REVIEW ARTICLE

CARDIOLOGY IN THE 21ST CENTURY

*ABDUS SAMAD**

While entering the 21st century there is no doubt in the minds of health workers of the developing countries especially, those of the subcontinent that ischaemic heart disease has become the major problem of middle aged adults in this region.

Cardiovascular disease accounted for about 15.3 million deaths all over the world in 1996 this was about 30% of all deaths in that year. 9.7 million deaths were recorded in the developing countries. While only 5.6 million occurred in the developed countries of the world. This is about 76% more in the developing countries than those in the developed world (Murray and Lopez Harvard School of health).

Table No. 1 shows that in 1990 63 % of all cardiovascular disease 48% of all coronary deaths occurred in the developing countries.

Table - 1
POPULATION BY AGE

	RURAL		URBAN	
AGE	**POPULATION**	**%**	**POPULATION**	**%**
0-34 years	65025000	76.54	32268	76.14
35-74 years	18801000	22.13	9737000	22.98
> 75 years	1135000	1.34	370000	0.87
Total	84,961		42,368	

Regional Difference in Burden of CVD

	Population Millions	**CVD Mortality Thousand**	**Coronary Mortality Thousand**
Developed Regions	11440	5328	2678.0
Developing Regions	4123.4	90167	2469.0
Middle East Crescent	503.1	992.3	2766

MURRAY & LOPEZ

Our country which is a developing country more clearly associated geographically and socially with the middle eastern crescent countries where coronary artery disease, is relatively lower is experiencing a rapid transition in health as described by Yousuf and Reddy(2) Review of the local literature shows clearly that as far back as 1962 Pirzada from Mayo Hospital Lahore, reported an increasing trend in coronary artery disease admissions (3) similar trends were reported by A Abbasi and Beg from Karachi (4) Nasir u ddin A khan from Peshawar (5) Sattar and Kareem reported a very high previllence of atheroma in patients dying of non coronry deaths. The 1st angiographic study was reported by our group (6) in 1991. A review of 1000 consecutive angiograms showed high prevalence of single and multi disease in men and women undergoing angiography for symptoms of IHD.

This study, reported in 1991, also found that a large number of patients undergoing angiography are 40 years of age and below.

Prevelance of Risk Factors

The four cities risk factor study published in 1992 conclusively showed (7) that HBP and Hypercholesterolemia as well as smoking were highly prevalant in the urban population of Pakistan Hypercholesterolemia, as defined by a cholesterol > 200mg, was present in 31.1% males and 29% of females. High blood pressure, as defined > 140190, was present in 31.52%. Table - 2 shows the details of these values. Smoking was present in 24%.

STRATEGIES for prevention of coronary artery disease in Pakistan (lessons from the developed countries):

The mortality from coronary artery disease has seen declining trends in the past 2 decades in many western countries including the U.S.A. In Finland the North KARELIA (8) project was launched in 1972. By 1992 the age adjusted mortality from coronary artery disease decreased by 55% in males and 68% in females. The mean age of first MI was also delayed from 50's to 70's. There was also a marked decrease of all cause and cancer mortality. There was marked decrease in the level of cholesterol and B.P as well as

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smoking in these years in North Karelia as well as all of Finland Smoking in females actually increased The finish experience shows that healthy life styles when applied to population in general yields more salutory results than when individual strategy is adopted.

Percentage of Male Individuals with cholesterol levels above 200 mg

Age group	T. No.	No.	%
15-20	137	5	3.65
21-30	530	91	17.17
31-40	442	169	38.24
41-50	274	109	39.78
51-60	191	78	40.84
Total	1437	447	31.11

Adopted from 4 Cities study

Percentage of females individuals with cholesterol levels above 200 mg

Age group	T. No.	No.	%
15-20	153	7	4.5
21-30	259	38	14.6
31-40	108	48	44.44
41-50	76	34	48.57
51-60	42	21	50.00
Total	470	141	1 29.44

Adopted from 4 Cities study

Mean cholesterol values in Pakistan

Karachi	159 mg/dl	S.D	S.E.M
Lahore	181 mg/dl	50.9	2.29
Islamabad	176 mg/dI	66.1	4.09
Peshawar	184 mg/dl	56.6	2.73
Mean	180+554.5 mg/dl	54.5	2.01

Adopted from 4 cities study

In Shanghai on the other hand an increase in the mean level of cholesterol from 152 mg/dl to 182mg/dI was associated with the fourfold increase in the occurrence of fatal coronary artery disease. In China the mean total cholesterol is 155mg while mean HDL cholesterol is 49mg/dI.

CHOLESTEROL AND SATURATED FATTY ACIDS

From the Finish and Chinese experience it is shown that preventive measures on a population basis to lower the cholesterol levels in Pakistan are urgently needed Saturated fats should be replaced by unsaturated fats and total calories from fats should be restricted (table 2) as well as salt intake. Definite recommendation in this field are the order of the day. It has been definitely shown that a reduction of 5% in the calories from saturated fatty acids and its substitution with poly or mono unsaturated fatty acids results in a 42 percent reduction in the risk of coronary artery disease . A 2% reduction in trans fatty acids results in 53 % reduction in coronary artery disease risks. Thus oils must replace hydrogented fats if a preventive strategy is to be effective in Pakistan.

T A B L E

Risk of New Native Lesions Relative to Fat Intake

Calories from Total Fat(%)	Relative Risk
<23	1
23-28	5.0
29-34	6.7
>34	12.3

Adapted from JAMA

Age Standardized Mortality (CANADA) Per 100,000

	E CANADA	S. ASIA	CHINESE
C.V.D.	308	320	147
C.H.D.	208	232	72

From Sheth etal

	Cvd Mortality	Coronary Mortality
EME	22%	30.3%
FSE	15 %	21.7%
DC	63%	48%

From Marray & Lopez

EME = Established Market Economy
FST = Former Socialist Territory
DC = Developing Countries

NCEP GUIDE LINES

Preventive Strategy	Atherosclerosis	>Risk Factors	LDLC Initiate	LDLC Target
Primary	No	No	>190	<160 mg
Primary	No	Yes	>160	<130 mg
Secondary	Yes		>130	< I 00mg

Diabetic Patients & Asian Population

LDL	< 100 mg
Cholesterol	< 160 mg

Smoking

34% of all males are smoking in Pakistan. This area of prevention could well result in a marked decline of

coronary artery disease related mortality.

Physical inactivity

Although data on prevalence of physical inactivity is lacking in Pakistan with urbanization and automobile culture both job related and leisure time physical activity are markedly restricted in both sexes more so in the female population. Specific recommendation for physical activity both job related and leisure time are needed to decrease the risk factor mentioned as well as coronary artery disease mortality in our country.

HIGH BLOOD PRESSURE

While in the rural population of Pakistan HBP prevelance is about 5 % in the urban population it is highly prevelant (table 4). Awareness is high in the urban population (table 5) especially in the females. However control of B.P in faily low. This is in part due to the inability of the target population to purchase HBP medications and in part due to the habits of the physicians prescribing costly medications which the poor patients can take only for a month or so at the most. Although guidelines for the management of HBP are available no effort has been made to address this very important issue.

Relative frequency of individuals with B.P>140/90

Age group	Number	No with HBP	%
21-30	789	126	15.97
31-40	550	179	32.55
41-50	344	157	45.64
51-60	233	142	60.94
Total			

Adopted from 4 cities study

EMEGING RISK FACTORS

(1) HOMOCYSTEINE

Homocysteine is a sulfur containing amino acid, a product of methionine metabolism, is associated with increased risk of premature atherosclerosis. Stampfer et al reported the risk of myocardial infarction associated with mild to moderate elevation of homocystine in the US physicians,(9) subsequently large number of trials in the Asian population showing the role of moderate elevation of homocysteine associated with atherosclerotic heart disease.

Folic acid, vit B6 and vit B12 are essential co-factors for further metabolism of homocystine. Factors responsible for mild to moderate elevation of homocystine levels are;

1. Nutritional deficiency of folic acid vit B6 and B12.
2. Genetic abnormalities involving the enzyme methionine tetrahydro folate reductase.
3. Combination of the above.

Homocystine and folate levels are being checked in the Aga Khan University lab. Which has pick up points in the major cities of Pakistan. However it is recommended that patients with coronary artery disease below the age of 55 years with mild to moderate hypercholesterolemia should be given folate, B6 and B12 supplements.

TRIGLYCERIDES: Majority of the patients of coronary artery disease in Pakistan have mixed Hyperlipidemid that is, Elevated TG, LDL and low HDL levels. Although high TG Levels are not conclusively proved to play major atherogenic role, nontheless recent reviews do show the beneficial effects of lowering TG levels. In our population, for the present time proper diet, fibrates and Niacin are recommended. More recent studies show that higher doses of statins also lower TG and raise HDL but cost is a major factor in providing the high doses of statins in our country.

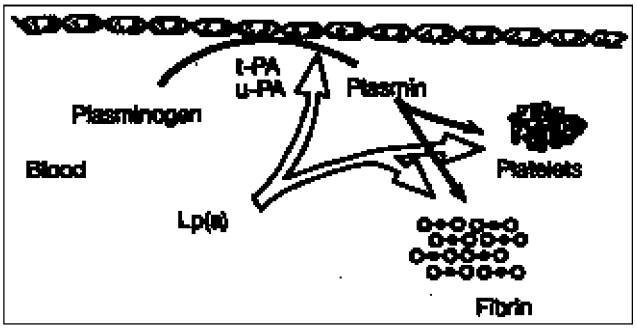
Small Dense LDL

Depending upon the size and density of LDL molecule circulating LDL exists either as small dense LDL or large and fluffy LDL. These patients whose LDL is small and dense are called phenotype B those with large and fluffy molecule are type A and mixed is called type C. Independent of TC and LDL levels, the presence of phenotype B is an independent risk of coronary artery disease. Pheno type B is also associated with high TG and low HDL. Pattern B is more common in males than females, fibrate and nicotanic acid are more effective is lowering the levels of small dense LDL. However their beneficial effects are yet to be proven in clinical trials.

Lp (a)

Apolipoprotein (a) when gets attached to apolipoprotin B the resultant molecule is called lipoprotein little a. Apolipoprotein (a) has structural

similarity with plasminogen and competes with it for cell surface binding. By displaying plasminogen from the cell surface t-PA formation is reduced thus limiting the endogenous process of fibrinolysis. Niacin and oestrogens can reduce Lp (a) levels but statins and fibrates are in effective in this regard. (figure)



Putative mechanisms of prothrombotic action of lipoprotien (a) [Lp(a)]. t-PA = tissue type plasminogen activator, u-PA = urokinase-type plasminogen activator

Specific recommendations at this time can not be made because of the lack of information on this particular lipoprotein in clinical setting.

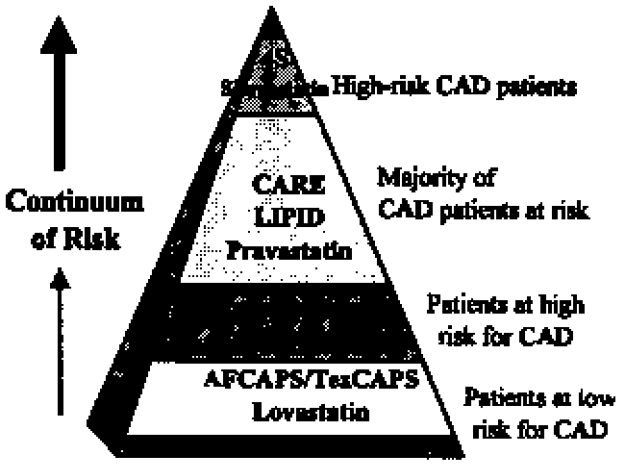
Circulatory Markers Of Inflamations

Circulatory markers of inflamation especially CRP is associated with high risk of complications, repeat events and adverse out come in acute coronary syndromes, as well as survivors of myocardial infarction. The specific cause of raised inflammatory markers is as yet not known but attempt to treat endogenous infections in teeths etc is recommended.

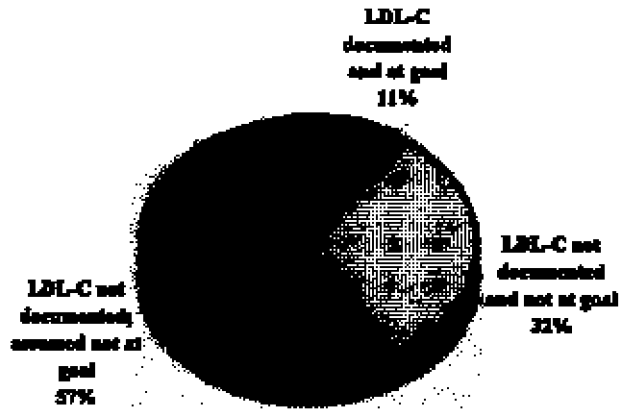
Myocardial Infarction:

Mortality from acute myocardial have registered a significant decrease from 30% to about 7-10% in the Aspirant thrombolytic era (7). However further reduction in mortality have not been achieved mainly because of the feasibility, cost considerations and even efficacy of Primary angioplasty and IIb IIIa inhibitors in such situation (11). The incidence of acute myocardial infarction in Pakistan is 199221, 00, 000 of male population age of 35-65 years. Because of the structure of the family (average family members 7.7) and only sole earner being the male, his demise or serious illness like MI has a devastating effect on the whole family.

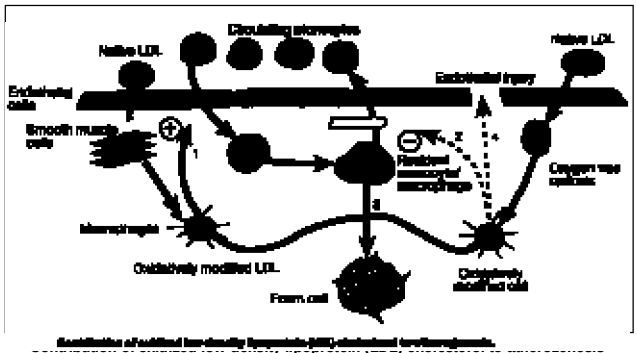
Acute Coronary Syndromes (12) and non q wave myocardial infarction are increasingly presenting to



Continuum of risk in primary prevention trials. 4S = Scandinavian Simvastatin Survival Study; AFCAPS/TexCAPS = Air Force/Texas Coronary Atherosclerosis Prevention Study; CAD = coronary artery disease.



Percentage of coronary artery disease (CAD) patients on lipid-lowering drug therapy. [10]LDL-C = low-density lipoprotien cholesterol.



Diametre of Coronary Arteries from 60 Pakistani Patients

	Non-Diabetics	Diabetics
LM	3.95 mm	4.07 mm
LAD	3.33 mm	2.92 mm
CX	3.025 mm	3.21 mm
RCA	2.85 mm	2.6 mm

Adopted from Mussarrt Jabeen etal
Pakistan J Med Sci 15, No 4 277-82

the cardiologist and still wait for a better management. The low molecular weight heparin are used commonly now as bail out to further intervention and surgical preceures. Coronary angioplasty/stenting with Aspirin and Ticlopidine and low molecular weight heparin. The diameters of coronary arteries are not different in Pakistani patients from these of the developed countries (table).

Interventional Cardiology

The field of Interventional cardiology is ever expanding with improvements in guide wire, balloons, stents and antiplatelet therapy. The primary success rate achieved is meanly 100% except 1-2%, in the experienced hands. Type C lesions are effectively treated currently with excellent initial results. Unprotected left main lesions, sphenous vain graft lesion, small vessels, bifurcation lesions and chronic total occlusions are the frontiers needing solution in the time frame. Due to smooth muscle proliferation, restenosis is a major problem at this time. Cutting balloon and Beta and Gamma rediation are being tested to treat in stent restenosis. Stent thrombosis in patients receiving radiation is a problem not yet solved Long term antiplatelet therapy with clopidogil (PLAVAX) is currently being tested. Stents coated with medication preventing smooth muscle. Proliferation are meanwhile making advances in this field and are the devices. The future of the stents will depend.

CABG

After enjoying leadership status for nearly 2 decades the cardiologist and patients alike have chosen the interventional procedures for revescularization. The current efforts of the surgeons to reduce the initial morbidity associated with CABG, Midcab surgery or surgery on the beating heart a thoraco scopic surgery has not received widespread acceptance. The 7-8 years follow up of angioplasty versus surgery, study (BARI) have shown the efficacy of angioplasty as much as bypass surgery except in-patients with treated diabetes mellitus. However medical management and preventive measures to delay or eliminate obstructive coronary artery disease is a challenge for the current medical scientists. Not wrongly this in the EPA of LIPID LOWERING.

TABLE

Odds Ratios (with Exact 95 Percent Confidence Intervals) for Disease among patients with Hyperthomocysteinemia or other Risk Factors.

Risk Factor	General Vascular Disease (N=38)	peripheral Vascular Disease (N=25)	Common Vascular (N=60)	Total Disease (N=123)
Hyperhomocysteinemia	40.3 (4.0-00)	22.3 (1.9-00)	23.9 2.5-00)	27.7 3.2-00)
Hypercholesterolemia	1.2 (0.4-3.9)	1.6 (0.5-5.5)	3.1 (1.1-9.1)	2.0 (0.8-5.4)
Hypertension	18.2 (2.5-822.7)	16.5 (2.0-780.3)	7.8 (1.1-347.2)	12.4 (1.9-526.3)
Cigarette smoking	3.6 (1.1-12.1)	3.5 0.9-13.2)	3.5 1.2-10.9)	3.6 1.4-10.2)

Odds ratios show the odds that persons with the risk factor will have the disease, as compared with the odds for normal subjects. These estimates are based on the addition of 0.5 to each cell of a two-by two table.

T A B L E

Geometric Means of Peak-Methionine-Loading Serum Homocysteine Levels in Patients with Vascular Disease, with Their Ratios to the normal Mean (13.4 umol per liter)

Variable	General Vascular Disease (N=38)	Pheripheral Vascular Disease (N=25)	Coronary Vascular Disease (N=60)	Total (N=123)
Homocysteine-umol/lit.	20.4	15.8	18.7	18.6
Ratio(95% CI)	1.52 (1.15-2.01)	1.18 (0.87-1.60)	1.40 (1.08-1.81)	1.39 (1.10-1.75)
Ratio adjusted for other factors (95% CI)	1.46 (1.07-1.98)	1.13 0.81-1.58)	1.34 (1.02-1.76)	1.33 (1.03-1.72)

CL denotes confidence interval.
Sec Methods section for a description of the adjustment

Angiogenesis:

VEGF and FGF are finding their way to develop collateral vessels to solve the problems of vascular

obstruction so for only experimental studies are in progress.

Left ventricular dysfunction:
Both systolic and diastolic dysfunction could be guantitated with non-invasive technique by 2-D and Doppler technique in the majority of patients. To accurately measure LV dysfunction arising from ischemic onshough and the component of reversibility is the foculs of wide spread research.

PET studies are most commonly used to identify reversibility at this time.

The terms hibernating stunned myocardium are occurred to define reversible myocardial dysfunction. New techniques are definitely needed to address these thorny problems. The greatest challenge of the coming decade is in the field of heart failure. Although Ace inhibitors and aldosterone antigonist as well as B blockers have shown a definite improvement in morbidity and mortality from coronary artery disease and hypertension. No doubt about it whether genetic modification of myocardial cells is a hope or reality only time will show.

Ventricular assist devices and cardiac transplantation have shown only very limited potential useful uptill now but received an immense enthusiasm.

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FORTHCOMING NEWS

16th Annual Congress of Cardiology

PAKISTAN CARDIAC SOCIETY

Faisalabad, Pakistan

October 28, 29, 2000

on

Saturday & Sunday

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International Conference Coronary Heart Disease in the New Millenium: Issues in Prevention, Diagnosis and Management, March 26-28, 2001 Kuwait City

Further Information: Conference 2001, Department of Pathology, Faculty of Medicine, Kuwait University, P.O. Box 24923 Safat, 13110 KUWAIT
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October 28, 2000-October 28, 2000
68th Annual
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October 29, 2000-November 01, 2000
Canadian Cardiovascular Society
Annual Meeting 2000
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October 29, 2000-November 03, 2000
47th Annual
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Update in the Treatment
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