Coronary Artery Disease
Heart Disease

• Heart disease is a general term that refers to a variety of acute and chronic medical conditions that affect one or more of the components of the heart

• It is either acquired at birth (congenital) or later in life and could result from:

  ✓ compromised status of the coronary artery that nourishes the heart muscle, as seen in coronary artery disease (CAD)

  or

  ✓ compromised status of the muscles and valves of the heart or its impulse conduction system
Coronary Artery Disease (CAD)

- CAD develops when a combination of fatty material, calcium, and scar tissue (plaque) builds up in the coronary arteries.

- The resulting condition, called **atherosclerosis**.

- The plaque often narrows the artery so that the heart does not get enough blood.
  - Partial block: it causes angina.
  - Full block: it causes a myocardial infarction or a heart attack!
Coronary Artery Disease - Bare Facts

• In 2001, 17 million people died of cardiovascular disease

• According to W.H.O report, an estimated 17.5 million people died from cardiovascular disease in 2005, representing 30% of all global deaths. Of these deaths, 7.6 million were due to heart attacks

• By 2015, almost 20 million people will die from CVDs mainly from coronary heart disease
Atherosclerosis

Deposition of Plaques Inside Vessels

Narrowing of Lumen

Compromised Blood Supply

Infarction / Ischaemia
Risk Factor for CAD

- High levels of cholesterol and Low-Density Lipoprotein (LDL) in the blood
- Low level of High-Density Lipoprotein (HDL) in the blood
- High Blood Pressure
- Sedentary life style
- Diabetes Mellitus
- Obesity
- Age
- Family History of Heart Disease - Genetic predisposition
- Stress, Smoking
Outcome......Acute coronary syndrome

• The process central to the initiation of an acute coronary syndrome is disruption of an atheromatous plaque

• Ischemia/Infarction occurs when an atherosclerotic plaque blocks or fissures, ruptures and lodges in a coronary artery

• Thereby, partially or fully blocking blood supply to the myocardium distal to it

  – Partial block ➔ Unstable Angina (UA)

  – Full block ➔ Myocardial Infarction (MI)
Progression of coronary plaque over time Clinical Findings

Acute Coronary Syndromes
Sudden Cardiac Death

Acute silent occlusive process

Endothelial dysfunction

Atherogenic risk factors

Thrombogenic risk factors

Age

20 years

60 years
CAD - an overview of how lab diagnosis may help

Cardiac markers to assess progression to MI

CAD

STABLE ANGINA

Risk Assessment tests

UNSTABLE ANGINA

Typical ECG changes

CARDIAC MARKERS+

NT proBNP to predict risk of HF

MYOCARDIAL INFARCTION

STEMI

No Suggestive ECG clue: Cardiac markers paramount

NSTEMI

Cardiac markers released
Acute Myocardial Infarction (AMI)

- MI is the irreversible necrosis of heart muscle secondary to prolonged ischemia
- This usually results from an imbalance of oxygen supply and demand
- The appearance of cardiac enzymes in the circulation generally indicates myocardial necrosis
Unstable Angina (UA)

- The term, unstable angina, meant to signify the intermediate state between myocardial infarction and the more chronic state of stable angina.
Some Facts

• ~50% of MI occurs in patients with no prior history of heart disease or risk factors
• 6% to 10% of men with STEMI have normal or non-obstructive coronary disease.
• 10% to 25% of women with ACS and STEMI have normal or non-obstructive atherosclerotic coronary
• About 30% of patients with unstable angina have an MI within 3 months of onset
• Overall mortality rate for NSTEMI and STEMI is about 30%, with 50-60% of those patients dying before reaching the hospital.
DIAGNOSTICS IN CAD
The Three Pillars

**Diagnosis**
Confirm Condition  Appropriate Therapy  Proper Levels of Care

**Risk Assessment**
Prevention  
Long Term Health  Cost  
Management  Lifestyle Changes

**Management**
Appropriate Drugs  Monitor Therapy  Minimize Damage  
Minimize Morbidity/Mortality
Screening for presence of CAD [Also known as Ischemic Heart Disease (IHD)]

- Electrocardiogram (ECG)
- Stress Test
- Coronary Angiography

Electrical impulses -> ECG

Blood supply -> TreadMill

Specific sites of narrowing in coronaries -> Coronary Angiography

Shows measures to heart
Role of Clinical Laboratories

**Diagnosis**
- Troponins
- CKMB, Myoglobin
- D-Dimer*

**Risk Assessment**
- Lipid profile
- hsCRP, IL-6#
- Homocysteine
- Diabetes profile
- NT proBNP

**Management**
- D-Dimer*
- hsCRP, IL-6#
- Homocysteine
- Troponin, CK-MB
- Myoglobin
- NT proBNP
Lipid Profile Assessment

- Total serum cholesterol and LDL-C measurements are most widely used in determining risk of CAD and deciding on cholesterol-lowering therapy, however other lipid fractions are also reliable indicators of risk.

- Many individuals who have CAD do not have substantially elevated LDL-C. They have derangement of other lipid fractions, most commonly low levels of high-density lipoprotein cholesterol (HDL-C).

- Both HDL-C and triglyceride are defined as risk factors for the metabolic syndrome, a secondary target of therapy.

- National Cholesterol Education Program (USA, 2002) confirmed that risk assessment with entire lipid profile identifies more high-risk individuals than evaluating LDL-C alone.
Cholesterol

- Cholesterol is a steroid that is essential for life.
- A small amount of the body’s cholesterol circulates in the blood in complex particles called lipoproteins.
- High serum cholesterol is one of the most important factors contributing to risk of Coronary Artery Disease (CAD).
- The death rate due to CAD increases steadily with increasing cholesterol concentration.

**Increased Cholesterol Levels**
- Familial Hypercholesterolemia
- Biliary Obstruction
- Nephrotic Syndrome
- Hypothyroidism

**Decreased Cholesterol Level**
- Severe Liver Insufficiency
- Malnutrition Hyperthyroidism
- Chronic Anemia
Triglycerides

- Triglycerides are the body's storage form for fat.

- Blood tests for triglycerides are usually part of a lipid profile used to identify the risk of developing heart disease.

- When triglycerides are very high (greater than 1000 mg/dL), there is a risk of developing pancreatitis also.

**Elevated Tg Levels**
- Coronary heart Disease
- Familial Hypertriglyceridemia
- Nephrotic Syndrome
- Liver Disease, Alcoholism
- Diabetes, Pancreatitis

**Decreased Tg levels**
- Malnutrition
- Betalipoproteinemia
Very Low Density Lipoprotein (VLDL)

- Very-low-density lipoprotein (VLDL) Cholesterol contains the highest amount of triglyceride.

- VLDL cholesterol is considered a type of "bad cholesterol" because elevated levels are associated with an increased risk of coronary artery disease.
Low Density Lipoprotein (LDL) Cholesterol

- LDL constitutes about 50% of the total lipoprotein mass in human plasma and is very rich in cholesterol.

- LDL is a type of lipoprotein that carries cholesterol in the blood.

- LDL is considered to be undesirable because it deposits excess cholesterol in walls of blood vessel and contributes to “hardening of the arteries” and heart disease.

- Hence, LDL cholesterol is often termed “bad cholesterol”.

- The test for LDL measures the amount of LDL cholesterol in blood.
Direct LDL measurement

**Advantages:**

1. Accurate measurements because of reduced interference from Triglycerides, VLDL even at high TG values.

   - Lab estimation of LDL cholesterol has been most commonly performed by the use of formulas, such as the Friedewald formula [indirect method].
   - However, if this formula is used to calculate LDL in fasting samples having triglycerides > 400 mg/dL, the estimation is incorrect. So the use of this formula is limited to fasting samples with TG <400 mg/dL.

2. Direct LDL value is independent of time of food digestion.

3. The method has high sensitivity and specificity.
Reference Range for Direct LDL

- Optimal: < 100 mg/dL
- Near or Above optimal: 100-129 mg/dL
- Borderline high: 130-159 mg/dL
- Very high: >190 mg/dL
High Density Lipoprotein (HDL) Cholesterol

- HDL carries excess cholesterol back to the liver from peripheral cells.

- Numerous studies demonstrate that low concentrations of HDL-C are associated with increased risk of CAD and myocardial infarction, independent of TC.

- Hence HDL cholesterol is often termed “good cholesterol”. The test for HDL measures the amount of HDL-cholesterol in blood.

- Low levels of HDL (less than 40 mg/dL) also increase the risk of heart disease.
These additional calculated values also help the physician in determining the risk for developing heart disease.

**Cholesterol/HDL Ratio**

**Interpretation**
- Low risk: 0.0 - 3.5
- Moderate risk: 3.5 - 5.0
- High Risk: > 5

**LDL/HDL Ratio**

**Interpretation**
- Normal range: 2.5 – 3
- High Risk: > 3.5
Apolipoprotein (apo) B

- Apo B-100 levels are used, along with other lipid tests, to help determine an individual's risk of developing atherosclerotic heart disease and coronary artery disease (CAD).

- Elevated levels of Apo B-100 correspond to elevated levels of LDL-C and are associated with an increased risk of CAD.

- Increased levels of Apo B-100 are seen in hyperlipidemia, diabetes, hypothyroidism, nephrotic syndrome etc.

- Lower levels are seen in hyperthyroidism, malnutrition, Reye syndrome, cirrhosis etc.

- A low ratio of Apo A-I to Apo B-100 (A/B) may indicate a higher risk of developing coronary artery disease.
Apolipoprotein a1

• It is the major protein component of high density lipoprotein (HDL) in plasma

• ApoA-1 helps to clear cholesterol from arteries. Thus its high level denotes “good” prognosis

• ApoA-1 was also isolated as a prostacyclin (PGI2) stabilizing factor, and thus may have an anticlotting effect.

Recently, the INTERHEART study established that the ApoB100 / ApoA1 ratio is more effective at predicting heart attack risk than either the ApoB100 or ApoA1 measure alone.

Remember, we have Apolipoprotein Evaluation Panel (Test Code 1900)
Normal Values

• Blood pressure (NORMAL) - <120/<80 mm of Hg

• Cholesterol - <200mg/dl

• Triglyceride - <150mg/dl

• LDL - <100mg/dl

• HDL - >40 mg/dl
### Risk Assessment Tests

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Diagnosis

Biochemical Cardiac Markers

Cardiac markers are substances released from heart muscle when it is damaged, and can be measured in blood samples.

Some of the common markers

Markers released from heart
- Myoglobin
- Creatine Kinase-MB
- Troponins (T & I isoforms)
- N-terminal proB-type Natriuretic Peptide

Markers for early diagnosis

Inflammatory markers present in blood
- Homocysteine
- C-reactive protein
- Apolipoprotein (apo) B

Long-term-risk assessment markers
Cardiac Markers

• The recent ACC/AHA guidelines (2007) for the treatment of patients with unstable angina and NSTEMI recommend a baseline sample testing for cardiac markers on Emergency Department arrival and a repeat sample 6-12 hours after symptom onset.

• The markers available with us:
  – Myoglobin
  – CK-MB
  – Trop I

Trop T measurement is generally done qualitatively on the bedside through TropT kits
Myoglobin

- Myoglobin, an oxygen carrying protein present in muscles.
- It is released in the presence of skeletal muscle injury as well as cardiac tissue necrosis.
- Its low molecular weight accounts for its early-release profile.
- Myoglobin typically rises 1-3 hours after onset of infarction and peaks at 6-12 h.
- It is rapidly excreted in the urine, so that blood levels return to the normal range within 24-36 h of the onset of infarction (hence, lacks specificity).
- Because of its rapid-release kinetics, myoglobin is an attractive marker for the early diagnosis of MI.
Creatine Kinase-MB

• CK-MB is the preferred, widely available cardiac biomarker for most patients with STEMI.

• CK-MB first appears 4-6 hours after symptom onset, peaks at 24 hours, and returns to normal in 48-72 hours.

• An early peak of CK-MB (12 to 18 hours) suggests reperfusion.
Troponin

- Cardiac troponins has been declared to be the preferred biomarker for diagnosing MI.

- Troponin is essential for the calcium-mediated regulation of skeletal and cardiac muscle contraction.

- It is a 3-unit complex (troponin I, T and C) with a half-life of about 2 hours.

- Cardiac troponin I and T are very sensitive and specific indicators of damage to the heart muscle (myocardium).

- They are measured in the blood to differentiate between unstable angina and myocardial infarction (heart attack) in patients with chest pain.

Given the nearly absolute myocardial tissue specificity and high sensitivity for even microscopic zones of myocardial necrosis, the American College of Cardiology and the European Society of Cardiology have declared cardiac troponins to be the preferred biomarker for diagnosing MI.
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<td><strong>Troponin I</strong></td>
<td><strong>Serum</strong></td>
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• Cardiac-specific troponins (cTnI/cTnT) should be used as the optimum biomarkers for the evaluation of patients with STEMI who have coexistent skeletal muscle injury.

• Serial biomarker measurements are useful to provide supportive noninvasive evidence of reperfusion of the infarct area after fibrinolytic therapy (i.e. with streptokinase) in patients not undergoing angiography within the first 24 hours after fibrinolytic therapy.

• A more rapidly rising and falling biomarker such as CK-MB or myoglobin is superior for diagnosing reinfarction.
B-type Natriuretic Peptide (BNP)

- B-type Natriuretic Peptide (BNP) produced principally in the cardiac ventricles in response to
  - increased diastolic pressure
  - ventricular stretch &/or stress

- MoA: A protective response
  BNP binds to the natriuretic peptide-A receptor (NPR-A), which, via 3',5' cyclic guanosine monophosphate (cGMP) mediates
  - Vasodilation
  - Natriuresis (Sodium excretion)
  - Diuresis (water excretion)

- Cleared by the natriuretic peptide-C receptor and degraded by the neutral endopeptidase both of which are widely expressed in kidney, lung, and vascular wall.

BP
N-terminal proB-type Natriuretic Peptide (NT-proBNP)

- PreproBNP originally produced in cardiomyocytes of ventricles
- Cleaved in cells to proBNP, secreted in blood and then cleaved in blood to N-terminal pro BNP (76 AA) and BNP (C-terminal, 32 AA); ideally the conc. of each should be equal in serum
- NT-proBNP is markedly more stable in blood and can be assayed from stored or delayed specimens (no need for bed side testing, so absolute quantification possible)
- Sample stability for estimation in Roche Elecsys 2010 system:
  - 3 days at 20-25 degrees C
  - 6 days at 2-8 degree C
  - 12 months at -20 degrees C

Clinical Significance of NT-proBNP

- Exclusion of heart failure: If the level of NT-proBNP is lower than a certain value (< 125 pg/ml) the diagnosis of heart failure is unlikely.
- Applied to:
  - New patients with suspected heart failure
  - Patients presenting with acute dyspnoea in emergency room (ER).
- Screening asymptomatic subjects with high BP, DM, CAD at risk of developing HF
- Screening for left ventricular systolic dysfunction after an acute myocardial infarction
- Prognostic marker in heart failure
  - Predicts mortality in acute coronary syndrome
- In monitoring of patients with heart failure
NT-proBNP Detection Method

- NT-proBNP is detected in serum sample by Electro Chemiluminescence Immuno-Assay (ECLIA) - a two step sandwich immunoassay where two polyclonal antibodies are used, which recognizes epitopes located in the NT-proBNP.

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Inflammation & CAD

- Risk factors for atherosclerosis are high blood pressure, high cholesterol, obesity, and smoking i.e. irritation and disturbance of the normal biology and activity of the arteries.

- This irritation in turn stimulates the production of cells and cytokines that initiate and fuel inflammation.

- There are no outward signs that inflammation is damaging arteries. But the most widely known and commonly used is C-reactive protein.

- CRP levels rise and fall with the intensity of inflammation in the body.
C Reactive protein (CRP)

- CRP is a protein produced by the liver and by adipocytes that is widely secreted during inflammation.

- Inflammation is now believed to represent the underlying mechanism leading to the formation of human atheroma and favouring both
  - the destabilization of vulnerable plaques and
  - the formation of occlusive thrombi.

- The CRP is for seemingly healthy people to determine their risk of cardiovascular disease. It measures CRP in the range from 0.5 to 10 mg/L.

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<td>hsCRP</td>
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hsCRP

- **Low risk** <1.0 mg/L
- **Average risk** 1.0 – 3.0 mg/L
- **High risk** >3.0 mg/L
- **Very high risk** ≥10.0 mg/L
What is the difference between regular CRP and hs-CRP tests?

• Both tests measure the same molecule in the blood.

• The hs-CRP test is for seemingly healthy people to determine their risk of cardiovascular disease. It measures CRP in the range from 0.5 to 10 mg/L.

• The CRP test is ordered for patients at risk for bacterial or viral infection (such as following surgery) or patients with chronic inflammatory diseases (such as rheumatoid arthritis). It measures CRP in the range from 10 to 1000 mg/L.

• There are two different tests for CRP. The standard test measures a much wider range of CRP levels but is less sensitive in the lower ranges. The hs-CRP test can more accurately detect lower concentrations of the protein (it is more sensitive), which makes it more useful than the CRP test in predicting a healthy person's risk for cardiovascular disease.
Homocysteine

- Homocysteine is a sulfur-containing amino acid formed from the metabolism of the essential amino acid, methionine.
- An elevated level of homocysteine has been demonstrated to be a potential risk factor for Coronary Artery Disease and Stroke.
Role of hyperhomocysteinemia in endothelial dysfunction and atherothrombotic disease

• An elevated level of homocysteine is thought to contribute to plaque formation by damaging the arterial wall.

• High levels may also act on platelets and increase the risks of platelet hyperactivity and subsequent clot formation.

• The adverse effects of homocysteine leading to CAD are:
  – oxidative damage to vascular endothelial cells,
  – increased proliferation of smooth muscle cells in the muscle part of vessel wall and
  – oxidative modification of LDL.
Clinical Significance of Homocysteine

- Homocysteine has emerged as a novel independent marker of risk for the development of CAD.

- Serum homocysteine is measured from a blood sample taken after a twelve hour fast.

- A normal homocysteine level is between 5 and 15 micromoles per liter (µmol/L).

- Abnormal levels are classified as moderate (16 to 30 µmol/L), intermediate (31 to 100 µmol/L) and severe (> 100 µmol/L).

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<tr>
<td>Homocysteine, Urine</td>
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Associated Tests for Homocysteinemia

• Vit B 12 and Folic Acid Estimation: These tests can be performed to rule out deficiency of either of these vitamins as cause for homocysteinemia.

• MTHFR Mutation Detection: Most common genetic defect in patients with homocysteinemia. Two mutations (C677T and A1298C) in this MTHFR gene leads to reduced enzyme activity and elevated level of homocysteine in blood. Patients with family history of homocysteinemia should get the test done for identifying the cause.
Lipoprotein, Lp(a)

- Lipoprotein(a) structure is similar to plasminogen and tPA (tissue plasminogen activator) and it competes with plasminogen for its binding site, leading to reduced fibrinolysis.

- Because Lp(a) stimulates secretion of PAI-1 it leads to thrombogenesis.

- High Lp(a) predicts risk of early atherosclerosis similar to high LDL, but in advanced atherosclerosis, Lp(a) is an independent risk factor not dependent on LDL.
Practical Clinical Utility of D-dimer

• When there is a suspicion of deep venous thrombosis (DVT) or pulmonary embolism (PE).

• In patients suspected of disseminated intravascular coagulation (DIC), D-dimers may aid in the diagnosis.

• Plasma D-dimer levels are associated with the presence of CAD in patients with stable angina pectoris.*

Comprehensive Cardio Vascular range at SRL

- Apoliprotein Evaluation
  - Apolipoprotein A-1
  - Apolipoprotein B
  - Lipoprotein A
- Serum Homocysteine
- NT proBNP
- Acute Coronary Syndrome Markers
  - CPK-MB
  - Trop I
  - Myoglobin
- TruCard Panel
  - hsCRP
  - Lipid Profile (TG, Chol total, HDL, LDL, VLDL, LDL/HDL ratio, Chol total/HDL ratio)
  - Direct LDL

All on advanced Electrochemiluminescence based Elecsys® system

Also, advanced LIPOPROTEIN ELECTROPHORESIS for in depth patient analysis and monitoring
THANK YOU