"Our thoughts create our reality — where we put our focus is the direction we tend to go."

Review of Literature
3: REVIEW OF LITERATURE

3.1 EPIDEMIOLOGY OF ISCHEMIC HEART DISEASE/CORONARY ARTERY DISEASE

Cardiovascular diseases (CVDs) are major contributors to the global burden of chronic diseases with 29.3% of global deaths and 9.9% of disability-adjusted life years (DALYs) lost, reported in 2003. In low and middle income countries it has accounted 78% and 86% of the global deaths and DALYs lost, respectively in 1998. In 2005, 80% of chronic disease deaths occurred in low and middle income countries (WHO, 2005). By 2020, burden of CVD is predicted to increase substantially in developing countries accounting for at least one in every three deaths. Major causes for the increase in disease burden are raising rates of hypertension, dyslipidemia, diabetes, overweight, obesity, physical inactivity and tobacco use. Ischemic heart disease and stroke are the two most common causes of CVD death worldwide (Murray et al 1996).

CAD is increasing in prevalence and is the leading cause of death and disability worldwide. In India by 2020, CVD is projected to be the largest cause of death and disability with 2.6 million Indians predicted to die due to coronary heart disease (CHD)/IHD, which constitutes 54.1% of all CVD deaths. Nearly half of these deaths are likely to occur among young and middle-aged individuals (30-69 years). This is because Indians experience CVD deaths at least a decade earlier than their counterparts in developed countries. This has the potential to adversely affect India's economy with 52% of CVD deaths occurring in those below the age of 70 years compared to 23% in countries having established market economies. Demographic and health transitions, gene-environmental interactions and early life influences of fetal malnutrition have been implicated as the causes of increasing CVD burden in India. However, the most important factors are changes in living habits, whereby behavioral risk factors are transformed into biological risk factors. Such environmentally determined risk factors are more amenable to change through public health and clinical interventions and, therefore, warrant early recognition at the individual level and surveillance at the population level.

In 2003, the prevalence of CHD/CAD in India was estimated to 3-4 percent in rural areas (two-fold higher than before 40 years) and 8-10 percent in urban areas (six-
fold higher than before 40 years), with a total of 29.8 million affected (14.1 million) in urban areas, and 15.7 million in rural areas which is comparable to the figure of 31.8 million affected, derived from extrapolations of the Global Burden of Diseases study (Murray et al 1996, Gupta 2005, Gupta 2004). However, these numbers are still likely underestimates as they do not account for those with silent myocardial infarction or otherwise asymptomatic IHD. By 2010, 60% of the world’s patients with heart disease will be in India (Gaziano et al 2006). In 1990, there were an estimated 1.17 million deaths from CHD in India, and the number is expected to almost double to 2.03 million by 2010 (Ghaffar et al 2004). An estimated 9.2 million productive years of life were lost in India in 2000, with an expected increase to 17.9 million years in 2030 (almost ten times the projected loss of productive life in the United States) (Leeder et al 2004).

3.1.1 Epidemiological studies and risk factors

There is steep rise in CVD risk factor burden in the proportion of urban inhabitants (currently at 30% with a projected rise to 43% in 2021 (Reddy et al 2005). Urbanization is characterized by a marked increase in the intake of energy-dense foods, a decrease in physical activity, and a heightened level of psychosocial stress, all of which promote the development of dysglycaemia, hypertension, and dyslipidaemia (Yusuf et al 2001).

Diabetes mellitus: The Indian subcontinent has a higher prevalence of diabetes mellitus than any other region in the world, and 2-3 times the reported prevalence in Western countries (Jafar 2006). In India alone, an estimated 19.3 million people had diabetes in 1995, which is expected to be almost triple to 57.2 million in 2025 (King et al 1998). The Indian Council of Medical Research (ICMR) estimates that the prevalence of diabetes is 3.8 per cent in rural areas, compared with 11.8 percent in urban areas (Reddy et al 2005). Recent studies in large cities in northern and southern India reported that the prevalence of diabetes among adults (>20 years) ranges from 8% to 15% (Gupta et al 2007, Mohan et al 2007).

Hypertension: It is even more prevalent (20-40% among urban and 12-17% among rural adults) (Gupta 2004), and was affecting an estimated 118 million inhabitants in India in 2000; which is projected to be almost double to 214 million in 2025 (Kearney et al 2005).
Chronic kidney disease (CKD): Concomitant with the rise in the prevalence of diabetes and hypertension is an increase in the prevalence of CKD, also recognized as an independent risk factor for CHD (Go et al 2004). CKD prevalence is estimated about 0.8-1.4 per cent in urban areas (Mani et al 2005, Agarwal et al 2005).

Cigarette smoking: In 2002, a national survey of tobacco use reported that the Indian subcontinent, second only to China in both the production and consumption of tobacco products, had an alarming rate of current tobacco use of 56 per cent among Indian men aged 12-60 yr (Reddy et al 2005). Reddy and colleagues observed that the prevalence of tobacco use (any history of use or current use) was 2-3 times higher among sixth graders compared with eighth graders (Reddy et al 2006) in an urban setting, suggesting a concerning new wave of smoking among India's youth that forebodes serious future public health consequences for the Indian subcontinent.

Other forms of tobacco use: Little data existed regarding the association between the use of other forms of tobacco and the risk of CVD; however, in the INTERHEART case-control study it has documented that risk associated for acute myocardial infarction (AMI) increased with all forms of smoked and smokeless tobacco (Yusuf et al 2004). Risk associated for AMI with smoking beedies was comparable to the risk of current cigarette smoking (Teo et al 2006).

Dyslipidaemia: The ICMR surveillance project reported a prevalence of dyslipidaemia (defined as a ratio of total to HDL cholesterol >4.5) of 37.5 percent among adults aged 15-64 yr, with an even higher prevalence of dyslipidaemia (62%) among young male industrial workers (Reddy et al 2005). The INTERHEART investigators reported that the prevalence of dyslipidaemia (abnormal apolipoprotein ApoB/ApoA1 ratio) among controls without AMI was higher among study participants living in the five South Asian countries (45%) compared with participants from the other 47 countries represented in the study (35%) (Yusuf et al 2004).

The ongoing Prospective Urban and Rural Epidemiologic (PURE) study that aims to understand the determinants and rates of several chronic diseases in over 1,35,000 people from about 15 countries worldwide, including 30,000 from India. This study will help quantify the impact of urbanization on risk factors for chronic diseases, and shape policy efforts to address risk factor profiles that are unique to urban versus rural areas.
The CREATE registry in South Asian population with 20,000 ACS studies the association between medical and socio-economic risk factors and AMI at both the individual patient and the site level (Yusuf et al 2004).

Other factors: Many small studies from India have evaluated unconventional cardiovascular risk factors, including lipid subfractions, platelet functional abnormalities, inflammatory markers, homocysteine and thrombotic factors (Khare et al 2006). However, larger studies are needed. Barker’s hypothesis focuses on the adverse long-term cardiovascular impact of fetal undernutrition and low birth weight has been proposed as a cardiovascular risk factor (Barker 1998).

Figure 3.1: Coronary heart disease (CHD) prevalence (%) in Indian urban and rural subjects aged >30 years as reported in epidemiological studies (Gupta et al 2008).

The diagnostic criteria used were either known CHD, or angina on the Rose questionnaire or electrocardiographic Q/ST/T wave changes. There is a significantly increasing trend of CHD in both urban and rural populations.

A high prevalence is consistently seen in studies at urban locations Chandigarh 6.6% (Sarvotham et al 1968, Rohtak 3.6% (Gupta et al 1975), Delhi 9.7% (Chadha et al 1990), Varanasi 6.5% (Sinha et al 1990), Jaipur 9.2% (Gupta et al 1995), Trivandrum 12.7% (Begom et al 1995), Chennai 11.0% (Mohan et al 2001), Jaipur 9.1% (Gupta et al 2002), and Goa 12.5% (Pinto et al 2004) as compared with the rural Haryana 2.1% (Deewan et al 1974) Haryana 2.7% (Chadha et al 1989), Punjab 3.1% (Wander et al 1994) and Rajasthan 4.3% (Gupta et al 1994). There are significantly increasing trends in urban ($r^2=0.60$) as well as rural ($r^2=0.31$) populations (Figure 3.1) (Gupta et al 2008).
Analyses of prevalence studies in various decades in India also provide significant information about the absolute number of CHD cases (Gupta 2005). Decadal variations indicate that the adult prevalence has increased in urban areas from about 6.5% in the mid-1960s to 7.0% in 1980, 9.5% in 1990 and 10.5% in 2000, while in rural areas it has increased from 2% in 1970s to 2.5% in 1980, 4% in 1990 and 4.5% in 2000. This would translate into 4.5 million urban subjects in 1970, 5.6 million in 1980, 9.7 million in 1990 and 14.1 million in the year 2000, and in rural populations into 4.1 million in 1970, 6.4 million in 1980, 11.8 million in 1990 and 15.7 million in 2000 (Gupta 2005) Thus, epidemiological studies show that there are at present 29.8 million patients with CHD in this country, which is similar to the numbers obtained by the National Commission on Macroeconomics and Health (Indrayan 2004). As epidemiological studies do not identify patients with silent and asymptomatic CHD the actual number of cases may be much greater.

3.1.2 DALYs and absolute burden of CHD in India

In India by 2020, DALYs lost due to CHD is projected to more than double (14.36 millions males and 7.66 millions females) as shown in the Figure 3.2 (Murray et al 1997, WHO report 2002).

Figure 3.2: Estimated DALYs lost due to Coronary Heart Disease in India (Murray et al 1997, WHO report 2002).

DALYs – Disability-adjusted life years
3.1.3 Economic and Social Burden

From the year 1995 to 2000, India has been spending about 5% of its gross domestic product (GDP) on health. Of this, direct expenditure on health is about 82-83% and the subsidized general government expenditure is 17-18% (World Health 2002). It is reported that in India 92% of patients with ST segment elevation myocardial infarction (STEMI) receive thrombolysis. A high use of other drugs was also reported; aspirin 98%, beta-blockers 70%, ACE inhibitors 74%, and statins 62% showing a good compliance (Yusuf et al 2004).

The average cost of generic forms of these drugs in India is about 15/day (Rs. 5500/y) (Gupta et al 2005). Considering 8.0 million CHD populations are on this therapy the total burden in terms of cost would be Rs. 44 billion/year. Additional 44 billion/year would be covered for ancillary services such as costs of investigations and hospital visits. For 1.27 million acute coronary events, the cost would be Rs. 6.5 billion. It has been reported that about, 20,000 coronary bypass surgeries and 30,000 coronary angioplasty procedures are performed in the country every year (Padmavati 2002). At the minimum cost of Rs. 0.1 million per procedure (many hospitals charge the patient more than 5-times this amount) - this would add burden of another Rs. 5 billion to the patient. All this adds up to Rs. 99.5 billion (~100 billion) of burden in terms of direct cost of therapy to the patient given in Table 3.1 (Gupta et al 2005). The National Family Health Surveys reported that direct medicine costs are about 45-50% of medical treatment costs in India (International Institute for Population Sciences 2000). Thus, a similar amount (Rs. 100 billion) could be spent by the healthcare system in caring for these patients in outpatient clinics, hospitals and other institutions. Therefore, at an underestimate the economic burden of CHD in India is about Rs. 200 billion. The total economy of India annually (GDP) is about Rs. 25000 billion. Thus the burden of CHD in India is about 0.8% of the GDP. In Indian, typically acute coronary events occur at least 10 years earlier than in Caucasian and Latin American countries and 5 years earlier than in China (Wald et al 2003, Franco et al 2004).
Table 3.1: Direct annual economic burden of CHD in India (Gupta et al 2005)

<table>
<thead>
<tr>
<th>Direct cost to populations for CHD treatment</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Known CHD</strong></td>
<td>~8.0 million</td>
</tr>
<tr>
<td>Pharmacotherapy (polypill approach) (Yusuf et al 2004)</td>
<td>@Rs. 5500/year</td>
</tr>
<tr>
<td>Direct cost to patients</td>
<td>Rs. 44.0 billion</td>
</tr>
<tr>
<td>For ancillary medical services</td>
<td>Rs. 44.0 billion</td>
</tr>
<tr>
<td><strong>Hospitalization procedures and costs to patients</strong></td>
<td></td>
</tr>
<tr>
<td>Acute coronary syndrome:</td>
<td></td>
</tr>
<tr>
<td>One million events per year @ Rs. 5000/year</td>
<td>Rs. 6.5 billion</td>
</tr>
<tr>
<td>PTCA, CABG, 50,000/year: @Rs 1 lakh</td>
<td>Rs. 5.0 billion</td>
</tr>
<tr>
<td>Total Costs:</td>
<td>Rs. 100 billion (range 40 –100)</td>
</tr>
<tr>
<td>Ancillary costs (staff, clinics, hospitalization)</td>
<td>Rs. 100 billion</td>
</tr>
<tr>
<td>Grant total /year</td>
<td>Rs. 200 billion (range 80-320)</td>
</tr>
<tr>
<td>Others and indirect costs</td>
<td>Undetermined</td>
</tr>
</tbody>
</table>

3.1.4 Prevention of Coronary Heart Disease

WHO estimated that deaths attributable to CVD have increased in parallel with the expanding population in India. CVD now accounts for the large population of DALYs lost in India as well as other developing countries. The average life expectancy has increased from 41 years in 1951 to 61 years in 1991 and it is projected to 72 years in 2030, which could lead to large increase in CHD prevalence (Deedwania et al 2005).
3.2 ISCHEMIC HEART DISEASE

IHD which is also known as CAD is a condition in which there is a hardening of the arteries on surface of the heart. Due to functional or actual constriction of the coronary arteries, the blood supply to the heart is hindered and thus there is an imbalance between oxygen demand, ultimately leading to complications like cardiac ischemia, angina or MI. The underlying cause of most CVs disease is atherosclerosis, a disease characterized by accumulation of lipid in the intima of large and medium sized arteries. The interaction between the vulnerable atherosclerotic plaque and thrombus formation, a process referred to as atherothrombosis, is the corner stone of ACS (Corti et al 2002). Angina is a common symptom of CAD (Pace 2000). Lesions that causes blockages of arteries may be stable or unstable (unstable lesions activate blood clotting). It may present as stable angina, acute coronary syndrome, or sudden cardiac death. ACS encompass patients who have evidence of myonecrosis, or are felt to be at high risk of myonecrosis in the immediate future, and thus include patients with unstable angina (UA), non-ST elevation myocardial infarction (NSTEMI), and ST elevation myocardial infarction (STEMI) (Braunwald et al 2000, Braunwald et al 1989, Braunwald et al 2000, Braunwald et al 2000).

<table>
<thead>
<tr>
<th>Ischemic Heart Disease/Coronary Artery Disease - Spectrum of conditions</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Silent Ischemia – asymptomatic patients</td>
</tr>
<tr>
<td>2. Chronic Stable angina/Angina pectoris</td>
</tr>
<tr>
<td>3. Acute Coronary Syndrome</td>
</tr>
<tr>
<td>a. Unstable angina (UA)</td>
</tr>
<tr>
<td>b. Non-ST elevation myocardial infarction (NSTEMI)</td>
</tr>
<tr>
<td>c. ST elevation myocardial infarction (STEMI)</td>
</tr>
<tr>
<td>4. Sudden Cardiac death</td>
</tr>
<tr>
<td>5. Complications (ischemic cardiomyopathy, heart failure, ventricular tachyarrhythmias)</td>
</tr>
</tbody>
</table>

3.2.1 Causes and Pathogenesis

The major risk factors are smoking, diabetes mellitus and high cholesterol levels (hypercholesterolemia); hypertension, genetic and hereditary factors may also be responsible for the disease. Males are more prone to IHD. However, in post-menopausal women, the risk is almost similar to that of men. Stress is also thought to be a risk factor. The disease process occurs when an atheromatous plaque forms in the coronary vessels,
leading to narrowing of the vessel walls and obstructing blood flow to the musculature of the heart.

Patients with ACS have one or more of the underlying etiologies: (a) a nonocclusive or an occlusive thrombus on a preexisting plaque, (b) vasoconstriction or dynamic obstruction, (c) progressive mechanical obstruction, (d) inflammation, and (e) secondary unstable angina (Fuster et al 1992). The inciting event in this cascade is typically plaque disruption, which with its attendant superimposed thrombosis and associated vasoconstriction impairs coronary blood flow and may be complicated by distal embolization (Falk 1985, Davies et al 1985). Work done in the 1970s demonstrated that platelets play a key role in unstable plaque with aggregation and release of vasoconstrictors contributing to further worsening of the ischemic cascade. Autopsy studies by Falk demonstrated a layered structure of the coronary thrombus suggesting episodes of thrombosis with progressive luminal encroachment and a final occlusive thrombus in a majority of patients with myocardial infarction (MI) (Falk 1985). Patients had evidence of platelet micro-embolization distal to the thrombus suggesting a period of thrombus instability and spontaneous recanalization. Based on this and corroborating evidence, it was recognized that platelet inhibition would provide therapeutic value in ACS and this in turn lead to the early investigations and the consequent widespread use of aspirin and heparin in ACS (Theroux et al 1988).

3.3 PATHOPHYSIOLOGY AND CLINICAL ASPECTS OF CAD/IHD

3.3.1 Plaque formation

The accumulation of atherosclerotic plaques is no longer considered to be the simple result of cholesterol storage. Inflammation is increasingly implicated in plaque formation. At the cellular level, plaque accumulates in response to many signals that cause blood cells, such as monocytes, to adhere to the endothelium of the arterial lumen. Inflammatory responses to insults such as bacterial toxins, in addition to traditional risk factors, such as dyslipidemia, hypertension, hyperglycemia and obesity, can initiate monocyteadherence (Libby et al 2005). Once adhered to the endothelium, monocytes migrate into the vascular wall to the arterial intima, the muscular layer closest to the vessel lumen. At this point, they transform into macrophages and begin to ingest the
modified lipoprotein particles, which accumulate in the intima naturally and at an accelerated rate in people with hyperlipidemia. These lipid-filled macrophages are also known as foam cells, which are the hallmarks of atherosclerotic plaques. Foam cells typically come together to form a plaque within the intima. Many foam cells die by apoptosis, disintegrate with debris becoming membrane-bound, and then are eliminated by phagocytosis or by shedding. The original modified lipoproteins, macrophages, foam cells, and apoptotic debris, in addition to other important factors, such as collagen and von Willebrand factor, form the core of the plaque (Figure 3.3) (Libby et al 2005).

3.3.2 Plaque progression

Ultrasound studies have shown that atherosclerotic plaques are widely distributed in the coronary arteries and that these plaques begin to form early in life (Schoenhagen et al 2000, Tuzcu et al 2001). Therefore, atherosclerotic plaques only become clinically evident when they gain enough bulk to obstruct coronary circulation, often resulting in stable angina, or they become physically disrupted and form an acute clot at the site, resulting in either UA or AMI (Figure 3.4) (Libby 2002). Studies using serial observations by angiography have suggested that plaque progression is not a linear process and more likely occurs as the result of physical disruption of plaques.

Patients presenting with ACS have more than one disrupted plaque that becomes symptomatic through several mechanisms (Goldstein et al 2000). First, erosion of the epithelial monolayer, separating the intima from the vessel blood flow, which produces a thrombus by exposing collagen and von Willebrand factor—factors that promote platelet aggregation (one of the first steps in thrombus formation) (Faggiotto et al 1984). Endothelial monolayer erosion can be initiated by cell death or subendothelial basement membrane (a supportive layer that exists in between the endothelium and the intima) degradation. Inflammatory activation of T cells subjects the endothelial cells to attack in addition to local signaling that may increase apoptosis (Rajavashisth et al 1999). Secondly, plaque growth also results from intraplaque hemorrhages. Inflammatory cells within the plaque promote angiogenesis (the creation of new blood vessels that will deliver nutrients to the plaque) by secreting mediators (Ramos et al 1998). These small, fragile new vessels are prone to rupture. Thrombin production upon rupture stimulates the release of platelet-
derived growth factor and transforming growth factor beta, which are potent stimulants for smooth muscle growth, further increasing plaque bulk (de Boer et al 1999). A third mechanism of plaque growth occurs when a plaque’s fibrous cap tears, permitting contact between the plaque core and circulating coagulation factors in the blood. Inflammatory mediators, such as interferon-gamma, inhibit new collagen production necessary to maintain integrity and weakening of cap (Libby 2002). In addition to the decreased collagen production, existing collagen is usually weakened because collagenases are overexpressed in plaque tissue (Herman et al 2001). These mechanisms leave the fibrous cap of many plaques vulnerable to physical insult. If this vulnerability results in a microtear, a small subclinical thrombus may be formed, reabsorbed into the plaque, and then covered by additional fibrous tissue that is stimulated to grow by the release of platelet-derived growth factor and transforming growth factor beta. This process results in a bulky, fibrous plaque instead of a fatty plaque (Libby 2002). If the tear exposes a substantial amount of the plaque’s prothrombotic core, a large, fatal acute thrombus may result.

![Figure 3.3: Inflammation-Mediated Arterial Plaque Formation (Libby et al 2005): Determinants of thrombosis in coronary atherosclerotic plaques. Formation, extent, and duration of coronary thrombi produced by mechanisms such as those outlined in the figure depend on both solid-state factors in plaque itself and fluid-phase determinants in blood.](image-url)
3.3.3 Thrombus formation

Disrupted plaques allow contact between the blood and collagen, which activates platelets. The tissue growth factors produced by macrophages and smooth muscle cells also initiate coagulation (Thom et al 2006). Platelet activation results in the transformation of the Glycoprotein IIb/IIIa receptors on the platelets. These receptors are vital to thrombus formation because they are the sites where fibrinogen connects, enabling a “mesh” or “aggregation” of platelets to grow, and initiating thrombus formation (Rajagopal et al 2004). These mechanisms work in conjunction to produce the interlinked, aggregated platelets that are the hallmarks of the coronary thrombus. Clot formation is augmented in the presence of factors that inhibit natural fibrinolytic action. Plasminogen-activating inhibitor-1 levels are increased in patients with conditions that predispose them to CAD, such as diabetes and hypertension (Vaughan 2003). This fibrinolytic inhibitor weakens the body’s natural defense against clot formation and increases the potential for thrombi to form larger, more damaging occlusions.
3.3.4 Pathology

When plaque disruption occurs, a sufficient quantity of thrombogenic substances is exposed, and the coronary artery lumen becomes obstructed by a combination of platelet aggregates, fibrin, and red blood cells. An adequate collateral network that prevents necrosis from occurring can result in clinically silent episodes of coronary occlusion. Disruption of plaques is considered to be the common pathophysiological substrate of the ACS (Boersma et al. 2003). Completely occlusive thrombi lead to a large zone of necrosis involving the full or nearly full thickness of the ventricular wall in the myocardial bed subtended by the affected coronary artery and typically produce ST elevation (STEMI) on the ECG. The infarction process alters the sequence of depolarization ultimately reflected as changes in the surface of QRS (Phibbs et al. 1999). Patients present with ischemic discomfort with or without ST-segment elevation on the ECG. The majority of patients (75%) with STEMI ultimately develop a Q wave acute myocardial infarction (QwMI) in the leads overlying the infarct zone, whereas a minority (25%) develops non Q wave MI (NQMI). Patients who present without STEMI are either experiencing UA or a non NSTEMI. The distinction between these two diagnoses is ultimately made based on the presence or absence of a cardiac biomarker detected in the blood. Most patients with STEMI do not evolve a Q wave on the 12-lead ECG and are subsequently referred to as having sustained an NWMI; only a minority of NSTEMI patients develops a Q wave MI and is later diagnosed as Q wave MI. The spectrum of clinical conditions ranging from unstable angina to non-Q wave MI constitutes the ACS (Figure 3.5) (Antman et al. 2005).

**Figure 3.5:** Clinical presentation of ACS (Antman et al. 2005)
3.4 CURRENT TRENDS IN THE MANAGEMENT OF IHD

- Preventive management of IHD: National Cholesterol Education Program's (NCEP's) has established the guidelines for cholesterol testing and management on detection, evaluation, and treatment of high blood cholesterol in adults (Adult Treatment Panel III, or ATP III). It focuses on the role of the clinical approach for prevention of CAD (NCEP, ATP III, 2002).

- Therapeutic management of IHD: ACC/AHA has established the clinical guidelines for the management of the AMI/STEMI which focuses on the numerous advances in the diagnosis and management of patients with STEMI since 1999 (Antman et al 2004). ACC/AHA has also established the clinical guidelines for the management of the UA (NSTEMI) to address the diagnosis and management of patients with UA and the closely related condition of NSTEMI. The optimal management has the twin goals of the immediate relief of ischemia and the prevention of serious adverse outcomes with an approach of anti-ischemic and antithrombotic therapies (Anderson et al 2007). Figure 3.6 depicted preventive as well as therapeutic management of IHD in context of physiopathology, phase of disease, and intensity of risk (depicted by yellow to red gradient from right to left). Preventive measures are applied to entire population. Higher-risk individuals and those with documented disease often deserve drug therapy as well. Antianginal therapy is added when disease becomes symptomatic, and full antithrombotic therapy is added in ACS (Antman et al 2004).

Figure 3.6: Management of IHD (Antman et al 2004):

![Management of IHD Diagram](image)

*In ATP III, CHD is defined as symptomatic IHD, including MI, stable angina or UA, demonstrated myocardial ischemia by non invasive testing and history of coronary artery procedure*
Preventive Management of IHD

3.4.1 Diagnostic Modalities in Hyperlipidemic Patients

Cholesterol is a fat like substance (lipid) that is present in cell membrane and is a precursor of bile acids and steroid hormones.

Table 3.2: ATP III Classification of TC, LDL, HDL AND TG (NCEP ATP III, 2002)

<table>
<thead>
<tr>
<th>Total Cholesterol (mg/dL)</th>
<th>LDL Cholesterol (mg/dL)</th>
<th>HDL Cholesterol (mg/dL)</th>
<th>TG (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;200</td>
<td>&lt;100</td>
<td>&lt;40 (&lt;50 for women)</td>
<td>&lt;150</td>
</tr>
<tr>
<td>200-239</td>
<td>100-129</td>
<td>≥60</td>
<td>150-199</td>
</tr>
<tr>
<td>≥240</td>
<td>130-159</td>
<td>Borderline High</td>
<td>200-499</td>
</tr>
<tr>
<td></td>
<td>160-189</td>
<td>High</td>
<td>≥500</td>
</tr>
<tr>
<td></td>
<td>≥190</td>
<td>Very High</td>
<td></td>
</tr>
</tbody>
</table>

3.4.1.1 LDL cholesterol:

LDL cholesterol typically makes up 60–70 percent of the total serum cholesterol. It contains a single apolipoprotein, namely Apo B-100 (Apo B). LDL is the major atherogenic lipoprotein and has been identified by NCEP as the primary target of cholesterol-lowering therapy. The role of LDL in atherogenesis is confirmed by genetic disorders in which serum LDL cholesterol is markedly increased in the absence of other CHD risk factors (NCEP ATP III, 2002).

a. Serum LDL cholesterol as a major cause of CHD:

Elevated LDL cholesterol plays a role in the development of the mature coronary plaque; this is the substrate for the unstable plaque. LDL cholesterol lowering stabilizes plaques and reduces the likelihood of ACS. Clinical intervention with LDL lowering therapy in patients with advanced coronary atherosclerosis (short-term risk reduction) thus aims to stabilize plaques and to prevent ACS (Brown et al 1995, Brown et al 2000). In contrast, LDL lowering earlier in life slows atherosclerotic plaque development, the foundation of the unstable plaque. This fact provides a rationale for long-term lowering of LDL cholesterol.

b. Serum LDL cholesterol as a primary target of therapy:
The initial encouraging findings of earlier trials have recently been reinforced by the robust findings of a large number of studies, especially those using HMG CoA reductase inhibitors (statins). Clinical outcomes in terms of CHD incidence and CHD mortality are summarized in Table 3.3 for pre-statin and statin trials in which LDL-cholesterol reduction was the major lipid response (Gordon 2000). Statin therapy reduced risk for CHD, analysis from two combined secondary prevention trials (CARE and LIPID) (Sacks et al 2000, Rubins et al 1999).

### Table 3.3: CHD Outcomes in Clinical Trials of LDL-Cholesterol-Lowering Therapy†

*Gordon 2000*

<table>
<thead>
<tr>
<th>Intervention</th>
<th>No. trials</th>
<th>No. treated</th>
<th>Person-years</th>
<th>Mean cholesterol reduction (%)</th>
<th>CHD incidence (%) change</th>
<th>CHD Mortality (%) change</th>
</tr>
</thead>
<tbody>
<tr>
<td>Surgery</td>
<td>1</td>
<td>421</td>
<td>4084</td>
<td>22</td>
<td>-43</td>
<td>-30</td>
</tr>
<tr>
<td>Sequestrants</td>
<td>3</td>
<td>1992</td>
<td>14491</td>
<td>9</td>
<td>-21</td>
<td>-32</td>
</tr>
<tr>
<td>Diet</td>
<td>6</td>
<td>1200</td>
<td>6356</td>
<td>11</td>
<td>-24</td>
<td>-21</td>
</tr>
<tr>
<td>Statins</td>
<td>12</td>
<td>17405</td>
<td>89123</td>
<td>20</td>
<td>-30</td>
<td>-29</td>
</tr>
</tbody>
</table>

† Not included among these clinical trials are those employing fibrates, nicotinic acid, and hormones. The major actions of fibrates and nicotinic acid are on triglyceride and HDL, whereas hormone trials have effects beyond serum lipids.

#### 3.4.1.2 Triglycerides (TG):

Persons with elevated triglycerides are at increased risk for CHD. The most likely candidates for atherogenic TG are remnant lipoproteins which include small very low density lipoproteins (VLDL) and intermediate density lipoproteins (IDL). VLDL cholesterol, as a marker for remnant lipoproteins, is a potential target of cholesterol-lowering therapy. Elevated TG represents one factor within a set of risk-factor targets in persons who are overweight, obese, sedentary, or cigarette smokers. Life-habit changes—weight control, exercise, and smoking cessation—will favorably modify multiple risk factors including elevated TG (National Institutes of Health 1998). Thus, elevated serum TG is a potential target for therapeutic lifestyle changes.

#### 3.4.1.3 Non HDL Cholesterol i.e. VLDL and LDL:

VLDL cholesterol is highly correlated with atherogenic remnant lipoproteins; it can reasonably be combined with LDL cholesterol to enhance risk prediction when serum TG is high. The sum of VLDL+LDL cholesterol is called non-HDL cholesterol. Non-HDL cholesterol was chosen as a preferred secondary target of therapy over total apo B
for three other reasons: (a) standardized measures of total Apo B are not widely available in clinical practice; (b) measures of total Apo B have not been shown in a large number of prospective studies to carry greater predictive power than non-HDL cholesterol in persons with elevated TG; and (c) measurement of total Apo B will constitute an added expense beyond the usual lipoprotein profile.

3.4.1.4 High density Lipoproteins (HDL):

HDL cholesterol normally makes up 20–30 percent of the total serum cholesterol. The major apolipoproteins of HDL are Apo A-I and Apo A-II. Population studies show a continuous rise in risk for CHD as HDL-cholesterol levels decline. Higher risk for CHD at lower HDL levels is multifactorial in causation. Although the inverse relationship between HDL cholesterol and CHD shows no inflection points, any reduction in HDL cholesterol from population means is accompanied by increased risk for CHD. Clinical trials provide suggestive evidence that raising HDL-cholesterol levels will reduce risk for CHD. However, it remains uncertain whether raising HDL-cholesterol levels per se, independent of other changes in lipid and/or non lipid risk factors will reduce risk for CHD. A specific HDL-cholesterol goal level to reach with HDL-raising therapy is not identified. However, non drug and drug therapies that raise HDL-cholesterol levels and are part of management of other lipid and non lipid risk factors should be encouraged.

3.4.2 Treatment Strategies in Hyperlipidemic Patients

NCEP guideline focuses on low-density lipoprotein (LDL) as the primary target of cholesterol-lowering therapy. The following is an abridged summary of some of the recommendations from this clinical practice guideline. Type A, evidence from major randomized controlled clinical trials (RCTs); Type B, Smaller RCTs and meta-analyses of other clinical trials; Type C, Observational and metabolic studies and Type D, Clinical experience.

The major classes of drugs for consideration are:

1. HMG CoA reductase inhibitors (statins)—lovastatin, pravastatin, simvastatin, fluvastatin, atorvastatin
2. Bile acid sequestrants—cholestyramine, colestipol, colesevelam
3. Nicotinic acid—crystalline, timed-release preparations, Niaspan®
4. Fibric acid derivatives (fibrates)—gemfibrozil, fenofibrate, clofibrate

Hormones are also discussed below:

5. Estrogen replacement

6. Selective estrogen receptor modulators

3.4.2.1 HMG CoA Reductase Inhibitors:

After diet and life-style change, statins [3-hydroxy methyl glutaryl coenzyme A (HMG-CoA) reductase inhibitors], introduced in the late 1980s, are widely used as first line agents for lipid lowering in individuals with or are at 'risk' of CVD including those with familial hypercholesterolaemia. Since their initial introductions, they have improved the prospects of effectively managing dyslipidemia and reducing CVD. Statins inhibits the rate limiting enzyme in cholesterol reduction and, hence, up-regulate hepatic LDL receptors increasing the removal of Apo-B containing lipoproteins from plasma.

To date, atorvastatin, pravastatin, lovastatin, simvastatin, fluvastatin and cerivastatin have been used around the world. Atorvastatin, fluvastatin, lovastatin, pravastatin and simvastatin are the currently available agents. However, cerivastatin was voluntarily withdrawn from the market by the company following reports of fatal rhabdomyolysis to the FDA on August 9, 2001. The effectiveness of statins has been demonstrated in many clinical trials (Table 3.4) (Klotz 2003, Brousseau 2003, Athyros et al 2002). Depending upon the specific statin and the dose administered, reductions in LDL cholesterol of 18-55 percent are observed (Stein et al 1998, Jones et al 1998). The reductions in LDL-C are dose-dependent and log-linear, so that with each doubling of the dose of statin, LDL-C levels fall by about 6 percent. HDL cholesterol generally rises by 5-10 percent, but greater increases usually occur in persons with low HDL and elevated TG (Lipid study 1998, Downs et al 1998, Scandinavian Simvastatin Survival Study Group 1994, Sacks et al 1996, LaRosa et al 1999, Jones et al 1998, Shepherd 1995, Stein 1998). The reductions in TG with the statins generally range from 7-30 percent (Lipid study 1998, Downs et al 1998, Shepherd et al 1995, Scandinavian Simvastatin Survival Study Group 1994, Sacks et al 1996, LaRosa et al 1999, Jones et al 1998, Stein 1998). In individuals with TG levels of <150 mg/dL, TG responses are inconsistent. But when TG levels are >200 mg/dL, TG fall in direct proportion to LDL-C lowering (Stein et al 1998). With very high TG levels, however, LDL-C lowering is less than that observed with low
TG levels. The statins reduce the concentration of all LDL particles, including the small LDL particles, as well as IDL and VLDL remnants (Vega et al 1990, Broyles et al 1995). The combined lowering of LDL and TGRLP with the statins makes them efficacious for reducing non-HDL cholesterol in persons with atherogenic dyslipidemia or combined hyperlipidemias. Following PROVE-IT (Cannon et al 2004) and REVERSAL (Nissen et al 2004), the National Cholesterol Education Program, Adult Treatment Panel III guidelines (NCEP ATP III), advices further lowering of LDL-C levels from the previous levels of 2.6-1.7 mmol/l in order to achieve an enhanced decrease of cardiovascular risk (NCEP ATP III guidelines). The increasing need for more aggressive lipid lowering has fuelled a need for more efficacious statins. Available worldwide are atorvastatin, fluvastatin, lovastatin, pravastatin, rosuvastatin and simvastatin, providing a choice of agents for the treatment of patients to evidence-based targets.

Pitavastatin is a new highly effective statin and is available for use in Japan. It is reported to be more effective in LDL-C reduction than pravastatin, simvastatin, or atorvastatin (Flores 2002, Saito et al 2002, Iglesias et al 2003), with a longer duration of action and similar or reduced potential for drug interaction. In a study on 240 patients with primary hypercholesterolemia, 2mg pitavastatin vs. 10 mg pravastatin, at 12 weeks, pitavastatin showed significant reduction in total and LDL-C by 28% and 38%, respectively, compared to 14% and 18% respectively in the pravastatin. Pitavastatin at 1, 2 and 4 mg doses appear to be as efficacious as 10, 20 and 40 mg atorvastatin.

In a short-term double blind three group, parallel comparison in primary hypercholesterolemia compared the efficacy of pitavastatin at the doses of 1, 2 and 4 mg over 12 weeks followed a 4-week placebo run in phase and followed by 4-week placebo run-out found to be dose related reduction in TC [(23, 29 and 33%) baseline mean 7.5 mmol/l] and LDL-C [(34, 42 and 47% baseline mean 5.35 mmol/l], with TG reduced by 7.7, 13.6 and 14.7% (baseline mean 1.92 mmol/l). The rise in HDL cholesterol was 6.8, 5.9 and 7.9% (baseline mean 1.34 mmol/l). The significant change in HDL levels does not seem to be dose dependent, and was similar to the effect observed with most other statins (Saito et al 2002). In another short-term study, in individuals with heterozygous familial hypercholesterolemia, pitavastatin at 2mg/day for 8 weeks significantly reduced total and LDL-C by 30 and 42% respectively (baseline levels total cholesterol 8.8±1.38
mmol/l, LDL-C 6.81±1.52 mmol/l). On further increased to 4mg/day for another 8 weeks found to be further significant reductions on TC and LDL levels by a 6% with TC achieved 37 and 48%. The drop in LDL-C levels were comparable to those produced by atorvastatin 20 and 40 mg daily, with the 6% additional fall in LDL-C levels with the doubling of statin doses (McKenney et al 2003). Mean LDL-C levels achieved (3.55±0.85 mmol/l) were close to the target levels set by the NCEP ATP III guidelines for individuals with two or more risk factors, 3.4 mmol/l. TG levels were reduced at both doses by 15 and 23% significant at the higher dose. Significant reductions in Apo B, CII, CIII and E were noted (41, 27, 19 and 37% from baseline, respectively) while levels of Apo A1 and A11 rose by 9.5 and 5.8% (Kajinami et al 2000, Kajinami et al 2000). After run-in placebo, the long term effect of 2 mg of pitavastatin was investigated in 25 individuals with heterozygous familial hypercholesterolemia for 8 weeks and then increased to 4 mg for a total of 104 weeks reported that the total mean cholesterol was reduced by 31% at the end of the initial phase and 37% at 12 weeks with the dose related changes being maintained to 2 years. LDL levels for the same time spans were reduced by 41% and 49% (Noji et al 2002). In another study on 308 patients with doses of 2, 4 and 6 mg for 44 weeks following an 8 week run-in on 2 mg od, mean LDL levels dropped from 5.22 to 3.13 mol/l by the end of 52 weeks. TG levels fell by 25-31% (baseline mean 2.9 mmol/l) and HDL-C levels rose by 11% (baseline mean 1.45 mmol/l). Adverse events were minimal. 4.8% of the subjects had raised CPK levels (1.5-5×ULN3), 2.9% had raised GGT and AST and only 2.6% were noted to have raised ALT levels (Kajinami et al 2000). Thus the safety profile was found to be similar with the currently available statins. The effect of pitavastatin in metabolic disorders associated with dyslipidemias was investigated in 13 men and 20 women with type 2 diabetes by giving 2 mg of pitavastatin for a total of 8 weeks. TC and LDL were reduced by 25 and 36%, respectively (baseline mean 6.48 and 4.36 mmol/l). TG levels were dropped by 29% (baseline mean 2.31 mmol/l). Furthermore, in these patients there was a reduction in atherogenic small LDL particles (10%) and remnant-like particle cholesterol (RLP-C) (31%) and a small increase in LDL particle size (3%). Both small dense LDL particles and RLP-C have been identified as independent risk factors for CHD (Sone et al 2002).
Table 3.4: Comparison of Low Density Lipoprotein Cholesterol and Coronary Event Reductions in Large Statin Trials (Klotz 2003, Brousseau 2003, Athyros et al 2002)

<table>
<thead>
<tr>
<th>Study</th>
<th>Statin</th>
<th>No. of subjects involved</th>
<th>Baseline LDL (mmol/L)</th>
<th>Reduction in LDL (%)</th>
<th>Reduction in coronary events (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>4S</td>
<td>Simvastatin</td>
<td>4444</td>
<td>4.86</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>CARE</td>
<td>Pravastatin</td>
<td>4159</td>
<td>3.59</td>
<td>25</td>
<td>24</td>
</tr>
<tr>
<td>LIPID</td>
<td>Pravastatin</td>
<td>9014</td>
<td>3.88</td>
<td>32</td>
<td>24</td>
</tr>
<tr>
<td>WOSCOPS</td>
<td>Pravastatin</td>
<td>6595</td>
<td>4.97</td>
<td>26</td>
<td>31</td>
</tr>
<tr>
<td>AFCAPS</td>
<td>Lovastatin</td>
<td>6605</td>
<td>3.88</td>
<td>25</td>
<td>37</td>
</tr>
<tr>
<td>HPS</td>
<td>Simvastatin</td>
<td>20,536</td>
<td>3.41</td>
<td>30</td>
<td>26</td>
</tr>
<tr>
<td>ASCOT-LLA</td>
<td>Atorvastatin</td>
<td>10,305</td>
<td>3.4</td>
<td>29</td>
<td>36</td>
</tr>
<tr>
<td>GREACE</td>
<td>Atorvastatin</td>
<td>1600</td>
<td>&gt;2.6</td>
<td>46</td>
<td>47</td>
</tr>
<tr>
<td>CARDs</td>
<td>Atorvastatin</td>
<td>2838</td>
<td>3.04</td>
<td>31</td>
<td>36</td>
</tr>
</tbody>
</table>

3.4.2.2 Bile Acid Sequestrants:

The bile acid sequestrants are the second most effective class of drugs for lowering LDL-C levels. They are particularly useful in combination with statins to achieve major reductions in LDL-C levels. They can either be added to a statin when maximal doses of statin have not achieved target goals, or they can be added to lower doses of statin if there are concerns about the tolerability and side effects of higher doses. The sequestrants bind bile acids in the intestine through anion exchange; this binding reduces the entero hepatic recirculation of bile acids, which releases feedback regulation on conversion of cholesterol to bile acids in the liver. The resulting decrease in hepatocyte cholesterol content enhances LDL-receptor expression, which in turn lowers serum LDL-C concentrations (Rudling et al 1990). In some persons, sequestrants increase hepatic VLDL production (Beil et al 1982) thereby raising serum TG levels (Knopp 1999) cholestyramine (8–16 g/day) or colestipol (10–20g/day) usually produce 10–20% reductions in LDL-C when administered as monotherapy, and colesevelam (2.6–3.8g/day) lowers LDL-C by 12–18%. Sequestrants add to LDL lowering when combined with other cholesterol-lowering drugs. Whereas doubling the dose of a statin produces only a 6% further reduction in LDL-C, adding a moderate dose of a sequestrant to a statin can further lower LDL-C by 12–16% (Knapp et al 2001, Davidson et al 2001, Denke et al 1995) Thus, sequestrants are useful in combined drug therapy with statins. For purposes of drug safety, bile acid sequestrants can be considered as monotherapy in younger...
persons, women considering pregnancy, and when only modest LDL lowering is needed. Bile acid sequestrants are not contradicted in patients with type 2 diabetes (Garg et al 1994). Sequestrants remain unabsorbed in their passage through the gastrointestinal tract and lack systemic toxicity. Their disadvantages are two-fold. Because of their bulk, they lack convenience of administration; they also cause various gastrointestinal symptoms, notably constipation.

3.4.2.3 Nicotinic acid:

It lowers serum TC, LDL-C and TG levels and also raises HDL-C levels. The LDL-C lowering effects of nicotinic acid are usually modest and can be quite variable. Reductions in LDL of 5–23% have been noted with doses of 1.5–4.5g of crystalline nicotinic acid and 10–20% at 2.0–3.0g of Niaspan® (Guyton et al 2000, Capuzzi et al 1998, Goldberg et al 2000, Morgan et al 1996). Nicotinic acid should be considered if additional LDL-C lowering is required after statin administration, especially in persons who do not tolerate sequestrants or who prefer to take medication in tablet form. Nicotinic acid is also considered if, in addition to LDL-C lowering, increases in HDL-C and decreases in TG and Lp(a) are needed. Decreased rates of atherosclerotic progression were also observed in three quantitative angiographic trials: FATS (Brown et al 1990) HATS (Brown et al 2001) and CLAS (Blankenhorn et al 1987). In all of these trials, nicotinic acid was combined with other LDL-lowering drugs and effects were compared to placebo. Extended-release nicotinic acid (Niaspan®), which is administered as a single bedtime dose, has been shown to reduce LDL-C by 15% at 2 g/day. (Guyton et al 2000, Guyton et al 1998, Knopp et al 1998, Capuzzi et al 1998). Nicotinic acid is typically not used primarily to lower LDL levels. Instead, it is generally used in combination with other drugs, especially the statins (Guyton et al 1998).

3.4.2.4 Fibric acid derivatives:

The fibrates usually do not significantly enhance LDL-C lowering when added to a statin. However, if a patient is not at LDL target level and has not tolerated a bile acid sequestrant or nicotinic acid, addition of fenofibrate may enhance LDL lowering in some patients; (Kiortisis et al 2000) it may also be useful if the patient has concomitant atherogenic dyslipidemia (Ellen et al 1998). Gemfibrozil (1.2 g/d), clofibrate (2g/d)
decreases TG 20-50% and increases HDL 10-15%. Fenofibrate is a new fibric acid derivative. Fibrates may protect against coronary atherosclerosis not only by reducing LDL levels but also by atherogenic phenotype. However, this beneficial effect on cardiovascular outcomes has not been observed in all large fibrate trials (Coronary Drug Project Research Group 1975, Bezafibrate Infarction Prevention (BIP) Study Group 2000). Nonetheless, to date no clinical trials have been published that compare statins vs. statins + fibrates on CHD outcomes.

3.4.2.5 n-3 (omega) fatty acids:

n-3 fatty acids (linolenic acid, DHA, and EPA) have two potential uses. In higher doses, DHA and EPA lower serum TG by reducing hepatic secretion of TG rich lipoproteins. They represent alternatives to fibrates or nicotinic acid for treatment of hypertriglyceridemia, particularly chylomicronemia. They are available in capsules of fish oil, and doses of 3–12 g/day have been used depending on tolerance and severity of hypertriglyceridemia. Recent clinical trials also suggest that relatively high intakes of n-3 fatty acids (1–2 g/day) in the form of fish, fish oils, or high-linolenic acid oils will reduce risk for major coronary events in persons with established CHD (Albert et al 1998, Daviglus et al 1997, Dolecek et al 1991). Although this usage falls outside the realm of “cholesterol management,” the ATP III panel recognizes that n-3 fatty acids can be a therapeutic option in secondary prevention. The n-3 fatty acids are recommended only as an option because the strength of the clinical trial evidence is moderate at present. In the view of the ATP III panel, more definitive clinical trials are required before relatively high intakes of n-3 fatty acids (1–2 g/day) can be strongly recommended for either primary or secondary prevention.

3.4.2.6 Hormone replacement therapy (HRT):

Risk for CHD is increased in postmenopausal women whether the menopause is natural, surgical, or premature (Rosenberg et al 1981, Colditz et al 1987, Kannel et al 1976). Loss of estrogen has been proposed as a cause for increased risk. This putative mechanism was strengthened by results of numerous case-control and epidemiological studies which suggested that either estrogen alone, or in combination with progestin, reduces risk for CHD in primary and secondary prevention. However, benefit of estrogen
replacement was not confirmed in a secondary prevention trial, the Heart and Estrogen/progestin Replacement Study (HERS) (Hulley et al 1998). A subsequent angiographic study also revealed no apparent benefit from HRT (Herrington et al 2000).

**Therapeutic Management of IHD**

3.4.3 Diagnostic Modalities in IHD patients presenting with ACS

(UA/NSTEMI/STEMI):

The initial presentation and early management of ACS (UA, STEMI, and NSTEMI) frequently are similar. Differentiating ACS from non cardiac chest pain is the primary diagnostic challenge. The initial assessment requires a focused history (including risk factor analysis), a physical examination, an electrocardiogram (ECG) and frequently, serum cardiac marker determinations (Figure 3.6).

⇒ **MI**: (Revised Definition of MI, Alpert et al 2000)

<table>
<thead>
<tr>
<th>Criteria for acute, evolving, or recent MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Either one of the following criteria satisfies the diagnosis for an acute, evolving, or recent MI:</td>
</tr>
<tr>
<td>1. Typical rise and gradual fall (troponin) or more rapid rise and fall (CK-MB) of biochemical markers of myocardial necrosis with at least one of the following:</td>
</tr>
<tr>
<td>a. Ischemic symptoms</td>
</tr>
<tr>
<td>b. Development of pathologic Q waves on the ECG reading</td>
</tr>
<tr>
<td>c. ECG changes indicative of ischemia (ST-segment elevation or depression)</td>
</tr>
<tr>
<td>d. Coronary artery intervention (e.g., coronary angioplasty)</td>
</tr>
<tr>
<td>2. Pathological findings of an acute MI</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Criteria for established MI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Either of the following criteria satisfies the diagnosis for established MI:</td>
</tr>
<tr>
<td>1. Development of new pathological Q waves on serial ECG readings. The patient may or may not remember previous symptoms. Biochemical markers of myocardial necrosis may have normalized, depending on the length of time that has passed since the infarct developed.</td>
</tr>
<tr>
<td>2. Pathological findings of a healed or healing MI</td>
</tr>
</tbody>
</table>

**UA/NSTEMI**: Unstable angina/NSTEMI constitutes a clinical syndrome subset of the ACS that is usually, but not always, caused by atherosclerotic CAD and is associated with an increased risk of cardiac death and subsequent MI. In the spectrum of ACS, UA/NSTEMI is defined by electrocardiographic (ECG) ST-segment depression or prominent T-wave inversion and/or positive biomarkers of necrosis (e.g., troponin) in the...
absence of ST-segment elevation and in an appropriate clinical setting (chest discomfort or anginal equivalent).

**Figure 3.7: ACS Risk Stratification –Diagnostic/Therapeutic Pathway (Hamm et al 2001)**

3.4.3.1 Electrocardiogram (ECG) Interpretation

The ECG provides information that assists in stratifying the patient's risk of having ACS, establishing the diagnosis, and determining the treatment strategy. Accuracy is enhanced when the ECG is obtained in a patient with ongoing chest pain. The 12-lead ECG in the Emergency Department is at the center of the therapeutic decision pathway because of the strong evidence that STEMI identifies patients who benefit from reperfusion therapy (Menown et al 200). Mortality increases with the number of ECG leads showing ST elevation. Important predictors of mortality on the initial 12-lead ECG include left bundle-branch block (LBBB) and anterior location of infarction (Mauri et al 1989, Antman et al 1986). The diagnosis of MI is confirmed with serial cardiac biomarkers in more than 90% of patients who present with STEMI of ≥1 mm (0.1 mV) in at least 2 contiguous leads and such patients are considered candidates for acute reperfusion therapy. Patients who present with ST-segment depression are initially considered to have either UA or NSTEMI; the distinction between the 2 diagnoses is ultimately based on the detection of markers of myocardial necrosis in the blood. Inverted T-wave indicates UA/NSTEMI.
3.4.3.2 Treadmill Test (TMT)

In UA/NSTEMI choice of TMT is based on the resting ECG, ability to perform exercise, local expertise, and technologies available. It is useful in patients able to exercise in whom the ECG is free of baseline ST-segment abnormalities, bundle-branch block, LV hypertrophy, intravenous conduction defect, paced rhythm, pre-excitation, and digoxin effect (Class I).

3.4.3.3 Laboratory findings

Serum cardiac marker determinations play a vital role in the diagnosis of AMI. Serum markers such as aspartate transaminase, lactate dehydrogenase, and lactate dehydrogenase subforms no longer are used because they lack cardiac specificity and their delayed elevation precludes early diagnosis (Braunwald et al 2000). Cardiac biomarkers like troponin I, troponin T, creatinine phosphokinase (CK), CK myocardial band (CK-MB), myoglobin of necrosis leak from cardiomyocytes after the loss of membrane integrity and diffuse into the cardiac interstitium, then into the lymphatics and cardiac microvasculature eventually are detectable in the peripheral circulation. Features that favor their diagnostic performance are high concentrations in the myocardium and absence in nonmyocardial tissue, release into the blood within a convenient diagnostic time window and in proportion to the extent of myocardial injury, and quantification with reproducible, inexpensive, and rapid and easily applied assays (Zimetbaum et al 2003). The cardiac troponins possess many of these features and have gained wide acceptance as the biomarkers of choice in the evaluation of patients with ACS for diagnosis, risk stratification, and treatment selection. Elevated level of these markers is identification of ACS. A cardiac-specific troponin (Tn) is the preferred assay. Tn is a highly sensitive and specific marker for myocardial necrosis, and it is predictive of short- and intermediate-term mortality in patients presenting with UA (Figure 3.6) CK-MB by mass assay is a second-choice marker, which is not quite as sensitive or specific as Tn. While both Tn and CK-MB generally begin to elevate 2-4 hours after ACS, this rise may be delayed. Therefore, for patients presenting <6 hours after symptom onset with negative biomarkers, reassessment is performed at 8-12 hours (Class Ila). The superior sensitivity makes troponin the preferred marker for patients with UA/NSTEMI (Class I). C-reactive
protein (CRP) and other markers of inflammation are measured (Class IIb). In contrast, patients with STEMI are recognized on the basis of the 12-lead ECG, and in general, subsequent confirmation of MI can be ascertained by measurement of any of the available cardiac biomarkers.

3.4.3.4 Imaging modalities

- **Two dimensional echocardiography**

  It is the tool in evaluation of patients with ACS, by assessing global and regional left ventricular function in the absence and presence of ischemia, as well as in establishing LV hypertrophy and associated valve disease. In the setting of the acute coronary ischemia, inadequate perfusion of the myocardium leads to a reduction in wall motion and systolic thickening of the myocardium which can be detected by echocardiography (Cheatlin et al 2003). Doppler echocardiography allows assessment of blood flow in the cardiac chambers and across cardiac valves is used in conjunction with the two dimensional echocardiography. It is helpful in detecting and assessing the severity of mitral or tricuspid regurgitation after STEMI by indicating abnormal regional wall motion (Reimold et al 1998, Spodick et al 2003). Echocardiographic evaluation is recommended for the initial evaluation of the patients in selected cases (Class IIa indication) as well as for the estimation of infarct size post AMI (Class I). When the clinical history and ECG are unavailable or not reliable and an adequate echocardiographic study can be performed during an episode of chest pain, documentation of transient segmental wall motion abnormalities that normalize with treatment supports the diagnosis of UA. By the two dimensional echocardiography regional walls motion is assessed normal in UA/NSTEMI. In UA/NSTEMI echocardiogram evaluates the LV function in patients with definite ACS and are not scheduled for coronary angiography and left ventricular angiography (Class IIa) (Zipes et al 2005).

- **Other Imaging modalities**

  Various imaging techniques like Computed Tomography (CT), Magnetic resonance imaging (MRI), Nuclear Imaging using Technetium (Tc) sestamibi SPECT approach can be useful for initial evaluation of STEMI (Class III), assessing infarct size
(Class I), collateral flow and jeopardized myocardium; determining the effects of the infarct on ventricular function; and establishing prognosis of AMI patients. It is recommended to evaluate LV function in patients with definite ACS who are not scheduled for coronary angiography and left ventriculography. The practical applications of these techniques is however limited because of the need to transport the patients in the emergency condition. However, imaging modality is added in the patients with resting ST segment depression (greater than or equal to 0.10mV), LV hypertrophy, bundle branch block, intraventricular conduction defect, preexcitation, or digoxin who are able to exercise. It also adds sensitivity for the patients who are undergoing low level exercise test (Zipes et al 2005).

3.4.3.5 Catheter Based Invasive Diagnostic Procedures

- **Coronary angiography**

  Angiography is an invasive test that may be performed on patients who have very incapacitating angina that does not respond to medical therapy and for planning surgical procedures. A narrow tube is inserted into an artery, usually in the leg arm, and then threaded up through the body to the coronary arteries. A dye is injected into the tube and an X-ray records the flow of dye through the arteries. This process provides a map of the coronary circulation, revealing any blocked areas. Major complications include stroke, heart attacks and kidney damage, but these risks are very low (about 0.1%) if the procedure is done in a center that performs at least 300 of these operations every year. Allergic reactions can also occur. Many experts believe this procedure is overused. The procedure is expensive, and 10-30% of patients who have this procedure have normal results. Coronary arteriography/angiography remains the "gold standard" for identifying the presence or absence of arterial narrowing in CAD and provides the most reliable anatomical information for determining the appropriateness of medical therapy, PCI or CABG surgery in patients with ischemic CAD (Popma et al 2005). Diagnostic angiography is recommended in all AMI patients who are candidates for revascularization (Class I). Prompt angiography without non invasive risk stratification is recommended in all UA/NSTEMI candidates who are failure of stabilization with intensive medical treatment (Class I) (Zipes et al 2005).
- Intravascular Ultrasound (IVUS) Imaging

Intravascular ultrasound technique is an advanced adjunctive invasive imaging modality that can be performed at the time of coronary angiography and provides precise characterization of the vessel wall and extent of atherosclerosis.

3.4.4 Treatment Strategies in IHD patients presenting with ACS (AMI/STEMI):

The management & therapy goals in AMI/STEMI are the expedient restoration of normal coronary blood flow and the maximum salvage of functional myocardium. These goals can be met by a number of medical interventions and adjunctive therapies. ACC/AHA has established the clinical guidelines for the management of the AMI (STEMI) (Antman et al 2004). This guideline has been incorporated in the overall management of the patients. The following is an abridged summary of some of the recommendations from this clinical practice guideline. The customary ACC/AHA classifications are used. Class I refers to conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class II refers to conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. For Class IIa, the weight of evidence/opinion is in favor of usefulness/efficacy while Class IIb is less well established by evidence/opinion. Class III refers to conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.

3.4.4.1 Oxygen

Supplemental oxygen should be administered to patients with arterial oxygen desaturation (SaO2 less than 90%) (Class I). It may be administered to all patients with uncomplicated AMI during the first six hours (Class IIa).

3.4.4.2 Nitroglycerin

Nitroglycerin may be administered to relieve ischemic pain and it is clearly indicated as a vasodilator in patients with STEMI associated with LV failure (Class I). Nitrates in all form should be avoided in patients with initial blood pressure <90 mm Hg or ≥30 mm Hg below baseline, in patients with marked bradycardia or tachycardia (Come
et al. 1976), and in patients with known or suspected RV infarction. In view of their marginal treatment benefits, nitrates should be used if hypotension limits the administration of beta-blockers, which have more powerful salutary effects.

3.4.4.3 Analgesic

Morphine sulphate is the analgesic of choice for the management of pain associated with ST elevation AMI (Class I).

3.4.4.4 Aspirin

In a dose of ≥162 mg, aspirin produce a rapid clinical antithrombotic effect caused by immediate and near-total inhibition of thromboxane A2 production. Aspirin should be given promptly and certainly within the first 24 hrs of AMI, at a dose between 162 and 325 mg and continued indefinitely at daily dose of 75-62 mg (Class I).

3.4.4.5 Beta blockers

Oral beta blockers are recommended in all AMI patients irrespective of the reperfusion strategy employed (Class I). Intravenous beta blockers are recommended in patients with tachyarrhythmia and hypertension (Class IIa). Immediate beta blockers therapy appears to reduce the magnitude of infarction and incidences of associated complications in subjects not receiving fibrinolytic therapy, and the frequency of life-threatening ventricular tachyarrhythmia.

3.4.4.6 Reperfusion therapy

Evidence exists that expeditious restoration of flow in the obstructed infarct artery after the onset of symptoms in AMI patients is a key determinant of short- and long term outcomes regardless of whether reperfusion is accomplished by fibrinolysis or PCI (Boersama et al. 2003, De Luca et al. 2004) (Class I). Pharmacological reperfusion is multipronged approach consisting of fibrinolytic agent that digest fibrin, antithrombin prevents the formation of thrombin and inhibit the activity of thrombin that is formed an antiplatelet therapy. Mechanical reperfusion on other hand comprised of PCI and CABG. Several issues like from time of onset of symptom, risk of mortality, risk of bleeding and
time to require to transport to skill PCI laboratories needs to consider before selecting the type of reperfusion therapy.

3.4.4.7 Thrombolytic therapy

Restoration of coronary blood flow in MI can be accomplished pharmacologically with the use of a thrombolytics/fibrinolytic agent (GISSI investigators 1996, The TIMI study group 1989, Franzosi et al 1998). Thrombolytic therapy is indicated for the patient with the presentation compatible with MI and ST segment elevation or new onset of a bundle branch block who presents <12 hr of onset of symptom (Class I). The available thrombolytic agent shares the common properties of plasminogen activation, which accelerates natural process of fibrinolysis. Streptokinase, prototype of non fibrin selective agent is bacterially derived product, whereas fibrin specific agent includes altiplase (t-PA), which is genetically produced, retiplace, tenecteplase and lanoteplase are its deletion and substitution mutants increasing their fibrin specificity other agents are urokinase, anistreplase and staphylokinase. The GUSTO trial established that an accelerated alteplase/heparin regimen was superior to two streptokinase/heparin regimens (GUSTO investigators 1993). Reteplase has shown to produce slightly higher 60 and 90 min angiographic patency rates than accelerated alteplase, while adverse events rate were equal (GUSTO III investigators 1997). Presently available and commonly used agents in Indian population, is streptokinase due to unavailability/cost factor of other agents. The most critical variable in achieving successful fibrinolysis is time from onset of symptom to drug administration. Bleeding is most common and potentially serious complication associated with this agent (Dubois et al 2003). Fibrinolysis agent is contraindicated (Class I) in patient with neurological contraindications, intracranial hemorrhage, uncontrolled hypertension or ischemic stroke. Combination of half dose of fibrinolytic therapy with platelet GP IIb/IIIa inhibitors is also recommended in selected patients (Class IIa), however not in patients with age >75 yr (Class III).

3.4.4.8 Percutaneous Coronary Interventions (PCI)

Reperfusion of the infarct artery can also be achieved by a catheter based strategy. This approach has evolved from passage of a balloon catheter over a guidewire followed by introduction of coronary stents (Van de Werf et al 2002). When PCI is used in lieu of
fibrinolytic therapy, it is referred to as direct or primary PCI. When fibrinolysis has failed to reperfuse the infarct vessel, or a severe stenosis is present in the infarct vessel, a rescue PCI can be performed. A more conservative approach of elective PCI can be used to manage acute STEMI patients only when spontaneous or exercise-provoked ischemia occurs, whether or not they have received a previous course of fibrinolytic therapy. Different approach for angioplasty in AMI is given in Table 3.5 (Antman et al 2004).

Table 3.5: Different approaches for Angioplasty in AMI (Antman et al 2004)

<table>
<thead>
<tr>
<th>Primary (direct)</th>
<th>Emergency PCI/Stent without prior thrombolytic therapy</th>
</tr>
</thead>
<tbody>
<tr>
<td>Facilitated</td>
<td>Reduce dose thrombolytic therapy with or without GP IIb/IIIa agents prior to emergency PCI</td>
</tr>
<tr>
<td>Rescue</td>
<td>Emergency PCI for failed thrombolysis</td>
</tr>
<tr>
<td>Immediate</td>
<td>PCI immediately after successful thrombolysis</td>
</tr>
<tr>
<td>Delayed</td>
<td>PCI 1-7 days after thrombolysis</td>
</tr>
</tbody>
</table>

3.4.4.8.1 Primary PCI:

Primary PCI refers to angioplasty that is performed as a primary reperfusion strategy without prior thrombolytic therapy. The goal is to achieve reperfusion and salvage of myocardium. Primary PCI achieves TIMI-3 flow in over 90% of AMI patients, which is an important predictor of mortality and partially reflects the survival advantage associated with primary PCI (Grines et al 1993, Zijlstra et al 2000). Current ACC/AHA guidelines favor primary PCI as the preferred reperfusion strategy in AMI patients if it can be done within 12 hours of onset of symptoms, performed in timely fashion (PCI balloon inflation within 90 minutes of presentation), by skilled operators and supported by experienced personnel in an appropriate laboratory environment (Class I); in patients with cardiogenic shock or heart failure, contraindications to thrombolysis, increase risk of bleeding and intracranial hemorrhage, and symptom duration >3 hours (Class I). It is also recommended within 12-24 hours, if ischemia symptoms persist, or patients develop congestive heart failure (CHF) or hemodynamic instability (Class Ila). Primary PCI has been compared with fibrinolytic therapy in 22 randomized clinical trials (Antman et al 2004). An additional trial, SHOCK (Should we emergently revascularize occluded coronaries for cardiogenic shock?) (Hochman et al 1999) compared medical stabilization with immediate revascularization for cardiogenic shock, was included along with the above 22 trials and overview of primary PCI versus fibrinolysis. These investigations
demonstrated that PCI-treated patients experienced lower short term mortality rates, less nonfatal reinfarction, and less hemorrhagic stroke than that treated with fibrinolysis but have an increased risk for bleeding (Keeley et al 2003). The C-PORT trial evaluated thrombolysis with primary PCI in 454 AMI patients revealing superior results with primary PCI (Aversano et al 2002). AIR PAMI trial investigated emergent transfer of PCI versus onsite thrombolysis in high-risks STEMI patients. Inspite of early termination of the trial, primary PCI group showed non-significant reductions in the events (Grines et al 2002). DANAMI and PRAGUE-2 trials have reported comparable benefits with primary PCI & thrombolytic therapy (Andersen et al 2003, Widimsky et al 2003). Time from symptom onset to reperfusion is an important predictor of patient outcome. Two studies (Berger et al 1999, Cannon et al 2000) have reported increasing mortality rates with increasing door to balloon time. Other studies have shown smaller infarct size, better LV functions and fewer complications when reperfusion occurs before PCI (Clement et al 1993, Brodie et al 2000, Stone et al 2001). An analysis of the randomized controlled trials comparing fibrinolysis within a fibrin-specific agent versus primary PCI suggests that the mortality benefits with PCI exists when treatment is delayed by no more than 60 minutes. Mortality increases significantly with each 15 minutes delay in the time between arrival and restoration of TIMI-3 flow (door to TIMI-3 flow time), which further underscores the important of timely reperfusion in patients who undergo PCI (Juliard et al 2003). If the expected door to balloon time exceeds the expected door to needle time by more than 60 minutes, fibrinolytic agents with fibrin specific agent should be considered unless it is contraindicated (Antman et al 2004). Randomized controlled trials evaluating the outcome of PCI for patients who present with STEMI but who are ineligible for fibrinolytic therapy have not been performed. Nevertheless, these patients are at increased risk for mortality (Cragg et al 1991), and there is a general consensus that PCI is an appropriate means of achieving a reperfusion in those who cannot receive fibrinolytics because of increase risk of bleeding (Grzybowski et al 2003).

Advantage of primary Angioplasty Strategy
1. Superior Restoration of blood flow
Restoration of the epicardial blood flow (TIMI-III flow) and achievement of tissue myocardial perfusion (TMP grade 3) is the goal of reperfusion strategy in AMI. The GUSTO-I trial confirmed the critical link between early establishment of TIMI-3 flow and myocardial salvage and subsequent survival (GUSTO Angiographic investigators 1993). A relationship between TIMI-3 flow and survival has also been verified for primary angioplasty (Berger et al 1999). Catheter-based reperfusion techniques attain TIMI-3 flow in 93-98% of patients (Griens et al 1999, Stones et al 2002). Despite restoration of epicardial flow, many patients exhibit suboptimal tissue level perfusion (TMP grade <3). The impaired perfusion is associated with adverse left ventricular remodelling, heart failure, and reduced survival (Roe et al 2001, Rezkalla et al 2002). Although the significant proportion of patients exhibit impaired perfusion (30-70%) (Van’t Hof et al 1998, Gibson et al 2000) after successful restoration of infarct artery flow, there appeared to be more preserve microvascular perfusion among patients undergoing primary angioplasty (Lane et al 2005).

2. Treatment of the inciting pathobiology in AMI

After successful thrombolysis, a significant residual stenosis remains in the majority of the patients (Llvedot et al 2000). Treatment of stenosis during primary angioplasty appears to the lower the risk of recurrent ischemic events. In the Meta analysis of randomized trials reinfarction was reduced to 3% with primary angioplasty compared with 7% for thrombolytic therapy (Keeley et al 2003). Stenting further reduced the risk of reocclusion and restenosis (Grines et al 2000).

3. Anatomical definition and risk stratification

The angiography and hemodynamic data obtained at the time of emergency catheterization impart valuable decision-facilitating information's and more precise risk stratifications. Stratifications of patients into a low risk group (age ≤70 years, LV ejection fraction >0.45, one or two vessel disease, successful angioplasty, no persistent arrhythmias) at the time of the procedures facilitates rapid safe recovery.

4. Reduction in complications

Treatment with primary angioplasty appears to reduce the complications of myocardial infarct rupture. In a combined analysis of the GUSTO-I and PAMI-I/II trials, primary angioplasty resulted in an 86% reduction in the risk of mechanical complications.
compared with that of patients undergoing thrombolysis (Stone et al 2000). Intracranial hemorrhage remains a serious complication of thrombolysis. One third of the mortality reduction with primary angioplasty compared with thrombolysis has been attributed to curtailment of intracranial hemorrhage (Weaver et al 1997).

5. Interhospital transfer for Primary PCI

To achieve optimal results, time from the first hospital door to the balloon inflation in the second hospital should be as short as possible, with a goal of within 90 minutes. Significant reduction in door to balloon times might be achieved by directly transporting patients to PCI centers rather than transporting them to the nearest hospital, if interhospital transfer will subsequently be required to obtain primary PCI (Antman et al 2004).

6. Primary Stenting for AMI

Stents have ascended to an essential role in interventional cardiology practice. A stent procedure is used along with balloon angioplasty. Stents are metallic mesh of coil splint, which are placed inside arteries to brace them, open and prevent collapse through dissections or elastic recoil. The stent is mounted on a balloon tipped catheter, threaded through an artery, and positioned at the blockage. The balloon is inflated, opening the stent. Then the catheter and deflated balloon is removed, leaving the stent in place. The stent may be used to support and maintain a stretch of a disease segment of the artery. It has been well demonstrated that there is improved procedural success with reduced long term restenosis and a reduced need for coronary revascularization (Fischman et al 1994).

The use of stent with PCI for MI is superior to the use of PCI without stents, primarily because stenting reduced the need for subsequent target vessel revascularization (TLR) (Grines et al 1993). Three small trials in the patients with AMI with vessel suitable for stenting have demonstrated significant reduction with stenting in early (in hospital or < 1 month) recurrent ischemic events and in a late composite end point of death, recurrent AMI or repeat target vessel revascularization (TVR) by 6 months. Sub optimal results after primary angioplasty are predictive of recurrent ischemia or reocclusion (Grines et al 1995). Initial use of stents was restricted to "bailout" indications, but several studies demonstrated the feasibility and safety of stents in AMI (Stone et al 1998). Several randomized trials have been conducted comparing primary stenting with primary balloon...
angioplasty. The stent PAMI trial reported a reduction in the cardiovascular endpoints, recurrent ischemia and restenosis or reocclusion in the stent group (Grines et al 1999). CADILLAC trial showed similar benefit with primary angioplasty vs. stenting with a lower target vessel revascularization rates in stent group (Stone et al 2002). A Meta analysis of reported trial confirms the advantage of stent deployment (Zhu et al 2001). Thus, as with other PCI indications stents are recommended to be routinely apply in AMI. In addition to the bare metal stent (BMS) (stainless steel or cobalt chromium alloy), drug eluting stents (DES) is a major advancement in the cardiology. DES contains pharmacological agent coated on the conventional BMS. DES can maximize local drug effects and minimize the potential for systemic toxic effects. With proven efficacy in other therapeutic arenas, many drugs aimed at inhibiting cell proliferation (paclitaxel, sirolimus, tacrolimus and everolimus), cell migration (batimastat, a matrix metalloproteinase inhibitor) and abnormal healing (estradiol) are currently under clinical investigation. Currently available DES includes sirolimus coated coronary stents (CYPHER®), ABT-578 coated cobalt chromium alloy stent (ENDEAVOR®), paclitaxel coated stent (TAXUS®) etc. Based on the various mechanism of action of these agents, drug released from these stents may be classified as immunosuppressive, antiproliferative, anti-inflammatory, or pro healing (Sousa et al 2003). The released of these agents further retard the risk of restenosis compared to BMS. Preliminary report suggested that compare with conventional BMS, DES are not associated with increase risk when use for primary PCI in STEMI patients (Lemos et al 2004).

3.4.4.8.2 Combining Thrombolysis and PCI as Reperfusion therapy

- Facilitated PCI

Facilitated PCI refers to a strategy of planned immediate PCI after an initial pharmacological regimen such as full dose fibrinolysis, half dose fibrinolysis, a GP IIb/IIIa inhibitor or a combination of reduced dose fibrinolysis and a platelet GP IIb/IIIa inhibitor. Facilitated PCI holds promising strategy in higher risk patients when PCI is not immediately available (Class IIb). Several randomized trials of facilitated PCI with variety of pharmacological regimen are in progress which induced ‘Facilitated Intervention with Enhanced Reperfusion to Stop Events’ (FINESSE) trial and
Assessment of the Safety and Efficacy of a New Thrombolytic (ASSENT) -4 Trial comparing facilitated PCI with primary PCI.

- Rescue PCI

Rescue PCI refers to PCI within 12 hours after failed fibrinolysis for patients with continuing or recurrent MI. Patients with an occluded infarct artery (TIMI grade 0 to 1 flow) or suboptimal flow (TIMI grade 2 flow) 90 min after thrombolytic therapy have worsed LV function, increased incidence of mechanical defects an increase early mortality (Ross et al 1989). Rescue PCI is performed in patients with failed thrombolysis to establish reperfusion and may salvage myocardium and improve prognosis. Few randomized trials including TAMI 5, RESCUE (Ellis et al 1994), GUSTO III (Miller et al 1999) and MERLIN (Sutton et al 2004) have shown benefits with rescue PCI following failed thrombolytic therapy. Persistent of ischemic chest pain, fail to resolve ST segment elevation, rise of baseline/60 min biomarker and hemodynamic or arrhythmic instability are general indicators of failed pharmacological perfusion and need to consider rescue PCI. The current ACC/AHA guidelines recommends rescue PCI for STEMI patients with cardiogenic shock, hemodynamic or electrical instability or persistent ischemic symptoms (Class 1). Patients requiring rescue PCI, however, remains at increased risk for reocclusion and early death, especially if the revascularization procedure is unsuccessful.

3.4.4.8.3 PCI Immediately After Successful Thrombolysis

A high grade (>70%) residual stenosis is usually present following successful thrombolysis. However trials, of immediate PCI following successful thrombolysis demonstrated that routine PCI was associated with high transfusion rates, increased need for bypass surgery, a trend toward increased mortality, and no improvement in predischarge LVEF (de Boer et al 1995, Gibbons et al 1993, Lieu et al 1996). Additional studies are needed to confirm clinical benefits and to determine the optimal timing for PCI.

3.4.4.8.4 Delayed PCI Following Thrombolysis

Delayed PCI refers to angioplasty performed electively (1-7 days following thrombolysis) in asymptomatic patients. As it with rescue of immediate PCI, the goal of this approval was to reduce the residual stenosis in the hope of preventing reocclusion.
and recurrent ischemia, and augmenting recovery of ventricular function. Trials for delayed PCI vs. conservative therapy demonstrated no difference in death, reinfarction or EF (The TIMI study group 1989, Barbash et al 1990, The SWIFT investigators 1991, Van en Brand et al 1992, Lieu et al 1996). Despite concerns over infarct arterial residual stenosis and late reocclusion, elective angiograph and revascularization should be more targeted to post STEMI patients with recurrent symptoms, positive non invasive stress test or high risk indicators (LVEF ≤0.40). Specially, elective revascularization may be consider in the patients with the history of prior MI, TIMI II flow, coronary stenosis ≥90% supplying a large amount of myocardium, and lesion documented to be physiologically significant by IVUS or Doppler.

3.4.4.8.5 Acute Surgical Reperfusion

CABG is also a treatment modality for IHD. In procedure, a blood vessel from another part of the body is used to bypass block region. The saphenous vein is used mainly for the distal branches of right and circumflex coronary arteries and for sequential graphs to these vessels and diagonal branches. Internal mammary artery is used, which is remarkable free of atheroma, especially in the patients under age of 65yr. Emergency or Urgent Coronary Artery Bypass Graft (CABG) surgery can be done for AMI or for one of the following indication; persistent or recurrent chest pain despite fibrinolysis or PCI, high risk coronary anatomy (e.g., left main stenosis) discovered and catheterization, or a complication of STEMI such as ventricular septum rupture or severe mitral valve regurgitation due to papillary dysfunction (Class I indication).

3.4.4.9 Assessment of Reperfusion

Persistence of unrelenting ischemic chest pain, absence of resolution of the qualifying ST segment elevation, and hemodynamic and/or electrical instability are generally indicators of failed pharmacological perfusion and need to consider the rescue PCI. Assessment of the epicardial blood flow and myocardial perfusion following primary PCI is the direct evidence of reperfusion achieved.

3.4.4.9.1 Epicardial blood flow
To provide the level of standardization for comparison of the various regimens, the blood flow in the infarct vessel is assessed angiographically according to the thrombolysis in the myocardial infarction trial (TIMI) grading system (Table 3.6). TIMI grade III flow is considered being goal when assessing flow in the epicardial infarct artery following reperfusion (Gibson et al 2003). TIMI frame count is more quantitative index for the briskness coronary blood flow. It is the simple count for the number of angiographic frames elapsed until the contrast material arrives in the distal bed of the vessel (Gibson et al 1996).

Table 3.6: TIMI Flow Grade Classification Scheme (Gibson et al 2003)

<table>
<thead>
<tr>
<th>Flow Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>No perfusion: No antegrade flow beyond the point of occlusion</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Penetration without perfusion: Contrast material passes beyond the area of obstruction but fails to opacify the entire coronary bed distal to the obstruction for the duration of the cine angiography filming sequence</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Partial reperfusion: Contrast material passes across the obstruction and opacify the coronary distal to the obstruction. However, the rate of entry of the contrast material into the vessel to the obstruction or its rates of clearance from the distal bed (or both) is perceptively slow than its flow into or clearance from comparable areas not perfuse by the previously occluded vessel</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Complete perfusion. Antegrade flow into the bed distal to the obstruction occurs as promptly as antegrade flow into bed proximal to the obstruction, and clearance to contrast material from the involved bed is as rapid as clearance from an uninvolved bed in the same vessel or the opposite artery</td>
</tr>
</tbody>
</table>

3.4.4.9.2 Myocardial perfusion

The goal of reperfusion therapy in AMI is not only the early, full early and sustained restoration of antegrade flow at the epicardial level but also the achievement of adequate perfusion at the myocardial level (Roe et al 2001). Abnormalities of increase in myocardial perfusion as assessed angiographically by the TIMI myocardial perfusion (TMP) grade (Gibson et al 2000) (Table 3.7) correlates with mortality risk even after adjusting for the presence of TIMI grade III flow or a normal TIMI frame count (Aneja et al 2002). Myocardial perfusion cannot be improved adequately even when there is restoration of flow in the occluded infarct related artery i.e. the patients with TIMI grade III flow may not achieve adequate myocardial reperfusion. Obstruction of distal microvasculature by thrombi, micro embolization, and spasm of the distal...
microvascular or reperfusion injury contributes to the tissue injury and inadequate myocardial perfusion. All these consequences may result in a phenomenon known as "No-reflow" (NR) which leads to failure to achieve myocardial reperfusion despite the presence of patent coronary artery (Rezkalla et al 2002). Diagnostic technique such as ST segment resolution, angiographic blush, nuclear scintigraphy, myocardial contrast echocardiography, coronary doppler, magnetic resonance imaging and positron emission tomography have been used to assess the NR phenomenon (Gibson et al 2004). The presence of NR in patients with AMI receiving reperfusion therapy has been associated with poor outcomes (Ito et al 1996).

<table>
<thead>
<tr>
<th>Perfusion Grade</th>
<th>Definition</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Minimal or no myocardial blush</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Dye stains the myocardial and this stain persists on the next injection</td>
</tr>
<tr>
<td>Grade 2</td>
<td>Dye enters the myocardium but washes out slowly so that dye is strongly persistent at the end of the injection.</td>
</tr>
<tr>
<td>Grade 3</td>
<td>There is normal entrance and exist of dye in the myocardium so that dye is mildly persistent at the end of the injection.</td>
</tr>
</tbody>
</table>

3.4.4.9.3 Keeping arteries open:

The 'open artery' principle is considering a vital one in improving the outcome after MI. The obstructed vessel should be unblocked as soon as possible, and patency should be maintained to improve the patient’s prognosis and reduce morbidity. Remimer et al (1977) showed that early restoration of blood flow improve the subsequent function of left ventricle. A more recent trial using graded outcomes determine by the thrombolysis in myocardial infarction trial (TIMI) showed that the higher the grade achieve, the lower the mortality at 30 days. Patients with TIMI grade 0 (complete occlusion) at 90 min had a 30 day mortality of 8.4% whereas mortality was 4% in patients with TIMI grade 3 (GUSTO angiography investigators 1993).

3.4.4.10 No Reflow (NR) & distal Embolization during PCI:

NR describes the persistence of reduced flow and associated myocardial perfusion despite the removal of mechanical epicardial coronary occlusion. Ames et al (1968) first coined the term in their experiment work on cerebral ischemia. Coronary NR was also
described first in experimental setting (Kloner et al 1974) but was later noted to occur clinically as well (Bates et al 1986).

The exact pathophysiologic mechanism behind this phenomenon has not been identified. The epicardial vessel is patent and the flow impairment is the result of pathology in the microcirculation. This microvascular dysfunction usually follows a direct injury. Potential mechanism of microvascular dysfunction include vasospasm, distal embolization of thrombus or other debris, oxygen free radical mediated endothelial injury, capillary plugging by erythrocytes and neutrophils and intracellular/interstitial edema with intramural hemorrhage. Electron microscopy performed on animal experiment shows the plugging of capillaries with neutrophils, myocyte edema, and endothelial blistering (Kloner et al 1974). Capillary resistance to flow is thus increased. It has also been postulated that activated platelets secrete potent vasoactive substances that promote distal microvascular constriction, thus impeding flow. In addition, particles from plaques or thrombi that are dislodged and embolized downstream by the revascularization procedure can lead to microvascular spasm. It is important to keep in mind that the responses of the endothelium of the distal microvasculature to those vasoactive substances may not be identical to those of intact endothelial cells. In other words, endothelium dependent vasoactive substances may lead to incomplete or even paradoxical responses once exposed to injured endothelium. No reflow in AMI may result due to ischemia reperfusion injury following the reperfusion of the infarcted artery.

Another most challenging scenario encountered in AMI is the presence of thrombus, and the subsequent distal embolization due to mechanical disruption of the culprit lesion (Topol and Yadav 2000), a scenario occurring during primary/rescue PCI. Resultant epicardial vessel and microvascular impedance to flow contributes to long term LV dysfunction, CHF and death (Ito et 1996, Henriques et al 2002, Morishima et al 2000). Embolization either spontaneous or following PCI has an important role in the development of the NR phenomenon after AMI (Rezkalla et al 2002).

3.4.4.11 Management of No-reflow (NR)

The best approach for management of NR phenomenon is probably to avoid it altogether. Therefore, strategies aiming at reducing the risk of its occurrence are perhaps
the most effective. Treatment of established NR phenomenon is mainly pharmacologic. The response of the coronary microvasculature to vasoactive substances varies with the location of the vascular bed. In general, subendocardial blood flow increases more than subepicardial blood flow in response to endothelium dependent vasodilators like acetylcholine, adenosine triphosphate, and arachidonic acid (Quillen and Harris 1992). The response of the coronary microvasculature to endothelium-dependent factors is reduced after ischemia-reperfusion (Quillen et al 1990). Endothelium independent substances like sodium nitroprusside are equivalent in the two regions of myocardium.

3.4.4.11.1 Drugs for the treatment of No-reflow (NR)

- Nitroglycerin: Intracoronary (IC) NTG has been used as a mainstay in the treatment of no-reflow. Although NTG is a potent vasodilator of the epicardial coronary artery, it has weak effects as a microvasculature/arteriolar vasodilator.
- Sodium nitroprusside: IC Nitroprusside may also effectively treat NR. This agent probably works via its action as a NO donor at the arteriolar level. The drug is most often administered via the distal lumen of a balloon catheter or on infusion catheter.
- Adenosine: Adenosine is perhaps the most potent arteriolar vasodilating drug available to reverse NR in degenerated SVG. Adenosine is generally considered an endothelium independent vasodilator. It is secreted locally to purinergic receptors and causes relaxation by activating adenylate cyclase. Adenosine is considered a possible auto-regulator of coronary blood flow. In the setting of intervention in AMI, adenosine has been found to decrease the incidence of NR by four-fold.
- Calcium Channel Blockers: It appears to have substantial efficacy in reversing NR. Verapamil, diltiazem and nicardipine have all been used successfully to reverse NR. The mechanism of action of verapamil is most likely a direct effect on arteriolar smooth muscle cells that promotes relaxation and consequently eases spasm.
- Papaverine: The reasoning behind the use of papaverine is that ischemia induces spasm, which, in turn, contributes to the development of NR, thus perpetuating, ischemia and tissue injury. Papaverine would break the ischemia-spasm cycle and this helps to resolve NR. Care must be taken through because papaverine may lead to QT-segment prolongation and has been known to cause Torsades de Pointes.
Antioxidants: Antioxidants such as superoxide dismutase and allopurinol (to decrease reperfusion injury) and mannitol (to reduce myocardial edema) have been studied in experimental MI, but their value for NR is unknown.

Platelet GP IIb/IIIa inhibitors: The use of potent receptor antagonist for preventing or reversing NR in controversial. They may play a role in the prevention of NR in SVG intervention and in AMI. The use of GP IIb/IIIa inhibitors is indicated in high-risk coronary interventions. They are probably not best used as a treatment once NR is established. Presently, there is relatively little data regarding the use of GP IIb/IIIa inhibitors in this setting.

3.4.4.11.2 Devices for Prevention of No-Reflow

There are a number of devices that are either approved or under investigation for the treatment of IC thrombus and/or the prevention of NR during coronary interventions. The major ones include Angiojet Rheolytic Thrombectomy System, Acolysis device and distal embolization protection device (DPD). Multiple devices of this type are in development and testing at Cordis/J&J, Microvena, Boston Scientific, and other companies. The filter devices, a kind of DPD has the potential advantage of allowing distal blood flow while the larger embolic debris is collected. Atherectomy and stenting may also cause NR. The best strategy is to avoid its occurrence by the use of DPD like PercuSurge GuardWire® system or aspiration catheters. Platelet GP IIb/IIIa inhibitors can be concomitantly used when indicated, although definitive data demonstrating their benefit in NR situations is lacking at the time. If NR does occur, there are number of pharmacologic options that appear to be effective in reversing NR and to relieve the element of spasm in the microcirculation in an attempt at breaking the cycle of continued microvascular injury. Rapid boluses of IC adenosine with or without adjunctive IC nicardipine, IC verapamil, diltiazem and nitroprusside appear to be effective agents. In high-risk thrombus laden lesions, prevention of NR may be feasible with clot debulking devices such as the angiojet and acolysis. Comparing drugs with mechanical devices should be carefully assessed in future clinical trials.

3.4.4.12 Management of Distal Embolization
Distal embolization of thrombus/plaque components during primary PCI may play a crucial role in limiting effective myocardial perfusion (Limbruno et al. 2003), thus it can be hypothesized that mechanical prevention of distal embolization might prevent NR during PCI.

The use of protection devices during stenting of stenotic venous grafts intended to prevent distal embolization appears feasible and may confer a potential role of these devices in the improvement of patient outcomes. Several new devices have been developed to prevent embolic particles from passing into the distal microcirculation during intervention. These are broadly into two categories: balloon occlusion devices and filter devices. Currently only two such devices approved by the FDA for use in PCI (Schomig et al. 2005): the PercuSurge GuardWire (Medtronic Corp, Santa Rosa, Calif) and FilterWire-Ex two guiding catheters and occluding the distal vessel with a balloon catheter and performing an aspiration thrombectomy using and aspiration device while a balloon was inflated within the vessel (Stein et al. 2000). The Export\textsuperscript{®} catheter is a component of the PercuSurge GuardWire\textsuperscript{®} distal protection system and has been used as an adjunctive therapy for the treatment of thrombotic lesions in saphenous vein grafts, no reflow during PCI, and AMI caused by plaque rupture thrombi. The results of the EMERALD trial showed that the PercuSurge GuardWire\textsuperscript{®} effectively retrieved embolic debris, but it failed to show improved micro vascular flow, greater reperfusion success, reduced infarction size, or enhanced event-free survival and associated with a longer procedural duration. The use of aspiration catheter was simple and cost effective.

Several aspiration and thrombectomy devices have been introduced to prevent distal embolization. These include the Diver (Invatec, Roncadelle, Italy), Export (Medtronic, Minneapolis, Minnesota), Probing (Boston Scientific, Natick, Massachusetts), Pronto (Vascular Solutions, Minneapolis, Minnesota), and Rescue catheters (Boston Scientific, Natick, Massachusetts) (Grines et al. 1999, Suryapranata et al 1998, Kastrati et al 2000, Kloner et al 1974, Topol et al 2000, Henriques et al 2002). The aspiration device (Export\textsuperscript{®}, Medtronic Inc., Minnesota, MN), is a 6-Fr rapid exchange catheter (1.37 mm internal lumen); a vacuum syringe is connected to the proximal end, while the distal tip is advanced on the guidewire until the thrombus. When the vacuum syringe is opened, simple mechanical aspiration removes the thrombus from the coronary
artery. Multiple aspirations can be performed until the operator is unable to aspirate further thrombus. Thrombus Aspiration during Percutaneous Coronary Intervention (TAPAS) study compared with conventional stenting showed improvement in myocardial perfusion, electrocardiographic variables of reperfusion, and clinical outcome as compared to conventional stenting (Svilaas et al 2008). In small study, thrombus aspiration with Export® catheter in STEMI demonstrated that the routine use of Export® catheter in patients with STEMI and coronary thrombus is feasible, safe, and was associated with significant improvements in flow-related angiographic parameters (Margheri et al 2007).

As an alternative to occlusion devices, a number of porous membrane filters mounted on the tip of coronary guidewires have been developed to capture and retrieve embolized materials during intervention. This includes devices like Angioguard®, Filterwire-Ex system and may other filters. The Filter Wire-Ex system is an intravascular filtration device that is placed distal to the PCI site without impeding antegrade blood flow. Distal filters allow perfusion and contrast injection, thus ensuring better angiographic control during angioplasty and stent deployment. However, the filters may fill with particulate debris and reduce anterograde flow. Simply removing the filter wire without aspiration may release a column of static particulate debris into the distal microcirculation in this circumstance, aspiration of the column of material with an aspiration catheter before filter removal may be useful. The recent, large, randomized FIRE trial compared distal balloon protection with a distal filter during SVG interventions. In this study the device success and the incidence of MI were reported to be similar (Rogers and Stone 2002).

As the market for embolic protection devices has increased, the spectrum of application of embolic protection devices has expanded to include primary PCI for AMI. There have been observations suggesting a beneficial impact of distal protection devices and aspiration catheters that have encouraged their use in patients with AMI in many centers (Limbruno et al 2003, Huang et al 2003, Yip et al 2003, Orrego et al 2003, Nakamura et al 2004, Taguchi et al 2005), but randomized clinical trials of the value of these devices in this setting have not been established.
3.4.4.13 Ancillary Therapy to Reperfusion Therapy

Reperfusion therapies including fibrinolysis and primary PCI attempt to rapidly obtain and sustain optimal flow in the infarct related artery. Adjunctive therapies are used along with thrombolysis or primary PCI to enhance the coronary reperfusion or alternatively to minimize the extent of ischemic myocardial injury. These include antiplatelet agents, nitrates (described above), beta blockers, calcium channel antagonists, ACE inhibitors and many more.

3.4.4.13.1 Antithrombotic Agents

- Unfractionated Heparin (UFH):

  UFH is recommended in all the patients undergoing percutaneous or surgical revascularization (Class I). It forms a chemical complex with antithrombin III. This complex inactivates both free thrombin and factor Xa; thus acting as an indirect thrombin inhibitor. The desired clinical effect of heparin is the inhibition of additional formation and propagation of thrombi. UFH is beneficial until the inciting thrombotic cause (ruptured plaque) has completely resolved or healed. Intravenous UFH is recommended in patients with a MI who undergo percutaneous revascularization or fibrinolytic therapy with alteplase. It is also recommended in patient with AMI who receive fibrinolytic therapy with a non-selective fibrinolytic agent (urokinase, streptokinase, anistreplase) and are at increased risk for systemic emboli (prior embolic event, large or anterior wall infarction, known left ventricular thrombus, or atrial fibrillation) (Ryan et al 1999).

- Low-molecular weight Heparin (LMWH)

  LMWH are considered as an accepted alternative to UFH in AMI patient receiving thrombolytic therapy (Class IIb). This class includes agents like enoxaparin, fondaparinux, etc. LMWH are formed by controlled enzymatic or chemical depolymerization, producing glycosaminoglycans of various length and less molecular weight than UFH (Antman et al 2001). Compared to UFH, the rate of early reperfusion is not enhanced by LMWH, but the rates of reocclusion of the infarct artery, reinfarction, or recurrent ischemic events appear to reduce with LMWH (Ross et al 2001, Simoons et al 2002, Antman et al 2002). LMWH can be administered to MI patients not treated with fibrinolytic therapy that have no contraindication to heparin.
Direct Thrombin Inhibitors:

UFH and LMWH are indirect inhibitors of thrombin and hence to overcome their limitations, direct thrombin inhibitors are being investigated (Antman et al 2001). These agents are recommended in case of known heparin induced thrombocytopenia in AMI patients as an alternative to heparin (Class IIa). The principal direct thrombin inhibitors are hirudin, bivalirudin, argatroban and lepirudin; however, have not shown to reduce mortality compared to heparin when used as adjuncts to fibrinolytics (Direct Thrombin Inhibitors Trialists’ Collaborative Group 2002). Efficacy of hirudin and bivalirudin in comparison to heparin is investigated in many trials. One unique advantage of these agents is that fact that they do not cause or worsen heparin induced thrombocytopenia. HERO-2 trial tested bivalirudin versus heparin as adjunctive therapy to streptokinase, did not reveal significant benefits, but was associated with a lower rate of adjudicated MI within 96 hr (1.6% vs. 2.3%, p=0.005) (White et al 2001). In the BIAMI trial use of bivalirudin showed safety and comparable efficacy with abciximab/stent arm of CADILLAC trial. Bivalirudin in AMI patients also offered economical benefit.

3.4.4.13.2 Antiplatelet agents

The pathology of an occlusive coronary thrombus is the adhesion of a small collection of activated platelets at the site of intimal disruption in an "unstable" atherosclerotic plaque.

Aspirin:

The rationale for the use of aspirin along with thrombolytic therapy lies in the relatively high risk of re-occlusion of 5-30% and a rate of reinfarction of about 4% when aspirin is not used (Fuster et al 1993). Aspirin, proved to be beneficial in AMI (collaborative group 1998), is given in a dose of at least 150 mg and up to 325 mg immediately on recognition of MI signs and symptoms and continued daily indefinitely (Class I) (Antman et al 2004).

Adenosine Di-Phosphate (ADP) Receptor Antagonists:

Other antiplatelet class of drugs namely thienopyridines – including clopidogrel, ticlopidine block the adenosine diphosphate (ADP)-mediated activation of platelet GP Iib/IIIa receptor and led to irreversible inhibition of platelet aggregation. Clinical studies
indicate that clopidogrel is at least as effective as aspirin in reducing vascular events (The CAPRIE Steering Committee 1996) and the combination appears to be more beneficial than aspirin alone (Yusuf et al 2001). Clopidogrel combined with aspirin is recommended for STEMI patients who undergo coronary stent implantation (Class I). There are no safety data available regarding the combination of fibrinolytic agents and clopidogrel, but ongoing trials will provide this information in the future. However, in patients whom aspirin is contraindicated because of aspirin sensitivity, clopidogrel is probably useful as a substitute for aspirin to reduce the risk of occlusion (Patrono et al 2004).

> GP IIb/IIIa Inhibitors:

Whatever the pathway of platelet activation, platelet-platelet interaction and thrombus formation is ultimately regulated by the GP IIb/IIIa Inhibitors. Abciximab, eptifibatide and tirofiban are intravenously administered agents that block the platelet GP IIb/IIIa inhibitors inhibiting crosslink formation between platelets and fibrinogen as the final common pathway of platelet aggregation. Efficacy of these agents in AMI has been extensively investigated (Katritsis et al 2003). The use of intravenous GP IIb/IIIa inhibitors during the PCI and in patients with MI and ACS has been shown to reduce the composite endpoint of death, reinfarction, and the need for target-lesion revascularization at follow up (Brener et al 1998). GUSTO V trial has reported the efficacy of abciximab in combination with half dose of streptokinase versus full dose streptokinase in AMI (Topol et al 2001). Adjunctive abciximab and tirofiban therapy have been investigated in the setting of primary PCI. Clinical results are more favorable in the ADMIRAL trial in AMI in which abciximab was administered during primary PCI. However, the largest randomized trials of primary PCI or stenting, CADILLAC, did not demonstrate a benefit of abciximab with regards, to angiographic and clinical endpoints (Stone et al 2002). Reduction in the rate of reinfarction using abciximab was driven in ACE study. The current ACC/AHA guidelines state that is “reasonable” to administer abciximab (Class IIa) or tirofiban/eptifibatide (Class IIb) prior to primary PCI (Antman et al 2004). Oral GP IIb/IIIa inhibitors are also under investigations.

3.4.4.13.3 Nitrates
Nitrates provide nitric oxide to vascular smooth muscles, thereby inducing vasodilation, and they likely have significant antiplatelet effects. Nitrates vasodilate coronary arteries and reduce coronary vasospasm, thereby increasing myocardial oxygen delivery (GISSI-3 investigators 1994). Two large placebo controlled trials, GISSI-3 and ISIS-4 investigators have shown mortality benefits with trinitroglycerin therapy as adjunctive to fibrinolysis (GISSI-3 Investigators 1994, ISIS-4 Collaborative group 1995). Low BP, headache, and tachyphylaxis limit the use of nitroglycerin. Nitrate tolerance can be overcome either by increasing the dose or by providing a daily nitrate-free interval of 8-12 hours (Ryan et al 1999).

3.4.4.13.4 Beta Blockers

Beta-blockers or beta-adrenergic antagonists reduce myocardial damage by decreasing the components of myocardial oxygen demand. In patients with AMI, they reduce infarct size, ventricular arrhythmias, and recurrent ischemia (Gheorghiade et al 2002). During the acute phase of MI, beta-blocker therapy may be initiated intravenously; later patients can switch to oral therapy for long-term treatment. This β-1 selective agents like metoprolol, atenolol, timolol, isomolol, acebutolol, etc. that have beneficial effects in AMI. Various trials (ISIS-1, BHAT, MIAMI and CAPRICORN) have proved mortality benefits in AMI with beta-blocker therapy.

3.4.4.13.5 Inhibitors of Renin Angiotensin Aldosterone system

Oral angiotensin converting enzyme inhibitor (ACEi) is recommended in MI patients within the first 24 hr of symptom onset, if no contra-indications exist (Class I). The beneficial effects of ACE inhibitors in AMI are particularly large in hypertensive (Borghi et al 1999) and diabetic (Zuanetti et al 1997, Gustafsson et al 1999) patients. ACE inhibitor tilt the fibrinolytic balance toward a profibrinolytic state by reducing plasma levels of PAI-1 (Brown et al 1999) and improve endothelial vasomotor dysfunction in patients with CAD (Mancini et al 1996). HOPE study demonstrated that patients who were at high risk of cardiovascular events benefited considerably from treatment with ACEi (Yusuf et al 2000). The potentially beneficial effects of ACEi include a reduction in left ventricular hypertrophy, vascular hypertrophy, and progression of atherosclerosis, plaque rupture and thrombosis, in addition to a potentially favorable
influence on myocardial oxygen supply/demand relationships, cardiac hemodynamics and a reduction of sympathetic activity (Lonn et al. 1994). Post-AMI ACE inhibition is also found to be associated with hypotension, renal insufficiency, and cardiogenic shock. Angiotensin receptor blockers (ARBs) like valsartan, losartan, telmisartan, candesartan are used as an alternative method in AMI patients intolerant to ACEi (Class I). However, use of ARBs has not been explored as thoroughly as ACEi in AMI.

3.4.4.13.6 Calcium Channel Blockers (CCBs):

CCBs lower blood pressure (BP), prolong treadmill exercise tolerance, and reduce myocardial ischemia episode in stable CAD patients. Multiple studies have been conducted with verapamil and diltiazem are recommended in AMI patients in whom beta-blockers are ineffective or contraindicated (Class IIa). Short acting nifedipine is contraindicated in AMI as it increased mortality risk.

3.4.4.13.7 Lipid lowering agents

Recent clinical trials demonstrated lipid-lowering therapy reduces total mortality, CV mortality, coronary events, and stroke in persons with AMI or established CHD. Treatment with statin drugs (3-hydroxy-3-methylglutaryl coenzyme A [HMG CoA] Reductase inhibitors) including agents like simvastatin, atrovastatin, rosuvastatin, pitavastatin has shown impressive benefit post-AMI. Various trials (4S, CARE, MIRACL) have demonstrated the benefits of these drugs.

3.4.4.13.8 Miscellaneous agents

The indications for long-term anticoagulation after STEMI remain controversial and are evolving. Although the use of warfarin has been demonstrated to be cost-effective compared with standard therapy without aspirin, the superior safety, efficacy and cost-effectiveness of aspirin has made it the antithrombotic agent of choice for secondary prevention (Cairns et al. 1995). Several investigators have attempted to reduce myocardial necrosis post infarction with metabolic modulation and agents designed to conserve myocardial intracellular adenosine triphosphate and other energy stores. Infusion of high- or low-dose glucose-insulin-potassium (GIK) versus usual care was studied in the ECLA GIK pilot trial, which revealed that high-dose GIK infusion had a neutral effect on
mortality, cardiac arrest, and cardiogenic shock patients with acute STEMI (Mehta et al 2005). Magnesium produces coronary vasodilatation, reduces platelet aggregation, stabilizes myocardial cell membranes and possible limits catecholamine and reperfusion related myocardial necrosis. Few reports including LIMIT-2 trial and ISIS-4 study have investigated the benefits of magnesium in AMI.

3.4.4.14 Intra-aortic balloon pump

Counter pulsation is preserved for AMI patients with severe refractory ischemia or with hemodynamic instability in patients before or after coronary angiography.

3.4.5 Treatment Strategies in IHD patients presenting with ACS (UA/NSTEMI):

There are 3 principal presentations of UA: rest angina (angina commencing when the patient is at rest); new onset (<2 months) severe angina and increasing angina (increasing in intensity, duration, and/or frequency) (Braunwald 1989). Criteria for the diagnosis of UA are based on the duration and intensity of angina as graded according to the Canadian Cardiovascular Society (CCS) classification (Table 3.8) (Campeau 1976). NSTEMI generally presents as prolonged, more intense rest angina or angina equivalent. ACC/AHA has established the clinical guideline for the management of the UA/NSTEMI (Anderson et al 2007). This guideline has been incorporated in the overall management of the patients. The following is an abridged summary of some of the recommendations from both of these clinical practice guidelines. The customary ACC/AHA classifications are used. Class I refers to conditions for which there is evidence and/or general agreement that a given procedure or treatment is useful and effective. Class II refers to conditions for which there is conflicting evidence and/or a divergence of opinion about the usefulness/efficacy of a procedure or treatment. For Class IIa, the weight of evidence/opinion is in favor of usefulness/efficacy while Class IIb is less established by evidence/opinion. Class III refers to conditions for which there is evidence and/or general agreement that a procedure/treatment is not useful/effective and in some cases may be harmful.
Table 3.8: Grading of Angina Pectoris According to CCS Classification (Campeau 1976)

<table>
<thead>
<tr>
<th>Class</th>
<th>Description of Stage</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>&quot;Ordinary physical activity does not cause angina,&quot; such as walking or climbing stairs. Angina occurs with strenuous, rapid, or prolonged exertion at work or recreation.</td>
</tr>
<tr>
<td>II</td>
<td>&quot;Slight limitation of ordinary activity.&quot; Angina occurs on walking or climbing stairs rapidly; walking uphill; walking or stair climbing after meals; in cold, in wind, or under emotional stress; or only during the few hours after awakening. Angina occurs on walking more than 2 blocks on the level and climbing more than 1 flight of ordinary stairs at a normal pace and under normal conditions.</td>
</tr>
<tr>
<td>III</td>
<td>&quot;Marked limitations of ordinary physical activity.&quot; Angina occurs on walking 1 to 2 blocks on the level and climbing 1 flight of stairs under normal conditions and at a normal pace.</td>
</tr>
<tr>
<td>IV</td>
<td>&quot;Inability to carry on any physical activity without discomfort—anginal symptoms may be present at rest.&quot;</td>
</tr>
</tbody>
</table>

The treatment objectives for patients with UA/NSTEMI are to stabilize and "passivate" the acute coronary lesion, to treat residual ischemia, and to employ long term secondary prevention. Antiischemic therapies (e.g. beta blockers, nitrates and calcium antagonists) are used primarily to reduce myocardial oxygen demand but also appear to have effects in preventing plaque rupture. Antithrombotic therapy (e.g., aspirin, clopidogrel, UFH or LMWH, and GP IIb/IIIa inhibitors) is used to prevent further thrombosis and allows endogenous fibrinolysis to dissolve the thrombus, reduce the degree of coronary stenosis and can continued in the long term to reduce the risk of developing future events or to prevent progression to complete occlusion of the coronary artery, or both. Coronary revascularization is frequently used to treat the severe stenosis of a culprit lesion, thereby preventing the thrombus from progressing and causing recurrent ischemia. (Cannon et al 2005).

3.4.5.1 Antiischemic therapies

3.4.5.1.1 Oxygen (O\textsubscript{2})

O\textsubscript{2} supplement is given to patients presenting with cyanosis, extensive rales, or documented hypoxemia (Class I). Oxygen saturation is determined by oxymetry (Cannon et al 2005).

3.4.5.1.2 Nitrates
Nitrates are endothelium independent vasodilators increases myocardial blood flow by coronary vasodilation thereby reducing myocardial oxygen demand. The latter effect is produced by venodilation, which leads to reduced myocardial preload reduction in ventricular wall stress and thereby reduced myocardial oxygen demand. NTG sublingual tablet or spray (0.3 to 0.6 mg) followed by intravenous administration, for the immediate relief of ischemia and associated symptoms (Class I). If pain persists after three sublingual tablets given 5 minutes apart, beta blockade and intravenous nitroglycerin is initiated. Consequently, the goal of nitrate therapy is relief of pain; chronic nitrate therapy can frequently be tapered off in the long-term management of patients, with primary therapy being aspirin, clopidogrel, beta blockers, and so forth with sublingual or buccal nitroglycerin given as needed for new episodes of pain. NTG or other nitrate within 24 hr of sildenafil (Viagra) use (Class III). Using nitrates no beneficial effect on the mortality is observed in the patients with NSTEMI in (GISSI)-3 and (ISIS-4) trials. Contraindications to the use of nitrates are hypotension or the use of sildenafil related compounds (Cannon et al 2005).

3.4.5.1.3 Morphine Sulphate

Morphine sulfate has potent analgesic, anxiolytic and hemodynamic effects are potentially beneficial in UA/NSTEMI (Class I to Class IIa). Morphine causes venodilation and can produce modest reductions in heart rate (through increased vagal tone) and systolic blood pressure to further reduce myocardial oxygen demand. Morphine sulfates is given intravenously when symptoms are not immediately relieved by NTG or when acute pulmonary congestion and/or severe agitation is present (Class I).

3.4.5.1.4 Beta Blockers

Oral beta blockers are given who do not have contraindication to beta blockade (bradycardia, advanced atrioventricular [AV block], persistent hypotension, known systolic dysfunction with acute pulmonary edema, history of bronchospasm) (Class I). If ischemia and chest pain is ongoing early intravenous beta blockade is used, followed by oral beta blockade. Beta blockers are recommended in ACC/AHA/UA/NSTEMI guidelines to be initiated orally, in absence of contraindications (e.g. HF), within 24 hr and should be avoided with HF, hypotension, and hemodynamically instability (Cannon et al 2005).
3.4.5.1.5 Calcium Channel blockers

Calcium antagonists are used in patients if needed for recurrent ischemia despite beta blockage or in patients in whom beta blockade is contraindicated. CCB have vasodilatory effects and reduces the blood pressure and some (verapamil and diltiazem) slows heart rates. Verapamil and diltiazem is given as initial therapy in the absence of severe LV dysfunction or other contraindications. CCB in UA/NSTEMI is predominantly limited to symptom control (Beevers et al 1996, Opie 1996).

3.4.5.1.6 Angiotensin-Converting Enzyme Inhibitors

ACEi is given when hypertension persists despite treatment with NTG and a beta blocker in patients with LV systolic dysfunction or CHF and in ACS patients with diabetes (Class I) and for all post-ACS patients (Class IIa). Long term use of ACE inhibition is beneficial in preventing recurrent ischemic events and mortality in a broad population of CAD. However, short term use of ACE inhibition does not appear to confer any benefits for patients with UA/NSTEMI (Cannon et al 2005).

3.4.5.1.7 Other Anti-ischemic therapy

$K_{ATP}$ channel openers have hemodynamic and cardioprotective effects that could be useful in UA/NSTEMI. Nicorandil is such an agent that has been approved in a number of countries but not in the United States. Ranolazine is a newly approved (January 2006) agent that exerts antianginal effects without reducing heart rate or blood pressure (Chaitman et al 2004). Currently, ranolazine is indicated alone or in combination with amlodipine, beta-blockers, or nitrates for the treatment of chronic angina that has failed to respond to standard antianginal therapy. The initial dose is 500 mg orally twice daily, which can be escalated as needed to a maximum of 1000 mg twice daily. The mechanism of action of ranolazine has not been fully characterized but appears to depend on membrane ion channel effects (similar to those after chronic amiodarone) (Antzelevitch et al 2004). It is contraindicated in patients with QT-prolonging conditions. The preliminary results suggestive of ranolazine may be safely administered for symptom relief after UA/NSTEMI, but it does not appear to significantly improve the underlying disease substrate (Morrow et al 2006 and Morrow et al 2007).
3.4.5.2 Antithrombotic therapies

Antithrombotic therapy is essential to modify the disease process and its progression to death, MI, or recurrent MI in the majority of patients who have ACS due to thrombosis on a plaque. A combination of aspirin, an anticoagulant, and additional antiplatelet therapy are the most effective therapy. The intensity of treatment is tailored to individual risk, and triple-antithrombotic treatment is used in patients with continuing ischemia or with other high-risk features and in patients oriented to an early invasive strategy (Table 3.9; Figure 3.8). Table 3.10 shows the recommended doses of the various agents. A problematic group of patients are those who present with UA/NSTEMI but who are therapeutically anticoagulated with warfarin. In such patients, clinical judgment is made with respect to initiation of the antiplatelet and anticoagulant therapy. Anticoagulant therapy is not initiated until the international normalized ratio (INR) is <2.0. However, antiplatelet therapy has to be initiated even in patients therapeutically anticoagulated with warfarin, especially if an invasive strategy is planned and implantation of a stent is anticipated. In situations where the INR is supratherapeutic, the bleeding risk is unacceptably high, or urgent surgical treatment is necessary, reversal of the anticoagulant effect of warfarin may be considered with either vitamin K or fresh-frozen plasma as deemed clinically appropriate on the basis of physician judgment (Anderson et al 2007).
**Figure 3.8:** Treatment algorithms for antiplatelet and anticoagulant therapies in UA/NSTEMI patients (Anderson et al 2007)

1. **Diagnosis of UA/NSTEMI is likely or definite**
   - ASA* (Class I); Clopidogrel if ASA intolerant (Class I)

2. **Select Management strategy**
   - **Invasive strategy**
     - Initiate anticoagulant therapy (Class I)*
       - Enoxaparin or UFH (acceptable options)
       - Bivalirudin or fondaparinux
     - Prior to angiography:
       - Initiate at least one (Class I) or both (Class II)
         - Clopidogrel*†
         - IV GP IIb/IIIa inhibitors*†
     - Factors favoring administration of both clopidogrel and GP IIb/IIIa inhibitor include:
       - Delay to angiography
       - High risk features
       - Early recurrent ischemic discomfort

   - **Initial conservative strategy**
     - Initiate anticoagulant therapy (Class I)
       - Enoxaparin or UFH* (Class I)
     - Fondaparinux
       (enoxaparin or fondaparinux are preferable)
     - Initiate conservative strategy
       - Initiate clopidogrel therapy (Class I)*
       - Consider adding L.V eptifibatide or tirofiban (Class IIb)*

   - Any subsequent event necessitating angiography‡

3. **Evaluate LVEF**
   - EF ≤0.40
     - Class IIa
   - EF >0.40
     - Class IIa

4. **Stress test**
   - Not low risk
     - Class I
   - Low risk
     - Class I

5. **Diagnostic angiography (cont..)**

---

*For dosing, refer Table 3.10

- *See table 3.9, for selection of management strategy
- †Evidence exists that GP IIb/IIIa inhibitors may not be necessary if the patient received a preloading dose of at least 300 mg of Clopidogrel at least 6 hr earlier
- ‡Low risk: Continue ASA indefinitely (Class I)*; continue clopidogrel for at least one month (Class I, LOE A) ideally up to 1 year (Class I, LOE B); discontinue IV GP IIb/IIIa inhibitors if started previously (Class I); discontinue anticoagulant therapy (Class I)
- ‡Recurrent symptoms/ischemia, heart failure, serious arrhythmia
Review of Literature

Diagnostic Angiography (cont...)

Select Post-Angiography Management Strategy

- Continue ASA (Class I)
- Discontinue clopidogrel 5 to 7 days prior to elective CABG (Class I)
- Discontinue IV GP IIb/IIIa 4 h prior to CABG (Class I)

CABG

- Continue ASA (Class I)
- Loading dose of clopidogrel if not given pre angio (Class I)* and
- IV GP IIb/IIIa if not started pre angio (Class I)**

PCI

- No significant obstructive CAD on angiography
- Antiplatelet and anticoagulant therapy at physicians’ discretion§

Medical therapy

- CAD on angiography
- Continue ASA* (Class I)
- LD of clopidogrel if not given pre angio (Class I)*
- Discontinue IV GP IIb/IIIa after at least 12 h if started pre angio (Class I)
- Continue IV UFH for at least 48 h (Class I) or enoxaparin or fondaparinux for duration of hospitalization (Class I); either discontinue bivalirudin or continue at a dose of 0.25 mg/kg/hr for up to 72 h at physician’s discretion (Class I)

UA/NSTEMI Patient groups at discharge (cont...)

- Continue ASA* (Class I)
- Loading dose of clopidogrel if not given pre angio (Class I)* and
- IV GP IIb/IIIa if not started pre angio (Class I)**

Discontinue anticoagulant after PCI for uncomplicated cases (Class I)**

No significant obstructive CAD on angiography

*For dosing, refer Table 3.10

- Evidence shows that GP IIb/IIIa inhibitors may not be necessary if the patient received a preloading dose of at least 300mg of clopidogrel at least 6 h earlier (Class I) and bivalirudin is selected as the anticoagulant (Class IIa).
- Additional bolus of UFH is recommended if fondaparinux is selected as the anticoagulant.
- For patients in whom the clinician believes coronary atherosclerosis is present, albeit without any significant, flow-limiting stenoses, long-term treatment with antiplatelet agents and other secondary prevention measures should be considered.
UA/NSTEMI Patient groups at discharge (cont...)

- **Medical therapy without stent**
  - ASA* 75 60 162 mg/d indefinitely (Class I) & Clopidogrel† 75 mg/d for at least 1 month (Class I) and ideally up to 1 year (Class I)

- **Bare-Metal Stent Group**
  - ASA* 162 to 325 mg/d for at least 1 month, then 75 to 162 mg/d indefinitely (Class I) & Clopidogrel† 75 mg/d for at least 1 month (Class I) and ideally up to 1 year (Class I)

- **Drug-Eluting Stent Group**
  - ASA* 162 to 325 mg/d for at least 3 to 6 months, then 75 to 162 mg/d indefinitely (Class I) & Clopidogrel† 75 mg/d for at least 1 month (Class I)

**Indication for Anticoagulation?**

- Add warfarin‡§ (Class IIb)
- Continue with dual antiplatelet therapy as above

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- *For aspirin (ASA) allergic patients, use clopidogrel alone (indefinitely), or try aspirin desensitization.
- †For clopidogrel allergic patients, use ticlopidine, 250 mg by mouth twice daily.
- ‡Continue ASA indefinitely and warfarin longer term as indicated for specific conditions such as atrial fibrillation; LV thrombus; cerebral, venous, or pulmonary emboli.
- §When warfarin is added to aspirin plus clopidogrel, an INR of 2.0 to 2.5 is recommended.
Table 3.9: Selection of Initial Treatment Strategy: Invasive Versus Conservative Strategy (Anderson et al, 2007)

<table>
<thead>
<tr>
<th>Preferred Strategy</th>
<th>Patient Characteristics</th>
</tr>
</thead>
</table>
| Invasive           | ■ Recurrent angina or ischemia at rest or with low-level activities despite intensive medical therapy  
                      ■ Elevated cardiac biomarkers (TnT or TnI)  
                      ■ New or presumably new ST-segment depression  
                      ■ Signs or symptoms of HF or new or worsening mitral regurgitation  
                      ■ High-risk findings from noninvasive testing  
                      ■ Hemodynamic instability  
                      ■ Sustained ventricular tachycardia  
                      ■ PCI within 6 months  
                      ■ Prior CABG  
                      ■ High risk score (e.g., TIMI, GRACE)  
                      ■ Reduced left ventricular function (LVEF less than 40%) |
| Conservative       | ■ Low risk score (e.g., TIMI, GRACE)  
                      ■ Patient or physician preference in the absence of high risk features |

3.4.5.2.1 Antiplatelet therapy:

- **Aspirin**

  Aspirin prevents the formation of thromboxane A2 by irreversibly inhibiting COX-1 within platelets thereby diminishing platelet aggregation. It should be administered to patients after hospital presentation at a dose between 75-1500mg depending on the different presentation and continued indefinitely at a daily dose of ≤75mg (Class I) (Cannon et al 2005) (Figure 3.8, Anderson et al 2007).

- **Thienopyridines analogs**

  Clopidogrel and ticlopidine is the irreversible ADP receptor (P2Y12) antagonist. Clopidogrel is given to all the hospitalized patients who are unable to take aspirin because of hypersensitivity or major gastrointestinal tolerance (Class I). Oral loading dose of clopidogrel is 300-600/900mg followed by daily oral maintenance dose of 75mg along with aspirin and anticoagulant as soon as after hospital admission and should be continued for at least one year (Class I) and also to those not at high risk of bleeding (Class I). Clopidogrel use has to be withheld for 5-7 days in those who have elective CABG planned (Figure 3.8, Anderson et al 2007).
3.4.5.2.2 Anticoagulant agents:

- Heparin

UFH exerts its anticoagulant effect by accelerating the action of circulating antithrombin, a proteolytic enzyme that inactivates factor IIa (thrombin), factor IXa, Xa. It prevents thrombus propagation but does not lyse existing thrombi (Hirsh 1991). The initial dose is 60 U/kg/bolus and 12 U/kg/infusion (Class I). The optimal duration of the therapy remains undefined. But in most of the trials the continued therapy of UFH in UA/NSTEMI is evaluated for 4-5 days.

Compare to UFH, LMWH induces a greater release of tissue factor pathway inhibitor and induces thrombocytopenia at lower rate. The SC administration of LMWH provides a longer duration of systemic anticoagulation so that dosing can be administered twice daily. Other agents like enoxaparin and fondaparinux both received a Class I recommendation in UA/NSTEMI. Fondaparinux is a new drug not yet officially approved for this indication. Enoxaparin or fondaparinux is preferable to UFH as anticoagulant therapy unless CABG is planned within 24 hr for UA/NSTEMI patients in whom an initial conservative strategy is selected (Class IIa) (Figure 3.8, Anderson et al 2007).

- Warfarin

Warfarin in addition to aspirin and clopidogrel are indicated for most high risk patients, arise occasionally after UA/NSTEMI (i.e. atrial fibrillation, mechanical prosthetic valve or left ventricular thrombus) (Class IIb). (Figure 3.8, Anderson et al 2007). Other oral factor Xa inhibitors are also in early stages of development.

- Direct Thrombin Inhibitors

  > Hirudin

It is polypeptide of 65 amino acids, binds directly to thrombin forming an irreversible complex and also inhibits clot-bound thrombin. Direct thrombin inhibitors have been shown to elicit a more stable and predictable anticoagulation than heparin (Topol et al 1994). A specific advantage of all direct thrombin inhibitors vs. heparin is their inability to induce severe thrombocytopenia. Hirudin was given as 0.1 mg/kg bolus followed by an infusion of 0.1 mg/kg/h, and the aPTT was adjusted to 60 to 85 seconds in both treatment groups (GUSTO IIb investigators 1996). The combined incidence of death and MI was 8.3% in the hirudin group and 9.1% in the heparin group. This small and
statistically non significant difference was mainly due to the prevention of MI (5.6% vs. 6.4%), whereas the death rates were similar (3.75% vs. 3.9%). The Organization to Assess Strategies for Ischemic Syndromes (OASIS-2) study in patients with UA or NQWMI demonstrated a small advantage of hirudin over heparin of the patients suffering death or MI within 7 days (OASIS-2 investigators 1999). In the doses tested, hirudin seems to be marginally better than heparin with respect to the clinical outcome of patients with UA. Three large-scale trials designed to investigate hirudin in relatively high doses as adjunct to thrombolysis for AMI were terminated early because of an excess of intracranial hemorrhages (GUSTO IIa investigators 1994, Antman et al 1994, Neuhans et al 1994). The high incidence of cerebral bleedings was not specific for hirudin, but the heparin-treated patients also have unexpectedly highly bleeding rates. As compared to the earlier GUSTO-I study (Grager et al 1996) using approximately 20% lower average doses of heparin, the bleeding risk was particularly high in patients treated with streptokinase irrespective of the anticoagulant given. The TIMI-9 and GUSTO-II studies were reinitiated with markedly lower doses of hirudin and the aPTT values were targeted at lower values also in the heparin groups. Both studies exhibited bleeding rates in the usually expected range for thrombolytic treatment of AMI and the risk was similar for hirudin and heparin to prevent death or reinfarction.

Therefore, the studies performed on hirudin in ACS do not show a relevant clinical benefit over heparin despite some pharmacological advantages. Presently, hirudin is only used in patients with heparin-induced thrombocytopenia as an alternative to heparin and primarily indicated by USFDA only for anticoagulation in patients with heparin induced thrombocytopenia as lepirudin. It should be administered as a 0.4 mg/kg IV bolus over 15-20s followed by a continuous IV infusion of 0.15 mg/kg/hr, with adjustment of the infusion to a target range of 1.5 to 2.5 times the control aPTT values.

- Argatroban

It is approved for the management of patients with HIT (argatroban package insert). The initial dose of argatroban is 2 mcg/kg/min i.v. infusions, with subsequent adjustments to be guided by the aPTT (medical management) or ACT (interventional management). It is ineffective antithrombin agent, hence generally not used in management of ACS.
Bivalirudin

Bivalirudin (formerly called hirulog) is a dodecapeptide derived from hirudin. It binds to the active catalytic site of thrombin via a Phe-Pro-Arg linker molecule. Like hirudin, hirulog inhibits free as well as clot-bound thrombin (Topol 1995). A recent meta-analysis of 6 studies performed until 1999 concluded that bivalirudin is at least as effective as heparin in IHD, with clearly superior safety (Knog et al 1999).

The TIMI-7 trial investigated bivalirudin to treat UA in 410 patients randomized to four groups of constant infusions over 72 hours with 0.02 to 1.0 mg/kg/h (Braunwald 1995). All patients received 325 mg aspirin. The primary endpoint was unsatisfactory outcome by 72 hours defined as death, MI, rapid clinical deterioration and between-group differences. The secondary endpoint, in-hospital death or nonfatal MI occurred in 10% of the patients in the lowest dose group vs. 3.2% of those treated with the three higher doses (p=0.008). The subsequent TIMI-8 trial was undertaken to compare the clinical efficacy of bivalirudin vs. UFH in patients with UA and NSTEMI (Antman et al 2002). The preliminary results were promising.

Four studies compared bivalirudin to heparin as adjunct to thrombolysis with streptokinase in patients with AMI. In an angiographic pilot study of 45 patients hirulog yielded a higher 90-minute patency rate of 77% vs. 47% of the patients treated with heparin (p<0.05). No reocclusions were seen at control angiography performed 4-7 days later (Lidon et al 1994). Theroux et al (1995) randomized 68 patients treated with streptokinase and aspirin for AMI to hirulog 0.5 mg/kg/h over 12 hours followed by 0.1 mg/kg/h (low dose), hirulog 1.0 mg/kg/h followed by placebo (high dose), or standard heparin treatment. At 90 minute angiogram TIMI grade 3 flow of the infarct vessel was found in 85%, 61%, and 31% of the low-dose, and heparin groups respectively (p=0.008). In the Hirulog Early Reperfusion Occlusion (HERO) trial of 412 patients treated with streptokinase for AMI, TIMI-grade 3 flow of the infarct artery was achieved in 46% and 48% of patients treated with low- or high-dose hirulog, vs. only 35% of patients treated with adjunctive heparin (White et al 1997). The combined incidence of death, shock, or reinfarction by day 35 was 12.5% (low dose) and 14.0% (high dose) in the hirulog groups vs. 18.0% in the heparin-treated patients (n.s.), major bleeding occurred in 14% (low dose) and 19% (high dose) with hirulog and in 28% with heparin. These promising
angiographic and clinical results gave rise to the subsequent HERO-2 study with 30-day mortality as the primary endpoint (HERO 2 investigators 2001). 17,073 patients with STEMI treated with streptokinase were randomized to bivalirudin or heparin. The mortality by 30 days was 10.8% (n.s). In-hospitalization due to reinfarction (2.8% vs. 0.5%, p=0.07) was lesser in the bivalirudin group.

Bivalirudin during coronary angioplasty was investigated in a study of 4,098 patients with interventions for unstable or postinfarction angina (Bittl et al 1995). Bivalirudin did not reduce the incidence of ischemic complications, but the bleeding risk was significantly lower on bivalirudin with 3.8% as compared to 9.8% with heparin. In the prospectively stratified subgroup of 704 patients with postinfarction angina, hirulog reduced the incidence of death, MI, or abrupt vessel closure to 9.1% vs. 14.2% in the heparin control group. After six months the rate of death, MI, or repeat revascularization was similar in both groups. This study was performed before the widespread use of coronary stents and of GP IIb/IIIa inhibitors, which attenuate the advantages of bivalirudin. After a promising pilot study of 268 patients (Licoff et al 2002), the REPLACE-2 trial compared bivalirudin and provisional GP IIb/IIIa inhibitors, with heparin and planned GP IIb/IIIa blockage during elective or urgent PCI in 6,010 patients from October 2001 to August 2002 (Lincoff et al 2003). Patients were randomly assigned to intravenous bivalirudin (0.75 mg/kg bolus plus 1.75 mg.kg/h infusion during the procedure) or a 65 U/kg bolus of UFH along with abciximab or eptifibatide. Provisional GP IIb/IIIa blockade was given to 7.2% of the patients on bivalirudin. The primary composite endpoint of 30-day mortality, MI, urgent revascularization, or in-hospital major bleeding occurred in 9.2% of the bivalirudin group vs. 10.0% in the heparin group (n.s.). Thus, the study satisfied prespecified statistical criteria for noninferiority of bivalirudin as compared to heparin plus planned GP IIb/IIIa blockade. The bleeding risk was lower in the bivalirudin group. As compared to patients of two earlier studies treated with heparin only during coronary stenting (ESPRIT investigators 2000, EPISTENT investigators 1998). Bivalirudin was significantly superior to prevent ischemic events and reduce the bleeding risk.
Taken together, the reported trials on bivalirudin demonstrate at least equal efficacy as compared to heparin in the conservative and interventional treatment of ACS with an improved safety reflected by lower bleeding risk.

Antithrombin therapy is of utmost importance in all types of ACS. In unstable angina pectoris the standard treatment consist of intravenous heparin given as a bolus of 5000 IU followed by an infusion of 1000 IU/h adjusted to an aPTT of 50 to 70 seconds. An alternative and at least equally effective treatment is subcutaneous application of LMW heparin; the best data exists for enoxaparin given BID in a dose of 1 mg/kg. The direct thrombin inhibitors are only marginally more effective than heparin, but bivalirudin has a better safety profile and therefore provides a net clinical benefit over heparin. This is especially true for patients with ACS treated interventionally, where bivalirudin with provisional GP IIb/IIIa inhibitors was equally effective as heparin with planned GP IIb/IIIa blockade.

3.4.5.2.3 GP IIb/IIIa inhibitors

The GP IIb/IIIa inhibitors are potent class of antiplatelet drugs. The GP IIb/IIIa receptors are abundant on the platelet surface. When platelets are activated this receptor undergoes a changes in conformation that increase in affinity for binding to fibrinogen and other ligands. The binding of molecules of fibrinogen to receptors on different platelet results in platelet aggregation. This mechanism is independent of the stimulus for platelet aggregation and represents the final and obligatory pathway for platelet aggregation (Lefkovits et al 1995). The platelet GP IIb/IIIa receptor antagonists act by occupying the receptors preventing fibrinogen from binding, and thereby preventing platelet aggregation. GP IIb/IIIa inhibitors should be administered, in addition to aspirin and heparin to those patients in whom catheterization and PCI are planned (Class I). Abciximab, eptifibatide and tirofiban are three agents available for used in UA/NSTEMI. Abciximab is a fab fragment of a humanized murine antibody that has a short plasma half-life but strong affinity for the receptor, which results in some receptor occupancy which persists in part for weeks. Platelet aggregation gradually returns to normal 24 to 48 h after discontinuation of the drug. Abciximab also inhibits the vitronectin receptor (□x,β3) on endothelial cells and the MAC-1 receptor on leukocytes (499,500). Intravenous
administration of GP IIb/IIIa inhibitor abciximab is indicated for PCI while eptifibatide or tirofiban is preferred choice for medical management in addition to initial conservative therapy with aspirin or clopidogrel (Class I, IIa, IIb & III). For UA/NSTEMI patients if recurrent symptoms/ischemia, HF or serious arrhythmias subsequently appears either I.V. GP IIb/IIIa inhibitors of clopidogrel are administered with initial conservatives therapy like aspirin and anticoagulants (Class I). The results of the CAPTURE trial showed a significant reduction in death, MI at six months using abciximab.

3.4.5.3 GP IIb/IIIa inhibitor and PCI/CABG

Relative benefit was seen in patients with GP IIb/IIIa inhibitor and undergoing PCI. From the results of PRISM-PLUS, PURSUIT, and CAPTURE showed a significant reduction in death and MI during a period of 24 hours of medical management (3.8% vs. 2.5%, p=0.001) with that benefit continuing up through the time of PCI. Patients who undergo CABG also appear to derive particular benefit from early treatment with GP IIb/IIIa inhibition.

3.4.5.4 Fibrinolysis

Intravenous fibrinolytic therapy showed no clinical outcome in patients with UA/NSTEMI (Class III).

3.4.5.5 Revascularization
3.4.5.5.1 Percutaneous Coronary Intervention (PCI):

PCI is an effective means of reducing coronary obstruction, impairing acute ischemia, and improving regional and global left ventricular function in patients with UA/NSTEMI (Class I). Current angiographic success rates are high generally >95%, although presence of UA/NSTEMI or visualized thrombus is associated with an increased risk of acute complications such as abrupt closure or MI (as compared with patients with stable angina or those without visualized thrombus) (Zhao et al 1999, Kamp et al 1989). Thus, use of GP IIb/IIIa inhibitors, clopidogrel and bivalirudin, or other antithrombotic drugs improves acute and long-term outcomes following PCI. Use of drug eluting stents has been shown to reduce the risk of restenosis (Moses et al 2003) further enhancing
the overall clinical benefit of an invasive approach (for details, refer procedure described in STEMI treatment strategies).

3.4.5.5.2 Percutaneous Coronary Intervention (PCI) versus Coronary artery bypass graft (CABG):

When revascularization is required in patients with UA/NSTEMI, the choice is between PCI and CABG. More than eight trials have compared PCI and CABG in patients with IHD, many of whom had UA/NSTEMI (BARI investigators 1996, Morrison 2002). On the basis of the results of these trials, CABG is recommended for patients with disease of left main coronary artery, multiple vessel disease, and impaired left ventricular function. For other patients PCI or CABG may be suitable. PCI is associated with a slightly lower initial morbidity and mortality than CABG but a higher rate of repeated procedures; CABG is associated with more effective relief from angina.

3.4.5.6 Intraaortic balloon counterpulsation (IABP)

IABP is an effective means of increasing diastolic coronary blood flow and reducing left ventricular after load, which act in concert to reduce ischemia. IABP is usually reserved for the patients with UA/NSTEMI who are refractory to maximal medical therapy, those with hemodynamic compromise who are awaiting cardiac catheterization, or those with very high risk coronary anatomy (e.g., left main stenosis) as a bridge of PCI or CABG (Class IIa). Although no randomized trials have documented the benefit of IABP, this method is effective in stabilizing patients with refractory ischemia.

3.4.5.7 Summary: Acute Management of UA or NSTEMI

The evaluation of patients with UA/NSTEMI begins with the clinical history; ECG, and measurement of cardiac biomarkers to assess the likelihood of coronary disease and the patient's risk of death or recurrent cardiac events. Patients with low likelihood of having UA/NSTEMI should undergo a "diastolic pathway" evaluation through serial ECGs, cardiac biomarkers, and early stress testing to evaluate for coronary disease. This evaluation can be frequently accomplished in an emergency department observation-chest pain unit. For patients with a clinical history strongly consistent with
UA/NSTEMI, those at low risk should be treated with antithrombotic therapy with aspirin, clopidogrel, and either heparin or LMWH, beta blocker, and nitrates. An early conservative strategy is equally clinically beneficial. For high-risk patients (e.g. those with positive troponin, ST segment changes, TIMI risk score>3), GP IIb/IIIa inhibitors are added to the preceding medications and an early invasive strategy is preferred.
Table 3.10: Dosing Table for Antiplatelet and Anticoagulant Therapy in Patients with UA/NSTEMI (Anderson et al 2007)

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Initial Medical treatment</th>
<th>Patient Received Initial Medical Treatment</th>
<th>During PCI Patient Did Not Receive Initial Medical Treatment</th>
<th>After PCI</th>
<th>At Hospital Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Oral Antiplatelet Therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>162 to 325 mg nonenteric formulation, orally or chewed</td>
<td>No additional treatment</td>
<td>162 to 325 mg Nonenteric formulation orally or chewed</td>
<td>162 to 325 mg daily should be given† for at least 1 month after BMS implantation, 3 months after SES implantation, and 6 months after PES implantation, after which daily chronic aspirin should be continued indefinitely at a dose of 75 to 162 mg</td>
<td>162 to 325 mg daily should be given† for at least 1 month after BMS implantation, 3 months after SES implantation, and 6 months after PES implantation, after which daily chronic aspirin should be continued indefinitely at a dose of 75 to 162 mg</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>LD of 300 to 600 mg orally; MD of 75 mg orally/day</td>
<td>A second LD of 300 mg orally may be given to supplement a prior LD of 300 mg</td>
<td>LD of 300 to 600 mg orally</td>
<td>For BMS: 75 mg daily for at least 1 month and ideally up to 1 year. For DES, 75 mg daily for at least 1 year (in patients who are not at high risk of bleeding)</td>
<td>For BMS: 75 mg daily for at least 1 month and ideally up to 1 year. For DES, 75 mg daily for at least 1 year (in patients who are not at high risk of bleeding)</td>
</tr>
<tr>
<td>Ticlopidine</td>
<td>LD of 500 mg orally; MD of 250 mg orally twice daily</td>
<td>No additional treatment</td>
<td>LD of 500 mg orally</td>
<td>MD of 250 mg orally twice daily (duration same as clopidogrel)</td>
<td>MD of 250 mg orally twice daily (duration same as clopidogrel)</td>
</tr>
</tbody>
</table>

**Anticoagulants**

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Initial Medical treatment</th>
<th>Patient Received Initial Medical Treatment</th>
<th>During PCI Patient Did Not Receive Initial Medical Treatment</th>
<th>After PCI</th>
<th>At Hospital Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bivalirudin</td>
<td>0.1 mg/kg bolus, 0.25 mg/kg/h infusion</td>
<td>0.5 mg/kg bolus, increase infusion to 1.75 mg/kg/h</td>
<td>0.75 mg per kg bolus, 1.75 mg/kg/h infusion</td>
<td>No additional treatment or continue infusion for up to 4 h</td>
<td></td>
</tr>
<tr>
<td>Dalteparin</td>
<td>120 IU/kg SC every 12 h (maximum 10,000 IU twice daily)</td>
<td>IV GP IIb/IIIa planned: target ACT 200 s using UFH, No IV GP IIb/IIIa planned: target ACT 250 to 300 s for</td>
<td>IV GP IIb/IIIa planned: 60 to 70U/kg§ of UFH No IV GP IIb/IIIa planned: 100 to 140 U/kg of UFH</td>
<td>No additional treatment</td>
<td></td>
</tr>
<tr>
<td>Drug*</td>
<td>Initial Medical treatment</td>
<td>Patient Received Initial Medical Treatment</td>
<td>During PCI Patient Did Not Receive Initial Medical Treatment</td>
<td>After PCI</td>
<td>At Hospital Discharge</td>
</tr>
<tr>
<td>-------</td>
<td>--------------------------</td>
<td>------------------------------------------</td>
<td>-----------------------------------------------------------</td>
<td>---------</td>
<td>---------------------</td>
</tr>
<tr>
<td>Enoxaparin</td>
<td>LD of 30 mg IV bolus may be given MD 1 mg/kg SC every 12 h; extend dosing interval to 1 mg/kg every 24 h if estimated creatinine clearance &lt;30 mL/min</td>
<td>Last SC dose less than 8 h: no additional Therapy. Last SC dose greater than 8 h: 0.3 mg/ kg IV bolus</td>
<td>0.5 to 0.75 mg/kg IV bolus</td>
<td>No additional treatment</td>
<td></td>
</tr>
<tr>
<td>Fondaparinux</td>
<td>2.5 mg SC once daily. Avoid for creatinine clearance &lt;30 mL/min</td>
<td>50 to 60 U/kg IV bolus of UFH is recommended by the OASIS 5 Investigators†</td>
<td>50 to 60 U/kg IV bolus of UFH is recommended by the OASIS 5 Investigators†</td>
<td>No additional treatment</td>
<td></td>
</tr>
<tr>
<td>UFH</td>
<td>LD of 60 U/kg (max 4,000 U) as IV bolus MD of IV infusion of 12 U/kg/h (max 1,000 U/h) to maintain aPTT at 1.5 to 2.0 times control (apprx 50 to 70 s)</td>
<td>IV GP IIb/IIIa planned: target ACT 200 s No IV GP IIb/IIIa planned: target ACT 250 to 300 s for HemoTec; 300 to 350 s for Hemochron</td>
<td>IV GP IIb/IIIa planned: 60 to 70 U/kg§ No IV GP IIb/IIIa planned: 100 to 140 U per kg</td>
<td>No additional treatment</td>
<td></td>
</tr>
</tbody>
</table>

**Intravenous Antiplatelet Therapy**

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Initial Medical treatment</th>
<th>Patient Received Initial Medical Treatment</th>
<th>During PCI Patient Did Not Receive Initial Medical Treatment</th>
<th>After PCI</th>
<th>At Hospital Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Abciximab</td>
<td>Not applicable</td>
<td>Not applicable</td>
<td>LD of 0.25 mg/kg IV bolus MD of 0.125 mcg/kg/min (max 10 mcg per min)</td>
<td>Continue MD infusion for 12 h</td>
<td></td>
</tr>
<tr>
<td>Eptifibatide</td>
<td>LD of IV bolus of 180 mcg/kg MD of IV infusion of 2.0 mcg/kg/min; reduce infusion by</td>
<td>Continue infusion</td>
<td>LD of IV bolus of 180 mcg/kg followed 10 min later by second IV bolus of 180 mcg/kg MD of 2.0 mcg/kg/min;</td>
<td>Continue MD infusion for 18 to 24 h</td>
<td></td>
</tr>
</tbody>
</table>
## Review of Literature

Additional considerations include the possibility that a conservatively managed patient may develop a need for PCI, in which case an intravenous bolus of 50 to 60 U per kg is recommended if fondaparinux was given for initial medical treatment; the safety of this drug combination is not well established. For conservatively managed patients in whom enoxaparin was the initial medical treatment, as noted in the table, additional intravenous enoxaparin is an acceptable option. This list is in alphabetical order and is not meant to indicate a particular therapy preference. In patients in whom the physician is concerned about the risk of bleeding, a lower initial ASA dose after PCI of 75 to 162 mg/d is reasonable (Class IIa, LOE: C). Dalteparin was evaluated for management of patients with UA/NSTEMI in an era before the widespread use of important therapies such as stents, clopidogrel, and GP IIb/IIIa inhibitors. Its relative efficacy and safety in the contemporary management era is not well established. Some operators use less than 60 U per kg of UFH with GP IIb/IIIa blockade, although no clinical trial data exist to demonstrate the efficacy of doses below 60 U per kg in this setting. For patients managed by an initial conservative strategy, agents such as enoxaparin and fondaparinux offer the convenience advantage of SC administration compared with an intravenous infusion of UFH. They are also less likely to provoke heparin-induced thrombocytopenia than UFH. Available data suggest fondaparinux is associated with less bleeding than enoxaparin in conservatively managed patients using the regimens listed. Personal communication to OASIS 5 Investigators on July 7, 2006. This regimen has not been rigorously tested in prospective randomized trials. ACT _ activated clotting time; BMS _ bare-metal stent; GP _ glycoprotein; h _ hour; IU _ international unit, IV _ intravenous, LD _ loading dose, MD _ maintenance dose; PCI _ Percutaneous coronary intervention; PES _ paclitaxel-eluting stent; SC _ subcutaneous, SES _ sirolimus-eluting stent; U _ units, UA/NSTEMI _ unstable angina/non-ST-elevation myocardial infarction, UFH _ unfractionated heparin.

<table>
<thead>
<tr>
<th>Drug*</th>
<th>Initial Medical treatment</th>
<th>Patient Received Initial Medical Treatment</th>
<th>During PCI Patient Did Not Receive Initial Medical Treatment</th>
<th>After PCI</th>
<th>At Hospital Discharge</th>
</tr>
</thead>
<tbody>
<tr>
<td>Tirofiban</td>
<td>LD of IV infusion of 0.4 mcg/kg/min for 30 min MD of IV infusion of 0.1 mcg/kg/min; reduce rate of infusion by 50% in patients with estimated creatinine clearance &lt;30 mL/min</td>
<td>Continue infusion</td>
<td>LD of IV infusion of 0.4 mcg/kg/min for 30 min MD of IV infusion of 0.1 mcg/kg/min; reduce rate of infusion by 50% in patients with estimated creatinine clearance &lt;30 mL/min</td>
<td>Continue MD infusion for 18 to 24 h</td>
<td></td>
</tr>
</tbody>
</table>
3.5 FUTURE TRENDS IN THE IHD/CAD PRESENTING WITH ACS:

Platelets are major players in arterial thrombosis and antiplatelet therapy has a clear benefit in the treatment and prevention of cardiovascular events. Antiplatelet agents are essential for the primary and secondary prevention of ACS. In particular, aspirin and clopidogrel have become cornerstones in the treatment of patients with atherothrombosis. However, despite the proven efficacy of antiplatelet drugs, cardiovascular events remain an important cause of morbidity and mortality in these patients (Depta et al 2009). Since the first angioplasty performed in 1977, improvements in techniques and devices have allowed a large diffusion of this revascularization procedure for CAD antherothrombosis and have also optimized the degree of reperfusion in STEMI. Intravascular metallic stents significantly reduced the risk of procedure-related complications but only provided a limited solution to the emerging problem of restenosis. DESs were introduced recently as an advanced alternative to BMS. DESs dramatically reduce the rate of restenosis; however, they may represent a trade-off with regard to the higher risks of stent thrombosis. Antiplatelet therapy is efficient in preventing DES thrombosis. However, this therapy could be optimized and may be improved in the future (Ducroq et al, 2007). Furthermore, a considerable variability in platelet reactivity during treatment with established oral antiplatelet therapy has prompted the search for novel drugs against platelet-dependent thrombosis. The concept of resistance to aspirin and clopidogrel is still an emerging and important clinical question. Newer ADP antagonists may be promising alternatives to currently available antiplatelet therapies for the treatment of ACS and for patients undergoing PCI. Possible benefits of upcoming drugs include a more efficient platelet inhibition and a reversible effect on platelet function (Depta et al 2009).

3.5.1 Novel trends in Biomarkers:

Besides markers of myocardial necrosis, markers of pathophysiological mechanisms implicated in ACS are under investigation and could become useful to determine pathophysiology, individualize treatment, and evaluate therapeutic effects. In considering the clinical application of new biomarkers, it is important to determine that they provide incremental value over existing biomarkers. A multimarker approach to risk
stratification of UA/NSTEMI (e.g., simultaneous assessment of cTnl, C-reactive protein [CRP], and BNP) has been advocated as a potential advance over single biomarker assessment. Further evaluation of a multimarker approach will be of interest (Anderson et al 2007).

3.5.1.1 Ischemia

Other new biochemical markers for the detection of myocardial necrosis are either less useful or have been less well studied than those mentioned above. An example is ischemia-modified albumin found soon after transient coronary occlusion and preceding any significant elevations in myoglobin, CK-MB, or cTnl. This modified albumin depends on a reduced capacity of human albumin to bind exogenous cobalt during ischemia. Choline is released upon the cleavage of phospholipids and could also serve as a marker of ischemia. Growth-differentiation factor-15 (GDF-15), a member of the transforming growth factor cytokine superfamily that is induced after ischemia and reperfusion injury, is a new biomarker that has been reported to be of incremental prognostic value for death in patients with UA/NSTEMI (Anderson et al 2007).

3.5.1.2 Coagulation

Markers of activity of the coagulation cascade, including elevated plasma levels of fibrinogen, the prothrombin fragments, fibrinopeptide, and D-dimers, are elevated in ACS but have little discriminative ability for a specific pathophysiology, diagnosis, or treatment assessments. In experimental studies, markers of thrombin generation are blocked by anticoagulants but reactivate after their discontinuation and are not affected by clopidogrel (Anderson et al 2007).

3.5.1.3 Platelets

Platelet activation currently is difficult to assess directly in vivo. New methods, however, are emerging that should allow a better and more efficient appraisal of their state of activation and of drug effects. Alternative markers of platelet activity are also being studied, including CD40L, platelet-neutrophil coaggregates, P-selectin, and platelet microparticles (Anderson et al 2007).
3.5.1.4 Inflammation

Systemic markers of inflammation are being widely studied and show promise for providing additional insights into pathophysiological mechanisms proximal to and triggering thrombosis, as well as suggesting novel therapeutic approaches. White blood cell counts are elevated in patients with MI, and this elevation has prognostic implications. Patients without biochemical evidence of myocardial necrosis but who have elevated CRP levels on admission or past the acute-phase reaction after 1 month and who have values in the highest quartile are at an increased risk of an adverse outcome. Elevated levels of interleukin-6, which promotes the synthesis of CRP and of other proinflammatory cytokines also, have been studied for their prognostic value. Other potentially useful markers are levels of circulating soluble adhesion molecules, such as intercellular adhesion molecule-1, vascular cell adhesion molecule-1, and E-selectin; the pregnancy-associated plasma protein-A, which is a zinc-binding matrix metalloproteinase released with neovascularization and believed to be a marker of incipient plaque rupture; myeloperoxidase, a leukocyte-derived protein that generates reactive oxidant species that contribute to tissue damage, inflammation, and immune processes within atherosclerotic lesions and others (Anderson et al 2007).

3.5.1.5 B-Type Natriuretic Peptides (BNP)

One newer biomarker of considerable interest that now may be considered in the guidelines recommendations is BNP. BNP is a cardiac neurohormone released upon ventricular myocyte stretch as proBNP, which is enzymatically cleaved to the N-terminal proBNP (NTproBNP) and, subsequently, to BNP. The usefulness of assessing this neurohormone was first shown for the diagnosis and evaluation of HF. Since then, numerous prospective studies and data from large data sets have documented its powerful prognostic value independent of conventional risk factors for mortality in patients with stable and unstable CAD. A review of available studies in ACS showed that when measured at first patient contact or during the hospital stay, the natriuretic peptides are strong predictors of both short- and long-term mortality in patients with STEMI and UA/NSTEMI. Increasing levels of NT-proBNP are associated with proportionally higher short- and long-term mortality rates; at 1 year, mortality rates with increasing quartiles
were 1.8%, 3.9%, 7.7%, and 19.2%, respectively ($p < 0.001$) in the GUSTO-IV trial of 6,809 patients. This prognostic value was independent of a previous history of HF and of clinical or laboratory signs of LV dysfunction on admission or during hospital stay. B-type natriuretic peptide and NT-proBNP levels can now be measured easily and rapidly in most hospital laboratories (Anderson et al 2007).

3.5.2 Novel trends in Drugs:

3.5.2.1 Cilostazol

Cilostazol selectively inhibits 5’3’-cyclic nucleotide phosphodiesterase III and has antiplatelet and vasodilating effects. This agent also inhibits smooth muscle cell proliferation in vitro (Ducroq et al, 2007).

3.5.2.2 Cangrelor

Cangrelor is an ATP analogue, and an intravenous reversible P2Y12 inhibitor. The short plasma half-life (3-5 min) results in a full recovery of platelet activity within 60 min. Cangrelor is a strong platelet inhibitor and results in a near complete inhibition of platelet aggregation (Ducroq et al, 2007). However, Phase III trial was recently discontinued (May 2009) because it failed to achieve primary endpoint. Cangrelor can only be administered intravenously, which will limit its utilization to the acute clinical conditions (cardisource.com).

3.5.2.3 Ticagrelor

It is P2Y12 receptor antagonist. It does not need metabolism to be active; however, it is metabolized into an active metabolite that participate its activity. This antithrombotic agent inhibits both platelet activation and aggregation in a reversible manner for the treatment of arterial thrombosis in patients with ACS. A Phase III study is ongoing “A study of Platelet inhibition and patient Outcomes (PLATO) comparing its efficacy with clopidogrel in ACS patients. The primary endpoint is composite of cardiovascular events (Ducroq et al, 2007).

3.5.2.4 Prasugrel
Prasugrel is an oral thienopyridine. Its antiplatelet action is due to irreversible and selective blockade of P2Y12 by its active metabolite. It exhibits more potent and rapid platelet inhibition than clopidogrel in vitro (Ducroq et al, 2007). It is recently (April 8, 2009) launched in UK for the treatment of ACS. In the pivotal trial TRITON-TIMI 38 compared against clopidogrel in ACS patients who are undergoing PCI, prasugrel has showed 19% reduction in relative risk for the composite endpoint of cardiovascular death, non-fatal heart attack or non-fatal stroke. Relative risk of CV complications was reduced by 30%, 21% and 18%, in patients with diabetes, STEMI and UA, respectively. The recurrence of stent thrombosis was reduced by 52%. However, major bleeding (2.4% vs. 1.8%), rate of life-threatening bleeding (1.4% vs. 0.9%), nonfatal bleeding (1.1% vs. 0.9%) and fatal bleeding (0.4% vs. 0.1%) was reported high in prasugrel (Wiviott et al 2007).

3.5.2.5 Platelet adhesion antagonists

Theoretically, all of the steps involved in platelet activation and coagulation are potential targets to prevent DES thrombosis after stent implantation. Blocking platelet adhesion to subendothelium (which is the first step of stent thrombosis) could be of particular interest. Since the interaction between GPIbζ is the very first step of platelet adhesion to subendothelium blocking the GPIb-IX-V/vWF pathway could be advantageous. This strategy was shown to be effective in different animal models. Blocking GPVI/collagen interaction could be another strategy of platelet adhesion inhibition. This target of therapy was shown to prevent thrombosis in rodent models. However, the efficacy of this strategy in the context of stenting has yet to be determined (Ducroq et al, 2007).

3.5.2.6 Rivaroxaban

It is factor Xa receptor antagonist, checking its activity in patients with deep vein thrombosis (DVT). It is ongoing two large scale multinational Phase III studies in ACS patients with prior MI and peripheral artery disease (PAD), and other one in NSTEMI patients for the treatment and prevention of cardiac events (Ducroq et al, 2007).

3.5.2.7 SCH 530348
It is PAR 1 receptor antagonists or thrombin inhibitors.

3.5.3 Novel trends in Devices:

3.5.3.1 Coronary Artery Stents

New DESs are under development and the safety of these devices has become of major clinical importance (Ducroq et al, 2007).

3.5.3.1.1 The Endeavor™ DES

It is a stent eluting zotarolimus (a drug from the same family as the sirolimus eluted from the Cypher stent) from a phosphorylcholine polymer developed by Medtronic. Its more rapid eluting profile could be critical for a better late endothelialization. The 2 year follow-up of the Endeavor III study presented at the recent ACC Congress in 2007 confirms no events of late stent thrombosis up to 2 years in the Endeavor group (Ducroq et al, 2007).

3.5.3.1.2 Bioresorbable materials

New concepts are emerging in order to increase the safety of DESs. Of the most interesting are bioresorbable polymers and bioresorbable stents. Bioresorbable materials for the stent itself are currently under development. To achieve such a goal magnesium could be the metal of choice. Poly-l-lactic acid could be even more promising. While the concept of such bioresorbable DESs is promising, larger studies are necessary to evaluate the future clinical utility of these devices (Ducroq et al, 2007).

3.5.3.1.3 Other strategies

‘Prohealing approaches’ are also of interest to reduce stent thrombosis. A preliminary study in humans assessed the implantation of stents coated with CD34 antibodies in order to ‘capture’ endothelial progenitor cells. This strategy was shown to be both feasible and safe; however, the efficacy still needs to be determined (Ducroq et al, 2007).

Coating stents with antiplatelet drugs could also be a promising way to prevent stent thrombosis. In a recent randomized study an acute STEMI context to an abciximab-coated stent or a BMS. During 1 year follow up, two patients in the BMS group had a
recurrent AMI whereas to patient in abciximab-coated stent suffered an AMI. Although this strategy seems intriguing, large studies are required to draw appropriate conclusions (Ducroq et al, 2007).

3.5.3.2 Atherectomy

Rotational atherectomy is the most common atherectomy procedure and is used to treat complex lesions and in-stent restenosis. Directional atherectomy is used rather infrequently but is useful for treating non-calcific ostial lesions. Orbital atherectomy has not been used extensively since it is a new procedure and TEC has fallen out of favor among cardiologists. Atherectomy can also prove very useful when used before stent placement or angioplasty. Removing atherosclerotic plaque before these procedures relieves stress applied to the artery walls when the plaque in compacted.

3.5.3.3 Excimer laser coronary angioplasty (ELCA)

ELCA offers a unique approach to the treatment of bifurcation lesions that continues to present a challenge in PCI. Debunking plaque prior to stenting or balloon angioplasty has demonstrated significant improvement in the treatment of bifurcation lesions. Clot dissolution properties of excimer laser combined with its ability to debulk, makes this device unique when applied to thrombus-laden bifurcation lesions. ELCA is the only debunking technique that allows retention of two guide wires with resultant protection of the bifurcation vessels during the debunking procedure.

3.5.3.4 Mechanical thrombectomy devices

The AngioJet® Xpeedior® Rheolytic™ Thrombectomy catheter is designed to offer the ultimate in thrombectomy performance. Powerful saline jets create a low pressure zone around the catheter tip causing a vacuum effect. Thrombus is drawn into the catheter, where it is fragmented by the jets, and removed from the body. AngioJet thrombectomy provides rapid restoration of flow in minutes, as opposed to hours with lytic therapy. In those patients non-responsive to pharmacotherapy, the application of mechanical thrombectomy devices (MTDs) is expanding to encompass a greater range of thrombotic sites. These devices fall into two broad categories, those that fragment the
thrombus, with or without clot removal and those that contact the vessel wall. The advantages of MTDs can include faster reperfusion of ischemic limbs, potentially shorter hospital stays than those required for lytic drug administration alone, and lower rates of rethrombosis. MTD therapy also may provide comparative advantages of safety by leading to fewer bleeding complications, because they can reduce lytic drug doses, or eliminate them altogether. This theoretical advantage, however, must be balanced against device risks such as distal embolization, hemolysis, and vessel wall damage, the likelihood of which varies with each specific device and application.

Mechanical thrombolytic devices have become the mainstay of percutaneous treatment of clotted dialysis grafts. Properly used, they are faster, safer and equally or more effective than chemical lysis. Surgical literature indicates that removing wall-adherent material (clot and pseudointima) is not only desirable but also essential for improved patency of these grafts. Currently, only two wall-contact devices are approved by the FDA for de-clotting synthetic dialysis grafts: the Arrow-Trerotola percutaneous thrombolytic device from Arrow International, Reading, Penna. and the Akonya Eliminator from IDev Technologies, Houston.

In a broader category, the AngioJet (Possis Medical, Inc., Minneapolis) is the only thrombectomy system currently approved for peripheral arterial applications; although many other MTDs have been used off-label for this purpose. The AngioJet is a dual lumen catheter designed to rapidly remove blood clots with minimal vascular trauma. AngioJet System removes blood clots in leg arteries, native coronary arteries and coronary bypass grafts and access grafts used by patients on kidney dialysis, respectively. The AngioJet System is typically used in conjunction with other medical devices, such as angioplasty balloons and stents (both bare metal and drug eluting), and drugs, such as thrombolytics and platelet inhibitors. When compared with urokinase in the randomized VeGAS 2 Trial, AngioJet therapy yields greater angiographic success with a lower incidence of 30-day major adverse events.

The Trellis, manufactured by Bacchus Vascular, Inc., Santa Clara, Calif., is a novel drug infusion device designed for isolated thrombolysis. A thrombus is isolated

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between two occlusion balloons while the thrombolytic is mechanically dispersed with an oscillating wire and then aspirated. Theoretically, isolated thrombolysis enables single-setting thrombolysis by delivering a high concentration of thrombolytic agent while preventing systemic dispersion. Adjunctive procedures may be performed in the same single setting. Data from a voluntary company registry for isolated thrombolysis have indicated lower hospital costs due to reduced ICU stay and lytic dosing, and no reported bleeding complications. Bacchus reports that a future registry is planned. The Trellis is approved for use in the peripheral vasculature. The AngioJet® Thrombectomy system is the most advanced catheter-based thrombectomy system available today. The intricately designed components of the system are designed to offer safety, power, performance and versatility. The AngioJet System offers many advantages over alternative treatments; the most important being safety monitoring and balanced, isovolumetric flow. In all, the AngioJet System provides the best method for rapid, decisive thrombectomy. HYDROLYSER Percutaneous Thrombectomy Catheter is a multi-lumen, over-the-wire thrombectomy catheter designed for rapid, effective and easy removal of fresh, soft thrombus in dialysis shunts. The HYDROLYSER provides an efficient, patient-friendly alternative to surgery and thrombolytic therapy. It is compatible with the existing contrast power injector. Fragments and thrombus is removed and helps to reduce the risk of embolization. It has no moving parts to minimize the potential for damage to the graft wall, accepts guidewires up to 0.025" to facilitate catheter introduction and positioning. A conventional contrast power injector is used to inject saline solution through the injection lumen. Resultant pressure reduction at the tip nozzle (Venturi Effect) created a 360° vortex that fragments and aspirates thrombus into the exhaust lumen. Thrombolytic material is discharged through the exhaust lumen into a collection bag. The X-SIZER® system is a single-use, disposable catheter system for thrombus removal in native coronary arteries and saphenous vein grafts. It is self-contained system featuring stainless steel cutter and continuous evacuation. It is available in two sizes: 1.5 mm and 2.0 mm.

3.5.3.5 Coronary ultrasound thrombolysis

This device is developed as a potential alternative to angioplasty that uses high frequency sound waves to dislodge and dissolve the fatty plaques on the walls of
coronary arteries. A long probe with three wires at the tip that transmit the ultrasound waves is inserted into the artery through a standard angioplasty catheter. High power pulses of high frequency ultrasound waves are delivered three times at one minute intervals. Initial experiments have found that this treatment effectively reopens clogged arteries with a relatively low restenosis rate.

3.5.3.6 Distal embolic protection devices

Preventing embolization of atheromatous plaques therefore seems to be a logical "first step" in avoiding complications of atherosclerosis. One of the most important events that trigger plaque embolization is removal of the atheroma during surgical or intervention, such mechanical disruption of the plaque often releases a shower of emboli downstream, sometimes with devastating intra- or post-operative complications. Creating a device that can prevent intra-operative embolization has been a major focus of effort over the past decade, and such "distal embolic protection devices" (DPDs) are quickly becoming an essential feature of interventional cardiology.

The concept of DPD was first demonstrated clinically by Jacques Theron, who used cerebral protection during carotid angioplasty and stenting. Since then, there has been an explosion of interest in DPDs. Current applications include carotid stenting as well as interventions on degenerated saphenous vein grafts. In addition, it is likely that indications for DPDs will soon expand to be used during intervention for the ACS. Two different types of DPDs are available in the United States. The first is a balloon system that temporarily occludes the vessel distal to the lesion during the intervention, thereby capturing and aspirating the atheromatous and thrombotic debris liberated by the lesion before it reaches the capillary bed. The second device is a filter system that does not occlude blood flow; instead, it preserves flow but captures thrombi (as little as 100 µm) through small pores. An alternative to DPD is a balloon placed proximal to the lesion and used to occlude the artery, thereby reversing the flow from the artery; such a device is available for reversing flow from the internal carotid artery (Parodi Anti-embolization catheter, ArteriA, San Francisco, CA).

Several landmark trials have demonstrated the capacity of DPDs to capture dislodged emboli and reduce complications. The Saphenous Vein Graft Angioplasty Free
of Emboli Randomized (SAFER) trial showed significant efficacy of a DPD towards reducing major adverse cardiac events in the treatment of degenerated saphenous vein grafts. More recently, data from the Stenting and Angioplasty with Protection in Patients at High Risk for Endarterectomy (SAPPHIRE) trial – which randomized 307 high-risk patients to either carotid artery stenting (CAS) with protection or carotid endarterectomy (CEA) – indicated that 30-day major adverse clinical event rates (e.g. stroke, death or MI) were 5.8% for CAS and 12.6% for CEA. Importantly, the FilterWire EX Randomized Evaluation (FIRE) trial has shown that similar results are obtained when distal balloon occlusive devices are compared with non-occlusive filter devices. While DPDs are quickly becoming standard of care for carotid artery stenting and interventions for degenerated saphenous vein grafts, their full potential is likely to be realized if they can be used successfully for the ACS. Several issues may need to be addressed in greater detail before these devices can be used routinely for ACS interventions. DPDs represent an exciting, useful new technology, and refinements to existing DPDs will continue to expand their use in interventional cardiology. The Guardwire Temporary Occlusion and Aspiration System have demonstrated a reduction in cumulative MACE events following saphenous vein graft interventions. This life-saving technology is easier to use, featuring the new EZ Adaptor device, which works seamlessly with the EZ Flator inflation device. The Guardwire System is a simple and elegant solution to distal protection. With the new EZ Adaptor device, just one turn of the knob clamps and seals the wire and opens the Microse.

The Rubicon Filter System is an embolic protection device that safely traps and removes much of the debris that may be dislodged during interventional procedures. The Rubicon Filter System comprises several components. The first is a guidewire-mounted filter, and the second is a capture catheter. Other ancillary components supplied with the system for convenience of use include an introducer, a syringe for flushing the capture catheter, and two torque devices.

3.5.3.7 Chronic Total Occlusion (CTOs) Crossing wires

The inability to pass a guidewire through an occluded segment into the distal lumen is a major cause of failure in CTOs. Several alternative devices have been
evaluated as adjuncts to conventional wires in patients with CTOs which includes excimer laser tipped wire, The safe-cross wire®, LuMend Frontrunner® Wire and FlowCardio CROSSER Ultrasound device.

3.5.4 Novel trends in therapy (Genome/Stem Cell)

Understanding the genomic influences ACS has recently emerged as a new avenue towards individualized therapy and the genetic variations in platelet biology which may change the course of antiplatelet therapy in the future. Advances in pharmacogenomics are on horizon and may change the landscape of how ACS and PCI should be managed in individualized antithrombotic regimens may include specific therapy based on patients’ platelet reactivity to that specific agent (Depta et al 2009).

The field of stem cell research has exploded in recent years. Several types of cells are currently being assessed for beneficial effects on myocardial damage resulting from MI. However, the most efficacious type of stem cell and the most beneficial mode of delivery remain unclear. These questions must be answered to optimize the eventual use of stem cells for the treatment of a wide array of CVDs (Wold et al 2005).

3.5.5 Others

From a strategic perspective, the single biggest issue looming on the horizon is an anticipated regulatory change. Specifically, there is a growing expectation that the ACC and other governing bodies will soon adopt a position that supports provision of primary angioplasty at facilities that do not have on-site open heart surgery programs.