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Review Article

BENEFITS OF EARLY INTERVENTION IN THE PROGRESSION OF CARDIOVASCULAR DISEASE —role of renin-angiotensin system blockade

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ATHEROSCLEROSIS – A VILLIAN

Atherosclerosis is a slowly progressive process. It begins early, progresses insidiously for many years, remains asymptomatic and by the time it manifests as coronary artery disease or stroke, the altherosclerotic burden is immense. The question is that why does it remain asymptomatic for so long? The answer lies in the fact that blood vessels are able to accommodate huge amount of plaque before the lumen becomes compromised. It is only when the plaque burden becomes severe that the lumen of the vessels becomes clogged and the symptoms start appearing.

In fact the atherosclerotic process begins after the first decade of life. More so in the recent years when the fast food culture has prevailed along with significant changes in life style with decreased physical activity and increasing trend towards obesity. The process progresses steadily over the third and fourth decade of life and beyond. The fatty streaks grow to form fibrous plaques which may narrow or occlude the arterial lumen. Complex lesions may become unstable and rupture, leading to acute coronary events such as unstable angina, myocardial infarction and stroke [1].

The primary event in atherosclerosis is thought to be the damage caused to the endothelium, resulting in endothelial dysfunction. The damage may be caused by a variety of factors; haemodynamic forces like hypertension, a number of vasoactive substances, mediators (cytokines), cigarette smoke, atherogenic diet, elevated glucose levels in blood and oxidised LDL cholesterol [2]. Endothelial damage causes the cells to produce cellular adhesion molecules such as cytokines (like IL-I, TNF-alpha), growth factors (like platelet – derived growth factor, PDGF), chemokines (like IL-8) etc. This encourages the inflammatory cells like monocytes and T-lymphocytes to attach to endothelial surface. Once attached they migrate through the intact endothelium into subendothelial space. Monocytes differentiate into macrophages and take up oxidised LDL which is more atherogenic and the macrophages become foam cells. Oxidised LDL stimulates the death of endothelial cells and an inflammatory response causes endothelial dysfunction. It also induces a prothrombotic state by influencing platelets and coagluation factors. (Table 1)

The endothelium thus responds to the damage by inducing a protective response which will eventually lead to formation of fibrofatty and fibrous lesions, the atherosclerotic plaque,

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preceded and accompanied by inflammation[3]. Migration of vascular smooth muscle cells to the intima and laying down of collagen fibre results in the formation of a protective fibrous cap over the lipid core. The fibrous cap is a crucial component in the mature atherosclerotic plaque. This plaque may cause complications as a result of its size, reducing lumen diameter and blood flow and its tendency to rupture. Plaque erosion or rupture occur in plaques which are intrinsically vulnerable. Erosion or rupture can lead to thrombus formation. Regression of atherosclerotic plaques can occur with lipid-lowering therapy and with dietary and life-style changes [4].

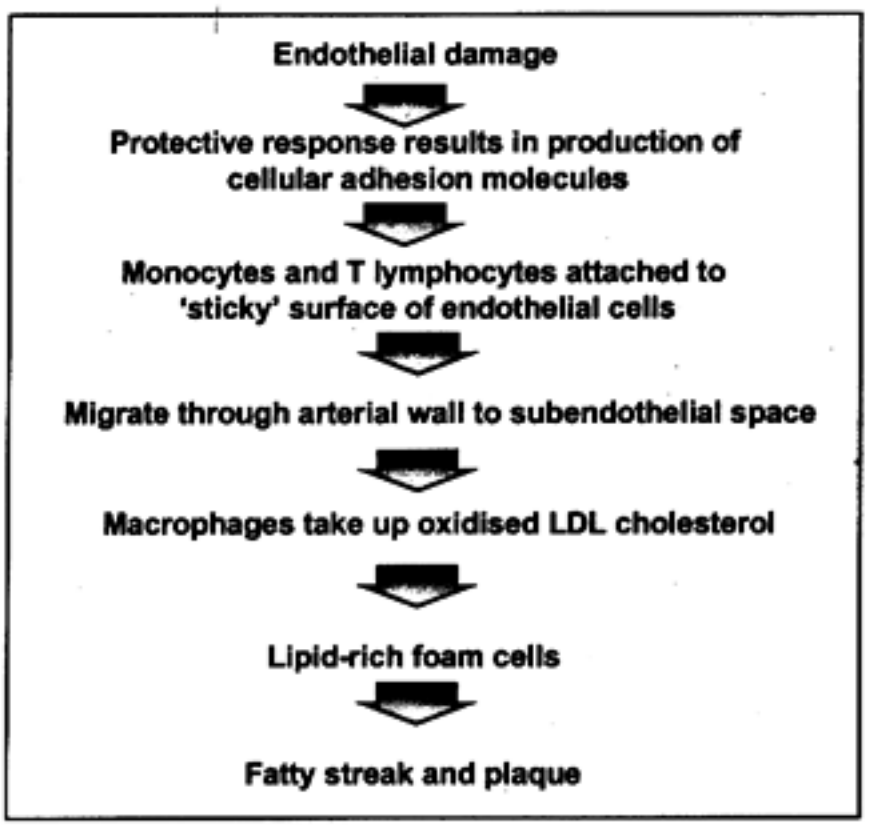
When the patients present with manifestation of atherosclerosis eg., coronary events like angina or myocardial infarction, the critical coronary stenosis is really the tip of the iceberg as it reflects the fact that diffuse atherosclerosis in most of the blood vessels in the body would already be established.

EARLY DIAGNOSIS OF ATHEROSCLEROSIS

Atherosclerosis must be identified and treated early by using all available means of diagnosis, especially in high risk individuals. High risk individuals include those with strong family history, overweight, smokers and sedentary life-style. Early identification of atherosclerosis is difficult to do. Coronary angiography is the gold standard for coronary artery disease. However, it can miss early atherosclerosis of coronary arteries. The reason being that angiography is a 'luminogram' and it does not image the vessel wall where atheroma through endothelial dysfunction and cholesterol deposition is taking place. Intravascular ultrasound (IVUS) is a good technique to detect the status of the vessel wall. However, this procedure is not routinely carried out.

Detection of CAD early may enable the initiation of anti-ischemic medication; patients could be advised to adhere to aggressive secondary prevention through weight control, cessation of smoking, exercise and other life-style changes. Patients with asymptomatic but severe CAD may benefit from early revascularisation. Patient education to recognize early coronary symptoms is another benefit, which they may otherwise consider atypical of symptoms of myocardial ischemia.

Table 1 : Pathogenesis of Atherosclerotic Plaques



RISK FACTORS FOR CARDIOVASCULAR DISEASE

Hypertension, diabetes mellitus, hypercholestrolemia, smoking, family history, obesity and sedentary habits are some of the prominent and well-documented risk factors for cardiovascular disease. The following section will focus on first three:

Hypertension

The Framingham Heart Study [5] represents one of the major milestones in the understanding of the cardiovascular risks of hypertension. This study has provided epidemiologic data in which a cohort of subjects from the general population have been followed biennially for almost four decades to observe development of cardiovascular events in relation to their blood pressure

and other risk factors. This study has found hypertension to be a major contributor to cardiovascular diseases.

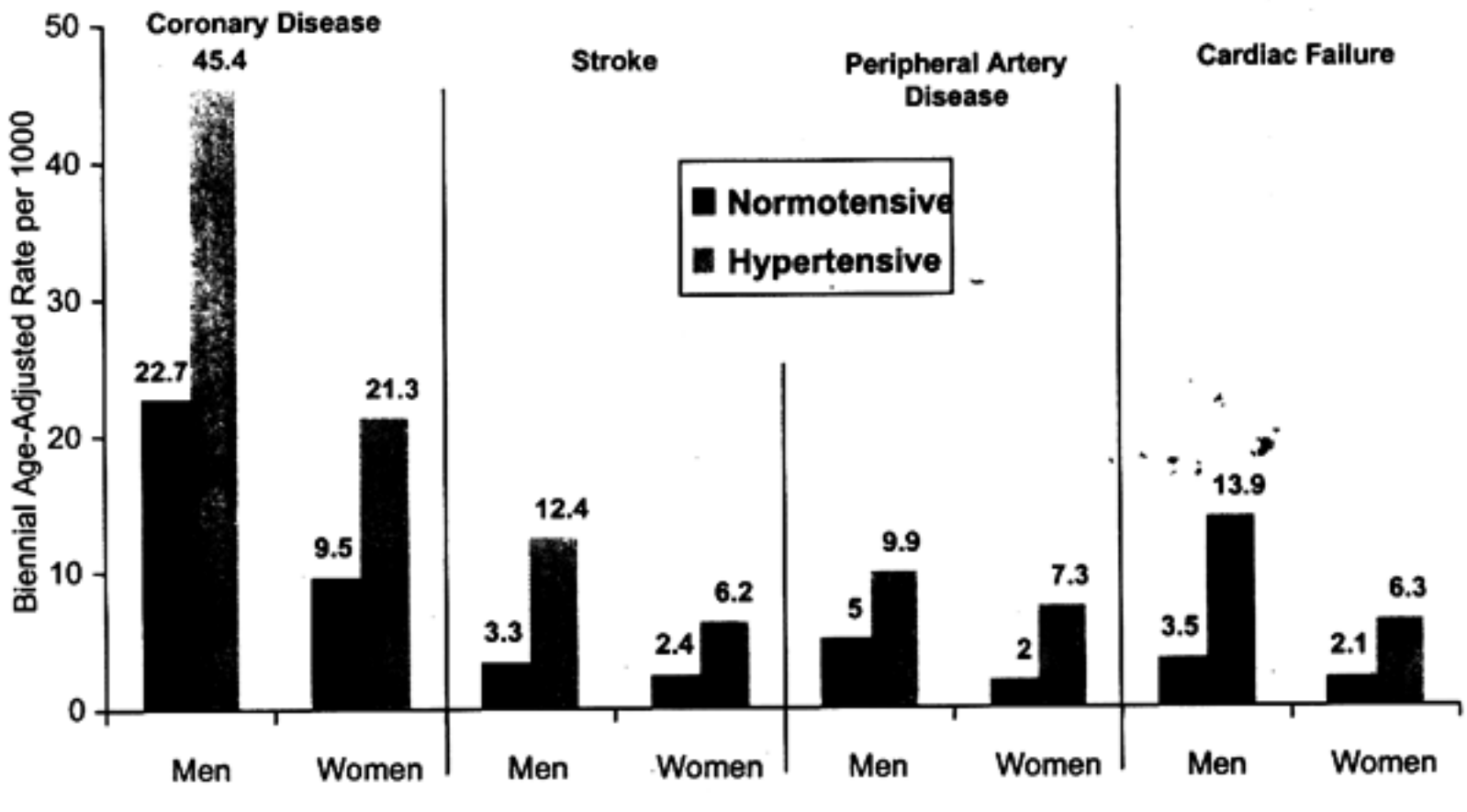
Hypertensive subjects in this study have been found to be at much greater risk for coronary artery disease, stroke, peripheral artery disease and heart failure, compared to normotensives, both in men and women (Fig 1). For example there is twice as much risk of CAD in hypertensive men and women compared to normotensives. There is almost four time more risk of stroke and heart failure in hypertensive men.

Multiple risk factors tend to cluster. Diabetes for example, can co-exist with hypertension. With the rising level of systolic blood pressure in the presence of diabetes in both sexes, the cardiovascular events rate rises in a linear fashion and twice as much as normotensives [6]. The data from Framingham Heart Study indicates that intensive blood pressure lowering in patients with diabetes would lead to reduction in the risk for cardiovascular events.

One of the early evidences of benefits of the treatment of hypertension in terms of significant reduction of morbidity and mortality was seen in VA cooperative study in 1970[7]. This study concluded that active treatment that included a diuretic-based regimen in patients with mild to moderate hypertension over a five year period prevented 37% of morbid events vs placebo, even though DBP averaged 90-114 mm Hg. More recently HOT study [8] showed that with optimal reduction of DBP to 83 mm Hg,

Fig 1 : Hypertensive Patients Are at Increased Risk for Cardiovascular Events

Framingham Heart Study - Risk of Cardiovascular Events by Hypertensive Status in Patients Aged 35-64 Years; 36-Year Follow-Up



Risk Ratio	2.0	2.2	3.8	2.6	2.0	3.7	4.0	3.0
Excess Risk	22.7	11.8	9.1	3.8	4.9	5.3	10.4	4.2

Kannel WB. *Eur Heart J* 1992 ; Suppl G : 34-42

risk of major cardiovascular events can be reduced by 30% (Fig 2).

Benefits of treatment of hypertension are very clear. However, the challenge lies in the early detection of the presence of raised BP, selection of appropriate antihypertensive therapy with minimal adverse events, maintaining the BP to the desired normal level and ensuring compliance. Majority of patients even in the best of environment do not have BP controlled less than 140 mm Hg [9] and only less than 50% are compliant with drug treatment over an extended period of time [10].

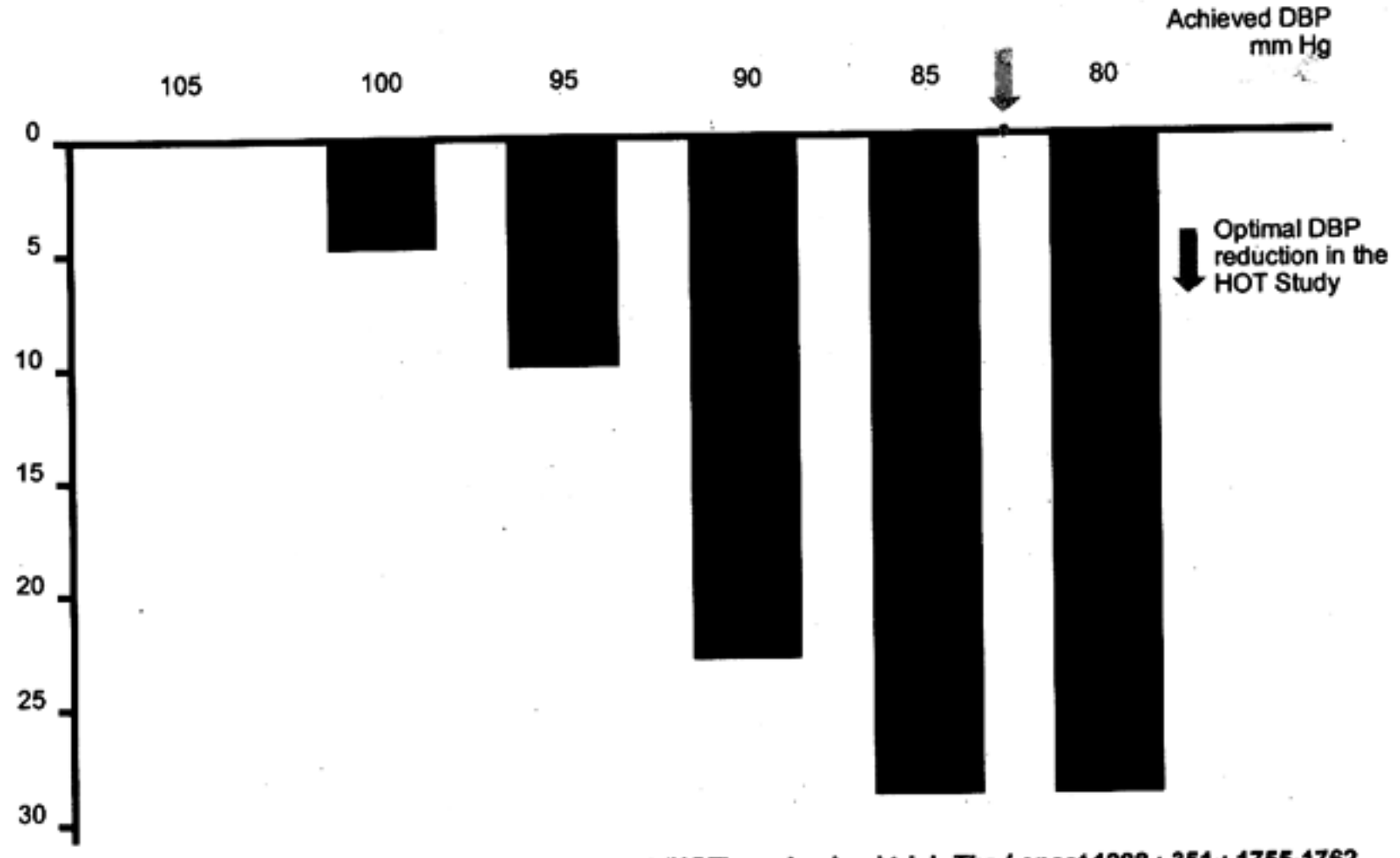
Hypercholestrolemia

There is a linear relationship of serum cholesterol levels with CHD mortality across cultures. Seven Countries Study [11] with twenty five years of follow up has clearly highlighted it. Diet also plays an important role and it also explains between-country differences in CHD-mortality rates. The linkage between cholesterol levels and CHD has also been shown in Multiple Risk Intervention study [12]. The relationship between cholesterol levels and incidence of CHD is for the best part dependent on LDL-cholesterol, a major atherogenic lipoprotein [13].

Results from the Framingham study [14] show that men have twice the incidence of CHD morbidity and mortality compared to women. After 45 years of age, however, cholesterol levels tend to plateau in men but increase steadily in women after menopause and by age 55, women tend to have higher levels then men [15].

Cholesterol is a modifiable risk factor for CHD and total mortality [16]. Cholesterol reduction pays definite dividends. A meta-analysis of 38 trials by Gould et al [17] has shown that for every 10% reduction in total cholesterol CHD mortality is reduced by 15% and total mortality by 11% ($p < 0.001$

Fig 2 : Risk of a major cardiovascular event reduced by 30% in the HOT Study



Hypertension Optimal Treatment (HOT) rendomised trial. *The Lancet* 1998 ; 351 : 1755-1762

for both). LDL-C has been recognized as the primary target for lipid intervention to prevent CHD. The intensity of intervention depends not only on raised cholesterol or LDL-cholesterol but also on the presence of a number of other risk factors for CHD. Recent Heart Protection Study [18] indicates that treatment of high risk patients with relatively normal level of lipids also reduces cardiac events.

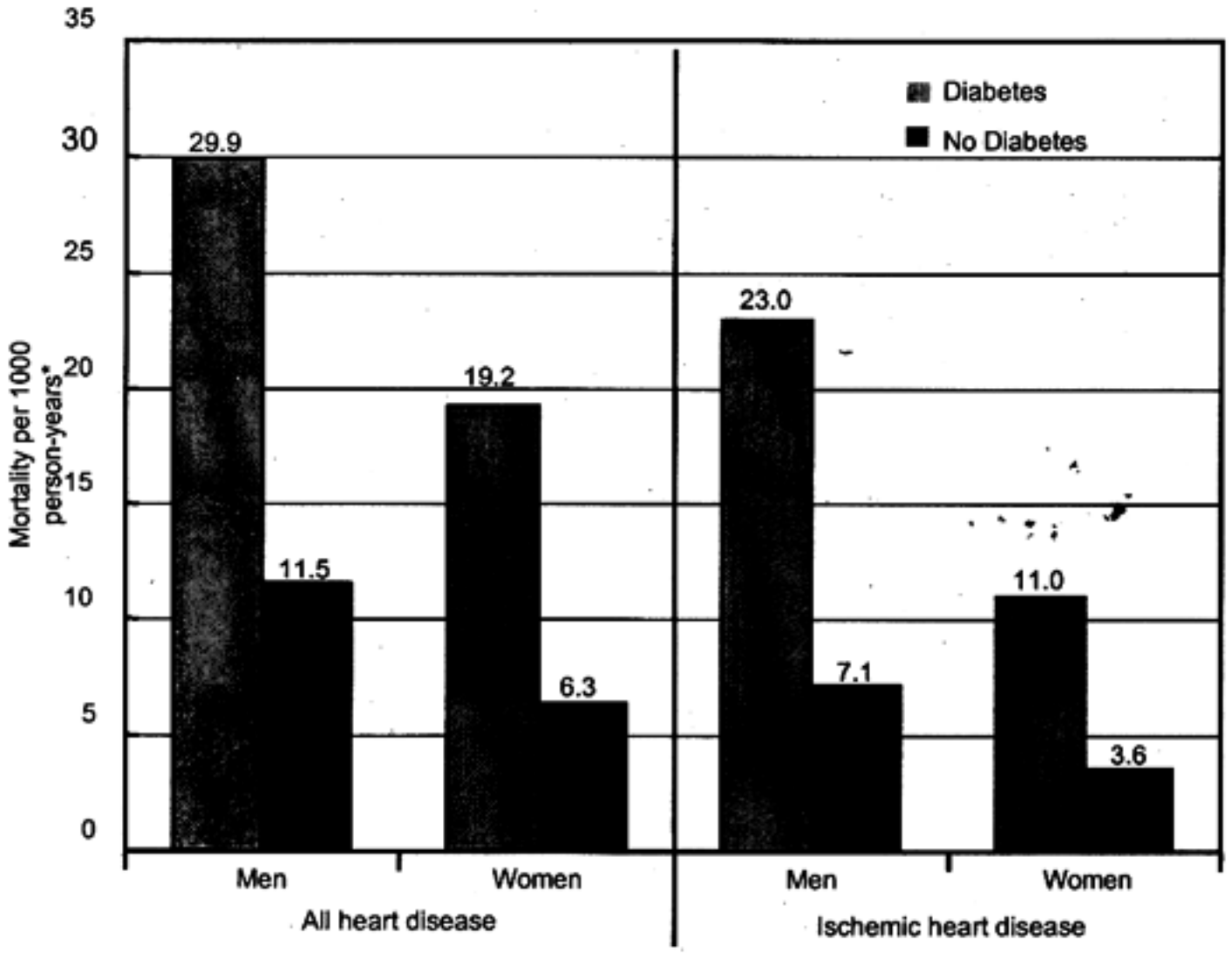
Cholesterol, amongst other factors, plays an important role in the progression of atherosclerosis. Early detection and control is thus expected to retard the progression towards cardiovascular disease.

In Pakistani population, the pattern of dyslipidemia has been determined. At the age of ≤ 40 years, 59% males and 63% females have hypercholestrolemia. 11.5% of the population surveyed have serum cholestrol ≥ 260 mg/dL [19]. This pattern is probably conducive to early onset of ischemic heart disease.

Diabetes

Mortality due to all heart disease and ischemic heart disease in diabetes, compared to non-diabetics, is significantly higher(3-4 times) in men and women [20] (Fig 3). There are several factors at play in diabetes which contribute to the increased atherosclerosis. These factors include dysplipidemia, hypertension, hyperinsulinemia, hyperglycemia, hemostatic abnormalities, advanced glycation end-products and oxidative stress. However, precise mechanism is still not well understood [21], but hyper-insulinemia with associated insulin resistance in type 2 diabetes seems to play a central role. Insulin resistance is also an integral part of metabolic syndrome and it is known to be highly

Fig 3 : Mortality Due to Heart Disease in Men and Women with or without Diabetes (US)



***Age-adjusted**
Adapted from Gu K et al. *Diabetes Care* 1998;21:1138-1145.

atherogenic. Interestingly atherosclerosis may be well advanced before diabetes first manifests, suggesting that insulin resistance is an independent risk factor for cardiovascular disease. According to "ticking clock" theory [22], the macrovascular complications of diabetes (stroke, CHD, PVD) the period of increased risk begins or clock starts ticking, even before the onset of hyperglycemia while microvascular complications (nerves, eyes, kidneys) develop after the onset of hyperglycemia.

Thus, for the prevention of microvascular complications of diabetes early and aggressive treatment of diagnosed diabetes is essential. However, prevention of type 2 diabetes and aggressive treatment of cardiovascular risk factors may be more important to prevent macrovascular complications. Cornerstone of the prevention and treatment include life-style modifications like exercise, weight control and a healthy diet. Insulin resistance has consistently been linked to overweight status (BMI > 25 in Western population, > 22 in Asians) and obesity (BMI > 30 in Western population, > 25 in Asians). Weight loss can improve insulin sensitivity and thus lower plasma glucose. Weight reduction has positive impact on other modifiable cardiovascular risk factors like hypertension and dyslipidemia.

Pharmacotherapy has a role to play to reduce insulin resistance. Metformin improves hepatic sensitivity to insulin as evidenced by diminished hepatic glucose production and decrease or unchanged plasma insulin level in hyperinsulinemia in type 2 diabetes.

In addition, metformin increases insulin-mediated glucose transport in muscles, promotes weight loss and decreases triglycerides and LDL-C by 10-15%.

New class of drugs, Thiazolidinediones (glitazones) has recently become available. Pioglitazone and Rosiglitazone are two members of this class while the third one, Troglitazone has been withdrawn due to hepato-toxicity and resultant deaths. These agents promote insulin sensitivity primarily in adipose tissue, muscle and liver. The net effect is diminished insulin and free fatty acid levels, as well improved insulin sensitivity and glycemic control. Triglycerides may be potentially reduced by 10-20%. HDL-C may increase by 10%; however LDC-C may increase by 10%. There is some evidence that glitazones may interfere with the atherosclerotic process as shown by decrease in carotid artery intimal-medical thickness. The down side is that glitazones may increase the weight by 3-7 pounds. Liver function testing may still be required periodically and oedema with precipitation of CHF has been recorded in some cases [23, 24].

ROLE OF RENIN-ANGIOTENSIN SYSTEM (RAS) IN THE PROGRESSION OF CARDIOVASCULAR DISEASE

RAS plays a central role in the pathogenesis and progression of coronary atherosclerosis and other organ damage. (Fig 4). Angiotensin II (Ang II), the end product of renin-angiotensin system causes several adverse effects, mediated through AT_1 receptors. Cerebral ischemia due to atherosclerosis may lead to stroke. By potentiating neurohormonal systems Ang II exerts harmful cardiovascular effects like vasoconstriction, vascular hypertrophy, LV hypertrophy, myocardial and vascular wall fibrosis, myocardial remodeling, thereby contributing to the development of hypertension, heart failure and myocardial infarction.

Ang II also has a role to play in the development of renal insufficiency. As cardiac function deteriorates, glomerular filteration rate decreases, and increased production of Ang II leads to proteinuria, increased aldosterone release and glomerulosclerosis. Overall there is an increase in morbidity and mortality [25-31].

RAS BLOCKADE AND ITS POSITIVE IMPACT

There is an overwhelming evidence that RAS

blockade leads to protection against end-organ damage attributed to the effects of Ang II, mediated through AT_1 receptors and thus reduces morbidity and mortality. Angiotensin Converting Enzyme Inhibitors (ACE-Is) have been available for over two decades and more recently Angiotensin Receptor Blockers (ARBs) have been introduced. Obviously the strongest evidence relates to ACE-Is and this evidence is emerging similarly for ARBs which seem to have an edge for their better tolerability. There is also an emerging evidence in favour of their combined use in certain clinical situations.

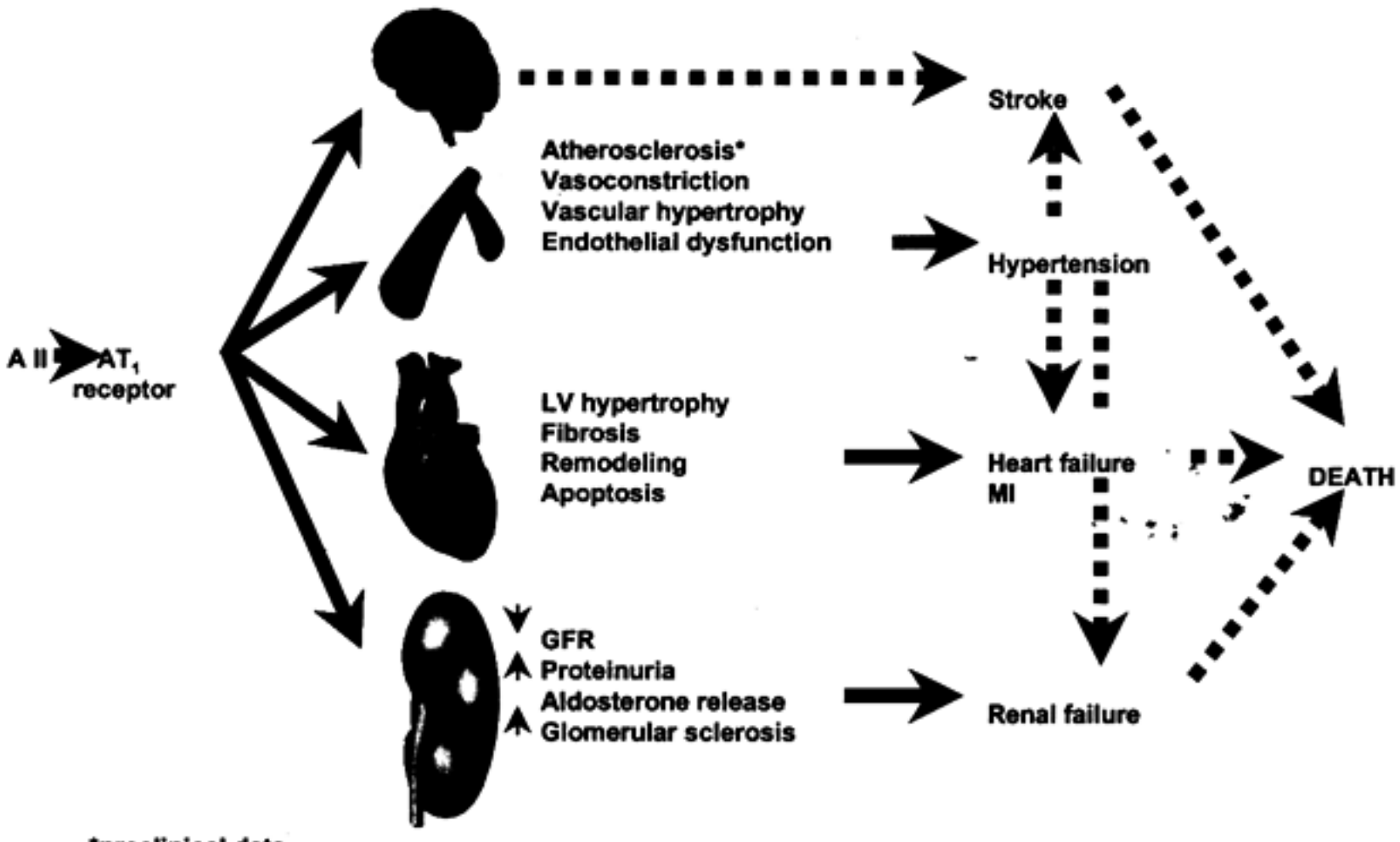
Hypertension and LV hypertrophy

ACE-Is and ARBs are already proven to be effective antihypertensive agents, similar to beta-blockers like atenolol and Calcium antagonists like amlodipine[32-34]. They reduce the left ventricular mass, somewhat better than diuretics and calcium antagonists[35]. They also correct endothelial dysfunction and vascular remodeling more effectively than beta-blockers [36].

Cardiovascular morbidity & mortality

Cardiovascular events like MI, stroke and death can significantly be reduced with ACE-Is. HOPE study with Ramipril[37] has shown significant risk reduction of composite of events by 22% ($p < 0.001$ vs placebo). SECURE, a substudy of HOPE study [38] has provided evidence of significant dose related reduction of atherosclerosis with Ramipril, through elegant B-mode carotid artery measurements of intimal-medial thickness ($p=0.028$). Conversely, Vitamin E,

Fig 4 : Angiotensin II Plays a Central Role in Organ Damage



*preclinical data

LV = left ventricular; MI = myocardial infarction; GFR = glomerular filtration rate

the comparative drug, failed to show any impact on carotid atherosclerosis (Fig 5 & 6).

Stroke

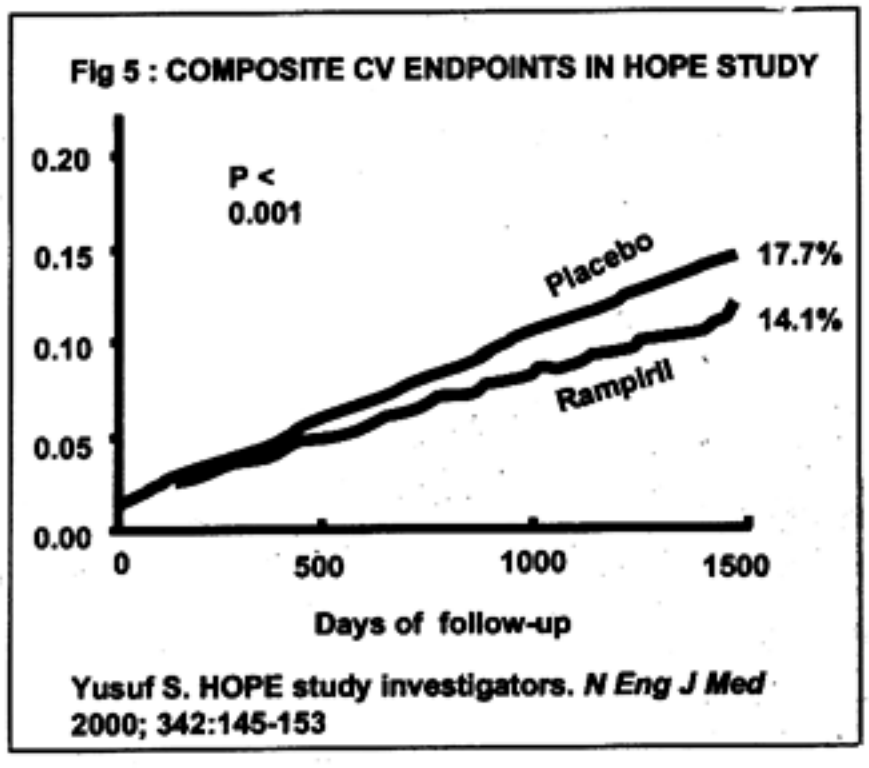
The evidence is now emerging for risk reduction in stroke. Perindopril based therapy vs placebo in PROGRESS trial [39] has shown a risk reduction of 29% in non-fatal stroke in individuals with previous stroke or TIAs. There was also an overall risk reduction of 26% in cardiac events and death. LIFE study [40], comparing losartan and atenolol in hypertensives with left ventricular hypertrophy, followed-up for 5 years, has shown reduction of cardiovascular morbidity and mortality, mostly driven by reduction in stroke (p=0.021). It has also shown risk reduction of onset of diabetes by 25% (p=0.001), in individuals without diabetes at entry into the study. VALUE, a mega trial, involving 15320 high risk hypertensives, is in progress to assess the morbidity and mortality comparing Valsartan with Amlodipine over 6 years [41]. Results are expected in 2004.

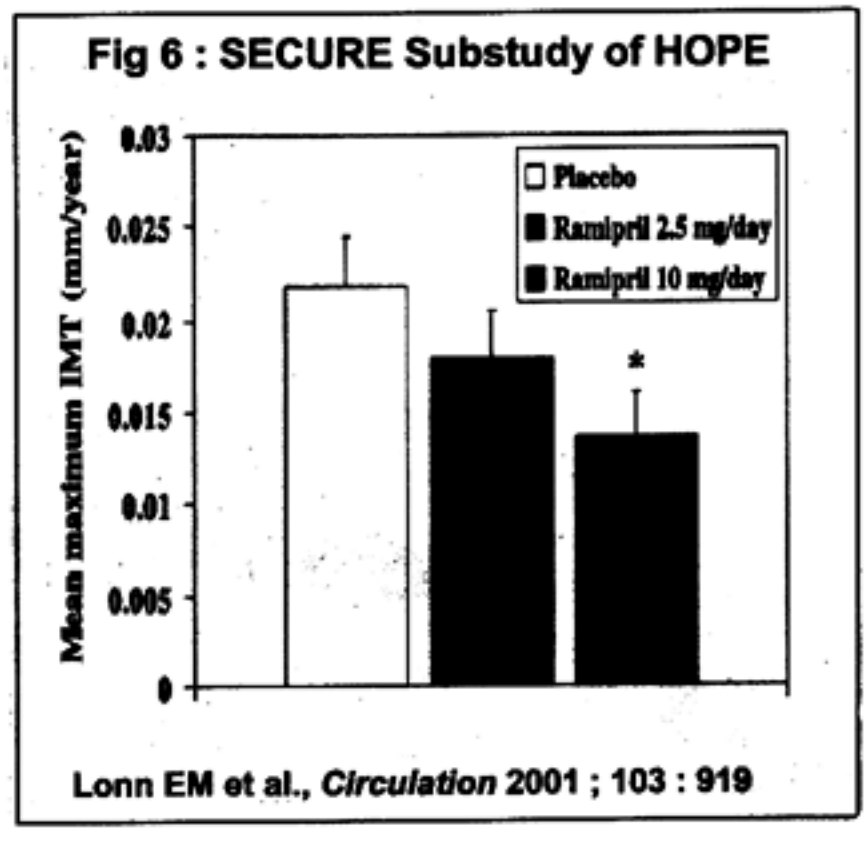
PCI and Heart Failure

Highly significant reduction (50%) in in-stent restonsis rate has been shown in 6 months follow-up, with Valsartan in patients with elective percutaneous coronary intervention (PCI) ($p < 0.005$) in Val-PREST study [42]. ACE-Is are already established effective therapy in heart failure. The evidence is emerging in favour of ARBs to be similarly effective in CHF. For example in Val-HeFT study [43], reduction in mortality by 33.1% (p=0.01) and event free survival by 44% (p=0.0002) has been shown with Valsartan in patients who were not taking ACE-I. Overall morbidity and mortality was reduced by 13.2% in patients taking Valsartan, over and above the regular therapy for heart failure including ACE-Is and beta-blockers. Valsartan has also been shown to favourably influence the reduction of norepinephrine and BNP in heart failure patients[44].

Post-myocardial Infarction

The potential beneficial effects of ARB's on all cause mortality are being explored in patients with acute MI coupled with left ventricular failure or dysfunction. For example VALIANT study is comparing Captopril, with Valsartan or combination of the two [45] in 14,500 such patients. OPTIMAAL is comparing Losartan with





Captopril [46] in a similar set of patients. CHARM study is evaluating Candesartan.

Renal Dysfunction and Diabetes

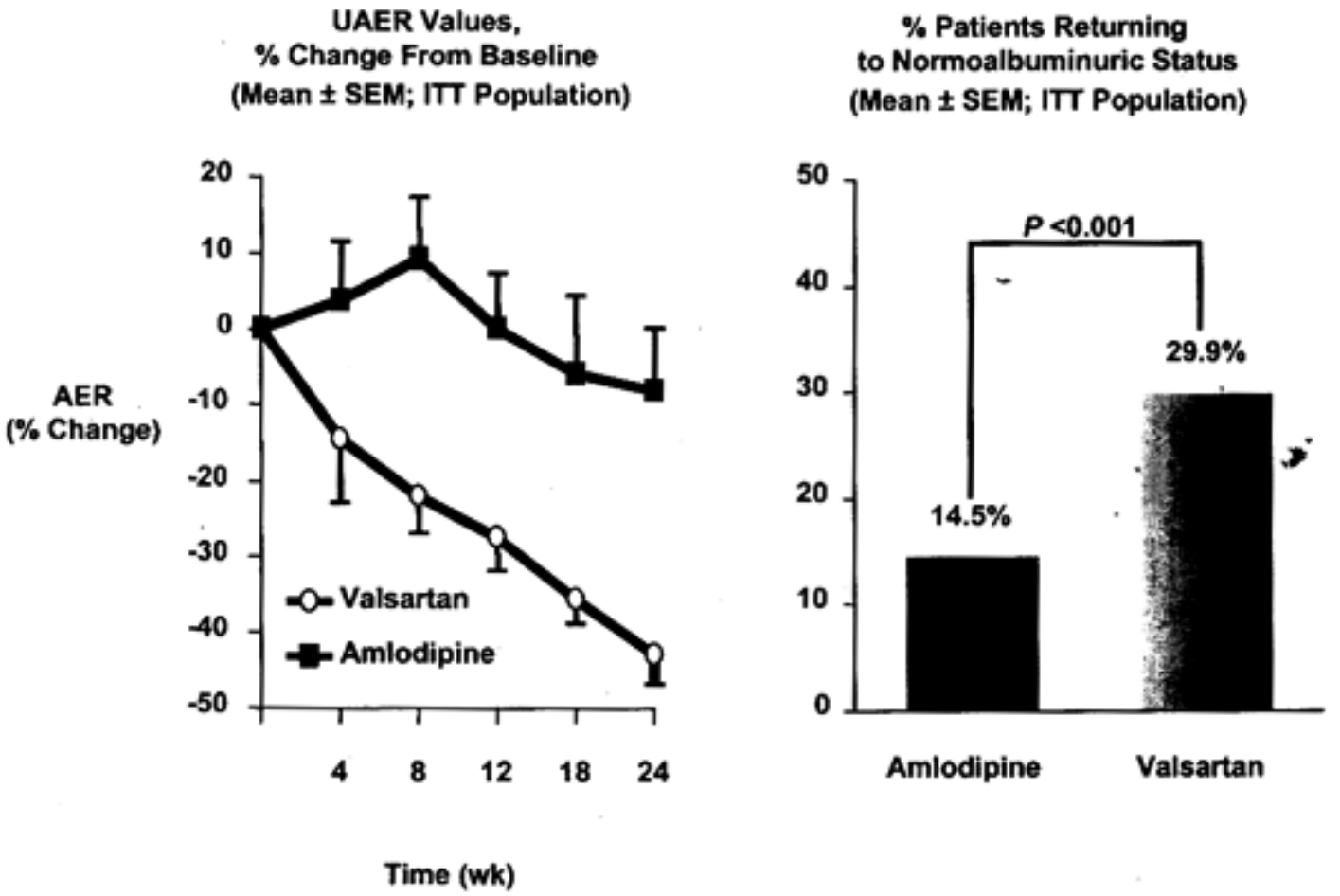
RAS inhibition has been shown to retard the progression of renal dysfunction and reduce cardiovascular morbidity and mortality. In hypertensive renal disease ACE-Is eg., captopril show a significant reduction in creatinine levels vs placebo over 4 years of follow-up [47]. Likewise, ARBs, Losartan and Valsartan have shown a significant reduction in proteinuria [48, 49]. Cumulative incidence of renal events and death in hypertensive patients has been reduced by 38% with Ramipril compared to Amlodipine in AASK study [50].

Enormous data has emerged regarding the renoprotective effects RAS blockade in nephropathy due to diabetes. In IRMA-2 study [51], ARB, Irbesartan reduced progression to nephropathy by 70% vs placebo in diabetes and increased the percentage of patients in whom microalbuminuria was abolished (34% vs 24%, p=0.006). When compared with Amlodipine, Valsartan reduced the albumin excretion rate by additional 40% and returned the normoalbuminuric status in 30% (vs 14.5%) in MARVAL study, (Fig 7) for the same level of blood pressure reduction by both agents [52]. RENAAL study with Losartan and IDNT study with Irbesartan show similar renoprotective effects.

Prehypertension and prediabetes

Animal data indicates that early blood pressure lowering with RAS blockade prevents long term hypertension. Study is in progress to assess the impact of treatment with Candesartan on subjects with high normal BP and to observe whether this intervention can reduce the incidence of hypertension after stopping the treatment [53] after 2 years.

Fig 7 : MARVAL Results (for Same Level of BP Reduction)



Wheeldon NM al al., *Am J Hypertens* 2001 ; 14 (n4, part 2) : 2A

Impaired glucose tolerance (IGT) is a prediabetic state. The subjects with IGT are at a higher risk to develop diabetes and cardiovascular events. NAVIGATOR study [54] has been designed to observe whether lowering of postprandial glucose with an antidiabetic, Nateglinide and blockade of vascular effects of Ang II with Valsartan can delay the onset of diabetes and decrease cardiovascular morbidity and mortality.

It can be concluded that atherosclerosis is an insidious disease and it takes years to develop, through vessel wall injury and lipid accumulation. Early detection of CHD and certain risk factors like hypertension and insulin resistance are highly important and thus an early treatment of risk factors may alter prognosis significantly. RAS plays a central role in atherosclerosis, end-organ damage and thus cardiovascular morbidity and mortality. RAS blockade significantly reduces the risk of end-organ damage. ACE-Is and ARBs have a positive impact on cardiovascular morbidity, mortality and renal dysfunction. Newer application of ARBs like prehypertension and prediabetes are under investigations, with interesting new possibilities in the near future.

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