Hypertension and Atherosclerosis - The Cardiovascular Risk Continuum

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INTRODUCTION

The concept of cardiovascular risk continuum was first proposed by Dzau and Braunwald as a new paradigm for cardiovascular disease pathogenesis. Atherosclerotic cardiovascular disease particularly coronary artery disease develops over decades and ill-effects of cardiovascular risk factors such as hypertension, dyslipidemia, obesity and insulin resistance accrues over a period of time leading to endothelial dysfunction, culminating in acute myocardial infarction or chronic coronary artery disease, left ventricular remodeling and ultimately to heart failure. Interruption of this chain of events with appropriate interventions at multiple sites along this continuum can substantially decrease the morbidity and mortality associated with cardiovascular disease. The development of HMG-CoA reductase inhibitors, or statins, that lower cholesterol effectively has transformed the management of lipid disorders. Large-outcome trials have conclusively proved that statins prevent myocardial infarction and mortality not only in patients who have already developed cardiovascular complications but also in individuals who have not had any cardiovascular events and who do not even have elevated cholesterol levels. Antihypertensive drugs and statins demonstrate the clinical utility of the cardiovascular continuum concept, namely, that the correction of cardiovascular risk factors prevents the escalation of cardiovascular disease and the downstream complications, including the ultimate event, death. Angiotensin-converting enzyme inhibitors, in particular, address different parts of the continuum, including hypertension, diabetes, left ventricular hypertrophy, remodeling, and heart failure. The ‘American Journal of Cardiology’ in a recent supplement issue revisited this concept in context of recent scientific developments and clinical trials. The present article will review the epidemiology of cardiovascular disease risk factors, progression of cardiovascular damage and the central role of Renin-Angiotensin system (RAS) in the continuum, the cardio-renal protection due to RAS blockade and finally the relevance of the continuum in Asian population. (Figure 1)

Epidemiology of cardiovascular risk factors

Modifiable risk factors of cardiovascular disease such as hypertension, abdominal obesity, abnormal lipids, smoking, diabetes mellitus as well as stress, low consumption of fruits and vegetables and lack of regular physical activity are the important risk factors and contribute to >90% of all myocardial infarctions. More recently, too little (<6 hours) or too much (>9 hours) sleep has been identified as another independent risk factor for hypertension and metabolic syndrome. Cardiovascular risk factors show a continuous association with overall cardiovascular risk with no minimum threshold for disease. Risk factors rarely occur in isolation and instead tend to cluster in individuals. The risk factors act synergistically to increase the cardiovascular disease risk by multiple times.

Hypertension which was identified in a recent World health Organization (WHO) report as among the most important causes of premature death, affected 972 million people worldwide in 2000 and is predicted to increase by around 60% to 1.56 billion people by 2025. Even though hypertension, hypercholesterolemia and tobacco use are the leading...
causes of death in developed nations like USA, similar trends are emerging in developing nations as well.

The global burden of cardiovascular disease is increasing as the world’s population ages and the lifestyle in lower and middle income countries become more similar to wealthier nations. The recently published Reduction of Atherothrombosis for Continued Health (REACH) Registry, which collected global data on atherosclerosis risk-factors from 67,888 patients aged ≥ 45 years in 44 countries, found that classic cardiovascular risk-factors (hypertension, diabetes, high cholesterol, obesity and smoking) confirm the findings from the INTERHEART study and are consistent and common in diverse ethnic populations, even if they do tend to be undertreated and under-controlled in many regions of the world. The prevention of cardiovascular diseases can be based on the same principles worldwide.

As cardiovascular risk factors tend to cluster, so an estimation of global cardiovascular risk score is more effective in implementing prevention strategies rather than single risk factor based approach. The importance of treating global cardiovascular risk rather than single factors has been corroborated by the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial. The study conducted in patients with myocardial ischemia and stable coronary artery disease (CAD), showed that intensive pharmaceutical treatment and lifestyle modification (optimal medical therapy) was as effective as percutaneous coronary intervention in lowering the composite cardiovascular end-point of death, myocardial infarction (MI) and stroke showing that systemic reduction in risk throughout the entire vascular tree was as effective as isolated surgical treatment of the acutely affected vessel.

Progression of cardiovascular damage-role of Renin-Angiotensin system (RAS) blockade.

The classical view of RAS system is shown in figure 2 below. Angiotensin II acts via specific receptors, of which 4 subtypes (AT₁-AT₄) have been identified. Pathologic effects as shown in the figure below are mediated by AT₁ receptors, activation of which results in vasoconstriction, sodium retention, aldosterone secretion, fibrosis, cellular proliferation,
Fig. 2: showing Renin-angiotensin-aldosterone system (RAAS) physiology.

superoxide formation, inflammation and thrombosis. By contrast AT₂ receptors results in potentially beneficial vasodilatory and antiproliferative effects but promotes apoptosis. The function of AT₃ receptor is not known and the AT₄ receptor primarily mediates release of plasminogen activator inhibitor 1 (PAI-1) and thus may be prothrombotic.

The angiotensin II can also be generated by a number of non-ACE pathways, through action of enzymes, such as the chymostatin-sensitive angiotensin II-generating enzyme and cathepsin G, which convert angiotensinogen directly to angiotensin II, and chymase, which cleaves angiotensin I to form angiotensin II. Chymase is responsible for generation of > 80% of tissue angiotensin II formation in human heart, and >60% in arteries. ACE 2, a homologue of ACE that has been found in heart, kidney, testis and gastrointestinal tract has been found to convert Angiotensin I to angiotensin (1-9) and it also converts Angiotensin II to angiotensin (1-7). Angiotensin (1-7) has been shown to have vasodilatory properties as it stimulates nitric oxide synthesis. Angiotensin (1-7) may also be generated through action of neutral endopeptidases. These pathways are potential therapeutic targets of RAS blockade in the future. ACE also catalyzes the breakdown of bradykinin which is a vasodilator and is thought to promote tissue plasminogen activator production.

Another important physiologic correlate is inhibition of aldosterone (by agents like spironolactone and eplerenone) which is directly stimulated by angiotensin II. (Figure 2)

ACE inhibitors has been shown to have beneficial effects on endothelial function, cardiovascular remodeling, the progression of atherosclerosis, and protection against clinical events such as myocardial infarction and heart failure.⁹

Effects on glucose metabolism and obesity
Obesity and hypertension are both closely related cardiovascular risk-factors and both conditions are associated with RAS activation. Higher levels of angiotensin II, renin, aldosterone and ACE have been found in obese women. Such activation in obese persons are thought to increase insulin resistance in skeletal muscle, resulting in induction of metabolic syndrome along with beta cell impairment leading to type 2 diabetes. ACE inhibitors have been shown to increase glucose uptake first by vasodilation and improved skeletal muscle perfusion and secondly by stimulating GLUT-4 mediated glucose uptake in skeletal muscle.¹⁰ The DREAM trial showed that ramipril reduced
incidence of diabetes by 9% in patients with impaired glucose tolerance or impaired fasting glucose over a period of 3 years (total participants 5269).\textsuperscript{11}

**Effects on endothelial function, lipid oxidation and monocyte adhesion**

Endothelial dysfunction is one of the earliest detectable functional abnormalities in the coronary circulation during the development of atherosclerosis. Effects of ACE inhibition have been studied extensively in trials like PERTINENT and EUROPA study. PERTINENT trial showed significant association between baseline von willebrand factor and coronary artery disease incidence and it also showed that patients treated with perindopril had a substantial reduction in von willebrand factor level and thereby cardiovascular risk. In the presence of perindopril endothelial nitric oxide levels were increased significantly in the patient group in EUROPA trial. A further study confirmed significantly improved flow mediated (endothelium-dependent) vasodilation in brachial artery in patients treated with either losartan, candesartan or irbesartan.\textsuperscript{12}

Oxidation of low-density lipoprotein(LDL) has been proposed as a key step in the development of atherosclerosis associated with hypercholesterolemia. The oxidized LDL are taken up by endothelial cells and vascular smooth muscle cells by a specific receptor, the lectin-like oxidized LDL receptor-1, on cell surface leading to activation of mitogen activated protein (MAP) kinase and of nuclear factor-κβ (NF-κβ), which in turn stimulates the expression of adhesion molecules that mediate adhesion and activation of inflammatory cells, such as monocytes and macrophages. Angiotensin II acting via AT1 receptor has been shown to promote LDL oxidation as well as increased expression of lectin-like oxidized LDL receptor-1 in human vascular smooth muscles.\textsuperscript{13}

**Effects on inflammation, cell proliferation, fibrinolytic balance and plaque dynamics**

Angiotensin II promotes the secretion of proinflammatory mediators and activation of inflammatory cells and thus plays a key role in development of the plaque. Angiotensin II also activates several pathways leading to cell proliferation including the c-fos, c-jun, and c-myc pathways resulting in in the expression of autocrine growth factors, such as platelet-derived growth factors, and hence cellular hypertrophy and proliferation. So RAS blockade should provide long lasting benefits. Mean left ventricular mass was significantly decreased in hypertensive patients (with left ventricular hypertrophy) taking losartan when compared to hypertensive patients taking atenolol in Losartan Intervention for Endpoint Reduction in Hypertension (LIFE) trial. Various studies have shown that RAS blockade also leads to reduced progression of atherosclerotic plaque and comparable results have been obtained in various major clinical trials. The SECURE trial has shown that treatment with 10 mg of ramipril compared to placebo over 4.5 years resulted in mean 37% reduction in carotid intima-media thickness in high-risk participants with vascular disease or diabetes, and ≥1 other cardiovascular risk factor. RAS activation also causes an increase in PAI-1 (Plasminogen activator inhibitor-1) levels in vascular smooth muscles and endothelial cells resulting in a prothrombotic state. RAS blockade has been shown to reverse this effect.

**RAS blockade: beyond blood pressure control**

In animal studies it has been shown that ramipril induces regression of left ventricular hypertrophy (L VH), reduction in coronary infarct area and improvement in survival, prevention of cerebrovascular and renal lesions, and reduction in urinary protein levels with enalapril in salt loaded stroke prone spontaneously hypertensive rats. A meta-analysis of 41 comparative clinical studies revealed that ACE inhibitors reduced proteinuria by 39.9% (95% confidence interval, 36.8-42.8%) versus a reduction of only 17% (95% confidence interval, 15.1-19 %) with other antihypertensives and blood pressure lowering was 12 % (95% confidence interval, 11.2-12.8 %) with ACE inhibitors versus 11.4 % (95% confidence interval, 11.1-11.7 %) with other antihypertensives.\textsuperscript{14} A recent study has shown that although enalapril 10mg and indapamide 2.5 mg given for 8 weeks produced similar reduction in brachial systolic and diastolic pressure, the reduction in aortic systolic pressure which is a better predictor of cardiovascular risk, was greater with enalapril.\textsuperscript{15} The recently published Incipient to Overt: Angiotensin II blocker, Telmisartan, Investigation on Type 2 Diabetic Nephropathy (INNOVATION) study also suggests that the effect of telmisartan on the prevention of the transition from incipient to overt nephropathy in patients with type 2 diabetic nephropathy was independent of blood pressure control.\textsuperscript{16}

**Renal and Cardiovascular protection and RAS blockade**

Currently three classes of RAS modulating agents are available-1) Angiotensin converting enzyme(ACE) inhibitors 2) Angiotensin Receptor blockers (ARBs) 3) Renin inhibitors like Aliskiren. The importance of diabetic nephropathy as a major cardiovascular risk factor has been established by a number of large epidemiologic and interventional studies. The United Kingdom Prospective Diabetes Study (UKPDS) showed that risk of mortality from cardiovascular causes increased progressively
with the degree of nephropathy (stage of microalbuminuria to macroalbuminuria to overt nephropathy with elevated plasma creatinine and renal replacement therapy) from 1.4% in patients without nephropathy to 19.2% in those with elevated plasma creatinine or renal replacement therapy. Several studies have shown that ACE inhibitors as well as ARBs has significant renoprotective effect in the setting of diabetic nephropathy. In terms of comparison among various ARBs with regard to antiproteinuric effects it has been shown in a recent study that the reduction in urine albumin creatinine ratio from baseline in patients with overt nephropathy, was significantly greater for Telmisartan than Losartan, despite comparable reductions in blood pressure. More recently, the ONTARGET trial that compared telmisartan with ramipril in 25,620 high-risk patients, showed that the incidence of primary renal outcome (a composite of dialysis, doubling of serum creatinine and death) was comparable between telmisartan and ramipril during a median follow-up of 56 months. Telmisartan had a significantly stronger antiproteinuric effect compared to ramipril but the decrease in estimated glomerular filtration rate (GFR) was lower for ramipril than telmisartan.

Several large trials including the HOPE study and EUROPA study have shown that ACE inhibitor therapy significantly reduces the risk of coronary artery disease in various at-risk patient populations. However available evidence suggests that combination of ACE inhibitor and ARB does not offer any additional benefits. The primary composite cardiovascular end-point (death from cardiovascular causes, MI, stroke or hospitalization for heart failure) in ONTARGET study was comparable between telmisartan and ramipril. It also showed that combination of telmisartan and ramipril did not offer any additional cardio- protection in high-risk patients.

Cardiovascular risk continuum in Asians

Asians particularly Indians are highly susceptible to cardiovascular risk and a carbohydrate based diet with less energy expenditure is one of the major causes of visceral adiposity, insulin resistance, systemic inflammation and endothelial dysfunction noted in Asians. A cross sectional survey done in rural Haryana in 1998 revealed a CAD prevalence rate of 6% in rural Indian aged 35-64 years. This CAD rate is 2 fold higher than contemporary US rates. The prevalence of CAD in urban India is about double the rate of rural India and about 4 fold higher than in the US. The rate appear to be higher in South India with Kerala having a prevalence of 13% in Urban area and 7% in rural. So, we can ready understand how the grave situation is. It is also noticed that CAD in India has some different Characteristics in comparison to global scenario, like premature onset, more symptomatic, higher association of with clinical CAD at a given degree of atherosclerosis. Polished rice, the staple food in much of Asia, is low in fiber and high in glycemic index. Rice-based meals have a place in rural societies where people walk more and do manual labor. Their appropriateness for an urbanized society is now questionable. Sumo wrestlers have a lot of subcutaneous fat but have little visceral fat because of heavy exercise. The same principles discussed above should in general be applicable in Asian population but large randomized trials needs to be conducted in Asians as the food habits, genetic predisposition, and threshold for risk factors are distinctly different in Asian population.

CONCLUSION

The cardiovascular risk continuum remains as relevant today as it was when the perspective was first launched in 1991. The recent large scale multi-centric clinical trials supports the principle that cardiovascular risk factors need to be treated as a composite whole and not each risk factor in isolation. The concept of therapeutic lifestyle change or TLC has been the clinical punch-line in this context. RAS system has emerged as the primary regulator of the cardiovascular continuum and modulation of RAS system by various drugs can halt the progression of the continuum.

REFERENCES


