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Risk factor control and medical therapy of coronary artery disease in Taiwan – Review and Recommendations – Part II: Blood pressure management for patients with coronary artery disease

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Abstract: Cardiovascular disease (CVD) is the leading cause of death in the world and the second important cause of death in Taiwan. Atherosclerosis CVD (ASCVD) especially coronary artery disease (CAD) is the major cause of CVD [1]. Clinically, the presentation of CAD can be divided into acute unstable disease, so-called acute coronary syndrome (ACS) and chronic stable disease. Up to now, the main risk factors for CAD are known as hyperlipidemia, hypertension, hyperglycemia, smoking and family history. The control of the above risk factors and lifestyle modifications can improve the prognosis of CAD patients [1,2]. Here, we described the blood lipid control, blood pressure control, blood glucose control, and lifestyle modifications for CAD in Taiwan. The followings are the part II for blood pressure control.

1. Optimal systolic and diastolic blood pressure for patients with CAD

Hypertension is a risk factor for CAD. High blood pressure (BP) can accelerate atherosclerosis and may lead to acute myocardial infarction. Many studies have shown that BP reduction can prevent cardiovascular disease in patients with CAD.

HOPE, EUROPA, and PEACE are three randomized controlled trials comparing angiotensin-converting enzyme inhibitors with control subjects in patients with CAD [1–3]. The baseline BPs were 139/79 mm Hg (HOPE), 137/82 mm Hg (EUROPA), and 133/78 mm Hg (PEACE), respectively. The final BPs were 136/76 mm Hg (HOPE), 132/80 mm Hg (EUROPA) and 129/74 mm Hg (PEACE), respectively. All three clinical trials had shown that angiotensin-converting enzyme inhibitors can reduce primary endpoints, including a 22% decrease in HOPE ($P < 0.001$), a 20% decrease in EUROPA ($P = 0.0003$), and a 4% decrease in PEACE ($P > 0.05$). The combined results of these three randomized controlled trials showed that angiotensin-converting enzyme inhibitors can reduce total mortality, non-fatal myocardial infarction, and stroke in patients with CAD [4].

The CAMELOT trial is a randomized controlled trial comparing patients with CAD using calcium channel blocker (amlodipine), angiotensin-converting enzyme inhibitor (enalapril), or the control group. The baseline BP was 129/78 mm Hg and the final BP was 124/75 mm Hg. The study showed that amlodipine can reduce the primary endpoint by 31% [5]. In the sub-study of the CAMELOT trial, intravascular ultrasound was used to compare the effects of amlodipine, enalapril, or the control groups on the volume of coronary atherosclerotic plaque in patients with CAD. BP 120-139/80-89 mm Hg had no significant effect on atherosclerotic plaque, but normal BP (<120/80 mm Hg) after treatment significantly reduced atherosclerotic plaque [6].

The COURAGE trial randomized patients with stable CAD to optimal medical treatment and optimal medical treatment plus coronary artery intervention. The baseline BP was 130/74 mm Hg and the final BP was 122/70 mm Hg. The optimal medical treatment included beta-blockers, calcium channel blockers, and angiotensin-converting enzyme inhibitors or angiotensin receptor blockers. The results showed that optimal medical treatment, including BP control, was comparable to optimal medical treatment plus coronary artery intervention in patients with stable CAD [7].

In a meta-analysis, 15 randomized controlled trials of patients with CAD treated with hypertension were included, including 66,504 patients with 276,328 person-years of follow-up. When comparing standard BP treatment (systolic BP $\leq$ 140 mm Hg Column) with intensive BP treatment (systolic BP $\leq$ 135 mm Hg), intensive BP treatment can reduce heart failure (-15%) and stroke (-10%). Further analysis found that more intensive BP control (systolic BP $\leq$ 130 mm Hg) can reduce myocardial infarction and angina [8].

In another meta-analysis of secondary prevention in patients with cardiovascular disease, a total of 64,162 patients with cardiovascular disease were enrolled in 25 studies with a pre-treatment BP <140/90 mm Hg. The study showed that antihypertensive drugs can reduce stroke by 23%, myocardial infarction by 20%, heart failure by 29%, cardiovascular events by 15%, cardiovascular death by 17%, and total mortality by 13% [9].

In another meta-analysis investigating the effects of antihypertensive drugs on CAD and stroke, a total of 464,000 patients in 147 clinical trials were analyzed and divided into three groups, including patients without histories of cardiovascular disease, patients with CAD, and patients with stroke. Studies have shown that antihypertensive drugs can reduce the incidences of CAD and stroke, regardless of pre-treatment BP values or histories of cardiovascular disease. Pre-treatment systolic BP of 110-119 mm Hg and diastolic BP of 70-74 mm Hg were also beneficial. The study also found that all of the hypertensive drugs had similar effects for CAD and stroke, except that beta-blockers may have additional protection in the early stages of myocardial infarction and calcium channel blockers may have additional protection for stroke [10].

In the meta-analysis of BP Lowering Treatment Trialists' Collaboration (BPLTTC), a total of 201,566 patients in 32 clinical trials were divided into systolic BP <140, 140-159, 160-179, and $\leq$ 180 mm according to the baseline BP before treatment. The study found that different antihypertensive drugs and different baseline BP groups did not affect the reduction of the primary endpoint [11].

The SPRINT trial [12] investigated the effects of intensive BP treatment (systolic BP less than 120 mm Hg) and standard BP treatment (systolic BP less than 140 mm Hg) on the future of patients with high cardiovascular risks without diabetes. After an average follow-up time of 3.26 years, patients receiving intensive BP treatment had fewer primary endpoints, including a reduction in cardiovascular events and overall mortality. However, the results of SPRINT trial still need more discussions, such as the way of BP measurement was different from previous clinical trials, using automatic office BP (AOBP).

Currently, the 2015 Taiwan's hypertension guideline [13], the 2017 US hypertension guideline [14], and the 2018 European hypertension guidelines [15] suggest that BP in patients with CAD should be controlled at systolic BP less than 130 mm Hg and the diastolic BP less than 80 mm Hg.

2. Increased cardiovascular risk with low systolic and diastolic blood pressure in patients with CAD

Although intensive BP treatment (systolic BP less than 120 mm Hg) reducing more future cardiovascular events in patients with high cardiovascular risk than standard BP treatment (systolic BP less than 140 mm Hg) in the SPRINT trial [12], other previous clinical trials showed that low BP treatment may have higher cardiovascular events [16–21].

In the INVEST trial [16,17], 22,576 patients with hypertension and CAD were enrolled to compare the effects of a calcium-channel blocker (verapamil sustained release) and a control group (atenolol) on cardiovascular events. Post hoc analysis showed a J-curve phenomenon of BP on primary endpoints, total death, and myocardial infarction, with nadir of 119/84 mm Hg.

In the TNT trial [18], 10,001 patients with CAD were enrolled and randomly assigned to atorvastatin 80 mg or 10 mg. After an average of 4.9 years of follow-up, the study showed that patients with too low BP (<110-120/<60-70 mm Hg) may increase the risk of future cardiovascular events.

In the PROVE IT-TIMI 22 trial [19], 4,162 patients with acute coronary syndrome were randomly assigned to pravastatin 40 mg or atorvastatin 80 mg. The study found a J-shaped curve of BP for both primary and secondary endpoints, with BP at 136/85 mm Hg (systolic BP 130-140 mm Hg and diastolic BP 80-90 mm Hg) with the lowest primary end point. However, if the BP is too low may increase the risk (especially less than 110/70 mm Hg).

In the CLARIFY trial, 22,672 patients with CAD who underwent hypertension treatment were enrolled in 45 countries. The primary endpoints included cardiovascular death, myocardial infarction, and stroke. After an average of 5 years of follow-up, patients with systolic BP greater than 140 mm Hg or diastolic BP greater than 80 mm Hg had increased risks of cardiovascular events. However, patients with systolic BP less than 120 mm Hg or diastolic BP less than 70 mm Hg also had increased risk of cardiovascular events [20].

In a multi-center study in Taiwan, 2,045 patients with CAD were enrolled in 9 medical centers [21], and 12-month and 24-month cardiovascular events were followed. The study found that patients with systolic BP greater than or equal to 160 mm Hg had increased risks of cardiovascular events. In addition, patients with systolic BP less than 120 mm Hg or diastolic BP less than 70 mm Hg may also have increased risks of cardiovascular events. The results were similar to the CLARIFY trial.

Although current Taiwan's hypertension guideline [13] and the 2017 US hypertension guidelines [14] have not mentioned about the avoidance of too low BP treatment, the 2018 European hypertension guidelines [15] suggested that BP in patients with CAD may not be controlled too low, defined as systolic BP lower than 120 mm Hg or diastolic BP lower than 70 mm Hg.

3. Recommendations

1. For patients with coronary artery disease (CAD), systolic blood pressure (BP) should be <130 mmHg and diastolic BP <80 mmHg (**Class I, LOE: B**).
2. For patients with CAD, systolic BP < 120 mm Hg and diastolic BP < 70 mm Hg may be avoided (**Class I, LOE: C**).

Conflicts of Interest:
The authors declare no conflict of interest.

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