



## Review of 2003 to 2015 Guidelines on Treatment of Hypertension in Patients with Coronary Artery Disease

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### Abstract

Patients with coronary artery disease should have their modifiable coronary risk factors intensively treated. Dietary sodium should be reduced. Hypertension should be treated with beta blockers and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. Long-acting nitrates are effective antianginal and antiischemic drugs. Calcium channel blockers may be added if angina persists despite beta blockers and long-acting nitrates. The American Heart Association/American Society of Cardiology 2015 guidelines recommend that the target blood pressure should be less than 140/90mmHg in patients with coronary artery disease and with an acute coronary syndrome if they are aged 80 years and younger but less than 150mmHg if they are older than 80 years of age. Octogenarians should be checked for orthostatic changes with standing, and a systolic blood pressure less than 130mmHg and a diastolic blood pressure less than 65mmHg should be avoided. Caution is advised in causing a diastolic blood pressure less than 60mmHg in patients with diabetes mellitus or in patients older than 60 years of age. In addition to the beta blockers carvedilol, metoprolol CR/XL, and bisoprolol, patients with hypertension and left ventricular systolic dysfunction should be treated with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers and also with an aldosterone antagonist if indicated. Management of hypertension in patients with coronary artery disease according to guidelines from 2003 to 2015 will be discussed.

### Keywords

Myocardial infarction, Coronary artery disease, Hypertension, Beta blockers, Angiotensin-converting enzyme inhibitors, Aldosterone antagonists, Calcium channel blockers, Nitrates

Hypertension is a major risk factor for coronary artery disease [1-9]. These guidelines recommend lowering the blood pressure to less than 140/90mmHg in patients younger than age 80 years and to less than 150/90mmHg in patients aged 80 years and older if tolerated [1-4,7-9]. Hypertension is present in approximately 69% of patients with a first myocardial infarction [10]. Hypertension is also a major risk factor for sudden cardiac death and for angina pectoris [3]. This paper will discuss the management of hypertension in patients with coronary artery disease recommended by hypertension guidelines from 2003 to 2015.

The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure (JNC 7) recommended that the blood pressure should be reduced to less than 140/90mmHg in patients with coronary artery

disease [1]. These guidelines recommended treating patients after myocardial infarction with a beta blocker and an angiotensin-converting enzyme inhibitor plus an aldosterone antagonist if a third drug is indicated [1]. In patients with hypertension and stable angina pectoris, the first drug of choice is a beta blocker. A long-acting calcium channel blocker should be added if angina persists [1]. In patients with an acute coronary syndrome, hypertension should be treated with a beta blocker plus an angiotensin-converting enzyme inhibitor with addition of other drugs such as a diuretic and calcium channel blocker if needed to control blood pressure [1].

The 2007 American Heart Association Hypertension Scientific Statement recommended that the blood pressure be reduced to less than 130/80mmHg in patients with coronary artery disease with consideration of lowering the blood pressure to less than 120/80mmHg if left ventricular systolic dysfunction is present [2]. Patients with stable angina pectoris should be treated with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker plus a long-acting nitrate plus a thiazide diuretic. If the angina or the blood pressure remains uncontrolled, a nondihydropyridine long-acting calcium channel blocker can be added if there is no left ventricular systolic dysfunction or a dihydropyridine long-acting calcium channel blocker can be added if there is left ventricular systolic dysfunction [2]. Patients with an acute coronary syndrome should be treated with a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker if the patient is hemodynamically stable [2]. If the angina or the blood pressure is not controlled, a long-acting calcium channel blocker (dihydropyridine if there is left ventricular systolic dysfunction) can be added. A thiazide diuretic can also be added for blood pressure control [2].

However, clinical trial data did not support the 2007 American Heart Association Hypertension Scientific Statement [11]. The Pravastatin or Atorvastatin Evaluation and Infection Therapy-Thrombolysis in Myocardial Infarction (PROVE IT-TIMI) 22 trial enrolled 4,162 patients with an acute coronary syndrome (acute myocardial infarction with or without ST-segment elevation or high-risk unstable angina pectoris) [12]. The lowest cardiovascular events rates occurred with a systolic blood pressure between 130 to 140mmHg and a diastolic blood pressure between 80 to 90mmHg with a nadir of 136/85mmHg with a J- or U- shaped curve at both low and high blood pressure values [12]. Randomized clinical trials of antihypertensive drug treatment provide evidence for a J-shaped relationship between systolic blood pressure and diastolic blood

pressure and all-cause death, cardiovascular death, nonfatal and fatal stroke, and congestive heart failure [13].

An observational subgroup analysis was performed in the 6,400 patients, mean age 66 years, with coronary artery disease and diabetes mellitus in the International Verapamil SR-Trandolapril Study (INVEST) [14]. Tight control of blood pressure was maintenance of a systolic blood pressure below 130mmHg. Usual control of blood pressure was maintenance of a systolic blood pressure between 130 to 139mmHg. Uncontrolled blood pressure was maintenance of a systolic blood pressure of 140mmHg or higher. During 16, 893 patient years of follow-up, compared to usual control of systolic blood pressure, uncontrolled systolic blood pressure increased the primary outcome event of all-cause mortality, nonfatal myocardial infarction, or nonfatal stroke by 46% ( $p<0.001$ ), and tight control of systolic blood pressure insignificantly increased the primary outcome event by 11% [14]. All-cause mortality was 11.0% in patients who had tight control of systolic blood pressure versus 10.2% in patients who had usual control of systolic blood pressure ( $p=0.06$ ). With extended follow-up to 5 years after the close of INVEST, all-cause mortality was increased 15% from 21.8% in the patients with usual control of systolic blood pressure to 22.8% in patients with tight control of systolic blood pressure ( $p=0.04$ ) [14].

A meta-analysis of 147 randomized trials of 464,000 adults with hypertension reported that except for the extra protective effect of beta blockers given after myocardial infarction and a minor additional effect of calcium channel blockers in preventing stroke, beta blockers, angiotensin-converting enzyme inhibitors, angiotensin receptor blockers, diuretics, and calcium channel blockers caused a similar decrease in coronary events and stroke for a given reduction in blood pressure [15]. The proportionate reduction in cardiovascular events was the same or similar regardless of pretreatment blood pressure and the presence or absence of cardiovascular events [15]. If beta blockers are used to treat adults with hypertension, atenolol should not be used [16-18].

The American College of Cardiology Foundation/American Heart Association 2011 expert consensus document on hypertension in the elderly recommended that the blood pressure in persons with coronary artery disease younger than 80 years be reduced to less than 140/90mmHg [3]. On the basis of data from the Hypertension in the Very Elderly trial [19], these guidelines recommended reducing the systolic blood pressure in persons with coronary artery disease aged 80 years and older to 140 to 145mmHg if tolerated in the standing position [3].

The American College of Cardiology Foundation/American Heart Association 2011 expert consensus document on hypertension in the elderly recommended as initial antihypertensive drug therapy in elderly patients after myocardial infarction use of beta blockers plus an angiotensin-converting enzyme inhibitor plus an aldosterone antagonist if needed [3]. Patients with angina pectoris should be treated with a beta blocker plus a calcium channel blocker [3]. Patients with coronary artery disease should be treated with a beta blocker plus an angiotensin-converting enzyme inhibitor with addition of a thiazide diuretic and calcium channel blocker if indicated to control blood pressure [3].

The 2013 European Society of Hypertension (ESH)/European Society of Cardiology (ESC) hypertension guidelines recommend that the systolic blood pressure should be reduced to less than 140mmHg in patients with coronary artery disease [4,12,14]. In hypertensive patients with a recent myocardial infarction, beta blockers are the drugs of choice [4]. In other patients with coronary artery disease, all antihypertensive drugs can be used, but beta blockers and calcium channel blockers are preferred in patients with angina pectoris [4].

The 2013 Canadian Hypertension Education Program guidelines recommend reducing the systolic blood pressure to less than 140mmHg in patients with coronary artery disease younger than 80 years and to less than 150mmHg in patients with coronary artery disease aged 80 years and older [7]. The American Society

of Hypertension/International Society of Hypertension 2014 hypertension guidelines recommend reducing the blood pressure to less than 140/90mmHg in patients with coronary artery disease [8].

The American Society of Hypertension/International Society of Hypertension 2014 hypertension guidelines recommend treating patients with coronary artery disease initially with a beta blocker plus an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker to reduce the blood pressure to less than 140/90mmHg [8]. If an additional drug is needed to control the blood pressure, a thiazide diuretic or calcium channel blocker should be added [8].

If a fourth antihypertensive drug is needed, it should be the alternative third antihypertensive drug (thiazide diuretic or calcium channel blocker) [8].

The American Heart Association/American Society of Cardiology 2015 guidelines recommend that the target blood pressure should be less than 140/90mmHg in patients with coronary artery disease and with an acute coronary syndrome if they are aged 80 years and younger but less than 150mmHg if they are older than 80 years of age [9]. Consideration can be given to reduce the blood pressure to less than 130/80mmHg with a class IIb C indication [9]. Octogenarians should be checked for orthostatic changes with standing, and a systolic blood pressure less than 130mmHg and a diastolic blood pressure less than 65mmHg should be avoided [9]. Caution is advised in causing a diastolic blood pressure less than 60mmHg in patients with diabetes mellitus or in patients older than 60 years of age [9].

## Coronary Artery Disease

Coronary risk factors should be controlled including smoking, hypertension, dyslipidemia, diabetes mellitus, obesity, and physical inactivity [9]. Dietary sodium should be reduced.

Beta blockers are the initial antihypertensive drugs to use in patients with coronary artery disease who have angina pectoris, who have had a myocardial infarction, and in those who have left ventricular systolic dysfunction unless contraindicated [9]. Patients with prior myocardial infarction and hypertension should be treated with beta blockers and angiotensin-converting enzyme inhibitors [1-4,8,9,15,18-32]. If a third drug is needed, aldosterone antagonists may be used based on the Eplerenone Post-Acute Myocardial Infarction Heart Failure Efficacy and Survival (EPHESUS) trial [33]. Patients treated with aldosterone antagonists should not have significant renal dysfunction or hyperkalemia.

Patients with left ventricular systolic dysfunction should be treated with the beta blockers carvedilol, metoprolol CR/XL, and bisoprolol [9,34-39] and with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers [9,34,40-47]. Drugs to avoid in patients with hypertension and a reduced left ventricular ejection fraction include verapamil, diltiazem, doxazosin, clonidine, moxonidine, hydralazine without a nitrate, and nonsteroidal anti-inflammatory drugs [9]. Aliskiren is contraindicated in patients treated with an angiotensin-converting enzyme inhibitors or angiotensin receptor blockers who have diabetes mellitus or an estimated glomerular filtration rate less than 60ml/min/1.73m<sup>2</sup> or in patients with hyperkalemia.

## Stable Angina Pectoris

Patients with hypertension and chronic stable angina pectoris should be treated with beta blockers plus nitrates as antianginal agents [9]. The hypertension in these patients should be controlled with beta blockers plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker with addition of a thiazide or thiazide-like diuretic if needed. If either the angina pectoris or the hypertension remains uncontrolled, a long-acting dihydropyridine calcium channel blocker can be added to the therapeutic regimen. Nondihydropyridine calcium channel blockers such as verapamil and diltiazem cannot be used if there is left ventricular systolic dysfunction. Combining a beta blocker with either verapamil or diltiazem must be

used with caution because of the increased risk of bradyarrhythmias and heart failure [9]. Beta blockers plus an angiotensin-converting enzyme inhibitor or an angiotensin receptor blocker are the initial drugs to use in hypertensive patients with coronary artery disease who have chronic kidney disease [9]. Hypertensive patients with vasospastic angina pectoris should be treated with nitrates plus calcium channel blockers [47].

## Acute Coronary Syndromes

In patients with an acute coronary syndrome, initial therapy of hypertension should include a short-acting beta<sub>1</sub> selective beta blocker without intrinsic sympathomimetic activity such as metoprolol tartrate or bisoprolol [9]. Treatment with beta blockers should be given initially within 24 hours of symptoms. In patients with severe hypertension or ongoing ischemia, intravenous esmolol may be considered [9]. In hemodynamically unstable patients or those with decompensated heart failure, treatment with beta blockers should be delayed until the patient is stabilized [9].

In patients with acute coronary syndromes with hypertension, nitrates can be used to lower blood pressure or to decrease ongoing myocardial ischemia or pulmonary congestion [9]. However, nitrates should not be administered to patients with suspected right ventricular infarction or in those with hemodynamic instability. Intravenous or sublingual nitroglycerin is preferred initially [9].

An angiotensin-converting enzyme inhibitor or angiotensin receptor blocker should be administered to patients with an acute coronary syndrome, especially in patients with an anterior myocardial infarction, if hypertension persists, if there is a reduced left ventricular ejection fraction, or if diabetes mellitus is present [9]. If hypertension persists after use of a beta blocker plus an angiotensin-converting enzyme inhibitor or angiotensin receptor blocker, a long-acting dihydropyridine calcium channel blocker may be added [9]. Aldosterone antagonists are indicated in patients receiving beta blockers plus angiotensin-converting enzyme inhibitors or angiotensin receptor blockers after myocardial infarction who have left ventricular systolic dysfunction and either heart failure or diabetes mellitus [9,18,33,48]. However, they should be avoided if the serum potassium is  $\geq 5.0$  mEq/L or if the serum creatinine is  $\geq 2.5$  mg/dL in men or  $\geq 2.0$  mg/dL in women [9,33]. Loop diuretics are preferred to thiazide and thiazide-type diuretics in patients with heart failure or in patients with chronic kidney disease and an estimated glomerular filtration rate less than 30 mL/minute [9]. Additional antihypertensive drugs may need to be administered to patients with uncontrolled hypertension despite use of beta blockers, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, calcium channel blockers, diuretics, and aldosterone antagonists [49].

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