
						BP ≤ 120/80 mmHg white women	9.9 (6.9–12.8)	8.6 (7–10.4)	
						BP ≤ 120/80 mmHg black men	-	13.9 (5.9–22)	
						BP ≤ 120/80 mmHg black women	6.7 (0 – 14)	6.9 (0–16.1)	
						BP ≥ 160/100 mmHg white men	9.8 (5.8–13.9)	16.3 (13.5–19.2)	6.5%
						BP ≥ 160/100 mmHg white women	9.9 (6.9–12.8)	13.3 (9.7–16.9)	3.4%
						BP ≥ 160/100 mmHg black men	–	12.7 (3.2–22.2)	
						BP ≥ 160/100 mmHg black women	6.7 (0–14)	16.0 (6.4–25.5)	7.3%

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Table 3 Continued

S. No	Reference	Study type	Country	Study objective	Sample size	Events/Outcomes	Life time risk		
							Normotensives	Hypertensives	Lifetime risk difference
3	Lloyd-Jones DM. *et al.* 2002[40]	Cohort	USA	To determine Lifetime Risk for Developing Congestive Heart Failure	8229	**Lifetime risk for CHF**			
						at 40 for men	14.8%	21.0% (18.7–23.2)	6.2% (RD)
						at 50 for men	17.3%	20.9% (18.6–23.2)	3.6%
						At 60 for men	17.4%	20.5% (18.1–22.9)	3.1%
						at 70 for men	15.1%	20.6% (17.8–23.4)	5.5%
						at 40 for women	12.0%	20.3 (18.2–22.5)	8.3%
						at 50 for women	12.4%	20.5 (18.3–22.6)	8.1%
						at 60 for women	14.4%	20.5 (18.3–22.8)	6.1%
						at 70 for women	14.3%	20.2 (17.8–22.6)	5.9%
4	Bowling CB. *et al.* 2019 [41]	Cohort	USA	To evaluate the impact of Sustained BP control (<140 mm Hg) on coronary heart disease,stroke, heart failure and mortality	24 309	**Sustained BP control rate ≥ 75–100%**			
						Fatal CHD or non-fatal MI		1.07 (0.83–1.39)	$P = 0.14$
						Stroke		1.13 (0.78–1.65)	$P < 0.01$
						Heart failure		1.11 (0.83–1.48)	$P < 0.01$
						Composite CVD outcomes*		1.08 (0.90–1.29)	$P < 0.01$
						All-cause mortality		1.04 (0.88–1.22)	$P = 0.06$
						Sustained BP control rate 50–75%			
						Fatal CHD or non-fatal MI		1.22 (0.97–1.52)	$P = 0.14$
						Stroke		1.05 (0.74–1.47)	$P < 0.01$
						Heart failure		1.30 (1.01–1.67)	$P< 0.01$
						Composite CVD outcomes*		1.16 (0.99–1.36)	$P < 0.01$
						All-cause mortality		1.00 (0.87–1.16)	$P = 0.06$
						Sustained BP control rate < 50%			
						Fatal CHD or non-fatal MI		1.16 (0.93–1.44)	$P = 0.14$
						Stroke		1.71 (1.26–2.32)	$P < 0.01$
						Heart failure		1.63 (1.30–2.06)	$P < 0.01$
						Composite CVD outcomes*		1.39 (1.20–1.62)	$P < 0.01$
						All-cause mortality		1.14 (0.99–1.30)	$P = 0.06$
5	Rodriguez CJ. *et al.* 2014 [42]	Cohort	USA	To examine the risk of incident cardiovascular (CV) events among adults with HTNaccording to 3 SBP levels: 140 mm Hg or higher; 120 to 139 mm Hg; and a reference level of lower than 120 mm Hg.	4480	**Heart failure (RR)**			
						SBP 120–139 mmHg	1.14 (0.97–1.34)	1.49 (1.23–1.81)	0.35
						SBP 120–139 mmHg men	1.08 (0.86–1.35)	1.44 (1.08–1.92)	
						SBP 120–139 mmHg women	1.15 (0.92–1.45)	1.54 (1.18–2.02)	
						SBP 120–139 mmHg blacks	1.43 (1.12–1.83)	1.57 (1.18–2.08)	
						SBP 120–139 mmHg whites	1.01 (0.82–1.25)	1.44 (1.09–1.90)	
						Stroke			
						SBP 120–139 mmHg	1.05 (0.83–1.32)	1.87 (1.43–2.44)	
						SBP 120–139 mmHg men	1.02 (0.73–1.43)	1.90 (1.27–2.85)	
						SBP 120–139 mmHg women	1.08 (0.78–1.49)	1.83 (1.28–2.61)	

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Table 3 Continued

S. No	Reference	Study type	Country	Study objective	Sample size	Events/Outcomes	Life time risk		
							Normotensives	Hypertensives	Lifetime risk difference
						SBP 120–139 mmHg African American	1.10 (0.80–1.52)	1.63 (1.15–2.32)	
						SBP 120–139 mmHg whites	1.09 (0.78–1.52)	2.03 (1.33–3.09)	0.94
						Myocardial infarction			
						SBP 120–139 mmHg	0.99 (0.82–1.20)	1.41 (1.12–1.78)	
						SBP 120–139 mmHg men	0.88 (0.68–1.14)	1.53 (1.10–2.13)	
						SBP 120–139 mmHg women	1.03 (0.78–1.36)	1.18 (0.85–1.65)	
						SBP 120–139 mmHg blacks	1.00 (0.74–1.34)	1.35 (0.97–1.88)	
						SBP 120–139 mmHg whites	1.00 (0.78–1.29)	1.45 (1.03–2.04)	0.45
6	Bangalore S. *et al*. 2014 [43]	Cohort	USA	To determine the prevalence, predictors, and outcomes among apparent treatment-resistant hypertension, especially in patients with coronary artery disease.	10 001	aTRH is associated with			
						Major cardiovascular event		1.64 (1.39–1.94)	$P < 0.001$
						Coronary heart disease death		1.69 (1.22–2.34)	$P = 0.001$
						Non-fatal MI		1.73 (1.39–2.16)	$P < 0.0001$
						Resuscitated cardiac arrest		1.72 (0.81, 3.64)	$P = 0.1544$
						Stroke		1.52 (1.05–2.19)	$P = 0.0714$
						Angina pectoris		1.68 (1.44–1.95)	$P < 0.0001$
						Heart failure		1.37 (0.88–2.13)	$P = 0.05$
						All case mortality		1.45 (1.12–1.89)	$P < 0.0011$
						Coronary re-vascularization		1.59 (1.35–1.87)	$P < 0.0001$
						All-cause mortality		1.45 (1.16–1.80)	$P = 0.0011$
						Transient ischemic attack		0.95 (0.62–1.45)	$P = 0.8009$
						Any coronary event		1.60 (1.43–1.78)	$P < 0.0001$
						Any CV event		1.53 (1.39–1.69)	$P < 0.0001$
7	Irvin MR. *et al*. 2014[44]	Cohort	USA	To evaluate the association of apparent (aTRH)with incident stroke, CHD and all-cause mortality	14 522	Non-resistant HTN ref. (Hazard ratio, 95% CI)			
						Ange-sex and race adjusted stroke		1.16 (0.76–1.77)	
						Multivariable adjusted stroke		1.07 (0.67–1.71)	$P > 0.05$
						Ange-sex and race adjusted CHD		1.91 (1.12–3.26)	
						Multivariable adjusted CHD		2.33 (1.21–4.48)	$P < 0.05$
						Ange-sex and race adjusted all-cause mortality		1.07 (0.84–1.36)	
						Multivariable adjusted all-cause mortality		1.15 (0.91–1.45)	$P > 0.05$
8	Sim JJ. *et al*. 2015) [45]	Cohort	USA	To compare the risk of end-stage renal disease (ESRD), ischemic heart event (IHE), CHF, cerebrovascular accident (CVA), and all-cause mortalityamong 470 386 individuals with resistant and nonresistanthypertension (non-RH).	470 386	**IHD (Adjusted hazard ratio, 95% CI)**			

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Table 3 Continued

S. No	Reference	Study type	Country	Study objective	Sample size	Events/Outcomes	Life time risk		
							Normotensives	Hypertensives	Lifetime risk difference
						RH (cRH+ uRH) versus non-RH		1.24 (1.20, 1.28)	$P < 0.05$
						cRH versus non-RH		1.21 (1.16, 1.26)	$P < 0.05$
						uRH versus non-RH		1.26 (1.21, 1.31)	$P < 0.05$
						cRH versus uRH		0.96 (0.91, 1.01)	$P < 0.05$
						Heart failure (**Adjusted hazard ratio, 95% CI**)			
						RH (cRH+ uRH) versus non-RH		1.46 (1.40, 1.52)	$P < 0.05$
						cRH versus non-RH		1.51 (1.43, 1.59)	$P < 0.05$
						uRH versus non-RH		1.42 (1.35, 1.50)	$P < 0.05$
						cRH versus uRH		1.06 (0.99, 1.12)	$P < 0.05$
						Cerebrovascular event (**adjust. HR, 95% CI**)			
						RH (cRH+ uRH) versus non-RH		1.14 (1.10, 1.19)	$P < 0.05$
						cRH versus non-RH		1.01 (0.95, 1.07)	$P < 0.05$
						uRH versus non-RH		1.24 (1.18, 1.30)	$P < 0.05$
						cRH versus uRH		0.81 (0.76, 0.88)	$P < 0.05$
						ESRD (**adjust. HR, 95% CI**)			
						RH (cRH+ uRH) versus non-RH		1.32 (1.27, 1.37)	$P < 0.05$
						cRH versus non-RH		1.16 (1.10, 1.22)	$P < 0.05$
						uRH versus non-RH		1.45 (1.39, 1.52)	$P < 0.05$
						cRH versus uRH		0.80 (0.75, 0.85)	$P < 0.05$
						All-cause mortality (**adjust. HR, 95% CI**)			
						RH (cRH+ uRH) versus non-RH		1.06 (1.03, 1.08)	$P < 0.05$
						cRH versus non-RH		1.05 (1.02, 1.09)	$P < 0.05$
						uRH versus non-RH		1.06 (1.03, 1.09)	$P < 0.05$
						cRH versus uRH		0.99 (0.95, 1.03)	$P < 0.05$
9	Song Y. *et al.* 2016[46]	Cohort	China	To examine the impact of differentlevels of SBP on the incidence ofcardiovascular and cerebrovascular events and all-causedeath in Chinese adults	97 013	Cardiovascular and cerebrovascular events HR)		1.20 (1.13 - 1.28)	
						SBP < 110 mm Hg (reference)	1		
						Adjusted for sex and age VS SBP 5	1.49 (1.11–2.00)	2.63 (2.00–3.46)	1.14
						Adjusted for multivariable	1.35 (1.00–1.82)	2.05 (1.55–2.72)	0.7
						MI			
						Adjusted for sex and age	1.47 (0.82–2.64)	2.08 (1.21–3.56)	0.61
						Adjusted for multivariable	1.35 (0.74–2.47)	1.58 (0.89–2.79)	
						Ischemic stroke			
						Adjusted for sex and age	1.49 (1.01–2.22)	2.61 (1.82–3.75)	1.12
						Adjusted for multivariable	1.35 (0.91–2.01)	2.00 (1.38–2.90)	
						Hemorrhagic stroke			
						Adjusted for sex and age	1.51 (0.77–2.96)	3.57 (1.93–6.60)	2.06
						Adjusted for multivariable	1.37 (0.69–2.72)	2.97 (1.59–5.56)	1.6

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Table 3 Continued

S. No	Reference	Study type	Country	Study objective	Sample size	Events/Outcomes	Life time risk		
							Normotensives	Hypertensives	Lifetime risk difference
						All-cause death			
						Adjusted for sex and age	0.95 (0.74–1.23)	1.22 (0.97–1.54)	0.27
						Adjusted for multivariable	0.92 (0.71–1.20)	1.18 (0.93–1.50)	
10	Redon J. *et al.* 2016 [47]	Cohort	Spain	To estimate the attributable risk associated to hypertension for all-cause mortality and cardiovascular hospitalization endpoints	52 007	Hypertension attributed (%)			
						Total mortality men (PAR %)		33.67 (17.24, 47.72)	RR = 1.59 (1.23 2.05)
						Total mortality women (PAR %)		37.84 (5.74, 61.51)	RR = 1.65 (1.03 2.63)
						CHD in-hospital admission in men		41.81 (28.02, 53.24)	RR = 1.80 (1.42 2.29)
						CHD in-hospital admission in women		44.4 (24.21, 59.82)	RR = 1.88 (1.33 2.64)
						Stroke in-hospital admission in men		35.11 (18.47, 49.04)	RR = 1.63 (1.26 2.10)
						Stroke in-hospital admission in women		39.14 (18.14, 55.44)	RR = 1.70 (1.23 2.34)
11	Lida M. *et al.* 2003[48]	Cohort	Japan	To clarify the relationship between BP and mortality from stroke, heart disease, CVD and all causes of death and to estimate category-specific excessmortality from stroke due to BP level	2345	**Men**			
						All-cause mortality	1.01 (0.66–1.53)	1.16 (1.09–1.23)	$P < 0.001$
						CVD	2.80 (0.87–9.05)	1.37 (1.23–1.52)	$P < 0.001$
						Heart disease	5.25 (0.83–33.0)	1.29 (1.11–1.51)	$P < 0.024$
						Stroke	1.36 (0.27–6.82)	1.45 (1.24–1.69)	$P < 0.001$
						Women			
						All-cause mortality	1.33 (0.92–1.93)	1.09 (1.03–1.17)	$P < 0.076$
						CVD	1.73 (0.91–3.29)	1.18 (1.07–1.31)	$P < 0.24$
						Heart disease	1.62 (0.70–3.72)	1.12 (0.97–1.28)	$P < 0.005$
						Stroke	3.00 (0.95–9.44)	1.27 (1.09–1.49)	$P < 0.004$
12	Ko MJ. *et al.* 2016[49]	Cohort	Korea	To estimate the proportion of hypertensive adults who would meet BP goals under SPRINT criteria and under JNC 2014 recommendations and to determine the related effects on cardiovascular morbidity and mortality	81 311	Age- and sex-adjusted MACE			
						Below SPRINT BP Goal (reference)	1		
						Above SPRINT but Below JNC 8 BP goal	1.02 (0.83–1.26)	1.48 (1.19–1.85)	$P < 0.001$
						Multivariable-adjusted MACE			
						Above SPRINT but Below JNC 8 BP goal	1.17 (0.94–1.45)	1.62 (1.29–2.02)	$P < 0.001$
						Age- and sex-adjusted CVD death			
						Above SPRINT but Below JNC 8 BP goal	1.06 (0.69–1.61)	1.24 (0.80–1.92)	$P = 0.19$
						Multivariable adjusted CVD death			
						Above SPRINT but Below JNC 8 BP goal	1.11 (0.71–1.73)	1.39 (0.87–2.20)	$P = 0.13$

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Table 3 Continued

S. No	Reference	Study type	Country	Study objective	Sample size	Events/Outcomes	Life time risk		
							Normotensives	Hypertensives	Lifetime risk difference
						Age- and sex-adjusted MI			
						Above SPRINT but Below JNC 8 BP goal	1.02 (0.74–1.42)	1.51 (1.08–2.12)	$P < 0.001$
						Multivariable adjusted MI			
						Above SPRINT but Below JNC 8 BP goal	1.22 (0.88–1.70)	1.68 (1.19–2.36)	$P < 0.001$
						Age- and sex-adjusted Stroke			
						Above SPRINT but Below JNC 8 BP goal	1.03 (0.78–1.35)	1.49 (1.12–1.99)	$P < 0.001$
						Multivariable adjusted Stroke			
						Above SPRINT but Below JNC 8 BP goal	1.14 (0.86–1.51)	1.61 (1.20–2.16)	$P < 0.001$
						Age- and sex-adjusted all-cause mortality			
						Above SPRINT but Below JNC 8 BP goal	0.71 (0.62–0.81)	0.86 (0.74–1.00)	$P = 0.96$
						Multivariable adjusted all-cause mortality			
						Above SPRINT but Below JNC 8 BP goal	0.83 (0.72–0.95)	0.98 (0.84–1.15)	$P = 0.22$
13	Li C. *et al.* 2018[50]	Cohort	China	To identify the relationship of SBP with all-cause mortality in Chinese menand women.	121 082	Multivariable adjust. Mortality rate (SBP 100-119mmHg reference)	1		
						In general population SBP < 100 mmHg		1.30 (1.03–1.64)	$P < 0.0001$
						In male SBP < 100 mmHg		1.46 (1.14–1.86)	$P < 0.0001$
						In female SBP < 100 mmHg		0.56 (0.24–1.29)	$P < 0.017$
						In general population SBP 120–139 mmHg		**1.13 (1.03–1.24)**	$P < 0.0001$
						In male SBP 120–139 mmHg		1.14 (1.04–1.26)	$P < 0.0001$
						In female SBP 120–139 mmHg		1.02 (0.75–1.39)	$P < 0.017$
						In general population SBP 140–159 mmHg		1.29 (1.17–1.44)	$P < 0.0001$
						In male SBP 140–159 mmHg		1.29 (1.16–1.44)	$P < 0.0001$
						In female SBP 140–159 mmHg		1.44 (1.01–2.07)	$P < 0.017$
						In general population SBP 160–179 mmHg		1.57 (1.39–1.78)	$P < 0.0001$
						In male SBP 160–179 mmHg		1.57 (1.38–1.79)	$P < 0.0001$
						In female SBP 160–179 mmHg		1.63 (1.04–2.55)	$P < 0.017$
						In general population SBP ≥ 180 mmHg		2.09 (1.79–2.44)	$P < 0.0001$
						In male SBP ≥ 180 mmHg		2.07 (1.76–2.43)	$P < 0.0001$
						In female SBP ≥ 180 mmHg		2.31 (1.27–4.20)	$P < 0.017$

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Table 3 Continued

S. No	Reference	Study type	Country	Study objective	Sample size	Events/Outcomes	Life time risk		
							Normotensives	Hypertensives	Lifetime risk difference
14	Holmqvist L. *et al.* 2018[51]	Cohort	Sweden	To assess CV outcome in patients with TRH compared with patients with non-TRH	4317	**TRHN compared with non-resistant HTN**			
						Age-sex adjusted total mortality risk		1.10 (1.01–1.20)	$P < 0.05$
						Multivariable adjusted total mortality		1.12 (1.03–1.23)	$P < 0.05$
						Age-sex adjusted CVD mortality risk		1.27 (1.10–1.47)	$P < 0.05$
						Multivariable adjusted CVD mortality risk		1.20 (1.03–1.40)	$P < 0.05$
						Age-sex adjusted IHD risk		1.16 (1.02–1.31)	$P < 0.05$
						Multivariable adjusted IHD risk		1.12 (0.99–1.27)	$P < 0.05$
						Age-sex adjusted Angina pectoris risk		1.27 (1.07–1.51)	$P < 0.05$
						Multivariable adjusted Angina risk		1.24 (1.03–1.48)	$P < 0.05$
						Age-sex adjusted MI risk		1.08 (0.93–1.25)	$P > 0.05$
						Multivariable adjusted MI risk		1.03 (0.89–1.20)	$P > 0.05$
						Age-sex adjusted HF risk		1.31 (1.15–1.49)	$P < 0.05$
						Multivariable adjusted HF risk		1.34 (1.17–1.54)	$P < 0.05$
						Age-sex adjusted stroke risk		1.11 (0.97–1.27)	$P > 0.05$
						Multivariable adjusted stroke risk		1.03 (0.90–1.19)	$P > 0.05$
						Age-sex adjusted TIA risk		1.12 (0.87–1.45)	$P > 0.05$
						Multivariable adjusted TIA risk		1.12 (0.86–1.46)	$P > 0.05$

Note: BP target used in the SPRINT criteria was defined as systolic BP <120 mm Hg, and BP targets used in the 2014 hypertension recommendations were defined as BP <140/90 mm Hg in subjects 18 to 59 years of age without CKD or diabetes, BP <150/90 mm Hg in subjects $60 years of age without CKD or diabetes, BP <140/90 mm Hg in subjects with CKD, and BP <140/90 mm Hg in subjects with diabetes.

MACE (Major cardiovascular events) or *composite outcomes: included nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes. Each component of myocardial infarction and stroke included fatal and nonfatal events.

Multivariable adjusted: adjusted for age, sex, smoking, diabetes mellitus, atrial fibrillation/flutter, BMI, SBP, estimated glomerular filtration rate, LDL, cancer, country of birth, level of education and annual income.

Abbreviations: ALLHAT, Antihypertensive and Lipid Lowering Treatment to Prevent Heart Attack Trial; ARIC, Atherosclerosis Risk in Communities; CHA, Chicago Heart Association Detection Project in Industry; CHS, Cardiovascular Health Study; HR, hazard ratio; IRR, incidence rate ratio; MACE, composite of fatal coronary heart disease, nonfatal myocardial infarction, resuscitated cardiac arrest, and stroke; RD, rate differences (events/10 000 person-years); REGARDS, REasons for Geographic And Racial Differences in Stroke; RD, risk difference; RR, relative risk.

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JNC-8 recommendations showed that the rate of CV death was [1.11 (95% CI, 0.71–1.73) and 1.39 (95% CI, 0.87–2.20), $P = 0.13$] above SPRINT but below JNC 8 BP goal, and above JNC-8 goal respectively. Similarly, rate of all-cause mortality was [0.83 (0.72–0.95) and 0.98 (95% CI, 0.84–1.15), $P = 0.22$] above SPRINT but below JNC 8 BP goal, and above JNC-8 goal respectively.[49]

A cohort study conducted to determine the prevalence and outcomes of apparent treatment-resistant hypertension (aTRH) showed that the relative risk of developing major cardiac events (MACE) 1.64 (95% CI, 1.39–1.94, $P < 0.001$), CHD death 1.69 (95% CI, 1.22–2.34, $P < 0.001$) and all-cause mortality 1.45 (95% CI, 1.12–1.89, $P = 0.005$).[43] Another cohort study conducted to assess CV outcome in patients with treatment-resistant hypertension (TRH) compared with patients with non-TRH in Sweden among 4317 showed that the relative risk of all-cause mortality was 1.12 (1.03–1.23) and CVD mortality was 1.20 (1.03–1.40).[51] A similar cohort study conducted to evaluate the association of apparent aTRH with CHD and stroke events in the USA among 14 522 patients with aTRH showed that the relative risk of developing CHD and all-cause mortality was 1.69 (95% CI, 1.27–2.24) and 1.29 (95% CI, 1.14–1.46), respectively. The risk of CHD in uncontrolled aTRH compared with controlled aTRH was 2.33 (95% CI, 1.21–4.48).[44] A cohort study conducted among 478 385 patients showed that patients with resistant hypertension [controlled resistant hypertension (cRH) and uncontrolled resistant hypertension (uRH)] had increased risk of ischemic heart event 1.24 (95% CI, 1.20–1.28), HF.46 (95% CI, 1.40–1.52), cardiovascular events (HR = 1.14, 1.10–1.19), end-stage renal disease (ESRD) 1.32 (95% CI, 1.27–1.37) and all-cause mortality 1.06 (95% CI, 1.03–1.08) when compared with the non-RH population.[45]

Association between hypertension and heart failure

A cohort study conducted to estimate the lifetime risk of HF by race and gender showed that the relative risk of developing HF among white men, white women and black women with BP ≤ 120/80 mmHg in 45 years old was 9.8%, 9.9% and 6.9%, respectively. The relative risk of developing HF among white men, white women, black men and black women with BP 140–159/90–99 mmHg at 45 years was 12.1%, 8.6%, 13.9% and 6.7%, respectively. Similarly, the relative risk of developing HF among white men, white women, black men and black women with BP ≥ 160/100 mmHg or treated at 45 years was 16.3%, 13.3%, 12.7% and 16.0%.[39] A cohort study conducted in the USA to examine the risk of CV events among adults with hypertension in reference to SBP < 120 mmHg among 4480 adults showed that RR of developing HF was 1.49 (95% CI, 1.23–1.81) at SBP ≥ 140 mmHg [i.e. 1.44 (95% CI, 1.08–1.92) in men and 1.54 (95% CI, 1.18–2.02) in women].[42] A cohort study conducted in the UK showed that HF was 1.5 times more common in patients with hypertension than in those with normal blood pressure 1.5 (95% CI, 1.44–1.55).[33] A cohort study conducted to determine the prevalence and outcomes of apparent treatment-resistant hypertension (aTRH) showed that the relative risk of developing HF 1.37 (95% CI, 0.88–2.13, $P = 0.1610$) when compared with non-resistant hypertension.[43]

Association between hypertension and angina pectoris

A cohort study conducted in the UK showed that the RR of developing stable angina among hypertensive adults, 30–59 years old normotensives, 60–79 years old normotensives and ≥80 years old normotensives were 1.41 (95% CI, 1.36–1.46); 0.63 (95% CI, 0.53–0.76); 0.77 (95% CI, 0.70–0.85); and 0.64 (95% CI, 0.47–0.87), respectively. Similarly, the relative risk of developing unstable angina among hypertensive adults, 30–59 years old normotensives, 60–79 years old normotensives and ≥80 years old normotensives were 1.25 (95% CI, 1.18–1.32); 0.70 (95% CI, 0.60–0.81); 0.78 (95% CI, 0.71–0.86); and 0.89 (95% CI, 0.70–1.13), respectively. Stable angina was 1.8 times more common in patients with hypertension than in those with normal blood pressure and stable angina with a lifetime risk ratio of 1.82 (95% CI, 1.76–1.87).[33] A cohort study conducted to determine the prevalence and outcomes of apparent treatment-resistant hypertension (aTRH) showed that the relative risk of developing angina pectoris 1.98 (95% CI, 1.58–2.47, $P < 0.0001$).[43]

Association between hypertension and myocardial infarction

A cohort study conducted in the USA to examine the risk of CV events among adults with hypertension in reference to SBP < 120 mmHg among 4480 adults showed a higher risk of developing MI at SBP ≥ 140 mmHg among men 1.53 (95% CI, 1.10–2.13) in men and 1.18 (95% CI, 0.85–1.65) in women.[42] A cohort study conducted in the UK showed that the relative of developing MI among hypertensive adults, 30–59 years old normotensives, 60–79 years old normotensives and ≥80 years old normotensive were 1.29 (95% CI, 1.25–1.34), 0.68 (95% CI, 0.58–0.80), 0.78 (95% CI, 0.70–0.87) and 0.86 (95% CI, 0.70–1.05), respectively.[33] Another cohort study conducted among 97 013 Chinese adults showed that risk of MI at age below 50 years and ≥50 years were 1.08 (RR = 1.09, 0.93–1.27), 1.04 (95% CI, 1.04–1.15) and 1.17 (95% CI, 1.14–1.19), respectively.[46] A cohort study conducted to determine the prevalence and outcomes of apparent treatment-resistant hypertension (aTRH) showed that the relative risk of developing MI was 1.73 (95% CI, 1.39–2.16, $P < 0.0001$).[43]

Association between hypertension and stroke and transient ischemic attack

A cohort study conducted in the USA to examine the risk of incident CV events among adults with hypertension in reference to SBP < 120 mmHg among 4480 adults showed that the relative risk of developing stroke at SBP ≥ 140 mmHg was 1.87 (95% CI, 1.43–2.44) [i.e. 1.90 (95% CI, 1.27–2.85) men and 1.83 (95% CI, 1.28–2.61) in women].[42] A cohort study conducted in the UK showed that higher risk of developing ischemic stroke was 1.35 (95% CI, 1.28–1.42), subarachnoid hemorrhage (SAH) 1.43 (95% CI, 1.25–1.63); and intracerebral hemorrhage (ICH) 1.44 (95% CI, 1.32–1.58) among hypertensive adults.[33] Another cohort study conducted among 97 013 Chinese adults showed that the risk of hemorrhagic stroke, ischemic stroke below 50 years, was 1.41 (95% CI, 1.29–1.54) and 1.23 (95% CI, 1.14–1.33), respectively. Similarly, the risk of hemorrhagic stroke, ischemic stroke at ≥50 years, was 1.22 (95% CI, 1.16–1.28) and 1.18 (95% CI, 1.14–1.21, $P < 0.01$), respectively.[46]

According to a cohort study conducted in Spain among adults aged ≥30 years of age, the risk of hypertension attributed stroke hospital admission was 40 (95% CI, 24.1–55.8) and 14.7 (95% CI, 2.3–27.0) in men and women, respectively.[47] A cohort study conducted in Japan to clarify the relationship between BP and mortality from stroke, heart disease, CVD, and all causes of death showed that the RR of stroke case mortality was 1.36 (95% CI, 0.27–6.82, $P < 0.001$), and 3.0 (95% CI, 0.95–9.44, $P = 0.004$) among men and

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women respectively at BP 120–129/80–84 mmHg when compared with BP < 120/80 mmHg.[48] A cohort study conducted in Korea to estimate the proportion of hypertensive adults who would meet BP goals under SPRINT criteria and JNC-8 recommendations showed that the rate of developing stroke was 1.49 (95% CI, 1.38–1.61), 1.36 (95% CI, 1.05–1.76) and 1.92 (95% CI, 1.69–2.18) among adults with hypertension, below systolic blood pressure intervention trial (SPRINT) BP goal and above Eighth Joint National Committee (JNC-8) goal, respectively.[49]

A cohort study conducted in the UK among 1.2 million adults showed that the RR of developing TIA among hypertensive adults, 30–59 years old normotensives, 60–79 years old normotensives and ≥80 years old normotensives were 1.15 (95% CI, 1.11–1.19), 1.06 (95% CI, 0.80–1.40), 0.92 (95% CI, 0.83–1.02) and 0.96 (95% CI, 0.82–1.11), respectively. Ischemic stroke, TIA was 1.1-times more common in patients with hypertension than in those with normal blood pressure.[33] A cohort study conducted to determine the prevalence and outcomes of apparent treatment-resistant hypertension (aTRH) showed that the relative risk of developing stroke 1.52 (95% CI, 1.05–2.19, $P < 0.025$).[43] Another cohort study conducted to assess CV outcome in patients with TRH compared with patients with non-TRH in Sweden among 4317 showed that the relative risk of incident stroke 1.03 (95% CI, 0.90–1.19), and TIA 1.12 (95% CI, 0.86–1.46).[51] A similar cohort study conducted to evaluate the association of apparent aTRH with CHD and stroke events in the USA among 14 522 patients with aTRH showed that the relative risk of developing stroke was 1.25 (95% CI, 0.94–1.6).[44]

Peripheral arterial disease and abdominal aortic aneurysm

A cohort study conducted in the UK among 1.2 million adults showed that the RR of developing PAD and AAA among hypertensive adults was 1.35 (95% CI, 1.30–1.40) and 1.08 (95% CI, 1.00–1.17), respectively.[33] The relative risk of developing PAD and AAA among 30–59 years old normotensives was 0.85 (95% CI, 0.71–1.03) and 0.93 (95% CI, 0.51–1.67), respectively.[33] The relative risk of developing PAD and AAA among 60–79 years old normotensive adults was 0.91 (95% CI, 0.82–1.01) and 0.95 (95% CI, 0.80–1.14), respectively.[33] The relative risk of developing PAD and AAA among ≥80 years old normotensives was 0.85 (95% CI, 0.68–1.07) and 0.88 (95% CI, 0.62–1.26), respectively. The AAA was 1.1-times more common in patients with hypertension than in those with normal blood pressure.[33]

Discussion

This systematic review described the risk of developing the following twelve vascular, cerebral and peripheral complications among hypertensive adults with treated and untreated hypertension. The included events were CHD and stroke mortality, unstable angina, stable angina, myocardial infarction, heart failure, cardiac arrest, transient ischemic attack, ischemic stroke, subarachnoid hemorrhage, intracranial hemorrhage, PAD and AAA.[33, 39–54]

The lifetime risk of total CVD at 30 years of age for people with hypertension and normal BP was 63.3% and 46.1%, respectively (absolute difference 17.2%). At age 60, the risk decreased to 60.2% and 44.6% for those with and without hypertension.[33] The relative risk of developing CHD events varies with the age and sex of patients. For example, in ≥60 years, SBP was no longer associated with subarachnoid hemorrhage or with AAA. In those aged ≥80 years, SBP is highly associated with stable angina, MI, intracerebral hemorrhage and PAD.[33] A cohort study showed that lifetime risks of developing CHD were 1.32 times higher at 50 years 51.7% (95% CI, 49.3–54.2) and 39.2% (95% CI, 37.0–41.4) for men and women, respectively [53]. A cohort study showed that at age 45 years, white men were at a six-fold increase of fatal CHD risk compared with white women, whereas black men had a two-fold increased risk of fatal CHD compared with black women.[55] A similar study showed that the lifetime risk of developing CVD at age 40 years was two in three in men and one in two in women. The prevalence of CHD is higher in men until after 75 years of age. After age 75, females have a longer life expectancy, and they account for a higher prevalence of CVD.[56]

The discrepancy was not explained by adjustment for CHD risk factors. This variation is also maintained across the general adult population. For example, a cohort study conducted among the general population showed that the relative risk of developing CHD events in men is 1.5 times higher than that of women across 40–60 years of age in the general population.[52]

Hypertension is associated with a higher risk of developing CHD death 1.26 (95% CI, 1.19–1.34) compared with normotensive adults.[33, 57] A cohort study conducted in Spain among adults aged ≥30 years showed that avoidable deaths attributed to hypertension were 41.8% and 37.84% in men and women, respectively.[47] A cohort study conducted relative risk of all-cause mortality at 40–59 years and 60–79 years was 5.99 (95% CI, 2.13–16.8) and 4.09 (95% CI, 1.70–9.85) respectively when compared with normotensive counterparts.[54] A rate of all-cause mortality was 1.3 (95% CI, 1.16–1.44) and 1.6 (95% CI, 1.38–1.79) times higher among adult men ≥18 years with SBP 140–159 mmHg and SBP 160–179 mmHg, respectively, when compared with when compared to SBP 100–119 mmHg.[50] A 20-year prospective cohort study conducted in Fangshan District, Beijing, China involving 7314 participants with a median follow-up a of 20 years showed that hypertension (BP ≥ 140/90 mm Hg) was significantly associated with mortality due to CVDs (HR = 2.49, 95% CI = 1.77–3.50) among people aged 35–59 years rather than people aged ≥60 years. However, stage 1 hypertension (BP 130–139/80–89 mm Hg) was not associated with an increased risk of CVDs mortality.[58]

A recent meta-analysis of 9 prospective cohort studies reported that achieving the most ideal cardiovascular health metrics including BP control is associated with a lower risk of all-cause mortality 0.55 (95% CI, 0.37–0.80), CV mortality 0.25 (95% CI, 0.10–0.63) and stroke 0.31 (95% CI, 0.25–0.38).[12, 13] BP control significantly reduced the rate of all-cause mortality.[59] For example, the rate of all-cause mortality was 4.45 (95% CI, 4.25–4.65) among hypertensives, 5.79 (95% CI, 5.11–6.57) among patients with uncontrolled BP and 4.08 (95% CI, 3.85–4.32) among those with uncontrolled BP.[49] Control of hypertension could reduce CVD mortality by 30.4% among males and 38.0% among females.[60] This difference could be explained by the longer life expectancy of women and the associated high prevalence of hypertension and associated chronic illness.

A meta-analysis of 61 prospective studies showed that at ages 40–69 years, each difference of 20/10 mmHg BP is associated with more than a two-fold difference in the stroke death rate and two-fold differences in the death rates from IHD and other vascular causes.[61] A systematic review and meta-analysis showed that reduction BP by 10 mm Hg of SBP or 5 mm Hg SBP was associated with the lower rate of CHD 0.73 (95% CI, 0.72–0.74) and all-cause mortality 0.86 (95% CI, 0.83–0.89) among 35–59 years hypertensives.[62] Another systematic review showed that average reduction of BP by 10 mm

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Hg of SBP or 5 mm Hg SBP was associated with a lower rate of CHD 0.77 (95% CI, 0.74–0.78), and all-cause-mortality 0.91 (95% CI, 0.91–0.92) among 60–74 years hypertensives.[63]

The lifetime risk of developing HF is higher among the adult hypertensive population across all ages.[40] The lifetime risk of developing heart failure at age 40 is 21% and 20.3% in men and women, respectively.[40] Hypertension is associated with an increased risk of heart failure, and 42% of patients with newly diagnosed CVD have HF.[64] A cohort study conducted in the USA among hypertensive adults showed that the relative risk of developing HF at SBP ≥ 140 mmHg was 1.44 (95% CI, 1.08–1.92) and 1.54 (95% CI, 1.18–2.02) among men and women respectively when compared with SBP < 120 mmHg.[42] Another study showed that the risk of developing HF at BP ≥ 160/100 mmHg is 2.3 and 1.3 times higher when compared with BP < 120/80 mmHg in black women and white women, respectively.[39] This could be explained by the greater prevalence of treatment-resistant hypertension in blacks.[65] In a large randomized trial of hypertension medication, black women had the lowest BP control rate (59%). In comparison with whites, blacks were more likely to be aware of their hypertension, those aware of their hypertension were more likely to be on treatment (OR, 1.69; 95% CI, 1.40–2.05), but those treated were still less likely to have their BP controlled (OR, 0.73; 95% CI, 0.64–0.83).[66]

A global congestive heart failure (G-CHF) cohort study conducted among 23 047 participants in 40 countries showed the most common causes of HF were ischemic (37.8%), hypertensive (20.0%), idiopathic (15.1%) and valvular disease (8.8%), respectively.[67] A large cohort study conducted in the UK showed that hypertension is associated with a higher risk of developing HF among hypertensive adults 1.27 (95% CI, 1.23–1.32) compared with normotensive adults aged ≥30 years.[33] The relative risk of developing HF was lower among patients with controlled BP 0.62 (95% CI, 0.45–0.84, $P = 0.002$).[59] Risk factors of HF vary substantially across world regions. Hypertension is highly associated with HF in all regions but most commonly in Latin America, the Caribbean, Eastern Europe and sub-Saharan Africa.[68] Therefore, it is important to consider HF in the cardiovascular disease policy model to evaluate the cost-effectiveness of hypertension treatment in Latin America, the Caribbean, Eastern Europe and sub-Saharan Africa.

Hypertension is a risk factor for all types of stroke. A cohort study conducted among 97 013 Chinese adults showed that the risk of hemorrhagic stroke, ischemic stroke below 50 years, was 1.41 (95% CI, 1.29–1.54) and 1.23 (95% CI, 1.14–1.33), respectively. Similarly, hemorrhagic stroke, ischemic stroke events ≥50 years were 1.22 (1.16–1.28) and 1.18 (95% CI, 1.14–1.21), respectively.[46] A cohort study conducted in Japan showed that RR of stroke case mortality was 1.36 ($P < 0.001$) and 3.0 ($P = 0.004$) among men and women respectively at BP 120–129/80–84 mmHg when compared with BP < 120/80 mmHg.[48] This is supported by evidence from a case–control study involving age-matched stroke-free, treated hypertensive patients in the USA, which showed that uncontrolled hypertension is associated with a higher risk of ischemic stroke 1.52 (95% CI, 1.2–1.94) and hemorrhagic stroke (HS) risk 3.0 (95% CI, 1.7–5.4).[69] A meta-analysis of 24 randomized trials among 47 991 individuals with high normal BP showed that BP-lowering treatment significantly reduced stroke risk.[70] A cohort study conducted in Sweden showed high BP was a stronger risk factor for stroke.[71] Hypertension is the major risk factor for all stroke types with an estimated population-attributable fraction (PAF) ranging from 35 to 52%, depending on the definition of hypertension and stroke subtypes.[72] Females have a higher lifetime risk of stroke than males. The lifetime risk of stroke among those 55–75 years of age was one in five for females and ≈1 in six for males.[73]

Another cohort study conducted in the USA showed that sustained BP control (<140/90 mmHg) had increased risk for nonfatal stroke 1.71 (95% CI, 1.26–2.32), transient ischemic attack 1.71 (95% CI, 1.26–2.32), respectively.[41] Cohort study conducted in USA among 4480 adults showed that RR of developing stroke at SBP ≥ 140 mmHg was 1.87 (95% CI, 1.43–2.44) [i.e. 1.90 (95% CI, 1.27–2.85), and 1.83 (95% CI, 1.28–2.61)] in men and women respectively when compared with SBP < 120 mmHg.[42] Another study showed that both treated and untreated hypertension were associated with higher odds of deep intracranial hemorrhage whites (OR = 2.13), blacks (OR = 4.45), and Hispanics (OR = 2.28). In patients with ICH, treated hypertension was a significant risk factor in Hispanics (OR = 7.07), but not in whites (OR= 1.53) or blacks (OR = 2.28). Untreated hypertension was a significant risk factor for ICH in all three ethnic groups: whites (OR = 11.64), blacks (OR = 5.11) and Hispanics (OR = 38.47).[16] The recent systematic review conducted to evaluate effects of intense BP control (<130/80 mmHg), which showed that relatively lower risk of stroke 0.81 (95% CI, 0.71–0.89), MI 0.76 (95% CI, 0.64–0.89), HF 0.80 (95% CI, 0.67–0.97) and CV death 0.88 (95% CI, 0.51–1.62) at BP below 130 mmHg when compared with SBP ≥ 130 mmHg.[74] A systematic review and meta-analysis showed that mean reduction BP by 10 mm Hg of SBP or 5 mm Hg DBP was associated with a lower rate of stroke 0.64 (95% CI, 0.61–0.66) among 35–59 years hypertensives.[62] Another systematic review showed that reducing SBP by 10 mm Hg or DBP 5 mm Hg was associated with the lower rate of stroke 0.69 (95% CI, 0.66–0.71) among 60–74 years of hypertensives.[63]

A meta-analysis of 34 studies, including a total of 73 184 patients with either ischemic stroke or TIA, the annual risk of recurrent stroke was 4.26% (95% CI, 3.43%–5.09%). The annual risk was 0.77% (95% CI, 0.45–1.10) for fatal stroke and 2.92% (95% CI, 2.22–3.62) for nonfatal stroke.[75] Transient ischemic attack contributes to a substantial short-term risk of stroke, hospitalization for CVD events and death.[76] Patients who survived the initial attack of transient ischemic attack have an estimated 10-year stroke risk of 19% and 43% combined 10-year risk of (stroke, MI or vascular death) (i.e. 4% per year).[77] A recent meta-analysis of nine trials showed that BP control to <150/90 mmHg reduces stroke 0.74 (95% CI, 0.65–0.84), and lower targets (≤140/85 mmHg) are associated with significant decreases in stroke 0.79 (95% CI, 0.59–0.99).[78] In a meta-analysis of clinical trials, antihypertensive therapy was associated with an average decline of 41% (95% CI, 33–48) in stroke incidence.[79] A standardized international age and sex-matched case–control study in 32 countries in Asia, America, Europe, Australia, the Middle East and Africa showed that history of hypertension or BP ≥140/90 mmHg significantly associated with all types of stroke (AOR = 2.98; 95% CI, 2.72–3.28).[80] A cohort study conducted in Korea showed that the risk of developing stroke was 1.49 (95% CI, 1.38–1.61), 1.36 (95% CI, 1.05–1.76) and 1.92 (99% CI 1.69–2.18) among hypertensives adults, patients with controlled BP and patients with uncontrolled BP, respectively.[49]

Hypertension is associated with the risk of acute coronary syndrome, including angina pectoris. Seventy percent of patients with angina had a previous history of hypertension.[81] Hypertension is associated with a higher risk of developing stable angina and unstable angina 1.41 (95% CI, 1.36–1.46) and 1.25 (95% CI, 1.18–1.32), respectively when compared with normotensive adults aged ≥30 years.[33] Concerning mortality implications of angina and BP

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in hypertensive patients with CAD, data from extended follow-up of the International Verapamil/Trandolapril Study (INVEST) showed that persistent-angina was significantly associated with an apparent protective effect (HR: 0.82, 95% CI, 0.75–0.89, $P < 0.0001$).[82] The systolic blood pressure intervention trial (SPRINT) was conducted to compare the safety and efficacy of intensive lowering of SBP to <120 mmHg versus routine management (i.e. <140 mmHg) among 9361 hypertensive patients aged 50 years and above with at least one of the following risk factors (i.e. presence of clinical or subclinical CVD other than stroke, or Framingham risk score for 10-year CVD risk ≥15%, or chronic kidney disease, or age > 75 years). The trial showed a lower relative risk of the composite outcome (MI, ACS, stroke, acute HF) in the intensive treatment group is 0.75 (95% CI, 0.64–0.89, $P < 0.001$).[59]

Concerning the association of hypertension with MI, a cohort study conducted in the UK showed that hypertension is associated with a higher risk of developing MI, 1.29 (95% CI, 1.25–1.34) compared with normotensive adults aged ≥30 years. MI had a stronger association with SBP in women than in men ($P < 0.0001$).[33] A cohort study conducted in Korea showed that the rate of developing MI was 1.02 (95% CI, 0.74–1.42) below JNC 8 BP goal and 1.51 (95% CI, 1.08–2.12) above JNC 8 BP goal.[49] Another cohort study conducted in the USA among 4480 adults showed that relative risk of developing MI at SBP ≥ 140 mmHg was 1.53 (95% CI, 1.10–2.13) and 1.18 (95% CI, 0.85–1.65) in men and women, respectively] when compared with SBP < 120 mmHg.[42] A study conducted to determine the association between antecedent hypertension and myocardial injury in patients with re-perfused ST-elevation MI showed that antecedent hypertension is associated with poor outcomes in patients with STEMI. MACE was more frequent in patients with hypertension as compared to patients without hypertension (HR = 3.42, 95% CI 1.45–8.08, $P < 0.01$).[83]

Concerning the mortality rate of MI, within one year after a first MI, 18% of males and 23% of females will die at ≥45 years of age. Similarly, in 45–64 years of age, 3% of white males, 5% of white females, 9% of black males and 10% of black females will die. Fourteen percent of white males, 18% of white females, 22% of black males and 21% of black females will die at 65–74 years of age. Twenty-seven percent of white males, 29% of white females, 19% of black males and 31% of black females will die at ≥75 years of age.[84] Within five years after a first MI: 36% of males and 47% of females will die at ≥45 years of age. Eleven percent of white males, 17% of white females, 16% of black males and 28% of black females will die at 45–64 years of age. Twenty-five percent of white males, 30% of white females, 33% of black males and 44% of black females will die at 65–74 years of age. Fifty-five percent of white males, 60% of white females, 61% of black males and 64% of black females will die at ≥75 years of age.[84]

A sudden cardiac death (SCD) is responsible for over 60% of all cardiovascular deaths. Hypertension is associated with a higher risk of developing sudden cardiac death 1.19 (95% CI, 1.10–1.29).[33] Each 20/10 mmHg increase in BP is associated with a 20% additional increase in SCD risk.[85] Antihypertensive treatment is expected to reduce the risk of SCD. However, a recent meta-analysis of 15 RCTs showed that antihypertensive treatment does not reduce the incidence of SCD.[86] A cohort study showed that LVH the highest risk for SCD (AOR = 2.99; 95% CI, 1.47–6.09; $P = 0.002$) after adjustment for age ($P < 0.0001$), sex ($P = 0.019$), diabetes mellitus ($P < 0.0001$) and 24-h ambulatory pulse pressure ($P = 0.036$).[87] Aggressive HTN control may lead, at least in part, to regression of LVH and thus lower the risk of AF and SCD.[88]

Regarding association of hypertension and PAD, hypertension is associated with a higher risk of developing PAD 1.35 (95% CI, 1.30–1.40) compared with normotensive adults aged ≥30 years.[33] About 35–55% of patients with PAD also having hypertension at presentation. A recent study among Chinese hypertensives showed that SBP, but not DBP, was an independent risk factor for low ankle-brachial pressure index.[89] Reanalysis of data from ALLHAT trial involving 33 357 patients showed that SBP < 120 mmHg was associated with a 26% (95% CI, 5–52; $P = 0.015$) higher hazard and SBP ≥ 160 mmHg was associated with a 21% (CI, 0–48; $P = 0.050$) higher hazard for a PAD event, in comparison with SBP 120–129 mmHg. Lower DBP was associated with a higher hazard of PAD events: for DBP < 60 mmHg (HR = 1.72, 95% CI, 1.38–2.16).[90] A cross-sectional study conducted to assess the prevalence and factors associated with PAD, and the usefulness of the ankle-brachial index (ABI) in evaluating cardiovascular risk in hypertensive patients showed that hypertension remained an independent factor associated with PAD (AOR = 3.20; 95% CI, 1.56–6.58).[91] Pooled data from 11 studies in six countries found that the pooled age-, sex, risk factor, and CVD adjusted RRs in people with PAD (defined by ABI < 0.9) versus those without were 1.45 (95% CI, 1.08–1.93) for CHD and 1.35 (95% CI, 1.10–1.65) for stroke.[92] The association between hypertension and PAD needs further strong results from a meta-analysis.

Hypertension is also associated with a higher risk of developing AAA 1.08 (95% CI, 1.00–1.17) when compared with normotensive adults.[33] However, the evidence concerning the association was not strong. For example, systematic review including data on 6619 AAA patients showed no association between hypertension and AAA ($P = 0.19$).[93] Another systematic review of 21 cohort studies showed that the RR of AAA in hypertensive patients is 1.66 times (95% CI: 1.49–1.85) of non-hypertensive patients. Besides, there was a 14% (95% CI: 6–23) and a 28% (95% CI: 12–46) increase in the RR of AAA for every 20 mmHg and 10 mmHg increase in SBP and DBP, respectively. Hypertension had increased the risk of developing AAA by 66%.[94] More strong evidence from the meta-analysis is required to justify the variation of risk between SBP and DBP. During modeling study, consistent relative risk and transition probabilities are required. Hence, the inclusion of AAA in CVD policy model during the cost-effectiveness evaluation of hypertension treatment is not reasonable.

Another important event not included in the previous CVD policy model was the issue of treatment-resistant hypertension. Apparent treatment-resistant hypertension (aTRH) is associated with a higher relative risk of developing MACE, CHD death, MI, stroke, angina pectoris and all-cause mortality.[43, 44, 51] A retrospective cohort study showed that patients with TRH were more likely to experience death, MI, HF, stroke or chronic kidney disease (CKD) compared to patients with controlled BP.[95] Another retrospective study conducted among patients with TRH showed that patients with TRH have a higher prevalence of comorbid conditions, including diabetes mellitus, ischemic heart disease (41% versus 22%) and cerebrovascular disease (16% versus 9%) compared to non-resistant hypertension.[45] In hypertensive patients with coronary artery disease (CAD), TRH's presence is associated with a higher risk of all-cause mortality, nonfatal MI and nonfatal stroke compared with treated hypertensive patients with controlled BP.[43, 96, 97] Therefore, it is important to consider the effect of treatment resistance on hypertension treatment outcomes during the analysis of hypertension treatment cost-effectiveness by using the CVD policy model. This can be done by either inclusion in the model structure on during setting model assumptions.

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Finally, the CVD policy model for evaluating cost-effectiveness is comprehensive to address the important variables (clinical states, secondary outcomes, treatment effects and costs).[27, 32] However, it is essential to consider HF in the CVD policy model to evaluate the cost-effectiveness of hypertension treatment, especially in Latin America, Caribbean, Eastern Europe and Sub-Saharan Africa as a strong association of hypertension and heart failure was reported from these regions. This should be done with due consideration of model complexity, diagnostic capacity of health facilities and data availability. Patients with TRH are exposed to three to a five-fold higher risk of cardiovascular events, including IHD, heart failure, stroke, CKD and peripheral vascular disease. Researchers should take the effect of treatment-resistant hypertension either through the basic model or setting the model assumptions.

Finally, hypertension is associated with the following 12 events CHD and stroke mortality, unstable angina, stable angina, myocardial infarction, heart failure, sudden cardiac death, transient ischemic attack, ischemic stroke, subarachnoid hemorrhage, intracranial hemorrhage, PAD and AAA. The exclusion of HF, PAD and AAA in the previous CVD policy model used to evaluate the cost-effectiveness of hypertension treatment was reasonable except for HF. Hypertension being highly associated with HF in Latin America, the Caribbean, Eastern Europe and Sub-Saharan Africa. Hypertension is associated with a higher risk of developing PAD. However, the association between hypertension and PAD needs further strong results from a meta-analysis. Hypertension increased the risk of developing AAA by two-third. The risk is highly associated with DBP than SBP, which requires further strong analysis to clear out this variation. Another critical concern not included in the previous CVD policy model was treatment-resistant hypertension. Treatment-resistant hypertension (aTRH) is associated with a higher relative risk of developing MACE, CHD death, MI, stroke, angina pectoris and all-cause mortality compared with non-treatment resistant hypertension.

Strengths and limitations

This review has the following strengths. First, it is the first systematic review conducted to address twelve CVD outcomes associated with hypertension in light of CVD policy model being used to evaluate the cost-effectiveness of hypertension treatment. Second, it suggested the inclusion of heart failure in the previous CVD policy model for cost-effectiveness evaluation of hypertension treatment in selected regions. Third, it also suggested consideration of apparent treatment-resistant hypertension during modeling or assumption setting. However, the findings of our study should be used in light of its limitations. We only included articles written in the English language, and articles in other languages could have an effect on the findings of the study.

Conclusion

In conclusion, the CVD policy model being used to evaluate cost-effectiveness is comprehensive to address the important variables in most regions. We recommend the inclusion of HF in CVD policy model for evaluating the cost-effectiveness of hypertension treatment in Latin America, Caribbean, Eastern Europe and Sub-Saharan Africa as a strong association of hypertension and HF was reported from these regions. This should be done with due consideration of model complexity, diagnostic capacity of health facilities and data availability. We do not recommend PAD and AAA's inclusion in the CVD policy model to evaluate the cost-effectiveness of hypertension treatment due to a lack of sufficient evidence. Researchers should also consider the effect of treatment-resistant hypertension either through including in the basic model or during setting the model assumptions.

Supplementary Material

Supplementary data are available at *Journal of Pharmaceutical Health Services Research* online.

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Authors' contributions

All authors read and approved the manuscript. *MM*, *MD and AK* have, framed the format design; conducted review and developed the manuscript for publication *NN and NS* participated in literature review and format design; *TS and SN* participated in literature review and polished the language of the manuscript; and *BF* has participated in quality appraisal and possibility of bias evaluation.

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Conflict of Interest

The authors declare that they have no competing interests.

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Data availability

Not Applicable. We used only published articles, and search strategy is provided in Supplementary file.

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