Medical angioplasty - Hope and expectations: An optimistic overview

Mohammed F. Abdul-Mohsen

Department of Internal Medicine, King Fahd Hospital of the University and Medical College, University of Dammam, Dammam, Saudi Arabia

Address for correspondence: Dr. Mohammed Fakhry Abdul-Mohsen, King Fahd Hospital of the University, PO Box 40032, Alkhobar 31952, Saudi Arabia. E-mail: mfakhriibrahim@yahoo.com

ABSTRACT

Primary and secondary prevention of cardiovascular diseases (CVD) are markedly overlooked worldwide. The use of these kinds of preventive methods will greatly improve outcome of or even reverse major CVD, especially coronary atherosclerosis. Comprehensive lifestyle changes combined with aggressive medical therapy [lipid lowering agents “statins”, antiplatelet agents, beta-blockers and angiotensin-converting enzyme inhibitors] for patients suffering from coronary heart disease significantly reduce all major adverse cardiovascular events (MACE), especially in those with stable coronary artery disease (CAD), even if their coronary lesions are significant. The main mechanistic pathways for the significant reduction of MACE are: Stabilization of atheromatous plaques through endothelial function repairation, strengthening of the fibrous cap of the atheromatous plaque and reduction of atheroma burden, i.e., reversal of the process of coronary artery stenosis, the great dream of “medical angioplasty”. Despite the compelling data indicating the great beneficial effects of both primary and secondary prevention of coronary atherosclerosis, the US national survey data reveals that only a minority of patients eligible by guidelines for these therapies in fact receive them. Hence, we strongly believe that our main duties as cardiologists is to improve the up-to-date knowledge of the practicing physicians about utility of aggressive medical therapy for both prevention and reversal of CVD, and also to promote useful primary and secondary prevention programs among physicians and patients. Meanwhile, further improvement and refinement of the current therapeutic modalities and introduction of new modalities for the management of lipid parameters other than LDL-C, such as HDL-C, triglyceride, lipoprotein (a), LDL particle size and susceptibility to oxidation may add further favourable effects in prevention and reversal of atherosclerotic process. Cardiologists should be just as aggressive with prevention as many have been with intervention. This optimistic overview is a valley cry to all practicing physicians; please depart from usual methods of intervention to preventive strategies which are largely overlooked.

Key words: Atheromatous plaque, endothelial function, hypercholesterolemia, high density lipoprotein cholesterol, low density lipoprotein cholesterol, nitric oxide, percutaneous coronary intervention, statins

INTRODUCTION

Coronary angioplasty is an invasive medical procedure for the reduction or elimination of coronary artery stenosis through reduction of atheromatous plaque volume. This procedure is usually done in the cardiac catheterisation laboratory with an angioplasty balloon (PTCA) and stent deployment in the majority of cases. Unfortunately, this invasive procedure is expensive and sometimes associated with a high incidence of early and late complications, such as coronary artery restenosis and in-stent thrombosis, especially if the patients did not have the proper medical care with dual antiplatelet therapy (e.g., clopidogrel bisulfate and aspirin) and effective lipid lowering therapeutic strategy. Nevertheless, the target of this invasive procedure is usually significantly stenosed segment(s) of the coronary arterial system, whereas, moderate size athermanous plaques causing 50%–65% stenosis are left alone. These types of plaques are usually unstable and more vulnerable to rupture, subsequently causing total occlusion and acute myocardial infarction (AMI) in about 70% of the cases of
AMI. It is now clear that the composition of the plaque, rather than the percent stenosis is a major determinant of vulnerability of the plaque.\textsuperscript{1-4} Inflammation (activation of monocytes/macrophages) is a major determinant of both the vulnerability of the plaque and thrombogenicity as they relate to its disruption and to future ischemic events. In one-third of acute coronary syndromes, there is, however, no plaque disruption but only superficial erosion of a markedly stenotic, fibrotic plaque.\textsuperscript{1-4} Hence, the real question addressed in this overview is this: Can comprehensive lifestyle change, aggressive lipid lowering therapy, antiplatelet drugs, beta adrenergic blockers, and renin-angiotensin–aldosterone system (RAAS) modifying therapy stabilize the vulnerable atheromatous plaques, reduce their volume and prevent cardiovascular events? The main objective and the territory to be covered by this review is to discuss both the primary and secondary prevention tools, with more emphasis on secondary prevention in order to slow down the progression or hopefully to induce regression of atheromatous plaque(s) volume and subsequently the ischemic burden of the CAD.

**REVERSIBILITY OF ATEROMATOUS PLAQUE**

The atheromatous plaque is usually formed in different arteries, especially the coronary arteries whenever risk factors for atherosclerosis cluster in certain individuals. These risk factors include age and gender, diabetes mellitus, smoking, hypertension, dyslipidemia, metabolic syndrome, lack of exercise, mental stresses, and some microbial infections with microorganisms such as *Chlamydia pneumonia*, cytomegalovirus, and *Helicobacter pylori*.

**CLINICAL EVIDENCE OF STABILIZATION AND REGRESSION OF ATEROMATOUS PLAQUE**

**Clinical trials comparing comprehensive medical treatment strategy with invasive strategies**

A plethora of research data has accumulated over the past two decades demonstrating not only reduction in atherosclerosis progression, but actual reversal of atherosclerotic process with aggressive medical therapy and lifestyle management. Four classes of drugs (statins, antiplatelet agents, beta-blockers, and angiotensin-converting enzyme (ACE) inhibitors/angiotensin II receptor blockers -ARBs) and three lifestyle components (cessation of cigarette smoking, nutrition, and physical activity) have produced life-saving reductions in cardiovascular (CV) risk by modulation of atherosclerosis and CV disease pathophysiology.\textsuperscript{15}

A large number of clinical trials have compared medical treatment strategy for patients suffering from coronary heart disease (CHD) with Percutaneous Transluminal Coronary Angioplasty (PTCA), Percutaneous coronary intervention (PCI), and coronary artery surgery (CABG) strategies. Many of these trials proved that comprehensive medical treatment was comparable to and in some subgroups of patients was better than invasive strategies regarding the primary and secondary end points. RITA-2 (Randomized Intervention Treatment of Angina trial, coronary angioplasty versus medical therapy) compared the long term outcome of coronary angioplasty (PTCA) with conservative medical therapy. The seven year outcome of death or myocardial infarction (MI) occurred in 14.5% in PTCA group compared to 12.3% in the medical treatment group. PTCA was associated with improved anginal symptoms and exercise tolerance but these differences had been narrowed over time. Therefore, in RITA-2 trial, the initial strategy of PTCA did not influence the risk of death or MI.\textsuperscript{16}

MASS II trial “The Medicine, Angioplasty, or Surgery Study” compared three therapeutic strategies for multi-vessel CAD (CABG, PCI and medical treatment [MT]) with a follow-up for 1 year. The one year survival was similar in the three treatment arms (96% for CABG patients, 95.6% for PCI patients, and 98.5% for MT patients). The one year survival free of Q-wave MI was 98% for CABG patients, 92% for PCI, and 97% for MT patients. However, patients who needed additional intervention within the one year follow-up period were much less in CABG patients compared to MT or PCI patients. It appears from this study that MT for multi-vessel CAD was associated with a lower incidence of short-term events and a reduced need for additional revascularization compared with PCI, and CABG was superior to MT for eliminating angina symptoms.\textsuperscript{17}

The Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial showed also a similar outcome. COURAGE was a randomized trial involving 2287 patients with stable but significant CAD who were randomized to either receive optimal medical therapy (OMT) and PCI or to receive OMT alone. The primary outcome of the study was a composite outcome of death from any cause and non-fatal MI. During a mean follow up of 4.6 years, there were no significant differences between the PCI group and the optimal medical-therapy group in the primary event rate (19% in the PCI group, 18.5% in the medical therapy group, $P = 0.62$).\textsuperscript{18} Similarly, in the BARI 2D trial, 2368 patients with diabetes and stable but significant CAD were randomized either to revascularization (PCI or CABG) with OMT or OMT alone. The mean follow-up was 5 years. There was no
difference in survival between PCI and OMT patients, or between CABG and OMT patients. Nevertheless, there was no difference in freedom of cardiovascular events in PCI versus OMT patients, but only between CABG versus OMT patients as it was found that CABG was associated with more freedom of cardiovascular events ($P = 0.01$). COURAGE and BARI 2D trials had some important limitations such as the low use of drug eluted stents (DES) and the high rate of cross-over from OMT to revascularization arm (21% in COURAGE trial and 42% in BARI 2D trial). The main conclusions of the two trials are: 1) OMT alone is safe initial treatment strategy for many patients with stable CAD. 2) Consider early revascularization in patients with left main disease >50% stenosis, left ventricular ejection fraction (LVEF) <40%, 3 vessel disease patients with diabetes, and patients with large burden of ischemia on myocardial perfusion imaging (PMI).

**Lipid lowering therapy**

**Apolipoprotein A-I Milano phospholipids complexes (ApoA-I Milano PL) and high density lipoprotein cholesterol (HDL-C) raising therapy**

Although low levels of high density lipoprotein-cholesterol (HDL-C) increase risk for CAD, no data exist on potential benefits of the administration of HDL-C or an HDL-C mimetic. In 2002, Chiesa et al., had reported the results of a very interesting animal study about the rapid removal of lipids from fatty streaks using a recombinant apolipoprotein A-I Milano infusion into rabbit carotid artery. Infusion of Apo A-I Milano-PL at the 2 highest doses (500 mg and 1000 mg) showed a reduction in the right carotid artery plaque area by the end of a 90 minute infusion, analyzed by intravascular ultrasound (IVUS). Plaque area regression was confirmed by histology of carotid arteries that received direct 500 or 1000 mg Apo-I Milano-PL. These results suggest that Apo-I Milano-PL complexes enhance lipid removal from arteries is the mechanism responsible for the observed atheromatous plaque regression. Several previous studies had revealed that recombinant Apo-I Milano-PL complexes infused to hypercholesterolemic animals significantly reduced neointimal formation after arterial injury, improved the endothelial function and reduced the progression of atherosclerosis in cholesterol-fed rabbits. Subsequently in 2003, Nissen et al., reported the results of their important human experiment in which they assessed the effect of intravenous recombinant ApoA-I Milano PL complexes (ETC-216) on atheroma volume measured by intravenous ultrasound (IVUS) in patients with acute coronary syndrome compared with those who had a placebo. The mean (SD) percent atheroma volume decreased by $-1.06\%$ in the ETC-216 group compared with baseline, ($P = 0.02$). In the placebo group, mean (SD) percent atheroma volume increased by 0.14% compared with baseline, ($P=0.97$). The absolute reduction of atheroma volume in the combined ETC-216 treatment group was $-14.1mm^3$ or 4.2% decrease from baseline ($P < 0.01$). Their conclusion was that recombinant ApoA-I Milano PL complexes had produced significant regression of coronary atherosclerosis as measured by IVUS. In another research direction, DEFINE (Determining the Efficacy and Tolerability of CETP Inhibition With Anacetrapib) investigators assessed the efficacy and safety profile of anacetrapib in patients with CHD or at high risk for CHD. Anacetrapib is a cholesteryl ester transfer protein inhibitor that raises HDL-C and reduces LDL-C. By 24 weeks, the LDL cholesterol level had been reduced from 81 mg/dl to 45 mg/dl in the anacetrapib group, as compared with a reduction from 82 mg/dl to 77 mg/dl in the placebo group ($P < 0.001$). In addition, the HDL cholesterol level had increased from 41 mg/dl to 101 mg/dl in the anacetrapib group, as compared with an increase from 40 mg/dl to 46 mg/dl in the placebo group ($P < 0.001$). Questions have also been raised about therapies that increase HDL cholesterol levels because of the conflicting results of epidemiologic studies examining the relationship between CETP activity and cardiovascular outcomes. However, a recent meta-analysis of 92 studies involving 113,833 participants concluded that the CETP genotypes that have been shown to have lower CETP activity were associated with a decreased coronary risk.

**Statin trials**

The launch of lovastatin in 1987, the first approved hydroxyl methylglutaryl-coenzyme A-reductase inhibitor, and the subsequent introduction of more therapeutically effective statins not only revolutionized treatment of patients with frank hyperlipidemia but also radically changed the treatment of patients at-risk for cardiovascular events. A solid body of evidence has demonstrated that statins reduce the risk of CV events in patients with established CV disease, patients at risk for CV disease due to cardiac risk factors, and even concomitant vascular disease. The magnitude of risk reduction is in the order of 30%, and cost analyses calculate superior cost utility over other CV treatments such as revascularization interventions. This risk reduction was clearly demonstrated in both primary and secondary prevention trials. Subsequently, in 2004, the National Cholesterol Education Program Adult Treatment Panel (NCEP - ATP) III guidelines released an update stating that a low-density lipoprotein cholesterol goal of <70 mg/dl is a reasonable therapeutic strategy for patients at very high cardiac risk, such as those with known coronary artery disease, diabetes, metabolic syndrome, or a recent cardiac event.
Role of statins in primary prevention of cardiovascular disease

Several primary prevention trials have shown that statins have favorable effects in the primary prevention of CV events and all-cause mortality. These trials: Air Force/Texas Coronary Atherosclerosis Prevention Study (AFCAPS/TexCAPS), West of Scotland Coronary Prevention Study (WOSCOPS), Anglo-Scandinavian Cardiac Outcomes Trial–Lipid-Lowering Arm (ASCOT-LLA), the Antihypertensive and Lipid-Lowering Treatment to Prevent Heart Attack Trial (ALLHAT) and Justification for the Use of statins in Prevention: An Intervention Trial Evaluating Rosuvastatin (JUPITER), have included patients who were clinically free of CAD. These trials revealed a significant reduction in CV events ranging from 31% to 44%. There was also a clear inverse relationship between the LDL-C level and the CV event rates.[21-28] A meta-analysis of 10 trials enrolled 70,388 people, 23,681 (34%) of whom were women and 16,078 (23%) had diabetes. Treatment with statins significantly reduced the risk of all-cause mortality by 12%, major coronary events by 30%, and major cerebrovascular events by 19%.[28]

Role of statins in secondary prevention of cardiovascular disease

Abundant evidence from clinical trials supports the beneficial effect of LDL-C lowering in decreasing CAD risk, both in angiographic trials, which measure atheromatous plaque volume progression, and in trials with morbidity and mortality endpoints.[29-34] A large number of secondary prevention trials, such as, Lescol Intervention Prevention Study (LIPS), Scandinavian Simvastatin Survival Study (4S), Heart Protection Study (HPS), Cholesterol and Recurrent Events (CARE) and The long-term intervention with Pravastatin in Ischemic Disease (LIPID) showed a significant reduction in LDL-C levels associated with a significant reduction in cardiac outcome [Table 1]. In these trials, the follow-up periods were relatively long, ranging from 3 to 4 years in LIPS trial to 6.1 years in LIPID trial. The degree of LDL-C reduction ranged from 25% in LIPID trial to 36% in 4S trial. The percentage reduction in cardiac death and myocardial infarction (MI) ranged from 24% in LIPID and CARE trials to 34% in 4S trial, and the percentage reduction in cardiac death alone ranged from 18% in HPS to 47% in LIPS trial.[29-33] In a meta-analysis of another group of secondary prevention trials, intensive LDL-C lowering with high doses of statins showed additional benefits compared with moderate doses. This meta-analysis involved 4 major trials, PROVE IT-TIMI 22 (Pravastatin or Atorvastatin Evaluation and Infection Therapy–Thrombolysis in Myocardial Infarction-22), A to Z (Aggrastat-to-Zocor), TNT (Treating to New Targets), and IDEAL (Incremental Decrease in End Points Through Aggressive Lipid-Lowering) revealed that there was a mean of 16% further reduction in the risk of coronary death or myocardial infarction in patients who received intensive statin treatment compared with patients given moderate statin doses (OR, 0.84, 95% CI, 0.77-0.91, P = 0.00003).[34-35] Furthermore, a very recent meta-analysis tried to answer the very important hypothetical question; Is the low-density lipoprotein cholesterol (LDL-C) “lower is better”? Twenty six statin trials enrolled 169,138 patients with median follow-up of about 5 years were analyzed to determine any further risk reduction in patients receiving intensive statin treatment compared with patients receiving less intensive regimens. More intensive regimens produced an average 15% further reduction in major CV events (coronary death or non-fatal MI, cardiac revascularization and ischemic stroke).[36]

### Table 1: Cardiac outcome benefits in some of the major statin in secondary prevention trials

| Study            | Statin                          | No of patients | % reduction in LDL-C | % reduction in cardiac death and MI | % reduction in cardiac death |
|------------------|---------------------------------|----------------|----------------------|------------------------------------|-----------------------------|
| LIPS             | Lescol® 80 mg/day for 3–4 years  | 1677           | 27                   | 31                                 | 47                          |
| ALERT            | Lescol® 40 mg/day for 5–6 years  | 2102           | 32                   | 28                                 | 38                          |
| 4S               | Simvastatin, 40 mg/day for a median of 5.4 years | 4444 | 36 | 34 | 42 |
| HPS              | Simvastatin, 40 mg/day for 5 years | 20,536 | 31 | 27 | 18 |
| CARE             | Pravastatin, 40 mg/day for 5 years | 4159 | 28 | 24 | 20 |
| LIPID            | Pravastatin, 40 mg/day for a mean of 6.1 years | 9014 | 25 | 24 | 24 |

LDL-C - low-density lipoprotein cholesterol, MI - myocardial infarction, LIPS - Lescol Intervention Prevention Study, 4S - Scandinavian Simvastatin Survival Study, HPS - Heart Protection Study, CARE - Cholesterol and Recurrent Events, LIPID - Long-term intervention with Pravastatin in Ischemic Disease
Regression of atheroma burden with statin treatment

LDL-C particles deposit into the arterial wall, whereas HDL-C particles remove cholesterol from the arterial wall and transport it to the liver for excretion in a process known as reverse cholesterol transport. The balance of transport between LDL and HDL in the sub-endothelial space determines the rate of atherosclerosis progression. It is thus possible to stop plaque formation and to induce regression.

Beginning in the late 1980s, clinical trials utilizing various imaging techniques have demonstrated that it is possible to halt atherosclerotic progression and, in some cases, induce regression. Early trials with quantitative coronary angiography have demonstrated an attenuation of atherosclerotic plaque progression. These include the Canadian Coronary Atherosclerosis Intervention Trial (CCAIT) and the Monitored Atherosclerosis Regression Study (MARS) with lovastatin; the Familial Atherosclerosis Treatment Study (FATS) with lovastatin, niacin, and a bile acid resin; the Lipoprotein and Coronary Atherosclerosis Study (LCAS) with fluvastatin; and the Pravastatin Limitation of Atherosclerosis in the Coronary Arteries (PLAC I) and the Regression Growth Evaluation Statin Study (REGRESS) with pravastatin.

Evidence from recent imaging studies suggests that statin therapy may beneficially affect plaque volume and composition within the arterial wall, possibly leading to increased plaque stability and a decreased likelihood of thrombotic events. In METEOR "Measuring Effects on Intima-Media Thickness: An Evaluation of Rosuvastatin" study, rosuvastatin reduced the rate of progression of carotid plaques over two years, although it did not induce regression. IntraVascularUltraSound (IVUS) trials examining the effects of intensive statin therapy on coronary atheroma burden have provided the strongest evidence that statins can slow or reverse the progression of atherosclerosis within the vessel wall. The reversal of atherosclerosis with aggressive lipid lowering (REVERSAL) trial enrolled approximately 600 patients with evidence of at least 20% narrowing of a coronary artery and compared treatment with atorvastatin 80 mg/day vs. pravastatin 40 mg/day. After 18 months of treatment, results indicated a non-significant halt in atherosclerotic progression in the atorvastatin group (intensive treatment) and a significant 2.7% progression in the pravastatin group (less intensive treatment), with significant between-group comparisons favoring intensive therapy. In ASTEROID "A Study to Evaluate the Effect of Rosuvastatin on IVUS-Derived Coronary Atheroma Burden" trial, rosuvastatin 40 mg/day reduced the mean LDL-C to 60.8 mg/dl, increased the mean HDL-C by 15% and demonstrated significant regression of atherosclerosis at 24 months. A post-hoc analysis by Nicholls et al., attempted to quantify the relationship between LDL-C, HDL-C, and atheroma burden. They combined data from REVERSAL, ASTEROID, and another two IVUS trials involving treatment with statins for 18 or 24 months. A substantial atherosclerotic regression (≥5% reduction in atheroma volume) was most likely to occur in patients who had achieved LDL-C levels below 87.5 mg/dl and who had increases in HDL-C greater than 7.5%.

The favorable effects of statin treatment on endothelium function and atheromatous plaque stability

Atherosclerosis is a very gradual process, the effect of which is that, the endothelium becomes more adherent and permeable to circulating monocytes and T-lymphocytes, acquiring increased thrombotic and vasoactive properties. Monocytes that adhere to the surface of endothelial cells are transported into the arterial wall, where they are converted into macrophages. Activated macrophages and leukocytes then release a variety of mediators that collectively increase inflammation and oxidative stress within the vessel wall. Meanwhile, patients with acute coronary syndrome (ACS) are at significantly heightened risk of recurrent events in the subsequent months compared to those with stable CAD. The majority of these recurrent events occur in non-culprit lesions and therefore, supports the current concept that ACS is a diffuse process that involve the entire coronary vasculature necessitating the need for systemic disease modifying therapy. Current understanding of the pathophysiology of ACS supports a potential role for immune activation, inflammation, endothelial activation/dysfunction and coagulation in its pathogenesis. Statins play an important role in a number of cell signaling pathways which in vitro alter the pathological triad of inflammation, endothelial activation and coagulation and are often referred to as "pleiotropic effects." Several large randomized controlled trials have provided information on the clinical benefits of statins within the first 4 months after ACS. Further analysis of the data suggested that the early benefits observed within 30 days were not related to the achieved LDL-C. In MIRACL study, among individuals randomized to intensive statin therapy C-reactive protein (CRP) levels were lower, suggesting that intensive statin therapy significantly reduces inflammation after an ACS event. In a meta-analysis of the A to Z and PROVE IT-TIMI 22 trials, a significant reduction of LDL-C associated with significant reduction of CRP levels was associated with fewer CV events. In JUPITER trial, rosuvastatin reduced LDL cholesterol levels by 50% and hs CRP levels by 37% at 12 months. That reduction was associated with 44% reduction in all primary end points of myocardial infarction, stroke, unstable angina or revascularization and CV...
Therefore, there is a large body of evidence indicating that statin in addition to LDL-C lowering, have further favorable effects, such as anti-inflammatory effect, reparation of endothelial function, and subsequent stabilization of atheromatous plaque.  

Antiplatelet therapy

Aspirin and other antiplatelet agents have been shown to be effective in preventing cardiovascular events at all CV risk levels studied. There is a large body of evidence documenting utility of aspirin for risk reduction in patients with established CV disease. The overall magnitude of risk reduction in terms of death and non-fatal MI is approximately 25%. The evidence of effectiveness among at-risk patients encompasses studies of more than 55,000 subjects with cardiac risk factors. Improvement of endothelial dysfunction with aspirin may improve vasodilatation, reduce thrombosis, and inhibit progression of atherosclerosis. This provides a pathophysiological basis for the beneficial effects of aspirin in atherosclerosis. 

Current American College of Cardiology/American Heart Association (ACC/AHA) guidelines indicate that low-dose aspirin therapy (75 to 162 mg daily) is indicated for all patients with established CV disease, as well as for patients deemed at moderate risk (10% 10-year calculated global risk).  

Beta-blocker therapy

More than 20 randomized controlled trials demonstrate the efficacy of beta-blocker therapy for the reduction of adverse events in patients with CV disease, as well as for at-risk patients undergoing surgery and anesthesia. Used in the setting of post-MI, unstable angina, and congestive heart failure, the overall risk reduction is 25%. Subgroup populations including diabetics and patients with heart failure also appear to benefit. The MIAMI (Metoprolol in Acute Myocardial Infarction) study, ISIS-1 (International Study of Infarct Survival) trial, and TIMI (Thrombolysis In Myocardial Infarction)-2B study demonstrated superiority of early intravenous beta-blocker therapy for patients with acute ST-segment elevation MI. Fortunately, not all studies have consistently demonstrated the benefit of early intravenous beta-blocker therapy. So it is advisable to defer acute beta-blockade in patients with acute coronary syndrome until hemodynamic stability is achieved. Obviously, beta-blockers are not all created the same. Fortunately, nebivolol (one of the third-generation cardioselective beta-blockers) has been shown to enhance nitric oxide bioactivity and improve endothelial function, which is the key element for halting the atherosclerotic process and stabilization of atheromatous plaque. Other third-generation beta-blockers, such as labetalol, carvedilol, and bisoprolol, vasodilate by different mechanisms, behaving differently than traditional beta blockers and offering different benefits. Bisoprolol, metoprolol, and carvedilol have shown great advantages in reducing the relative risk for death in patients with heart failure ranging from 34% in CIBIS II trial to 35% in MERIT-HF and COPERNICUS trials each. It is therefore, becoming obvious that beta-blocker therapy has a great role in plaque stabilization, and in both primary and secondary prevention of CV events.

ACE inhibitor/ARB therapy

Current ACC/AHA guidelines for secondary prevention in established coronary heart disease, include the use of beta-blockers and strong consideration of the use of Angiotensin Converting Enzyme inhibitor (ACE-I) independent of hypertensive status. The seventh report of the Joint National Committee (JNC-7) expanded this primary ACE inhibitors recommendation to hypertension in the setting of heart failure, post-MI, high coronary risk, diabetes, chronic kidney disease, and the prevention of recurrent stroke. The overall magnitude of risk reduction in terms of death and non-fatal MI is approximately 25%. It has also been known that long-term treatment with ACE inhibitors as well as Angiotensin II type 1 (AT(1)) receptor blockers (ARBs) and statins reduces cardiovascular mortality in patients with CAD as well as chronic heart failure. However, little is known about the acute effects of these compounds on vascular reactivity of coronary resistance vessels. Tiefenbacher et al., (2004) had undertaken an experiment on coronary arterioles obtained from patients undergoing coronary bypass surgery (atherosclerosis group) or valve replacement (control group). They found that in atherosclerosis, endothelium-dependent relaxation of coronary resistance arteries was severely compromised,
Importance of comprehensive life style changes

Comprehensive lifestyle changes can sharply reduce CV risk. Specifically, cessation of cigarette smoking, nutrition, and physical activity can reduce risk of adverse events to a greater magnitude than medications, ranging from 50% for smoking cessation and nutrition, to 25% for exercise. By controlling food intake and increasing exercise, patients can meaningfully alter their body mass index and affect their debilitating obesity. Such a rigorous combined effort also has a direct and positive impact on other manageable disease states, such as diabetes, that have been linked to CVD. In a Systematic Review of the Evidence Supporting a Causal Link Between Dietary Factors and Coronary Heart Disease, Mente et al., retrieved 146 prospective cohort studies. Most of the cohort studies (86%) were primary prevention studies, whereas 14% were secondary prevention trials. Strong evidence supports valid associations of protective factors, including the intake of vegetables, nuts, and “Mediterranean” dietary patterns with lower incidence of CHD, while there is association with of harmful factors, including intake of trans-fatty acids and foods with a high glycemic load with a higher incidence of CHD. There is also a moderate evidence of association for the intake of fish, marine omega-3 fatty acids, folate, whole grains, dietary vitamins E and C, beta carotene, fruit, liberal intake of monounsaturated fats (e.g., olive oil) and fiber diet and lower incidence of CHD.

Nevertheless, during the past half-century, prospective epidemiological studies of occupational and leisure-time physical activity have consistently documented a reduced incidence of CAD events in the more physically active and fit subjects. More recent studies have provided similar data by using measures of exercise capacity such as treadmill performance as an indicator of habitual physical activity. There is also strong evidence indicating that the most physically active subjects generally have half the CAD rates of those who are sedentary. Multiple studies were prospective and thereby demonstrated appropriate sequencing because the lower physical activity levels preceded the development of CAD rather than resulted from the disease itself. Encouraging and achieving sustained lifestyle changes remains a challenge for the physician and patient. However, because of its unequivocal beneficial effects in preventing CVD, it is always worth trying.

CONCLUSIONS AND FUTURE PERSPECTIVES

Surprisingly, summary studies document the potent utility of optimal medical therapy combined with comprehensive life style changes as safe initial treatment strategy for many patients with stable CAD, even if they have angiographically significant coronary lesions. However, we have still to consider early revascularization in patients with left main disease >50% stenosis, left ventricular ejection fraction (LVEF) <40%, 3 vessel disease patients with diabetes, and patients with large ischemic burden on myocardial perfusion imaging (PMI). Despite this large body of evidence documenting the utility of aggressive medical management for both prevention and reversal of CVD, there is a treatment gap which has enormous implications for the training and practice of cardiology. The US national survey data indicate that only a minority of patients eligible by guidelines for these therapies in fact receive them. So, it is becoming essential for the cardiology training programs worldwide to allocate enough time and expertise for the formal training of the cardiology fellows in the different areas related to primary and secondary prevention. Meanwhile, we strongly believe that one of the main duties of cardiology organizations worldwide is to promote the up-to-date knowledge about the great usefulness of primary and secondary prevention of CVD among physicians and patients. Indeed, we all need to shift the paradigm from intervention to prevention, working together to protect subjects who are still healthy rather than wait and have to treat patients with
complicated CVD. Let us do it, and change our hope and great expectations into reality.

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