The Dual Burden of Hypertension and Hyperlipidemia

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Abstract

Hypertension and hyperlipidemia are chronic diseases with high socioeconomic burdens. They contribute significantly to mortality and morbidity amongst populations. Globally, hypertension is estimated to cause 7.1 million deaths and hypercholesterolemia contributes to 4.4 million deaths. They share common pathophysiological pathways and the combination of hypertension and hyperlipidemia predisposes individuals to higher risk of cardiovascular events. Despite this knowledge, we are far from attaining the target treatment goals and these dismal results are sobering in the face of cardiovascular morbidity and mortality.

Key words: Hypertension, Hyperlipidemia, Cardiovascular, Mortality

Introduction

Hypertension and hyperlipidemia are rapidly becoming chronic diseases with high health care and socioeconomic burdens. Globally, hypertension is estimated to cause 7.1 million deaths and hypercholesterolemia contributes to 4.4 million deaths.¹ The prevalence of hypertension and hyperlipidemia in Singapore is 23.5% and 17.4%, respectively.² Data from the Framingham Heart Study³ have shown that increases in blood pressure double the risk of cardiovascular events. Hyperlipidemia has also been found to be an important risk factor in the development of cardiovascular disease in the same study. The combination of these risk factors results in a multiplicative effect on endothelial dysfunction, leading to accelerated atherosclerosis and resultant cardiovascular disease.⁴ Cardiovascular disease accounted for 17.9 million deaths worldwide in 2016.⁵ Understanding the dual burden of hypertension and hyperlipidemia on cardiovascular health is especially pertinent as cardiovascular disease (including deaths from ischemic heart disease, cerebrovascular disease, hypertensive, and other cardiac diseases) as a whole accounted for 30.1% of all deaths in Singapore in 2017.⁶

Combined Cardiovascular Risk With Hypertension And Hyperlipidemia

Hyperlipidemia is more commonly present in hypertensive than in normotensive patients.⁷ Both hypertension and hyperlipidemia share common complex pathophysiology with environmental and genetic influences. Alayee et al. previously conducted a genome-wide scan in 18 Dutch families with familial combined hyperlipidemia and found evidence that support the presence of multiple genetic factors that affect both blood pressure and plasma lipid parameters.⁸ Sprecher et al. observed that lipoprotein lipase mutations were associated with elevated triglyceride levels and higher blood pressures.⁹ Insulin resistance contributes to the development of both hypertension and hyperlipidemia through various mechanisms. Activation of the sympathetic nervous system, renal sodium retention, altered transmembrane cation transport, growth-promoting effects of vascular smooth muscle cells, and vascular hyperreactivity have been reported as contributory mechanisms. Physiological studies purport that insulin predisposes to hypertension by the stimulation of renal sodium absorption and the sympathetic nervous system. Both of these, in turn, result in higher blood pressures.¹¹

Endothelial dysfunction also plays an important role in the pathogenesis of both hypertension and hyperlipidemia. The vascular endothelium functions to regulate vascular tone. It synthesizes and releases several vasoactive substances, including nitric oxide, which is a potent vasodilator. Hypertensive patients have impaired vascular endothelial vasodilatation. Lectin-like ox-low-density lipoprotein (LDL) receptor 1 (LOX-1) is the oxidative form of LDL. The upregulation of LOX-1 in patients with hyperlipidemia results in...
the generation of reactive oxygen species and decreases nitric oxide release from endothelial cells. This leads to reduced vasodilation, increased vascular tones, and increased peripheral vascular resistance which contribute to higher blood pressures.

Due to the common pathogenetic pathways, patients with hyperlipidemia are more often found to be hypertensive. The clustering of hypertension and hyperlipidemia has been shown to increase cardiovascular disease risk. In a study performed by the French, published in European Heart Journal in April 2012, patients with the highest systolic blood pressure (SBP) and highest cholesterol levels were found to have the highest cardiovascular disease mortality as well as coronary heart disease mortality.\(^{[7]}\) The combination of hypertension and hyperlipidemia is also associated with increased health-care cost burden.\(^{[12]}\) Cardiovascular risk assessment is, hence, of utmost importance and the various tools available consider the additive effects of hypertension and hyperlipidemia. For example, the European systemic coronary risk evaluation (SCORE), risk assessment tool predicts the 10-year risk of fatal cardiovascular disease [Figure 1]. It takes into account an individual’s gender, age, smoking status, blood pressure, and cholesterol levels. For the same level of SBP, the higher the total cholesterol level, the higher the risk score for every defined age groups. In the same manner, a higher SBP will add to the overall cardiovascular risk of a given total cholesterol level at a defined age group. Cardiovascular risk assessment based on the Framingham heart study also similarly takes into consideration the individual’s blood pressure and cholesterol levels.

**Effect of The Treatment of Hypertension on Lipid Levels**

Reduction of cardiovascular risk requires appropriate management of both blood pressure and lipid levels. Medications used for the treatment of hypertension and hyperlipidemia can provide independent and additive reductions in cardiovascular risk. However, some medications used in the treatment of hypertension can affect the lipid profile in an unfavorable manner.

The use of diuretics, especially thiazides in the treatment of hypertension, has been found to have dose-dependent deleterious effects on total cholesterol, LDL cholesterol, and triglyceride levels.\(^{[13]}\) In the antihypertensive and lipid-lowering treatment to prevent heart attack trial, patients on chlorthalidone had higher serum cholesterol levels than the lisinopril group at 2 years and 4 years of follow-up. Similar results were seen when compared with patients taking amlodipine - total cholesterol levels were higher in chlorthalidone group at 2 years.\(^{[14]}\) Beta-blockers with cardioselectivity and intrinsic sympathomimetic activity decreased total cholesterol and LDL cholesterol levels and increased high-density lipoprotein (HDL) cholesterol.\(^{[15]}\) Alpha-blockers decreased total and LDL cholesterol levels and increased HDL cholesterol levels. Of the antihypertensive medications, this class provides the greatest lipid-lowering benefit.\(^{[13]}\) Angiotensin-converting enzyme inhibitors are especially useful in the diabetic population where they have been found to be associated with reductions in total cholesterol.\(^{[13,15]}\) In the RENAAL study, losartan resulted in a statistically greater fall in total and LDL cholesterol levels compared to placebo.\(^{[16]}\)

**Effects of Lipid-Lowering Therapy on Hypertension**

Similarly, lipid-lowering medications were also found to have beneficial effects on blood pressure control. In a randomized, double-blind, placebo-controlled trial - the UCSD statin study, participants were randomized to take either 20 mg simvastatin, 40 mg pravastatin, or placebo for 6 months. The study found that statins modestly but significantly reduced blood pressure relative to placebo, by 2.2 mmHg for SBP and 2.4 mmHg for diastolic blood pressure.\(^{[17]}\)

LDL has been shown to upregulate angiotensin 2 Type 1 receptor (AT1) in animal studies and cell cultures, resulting in elevated blood pressures in hypercholesterolemic patients.\(^{[18]}\)
Nickenig et al. studied the effects of cholesterol-lowering therapy on AT1 receptor overexpression and found that statins reversed the elevated blood pressure response to angiotensin 2 and downregulated AT1 receptor density. This is in concordance with the findings that statins improve blood pressure control in the UCSD study mentioned earlier.

The Anglo-Scandinavian cardiac outcomes trial-lipid-lowering arm (ASCOT) trial went further to study the effects of lipid-lowering therapy in hypertensive patients who were not traditionally deemed dyslipidemic. The study was stopped prematurely as participants who were receiving atorvastatin compared to placebo had highly significant reduction in the primary endpoint of cardiovascular events compared with placebo. They were also observed to have a significant reduction in the incidence of stroke.

ASCOT legacy study results recently published in 2018 revealed sustained long-term benefits of improved cardiovascular outcomes in patients treated with both antihypertensive and lipid-lowering therapy. These patients were followed up for a median of 15.7 years, demonstrating long-term cardiovascular benefits up to >10 years.

Treatment Targets

Hypertension

The 2018 European Society of Cardiology/European Society of Hypertension guidelines recommend that the first target for all patients on pharmacotherapy for hypertension would be ≤140/90 mmHg. If such a target is well tolerated, treated blood pressure should be targeted to 130/80 mmHg or lower in most patients. In elderly patients (>65 years old), SBP should be targeted to between 130 and 140 mmHg and diastolic blood pressure to <80 mmHg. In diabetics receiving pharmacotherapy for hypertension, office SBP should be targeted to ≤130 mmHg and diastolic blood pressure <80 mmHg. In older patients with diabetes, an SBP target range of 130–140 mmHg is acceptable.

The 2017 American Heart Association (AHA) guidelines suggested a blood pressure goal of <130/80 mmHg in majority of patients. The threshold blood pressure is slightly higher in individuals with no clinical cardiovascular disease and a 10-year atherosclerotic cardiovascular disease risk of <10% and patients on antihypertensive therapy for secondary stroke prevention. These individuals have a blood pressure threshold of ≤140/90 mmHg. In other individuals, blood pressure threshold is set at ≤130/80 mmHg.

The Eighth Joint National Committee (JNC 8) guidelines recommend a blood pressure target of <150/90 mmHg in patients 60 years or older without diabetes or chronic kidney disease. Patients with diabetes and hypertension should be treated to a target of <140/80 mmHg. In patients aged 18–50 years with no major comorbidities and in patients 60 years or older with diabetes, chronic kidney disease or both, the target blood pressure is <140/90 mmHg. It is important to note that the recommendations for JNC 8 were published early in 2014. The final draft of the guidelines was circulated in January 2013 for external peer review and various comments were incorporated in the second half of 2013.

Studies have been performed to study the effects of intensive blood pressure lowering therapy (SBP <120 mmHg) versus patients treated to standard targets (SBP <140 mmHg). The SPRINT study, which studied hypertensive patients without diabetes, showed that relative risk of death from cardiovascular causes was lower in the intensive treatment group compared to the standard treatment group. However, patients in the intensive treatment group also encountered higher incidence of adverse events such as acute kidney injury. The result from systolic blood pressure intervention trial (SPRINT) was published in November 2015, 2 years after JNC 8 was finalized.

The ACCORD study, which studied hypertensive patients with Type 2 diabetes, revealed that targeting an SBP of <120 mmHg in comparison to <140 mmHg did not reduce the rate of the prespecified combined cardiovascular events. Lowering blood pressure to <120 mmHg did reduce the incidence of stroke by 40%. Similar to the SPRINT study, it also reported higher incidence of serious adverse events in the intensive blood pressure lowering arm.

In Singapore, the Ministry of Health Singapore (MOH) hypertension clinical practice guidelines (CPG) recommend a target blood pressure of <140/90 mmHg in patients under 80 years and <150/90 mmHg in patients aged 80 years or older. In addition, in patients with moderate-to-severe albuminuria, the target blood pressure advised is <130/80 mmHg. Patients with diabetes mellitus should be treated to a blood pressure target of <140/80 mmHg. The final draft of the guidelines was finalized before the SPRINT result being published.

Hyperlipidemia

A meta-analysis conducted by the Cholesterol Treatment Trialists’ Collaboration in 2010 revealed a reduction in all-cause mortality of 10% per 1.0 mmol/L (38 mg/dL) LDL cholesterol reduction. This was primarily due to significant reductions in deaths related to coronary heart disease and other cardiac causes.

The 2017 American Association of Clinical Endocrinologists medical guidelines for the management of dyslipidemia recommend personalized treatment targets for dyslipidemia according to patients’ level of risk. This is determined by the presence of atherosclerotic cardiovascular risk factors as well as 10-year cardiovascular risk estimated by various tools such as the Framingham Risk Assessment tool.

For low-risk individuals with no risk factors, the recommended target LDL cholesterol level is <130 mg/dL. For individuals with moderate or high risk, an LDL cholesterol level target of <100 mg/dL is recommended. Treatment target goals for patients at very high and extreme risk are <70 mg/dL and <55 mg/dL, respectively. The guidelines recommend a triglyceride goal of <150 mg/dL and total cholesterol targets <200 mg/dL.
The American College of Cardiology (ACC) and AHA deliberated and proposed a cholesterol treatment guidelines that are quite distinctly different for the fact that it no longer advocates a “treat to target” strategy that has been the mainstay of most cholesterol treatment guidelines but instead recommends to match the intensity of the statin therapy according to the overall cardiovascular risks of the patient. The greater the risk category, the stronger the intensity of statin to be used for treatment in a given patient.\(^{[30]}\)

The Singapore MOH CPG 2016\(^{[31]}\) for dyslipidemia recommends similar LDL cholesterol target levels. It recommends target LDL cholesterol levels of <80 mg/dL for very high-risk individuals and <100 mg/dL for high-risk patients. Recommended LDL cholesterol target for moderate risk is <130 mg/dL or <100 mg/dL if benefits of more intensive therapy are deemed to outweigh risks. Similarly, for low-risk patients, recommended target LDL cholesterol level is <160 mg/dL or <130 mg/dL if deemed beneficial.

**Impact on Clinical Practice**

As physicians, attention to patients’ cardiovascular health is extremely important, regardless of setting of practice. Screening of individuals for hypertension and hyperlipidemia should be routinely performed as mitigation of these risk factors has been proven to improve outcomes and reduce incidence of cardiovascular disease. The dual burden of hypertension and hyperlipidemia predisposes an individual to higher risks of accelerated atherosclerosis and subsequent cardiovascular disease. This highlights the importance of assessing each patient’s cardiovascular risk and individualizing each patient’s target lipid and blood pressure targets based on their comorbidities and risk profiles. Cardiovascular risk assessment can be rapidly and easily performed with the aid of a variety of tools.

There are many well-established modifiable cardiovascular risk factors and as each contributes to the combined risk, they should be considered as a whole. Most available tools incorporate combinations of multiple risk factors in the determination of an individual’s absolute cardiovascular risk. These include the QRSK, QRSK 2, the World Health Organization score, and the ACC/AHA 2013 Pooled Cohort risk equations. The SCORE and Framingham risk assessment tools were previously discussed.\(^{[32]}\)

Educating patients on their cardiovascular risk allow physicians to work in tandem to prevent the development of cardiovascular disease and avoid adverse cardiovascular outcomes. The personalization of treatment goals helps physicians tailor treatment for optimal results while at the same time reducing unwanted adverse effects of treatment. Modification of these risk factors known to be a major contributory factor toward cardiovascular disease and death can help to reduce morbidity and mortality.

Despite the compelling evidence that pushes us toward modifying these risk factors, it seems that we are still far behind our intended targets. In a study conducted to assess the burden of hypercholesterolemia in Singapore, the authors found that in patients who were assessed to be at high risk of coronary heart disease by the National Cholesterol Education Program Adult Treatment Panel III risk determinants and Framingham risk score, only 39.6% of them were on lipid-lowering therapy. In those receiving lipid-lowering therapy, less than half met the group-specific LDL-C treatment goal.\(^{[33]}\) The return on expenditure achieved for lipid therapy-Asia study also showed that attainment of target goal of LDL-C is poor among the Asian population.\(^{[34]}\) This is in spite of the well-known fact that hyperlipidemia is a major risk factor for cardiovascular disease.

On the hypertension front, a study performed by the Japanese revealed that only 52% of diabetic patients achieved the blood pressure target of <130/80 mmHg.\(^{[35]}\) Similar rates of optimal blood pressure control were reflected in the National Health and Nutrition Examination Survey 2015–2016, where only 48.3% of patients were attaining recommended blood pressure goals.\(^{[36]}\)

These dismal results bring to our attention the need for more action. Various reasons have been cited in the above studies for the suboptimal control of blood pressure and lipid targets. These include obesity, smoking, lower education levels, and patients with greater number of cardiovascular risk factors. More studies are needed to elucidate the link between these risk factors and poor control of hypertension and hyperlipidemia.

**Conclusion**

The combination of hypertension and hyperlipidemia translates into a higher risk of cardiovascular disease and higher healthcare costs. Considering the prevalence and rising rates of hypertension and hyperlipidemia, these costs will contribute to a large portion of the health-care budget. Medications used in the treatment of either of these cardiovascular risk factors have unique effects on the other. The additive effect on cardiovascular disease and the effect of pharmacological therapy must be taken into consideration in the management of both conditions. The suboptimal attainment of treatment goals is sobering in the face of cardiovascular morbidity and mortality. Greater vigilance should be called upon in the management of these established risk factors.

**References**


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