Secondary prevention of coronary artery disease (CAD): Evidences, evidence based guidelines, and real life practices.

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Received - 22-3-2011
Revised- 23-3-2011
Accepted- 25-3-2011

Introduction

Cardiovascular diseases (CVDs) are the most prevalent cause of death and disability worldwide. This is true for developed countries, as well as developing countries like India, which are expected to face a phenomenal increase in the burden of chronic diseases in the near future. In 2005, CVD caused 17.5 million deaths worldwide, which is 3.3 times more than AIDS, tuberculosis and malaria combined. The problem is even worse in low-income and middle-income countries; four fifths of all cardiovascular related events occur in these parts of world.[1] Although, cardiovascular-related mortality in high-income countries is projected to increase from 5 million in 2000 to 6 million in 2020, the corresponding figures for low-income and middle-income countries are set to rise from 10 million to 19 million.[1]

While CVDs are currently a dominant cause of death in India, they are likely to be the overwhelming cause of mortality and morbidity in the future.[2] Of all CVDs, the predominant cause of mortality and morbidity is coronary heart disease (CHD). The likely cause of this epidemic, a part of the surge in chronic diseases, lies in the country's epidemiologic transition.[2] This transition is characterized by rapid urbanization and its accompanying adverse lifestyle changes (eg, drug and alcohol addictions, unhealthy diet, physical inactivity, and increasing psychosocial ailments) and by increasing longevity.

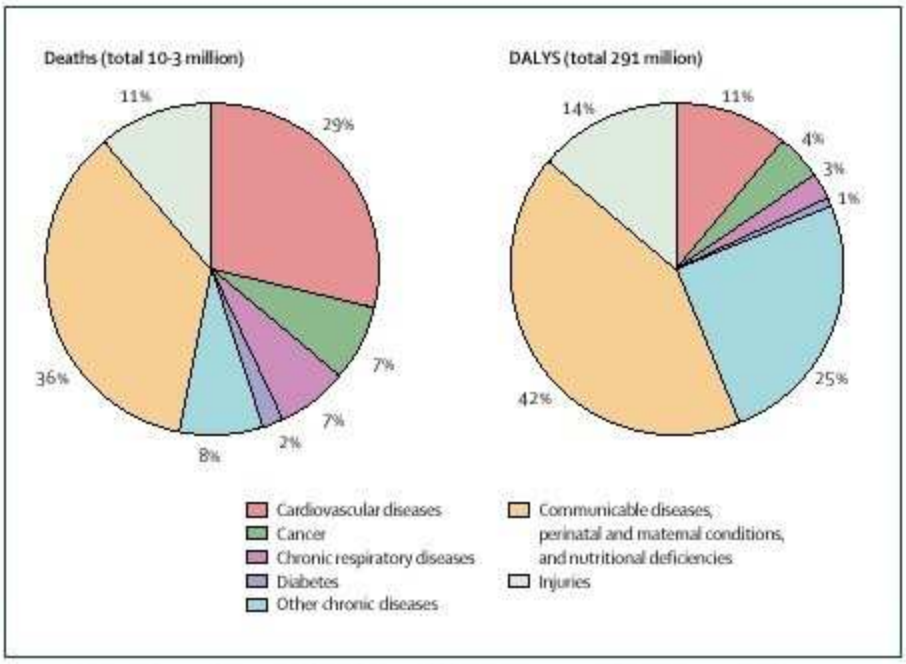

Fig 1: Estimated proportion of total deaths and Disease-adjusted life years (DALYs) lost by cause in India (all ages, 2005). [2]

What are the risk factors for CHD?

Common risk factors are hypertension, hyperlipidemia, smoking, diabetes, obesity, sedentary life style, psychosocial factors, family history and age.

Table 1: Prevalence of CHD in India. [3]

Urban India	1960	1%
	1995	8-10%
Rural India	1974	2%
	1995	4%

- About 29.8 million people were estimated to have CHD in India in 2003
  - 14.1 million in urban areas and
  - 15.7 million in rural areas.

- Approximately 14% of all deaths in India in 2000 were due to ischemic heart disease,[4] while an estimated 1.6 million deaths from CHD occurred in the same year (approximately 1.3 million due to acute coronary syndromes).[3] Even in rural areas, a recent study in Andhra Pradesh has shown that the predominant cause of death is vascular (32% of total deaths), with half due to CHD.[5]

One of the major factors influencing the high rate of CHD is the high prevalence of traditional risk factors like hypertension, diabetes, tobacco smoking, dyslipidemia, and obesity.

Table 2: Burden of Risk Factors in India. [6]

	Prevalence, %	Mortality/Y, millions	Burden, Millions	Projection, Millions
Diabetes	Urban: 11.8 Rural: 3.8	0.2	19.3 in 1995	57.2 in 2025
Hypertension	Urban: 20-40 Rural: 12-17	1.5	118 in 2000	213 in 2025
BMI≥25kg/m2	29-34	0.25	na	na
TC:HDL cholesterol ratio≥4.5	36-46	na	na	na
Metabolic syndrome	21-36	na	na	na

na: not available

- A retrospective study of Indian patients with recently diagnosed coronary artery disease to assess major risk factors.[7]

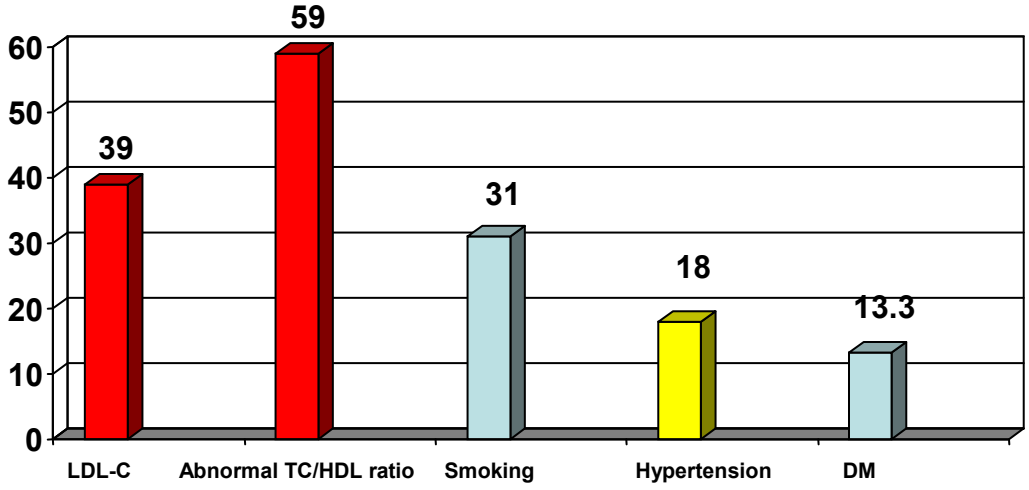

Fig 2: Fraction of patients (with CAD) with various risk factors.

Among the risk factors assessed, dyslipidemia (particularly abnormal TC/HDL ratio and elevated LDL cholesterol), smoking hypertension and diabetes were associated with coronary artery disease in decreasing order of prevalence.[7]

What are the evidence-based drugs for secondary prevention of CAD?

These drugs are as follows

1. Lipid modifying agents, statins.
2. Aspirin
3. Angiotensin converting enzyme inhibitors (ACE-I)
4. Beta-blockers

AHA/ACC guidelines for secondary prevention of CAD.[8]

- Lipid lowering drug:
  - ☐ LDL-C should be < 100mg/dL.
  - ☐ Further reduction of LDL-C to <70mg/dL is reasonable.
  - ☐ If baseline LDL-C is ≥100mg/dL, initiate LDL-C lowering drug therapy.

- Antiplatelet drugs: Start aspirin 75-162 mg/d and continue indefinitely in all patients unless contraindicated.

- ACE-I:
  - ☐ Start and continue in all patients with LVEF ≤40% and in those with hypertension, diabetes, or chronic kidney disease, unless contraindicated.
  - ☐ Consider for all patients.

- Beta-blockers: Start and continue in all patients who have had MI, acute coronary syndrome, or left ventricular dysfunction with or without HF, unless contraindicated.

WHO guidelines (2007) for secondary prevention of CAD.[9]

- Statin: it is recommended for all patients with established CHD. Treatment should be continued in the long-term, probably lifelong.

- Antiplatelet drugs: all patients should be treated with regular aspirin in the absence of contraindications. Treatment should be initiated and continued lifelong.

- ACE-I: recommended for all patients following MI, which should be initiated as early as possible and continued long-term, probably lifelong.

- Beta-blockers: recommended in all patients with a history of MI and those with CHD who have developed major left ventricular dysfunction leading to heart failure. Treatment should be continued long-term, probably lifelong.

NICE guidelines. [10]

- All patients should be offered combined treatment with the following:
  - Statin
  - ACE-I
  - Aspirin
  - Beta-blocker

What is the preferred dose of aspirin for prevention of CAD?

Currently available clinical data do not support the long term use of aspirin in dose greater than 75-81 mg/d in the setting of cardiovascular disease prevention. Higher dosages, which may be commonly prescribed, do not better prevent events, but are associated with increased risk of GIT bleeding.[11]

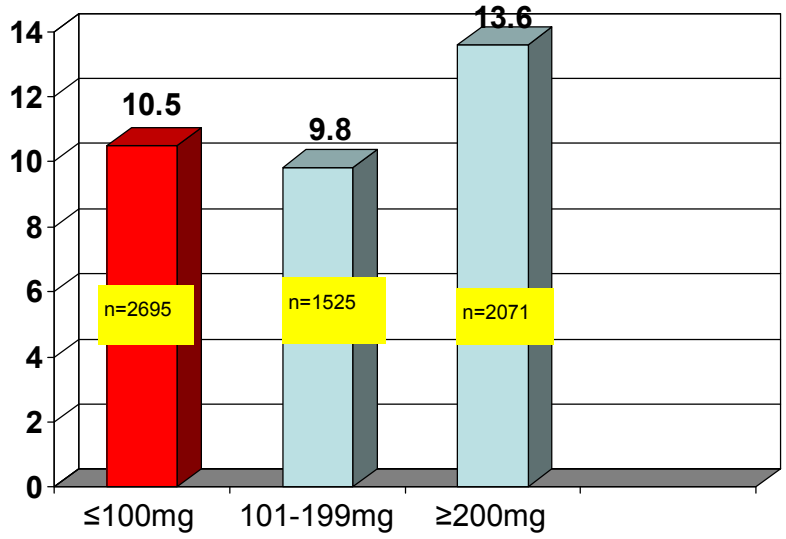

Fig 3: Aspirin dose and incidence (%) of first co-primary outcome (CV death, nonfatal MI, and stroke).[12]

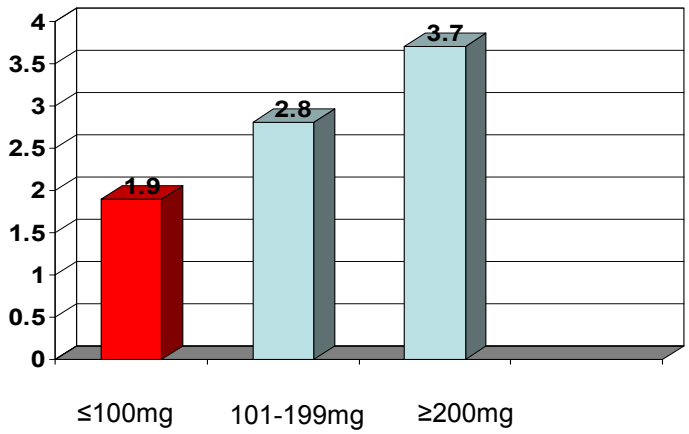

Fig: 4, Aspirin dose and the incidence (%) of major bleeding.[12]

In patients with ACS, bleeding risks increase with increasing aspirin dose, with or without clopidogrel, without any increase in efficacy. These findings suggest that the optimal daily dose of aspirin may be between 75 and 100 mg, with or without clopidogrel.[12]

What are the clinical benefits when optimal medical therapy (aspirin, statin, ACE-I and beta-blocker) is given to post-MI patients?

Ans: Aspirin, beta blockers, statin, RAS blockers have been shown to improve the prognosis of acute MI in clinical trials. In a recently concluded clinical trial, benefits of optimal medical therapy (combination of aspirin, beta blocker, statin, RAS blocker along with thienopyridine) was assessed in 5353 patients with acute MI.[13] At hospital discharge 89% received aspirin, 90% beta-blockers, 84% statins, 81% RAS blockers, 70% thienopyridine and 46.2% received all of these drugs. Results: Total mortality was reduced by 74% in patients receiving all these drugs versus patients receiving one or no drug.[13] This was consistent in subgroups defined by STEMI/NSTEMI, diabetes and gender. Mortality was also reduced by 51% in patients receiving 2-4 drugs.[13] It was concluded that optimal medical therapies over 1 year period is associated with a significantly lower mortality of patients with acute MI in clinical practice.[13]

Effect of combination of drugs on all cause mortality in patients with ischemic heart disease: [14]

- Combination of statins, aspirin, beta-blockers, and ACE-I was associated with 75% reduction in all cause mortality.
- Alone beta-blocker was associated with 19% reduction in all cause mortality.
- Alone ACE-I was associated with 20% reduction in all cause mortality.
- Combined use of statins and ACE-I was associated with 31% reduction in all cause mortality.

In one more study, the effect of optimal medical therapy (aspirin, beta-blocker, statin and ACE-I) at discharge in patients with acute coronary syndrome (ACS) was assessed.[14] Total 5833 patients with ACS were evaluated in this study. Results: Patients receiving optimal medical therapy with these 4 drugs had significantly lower 1-year mortality by 46% compared with those given 0 or 1 drug at discharge.[15]

All above mentioned studies are endorsing the mortality benefits of optimal medical therapy with statins, aspirin, ACE-I and beta blockers.

What are the common problems faced while attempting secondary prevention of CAD?

Although secondary prevention measures are a key component of any public-health strategy to reduce the burden of cardiovascular disease, a large proportion of potential candidates do not receive adequate treatment.

Three crucial reasons for this treatment gap have been identified:

1. Inadequate prescription of medication
2. Poor adherence to treatment
3. Unaffordable cost of medication.

What are the data on inadequate prescription of medications for CAD prevention?

Almost all the national and international guidelines for prevention of CAD recommends multiple drug therapy like aspirin, beta-blockers, statins, ACE-I. These are the evidence based recommendations. But the question is "Are we doing enough in our routine clinical practice to prevent CAD?"

The problem of insufficient treatment in patients who have suffered a MI has been documented by numerous registries and studies in different countries.

(EUROASPIRE) II survey [16]: included patients from nine European countries. In this survey, the use of angiotensin-converting-enzyme (ACE) inhibitors and statins was less than expected —43% and 57.7%, respectively.

Similar results have been observed in the EUROASPIRE III study, [17] as well as the Global Registry of Acute Coronary Events (GRACE) [18] and the Proyecto de Registro de Infarto Agudo de Miocardio Hospitalario (PRIAMHO) registries.[19]

Government-driven initiatives to improve prescribing practices have been launched in some European countries; in the UK, for example, GPs are paid for preventive efforts, and in Spain the government carries out periodic evaluation of prescriptions for the secondary prevention of cardiovascular disease in primary care. [20]

Situation in low-income and middle-income countries: The WHO study on Prevention of Recurrences of Myocardial Infarction and Stroke (WHOPREMISE) has documented an even worse situation for secondary prevention in low-income and middle-income countries.[21] In this crosssectional survey of 10,000 patients with cardiovascular disease, the percentage of those with coronary heart disease who received:

- Beta blockers was 48.1%,
- ACE inhibitors 39.8% and
- Statins only 20.8%.

Indian Data: A prospective epidemiologic survey, was conducted by 134 primary care physicians from 50 randomly selected cities distributed throughout India.[22]
Results: In 406 patients with CAD, the percentage of patients receiving various medications were as below:

- ACE-I: 15.5%
- Beta-blockers: 53%
- Statins: 69%
- Aspirin: 82.5%

Above Indian data establishes that secondary prevention is under utilized in Indian patients with CAD. Against the background of an emerging epidemic, physicians in primary care need to increase the use of widely available specific secondary preventive agents recommended by guidelines.[22]

How common is the problem of adherence to the treatment for preventing CAD?

As we have discussed in question no. 4, optimal medical therapy (with aspirin, statins, beta-blockers, and ACE-I) is associated with almost more than 70% reduction in mortality. "Are we getting the similar benefits of this optimal medical therapy in our daily real life clinical practice?" Most probably, answer is NO.[23]

What may be the reason behind this gap in clinical data and real life clinical practice? Answer may be the poor adherence to the treatment.[23] The efficacy of cardiovascular drugs in secondary prevention is limited by poor adherence to treatment.[23] End numbers of clinical data are endorsing the problem of adherence to the long term chronic treatment for prevention of CAD.

Several studies have shown that compliance to treatment in chronic conditions approaches only 50%.[24] However, poor adherence is frequently under-recognized as it is not often directly assessed by physicians.

In 2008, a report indicated that 40% of the almost 45 million patients treated for hypertension in the US did not adhere to treatment, and a similar proportion was observed for those treated with lipid-lowering agents.[25]

Poor adherence to statins: Reported discontinuation rates at 1 year ranged from 15-60%.[26]

Poor adherence to antihypertensive agents: full adherence is only approximately 20%.[27]

Poor adherence to concomitant statins and antihypertensive drugs: adherence rate is only 36% at 12 months.[28] Only 1 in 3 patients adhere to preventive therapy after 6 months. [28]

What are the reasons behind poor adherence to the chronic therapy?

Important reasons are –

1. Complexity in regimen
2. Cost burden
3. Pill burden
4. Memory burden

Cost of the chronic long term poly-pharmacotherapy in low-income or middle-income countries plays important role in defining patient's compliance. Patients with established CAD are on multiple medications, like antihypertensive agents, lipid modifying agents, antiplatelet therapy, antidiabetic agents (in patients with diabetes) etc. In countries like India, insurance policies like mediclaim do not reimburse the daily prescription based cost of therapy. In such case, total cost of therapy per day is a big economical burden on patients which plays a major role towards poor compliance to the medications. Any strategy towards reducing cost of therapy without reducing number of evidence based drugs will improve adherence to the treatment and hence the clinical outcome.

What are the consequences of discontinuation of evidence based drugs in patients with CAD?

Withdrawal of secondary prevention treatment translates into increased morbidity and mortality, and is associated with a large economic burden. Bosworth suggested that a lack of adherence to therapy is responsible for almost 10% of all hospital admission.[29]

In a French registry that included 2119 patients who had suffered a myocardial infarction; 1-year survival was 97% in patients who received statins, aspirin, beta-blockers, compared with 88% in those who received none, one or two of these medications.[30]

Ho and coworkers [31] analyzed the effect of medication discontinuation on mortality after a myocardial infarction in a series of 1,521 patients. This survival analysis found that discontinuation of secondary prevention therapy was independently associated with almost three-fold increased 1-year mortality (hazard ratio 3.81, 95% CI 1.88–7.72).

What is the effect of fixed dose combination (FDC) on patient's compliance in chronic therapy?

The use of fixed-dose combination therapy, in the form of a polypill, for cardiovascular prevention was first proposed by Wald and Law in 2000. These authors developed the concept which claimed that a polypill comprising six components and administered to each individual older than 55 years would reduce the incidence of cardiovascular disease by more than 80%.[32] Since then, controversy has surrounded the true value of this idea. Despite criticism, the potential value of applying the polypill concept for secondary

prevention has been recognized by different expert panels, including the WHO and the Combination Pharmacotherapy and Public Health Research Working Group. Research in this area is seen by these panels as an important breakthrough. [33]

Multiple pill burden, complexity in of treatment regimen and excessive total cost of therapy are the important determinants of poor medication compliance, efforts have been made to simplify the drug regimen and to reduce the total cost of therapy. Intervention aimed at simplifying the drug regimen for patients have been shown to improve patients' compliance in studies. The efficacy and safety of fixed dose combination is well established.[34]

The effect of FDC vs. free drug combinations on patient's compliance has been evaluated in a meta-analysis.[35] In this meta-analysis, 9 studies on chronic therapies (4 in hypertensive population, 2 in tuberculosis, 1 in HIV, 2 in diabetic population) were included. A total 11925 patients on FDC were compared against 8317 patients on free-drug component regimen.

FDC resulted in a 26% decrease in risk of non-compliance compared with free-drug component regimen (p<0.0001). [35]

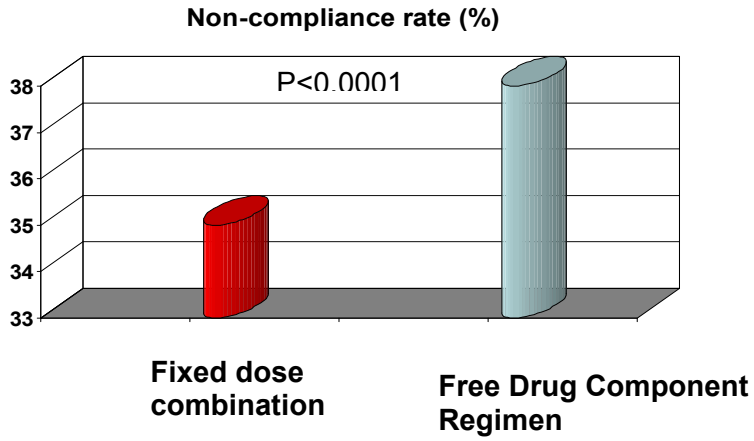

Fig 5: Non-compliance rate (%) in FDC and free drug-component regimen.[35]

How does FDC improve patients' compliance?

FDC have the potential to improve compliance by:

1. Reducing pill burden
2. Simplifying treatment regimen
3. Reducing memory burden on patients
4. Reducing total cost of therapy

Is there any drug-drug interaction when statin, aspirin and antihypertensive agents (like ACE-I, beta-blocker, and thiazide diuretic) are combined in a FDC?

No significant drug-drug interactions have been observed in an Indian trial on polypill.

An Indian study, TIPS study [36] on polypill, has established that:

1. The Polypill is similar to the added effects of each of its BP lowering components. There is greater BP lowering with incremental components. Aspirin does not interfere with the BP lowering effects.
2. The Polypill reduces LDL.
3. The Polypill lowers thromboxane B2 to a similar extent as aspirin alone.
4. The Polypill is well tolerated.
5. The Polypill could potentially reduce CVD risk by about half.

Conclusion

The prevalence of cardiovascular diseases is rapidly rising. In India, coronary artery disease is one of the leading causes of death. Evidence based guidelines are recommending multiple drug therapy (statins, aspirin, ACE-I and beta-blockers) for the prevention of CAD. Clinical data for the secondary prevention of CAD are endorsing significant mortality benefits with these evidence based therapy. In real life clinical practice, there is inadequacy of prescription for these evidence based poly-pharmacotherapy for the prevention of CAD. Further, chronic poly-pharmacotherapy is associated with poor adherence to the treatment. This poor adherence to the chronic preventive therapy has been found to be one of the major indicators for poor clinical outcome. Various clinical studies have established that FDC are associated with better patients' compliance which can translate into better clinical outcome.

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