ATHEROSCLEROTIC CARDIOVASCULAR DISEASE: AN OVERVIEW

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ATHEROSCLEROSIS

2009; WORLD HEALTH ORGANISATION:

"Coronary heart disease is now the leading cause of death worldwide; it is on the rise and has become a true pandemic that respects no borders."

ATHEROSCLEROSIS

1969; WORLD HEALTH ORGANISATION:

"Mankind's greatest epidemic, coronary heart disease, has reached enormous proportions striking more and more at younger and younger subjects. It will result in coming years in the greatest epidemic mankind has faced unless we are able to reverse the trend by concentrated research into its cause and prevention."

PAST PANDEMICS

- **1347 – 1351: THE "BLACK DEATH"**
  BUBONIC PLAGUE: 75 million people died

- **1918: THE "SPANISH FLU"**
  50 million people died

- **1981 – 2011: HIV/AIDS: 60 million people infected**
  25 million people died

CARDIOVASCULAR DISEASE

- Currently the leading cause of death worldwide
- 75% of these deaths are in low and middle income countries
- In 2012 17.5 million people died from CVD
- =31% of all global deaths
- 7.4 million deaths due to coronary heart disease
- 6.7% due to stroke

CARDIOVASCULAR DISEASE

- **16 million deaths occur in people below 70 years of age**
- **In Africa CVD deaths mostly occur in people between 30 and 69 years of age**
- **CVD cost in the US: US$ 300 billion pa**

CARDIOVASCULAR DISEASE

IN SOUTH AFRICA

- Coronary heart disease is the leading cause of death among white and Indian people
- White people: 165.3 per 100 000 people
- Indian people: 101.2 per 100 000 people
- Coloured people: 55.01 per 100 000 people
- Black African people: 5.03 per 100 000 people

CARDIOVASCULAR DISEASE

- Cerebrovascular disease is the commonest cause of death among Coloured people
- Coloured people: 73.6 per 100 000 people
- White people: 62.5 per 100 000 people
- Indian people: 36.5 per 100 000 people

EPIDEMIOLOGIC TRANSITION

Term coined by Omran in 1971

Changes in patterns of disease as a result of societal, socioeconomic developments in different countries

Developing countries are faced with a hostile cardiovascular environment characterised by changes in diet, exercise, tobacco , socioeconomic stressors, economic constraints at both the national and personal levels

EPIDEMIOLOGIC TRANSITION

STAGE 1 The age of pestilence and famine

- From pre-historic age (10 000years ago)
- Transition of mankind from hunter-gatherer to settled communities, domesticated animals
- Exposure to human and animal waste, reciprocal transmission of micro-organisms between humans and animals
- Microbial exposure
- Nutritional deficiencies
- Inadequate food storage

EPIDEMIOLOGIC TRANSITION

STAGE 2 The age of receding pandemics

- **In Europe & USA: late 18th to 19th century**
- **Declining mortality rates, increase in average life-expectancy from 30 years to 50 years, a shift from infectious diseases to chronic non-infectious diseases**
- **Sanitation**
- **Improved nutrition, medical and public health services**
- **Many developing countries are still at this stage in part. Tb, HIV/AIDS, Ebola**

EPIDEMIOLOGIC TRANSITION

STAGE 3 The age of degenerative and man-made diseases

- **Improvements in socioeconomic status, urbanisation lead to marked changes in risk factors**
- **Infectious diseases replaced by degenerative diseases as the leading cause of death**
- **Life expectancy >50 years**
- **Late 19th and 20th centuries**

EPIDEMIOLOGIC TRANSITION

- USA: 1930 – 1965
- Western Europe: 10 years later
- China, Eastern Europe, Middle East, Latin America, parts of India and parts of Africa today

STAGE 4 The age of delayed degenerative diseases

- Current stage in most wealthy countries

Life expectancy >70 years

Leading causes of death: CVD and cancer

EPIDEMIOLOGIC TRANSITION

Is there a Stage 5?

- Epidemic of obesity, diabetes and hypertension
- Is there a reversal of the trends from the 1970s and 1980s?

EPIDEMIOLOGIC TRANSITION

SOUTH AFRICA

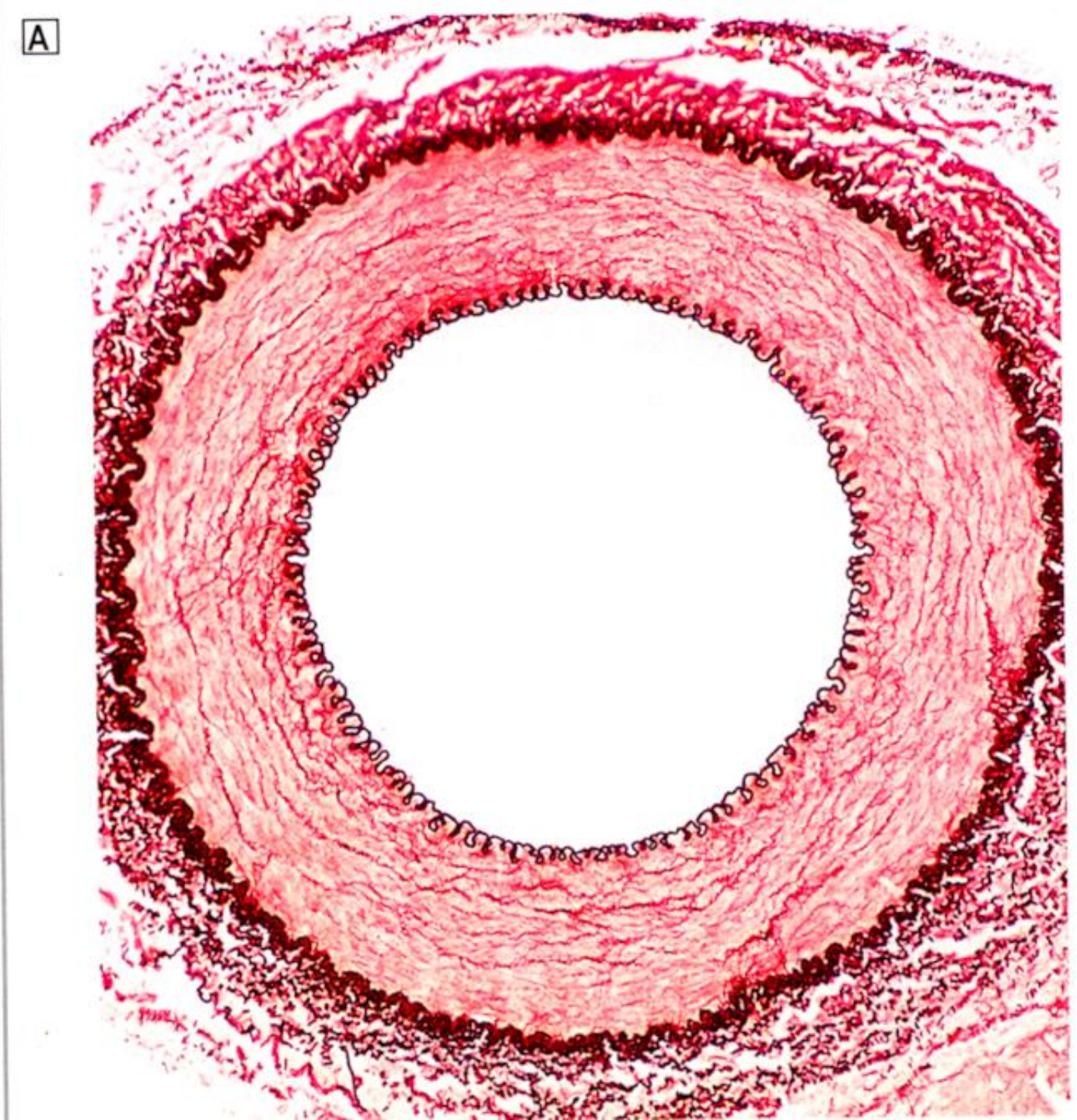
4 excessive health burdens:

- Communicable diseases: HIV/AIDS, Tb
- Maternal, neonatal and child mortality
- Non-communicable diseases
- Trauma and violence

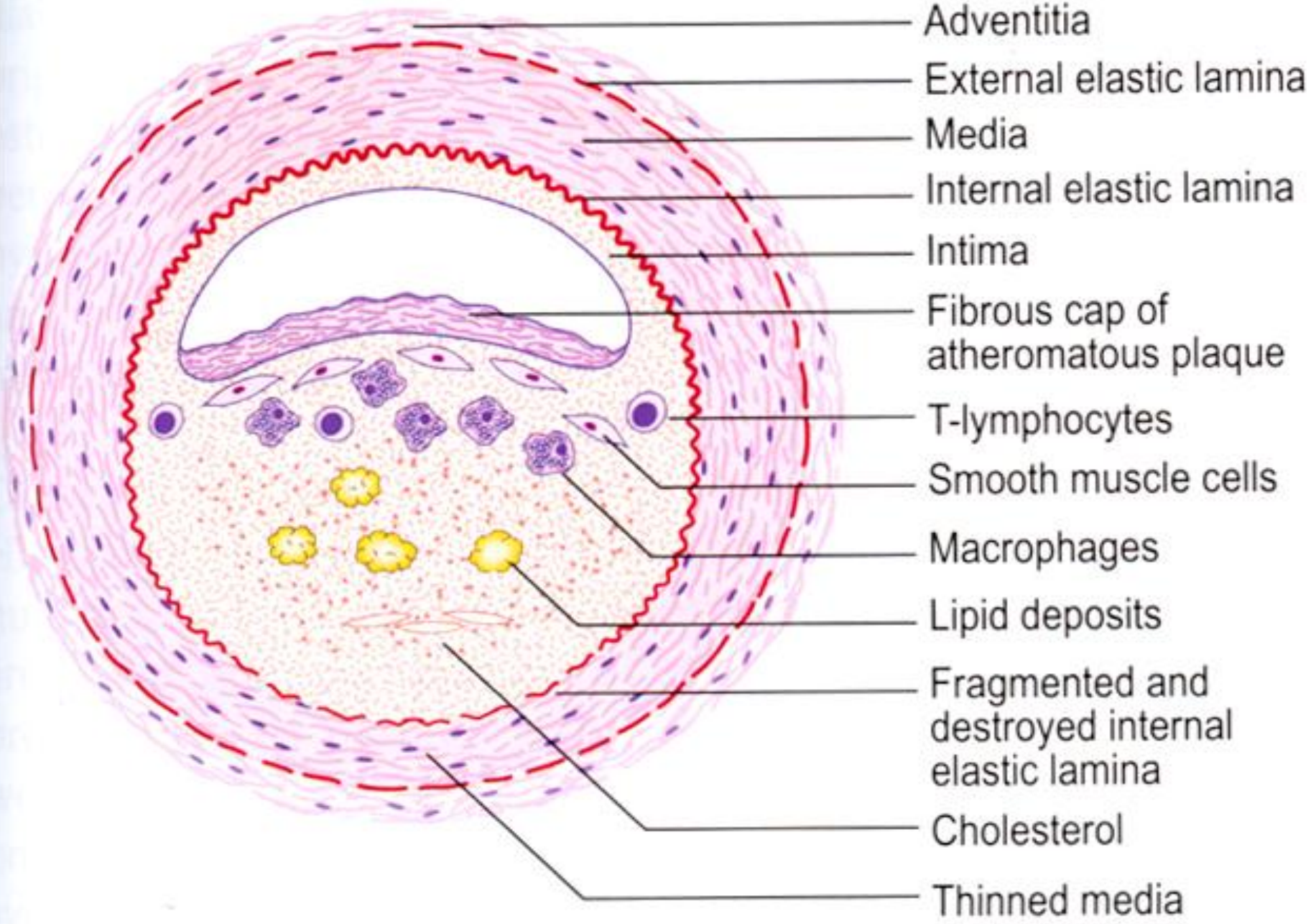
ATHEROSCLEROSIS

- An inflammatory disease of large and medium sized arteries
- Fibro-proliferative disease within the arterial walls
- Atherosclerosis involves ongoing inflammation from its initiation, to its progression and complications
- Preceded by endothelial dysfunction

Normal muscular artery

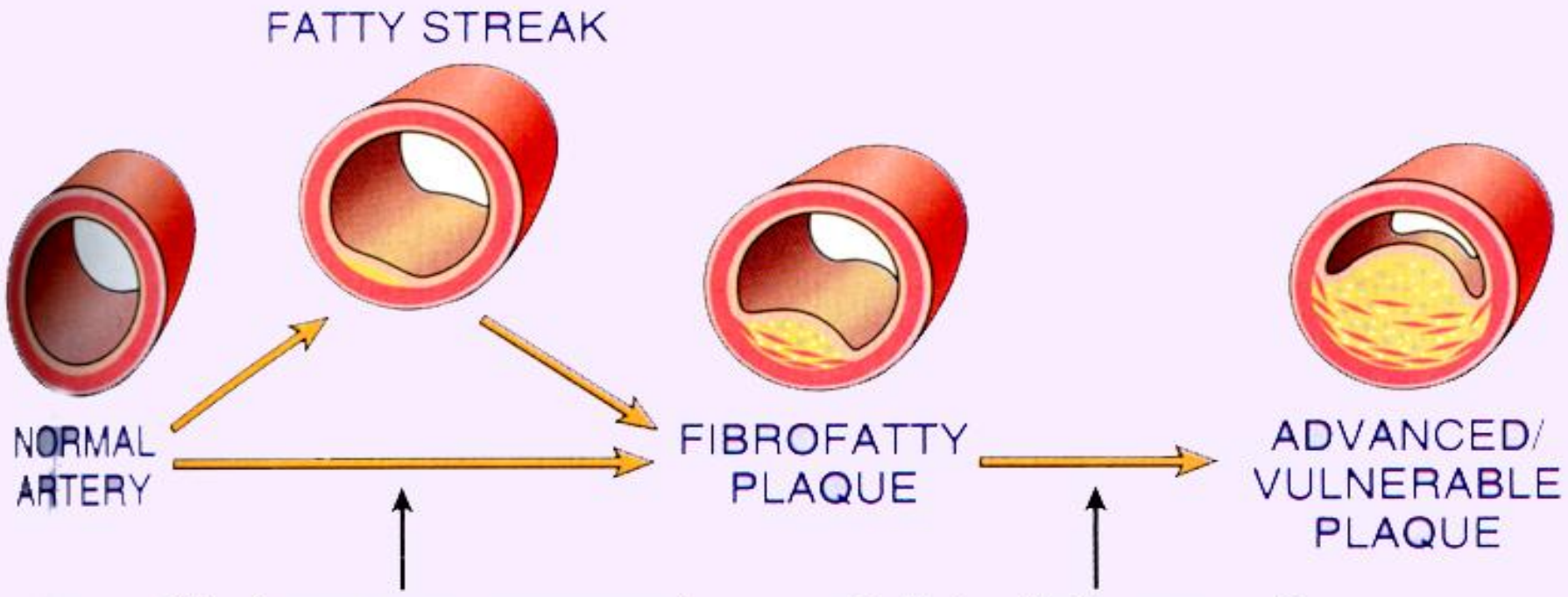


A


Adventitia
External elastic lamina
Media
Internal elastic lamina
Intima
Fibrous cap of atheromatous plaque
T-lymphocytes
Smooth muscle cells
Macrophages
Lipid deposits
Fragmented and destroyed internal elastic lamina
Cholesterol
Thinned media

Pre-Clinical Phase
Usually young age

Clinical



At lesion-prone areas, and accelerated by risk factors:
Endothelial dysfunction
Monocyte adhesion/emigration
SMC migration to intima
SMC proliferation
ECM elaboration
Lipid accumulation

Cell death/degeneration
Inflammation
Plaque growth
Remodeling of plaque and wall ECM
Organization of thrombus
Calcification

horizon

Clinical Phase

Usually middle age to elderly

Mural thrombosis
Embolization
Wall weakening

↓

ANEURYSM AND RUPTURE

Plaque rupture
Plaque erosion
Plaque hemorrhage
Mural thrombosis
Embolization

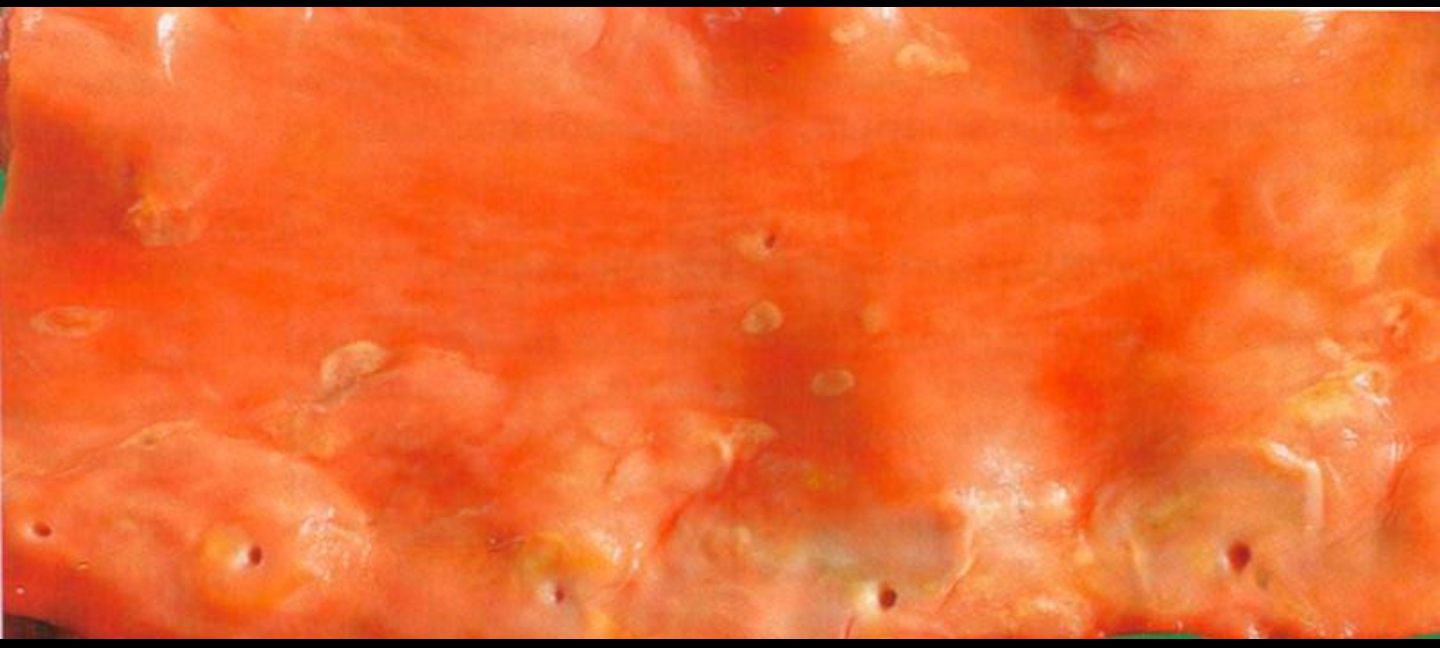
↓

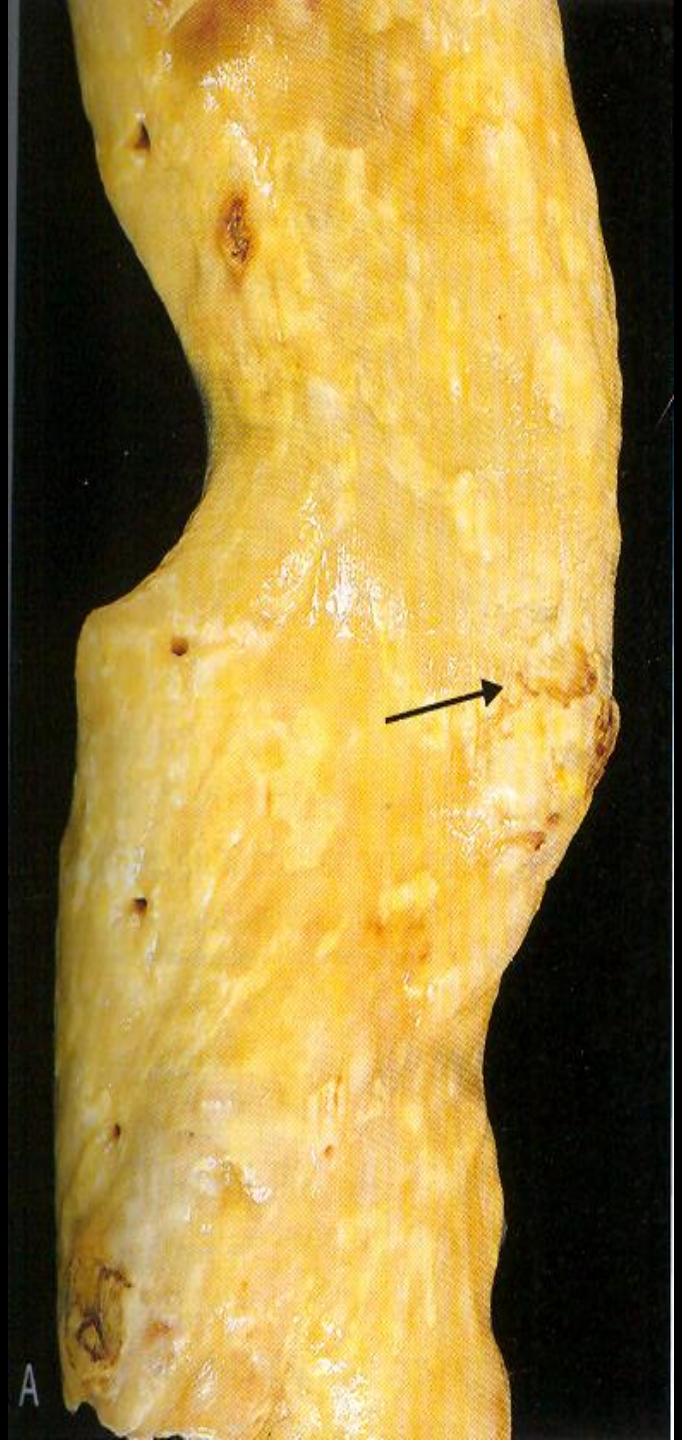
OCCLUSION BY THROMBUS

Progressive plaque growth

↓

CRITICAL STENOSIS

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B

THE ENDOTHELIUM

- Monolayer lining arteries, veins and lymph vessels
- Attached to basement membrane
- Endothelium covers 300 – 1000 sqm
- (a tennis court measures 260 sqm)

THE ENDOTHELIUM

FUNCTIONS

- Permeability barrier
- Thromboresistant: maintains fluidity of blood
- Maintains vascular tone
- Regulates cell growth
- Controls inflammatory and immune response
- Controls metabolism: endocrine, paracrine and autocrine organ

ENDOTHELIAL DYSFUNCTION

- Toxic, hostile internal mileu upset the intravascular homeostasis and cause endothelial dysfunction
- Precursor of atherosclerosis
- CAUSES OF ENDOTHELIAL DYSFUNCTION:

  Haemodynamic stress

  Hypertension

  Hypoxia

  Insulin resistance, Obesity

  Hyperglycaemia producing AGEs

  Infection

  Inflammation: TNF-a, cytokines, Reactive oxygen species, superoxide

ENDOTHELIAL DYSFUNCTION

Diabetes

- Adipocytes secrete inflammatory mediators TNFa, IL-6
- Chemoattractants
- Decreased NO
- Increased FFA
- AGEs
- Increased oxidative stress
- Platelet abnormalities: prothrombotic
- Increased PAI-1

ENDOTHELIAL DYSFUNCTION

- An atherogenic diet makes the endothelium adherent to leukocytes
- Inflammatory markers activate macrophage scavenger receptors leading to uptake of oxidised lipoproteins
- Vascular cell adhesion molecules (VICAM-1) binds to leucocytes and monocytes
- Macrophages express scavenger receptors for modified lipoproteins
- Ingest lipoproteins and become foam cells
- Monocytes secrete inflammatory cytokines: TNF-B, interferon

ENDOTHELIAL DYSFUNCTION

Nicotine effect

- Vasoconstriction
- Rise in blood pressure
- Increased LDL oxidation
- Increased platelet aggregation
- Increased CRP levels
- Increased ICAM-1

ENDOTHELIAL DYSFUNCTION

- Increased permeability to macromolecules
- Decreased availability of nitric oxide: Impaired vasoreactivity
- Thrombogenic surface
- Adherence to inflammatory cells
- The number of risk factors is related to the risk of endothelial dysfunction

ATHEROSCLEROSIS

- Oxidised LDL now penetrates the endothelium
- Intima exposed to mechanical stress
- Lipoproteins accumulate because of increased permeability
- Monocytes and lymphocytes migrate to intima
- Monocytes ingest oxidised LDL and become foam macrophages
- Secrete inflammatory cytokines
- Smooth muscle cells migrate
- Fibrosis
- Formation of atheromatous plaque

ATHEROSCLEROSIS

- Platelets adhere to endothelium
- Lesions grow in size
- Advanced lesions can rupture, ulcerate or erode
- Haemorrhage and thrombosis
- Progressive narrowing of vessel lumen
- Aneurysmal dilatation

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

- A disease that can affect any arterial vascular bed:
- The coronary arteries: Coronary or ischaemic heart disease
- The cerebral arteries: ischaemic stroke
- The peripheral arteries: peripheral artery disease
- The aorta: Aortic aneurysm and dissection

ATHEROSCLEROTIC CARDIOVASCULAR DISEASE

- The same disease process in the arteries supplying different organs
- Similar risk factors
- Often one person will have more than one vascular bed affected; “vasculopath”
- Progressive disease, patients return with recurrent acute episodes
- Prevention strategies take all the different diseases into consideration

CORONARY HEART DISEASE SYNDROMES

- Symptoms appear when the coronary artery diameter is reduced by 50% or more
- Chronic stable angina: stable symptoms brought about by a known level of physical exertion. Subside with rest
- Heart failure symptoms when there is left ventricular systolic or diastolic dysfunction

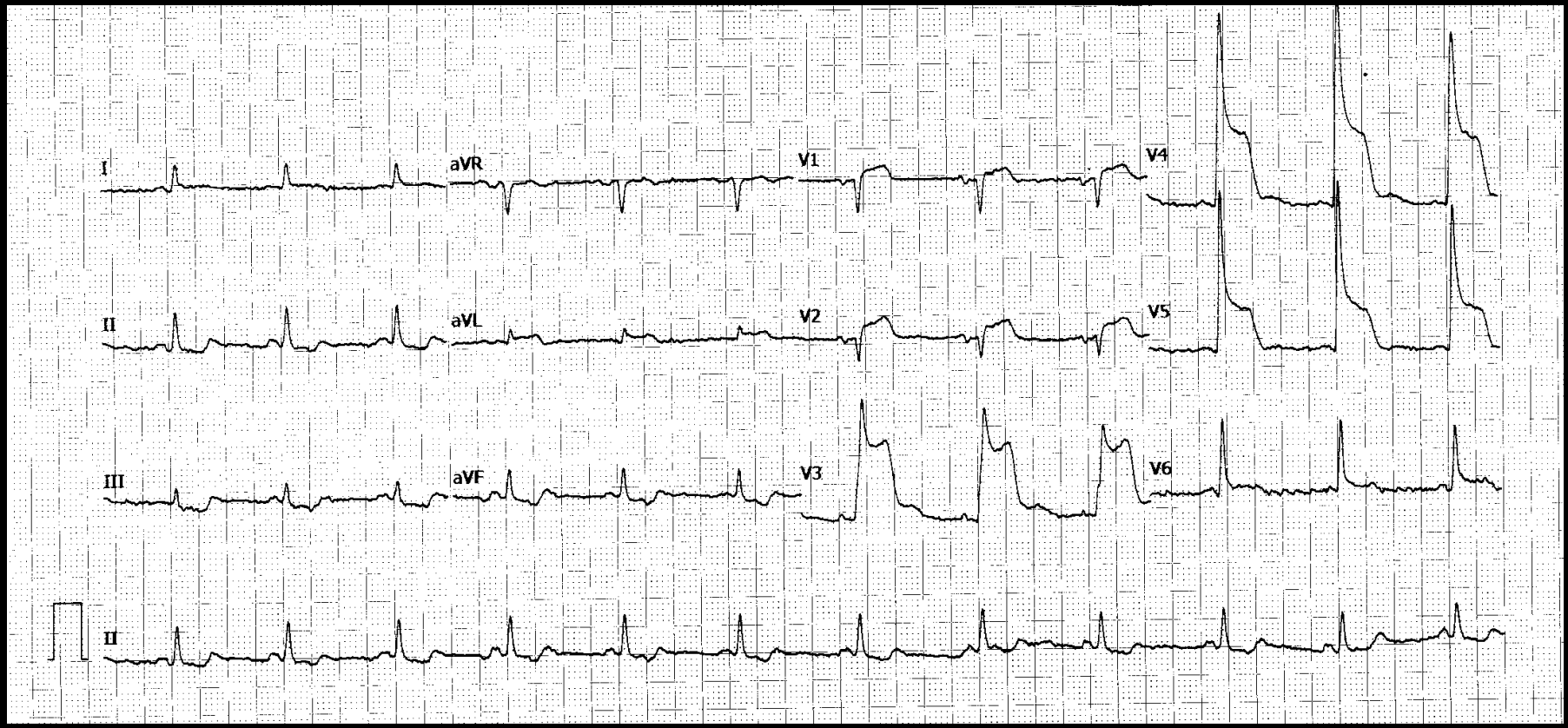
ACUTE CORONARY SYNDROMES

Acute rupture of an unstable atherosclerotic plaque followed by thrombus formation

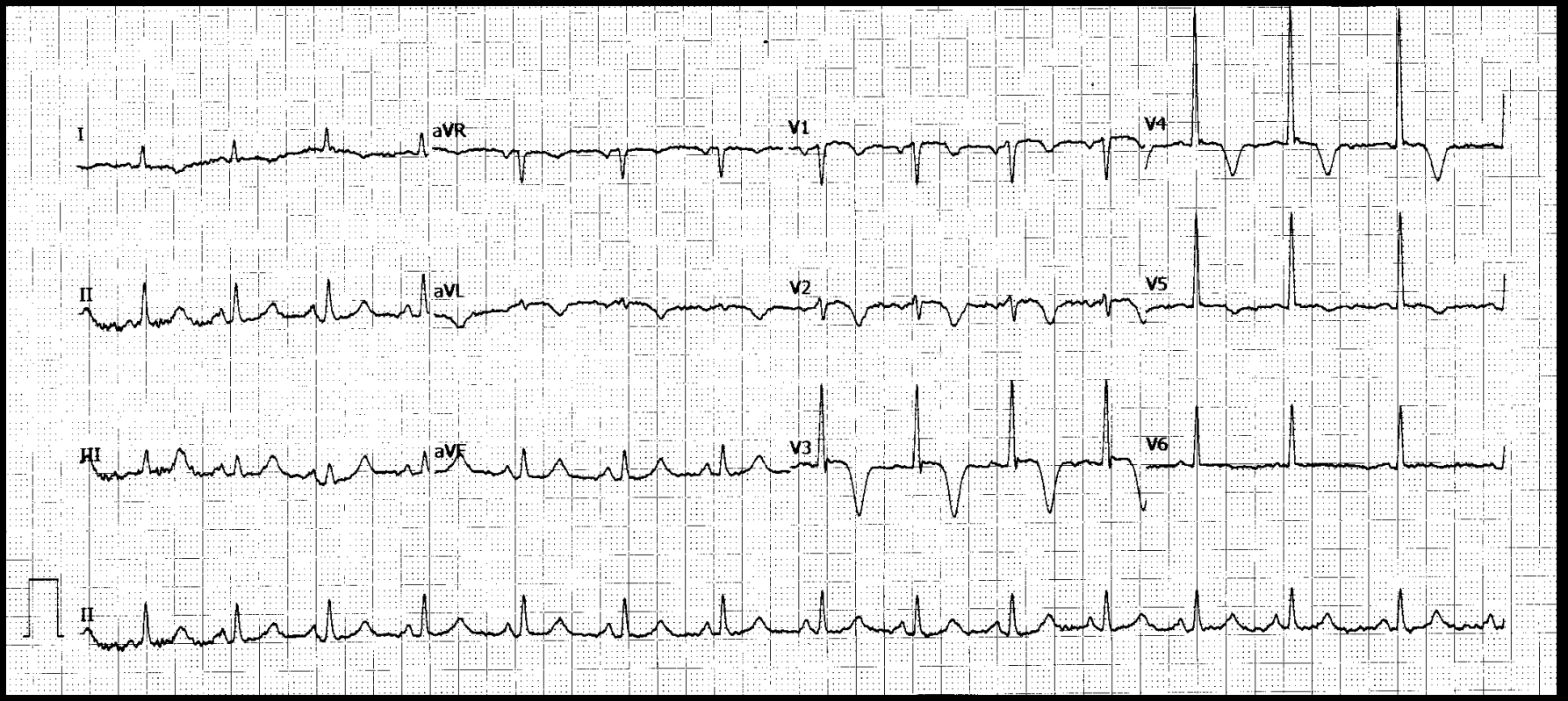
Critical or total artery occlusion often associated with myocardial damage

- Unstable Angina
- Non-ST elevation Myocardial Infarction (Non-STEMI)
- ST elevation Myocardial Infarction (STEMI}

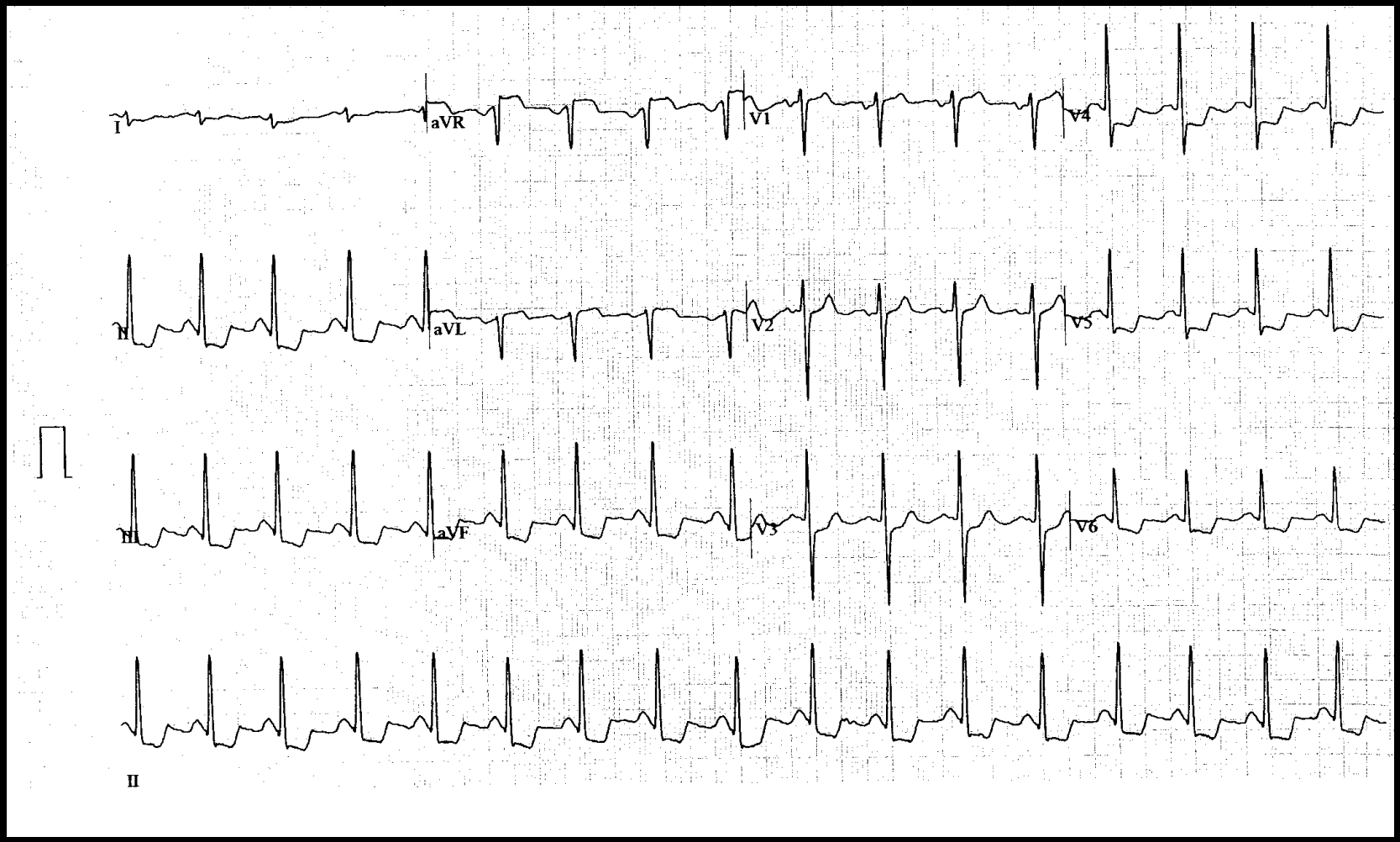
STEMI



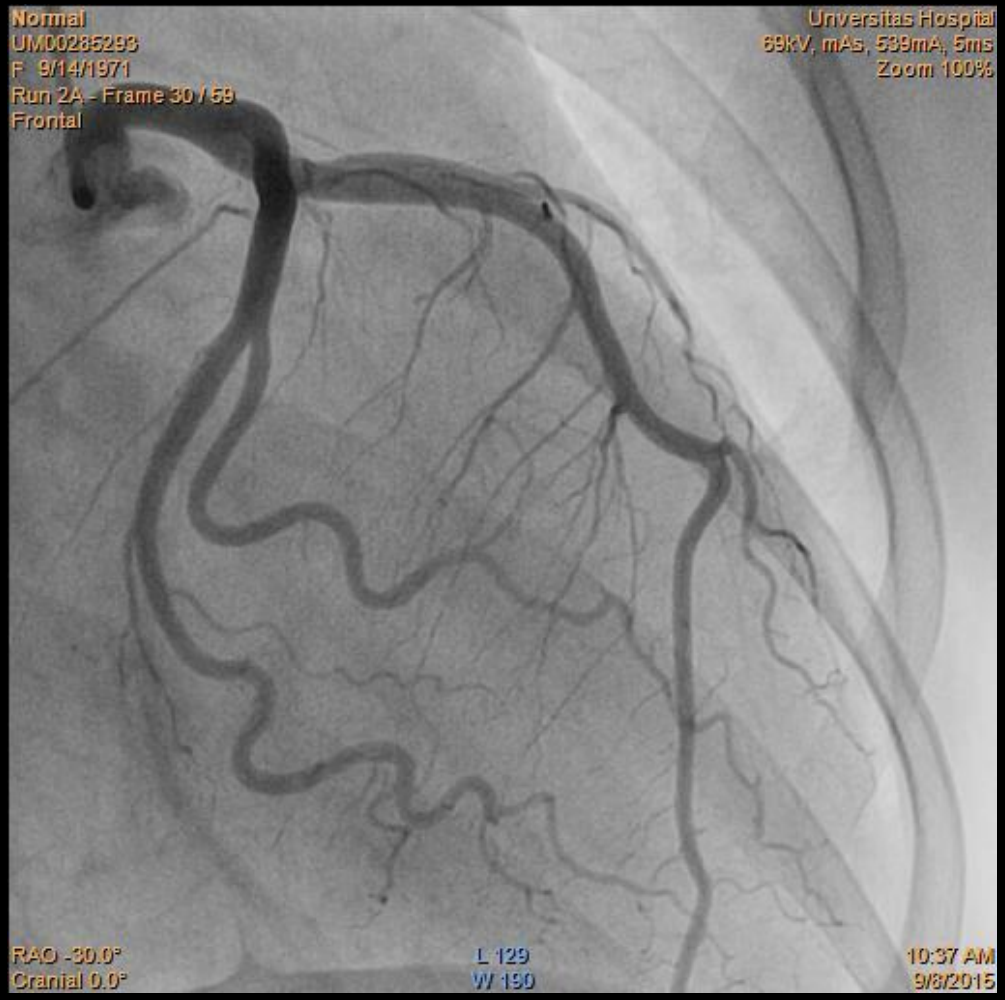
STEMI Streptokinase given



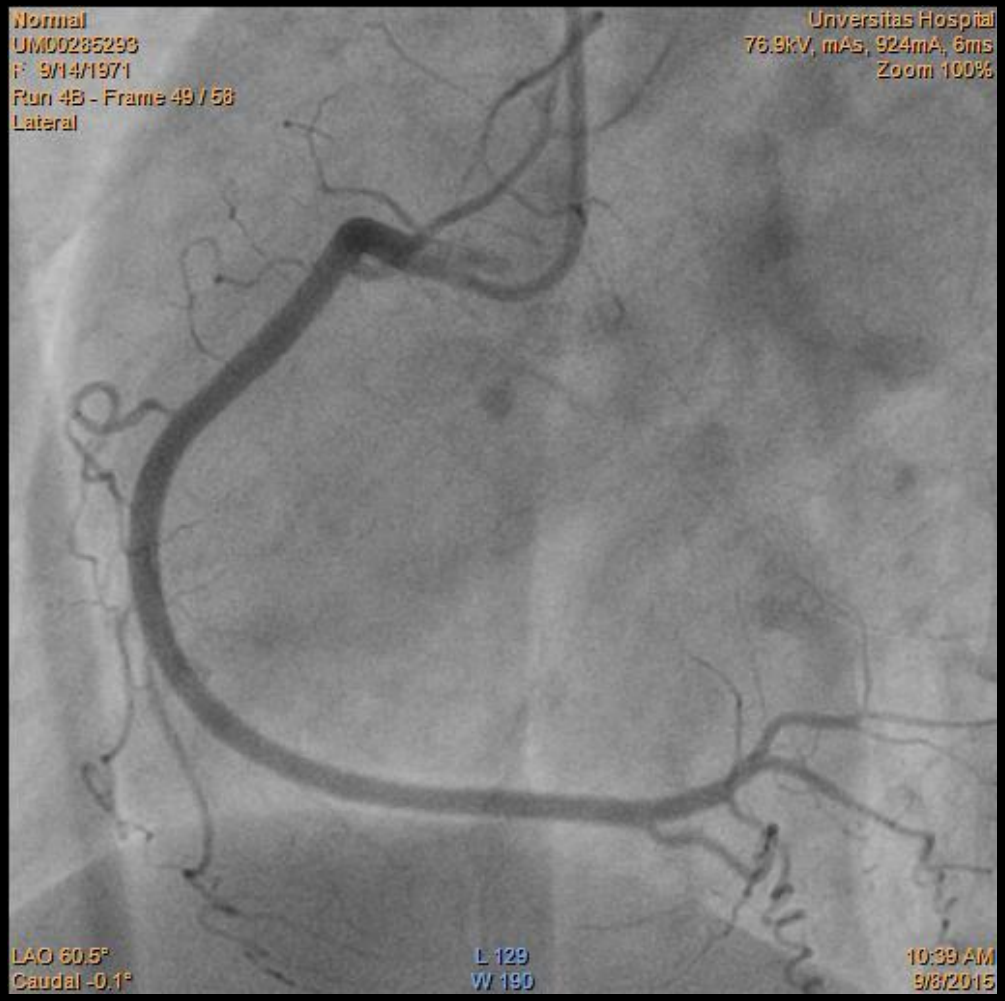
Unstable Angina



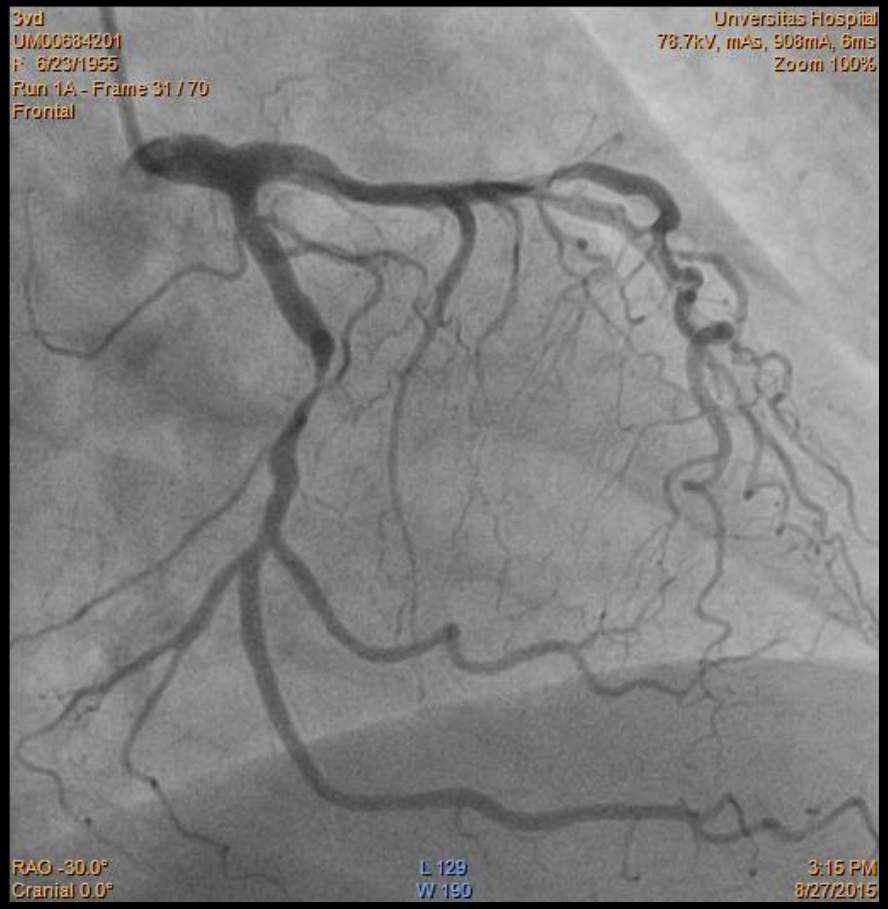
Normal left coronary artery

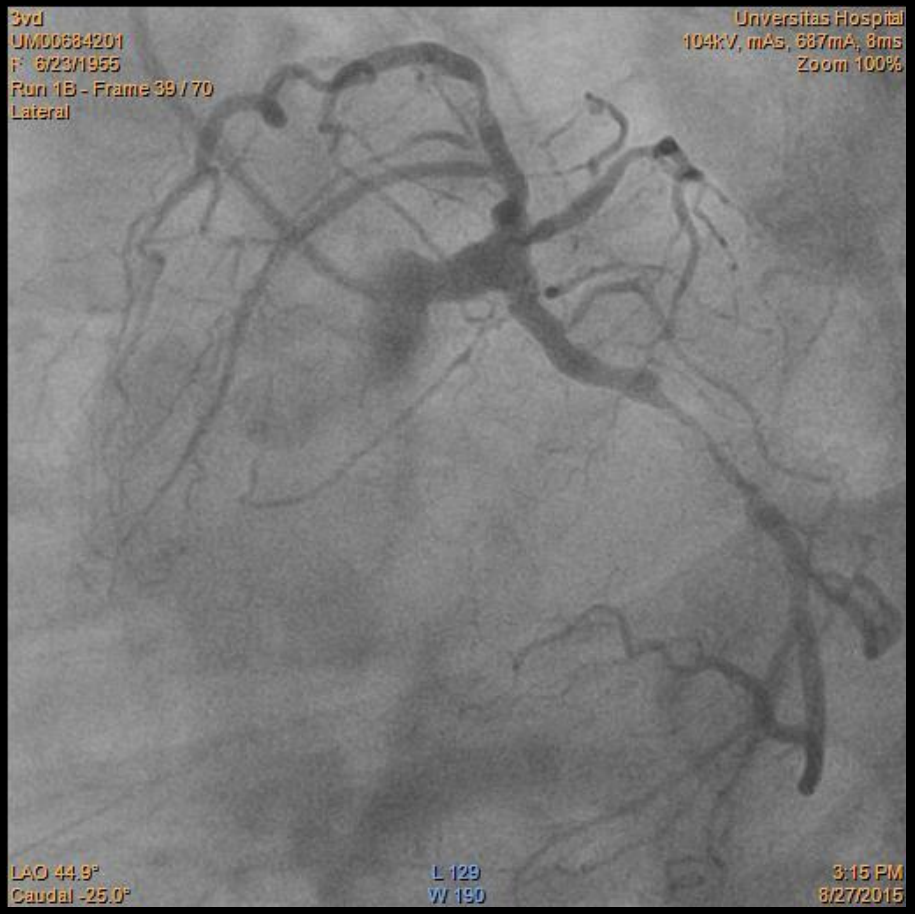


Normal right coronary artery

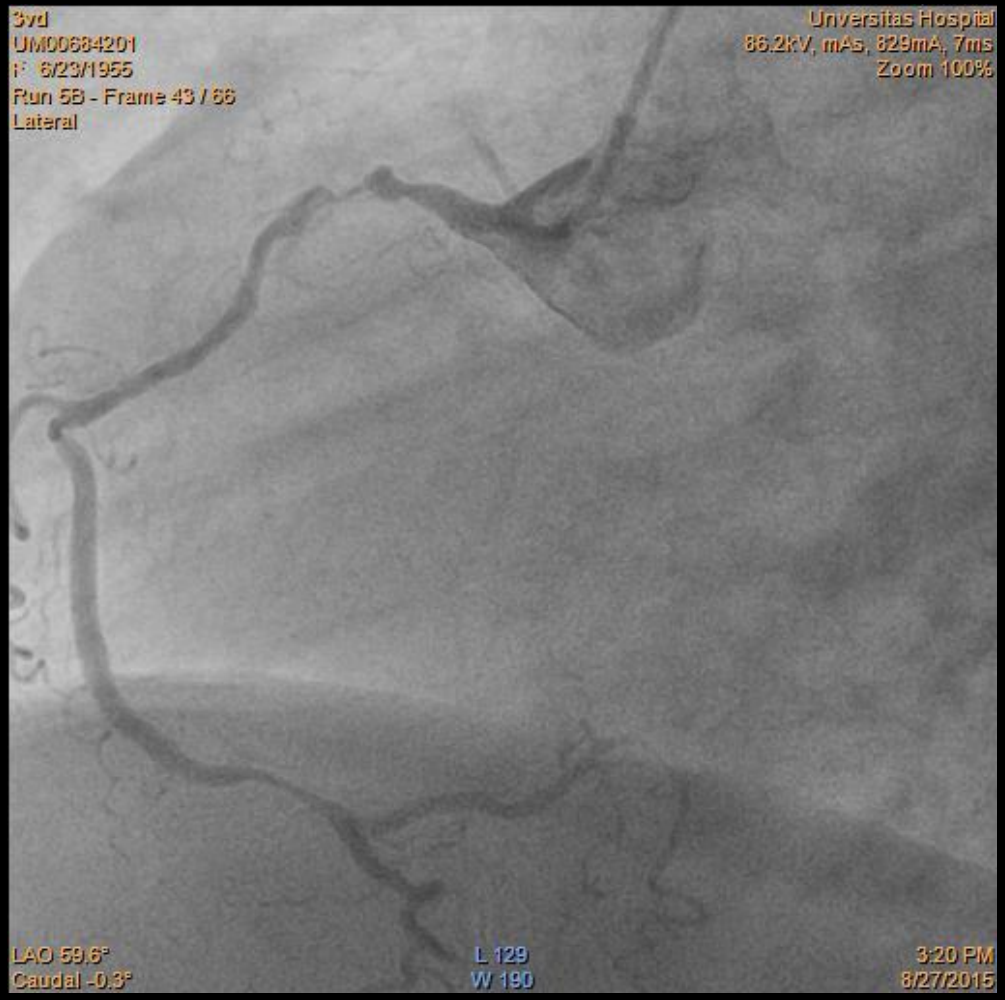


3 Vessel disease: LCA

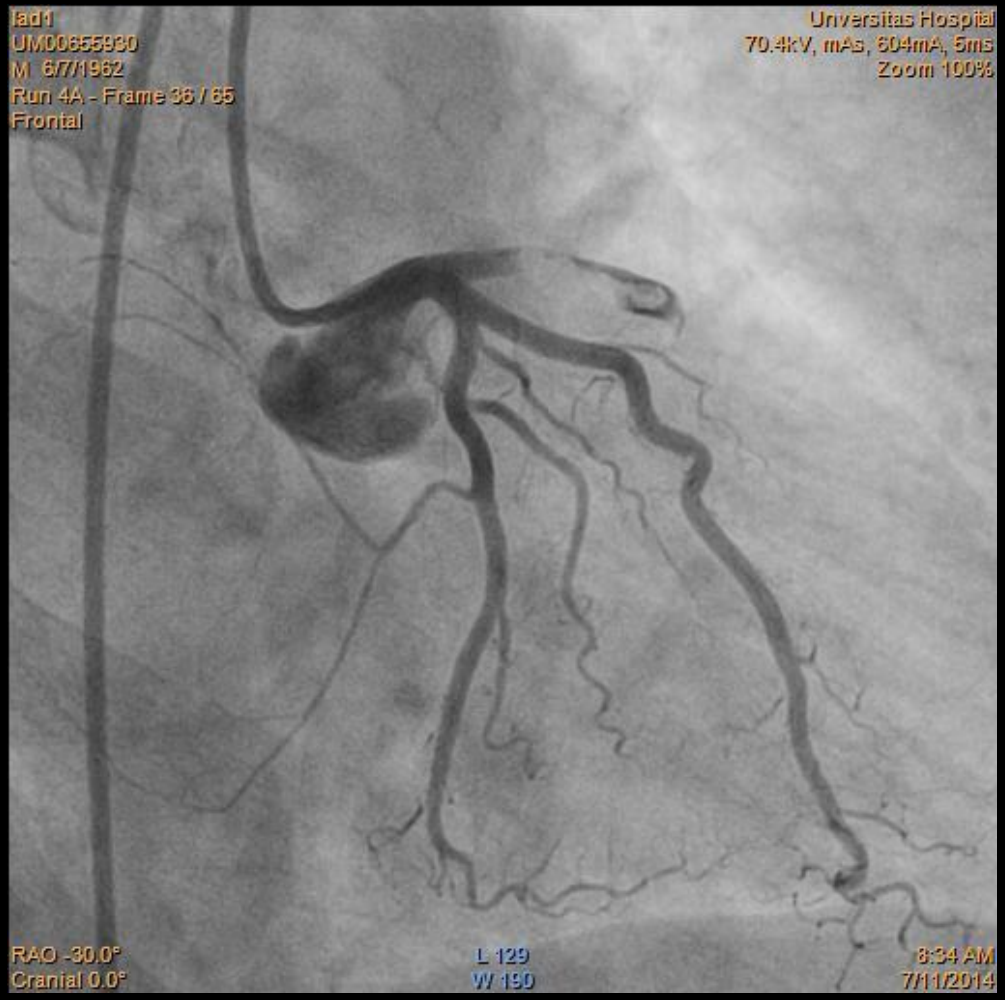




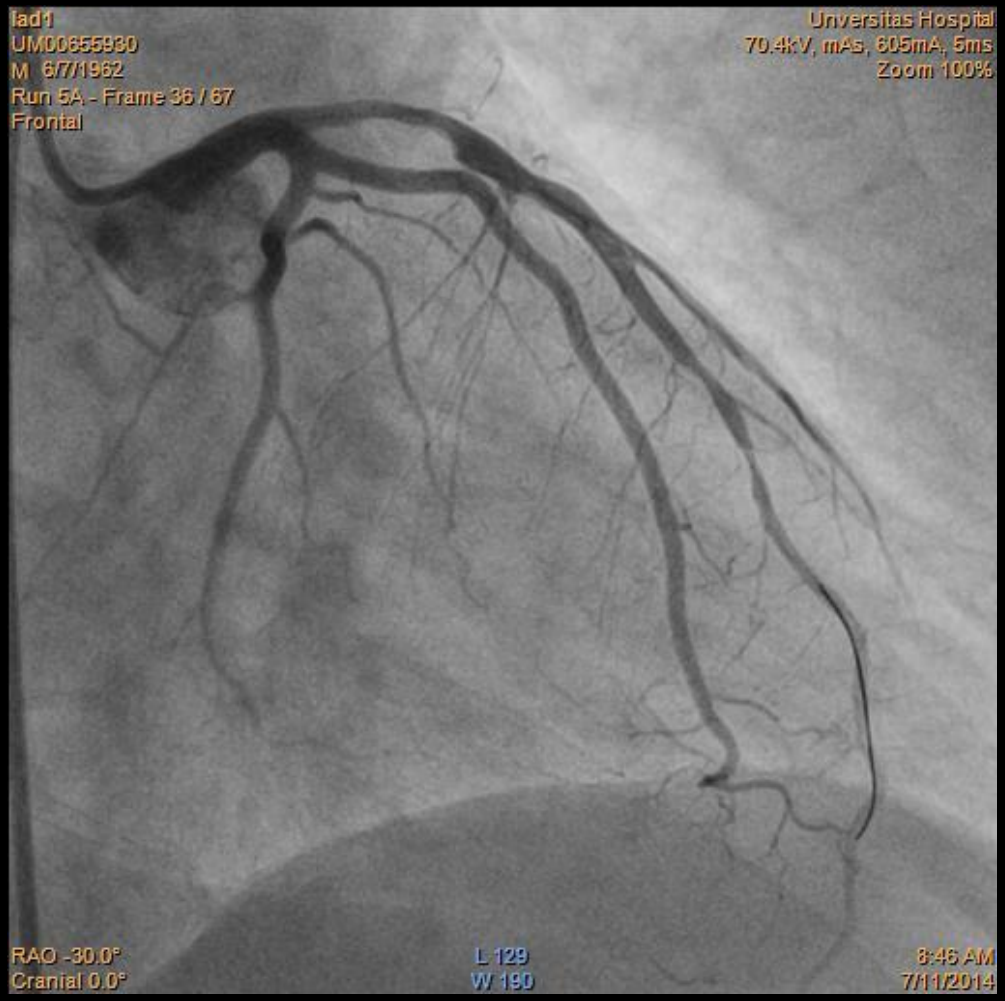
3 Vessel disease: RCA



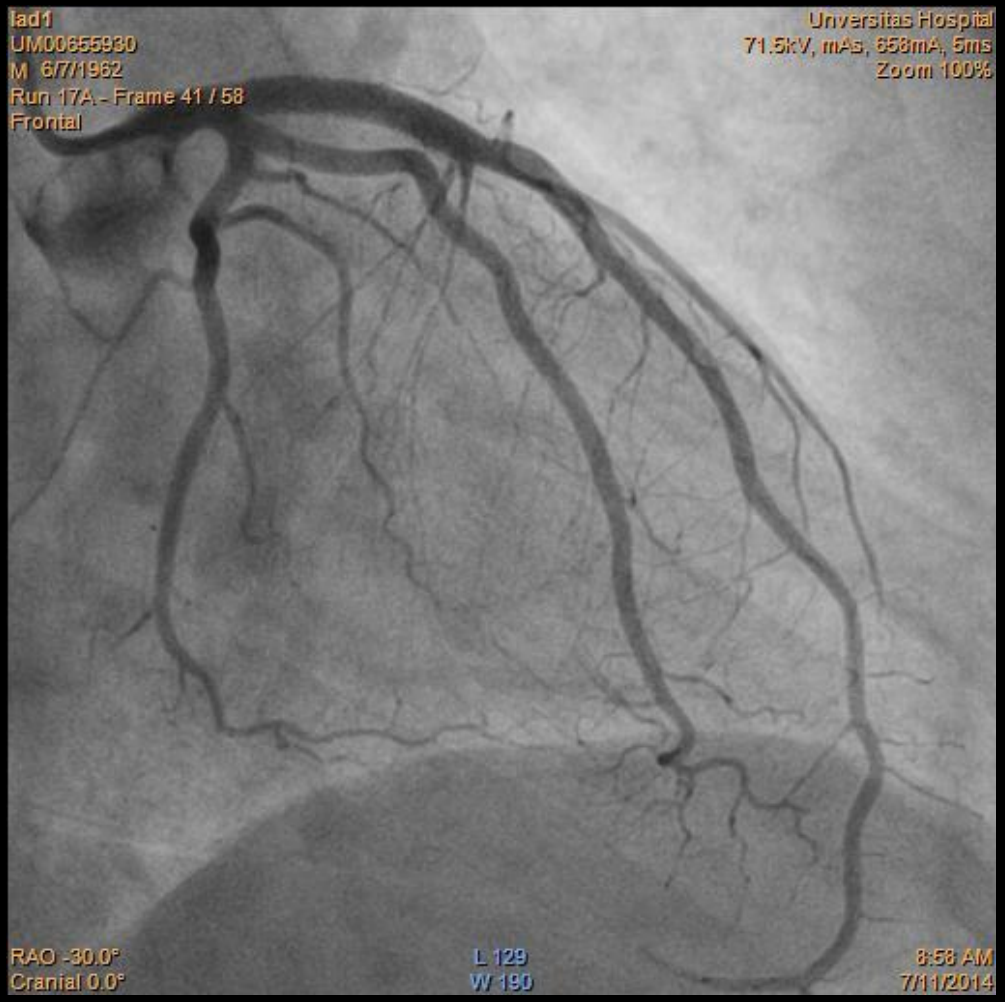
LAD occluded



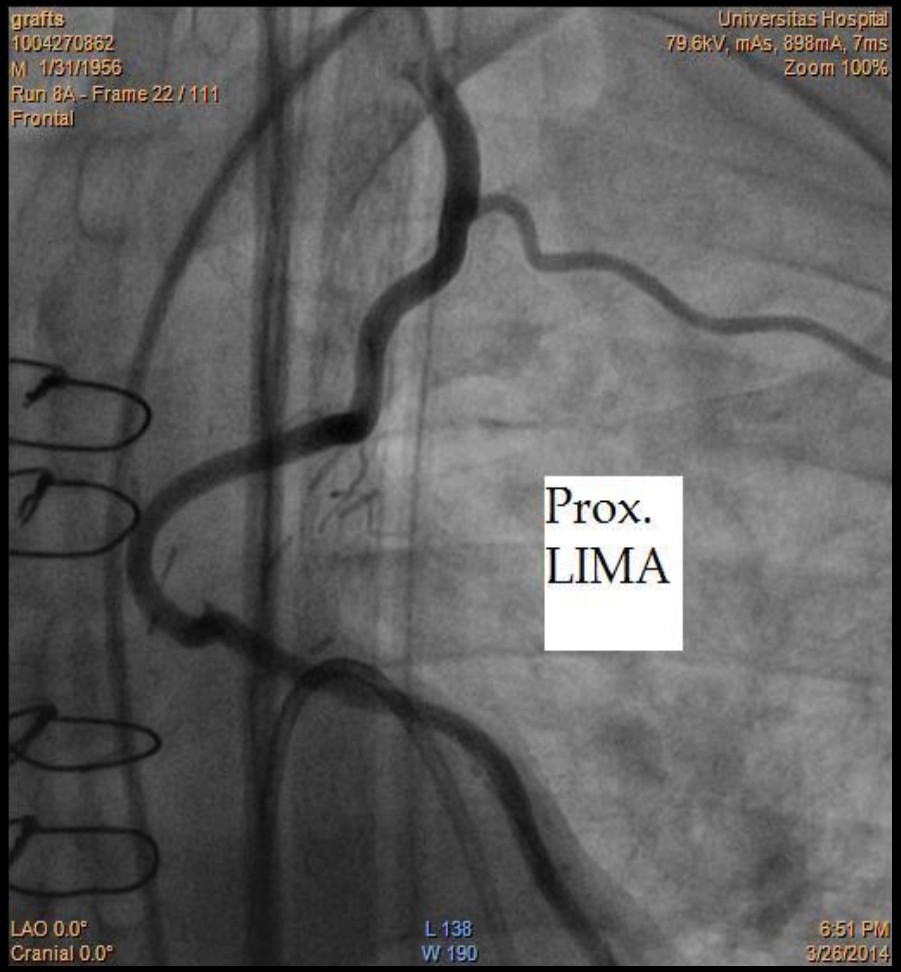
LAD after export

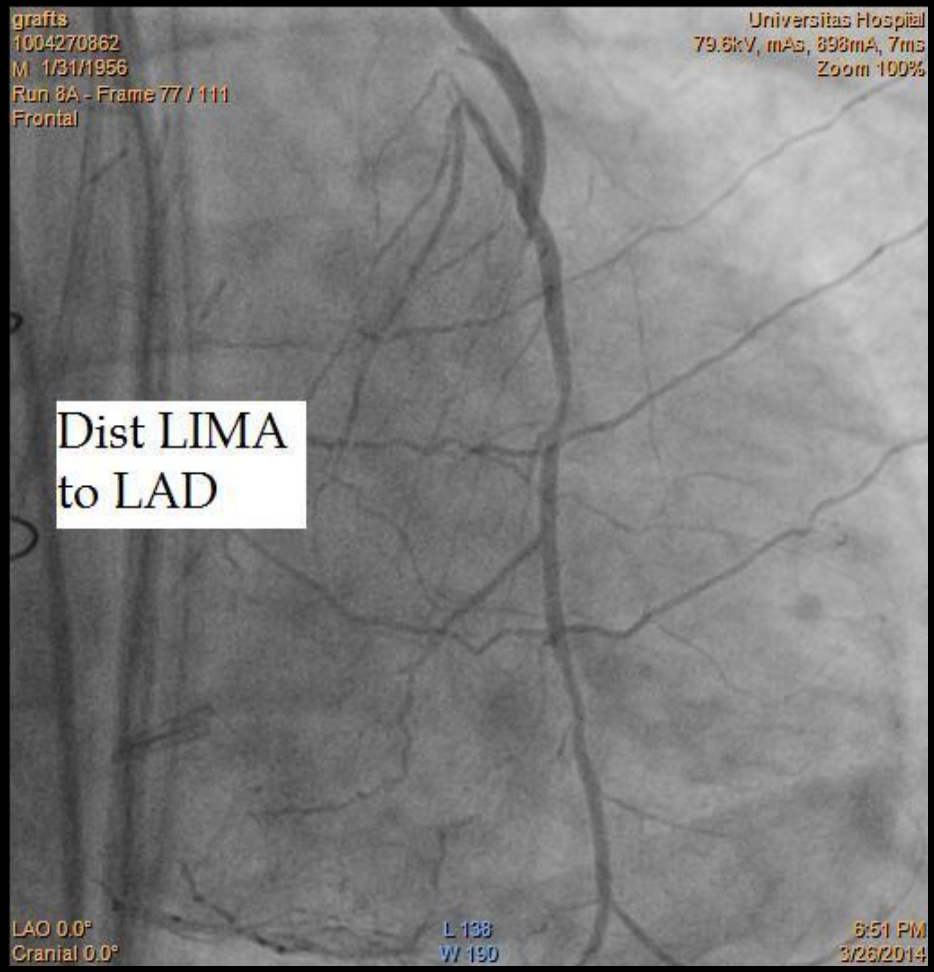


LAD after stent

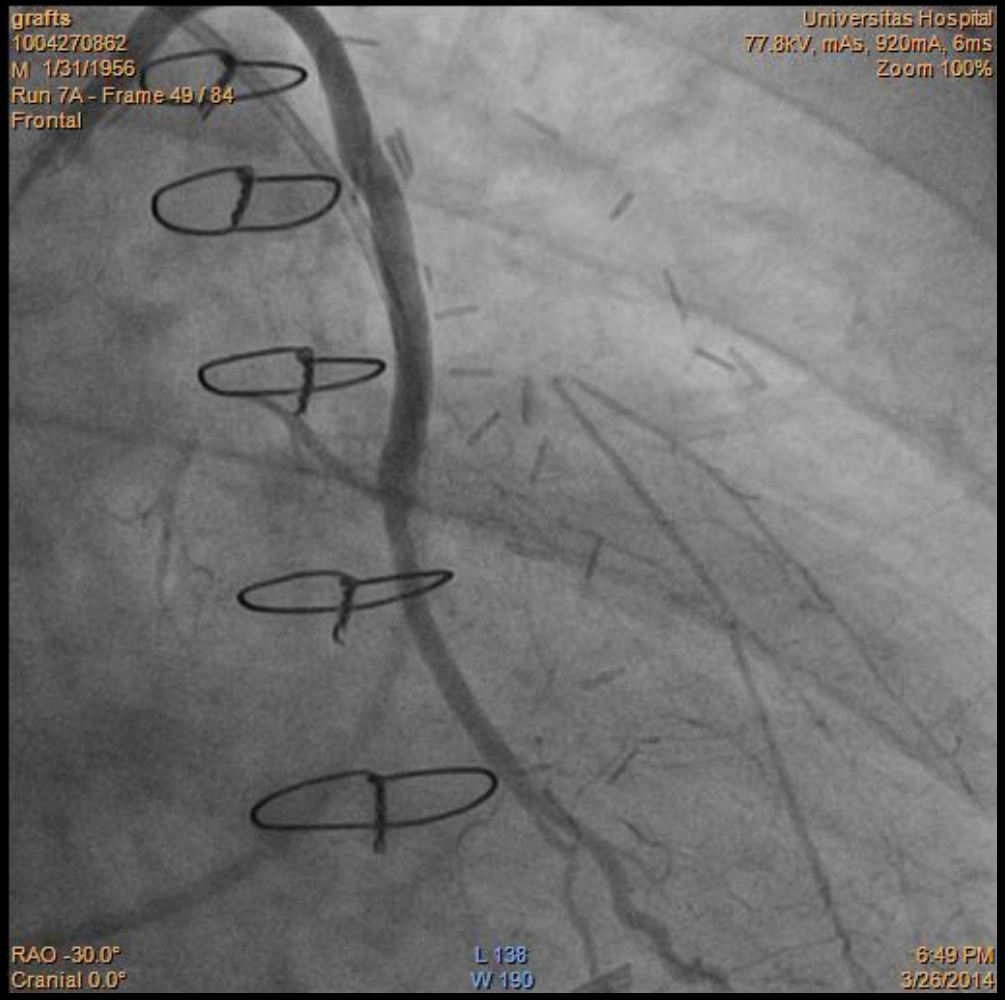


Bypass graft LIMA-LAD

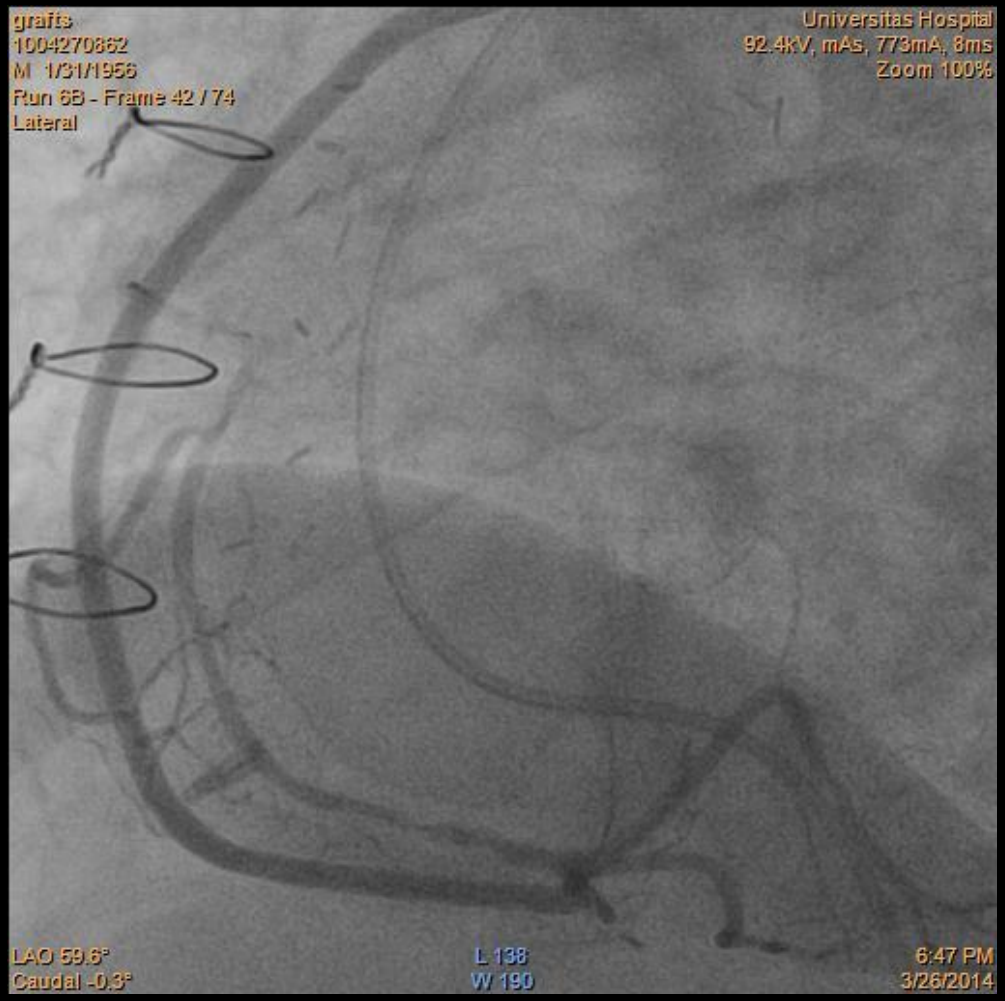




Bypass graft to LCX



Bypass graft to RCA



2012 EUROPEAN SOCIETY OF CARDIOLOGY (ESC) GUIDELINES ON CARDIOVASCULAR DISEASE PREVENTION

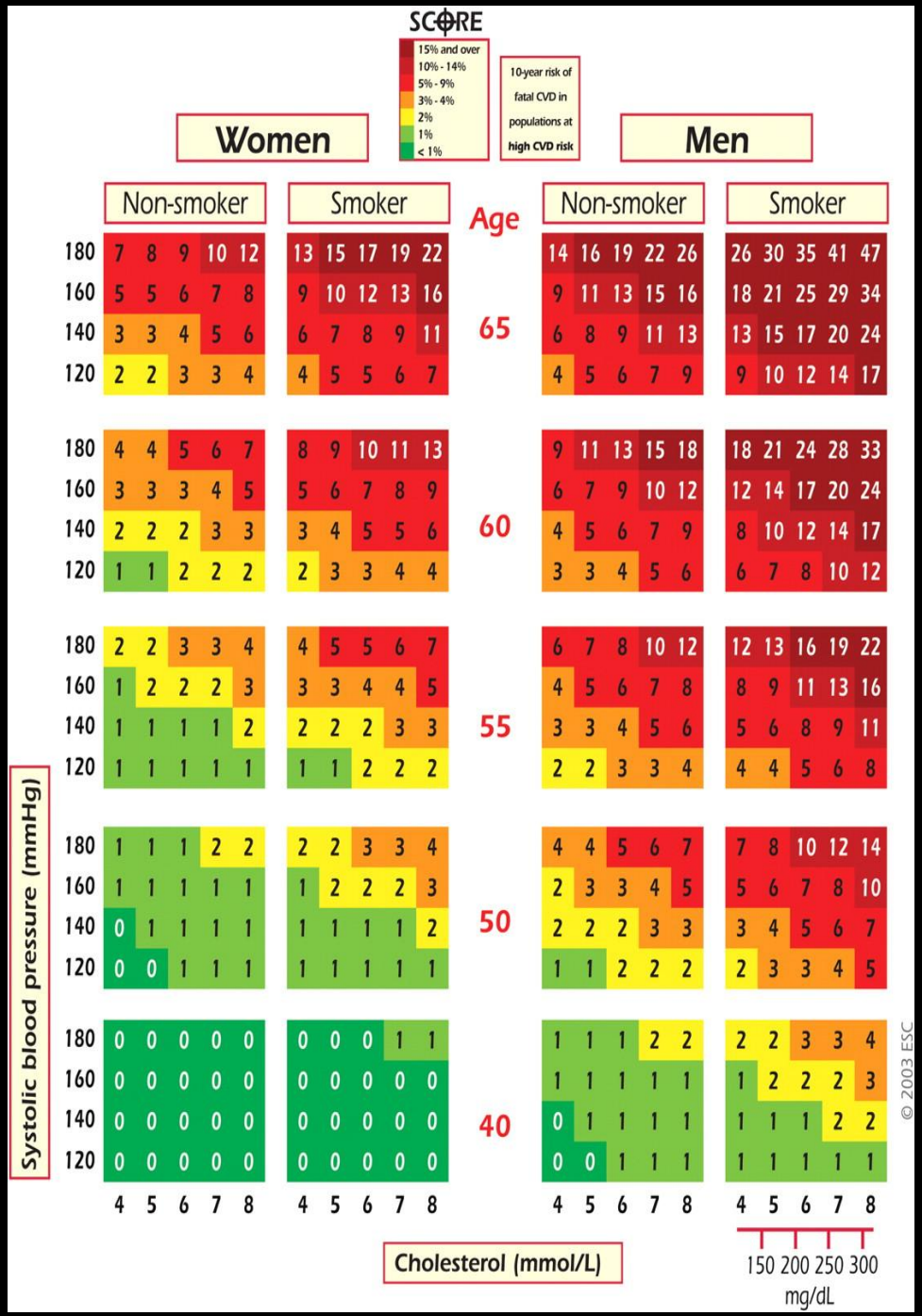
- **ESC Guidelines adopted by The South African Heart Association which is affiliated to the ESC**
- **Take into cognisance all the known risk factors for atherosclerosis**
- **Preventative strategies:**
  Primordial prevention
- **Primary prevention**
- **Secondary prevention**

PRIMORDIAL PREVENTION

- Government policies:
- Banning of smoking in public places
- Heavy “sin taxes”
- Policies preventing high fat foods and sugary drinks at school cafeterias and shops
- Policy to encourage exercise programmes at schools

PRIMARY PREVENTION

- Risk factor control in people without CVD
- Risk stratification will determine treatment targets



SCORE chart: 10-year risk of fatal cardiovascular disease (CVD) in countries at high CVD risk based on the following risk factors:

Age,
Sex,
Smoking,
Systolic blood pressure and
Total Cholesterol

VERY HIGH RISK GROUP

- People with documented CVD:
  coronary angiogram / nuclear imaging / stress echocardiogram
- Carotid plaque by ultrasound
- Coronary revascularisation by PCI or CABG
- Other arterial revascularisation procedure
- Ischaemic stroke
- Peripheral artery disease

VERY HIGH RISK GROUP

- Diabetes mellitus type 1 or 2 with one or more CV risk factors &/or target organ damage, eg microalbuminuria 30 – 300mg/24 hours
- Severe chronic kidney disease: GFR <30 ml/ 1.73m2
- A calculated SCORE of >10% risk of a fatal CVD in 10 years

HIGH RISK GROUP

- Type 1 or 2 Diabetes mellitus without CV risk factors and without target organ damage
- Markedly elevated single risk factor, eg severe hypertension, hypercholesterolaemia
- Moderate chronic kidney disease:
- GFR 30 – 59 ml/1.73m2
- A calculated SCORE of >5% <10% risk for 10 year risk of a fatal CVD

MODERATE RISK

- **SCORE >1% <5% risk of fatal CVD in 10 years**
- **Many "healthy" middle aged people are in this category**

LOW RISK

- **SCORE 1%< risk of fatal CVD in 10 years**

TOTAL RISK ASSESSMENT

Who should have it?

- **The person who asks for it**
- **One with one or more risk factor:**
  - **hypertension**
  - **diabetes mellitus**
  - **dyslipidaemia**
  - **smoker**
  - **family history**
  - **overweight**
- **Family history of premature CHD**
- **Symptoms suggestive of CVD**

TESTS FOR EARLY ATHEROSCLEROSIS

- Intima – Media thickness by carotid ultrasound
- Affected early
- Smooth muscle hypertrophy
- >0.9mm is abnormal

- Ankle-Brachial Index
- Difference between systolic blood pressure at the posterior tibial artery and at the brachial artery

1.00 – 1.29	normal
0.9 – 0.99	borderline
0.41 – 0.9	mild to moderate PAD
0.00 – 0.40	severe PAD

HYPERTENSION

BLOOD PRESSURE GRADES

Grade	Systolic	Diastolic
Optimal	<120mmHg	<80mmHg
Normal	120-129mmHg	80-84mmHg
High Normal	130-139mmHg	85-89mmHg
Grade 1	140-159mmHg	90- 99mmHg
Grade 2	160-179mmHg	100-109mmHg
Grade 3	>180mmHg	>110mmHg
ISH	>/=140mmHg	<90mmHg

HYPERTENSION

Investigations:

- **ECG**
- **Fasting plasma glucose**
- **Total cholesterol,LDL,HDL,TG**
- **K+, uric acid, creatinine and creatinine clearance**
- **Hb & haematocrit**
- **Urine analysis**

HYPERTENSION

Recommended Investigations:

- **Echocardiography**
- **Carotid ultrasound**
- **ABI**
- **Fundoscopy**
- **Pulse wave velocity**

HYPERTENSION

Non – Pharmacological Management:

- **Weight reduction**
- **Salt restriction to <5g/day**
- **Alcohol consumption to <20g/day for men, <10g/day for women**

HYPERTENSION

TREATMENT

- **ACE-Inhibitors & ARB:**
  - **reduce LVH**
  - **reduce microalbuminuria**
  - **preserve renal function & delay end-stage kidney disease**

- **CALCIUM CHANNEL BLOCKERS:**
  - **slow down progression of carotid hypertrophy & atherosclerosis**

HYPERTENSION

- 15 – 30% of patients will need 3 or more antihypertensive drugs to control the blood pressure
- Treatment target: </ 140/90mmHg
- < 130/85mmHG target in diabetics is not supported by evidence in recent trials

DIABETES MELLITUS

- CVD is the commonest cause of death in diabetics
- Intensive control of hyperglycaemia in diabetes reduces risk of macrovascular and microvascular outcomes
- Target HbA1c <7%
- LDL cholesterol <2.5 in diabetics without atherosclerosis
- LDL cholesterol <1.8 in very high risk diabetics
- In the Heart Protection Study, 40mg simvastatin reduced the risk of CHD and stroke in diabetics and non-diabetics without prior MI or angina
- TNT trial, Atorvastatin 80mg vs 10mg: reduction of risk of primary events

DYSLIPIDAEMIA

- Cholesterol and triglycerides bound to apoproteins to form lipoproteins
- Small, dense LDLs are atherogenic
- Oxidised LDL penetrates endothelium to form atheromatous plaques
- Epidemiological studies have shown that reducing LDL cholesterol reduces risk of CVD
- Every 1mmol/l reduction in LDL cholesterol is associated with a 20-25% reduction in CVD mortality and non-fatal MI

DYSLIPIDAEMIA

Treatment Targets:

- **LDL cholesterol is the treatment target**
- **<1.8mmol/l in very high risk subjects**
- **<2.5mmol/l in high risk people**
- **<3.0 in moderate risk people**

DYSLIPIDAEMIA

- **Secondary Dyslipidaemia:**
  - **Alcohol abuse**
  - **Liver and kidney disease**
  - **Cushing's syndrome**
  - **Hypothyroidism**
  - **Corticosteroids**
  - **Cyclosporin**

DYSLIPIDAEMIA

3-hydroxy-.methylglutaryl-co-enzyme A reductases (STATINS)

- Changed the epidemiology of coronary heart disease
- Major RCT in the 1980s showed that lowering LDL cholesterol reduced the risk of first ischaemic events and recurrent events
- Statins also decrease plaque burden in affected arteries

STATINS

- 5 – 10% of people using statins develop myalgia
- Drugs that interact with statins and increase the risk of myopathy and rhabdomyolysis
- CYP3A4 inhibitors:
- Protease inhibitors saquinavir, ritonavir
- Sildenafil
- Azole antifungals: itraconazole, fluconazole
- Macrolides: clarithromycin, erythromycin, azithromycin
- Calcium antagonists: diltiazem, verapamil

OTHER CHOLESTEROL LOWERING DRUGS

- **Fibrates**
- **Bile acid sequestrants**
- **Niacin**
- **Selective cholesterol absorption inhibitors**

WEIGHT CONTROL

Body Mass Index = weight (kg) / height (m)

- Normal: 18.5 – 25
- Overweight: 25 – 29.9
- Obese: >30

Waist circumference

- <80 cm women
- <94 cm men

SMOKING CESSATION

- Cigarette smoking is the single most powerful determinant of atherosclerotic cardiovascular disease apart from age
- 1 billion people smoke world-wide
- Rates increasing in developing countries, among adolescents, young people and women
- 20 cigarettes a day increase CVD risk x3
- Smoking cessation is highly beneficial
- Confers a 35 – 40% risk reduction
- 36% reduction in mortality

SMOKING CESSATION

- Smoking cessation exceeds the benefit of taking statins, Aspirin, ACE-inhibitors and B-blockers
- Patient support programmes are needed as nicotine is highly addictive

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