

## Optimal Blood Pressure Goals in Patients with Hypertension at High Risk for Cardiovascular Events

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### Abstract

The 2013 European Society of Hypertension guidelines recommended that lowering the blood pressure to less than 130/80 mmHg in patients with hypertension at high risk for cardiovascular events was unsupported by prospective trial data, and that the systolic Blood Pressure (BP) should be decreased to less than 140 mmHg in these patients and the systolic BP reduced to between 140 to 150 mmHg in patients aged 80 years and older with an initial systolic BP of 160 mmHg or higher provided they are in good physical and mental condition. The American College of Cardiology Foundation/American Heart Association 2011 expert consensus document on hypertension in the elderly recommended that the BP should be lowered to less than 140/90 mmHg in adults with hypertension younger than 80 years at high risk for cardiovascular events. On the basis of data from the Hypertension in the Very Elderly trial, these guidelines recommended that the systolic BP should be reduced to 140 to 145 mmHg if tolerated in adults aged 80 years and older. This article discusses the clinical trial data supporting these guidelines in patients at high risk for cardiovascular events because of coronary artery disease, diabetes mellitus, chronic kidney disease, and heart failure.

**Keywords:** Hypertension; Coronary artery disease; Diabetes mellitus; Chronic kidney disease; Stroke; Heart failure

### Introduction

The 2013 European Society of Hypertension guidelines recommended that lowering the blood pressure to less than 130/80 mmHg in patients with hypertension at high risk for cardiovascular events was unsupported by prospective trial data, and that the systolic Blood Pressure (BP) should be decreased to less than 140 mmHg in these patients and the systolic BP reduced to between 140 to 150 mmHg in patients aged 80 years and older with an initial systolic BP of 160 mmHg or higher provided they are in good physical and mental condition [1]. The American College of Cardiology Foundation/American Heart Association 2011 expert consensus document on hypertension in the elderly recommended that the BP should be lowered to less than 140/90 mmHg in adults with hypertension younger than 80 years at high risk for cardiovascular events [2]. On the basis of data from the Hypertension in the Very Elderly trial these guidelines recommended that the systolic BP should be reduced to 140 to 145 mmHg if tolerated in adults aged 80 years and older [3].

### Studies of Optimal Blood Pressure in High-Risk Patients

The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trials enrolled 4,162 patients with an acute coronary syndrome (acute myocardial infarction with or without ST-segment elevation or high-risk unstable angina) [4].

At 24-month mean follow-up, the lowest cardiovascular events rates occurred with a systolic BP between 130 to 140 mmHg and a diastolic BP between 80 to 90 mmHg with a nadir of 136/85 mmHg [4].

An observational subgroup analysis was performed in 6,400 patients with diabetes mellitus and coronary artery disease enrolled in the International Verapamil SR-Trandolapril Study (INVEST) [5]. These patients were categorized as having tight control of BP if they could maintain their systolic BP below 130 mmHg and their diastolic BP below 85 mmHg, usual control if they could maintain their systolic BP between 130 to 139 mmHg, and uncontrolled if their

systolic BP was 140 mmHg or higher. During 16,893 patient-years of follow-up, a cardiovascular event rate of 12.6% occurred in patients with usual control of BP versus 19.8% in patients with uncontrolled hypertension (adjusted hazard ratio=1.46,  $p<0.001$  [5]. The incidence of cardiovascular events was 12.6% in patients with usual control of BP versus 12.7% in patients with tight control of BP,  $p$  not significant (NS). All-cause mortality rate was 11.0% with tight control of BP versus 10.2% with usual control of BP ( $p=0.06$ ). When extended follow-up to 5 years following the close of INVEST was included, all-cause mortality was 22.8% with tight control of BP versus 21.8% with usual control of BP (adjusted hazard ratio=1.15,  $p=0.04$ ) [5].

The Action To Control Cardiovascular Risk in Diabetes (ACCORD) blood pressure trial randomized 4,733 patients with type 2 diabetes mellitus to intensive BP control with a target systolic BP of less than 120 mmHg or to standard BP control with a target systolic BP less than 140 mmHg [6]. Mean follow-up was 4.7 years. The annual rate of nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes was not significantly different between both groups.

The annual rate of all-cause mortality was 1.18% with intensive BP control versus 1.19% with standard BP control ( $p$  not significant). The annual rate of stroke was 0.32% with intensive BP control versus 0.53% with standard BP control ( $p=0.01$ ). The number needed to treat for 1 year for intensive BP control to prevent 1 stroke was 476 patients. However, serious adverse events attributed to BP treatment were 3.3% with intensive BP control versus 1.27% with standard BP

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control ( $p < 0.001$ ). The number needed to treat for intensive BP control to increase 1 serious adverse event was 49 patients [6].

The Ongoing Telmisartan alone and in combination with Ramipril Global Endpoint Trial (ONTARGET) included 9,603 diabetics, mean age 66.1 years, and 15,981 non-diabetics, mean age 66.6 years, with hypertension at high risk for cardiovascular events [7,8]. A progressive increase in the proportion of visits in which the blood pressure was lowered to less than 140/90 mm Hg or to less than 130/80 mmHg was associated with a progressive decrease in stroke, new onset of microalbuminuria or macroalbuminuria, and return to normal albuminuria in persons with albuminuria [7]. However, the adjusted risk of cardiovascular events was decreased by increasing the frequency of blood pressure control to less than 140/90 mmHg but not to less than 130/80 mmHg [7].

The primary outcome in ONTARGET was a composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, or hospitalization for heart failure. Mean follow-up was 4.6 years. Compared with non-diabetics, diabetics had a 48% increase (95% CI, 1.38 to 1.57) in the primary endpoint, a 56% increase (95% CI, 1.42 to 1.71) in cardiovascular death, a 30% increase (95% CI, 1.17 to 1.46) in myocardial infarction, a 39% increase (95% CI, 1.23 to 1.56) in stroke, and a 206% increase (95% CI, 1.82 to 2.32) in hospitalization for congestive heart failure [8].

In both diabetics and non-diabetics, antihypertensive drug treatment decreased the primary outcome if the baseline systolic blood pressure was between 143 to 155 mmHg [8]. Except for stroke, there was no benefit in reducing fatal or nonfatal cardiovascular outcomes by lowering the systolic blood pressure below 130 mmHg in diabetics and in non-diabetics. The lowest incidence of death from cardiovascular causes in diabetics occurred with a systolic blood pressure of 135.6 mmHg (range 130.6 to 140.5 mmHg). The lowest incidence of death from cardiovascular causes in non diabetics occurred with a systolic blood pressure of 133.1 mmHg (range 128.8 to 137.4 mmHg). For the primary outcome, the highest risk in both diabetics and in non-diabetics occurred in patients with the lowest or highest in-trial diastolic blood pressure (67.2 mmHg and 86.7 mmHg, respectively) [8].

A meta-analysis was performed of the 2,272 patients with hypertensive chronic kidney disease without diabetes in the African American Study of Kidney Disease and Hypertension (AASK), the Modification of Diet in Renal Disease (MDRD) and the Ramipril Efficacy in Nephropathy 2 (REIN-2) trials [9-12]. This meta-analysis demonstrated that a BP of less than 125/75 to 130/80 mmHg did not improve clinical outcomes more than a target BP of less than 140/90 mmHg [12]. Whether a BP of less than 130/80 mmHg benefits patients with proteinuria greater than 300 to 1,000 mg per day suggested by a subgroup analysis from the AASK trial requires further study [9,12].

The Prevention Regimen for Effectively Avoiding Second Strokes (PROFESS) trial included 20,330 patients with a recent non-cardio embolic ischemic stroke [13]. Mean follow-up was 2.5 years. Compared with patients with a systolic BP of 130-139 mmHg, the risk of recurrent stroke was increased in patients with a systolic BP less than 120 mmHg (adjusted hazard ratio=1.29; 95% CI, 1.07 to 1.56), increased in patients with a systolic BP of 140 to 149 mmHg (adjusted hazard ratio=1.23; 95% CI, 1.07 to 1.41), and increased in patients with a systolic BP of 150 mmHg or higher (adjusted hazard ratio=2.08; 95% CI, 1.83 to 2.37). Compared with patients with a systolic BP of 130-139 mmHg, the risk of stroke, myocardial infarction, or death from vascular causes was increased in patients with a systolic BP less than 120 mmHg (adjusted

hazard ratio=1.31; 95% CI, 1.13 to 1.52), increased in patients with a systolic BP of 120 to 129 mmHg (adjusted hazard ratio=1.16; 95% CI, 1.03 to 1.31), increased in patients with a systolic BP of 140 to 149 mmHg (adjusted hazard ratio=1.24; 95% CI, 1.11 to 1.39), and increased in patients with a systolic BP of 150 mmHg or higher (adjusted hazard ratio=1.94; 95% CI, 1.74 to 2.16) [13].

We investigated in 7,785 patients with mild to moderate chronic systolic and diastolic congestive heart failure in the Digitalis Investigation Group trial the impact of baseline systolic BP on outcomes using a propensity-matched design [14]. The mean follow-up was 5 years. Compared to a baseline systolic BP higher than 120 mm Hg, a systolic BP of 120 mmHg or lower was associated with a 10% insignificant increase in all-cause mortality, a 15% increase in cardiovascular mortality ( $p=0.031$ ), a 30% increase in heart failure mortality ( $p=0.006$ ), a 13% increase in cardiovascular hospitalization ( $p=0.008$ ), a 10% increase in all-cause hospitalization ( $p=0.017$ ) and a 21% increase in heart failure hospitalization ( $p=0.002$ ) [14].

## Conclusion

In conclusion, existing epidemiologic and clinical trial data suggest that the BP in patients with hypertension at high risk for cardiovascular events because of coronary artery disease, diabetes mellitus, chronic kidney disease, stroke, or heart failure should be reduced to less than 140/90 mmHg in patients younger than 80 years and the systolic BP reduced to 140 to 145 mmHg if tolerated in patients aged 80 years and older [1,2].

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