Treatment of Hypertension in Patients with Coronary Artery Disease

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Abstract

Hypertension is among the leading causes of mortality worldwide, both in the developed and developing world. Most deaths occur due to cardiovascular complications such as myocardial infarction (MI) and stroke. In the Asia Pacific Region, hypertension alone contributes to 66% of all cardiovascular deaths, more than it does worldwide.

The most recent meta-analysis on the benefits of treating hypertension showed that tighter control of blood pressure (133/76 mmHg) leads to a significant 14% reduction in myocardial infraction. In patients with concurrent Coronary Artery Disease (CAD) the two issues which need to be addressed are: 1) to determine the target of blood pressure (BP), and; 2) to determine the drug of choice in hypertensive patients with concurrent CAD.

Up to five years ago, most Clinical Practice Guidelines suggested that target BP to be achieved was <130/80 mmHg. This however was revised recently to <140/90 mmHg. The new cut-off was mainly due to lack of evidence from randomized controlled trials on the lower BP of <130/80 mmHg and the persistence concern about the J curve.

This article reviewed recommendations made by the latest Hypertension Guidelines across major hypertension societies in North America, Europe and the Asia Pacific Region published over the last 3 years in the English language. These were than compared with major clinical outcome studies investigating phenotype of patients with hypertension and CAD. The treatment of choice for patients with CAD depends on clinical circumstances. In patients with underlying CAD, calcium channel blockers (verapamil) and beta blockers (atenolol) are indicated based on the INVEST trial. Besides, ACE I should also be the treatment of choice as indicated by the EUROPA trial especially in patients with minimal symptomatic angina. Beta blockers and dihydropyridine calcium channel blockers are indicated for symptomatic angina although there is no evidence of their impact on prognosis. For patients with previous myocardial infarction and normal left ventricular ejection fraction , ACE I and beta blockers are the drugs of choice to improve prognosis and clinical outcome although doubt has been raised on the benefits of beta blockers especially for mortality reduction. As for post-MI patients with reduced left ventricular ejection fraction, ACE I (or ARB), beta blockers and aldosterone antagonist are indicated.

Keywords: Hypertension; Coronary artery disease; Treatment target

Introduction

Hypertension is a major contributor to cardiovascular events and total mortality. For more than a decade now, the World Health Organization (WHO) has identified hypertension as a leading cause of total mortality worldwide [1]. This is true not just for the developed world but also for the developing and under-developed regions. In the world's most populous country, China, hypertension has been identified as the main cause of premature death [2]. The Asia Pacific Cohort Collaborative Study which covered almost half a million individuals in the region showed that hypertension per se contributed to 66% of all cardiovascular events [3].

The worldwide prevalence of hypertension ranged from as low as 3.4% and 6.8% among men and women in rural India respectively, to 68.9% and 72.5% among Polish males and females [4]. In North America, it was reported that 28% of its adult population had hypertension as compared to 44% in Europe [5] and 21.7% in the Middle East [6], with differences across countries. The prevalence of hypertension in China was 27.2% [7] whereas in Asia Pacific it ranged from 5% to 47% in men and 7% to 38% in women [3]. In Malaysia, 32.9% of adults were said to have high blood pressure in 1996 [8] and this increased to 42% in 2011 [9]. Overall, with the exception of few countries, an upward trend is expected to continue with an increase of hypertension prevalence by 60% 2020, in and the number of adults affected by it growing from 972 million in 2000 to 1.56 billion in 2025 [10].

On the other hand, Coronary Artery Disease (CAD) is a complication of hypertension and the most common type of heart disease. CAD has been described as an international epidemic due to its increasing incidence worldwide [11]. Not only CAD is a major cause of death, but its massive impacts on morbidity and quality of life have equally been recognized, in addition to the high cost exerted. In 2003 alone, the cost of CAD was 45 billion Euro in the European Union [12]. The lifetime risk for Coronary Heart Disease (CHD) at age 40 was reported to be one in two for men, and one in three for women [13]. Besides hypertension and high cholesterol as the leading causes of CHD, other important contributors include tobacco, obesity, physical inactivity and diabetes [14].

Age-adjusted death rates for CHD have been declining in developed countries, and this is largely driven by preventive measures and advanced treatment modalities. Conversely, mortality in low and middle-income regions is on the rise due to increasing prevalence of risk factors, and relative lack of access to similar medical interventions [14]. A study by Ford et al. demonstrated that half the decline of CHD deaths in the United States from 1980 to 2000 was due to reductions in risk factors, and half due to evidence-based medical therapies [15]. This emphasizes the important role of medical therapies in preventing CHD-related mortality, along with the need to address the major risk factors. This article therefore aims at highlighting and discussing available evidences on treatment modalities with regards to hypertension among CAD patients.

This article reviewed all the latest hypertension guidelines published in the English language over the last 3 years (2013-2016). A particular emphasis was to focus on what was recommended as regards blood pressure targets and drug of choice in patients with hypertension and concurrent CAD. Search engine used were Pub Med, Google Scholar and official websites of the relevant societies. Guidelines from the United States, Canada, Europe, Japan, and Malaysia were retrieved and scrutinized. A search was also done on clinical outcome trials using key words Hypertension, Coronary Artery Disease, Treatment.

Hypertension and Coronary Artery Disease: From Pathophysiology to Population

Elevated Blood Pressure, once thought to be benign and 'essential' is now known to be a major risk factor for cardiovascular diseases including CAD. The pathophysiological cascade in the pathogenesis of CAD begins with endothelial dysfunction well before the onset of atheroma in the endothelial lining of arterial vasculature. Hypertension is a major risk factor contributing to endothelial dysfunction [16]. Hypertension also leads to reduced arterial compliance or increase arterial stiffness. The vascular effects of hypertension can pre- date the onset of elevated blood pressure including in the offspring of hypertensives who are still normotensive [17].

A high percentage of patients with CAD typically have hypertension. In the Malaysian Acute Coronary Syndrome Registry, up to 72% of CAD patients have underlying hypertension [18]. Hypertension also commonly co- exist with another major risk factor of CAD namely diabetes mellitus. In two recent mega trials on diabetes [19,20], 80% of the patients recruited have underlying hypertension. Incidence of hypertension among patients post myocardial infarction (MI) and among those with heart failure is usually underestimated because these patients may have reduced left ventricular function compromising cardiac output and reducing blood pressure.

Blood pressure targets in patients with hypertension and CAD

The latest round of hypertension guidelines were published in 2011 by NICE UK [21]. No specific recommendation was made for target blood pressure in patients with CAD. All other subsequent guidelines which have been published since recommended that the target blood pressure is <140/90 mmHg. Table 1 shows all the major guidelines on treatment of hypertension published from 2013. These include the European Society of Hypertension / European Society of Cardiology (ESH/ESC) [22] in 2013, and two other Guidelines published in the same year; The Canadian Hypertension Education Programme [23]

and the Japanese Society of Hypertension [24]. In 2014, three more major Guidelines were published, The American Heart Association / American College of Cardiology (AHA/ACC) [25], the American Society of Hypertension/ International Society of Hypertension (ASH/ISH) [26] and the 8th Joint National Committee (JNC 8) [27]. Both the AHA/ACC and ASH/ISH recommended that target BP in the hypertensive patients with CAD be <140/90 mmHg while the JNC 8 did not make any specific recommendations on the issue.

Guidelines	Year Published	BP Targets (mmHg)	Drug of Choice
Japanese	2013	<140/90	CCB or BB for angina ARB/ACEI + BB for post MI
Canadian	2013	<140/90	ACE I or ARB BB or CCB for stable angina ACEI + CCB for high risk patients ACEI + BB for post MI
Malaysian Hypertension	2014	<130/80	BB or CCB for angina BB , ACE I and ARB post myocardial infarction BB, ACE I and Aldosterone antagonist post myocardial infarction and reduced systolic function
ESH/ESC	2013	<140/90	All can be used BB or CCB for angina BB for post MI
ASH/ISH	2014	<140/90	BB + ARB/ACEI
JNC 8	2014	<140/90	Not mentioned

Table 1: Published guidelines on treatment of hypertension since 2013.

Evidence from Clinical Trials

Clinical trials on primary prevention of CAD in patients with hypertension are far and few in between. This is mainly because such a trial, especially on mild hypertension will have to recruit tens of thousands of patients to be studied over many years to show a difference in clinical outcomes. This has led to researchers pulling in data from smaller studies in the form of meta-analysis. The latest meta-analysis showed that for primary prevention, treatment of mild hypertension (BP 140-150/90-99 mmHg) over five years did not prevent CAD [28]. This was however associated with a Number Needed to Harm (NNH) of twelve patients (1 in every 12 patients will be harmed mainly because of side effects or discontinuation of treatment). There remain no trials published so far addressing this issue definitively. It will be difficult to organize a placebo-controlled trial on primary prevention in mild hypertension for reasons mentioned above. The answer may be provided by an on-going large trial from China which is studying patients with pre-hypertension and randomizing them into three treatment groups and is placebo-controlled. If this trial shows that treating pre hypertension can prevent CAD (primary prevention), there is a case for conducting a similar trial for mild (stage 1) hypertension.

Meta-analysis on the benefits of treating moderate hypertension from placebo-controlled trials was more forthcoming. Treating patients with moderate hypertension (stage 2) has the benefits of

preventing myocardial infarction for every 100 patients treated (NNT 100) with NNH of ten (1 patient in every 10 will either develop side effects or stop treatment) [28].

The meta-analyses mentioned above are from placebo-controlled trials conducted more than thirty years ago. More recent trials however are no longer placebo-controlled due to ethical concerns although for primary prevention in mild hypertension, the question remained unanswered as discussed above. Subsequent trials over the last 20 years were all comparative trials comparing two active treatments. These more recent trials were also designed to investigate if there were more than blood pressure reduction per se to prevent cardiovascular events.

Of more recent trials, the best one to address primary prevention was the ASCOT trial [29] which looked at patients whose baseline blood pressure was 164/95 mmHg. This trial of 19,257 patients, all without clinical cardiovascular disease, was designed to investigate two drugs combination with the primary endpoint of preventing coronary artery disease (non-fatal MI and fatal CHD). The trial was inconclusive for the primary endpoint because it was prematurely stopped by the Data Safety and Monitoring Board. This was because patients assigned to amlodipine with or without perindopril as the second drug had significantly lower all-cause mortality compared to those receiving atenolol with or without thiazide as a second drug. There was a clear trend in CAD prevention which favored the amlodipine combination but failed to reach statistical significance for reasons given above. Another trial which may be cautiously classified as a primary prevention trial is the LIFE trial [30]. This trial studied 9,222 hypertensives with ECG changes of left ventricular hypertrophy and a baseline blood pressure of 174/98 mmHg. The vast majority of these patients (86.4%) did not have CAD at baseline. Patients were randomized to receiving either losartan or atenolol with thiazides added as a second drug if target blood pressure is not reached. The primary outcome was a composite of cardiovascular events. Although losartan was superior to atenolol for the composite endpoint, there was no difference in CAD. This trial contradicted the common practice of that time which adopted beta-blockers as the treatment of choice for hypertension with left ventricular hypertrophy. This was because theoretically beta blockers have negative chronotropic, inotropic and positive lusitropic (relaxes the left ventricle) effects.

In patients with hypertension and established CAD, trials are also lacking. The only dedicated one for such clinical phenotype, the INVEST trial [31] studied 22,576 hypertensives, all with CAD. Patients were randomized into either verapamil with trandolapril as a second drug or atenolol with thiazide as a second drug. Baseline blood pressure in the INVEST trial was 151/87 mmHg. There was no difference in CV events rate (including CAD) between the two treatment groups. Besides the INVEST trial, two other trials studied patients with established CAD and randomized them into either antihypertensive agent or placebo. In the EUROPA trial [32], 12,218 patients with a baseline BP of 137/82 mmHg were randomized into perindopril or placebo. Only about a quarter (27%) of patients in the EUROPA trials were hypertensive. Perindopril significantly reduced primary endpoint (CV death, myocardial infarction and cardiac arrest) by 20%. Non-fatal myocardial infarction itself was significantly reduced by 22%. The benefits of perindopril were seen both in normotensive and hypertensive patients. Since EUROPA was a placebo-controlled trial, it may be argued that the impact of perindopril was due to the blood pressure lowering effects. Blood pressure in EUROPA was lowered by 5/2 mmHg in the perindopril arm compared to the placebo arm.

This however was not the case with another placebo-controlled trial on CAD patients using another antihypertensive drug. In the ACTION trial [33], 7,665 patients were randomized either to Nifedipine GITS or placebo. The baseline characteristics of the patients were not far different from the EUROPA trial, with a baseline blood pressure of 138/80 mmHg. Slightly more than half (52%) of the patients in ACTION were hypertensive at baseline. Blood pressure dropped by a similar magnitude in the ACTION trial as seen in EUROPA (5/2 mmHg). Rather unexpectedly, there was no difference between the Nifedipine GITS treated group and the placebo treated group in clinical outcome including MI.

Both the EUROPA and ACTION were however, strictly speaking, not hypertension trials (baseline BP for both were <140/90 mmHg). They were trials on secondary prevention of CAD (all patients had CAD at baseline) with blood pressure lowering drugs, one which is not known to have anti-anginal effect (perindopril) while the other with well documented anti-anginal effect (nifedipine GITS). The findings however lead to a rethink of our practice of focusing on symptom relief in secondary prevention of CAD (92% of ACTION compared to 24% in EUROPA patients had symptomatic angina). Treatment of CAD should also and more importantly focus on anti-ischaemic properties which will likely have a positive impact on clinical outcomes.

As regards hypertensive patients with previous myocardial infarction (MI) and normal left ventricular function, there are no such dedicated trials. There are however, trials looking at post-MI patients with or without hypertension, who were given drugs with antihypertensive properties. The sum of evidence from meta-analysis suggests that these patients should be on a beta blocker and ACE I with ARB as a substitution for ACE I-intolerant patients. Duration of beta blocker therapy should be for one year if the patients are symptom-free and have normal left ventricular function, while ACE I should be continued for its anti-ischemic properties and their positive effects on clinical outcomes. For post-MI, hypertensive patients with reduced left ventricular function, there are also no dedicated studies. There are however many trials investigating post-MI patients (both normotensive and hypertensive at base line) with reduced left ventricular ejection fraction. Trials with beta blockers, ACE I and aldosterone antagonists have demonstrated positive impacts on clinical outcomes. These drugs should therefore be the treatments of choice. On the other hand, dihydropyridine calcium antagonist has a neutral effect on these patients while non-dihydropyridine is contra-indicated because of their negative impact on clinical outcome.

Recommendations from Clinical Practice Guidelines

Based on the studies involving patients with established CAD as discussed above, it is interesting to scrutinize the recommendations made on anti-hypertensives of choice in primary and secondary preventions, and in patients with prior MI with normal or abnormal left ventricular ejection fractions.

For primary prevention, the ESH/ESC recommended all antihypertensive agents as suitable. The Canadian Guideline meanwhile recommended either ACEI or ARB while the ASH/ISH recommended a combination of beta blockers and ARB/ACE I. Both the Japanese and JNC 8 did not make any specific recommendation. These however did not take into consideration that the best (and only) evidence to quote for this particular patient phenotype is the ASCOT trial which clearly showed that amlodipine-based treatment was clearly superior to atenolol-based. There was no evidence from ARB-based

trials on primary prevention and it should only be reserved for ACE I-intolerant patients as suggested by the Canadian Guideline. There are no outcome trials on primary prevention with a combination of beta blockers and ACEI or ARB. The closest to a primary prevention outcome trial is the LIFE trial where 9,193 high risk hypertensive patients (baseline blood pressure of 174/98 mmHg, all with left ventricular hypertrophy on ECG) were randomized to losartan or atenolol. Only 17% of the patients had CAD at baseline. Losartan and atenolol had similar effects on myocardial infarction (both fatal and non-fatal). Another outcome trial on high risk hypertensive was the VALUE trial [34]. In this trial, 15,245 patients with a baseline blood pressure of 155/88 mmHg were randomized to either valsartan or amlodipine. Thiazide was added as a second drug to achieve blood pressure control. There was significantly less MI in the amlodipine treated group. This trial is also not strictly speaking a primary prevention trial because 46% of the patients had CAD at baseline. There was also a significant difference in BP between the two treatments, favoring amlodipine.

As regards patients with symptomatic angina, The Japanese, Canadian, Malaysian [35] and ESH/ESC Guidelines recommended calcium channel blockers or beta blockers. This is despite the fact that the ACTION trial showed that calcium channel blockers did not have any positive impact on clinical outcomes, and there have been no clinical outcome trials in hypertensive patients with symptomatic angina randomized to beta blockers to date. These two anti-hypertensives are also licensed as anti-anginals but they lack clinical trial evidence in reducing clinical outcomes.

Treatment of a hypertensive patient post myocardial infarction is less controversial. All the available guidelines recommended beta blockers plus RAS inhibitor. The Canadian Guidelines specified ACE I as the RAS blocker, while the Japanese and ASH/ISH recommended either ARB or ACE I and the Malaysian Guideline recommended beta blockers, ACE I and ARB. The ESH/ESC meanwhile recommended beta blockers. The evidence for beta blockers is however not as exhaustive as for ACE I. Indeed, a more recent meta-analysis of 60 trials involving 102,003 patients showed that while beta blockers do significantly reduce myocardial infarction and angina, there was no reduction in mortality especially in the post thrombolytic era [36]. Evidence for ARB meanwhile is limited to valsartan (VALIANT trial) which showed that post myocardial infarction, valsartan is non-inferior to captopril in terms of clinical outcome [37] The OPTIMAL trial meanwhile did not show that losartan was superior to captopril and it was also not equivalent [38]. Evidence for ACE I meanwhile has been shown with captopril, enalapril, ramipril, zofenopril and trandolapril. Another class of drug shown to be of benefit post-MI was aldosterone antagonists; both spironolactone [39] and eplerenone [40]. It has to be remembered that most of the patients studied post-MI were not hypertensive (mean BP around 122/75 for RALES and 119/72 mmHg for EPHESUS). In RALES only slightly more than half (54%) had CAD while in EPHESUS all were on average seven days post-MI. Therefore the recommendations for the treatment of hypertensive patients for post-MI were extrapolations from post-MI trials.

Conclusion and Recommendations

Target BP to prevent complication has been a subject of debate. The recently concluded SPRINT [41] trial suggest that SBP <140 mmHg was as good as SBP <120 mmHg for MI prevention. The SPRINT trial however was not a primary prevention trial because 20% of the patients already had CVD. A recent meta-analysis showed that hypertensive patients treated to BP of 133/76 mmHg has significantly less MI compared to those treated to BP of 140/81 mmHg [42].

For primary prevention, the ASCOT trial provided the only credible evidence showing that calcium channel blocker based therapy (amlodipine) was superior to beta blocker based therapy (atenolol). For patients with documented CAD, calcium channel based therapy (verapamil) is equivalent to beta blocker based therapy (atenolol) in reducing clinical outcome. Meanwhile, findings from the EUROPA trial showed that ACE I based therapy (perindopril) is indicated for patients with CAD and minimal symptomatic angina. Conversely, the ACTION study demonstrated that in patients with CAD and symptomatic angina, calcium channel blockers based therapy (nifedipine GITS) did not improve clinical outcome. For post-MI patients with normal left ventricular ejection fraction, although beta blockers are recommended , more recent meta-analysis incorporating post thrombolytic studies cast doubt on this class of drugs especially in reducing mortality, although it did reduce MI and angina. ACE I had better evidence base in post-MI patients with ARB as an alternative for ACE I-intolerant patients. In patients with reduced left ventricular ejection fraction post-MI, ACE I has the best evidence base in reducing clinical outcome (including mortality), with ARB as an alternative in case of intolerance. Beneficial outcomes were also seen with aldosterone antagonists and beta blockers.

Not all the evidences we have at the moment on the treatment of hypertension with CAD are definitive especially for post MI patients Studies specifically dedicated to this patient phenotype need to be performed. Until such evidence is generated, the recommendation will continue to be based on extrapolations from existing post-MI studies. Meanwhile doctors should treat patients with hypertension and concurrent CAD with evidenced-based combination therapy [43]. Patients' wrong perception on BP control also needs to be addressed [44].

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