Most Important Outcomes Research Papers on Hypertension

Ruijun Chen, BA; Kumar Dharmarajan, MD, MBA; Vivek T. Kulkarni, AB; Natdanai Punnanathinont, MD, MPH; Aakriti Gupta, MBBS; Behnood Bikdeli, MD; Purav S. Mody, MBBS; Isuru Ranasinghe, MBChB, MMed, PhD, for the Editor

The following are highlights from the new series, Circulation: Cardiovascular Quality and Outcomes Topic Review. This series will summarize the most important manuscripts, as selected by the Editor, which have published in the Circulation portfolio. The objective of this new series is to provide our readership with a timely, comprehensive selection of important papers that are relevant to the quality and outcomes, as well as general cardiology audience. The studies included in this article represent the most significant research related to hypertension. (Circ Cardiovasc Qual Outcomes. 2013; 6:e26–e35.)

Essential or primary hypertension, the world’s leading risk factor for global disease burden, is expected to cause more than half of the estimated 17 million deaths per year resulting from cardiovascular disease (CVD) worldwide. Defined as an elevation of blood pressure (BP) beyond 140/90 mm Hg, hypertension is strongly correlated with adverse outcomes such as stroke, ischemic heart disease, heart failure, and end stage renal disease. The challenges of managing hypertension and preventing the development of these latter outcomes are unlikely to relent; the global burden of hypertension is projected to increase by 60% to affect approximately 1.6 billion adults worldwide by 2025. In this month’s topic review in Circulation: Cardiovascular Quality and Outcomes, we concentrate on this highly prevalent condition.

Considerable hurdles remain in overcoming the burden of hypertension. First, the insidious nature in which hypertension develops means that hypertension is frequently undiagnosed, and early detection prior to the development of end-organ damage remains a challenge. Second, many patients appropriately diagnosed with hypertension fail to achieve the treatment targets recommended by guidelines. This highlights the considerable challenges in implementing risk factor modification and appropriate adherence to antihypertensive therapies long term. Third, uncertainty remains as to the appropriate BP treatment target for high-risk patients. While a target BP <140/90 mm Hg is generally recommended, a lower threshold of <130/80 mm Hg is recommended for patients at high risk of CVD, such as patients with diabetes. Whether such intensive BP lowering leads to improved outcomes remains uncertain. Fourth, even among patients who receive appropriate care, a proportion of patients remains resistant to treatment despite multiple medications. These patients with resistant hypertension carry substantial risk of adverse events. The emergence of renal artery de-innervation may herald a novel and effective procedural option to treat these patients.

The challenges highlighted are pertinent to many populations. Many low- and middle-income countries, most of which are in the midst of the epidemiological transition, face rapidly increasing prevalence of hypertension in the context of limited healthcare resources. In these countries, diagnosis and appropriate management of hypertension remains disconcertingly low. Developing innovative and cost-effective solutions to improve hypertension diagnosis and control thus remains a key priority. These issues are not limited to developing countries alone; less than 50% of the US patients have appropriate BP control despite good access to care, a wealth of evidence surrounding lifestyle modification, and the presence of highly efficacious anti-hypertensive therapies. Indeed, such persistent deficiencies have fueled national initiatives such as the HealthyPeople 2020 and the Million Hearts initiative to focus on improving awareness, treatment, and, ultimately, outcomes of this common disorder.

Blood Pressure Targets Recommended by Guidelines and Incidence of Cardiovascular and Renal Events in the Ongoing Telmisartan Alone and in Combination With Ramipril Global Endpoint Trial (ONTARGET)

Summary: Guidelines recommend treatment of hypertension when BP exceeds 140/90 mm Hg or 130/80 mm Hg for patients at high risk of cardiovascular (CV) events. However, whether this lower threshold for treatment in patients at high risk necessarily leads to fewer CV events is uncertain with a few studies suggesting no benefit or even harm from the excessive lowering of BP. The Ongoing Telmisartan Alone and in Combination with Ramipril Global Endpoint Trial (ONTARGET) compared telmisartan with telmisartan plus ramipril for treatment of hypertension with a median follow-up of 56 months using a randomized control trial design. Using pooled data from this study, the authors performed an observational analysis to compare patients with an in-trial pre-event BP of <140/90 mm Hg with patients those who achieved an in-trial pre-event BP of <130/90 mm Hg. The study findings show that a progressive increase in the proportion of visits in which BP was reduced to <130/80 mm Hg, compared to reduction to <140/90 mm Hg, was associated with a reduction in the risk of stroke and renal events (defined as new onset of microalbuminuria or macroalbuminuria and return to normoalbuminuria in albuminuric patients). In contrast, tighter BP control to <140/90 mm Hg or <130/80 mm Hg did not have any consistent effect on the adjusted risk of myocardial infarction and heart failure. The composite of CV events was reduced by lowering BP to <140/90 mm Hg, but no additional benefit was observed with lowering to <130/80 mm Hg.
Conclusions: Data from the ONTARGET study suggests that tightly controlled BP <130/80 mmHg does not necessarily lower cardiovascular events compared to a target BP of <140/90mmHg, raising debate as to the appropriateness of the targets recommended in current guidelines. However, many patients fail to meet either of these targets in clinical practice and achieving any form of BP control remains a challenge. As indicated in this study, tight BP control does have additional non-cardiac benefits including reducing the risk of stroke and renal events, which are important endpoints from a patient perspective. Furthermore in these high risk individuals, tighter BP control <130/80 was not necessarily associated with adverse patients outcomes and thus may be an appropriate goal for these patients. These results must also be interpreted with caution; this study is a non-randomized post-hoc observational analysis, subject to potential bias, and is not a substitute for a well-designed randomized trial.

Blood Pressure Targets in Subjects With Type 2 Diabetes Mellitus/Impaired Fasting Glucose: Observations From Traditional and Bayesian Random-Effects Meta-Analyses of Randomized Trials

Summary: Guidelines recommended aggressive lowering of BP in patients with diabetes with a target BP <130/80 compared with a target BP of <140/90 for the general population. Whether this leads to better outcomes among diabetic patients has been debated. In this study, the authors performed a meta-analysis of randomized clinical trials (RCTs) from 1965 to 2010 of antihypertensive therapy in patients with type 2 diabetes mellitus or impaired fasting glucose/impaired glucose tolerance. RCTs were included if they enrolled at least 100 patients who achieved systolic BP (SBP) of ≤ 135 mmHg in the intensive BP control group and ≤ 140 mmHg in the standard BP control group. Thirteen trials with 37,736 participants met the inclusion criteria. Intensive BP control was associated with a 10% reduction in all-cause mortality (odds ratio, 0.90; 95% CI 0.83 to 0.98) and a 17% reduction in stroke. A 20% increase in serious adverse effects was noted with intensive BP control but with no difference in other macrovascular and microvascular (cardiac, renal, and retinal) events, as compared with standard BP control. Lowering of BP below ≤130 mmHg was associated with further reductions in stroke risk, a trend which continued to a SBP of <120 mmHg. However, lowering of BP <130 mmHg was associated with 40% increase in serious adverse events and showed no benefit for other outcomes. The 10% reduction in all-cause mortality was largely driven by trials that achieved a SBP between 130–135 mmHg.

Conclusions: Continued debate persists about the appropriate target BP for hypertensive patients with diabetes. This meta-analysis suggests a treatment goal of 130-135 mmHg is associated with better outcomes compared to a target BP of <140/90 mmHg. Lowering of BP below <130/80 leads to reduced risk of stroke, at the expense of increased adverse events, and showed no benefits with regard to other micro or macrovascular events. As with most meta-analyses, there are some limitations which should be considered when interpreting these findings. Only 5 of the 13 trials were designed to specifically test a strategy of intensive versus standard BP lowering. Furthermore, the heterogeneity of the patient populations, comorbid conditions, and variations in the treatments used are potential drawbacks. However, despite these limitations, this study raises concerns about the current guideline recommendation of universal lowering of BP <130/80 in all diabetic patients to reduce cardiovascular risk.

National Surveillance Definitions for Hypertension Prevalence and Control Among Adults

Summary: Epidemiologic estimates of hypertension and hypertension control have been quite varied due to differences in cohort definitions and adjustment methodologies, even when the same data set has been used. The authors sought to characterize this variation using recent survey cycles of the National Health and Nutrition Examination Surveys (NHANES) from 2003 to 2008. They identified 19 studies that used various criteria for defining hypertension and hypertension control. Although the definition of hypertension was uniformly a systolic blood pressure (SBP) ≥140mmHg or a diastolic blood pressure (DBP) ≥90mmHg, studies varied in: (1) the use of patient self-report to define the presence of hypertension; (2) the inclusion of all individuals with hypertension or just treated patients when assessing hypertension control; (3) the age range of included patients; (4) the decision to include pregnant women; (5) report of crude versus age-adjusted rates; and many other parameters. As a result of these differences, crude prevalence of hypertension among adults varied from 28.9% to 49.9%, and age-adjusted prevalence varied from 28.9% to 32.1%. Crude hypertension control varied from 37% to 52.9%, and age-adjusted hypertension control varied from 35.1% to 64%. Using standard surveillance definitions proposed by the American Heart Association, the authors found the age-standardized prevalence of hypertension to be 29.8% and rate of hypertension control to be 45.8%.

Conclusions: The authors found significant variation in estimates of hypertension prevalence and control in the current medical literature even when using the same baseline data from NHANES because of different definitions. These findings demonstrate the need to standardize definitions in epidemiologic surveys in order to permit valid comparisons between populations and calculation of trends over time. Readers of the hypertension literature should be made aware that study definitions and methodology can significantly influence epidemiologic estimates. Although not tested in this study, it is possible that significant variability in the definitions of hypertension and hypertension control is also present in clinical trials. It may therefore be prudent to standardize definitions of hypertension-related parameters for trials in a parallel way to what has been done by the Bleeding Academic Research Consortium and Valve Academic Research Consortium.

Epidemiology of Diagnosis and Management of Hypertension

Significant advances have been made in the diagnosis and management of hypertension as contemporary studies have increased our understanding of the risk factors and the effectiveness of treatments. Large clinical trials have screened for and confirmed the BP lowering effects of weight loss, sodium reduction, dietary modification, exercise, and alcohol reduction. Such findings led to the ongoing promotion of healthier lifestyles to protect against the development of hypertension, achieved through enhanced public understanding and community-based strategies sponsored by non-profit and government organizations such as the National Heart, Lung, and Blood Institute (NHLBI). Coincident with these lifestyle changes which serve as both preventative measures and early treatment of hypertension, extensive research has been performed on drug development and optimal drug regimens, resulting in multiple highly effective therapeutic options for the treatment of hypertension. Clinical management has benefited from the rapid testing of new treatment strategies and evolving guidelines which are frequently updated to maximize positive outcomes for patients. Additional studies have similarly guided the incorporation of angiotensin converting enzyme inhibitors, angiotensin II receptor antagonists, and calcium channel blockers into our treatment arsenal, optimized their use in different clinical scenarios, and identified combination therapy as both a highly necessary and effective means of BP management.

As a result of these advancements in the scientific literature, we may expect to observe changes in the epidemiology and trends in the awareness, treatment, and effective BP control of hypertensive patients along with their associations with outcomes. Here, we summarize a number of papers which investigate contemporary
epidemiology and trends over time in the diagnosis and management of hypertension across a variety of patient populations.

**Trends in Antihypertensive Medication Use and Blood Pressure Control Among United States Adults with Hypertension: The National Health and Nutrition Examination Survey, 2001 to 2010**

**Summary:** Previous research has suggested that rates of treatment and control of hypertension in the US have been suboptimal. The authors therefore examine recent trends in antihypertensive medication use and its impact on blood pressure control using the National Health and Nutrition Examination Survey from 2001 to 2010. Blood pressure control was defined as <140/90 mmHg for the general population and BP < 130/80 mmHg for patients with diabetes mellitus or chronic kidney disease. The prevalence of antihypertensive medication use increased from 64% to 77% during this decade, and blood pressure control rates improved from 29% to 47%. Antihypertensive polytherapy regimens appeared to control blood pressure significantly better than monotherapy regimens. The study also shows that younger people, Mexican-Americans, and those without health insurance were undertreated. In contrast, hypertension in older people, non-Hispanic blacks, persons with diabetes mellitus, and persons with chronic kidney disease was more likely to be controlled with treatment.

**Conclusions:** The study is the most recent nationally representative study to document trends of antihypertensive medication use and disease-specific rates of blood pressure control. The authors found encouraging evidence of improvement in blood pressure control in the US adults during the past decade, which appears to have been facilitated by increased use of combination therapy regimens in the treated hypertensive population. However, disparities remain in blood pressure control among specific subpopulations such as younger persons. Furthermore, despite these encouraging improvements, less than one-half of the population appears to have adequate blood pressure control, which presents substantial opportunities for improvement.

**Trends in Blood Pressure and Hypertension Detection, Treatment, and Control 1980 to 2009: The Minnesota Heart Survey**

**Summary:** Recent national preventative health initiatives such as Healthy People 2020, have set high goals for improvement in the detection, treatment, and control of hypertension. This study evaluated trends in population blood pressure and hypertension detection, treatment, and control using the Minnesota Heart Survey from 1980 to 2009. In total, 23978 adults (11 192 men, 12 795 women) aged 25 to 74 years participated in six cross-sectional surveys taken 5 yearly, representing the Minneapolis/St. Paul metropolitan area. Over the 30 year study period, systolic and diastolic blood pressures decreased significantly over time for both men (SBP from 124.9 mmHg to 121.1 mmHg; DBP from 78.1 mmHg to 75.5 mmHg) and women (SBP from 120.1 mmHg to 114.7 mmHg; DBP from 74.0 mmHg to 70.6 mmHg), with most of the differences occurring among treated hypertensive patients (p<0.0001). There was also a dramatic increase in the population who were aware, treated with medications, and had their blood pressure controlled, accounting for 66% of men and 72% of women in the 2007–2009 survey. The number of individuals with uncontrolled blood pressure (BP ≥140/90), irrespective of anti-hypertensive therapy, declined from 20.3% to 5.8% for men and from 13.1% to 2.7% for women (p<0.0001). Stroke mortality trends from 1990–2009 declined in parallel with the observed decline in BP during the study period.

**Conclusions:** This study shows that the diagnosis, treatment, and control of hypertension have improved drastically from 1980 to 2009 in the Minneapolis/St. Paul region, with better levels of treatment and control along with lower average blood pressures than observed nationally. It is important to note that compared to the entire US, survey population is 90% white, has one of the highest levels of health insurance coverage, fewer people in poverty, and higher average educational levels. Despite these differences, these results demonstrate that high levels of control are already possible in certain regions, providing support that in time, the Healthy People 2020 goal of having 61.2% of the hypertensive population aware, treated, and controlled may be achievable nationwide.

**Blood Pressure Control Among US Veterans: A Large Multiyear Analysis of Blood Pressure Data from the Veterans Administration Health Data Repository**

**Summary:** Control of blood pressure among patients with hypertension has been associated with improved cardiovascular outcomes. The authors sought to assess improvements in hypertension control from 2000 to 2010 among a large cohort of hypertensive patients treated at 15 Department of Veterans Affairs medical centers. The main outcome measure was the percentage of hypertensive patients with controlled blood pressure, which was defined as those patients with 23 days of BP readings but no days with BP elevated. The average SBP during the 10 year period decreased from 143/77 mmHg in 2000 to 131/75 mmHg in 2010. Correspondingly, the proportion of patients with controlled blood pressures increased over time from 45.7% in 2000 to 76.3% in 2010. On average, control rates increased by 3.0% per year. Improvement was similar across all age, sex, and race groups. Interestingly, both systolic and diastolic blood pressures were lower in the summer compared with the winter for the whole period of the study, and blood pressure control rates were 6.8% better during the summer months.

**Conclusions:** The authors found a steady improvement in blood pressure control among US veterans over a 10-year period; control did not significantly vary by patient age, sex, or race. The degree of improvement in blood pressure control in this patient cohort greatly outstrips that of the US in general, which was from 35% to 50% over a similar time period. The source of this substantial difference is unknown, though may relate to the implementation of electronic medical records into the VA system that automatically notify doctors of patients' blood pressure elevation as well as significant outpatient capacity in which to schedule frequent follow up appointments until blood pressure is adequately controlled.

**Prevalence, Awareness, Treatment, and Control of Hypertension Among Residents in Guangdong Province, China, 2004 to 2007**

**Summary:** Hypertension in China has become a major public health problem, but little is known about trends in hypertension at the provincial level. Such provincial trends are important for identifying areas of need and future public health planning in the context of limited national healthcare resources. This study described the trends in the prevalence and rates of hypertension awareness, treatment, and control in Guangdong Province, the most populous Chinese province. Data were derived from the Guangdong Provincial Chronic Disease Risk Factor Surveillance, a representative cross-sectional survey of residents 18 to 69 years of age and compared 7633 participants in 2004 with 6447 participants in 2007. During this period, the age-standardized prevalence of hypertension increased from 12.2% to 15.4% (p<0.001), with the greatest increase in the rural population. Hypertension awareness and treatment was poor and did not differ significantly (25.6% to 25.8%; 21.7% to 22.2%, respectively). Hypertension control was rarely achieved and in fact worsened from 7.1% to 4.5% (p<0.01). Over the study period, mean body mass
index, systolic and diastolic blood pressure, and mean waist circumference all significantly increased (p<0.01).

**Conclusions:** Recent trends in Guangdong Province show that adverse markers of health outcomes including blood pressures, body mass index, and waist circumference have increased along with the prevalence of hypertension. However, awareness, treatment, and control of hypertension are poor, remaining unchanged or worse, suggesting that clinical care in the region has not improved to meet the increased needs of the population. Similar findings have been shown from national surveys which have indicated a prevalence of hypertension at 17% to 27%, awareness at 24% to 45%, treatment at 28% to 78%, and control at 8% to 19%. These national findings together with the results of this study highlight the major challenges in detecting and managing hypertension in China, as they lag far behind the 77% treated and 47% controlled seen in the US population. With numbers comparable to the lower end of the national spectrum or worse, Guangdong Province may be an important underperforming region which requires particular attention and resources in the future.

Guangdong Province may be an important underperforming region.

**Hypertension Control Among Patients Followed by Cardiologists**

**Summary:** Despite the high numbers of patients with hypertension treated by cardiologists, most studies on hypertension control have focused on primary care settings. This study evaluated hypertension control rates of patients cared for longitudinally by cardiologist in the cardiology clinics at Duke University Medical Center. It also assessed physician-level variation in these control rates and clinician response to elevated BP in the clinic. A total of 5979 patients with diagnosed hypertension in 47 cardiologists’ clinics were included in the study period from June 2009 to June 2010. The rate of sub-optimally controlled BP $\geq$140/90 among these patients was 30.3% and varied across cardiologists’ clinics with a range from 16% to 44%. These variations remained significant after risk adjustment for patient characteristics. Cardiologists failed to document a response to a finding of an elevated BP in the medical record in 38% of patients.

**Conclusions:** A large proportion of patients with hypertension seen in cardiology clinics have suboptimally controlled BP which varies widely across cardiologists and is often not addressed during the course of the clinic visit. These results may not be generalizable since the study was performed at a single center and 98% of these patients had health insurance. However, given the co-morbid effects that hypertension has on a large number of cardiovascular diseases, cardiologists should not overlook the importance of BP management and need take on an active role, sharing responsibility for effective control together with primary care providers.

**Trends in Mortality from All Causes and Cardiovascular Disease Among Hypertensive and Nonhypertensive Adults in the United States**

**Summary:** Despite improvement in the identification and control of hypertension over the past decades, relatively little is known about trends in mortality among persons with hypertension in the United States. This study aims to examine trends in all-cause and cardiovascular mortality among persons with and without hypertension over the past 4 decades. The authors used the data from the National Health and Nutritional Examination Survey (NHANES) I Epidemiological Follow-Up Study (1971 to 1975) and NHANES III Linked Mortality Study (1988 to 1994). Follow up was for a mean of 17.5 and 14.2 years, respectively. Not surprisingly, the authors found higher mortality among hypertensive adults compared with nonhypertensive adults in each cohort. Among hypertensive adults, adjusted mortality rate from all causes decreased by 4.6 per 1,000 person-years and adjusted mortality rate from CVD decreased by 3.6 per 1,000 person-years.

Among non-hypertensive adults, adjusted mortality rate from all causes decreased by 4.2 per 1,000 person-years and the adjusted mortality rate from CVD decreased by 2.6 per 1,000 person-years. Over the study period, reduction in adjusted mortality was highest among hypertensive men and hypertensive blacks and lowest among hypertensive women, in particular.

**Conclusions:** Although both all-cause and cardiovascular mortality declined significantly for adults with hypertension over the study period, it is unclear whether these results are due to improved hypertension control or rather reflect population wide-trends, as non-hypertensive adults also experienced significant declines in mortality. In addition, the reasons for greatest mortality reduction among hypertensive men and blacks compared with hypertensive women is unknown but may reflect the fact that compared with women and whites, men and blacks with hypertension have higher absolute cardiovascular risk and may therefore have greater opportunity for improvement.

**Interventions and Treatment Programs for Hypertension**

Despite the demonstrated efficacy of lifestyle changes and pharmaceutical agents in lowering blood pressure, hypertension remains poorly controlled in many populations and practice settings due to ineffective implementation of prevention and treatment strategies. On the other hand, even among patients receiving intensive pharmacotherapy, some patients’ hypertension remains resistant to treatment. Regardless of the cause, patients with suboptimally controlled hypertension remain at elevated risk for cardiovascular events, and efforts should be directed towards improving hypertension control in these patients.

In the following section, we review research aimed at improving hypertension control by implementing standardized prevention and treatment strategies across various practice settings—including pharmacist-led interventions, educational programs in Pakistan, and dietary protein supplementation—as well as the Symplicity HTN-2 trial of renal denervation for drug-resistant hypertension.

**A Pharmacist-Led, American Heart Association Heart360 Web-Enabled Home Blood Pressure Monitoring Program**

**Summary:** Home blood pressure monitoring (HBPM) is a promising modality for improving blood pressure control in patients with hypertension. In this study, the authors conducted a randomized, controlled trial to evaluate a HBPM program utilizing the American Heart Association’s Heart360 web application, a free tool to help patients and providers monitor cardiovascular risk factors. Adult patients in the Kaiser Permanente system with BPs above goal (BP $\geq$140/90 mm Hg or $\geq$130/80 mm Hg for patients with diabetes mellitus (DM) or chronic kidney disease (CKD) were randomized to a HBPM group or a usual care group. Patients in the usual care group (n=175) received written educational materials and instructions to follow up with their physicians. Patients in the HBPM group (n=171) additionally received a home BP monitor, pharmacist-led instruction in proper use, assistance with the Heart360 website, and instructions on how to upload their home BP readings to the site. These patients then took 3 BP measurements weekly. For patients in the HBPM group, clinical pharmacists made medication adjustments as needed and communicated via telephone or e-mail. The 2 groups did not differ in their demographic characteristics or their initial BP readings. After 6 months, the proportion of patients with achieving BP goal was 54.1% in the HBPM group compared with 35.4% in the usual care group (adjusted risk ratio (aRR), 1.5; 95% confidence interval (CI), 1.2–1.9). In the subset of patients with DM or CKD, the difference was even larger (51.7% v. 21.9%; aRR, 2.5; 95% CI, 1.6–3.8). Patients in the HBPM group also experienced significantly larger drops in SBP (20.7 mm Hg versus 8.2 mm Hg) and DBP (10.5 mm Hg versus 4.8 mm Hg) compared with the usual care group.
There was no difference between the groups in the number of clinic visits, emergency department visits, or hospitalizations, but patients in the HBPM group had significantly more telephone and e-mail encounters and a larger fraction reported being very or completely satisfied with their hypertension care than those in the usual care group.

Conclusions: This study shows promise that a pharmacist-led HBPM program can substantially improve BP control in a diverse group of patients in routine clinical practice, including those with DM or CKD. Free online tools such as the Heart360 website (https://www.heart360.org/) may facilitate these efforts. Nevertheless, substantial resources may be required to effect these changes. Most importantly, substantial time and interaction from clinical pharmacists was required to implement the study protocol, and it is difficult to distinguish the effects of home monitoring itself from the effects of pharmacist intervention.48

Effect of Dietary Protein Supplementation on Blood Pressure: A Randomized, Controlled Trial
Summary: Dietary modification is recommended for the prevention and treatment of hypertension. Previous observational data have suggested that increasing dietary intake of vegetable protein leads to lowering of blood pressure47 although this has not been evaluated in a randomized fashion. In this study, the authors evaluated whether the intake of vegetable protein (40 g soy protein/day) or animal protein (milk protein 40g/day) compared to placebo (40g/day carbohydrate supplementation) leads to a short-term reduction in BP using a randomized double-blind cross-over design. Patients with SBP of 120-159 mmHg and DBP of 80-95 mmHg were included. Patients on anti-hypertensive therapy were excluded. The study results show that in the 352 patients randomized, compared with controls, soy and milk protein supplementation was associated with 2.0 mmHg (95% CI 3.2 to 0.7 mmHg, p=0.002) and 2.3 mmHg (95% CI 3.7 to 1.0 mmHg, p=0.0007) reduction in SBP, respectively, with no change in DBP over the 8 week trial period. No significant difference in the magnitude of BP reduction was observed between soy and milk protein. Other markers such as weight, body mass index, blood glucose, total cholesterol, and LDL levels were unchanged with the exception of HDL, which was increased with soy protein intake.

Conclusions: This clinical trial provides intriguing data that suggest dietary modification with soy or milk protein may lead to a statistically and clinical significant reduction in SBP, but not DBP, in the short term. These findings must be interpreted with caution as these observations are yet to be replicated. Furthermore, it remains to be seen whether the BP reduction can be sustained long-term with improvements cardiovascular outcomes and whether the reduction in BP will extend to patients with more severe hypertension or those already receiving anti-hypertensive therapy. Nevertheless, this well designed study provides promising early evidence for dietary modification of protein as a viable population strategy for lowering systolic hypertension for primary and secondary prevention.49

Improving Blood Pressure Control Through a Clinical Pharmacist Outreach Program in Patients With Diabetes Mellitus in 2 High-Performing Health Systems: The Adherence and Intensification of Medications Cluster Randomized, Controlled Pragmatic Trial
Summary: This study evaluated the real-world viability of the Adherence and Intensification of Medications (AIM) intervention, a multifaceted strategy to improve medication adherence, in improving blood pressure control among patients with diabetes mellitus (DM). Diabetic patients with poor BP control and poor refill adherence were enrolled from 3 urban VA facilities in the Midwest and 2 Kaiser Permanente facilities in California. These patients were then randomized to either an AIM intervention group—which consisted of pharmacist-led motivational interviewing, medication adherence assessment, and changes to BP medications when appropriate—or a usual care group, with no staff contact. The AIM intervention has been described in detail elsewhere in the literature.45 The primary outcome was the change in SBP measurements at 6 months after the 14 month intervention period. There were no demographic or clinical differences between the intervention group (n=1797) and the usual care group (n=2303) at the time of randomization. At 3 months after the intervention period, mean SBP in the intervention group had dropped 9.7 mmHg versus 7.2 mmHg in the control group, a difference of 2.4 mmHg (p<.0001). However, at 6 months after the intervention period, the decline in SBP was not different in the intervention group (8.9 mmHg) compared to the usual care group (9.0 mmHg).

Conclusions: This pharmacist-led intervention aimed at improving BP control in patients with DM failed to show sustained improvement of SBP compared with usual care. As the authors acknowledge, the VA and Kaiser Permanente health systems are already “high-performing” with respect to BP control, in that more than 80% of patients are currently at goal. Thus, targeted interventions such as the AIM intervention may be more efficacious in populations for whom baseline control is poor, while the marginal benefit of such interventions in high-performing practices may be minimal.48

Cost-Effectiveness of Community-Based Strategies for Blood Pressure Control in a Low-Income Developing Country: Findings from a Cluster-Randomized, Factorial-Controlled Trial
Summary: Studies of cost effectiveness of interventions to reduce BP in low and middle income countries are limited in number. In this study, the authors performed a cost-effectiveness analysis of the Control of Blood Pressure and Risk Attenuation (COBRA) trial, which evaluated community based strategies to reduce BP by randomizing 1341 hypertensive subjects in 12 randomly selected communities in Karachi, Pakistan, to 3 intervention programs: (1) home health education (HHE) by community health workers focusing on risk factor modification (2) training of general practitioners (GP) in guideline-based BP management, and (3) combined HHE and GP training. The comparator was no intervention (usual care). The primary results of this study showed that the combined intervention (HHE and GP training) was associated with greater medication adherence and led to the most significant decline in SBP (10.8 mmHg reduction, 95% CI 8.9 to 12.8 mmHg) at 2 years.44 The cost-effectiveness considered the cost of the medications, costs to the patient in the health care received and the lifestyle changes advised, and losses in productivity. The results show that the combined intervention was the most cost-effective, with an incremental cost-effectiveness ratio (ICER) of US$23 (95% CI, 6–99) per 1 mmHg reduction in systolic BP compared with usual care. This estimate translated to an incremental per-capita cost of $0.43 per 1 mmHg reduction in SBP and an estimated US$1226 per CV disease related disability-adjusted life-year (DALY) averted from a societal perspective (or $0.49 per-capita cost per DALY averted).

Conclusions: This well conducted cost-effectiveness analyses, conducted from a societal perspective, suggest community based interventions are both effective and affordable in Pakistan. The reported ICER, per capita cost, and cost per DALY averted fall within the accepted ranges qualifying it to be cost-effective for developing countries, as set by the World Health Organization and other agencies.45,46 These findings have broad implications for other low and middle income countries facing the constant challenge of how best to care for people with high BP in the context of the rapidly increasing prevalence of hypertension and limited healthcare resources.8

Cluster-Randomized, Factorial-Controlled Trial
Performing Health Systems: The Adherence and Intensification of Medications Cluster Randomized, Controlled Pragmatic Trial

Conclusions: This study shows promise that a pharmacist-led HBPM intervention may be more efficacious in populations for whom patients are currently at goal. Thus, targeted interventions such as the AIM intervention may have a short-term benefit in improving BP control among patients with diabetes mellitus (DM). Diabetic patients with poor BP control and poor refill adherence were enrolled from 3 urban VA facilities in the Midwest and 2 Kaiser Permanente facilities in California. These patients were then randomized to either an AIM intervention group—which consisted of pharmacist-led motivational interviewing, medication adherence assessment, and changes to BP medications when appropriate—or a usual care group, with no staff contact. The AIM intervention has been described in detail elsewhere in the literature.45 The primary outcome was the change in SBP measurements at 6 months after the 14 month intervention period. There were no demographic or clinical differences between the intervention group (n=1797) and the usual care group (n=2303) at the time of randomization. At 3 months after the intervention period, mean SBP in the intervention group had dropped 9.7 mmHg versus 7.2 mmHg in the control group, a difference of 2.4 mmHg (p<.0001). However, at 6 months after the intervention period, the decline in SBP was not different in the intervention group (8.9 mmHg) compared to the usual care group (9.0 mmHg).

Conclusions: This pharmacist-led intervention aimed at improving BP control in patients with DM failed to show sustained improvement of SBP compared with usual care. As the authors acknowledge, the VA and Kaiser Permanente health systems are already “high-performing” with respect to BP control, in that more than 80% of patients are currently at goal. Thus, targeted interventions such as the AIM intervention may be more efficacious in populations for whom baseline control is poor, while the marginal benefit of such interventions in high-performing practices may be minimal.48

Effect of Dietary Protein Supplementation on Blood Pressure: A Randomized, Controlled Trial
Summary: Dietary modification is recommended for the prevention and treatment of hypertension. Previous observational data have suggested that increasing dietary intake of vegetable protein leads to lowering of blood pressure47 although this has not been evaluated in a randomized fashion. In this study, the authors evaluated whether the intake of vegetable protein (40 g soy protein/day) or animal protein (milk protein 40g/day) compared to placebo (40g/day carbohydrate supplementation) leads to a short-term reduction in BP using a randomized double-blind cross-over design. Patients with SBP of 120-159 mmHg and DBP of 80-95 mmHg were included. Patients on anti-hypertensive therapy were excluded. The study results show that in the 352 patients randomized, compared with controls, soy and milk protein supplementation was associated with 2.0 mmHg (95% CI 3.2 to 0.7 mmHg, p=0.002) and 2.3 mmHg (95% CI 3.7 to 1.0 mmHg, p=0.0007) reduction in SBP, respectively, with no change in DBP over the 8 week trial period. No significant difference in the magnitude of BP reduction was observed between soy and milk protein. Other markers such as weight, body mass index, blood glucose, total cholesterol, and LDL levels were unchanged with the exception of HDL, which was increased with soy protein intake.

Conclusions: This clinical trial provides intriguing data that suggest dietary modification with soy or milk protein may lead to a statistically and clinical significant reduction in SBP, but not DBP, in the short term. These findings must be interpreted with caution as these observations are yet to be replicated. Furthermore, it remains to be seen whether the BP reduction can be sustained long-term with improvements cardiovascular outcomes and whether the reduction in BP will extend to patients with more severe hypertension or those already receiving anti-hypertensive therapy. Nevertheless, this well designed study provides promising early evidence for dietary modification of protein as a viable population strategy for lowering systolic hypertension for primary and secondary prevention.49
Renal Sympathetic Denervation for Treatment of Drug-Resistant Hypertension: One-Year Results From the Symplicity HTN-2 Randomized, Controlled Trial

**Summary:** The randomized Symplicity HTN-2 trial demonstrated that catheter-based renal denervation significantly lowered blood pressure 6 months post-procedure among patients with treatment-resistant hypertension (defined as a baseline SBP $\geq 160$ mm Hg and use of at least 3 anti-hypertension medications). This study reports on 1-year follow up of initial trial patients as well as 6-month follow up of control patients allowed to cross-over to catheter denervation. At 12 months post-procedure, the mean fall in office SBP in the initial renal denervation group ($n=47$, 28.1 mm Hg; 95% CI, 35.4 to 20.7; p<0.001 versus initial baseline BP) was similar to the 6-month fall (31.7 mm Hg; 95% CI, 38.3 to 25.0; p=0.16 versus 6-month change). The mean SBP of the crossover group 6 months post-procedure was significantly lowered (from 190.0±19.6 to 166.3±24.7 mm Hg; change, -23.7±27.5; p<0.001). In the crossover group, there was 1 renal artery dissection during guide catheter insertion, before denervation, and 1 hypotensive episode, which resolved with intravenous fluids.

**Conclusions:** In patients with treatment-resistant hypertension, renal denervation appears to be relatively safe and result in a significant drop in blood pressure both 6 and 12 months post-procedure. However, limitations with trial design of Symplicity HTN-2 preclude the ability to make strong recommendations in favor of renal denervation. Methodological shortcomings include the use of clinic blood pressure readings rather than 24 hour monitoring as the primary endpoint, lack of blinding of patients and staff measuring blood pressure to treatment allocation, and absence of a sham renal denervation procedure among control patients. Although incompletely recorded, ambulatory blood pressure readings from Symplicity 2 did indeed show lower benefit as compared with clinic readings. These limitations will be addressed in the ongoing Symplicity HTN-3 trial. Futhermore, outcomes data showing an improvement in cardiovascular and other relevant endpoints are needed prior to the widespread adoption of this novel approach.42

**Health Risks of Hypertension**

At a population level, hypertension is the most important risk factor for premature cardiovascular disease. On a global basis, hypertension accounts for approximately 50% of all strokes and ischemic cardiac events.43 The risks for both of these outcomes increase progressively with incremental rises in both systolic and diastolic blood pressure above 115/75 mm Hg.43 Similarly, progressive increases in pulse pressure (difference between systolic and diastolic blood pressures) are likewise associated with heightened cardiovascular risk.50

Harms of hypertension are also seen among specific sub-populations of patients. For example, for patients with chronic kidney disease, hypertension can further damage the kidney and accelerate the progression of a variety of underlying renal diseases.51,52 In addition, hypertension during pregnancy, when severe, can result in complications to the fetus and mother such as an elevated incidence of preterm delivery, small for gestational age infants, and abruptio placenta.53 Gestational hypertension is also associated with an increased risk of chronic hypertension later in life.53

It is critical, however, to interpret the potential harms of hypertension in the context of a patient’s overall risk profile for CVD. The presence of other risk factors such as hyperlipidemia, cigarette smoking, diabetes, and elevated age can greatly increase the risks associated with even mild hypertension, while in the absence of these factors, elevated blood pressure may be associated with only a minimal increase in absolute cardiovascular risk.53 In addition, knowledge of a patient’s lifelong exposure to elevated blood pressure may help further refine cardiovascular risk assessment.54,55

In the following section, we review research relating to cardiovascular, cerebrovascular, and cognitive harms associated with hypertension.56,59 We also present research related to risk in specific populations such as pregnant women and the elderly.60,61

**Incidence and Prognosis of Resistant Hypertension in Hypertensive Patients**

**Summary:** Patients with treatment-resistant hypertension constitute a high-risk subset for cardiovascular complications such as myocardial infarction and stroke. However, the incidence and prognosis of this condition are largely unknown. Using patient data collected from 2002 to 2006 in the Kaiser Permanente Colorado and Northern California healthcare systems, the authors of this retrospective cohort study identified 205,750 patients who were started on anti-hypertensive treatment for newly diagnosed hypertension. Patients were followed up for the development of resistant hypertension based on AHA criteria of failure to achieve goal BP despite use of ≥3 antihypertensive medications. Within a median of 1.5 years from initial treatment, 1.9% of patients developed resistant hypertension (0.7 cases per 100 person-years of follow-up). These patients were more often men, were older, and had higher rates of diabetes mellitus than patients who were responsive to treatment. Over 3.8 years of median follow-up, cardiovascular event rates (composite endpoint of death or incident cardiovascular events including myocardial infarction, heart failure, stroke, or chronic kidney disease) were significantly higher in those with resistant hypertension (unadjusted 18.0% versus 13.5%, p<0.001). After adjustment for patient and clinical characteristics, resistant hypertension was associated with a higher risk of cardiovascular events (hazard ratio, 1.47; 95% CI, 1.33–1.62).

**Conclusions:** Using rigorous longitudinal follow-up data, the authors of this study showed that resistant hypertension is common and have significant adverse outcomes; 1 in 50 newly diagnosed hypertensive patients become resistant to treatment within a median of 1.5 years of treatment initiation and have approximately 50% higher risk of cardiovascular events. This suggests the need to guide our efforts toward improving recognition, management and outcomes of patients with resistant hypertension. Numerous questions about this condition still remain that may relate to its optimal medical and surgical management, role of renin profiling, and cost effectiveness of various treatment methods. The Ongoing Prevention and Treatment of Resistant Hypertension With Algorithm Guided Therapy (PATHWAY)42 and the Resistant Arterial Hypertension Cohort Study (RAHyCo)53 studies would help answer some of the fundamental questions still outstanding.5

**Visit-to-Visit Blood Pressure Variability, Carotid Atherosclerosis, and Cardiovascular Events in the European Lacidipine Study on Atherosclerosis**

**Summary:** The authors sought to investigate whether visit-to-visit blood pressure variability in patients treated for mild to moderate hypertension was important in avoiding cardiovascular events and preventing or delaying progression of end organ damage. The authors pooled data (n=2784 patients) from the European Lacidipine Study on Atherosclerosis (ELSA), a randomized, double-blind 4-year trial of the effect of lacidipine or atenolol on echocardiographic carotid intima-media thickness.54 Visit-to-visit BP variability was assessed by the coefficient of variation or the standard deviation (SD) of the mean of the on-treatment SBP obtained at 6-month intervals (clinic BP) and 12-month intervals (ambulatory or 24-hour BP), respectively. The outcomes of interest included the impact of variability on carotid intima-media thickness, major cardiovascular events (including fatal and nonfatal myocardial infarctions, stroke and cardiovascular death), minor cardiovascular events (hospitalized heart failure, angina, atrial fibrillation, and claudication) and death from any cause. The results
show that the intima-media thickness increased progressively from the lowest to highest quartile of mean on-treatment clinic or 24-hour SBP (adjusted P for trend=0.046 and 0.048) but not along similar quartiles of SBP coefficient of variation or SD. In a multivariable logistic regression model, mean clinic BP (odds ratio 1.03; 95% CI, 1.01–1.05) and 24-h clinic BP (odds ratio 1.04; 95% CI, 1.02–1.07) but not variability, was associated with reduced incidence of cardiovascular outcomes.

Conclusions: The authors demonstrate that in patients with mild to moderate hypertension, the mean reduction in blood pressure is prognostically important in improving cardiovascular outcomes such as stroke, myocardial infarction or mortality. In contrast, the variation in blood pressures has no effect on pertinent cardiovascular outcomes. These findings differ from recent studies that have suggested high BP variability leads to adverse CV outcomes, especially stroke.66–67

Elevated Blood Pressure in Pregnancy and Subsequent Chronic Disease Risk

Summary: Preeclampsia/eclampsia is strongly associated with increased CVD risk, but the effects of other forms of hypertension during pregnancy on CVD risk are not well established. The authors evaluated the prognostic importance of any form of hypertension during pregnancy on the future CVD risk using the Northern Finland Birth Cohort 1966 that included all births in the year 1966 with a mean follow-up of 39.4 years. Blood pressure measurements and clinical data were determined from prenatal care records and questionnaires for 10,314 women. Patients were classified into 7 mutually exclusive hypertensive disorders based on guideline definitions (isolated systolic hypertension, isolated diastolic hypertension, isolated systolic/diastolic hypertension with proteinuria, gestational hypertension, eclampsia/pre-eclampsia, chronic hypertension, and chronic hypertension with superimposed eclampsia/preeclampsia). The results show that most forms of hypertension during pregnancy (except isolated systolic/diastolic hypertension with proteinuria) were associated with an elevated risk of CVD events when compared with normotensive women. In order of increasing hazard ratios, higher risk was found in isolated systolic hypertension (1.14), isolated diastolic hypertension (1.18), preeclampsia/eclampsia (1.40), gestational hypertension (1.45), chronic hypertension (1.66), superimposed preeclampsia/eclampsia (2.06). New onset hypertension during pregnancy was also associated with a marked increase in risk of developing future hypertension. Results were similar among women without known risk factors for CVD, such as smoking, overweight/obesity, advanced age, and diabetes mellitus.

Conclusions: This study highlights the importance of hypertension during pregnancy on future cardiovascular risk in addition to traditionally known risk factors such as preeclampsia/eclampsia. These results are highly relevant given that cardiovascular disease has been recognized as the leading cause of death in women in the United States. Since pregnancy seems to unmask patients at high risk of developing hypertension and other CVD long-term, patients who develop hypertension during pregnancy should be counseled on appropriate lifestyle modification to prevent future hypertension and CVD as well as to undertake intermittent BP monitoring for early detection.50

Impact of Blood Pressure and Blood Pressure Change During Middle Age on the Remaining Lifetime Risk for Cardiovascular Disease: The Cardiovascular Lifetime Risk Pooling Project

Summary: Prior studies have evaluated the lifetime risk (LTR) of CVD by hypertensive status at set points in time (index age) but have failed to examine if changes in BP alter the LTR of CVD. In this study, using data from the Cardiovascular Lifetime Risk Pooling Project,68 the authors examined how changes in BP affect the LTR for CVD. Defined as fatal coronary heart disease, hospitalized myocardial infarction, non-hospitalized myocardial infarction, and stroke. From 55 years of age, 61,585 men and women were followed up for 70,000 person-years for development of CVD events. The study results show that from 55 years of age onward, the remaining LTR for CVD was 52.5% (95% CI, 51.3–53.7) for men and 39.9% (95% CI, 38.7–41.0) for women. LTR for CVD was higher for blacks and increased with increasing BP at index age. Individuals who maintained or decreased their BP to normal levels (<120/80) had the lowest remaining LTR for CVD (22% for women, 41% for men). In contrast, individuals who had or developed hypertension by 55 years of age had the highest LTR of CVD (42% for women, 69% for men).

Conclusions: The findings of this study suggest the presence of a dose-response effect for the length of time at high BP levels and risk
of adverse cardiac events. These study findings re-iterate the importance of maintaining a blood pressure within normal limits for prevention of hypertension which minimizes the LTR of cardiovascular disease. Furthermore, these findings are relevant to secondary prevention efforts as lowering of BP to normal levels in a person with established hypertension also leads to a reduction in risk of CVD.61

Disclosures

Dr Dharmarajan is supported by grant HL007854 from the National Heart, Lung, and Blood Institute; he is also supported as a Centers of Excellence Scholar in Geriatric Medicine at Yale by the John A. Hartford Foundation and the American Federation for Aging Research. Dr Ranasinghe is supported by a research fellowship from the Australian National Health and Medical Research Council with cofunding by the National Heart Foundation of Australia. The other authors report no conflicts.

References


Most Important Outcomes Research Papers on Hypertension
Ruijun Chen, Kumar Dharmarajan, Vivek T. Kulkarni, Natdanai Punnanithinont, Aakriti Gupta, Behnood Bikdeli, Purav S. Mody and Isuru Ranasinghe
for the Editor

Circ Cardiovasc Qual Outcomes. 2013;6:e26-e35; originally published online July 9, 2013; doi: 10.1161/CIRCOUTCOMES.113.000424
Circulation: Cardiovascular Quality and Outcomes is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2013 American Heart Association, Inc. All rights reserved.
Print ISSN: 1941-7705. Online ISSN: 1941-7713

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circoutcomes.ahajournals.org/content/6/4/e26

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation: Cardiovascular Quality and Outcomes can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation: Cardiovascular Quality and Outcomes is online at:
http://circoutcomes.ahajournals.org//subscriptions/