Ulster University

East Lancashire Hospitals NHS
NHS Trust

PATHOGENESIS OF LOWER LIMB ARTERIAL DISEASE

Professor Mark E. O'Donnell
DipSEM(GB&I) MB BCH BAO(Dist) MFSEM(UK) MFSEM(RCSI&RCPI) MFSTEd MMedSc(Dist) MD ECFMG RPVI(ARDMS) FRCSEd(Gen&VascSurg) FEBVS(Hon)

Consultant Vascular and Endovascular Surgeon, Royal Blackburn Hospital, East Lancashire Hospitals NHS Trust & Sport and Exercise Sciences Research Institute, Faculty of Life and Health Sciences, Ulster University, Northern Ireland.

Allied Healthcare Professions Teaching – Ulster University
Wednesday 1st March 2017

Safe | Personal | Effective

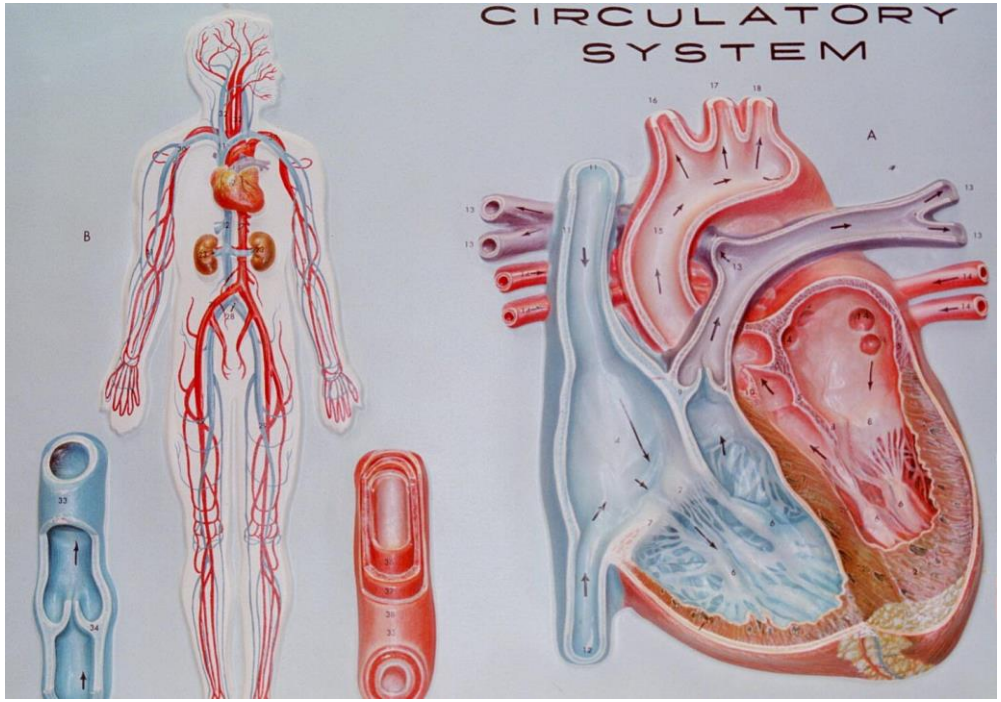
Learning Outcomes

East Lancashire Hospitals NHS
NHS Trust

- Describe vascular histology.
- Identify cardiovascular risk factors for atherosclerotic pathogenesis.
- Explore atherosclerotic and neuropathic pathogenesis.
- Discuss the physiological response to vascular disease and subsequent systemic clinical consequences.
- Evaluate the influence of atherosclerosis and diabetes on the lower limb.
- Explore other systemic manifestations of vascular disease.

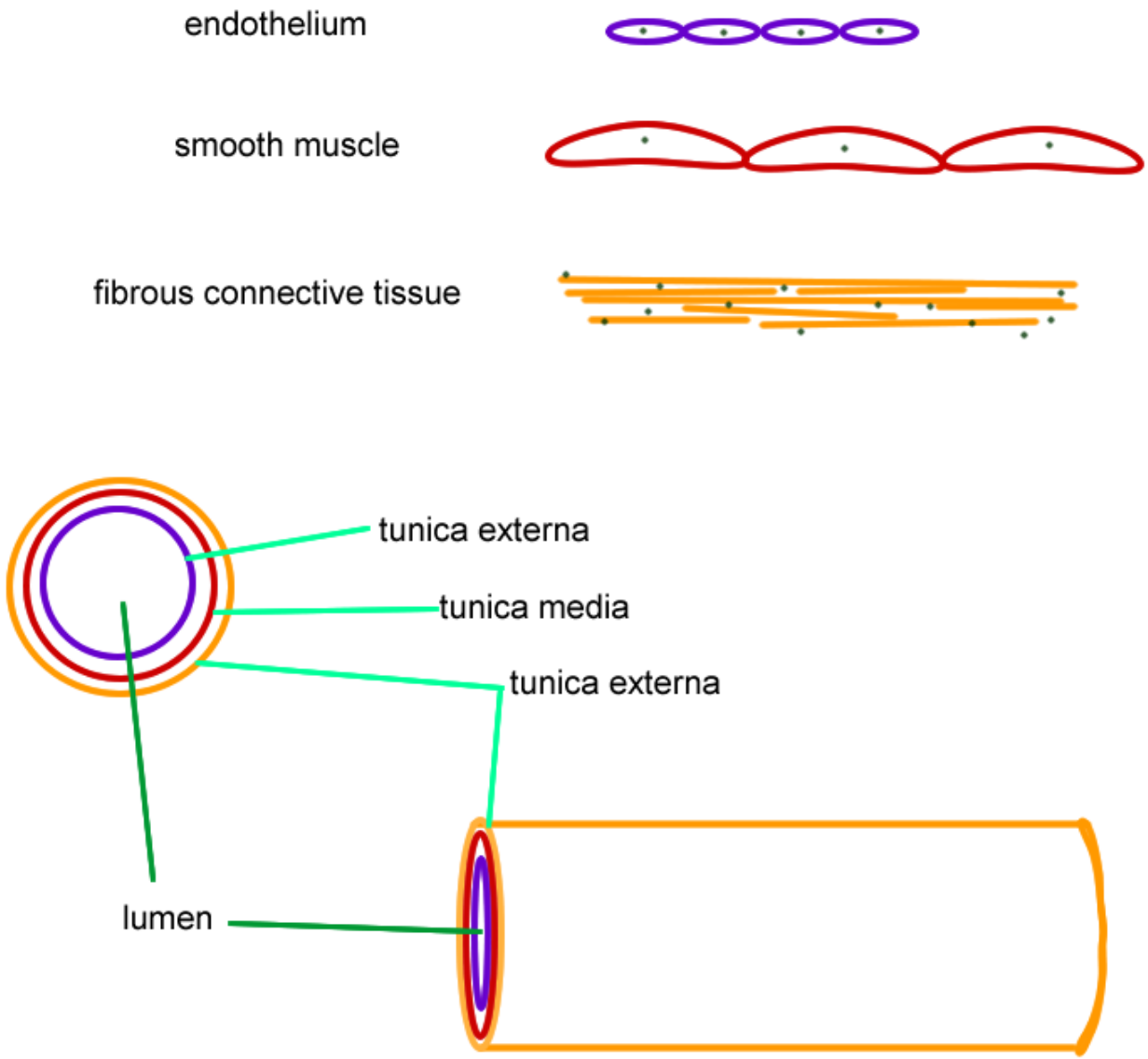
Vascular Histology

- Arteries.
- Veins.
- Lymphatics.



Arterial Wall

- **Tunica Intima**
  - Thin single layer of squamous epithelium called the endothelium with little collagenous tissue and an internal elastic lamina.
- **Tunica Media**
  - Thick layer of smooth muscle and elastic connective tissue. Varying amounts dependant on vessel.
  - Aorta more elastic whereas smaller vessels more musculature.
- **Tunica Adventitia**
  - External elastic lamina surrounded by collagenous connective tissue.

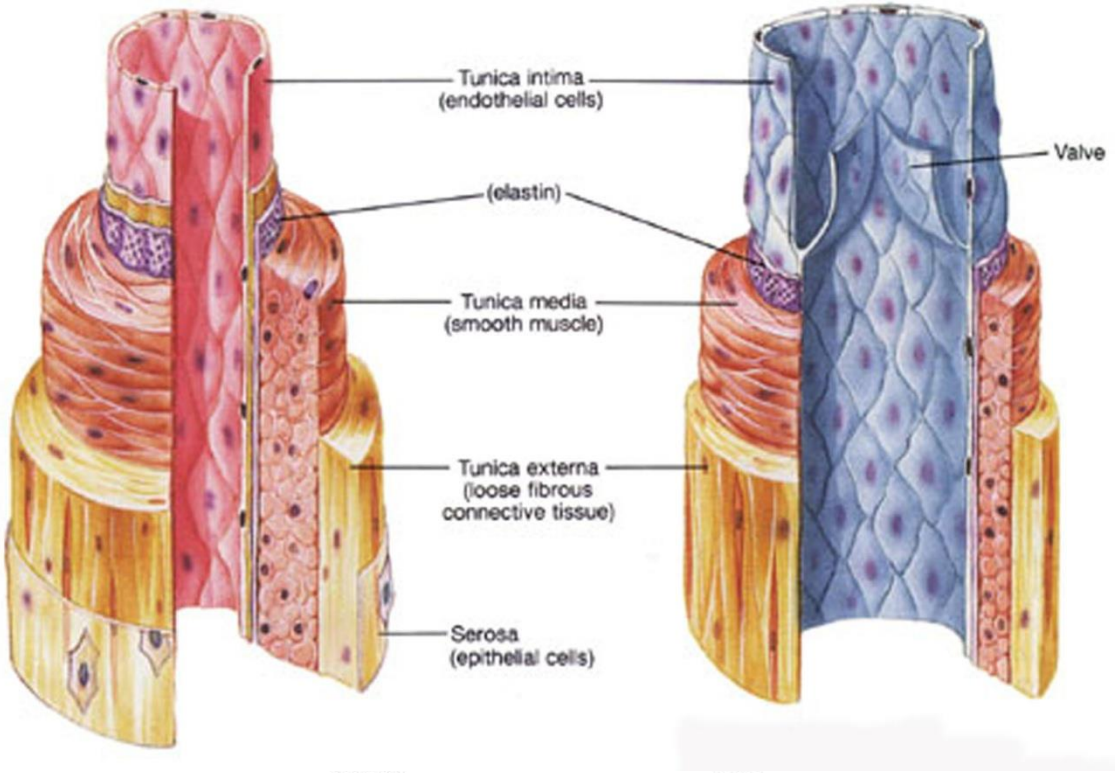

endothelium
smooth muscle
fibrous connective tissue
tunica externa
tunica media
tunica externa
lumen

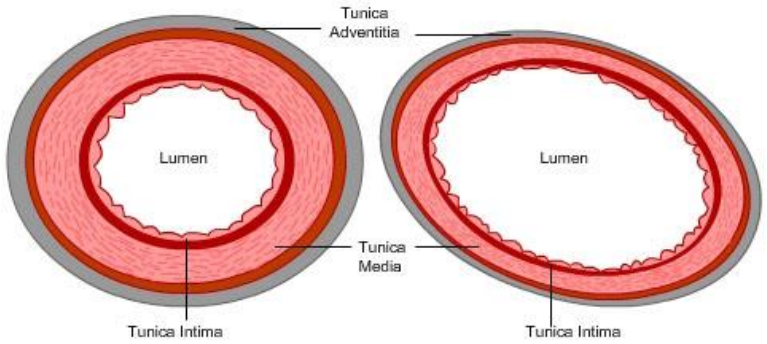
Venous Wall

- Thinner walls.
- Larger diameter.
- Similar three layers but less muscle in tunica media and internal elastic lamina absent.
- All veins have valves except those in the thorax and abdomen.

Artery

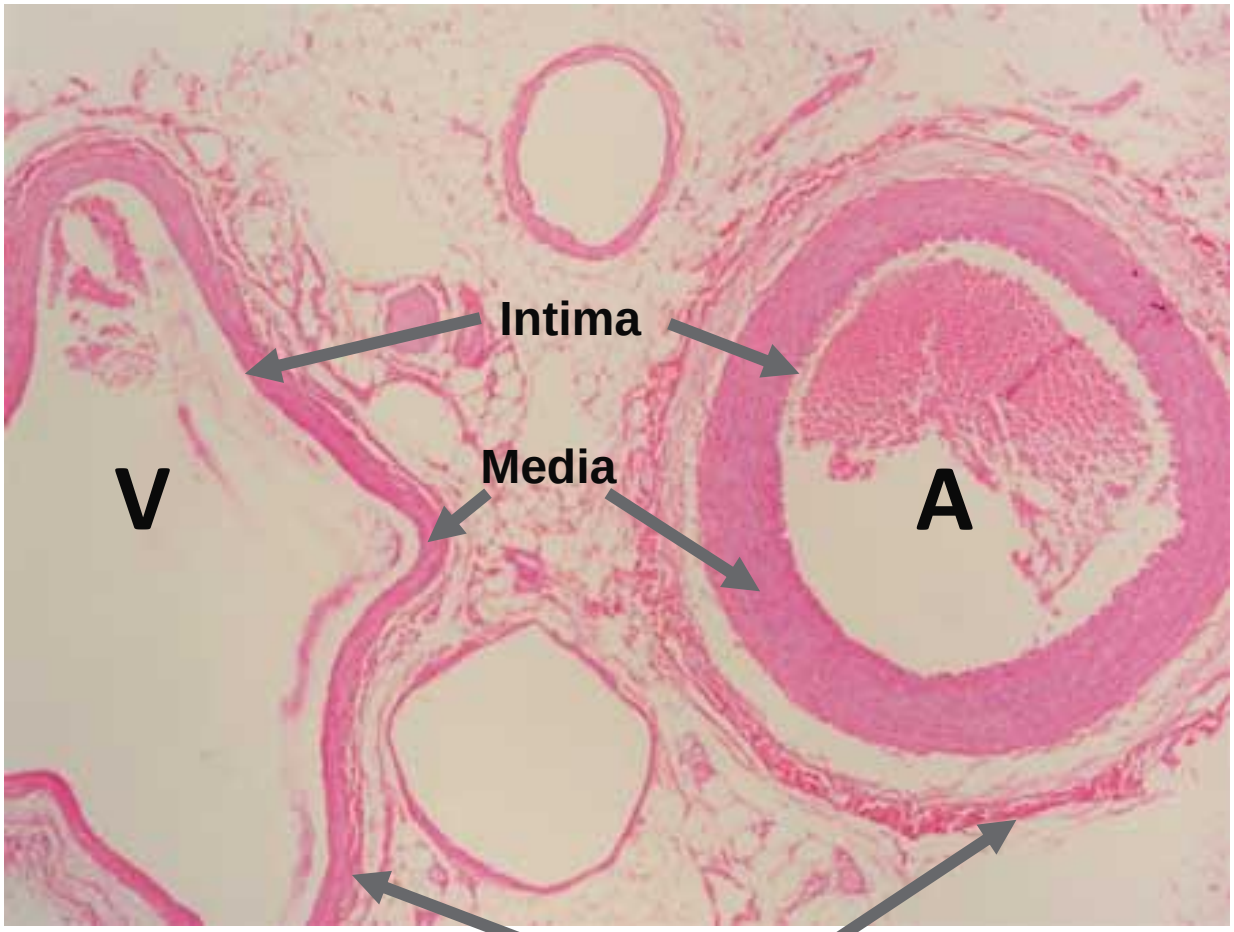
Vein

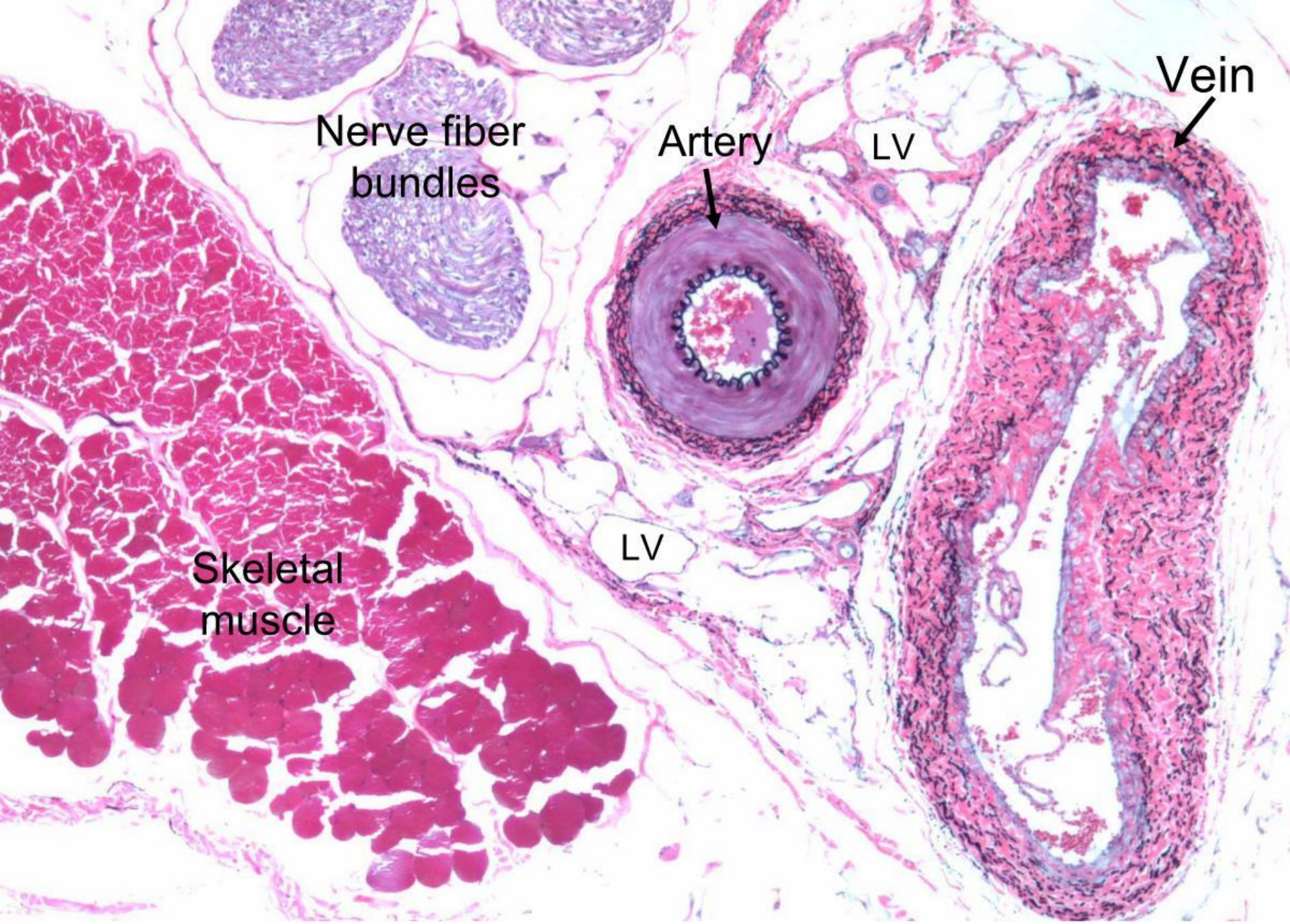

Tunica intima
(endothelial cells)
(elastin)
Tunica media
(smooth muscle)
Tunica externa
(loose fibrous
connective tissue)
Serosa
(epithelial cells)
Valve


Tunica
Adventitia
Lumen
Lumen
Tunica
Media
Tunica Intima
Tunica Intima


CAPILLARY
Single layer of
Endothelial Cell
Nucleus of
Endothelial Cell

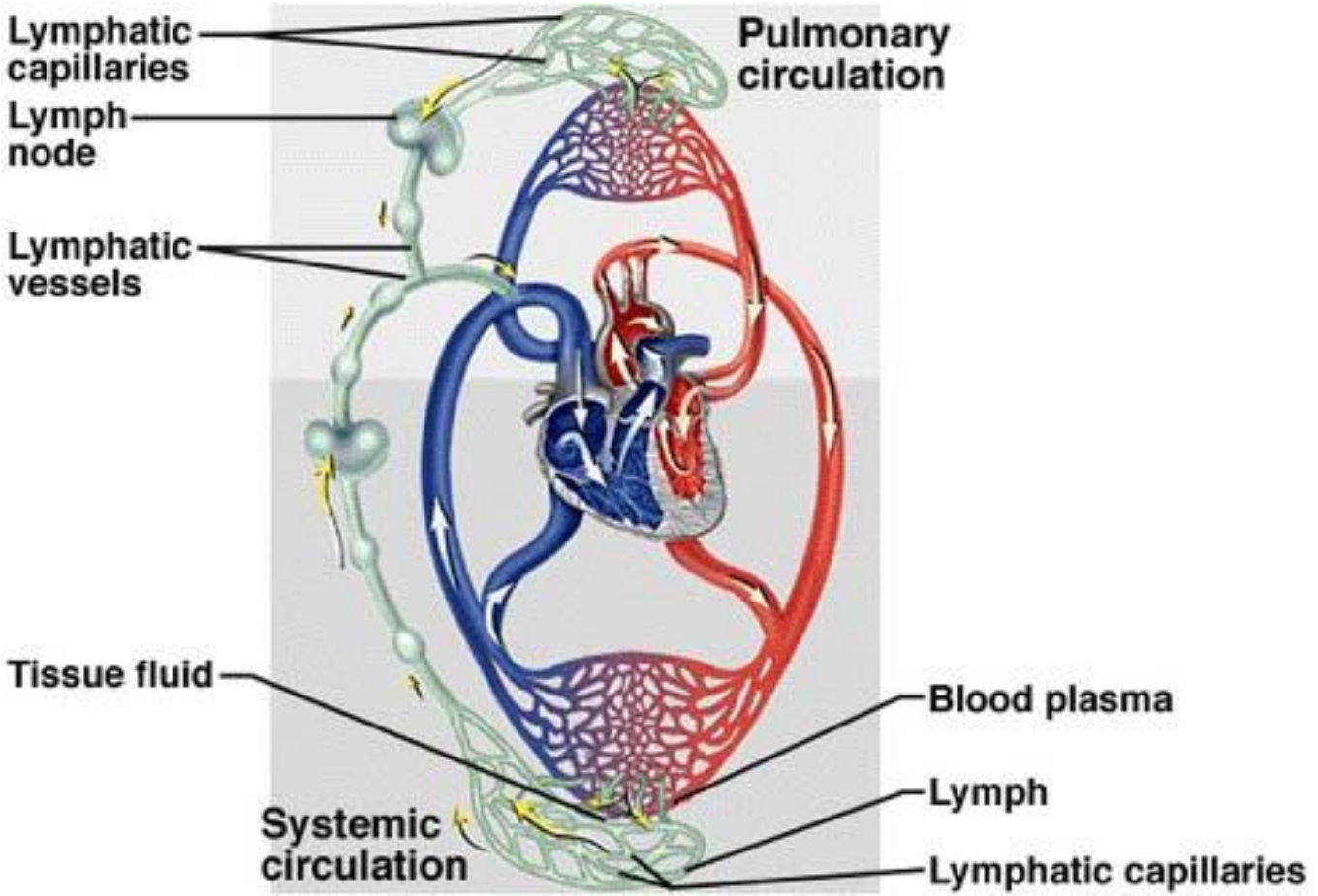
Normal Artery and Vein

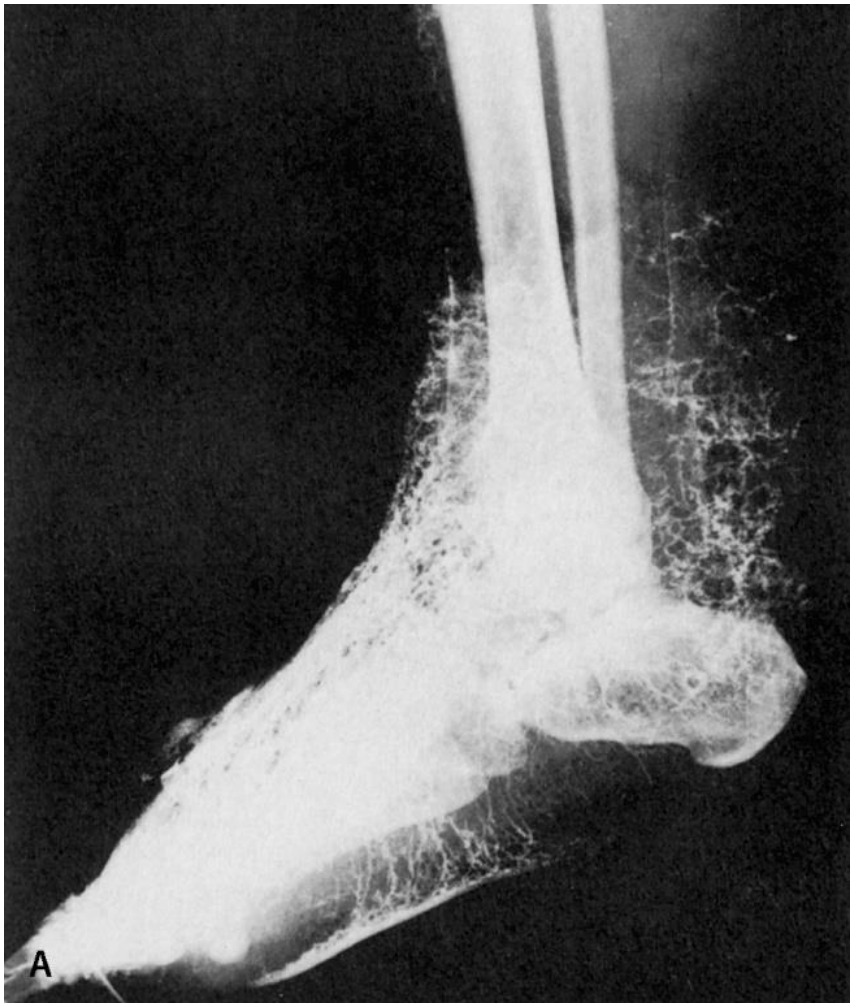



Nerve fiber bundles
Artery
LV
Vein
LV
Skeletal muscle

Lymphatics

- Simple endothelial tubes that originate in nearly all parts of the body as lymph capillaries.
- Lead to larger collecting channels which have walls similar to vein **BUT without the distinct 3 layers**.
- Contain more valves.
- The lymphatic system is a slow rhythm, low velocity and low pressure system.
- Lymph is propelled through the vessels primarily by the rhythmic contractions of tiny muscular units (lymphangions) which form the lymph collectors which can increase the flow through the lymphatic system by 20 - 30 times when stimulated.


Lymphatic capillaries
Lymph node
Lymphatic vessels
Tissue fluid
Systemic circulation
Pulmonary circulation
Blood plasma
Lymph
Lymphatic capillaries


A

East Lancashire Hospitals NHS
NHS Trust

Vascular Disease – What Lies Beneath

Safe | Personal | Effective

Vascular Disease – Key Risk Factors

- Hypertension.
- Hypercholesterolaemia.
- Diabetes.
- Smoking.
- Others.

Hypertension

- Exact mechanisms unknown.
- Elevation of oxidative stress and associated oxidative damage.
- Angiotensin II;
  - A multifunctional peptide regulating vascular contraction, growth and fibrosis.
  - Recently identified as proinflammatory mediator.
  - Angiotensin II increases vascular permeability, promotes recruitment of inflammatory cells into tissues, and directly activates infiltrating immune cells, which further contribute to the inflammatory process.
  - Moreover, angiotensin II participates in tissue repair and remodeling, by stimulating cell growth and fibrosis.
  - Many of these processes are mediated through increased generation of reactive oxygen species (oxidative stress).
    - *Rhian M* 2005

Hypercholesterolaemia

- Hypercholesterolaemia;
  - Progressive lipid accumulation within lipid-laden macrophages is believed to represent a dominant mechanism of subintimal fatty streak evolution that characterizes the earliest manifestations of atherosclerosis.
  - ↑ serum cholesterol has the ability to promote and sustain proatherogenic inflammation of vascular wall.
    - Desideri G *Curr Pharm Des* 2005

Hypercholesterolaemia

- Oxidised Low Density Lipoprotein (Ox-LDL);
  - Fuels lipid accumulation in foam cells.
  - Ox-LDL stimulates expression of proinflammatory signals including monocyte chemotactic protein-1 and intercellular adhesion molecule-1 that facilitate monocyte recruitment and adhesion to the vessel wall.
  - Further, ox-LDL directly inactivates nitric oxide, is cytotoxic to endothelial cells, stimulates vascular smooth muscle cell proliferation, and upregulates tissue factor and plasminogen activator inhibitor-1 expression that have the potential to support atherothrombosis.
    In addition to LDL oxidation, reaction of reactive oxygen species with cell membrane bound fatty acids can promote a vicious cycle of continued oxidative damage, resulting in alterations in cell membrane permeability and functional impairment in cellular transport and signaling.
    - *Nedeljkovic J Postgraduate Medical Journal* 2003

Hypercholesterolaemia

- Effects of Statins;
  - Inhibition of Smooth Muscle cell proliferation.
  - Improves endothelial and vasomotor function.
  - Reduced platelet aggregation.
  - Reduced modified LDL & oxidative stress.
  - Reduction in coagulation factors.

East Lancashire Hospitals NHS
NHS Trust

Diabetes

- 15% of diabetics are affected by PAD at 10 years following diagnosis, rising to 45% at 20 years.
  - Kreines *Diabetes Care* 1985.
- 20% of patients with PAD have diabetes.
  - Muribato *Circulation* 1997.
- PAD disease distribution different in diabetes.
  - Strandness *Diabetes* 1961.
- PAD more aggressive in diabetics with an 11-times higher rate of major lower limb amputation and a doubling of the five-year mortality.
  - Elhadd *Pract Diabetes Int* 1999.
- Diabetic ulcers heal more slowly and are the main cause of non-traumatic lower limb amputation in developed countries.
  - Caputo *N Engl J Med* 1994.

Smoking

- Vasospasm;
  - Anoxia of vessel wall.
  - Subsequent stimulation of inflammatory cells.
- Alteration in clotting factors;
  - ↑ fibrinogen levels which ↑ plasma viscosity.
  - Exudation of fibrinogen into arterial wall.
  - Tendency to thrombosis.
- Impairment of normal platelet function;
  - Increased platelet aggregation.
  - Release of vasoconstrictors.
- Greenhalgh RM *Inflammatory and Thrombotic Problems in Vascular Surgery* 1997

Homocysteine

- Amino – Acid intermediate in the metabolism of methionine.
- Excessive homocysteine in the vessel wall reacts with low density lipoproteins to create damaging reactive oxygen species.
- Elevated levels correlate with cardiovascular disease.
- 10% of coronary artery disease attributable to homocysteine.

Chlamydia

- First linked to cardiovascular disease by venerologists in South America in the 1940's.
- Ubiquitious respiratory organism that was the predominant species in cardiovascular lesions.
- More than 50% of people have anti-chlamydial antibodies by the age of 50 without the presence of a sexually transmitted disease.

Pathogenesis of Arterial Disease

- Pathophysiology:
  - Atherosclerosis.
  - Ischaemia-Reperfusion Injury.
- Key Mediators:
  - Endothelium.
  - Platelets.

Pathogenesis of Arterial Disease

- Pathophysiology:
  - Atherosclerosis.
  - Ischaemia-Reperfusion Injury.
- Key Mediators:
  - Endothelium.
  - Platelets.

Atherosclerosis

- Derived from Greek.
- *Athere* meaning porridge or gruel.
- *Sclerosis* meaning induration or hardening.

History of Atherosclerosis

- Battle casualities from Korea.
- Average age 22.
- 45 - 77% already had atherosclerosis.
- 39% had coronary luminal narrowing from 10-90%.
- 3% had complete occlusion of 1 or more coronary vessels.
  - Enos *JAMA* 1953

Pathogenesis of Arterial Disease

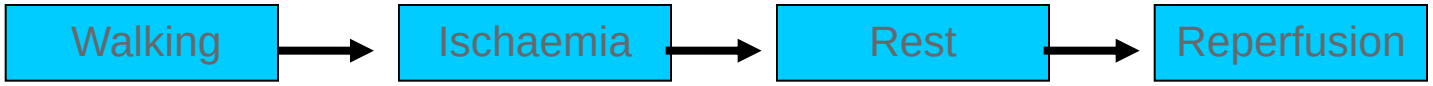
- Pathophysiology:
  - Atherosclerosis.
  - Ischaemia-Reperfusion Injury.
- Key Mediators:
  - Endothelium.
  - Platelets.

Ischaemia-Reperfusion Injury

- First reported in 1960;
  - Two patients with acutely ischaemic lower limbs developed acute massive ischaemic myopathy and myoglobinuria following revascularisation.
    - Haimovici *Surgery* 1960.
  - After a short ischaemic period, lower limb muscles can be salvaged by reperfusion.
    - McCord *Fed Proc* 1987.
  - However, re-introduction of oxygen to these hypoxic tissues can lead to oxygen derived free radical (ODFR) mediated damage.
    - Halliwell and Gutteridge *Free Radicals in Biology and Medicine* 1989
  - Triphasic revascularisation period following lower limb ischaemia.
    - Homer-Vanniasinkam *Eur J Vasc Endovasc Surg* 1997

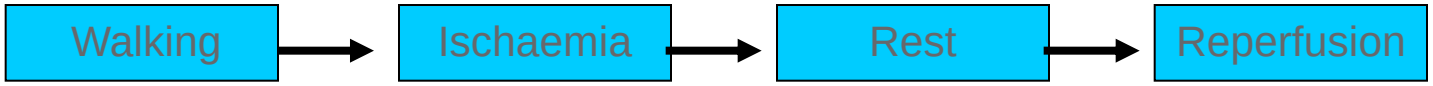
Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust



Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust

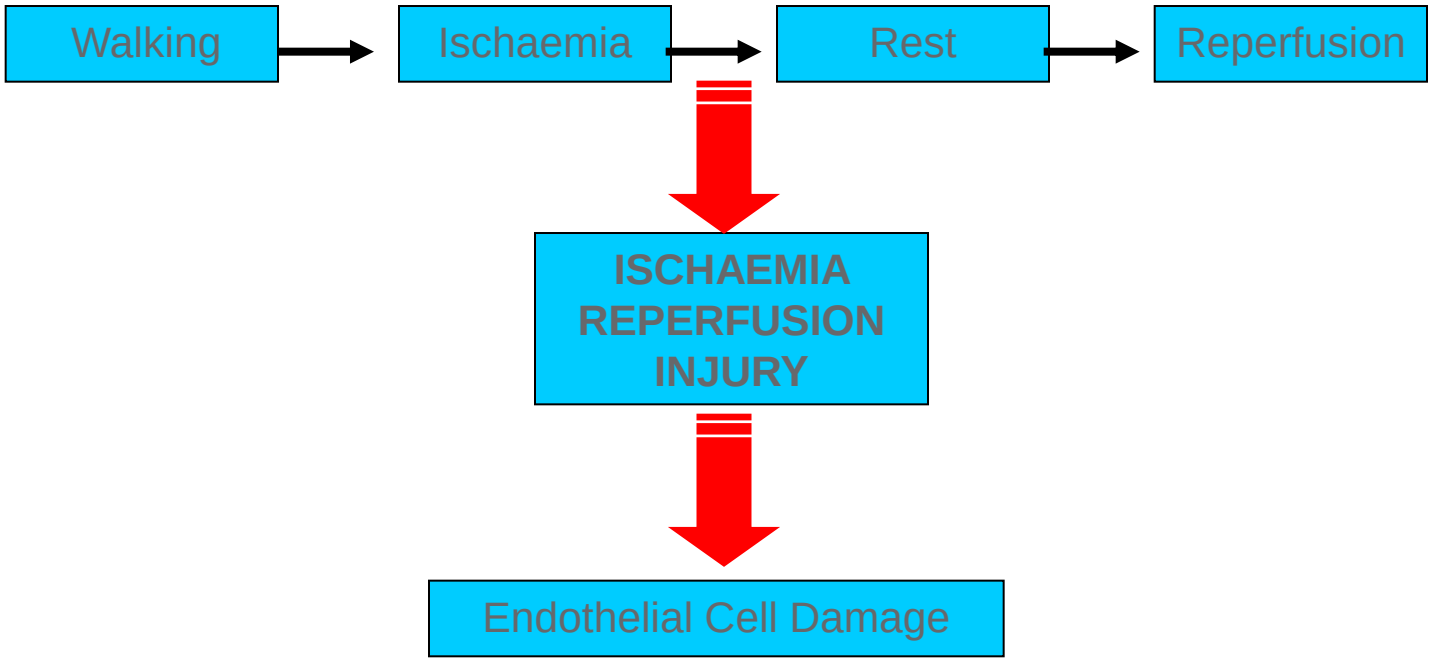


Free Radical Production

Antioxidant Consumption

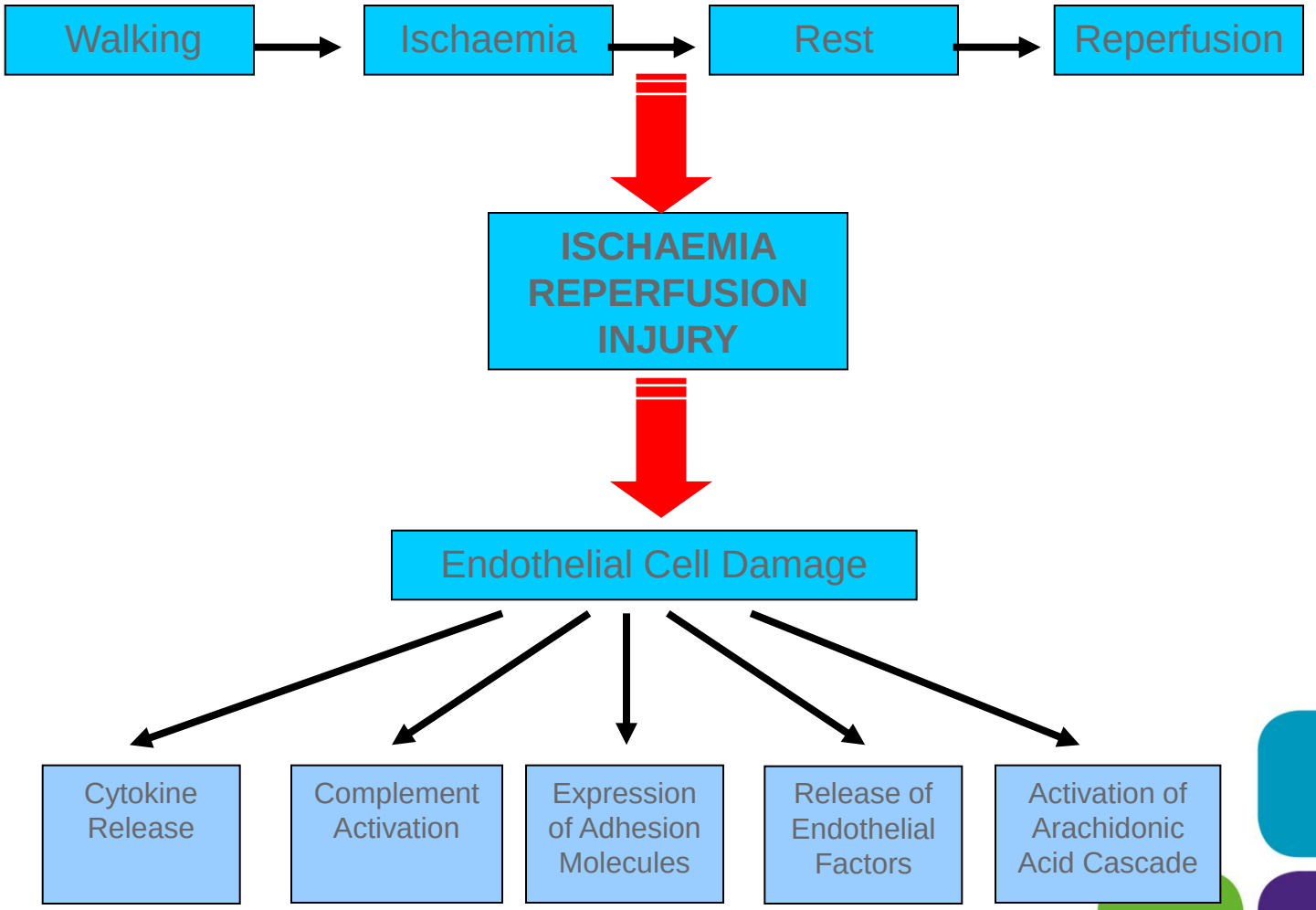
Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust



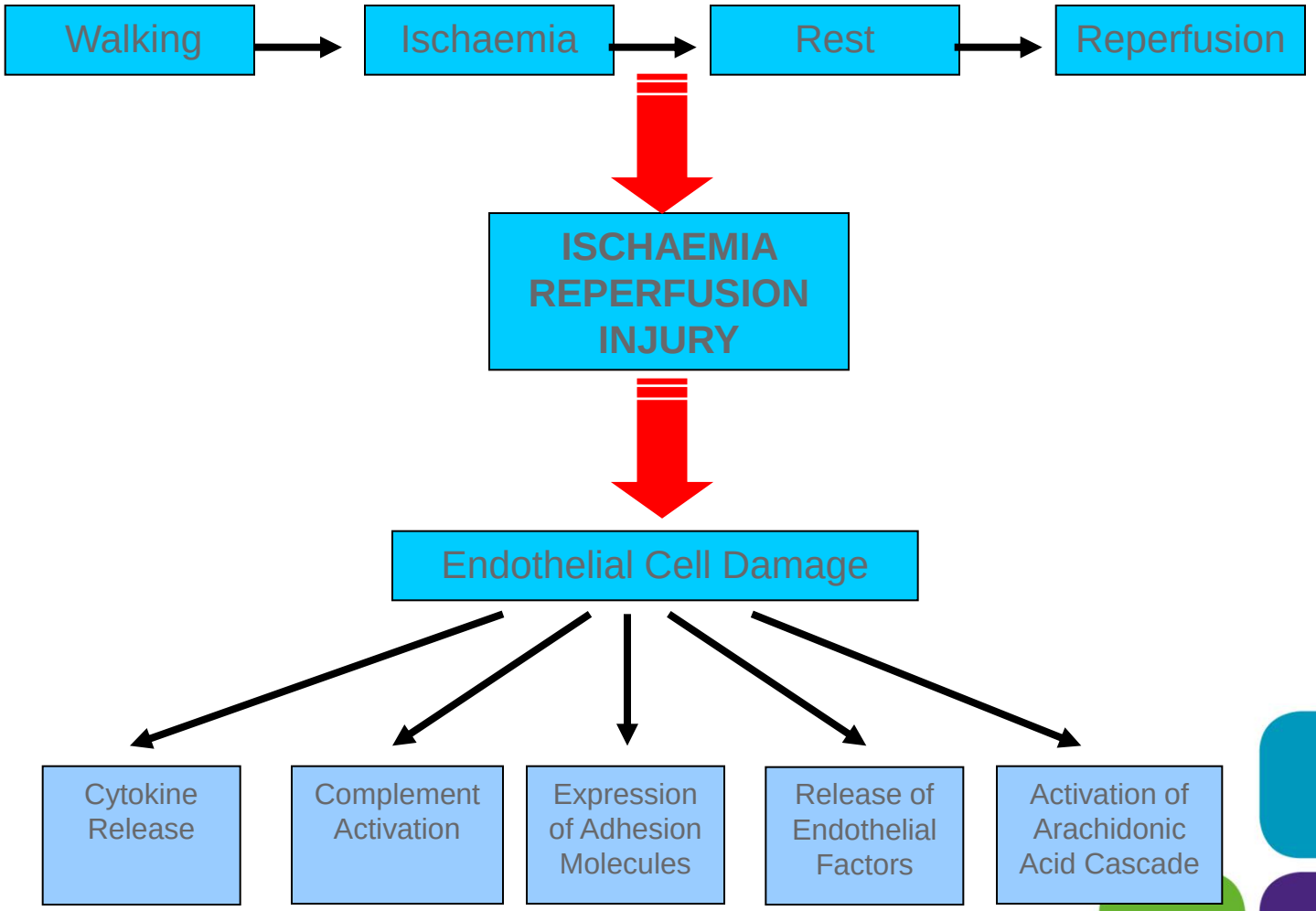
Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust



Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust



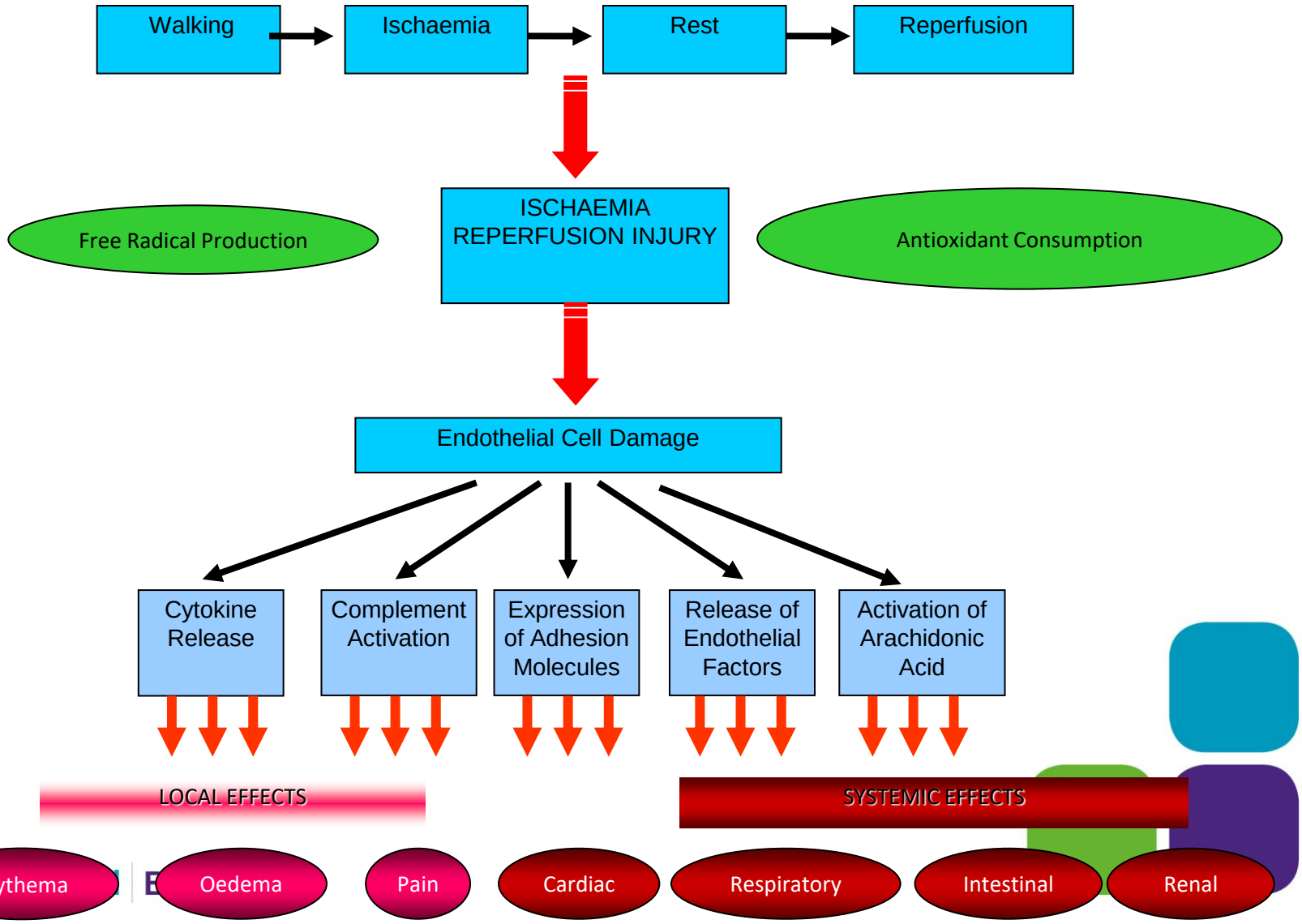
Safe | Personal | Effective

LOCAL

SYSTEMIC

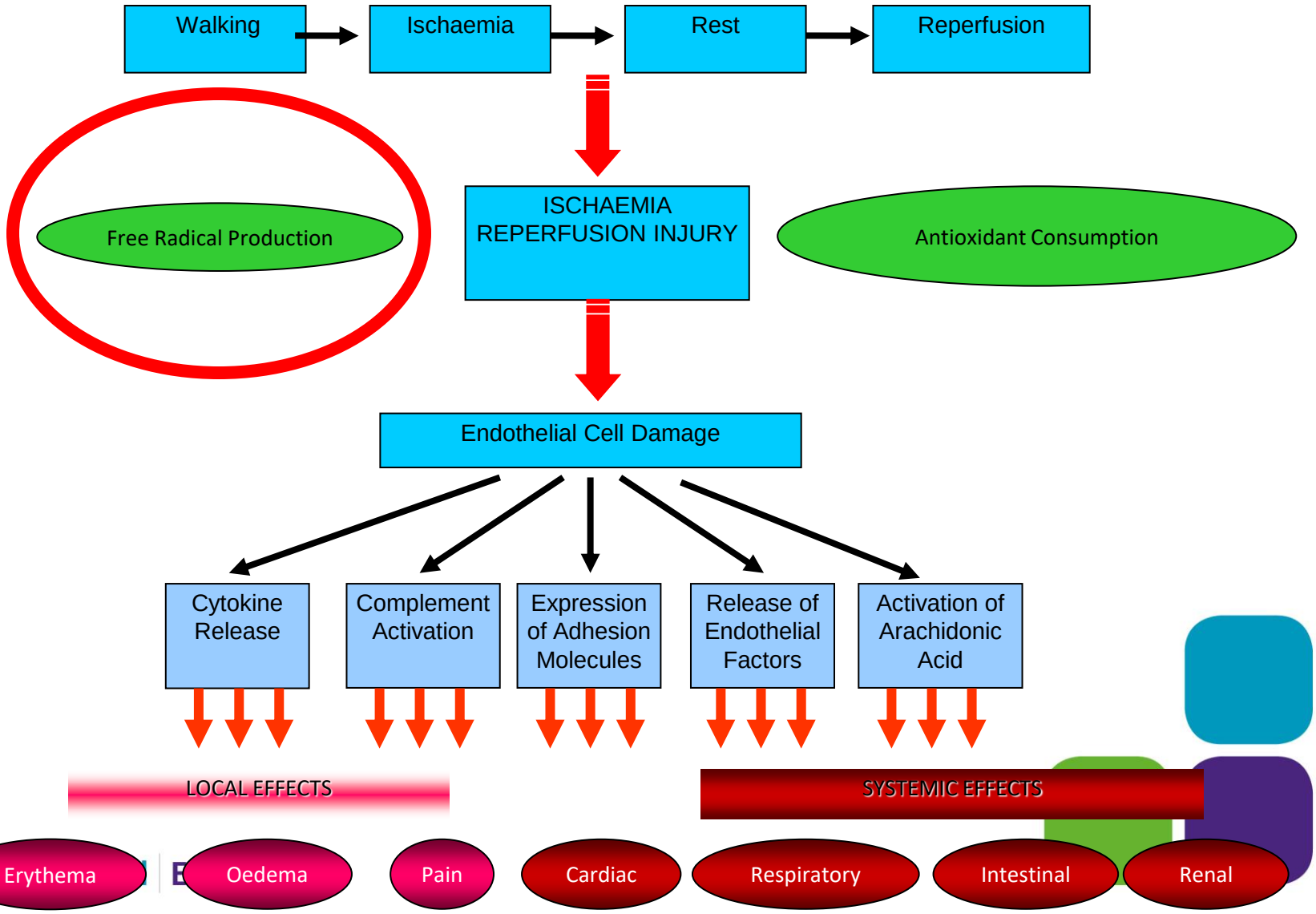
Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust



Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust

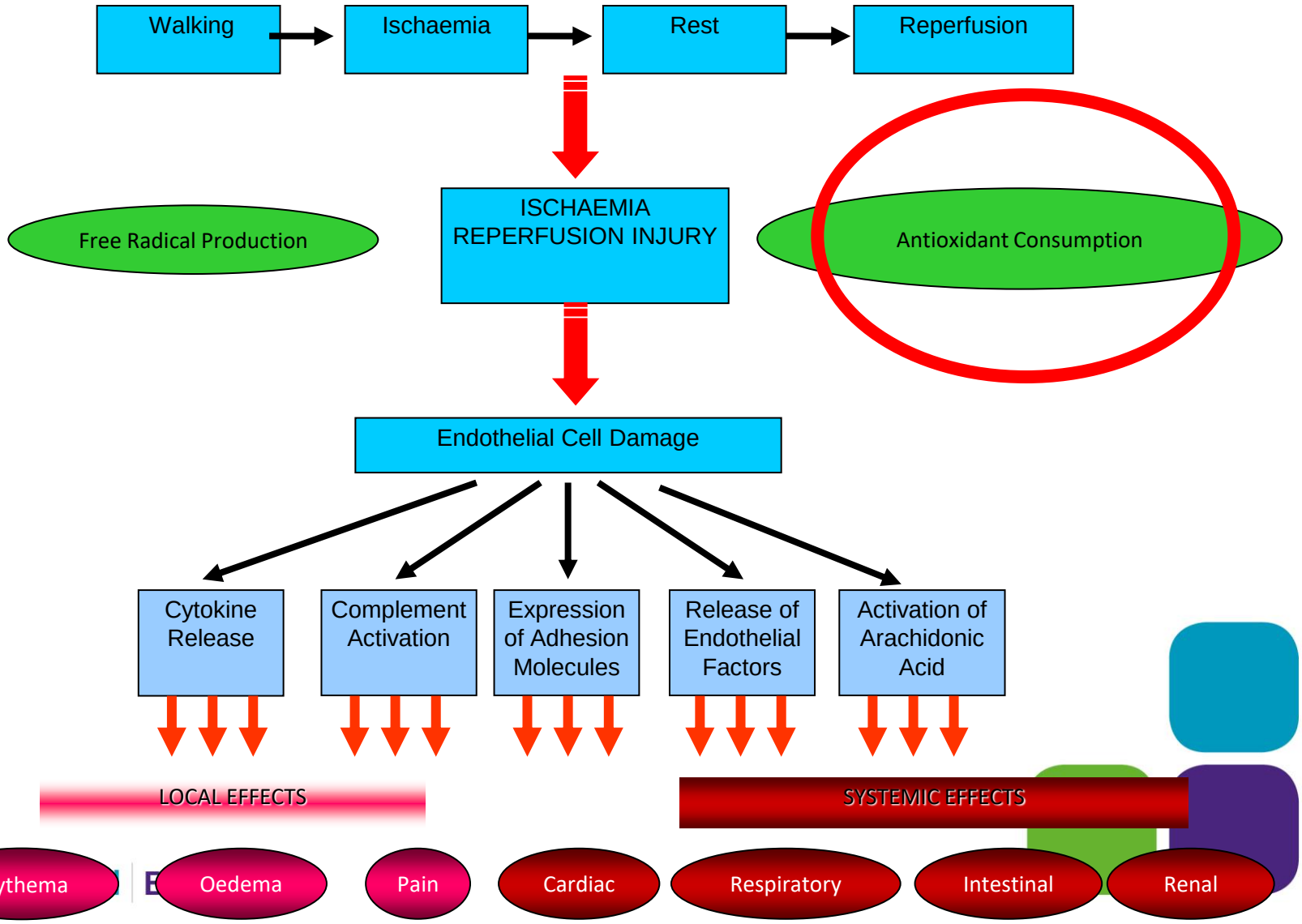


Oxygen-Derived Free Radicals

- Unstable molecule containing one or more unpaired electrons.
- The ODFR's implicated in PAD pathophysiology include;
  - The superoxide ion (O_2-).
  - Hydrogen peroxide (H_2O_2).
  - Hydroxyl radicals (OH-).
- Inactivation of nitric oxide or the oxidation of low density lipoproteins (LDL)
  - Gryglewski *Nature* 1986; Steinberg *N Engl J Med* 1989.
- The oxidized LDL damages the vascular endothelium and promotes foam cell formation.

Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust



Antioxidants

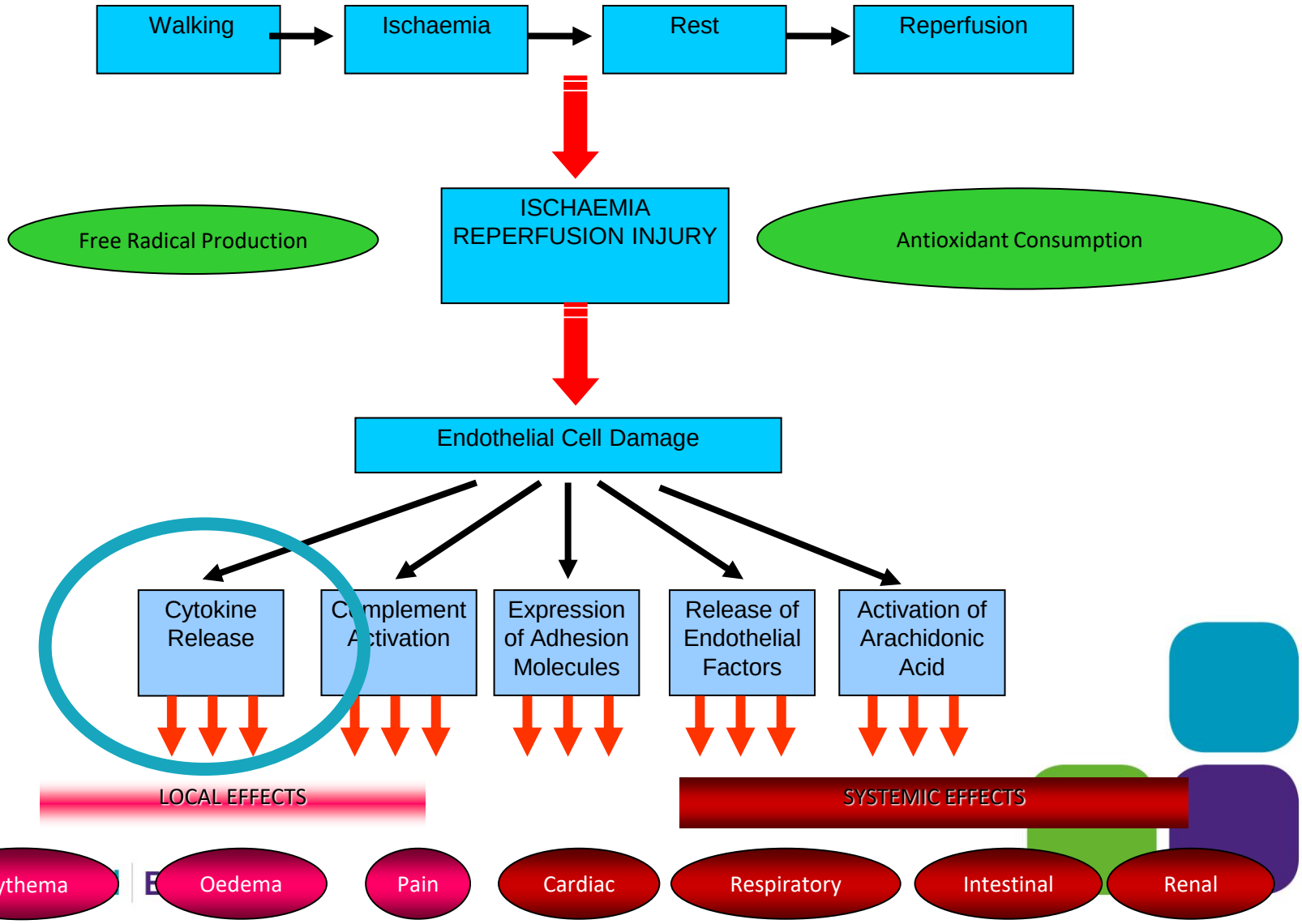
- Defined as any substance that, when present at low concentrations compared to those of an oxidizable substrate, significantly delays or inhibits oxidation of that substance.
  - Vitamins C (ascorbate).
  - Vitamin E (α-tocopherol).
  - Other low-molecular weight antioxidants such as urate and thiols.
- Act as the first line of defence against oxidative stress in the extracellular environment.
  - Stocker and Frei *Proc Natl Acad Sci USA* 1991; Ulker *Hypertension* 2003).

Antioxidants

- Antioxidants work at multiple levels in the oxidative sequence;
  - Attenuation of lipid peroxidation.
  - Can act as a “scavenger”.
  - Restorative role via rapid repair of oxidation damage.
- Role of ODFR scavenging to prevent oxidisation of proteins and lipids occurs at the expense of antioxidant consumption.
  - Soong *Eur J Vasc Surg* 1993; Stocker and Frei *Proc Natl Acad Sci USA* 1991.

Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust



Cytokines

- Small proteins released by cells which have a specific effect on the interactions between cells, on communications between cells or on the behavior of cells.

- The cytokines include interleukins, lymphokines and cell signal molecules, such as tumor necrosis factor and the interferons, which trigger inflammation and respond to infections.

    - Interleukin-6.
    - Interleukin-10.
    - Tumour Necrosis Factor.

Interleukin-6

- Interleukin-6 (IL-6);
  - Pro-inflammatory cytokine produced by macrophages, lymphocytes and endothelial cells.
  - Acts to promote B lymphocyte growth and differentiation and for T lymphocyte activation, proliferation and differentiation, and stimulation of granulocyte and macrophage colony formation.
    - Hack *Adv Immunol* 1997.
  - IL-6 production is stimulated by tumour necrosis factor, IL-1 and endotoxins during sepsis. IL-6 induces phospholipase A2 synthesis and promotes the complement and coagulation cascades

Interleukin-10

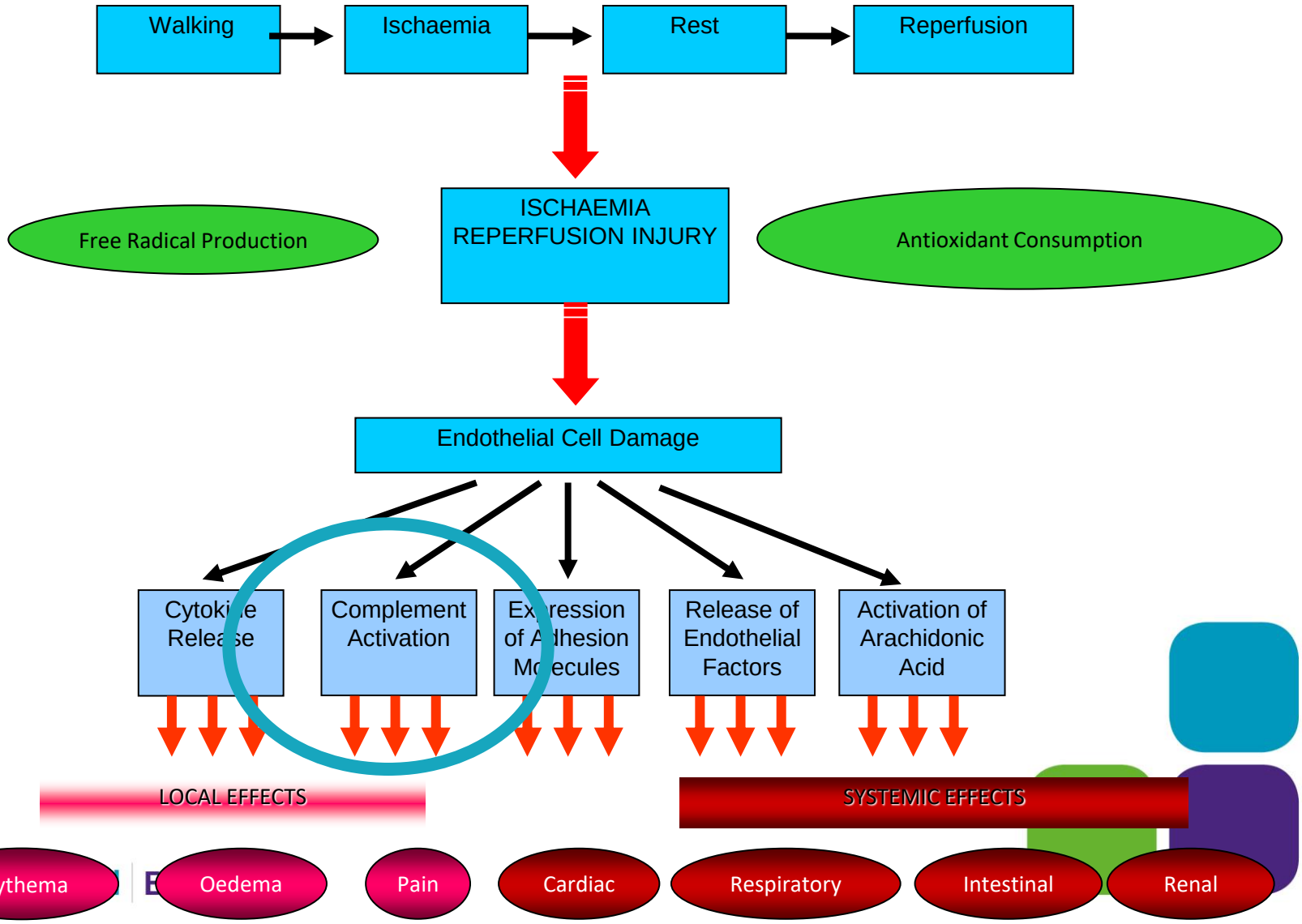
- Interleukin-10 (IL-10);
  - Anti-inflammatory cytokine which is primarily produced by the type-2 helper cells.
  - IL-10 regulates inflammatory cytokine production and major histocompatibility complex class II (HLA-DR) expression *in vitro.*
    - Klava *Arch Surg* 1997.
- It acts as an inhibitor of pro-inflammatory cytokine production and in patients following surgical or traumatic injuries

Tumour Necrosis Factor

- Tumour necrosis factor (TNF or cachectin);
  - Produced by monocytes, macrophages, T lymphocytes, natural killer, endothelial, mast, Kupffer and smooth muscle cells.
  - Involved in the acute phase reaction which can result in apoptotic cell death, cellular proliferation, differentiation, inflammation, tumorigenesis and viral replication.
  - Primary role is in the regulation of immume cells where dysregulation and overproduction may lead to a variety of human disease including cancer.
    - Locksley *Cell* 2001.
  - TNF-α is the main mediator released following the stimulation of endotoxin on leucocytes and endothelial cells.
  - It is responsible for the multiple cellular effects such as the induction of E-selectin expression, promotion of leucocyte-endothelial adhesion, activation of neutrophils and coagulation via an induction of tissue factor and plasminogen activator inhibitor in combination with protein C inhibition

Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust



Complement Activation

- Complex system of serum proteins which interact in a cascade, many of the early components are serine proteases which activate each other sequentially.

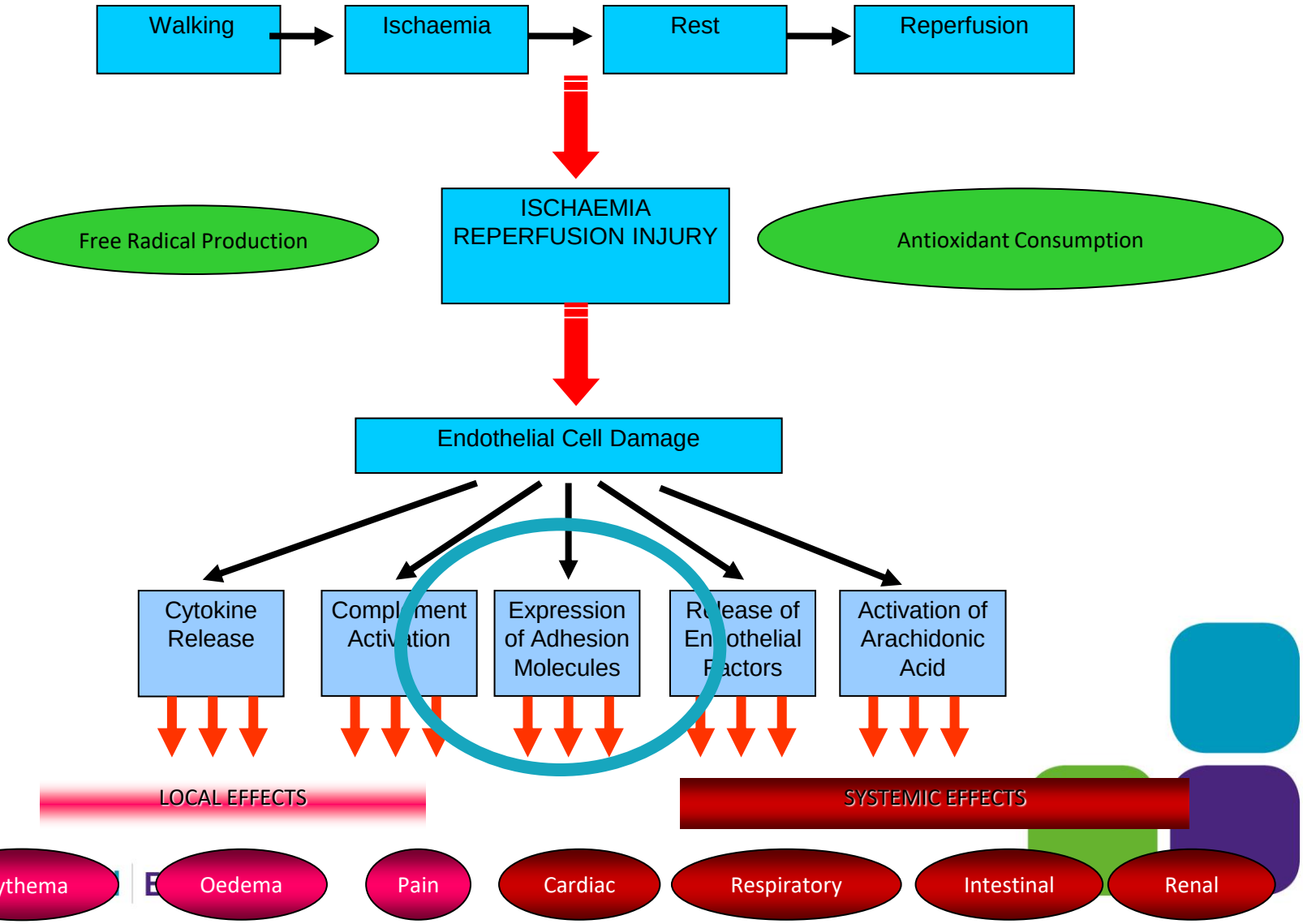
- There are two pathways by which complement activation is initiated.

  - **Classical pathway** is activated by antibody-antigen complexes.
  - **Alternative pathway** is initiated when a previously activated complement component binds to the surface of a pathogen, where it is **protected**.

- Activation of complement has a number of important biological effects.

Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust



Adhesion Molecules

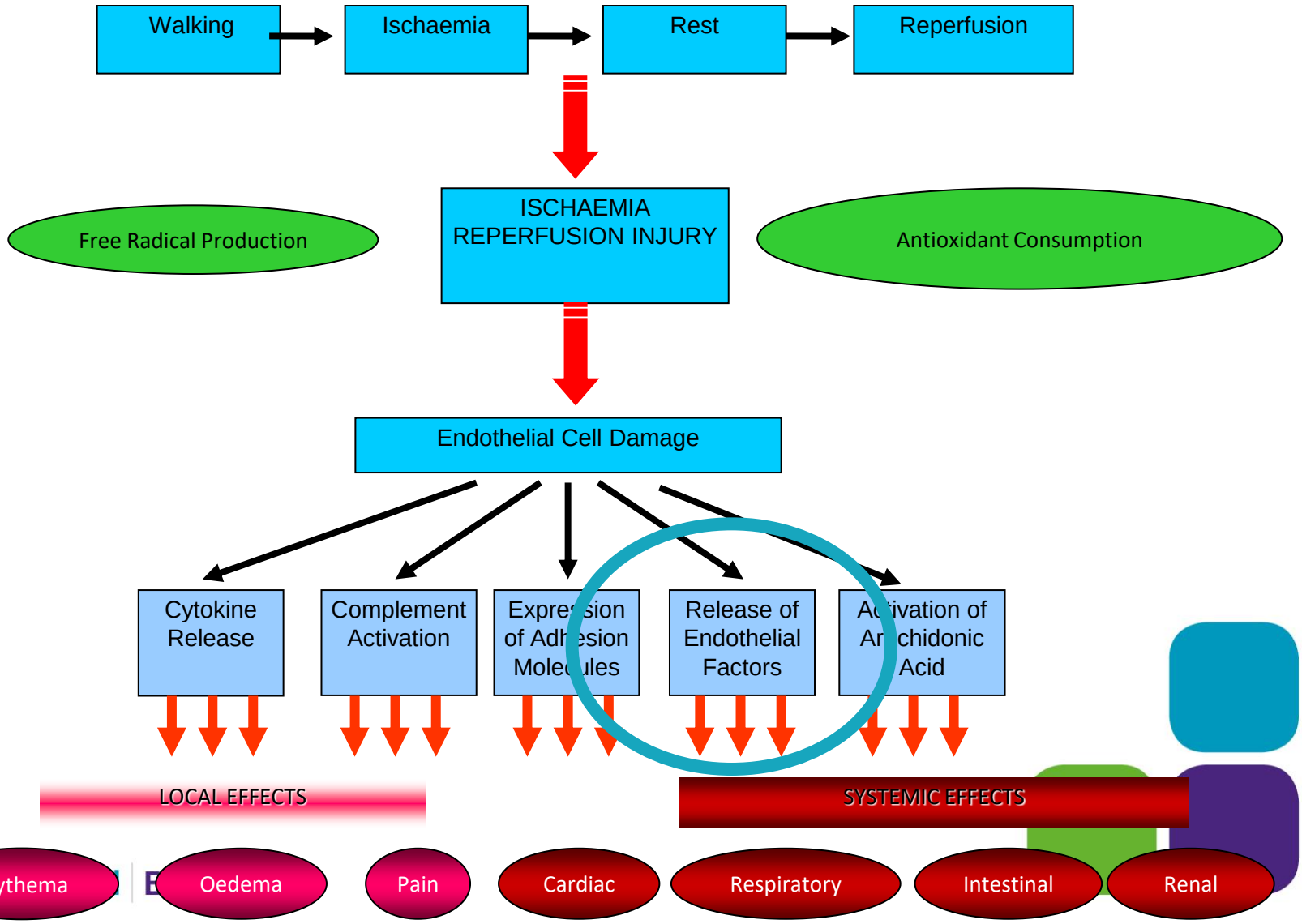
- Adhesion molecules, such as the selectins and cell adhesion molecules, recruit leucocytes to areas of inflammation.
  - Springer *Cell* 1994.
- Transient margination of leucocytes along the endothelium is mediated by both P- and E-selectins.
  - Tedder *Faseb J* 1995
- P-selectin can be identified in both the endothelial cells and α-granules of platelets.
  - Malik *Lancet* 2001; Ridker *Circulation* 2001.
- P-selectin is involved in platelet-leucocyte and inflammatory cell-endothelial interactions but not in platelet-platelet interactions.
  - Tsiara *Clin Appl Thromb Hemost* 2003

Adhesion Molecules

- A stronger attachment of leucocytes to the endothelium is mediated by intracellular adhesion molecule-1 (ICAM-1) and vascular cell adhesion molecule-1 (VCAM-1).
  - Springer *Cell* 1994.
- These molecules are more common in human atherosclerotic lesions than in healthy arterial disease.
  - Davies *J Pathol* 1993; Poston *Am J Pathol* 1992.
- There is a 5-times greater risk of CAD in patients with raised values of serum ICAM-1.
  - Hwang *Circulation* 1997

Ischaemia Reperfusion Injury

East Lancashire Hospitals NHS
NHS Trust

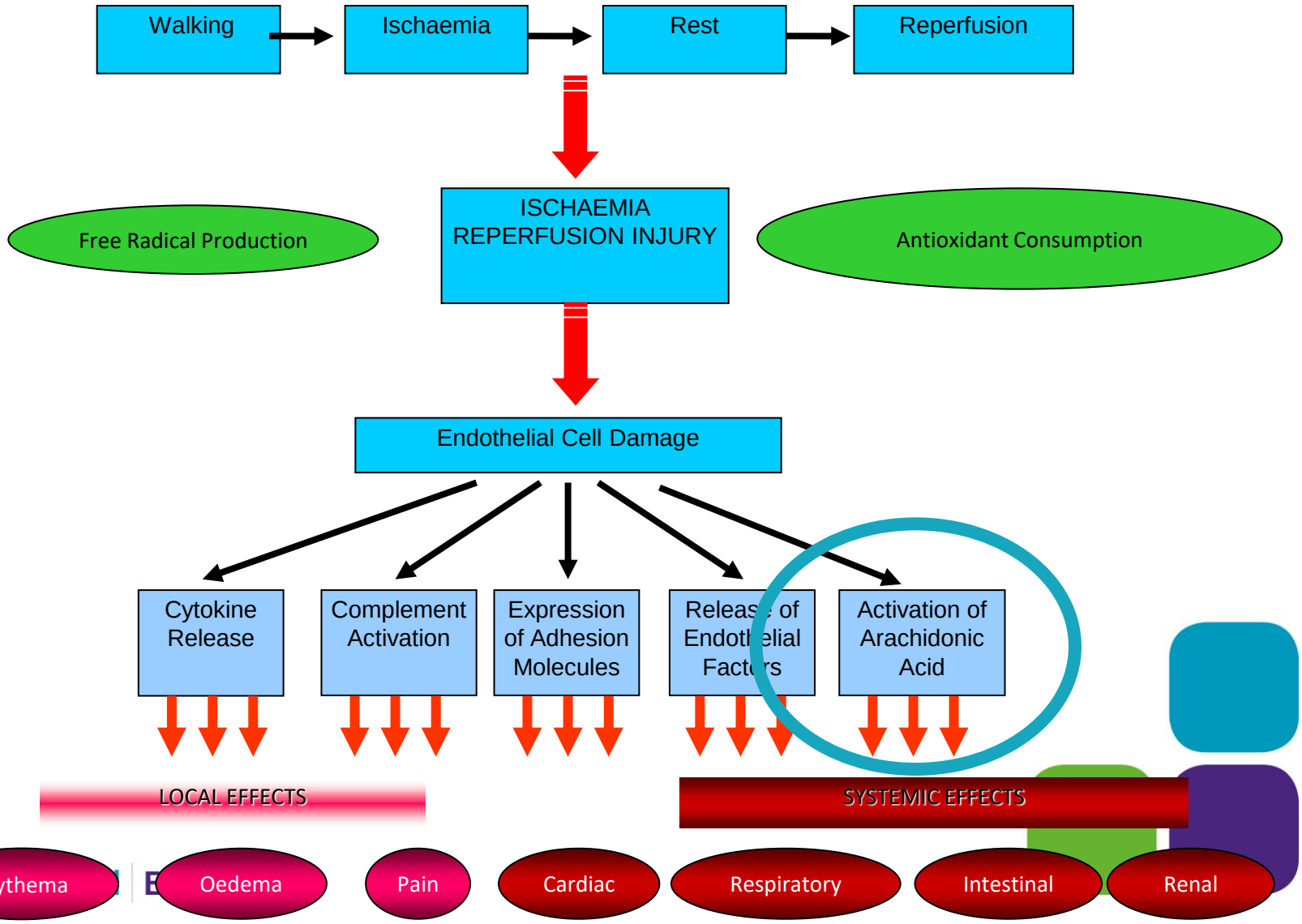


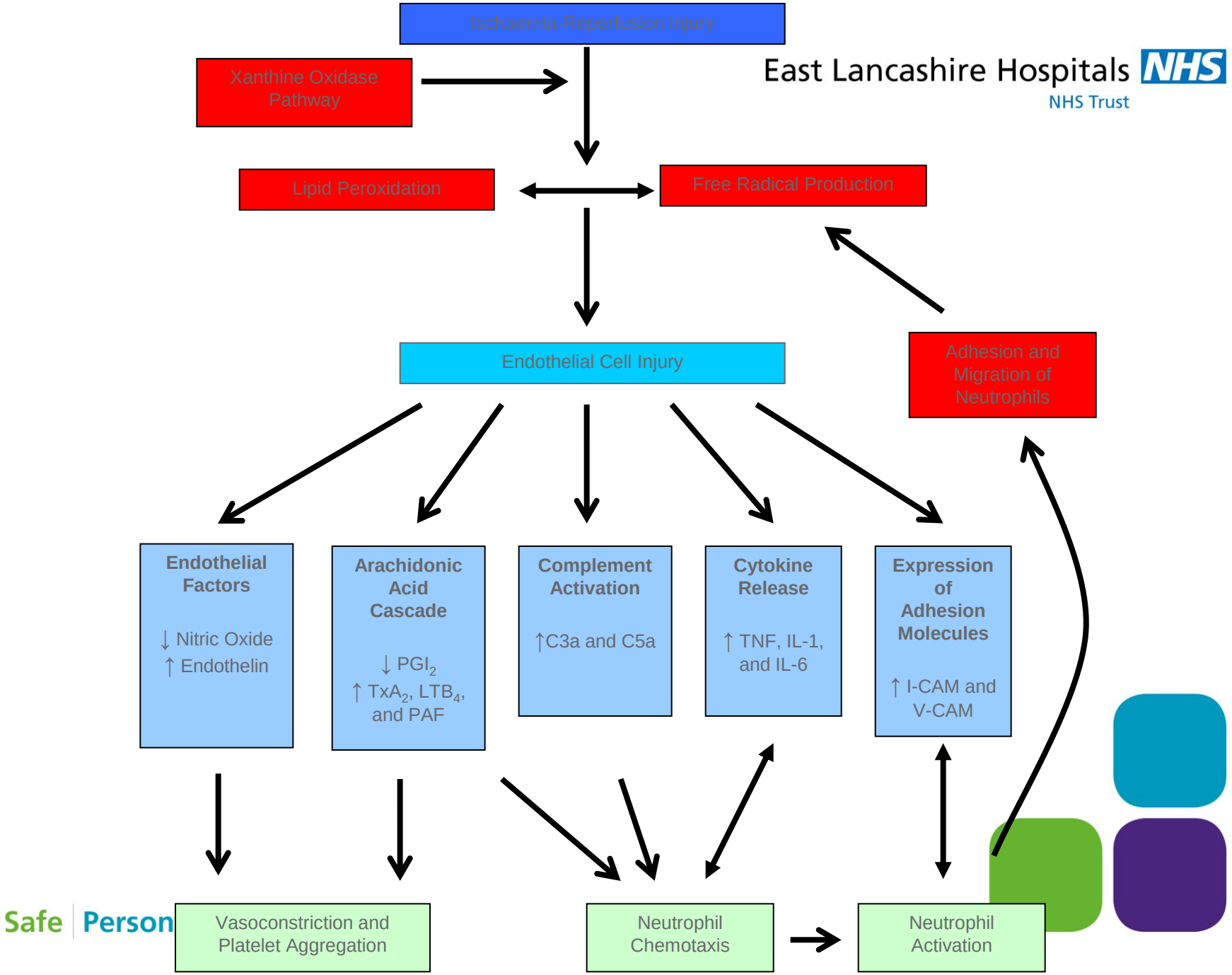
Endothelial Factors

- Thromboxane A_2 (TxA_2);
  - Arachidonic acid metabolite synthesized by the platelets via the cyclo-oxygenase pathway.
    - Vane *N Eng J Med* 1990.
  - Stimulant of platelet aggregation and vasoconstriction.
  - However, during ischaemia-reperfusion injury it acts as a powerful chemoattractant that can further induce neutrophil adhesion to the endothelium.
    - Spagnuolo *J Clin Invest* 1980.
  - An increase in vascular permeability resulting in muscle oedema following ischaemia-reperfusion injury has been attributed to TxA_2.
    - Lelcuk *Ann Surg* 1985.

Endothelial Factors

- Leukotriene B_4 (LTB_4);
  - Another arachidonic acid metabolite which plays an important role in endothelial function.
  - The stimulation of LTB_4 production by free radicals from ischaemia-reperfusion injury results in the activation of adhesion molecules on neutrophils and their subsequent adherence to endothelial cells.
    - Karasawa *Am J Physiol* 1991.


Walking
Ischaemia
Rest
Reperfusion
Free Radical Production
ISCHAEMIA REPERFUSION INJURY
Antioxidant Consumption
Endothelial Cell Damage
Cytokine Release
Complement Activation
Expression of Adhesion Molecules
Release of Endothelial Factors
Activation of Arachidonic Acid
LOCAL EFFECTS
SYSTEMIC EFFECTS
Erythema
Oedema
Pain
Cardiac
Respiratory
Intestinal
Renal



East Lancashire Hospitals NHS
NHS Trust

Safe | Person

Pathogenesis of Arterial Disease

- Pathophysiology:
  - Atherosclerosis.
  - Ischaemia-Reperfusion Injury.
- Key Mediators:
  - Endothelium.
  - Platelets.

The Body's Response

- Atherogenesis represents an exaggerated inflammatory, fibroproliferative response to injury.

- Common denominator is the endothelial cell.

The Body's Response

- Disruption of the endothelium also allows adhesion and transmigration of circulating monocytes, platelets and T-lymphocytes.
- Within the developing lesion, the activated cells release potent growth-regulatory molecules that may act in both a paracrine and autocrine manner.
- Under the influence of cytokines and growth factors, vascular smooth muscle cells begin proliferation and migration across the internal elastic lamina into the intimal layer.
- Stimulated vascular smooth muscle cells then allow the deposition of extracellular matrix, thus converting the initial lesion to a fibrous plaque.

Role of Endothelium

- Acts as a physical barrier to protect the underlying vessel and allows formed blood elements to flow freely, thus preventing thrombosis.

- Key docking point for monocytes, neutrophils and lymphocytes by virtue of cell-specific adhesion molecules.

- Source for cytokine and peptide growth factors that act in both autocrine and paracrine fashion to promote atherogenesis.

Role of Endothelium

- Vascular Relaxation:
  - Nitric Oxide.
  - Prostacyclin.

- Vascular Constriction:
  - Thromboxane.
  - Leukotrienes.
  - Free radicals.
  - Endothelins.
  - Cytokines (tumour necrosis factor, interleukin-6).

Pathogenesis of Arterial Disease

- Pathophysiology:
  - Atherosclerosis.
  - Ischaemia-Reperfusion Injury.
- Key Mediators:
  - Endothelium.
  - Platelets.

Role of Platelets

- Platelet activation in the formation of thrombus has three main phases;

Role of Platelets

- 1) Platelet adhesion:
  - After vascular injury, the subendothelial space is exposed.
  - Platelets then adhere to basement membrane proteins especially collagen.
  - Adhesion depends on binding of endothelial or circulating von Willebrand factor to the platelet membrane glycoprotein 1b receptor.

Role of Platelets

- 2) Platelet aggregation:
  - Energy-dependant process requiring adenosine triphosphate (ATP).
  - Predominant mechanism involves binding of fibrinogen to the platelet glycoprotein IIb-IIIa receptor.

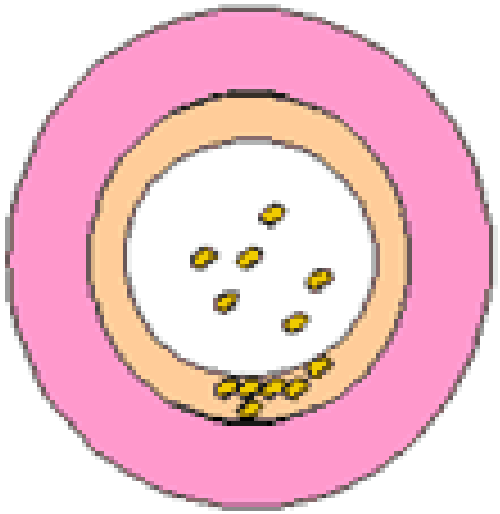
Role of Platelets

- 3) Platelet secretion:
  - Release products include the contents of dense bodies (serotonin, calcium, ATP).
  - Also released are alpha granules (vWF, fibrinogen, growth factors, platelet-4 and coagulation factors).
  - All serve to continue the thrombotic process.

Atherosclerosis

- Pathophysiology:
  - Atherosclerosis.
  - Ischaemia-Reperfusion Injury.
- Key Mediators:
  - Endothelium.
  - Platelets.

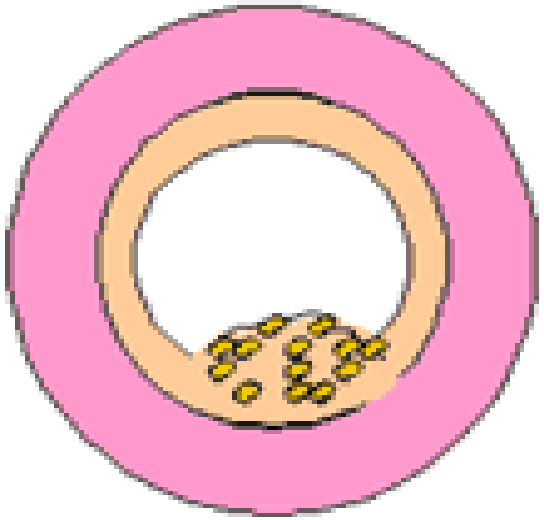
Atherosclerosis



I

Lipid deposits in the intima which can start in infants and children.

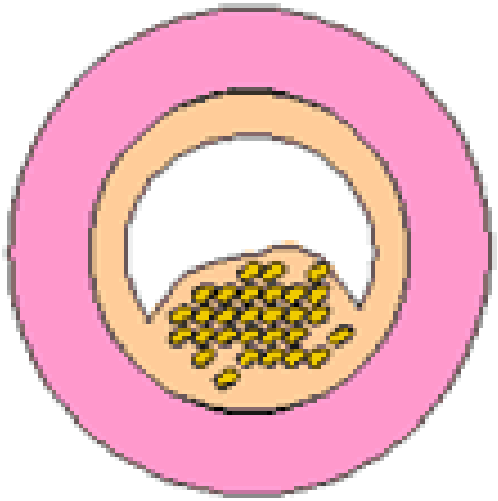
Atherosclerosis



II

Fatty streaks visible as yellow-coloured streaks, patches or spots on the intimal surface.

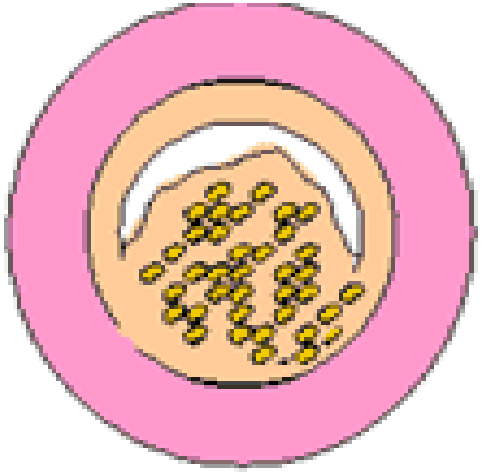
Atherosclerosis



III

Fatty streaks progress to intermediate lesions called Foam Cells. These are characterised by extracellular pools of lipid which are generally clinically occult.

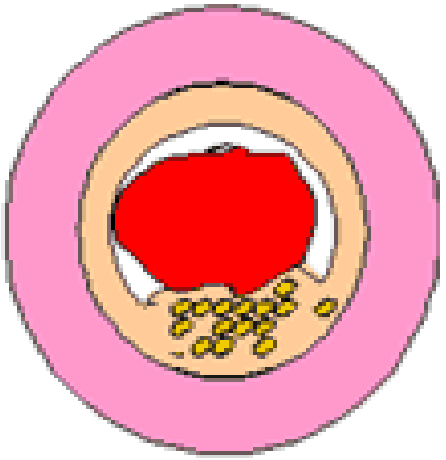
Atherosclerosis



IV

A type IV lesion is termed an atheroma and occurs when these extracellular pools of lipid coalese to create a core of extracellular lipid. The blood vessel architecture has been altered sufficiently to become clinically overt.

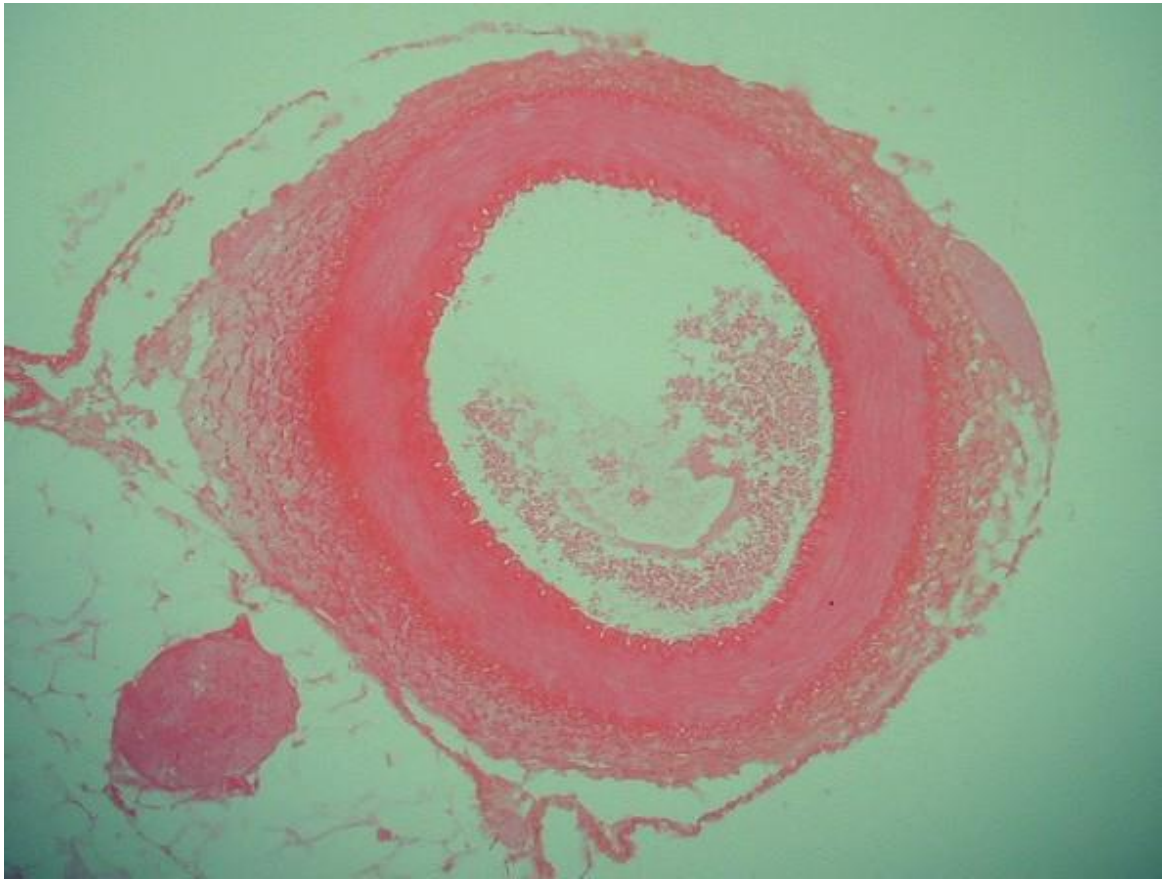
Atherosclerosis



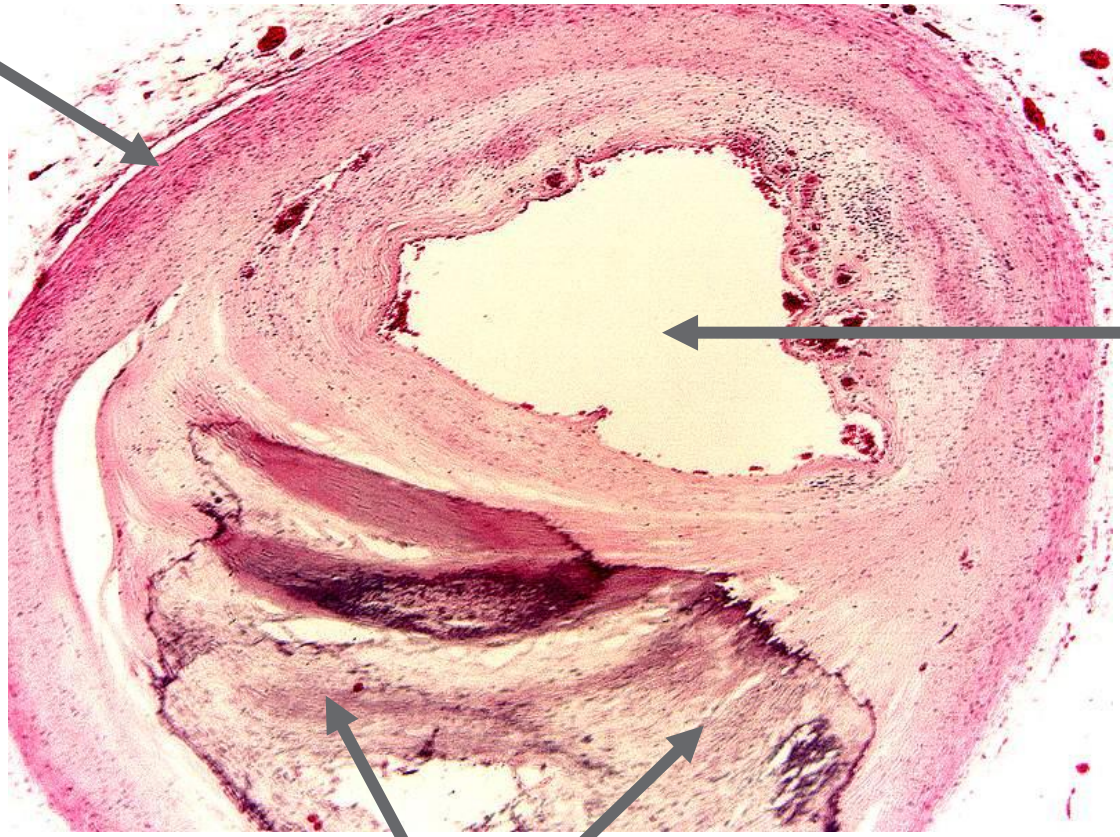
V

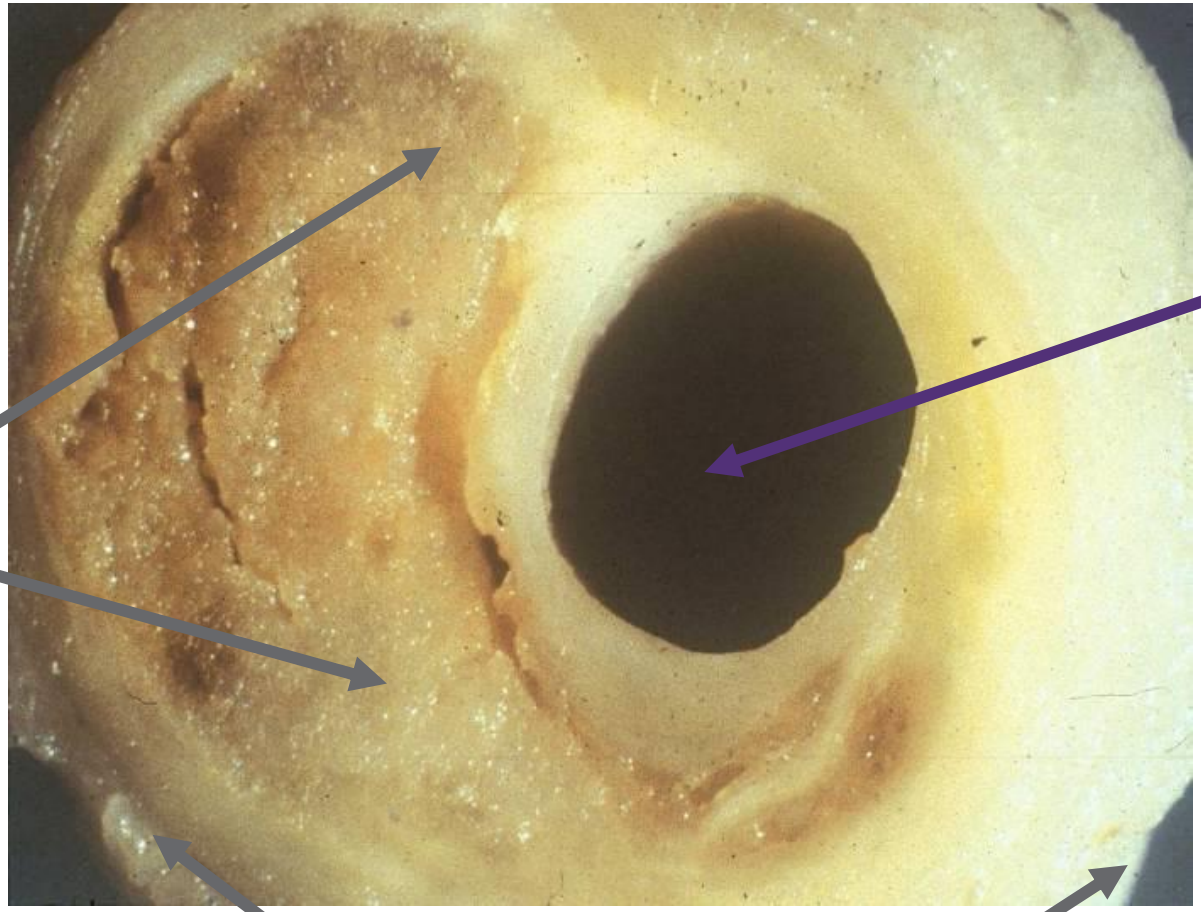
When the atheroma undergoes smooth muscle cell proliferation and collagen deposition it progresses to a fibroatheroma.

The fibroatheroma is then susceptible to thrombogenic surface defects with subsequent haemorrhage or thrombus, thus resulting in vessel occlusion and subsequent clinical sequelae.



Atheroma




Lumen
Atheroma
Vessel Wall

East Lancashire Hospitals NHS
NHS Trust

Clinical Consequences

Safe | Personal | Effective

Atherosclerosis – A Systemic Process

Cerebrovascular disease

- Ischaemic stroke.
- Transient Ischaemic Attack (TIA).

Cardiovascular disease

- Myocardial Infarction (MI).
- Angina (stable/unstable).

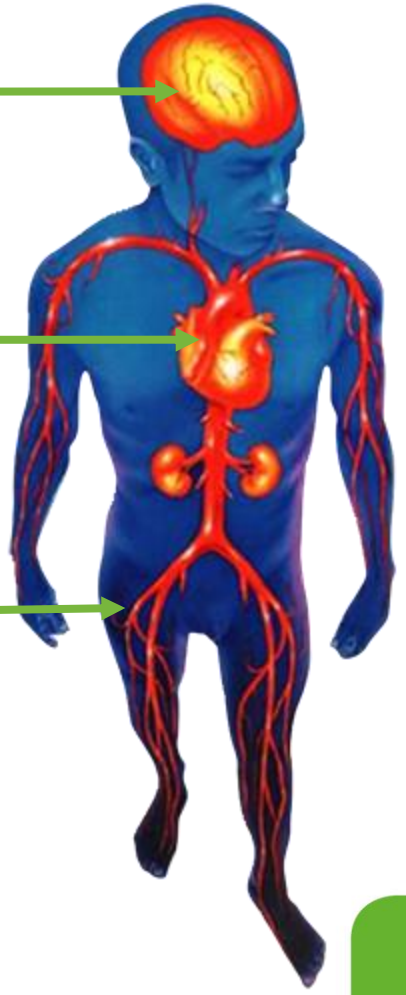
Peripheral arterial disease (PAD)

→ Intermittent claudication

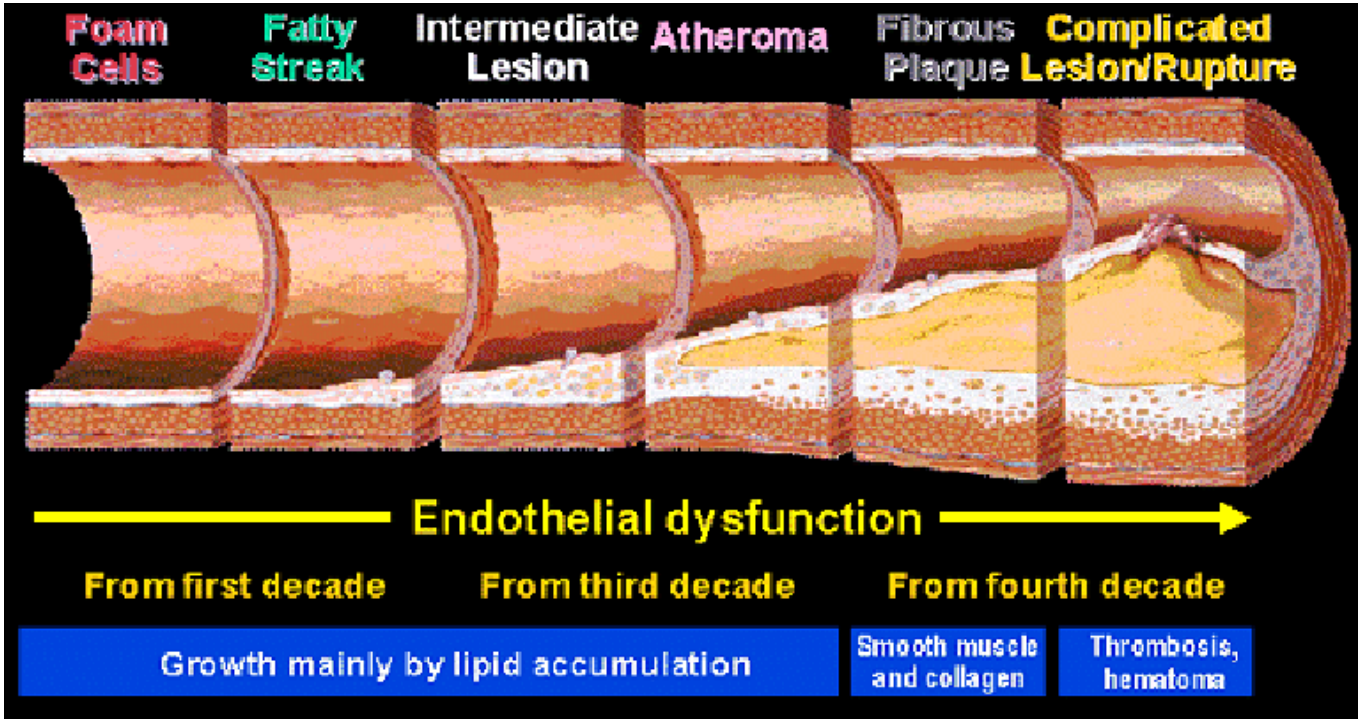
- Pain on walking.

→ Severe limb ischaemia

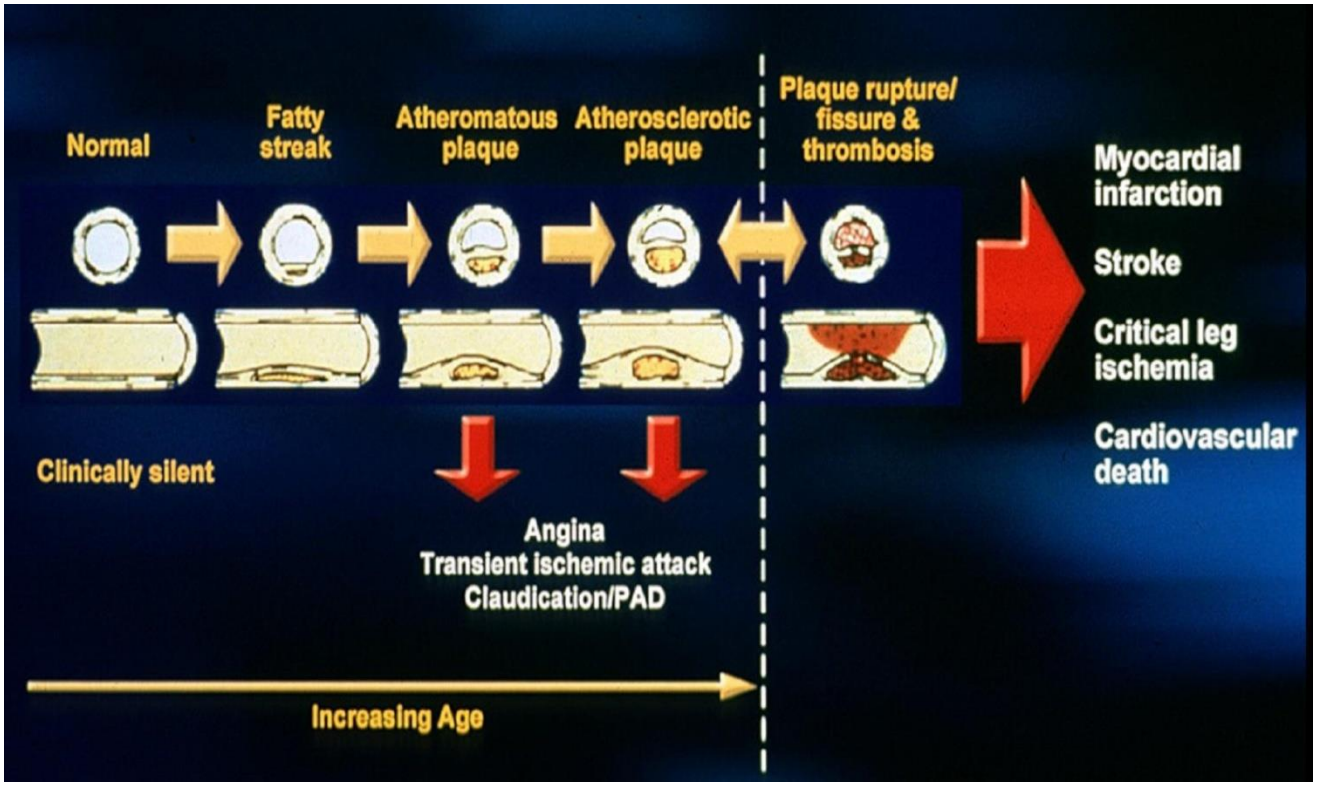
- Rest pain.
- Gangrene, necrosis.



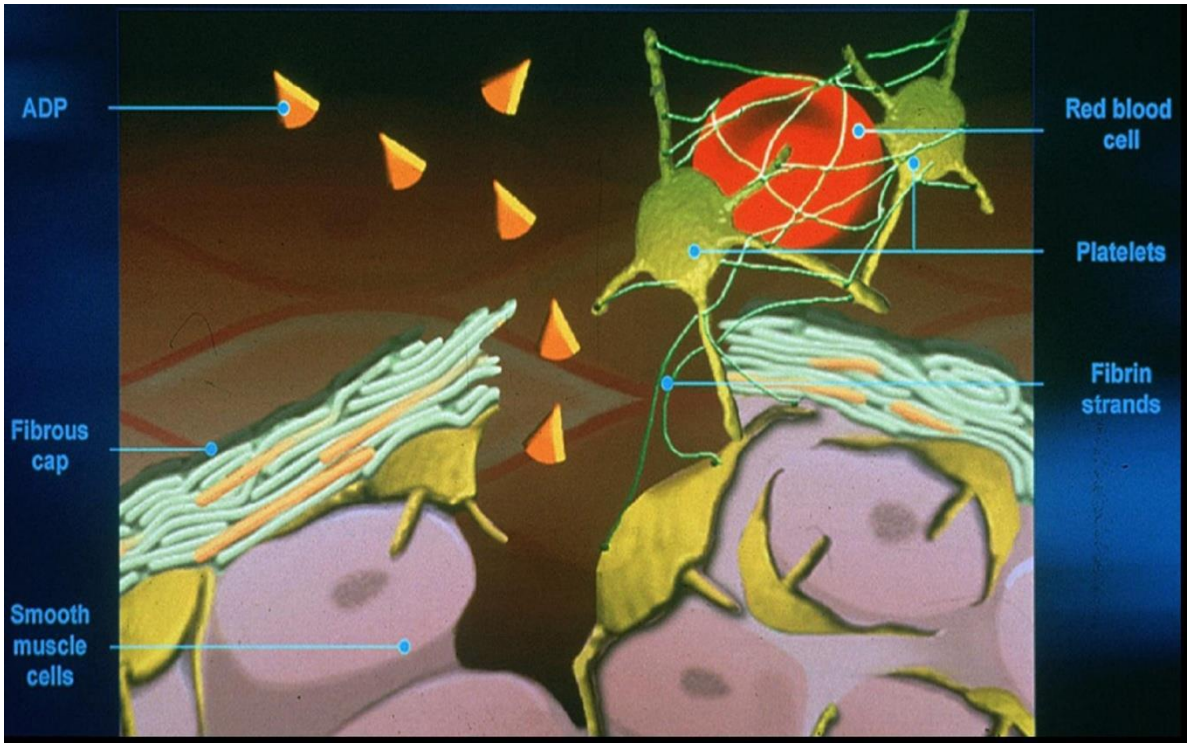
Atherosclerosis Timeline



A Progressive Process



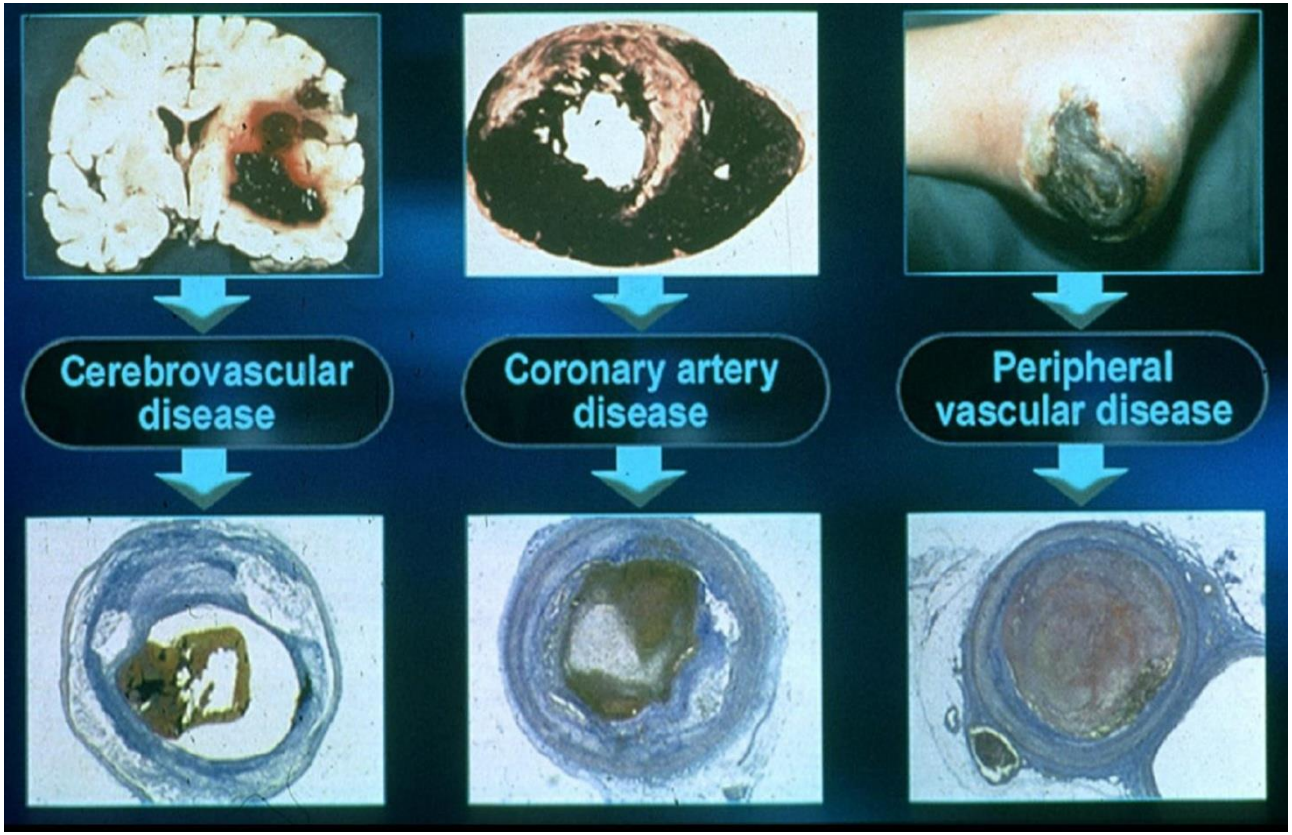
Plaque Rupture and Thrombus Formation



Acute Events

- Superficial Intimal Injury:
  - Lipid pool and fibrous cap remains intact.
  - 25% of acute events.
- Deep Intimal Injury:
  - Fissuring of fibrous cap and exposure of collagen.
  - 75% of events.

End-Organ Outcomes



Peripheral Arterial Disease

- 20% of people over 55 years of age.
  - Hankey GJ, *JAMA* 2006
- 27 million people affected in Europe and USA.
  - Hankey GJ, *JAMA* 2006
- Only 10-30% of patients will have symptoms.
  - McDermott MM, *Cleve J Clin Med* 2006
- Symptoms deteriorate in 25% of patients.
  - Schmieder FA, *Am J Cardiol* 2001
- 2% to 4% will require amputation.
  - Dormandy J, *Semin Vasc Surg* 1999

Diabetes - Epidemiology

- Worldwide - 285 million in 2010 expected to rise to 438 million in 2030. UK - 2.9 million 2011 rising to 4 million by 2025.
  - *Diabetes UK* 2010.
- Annual incidence of foot ulceration 2.2%.
  - Abbott *Diabet Med 2002*.
- Ulcers:
  - 45-60% neuropathic.
  - 10% purely ischaemic.
  - 25-45% mixed.
- Worldwide every 30 seconds a leg is lost to diabetes.
  - International Diabetes Federation 2005

East Lancashire Hospitals NHS
NHS Trust

Diabetes & Peripheral Arterial Disease

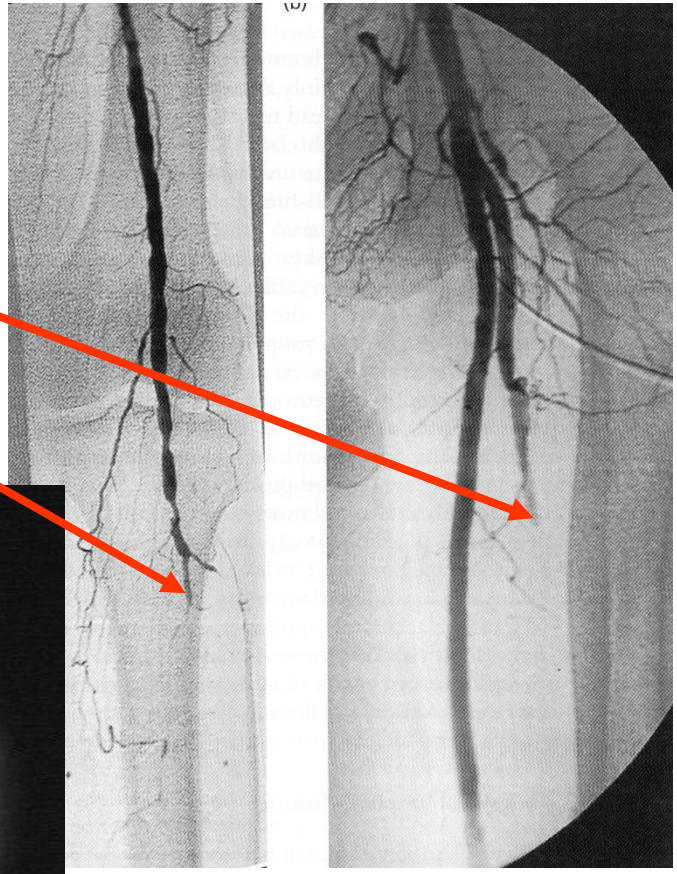
- 15% of diabetics are affected by PAD at 10 years following diagnosis, rising to 45% at 20 years.
  - Kreines *Diabetes Care* 1985.
- 20% of patients with PAD have diabetes.
  - Muribato *Circulation* 1997.
- PAD disease distribution different in diabetes.
  - Strandness *Diabetes* 1961.
- PAD more aggressive in diabetics with an 11-times higher rate of major lower limb amputation and a doubling of the five-year mortality.
  - Elhadd *Pract Diabetes Int* 1999
- Diabetic ulcers heal more slowly and are the main cause of non-traumatic lower limb amputation in developed countries.
  - Caputo *N Engl J Med* 1994

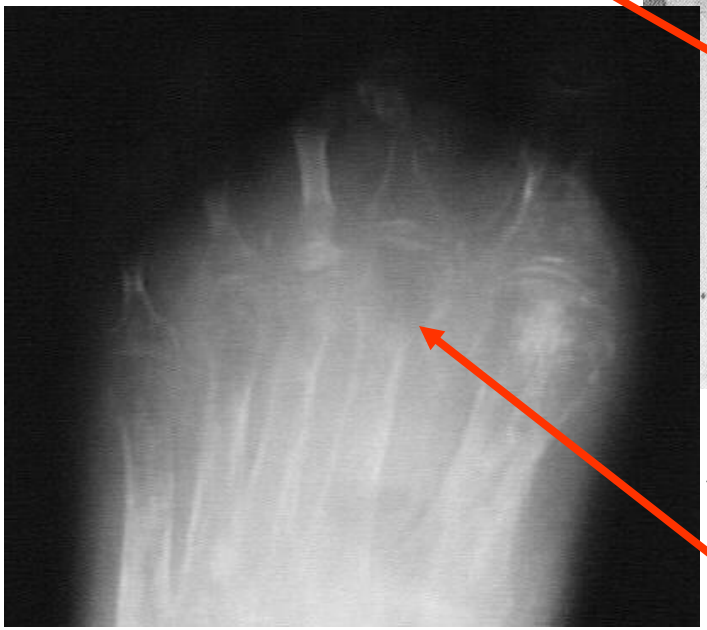
Diabetic Vascularity

East Lancashire Hospitals NHS
NHS Trust

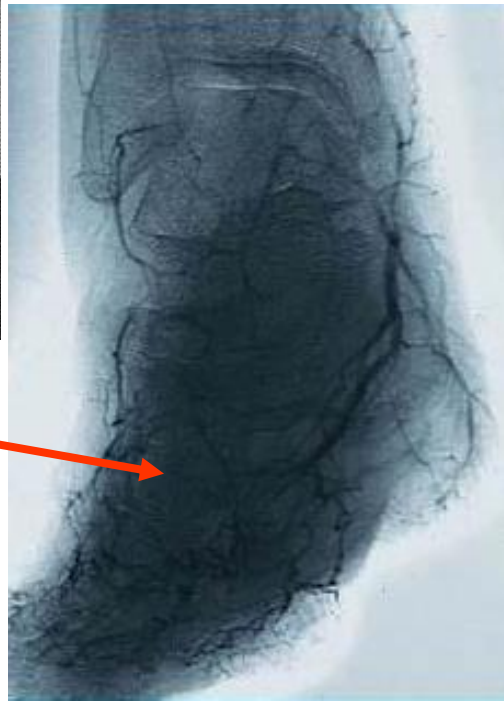
Profunda

Below knee





Small vessel disease



Calcification

Safe | Personal | Effective

Diabetes

- Peripheral Neuropathy;
  - Unfortunately, one of the least well understood of diabetic complications.
  - Heterogeneous disorder that encompasses a wide range of abnormalities affecting the sensory and motor components of both proximal and distal peripheral nerves as well the autonomic nervous systems.
  - True prevalence of DPN is unknown with reports varying from 10% to 90%, depending on the criteria and methods used to define diabetic neuropathies.
    - Ward *Diabetes Care* 1999
    - Boulton *Diabetes/Metabolism Res Rev* 2000

Diabetes

- The underlying mechanisms of DPN remain unclear and, as yet there is no definitive treatment.

- It is not clear whether;
  - hyperglycaemia induced metabolic and redox abnormalities such as the polyol pathway alone are sufficient.
  - or whether an intermediate tissue abnormality such as microangiopathy plays an important and perhaps permissive role.

- Hyperglycaemia is present in all diabetic patients, yet not all diabetic patients develop severe neuropathy.
  - Tesfaye *Diabetologia* 1994

Cellular Effects of Diabetes

- Hyperglycaemia interferes with the activity and function of endothelial cells.
  - *In vitro* data show that high glucose concentrations can activate protein kinase C (PKC) in endothelial cells, specifically PKC.
  - This activation appears to stimulate expression of adhesion molecules on endothelial cells, facilitating the adhesion and uptake of leukocytes into the endothelium.
  - In addition, high glucose concentrations affect the permeability of tight junctions between endothelial cells, which also seems to be mediated by PKC.
  - Thus, PKC activation may be central to the effects of glucose-stimulated vascular changes.

- Evidence for direct stimulation of endothelial cells by glucose may support the hypothesis that postprandial glucose spikes are important in the early development of micro- and macrovascular disease.
  - Haller H *Diabetic Medicine* 2004

East Lancashire Hospitals NHS
NHS Trust

Systemic Vascular Disease

- Stroke.
- Abdominal Aortic Aneurysm.
- Varicose Veins.
- Deep Venous Thrombosis.
- Lymphoedema.

Stroke


FACE.
Has their face fallen on one side? Can they smile?
ARMS.
Can they raise both arms and keep them there?
SPEECH.
Is their speech slurred?
TIME.
Time to call 999 if you see any single one of these signs.

Definition

- Transient Ischaemic Attack (TIA):
  - Acute loss of focal cerebral function with symptoms lasting less than 24 hours.

- Stroke:
  - Acute loss of focal cerebral function with symptoms lasting more than 24 hours.

Stroke Epidemiology

- Third most common cause of death responsible for 12% of UK deaths.
- Annual UK incidence of first-ever stroke is 2.4 per 1000 and TIA is 0.5 per 1000.
- 125,000 people suffer their first stroke each year while 36,000 suffer a TIA each year.
- Half of strokes affect patients greater than 75 years of age.
- Accounts for 10% of in-patient beds and 5% of health care expenditure.

Clinical Presentation

- Anterior cerebral artery:
  - Leg>arm weakness, grasp.
  - Cognitive: muteness, perseveration, abulia, disinhibition.

- Middle cerebral artery:
  - Arm>leg weakness.
  - Left – aphasia.
  - Right – cognitive dysfunction and neglect, topographical difficulty, apraxia, constructional impairment.

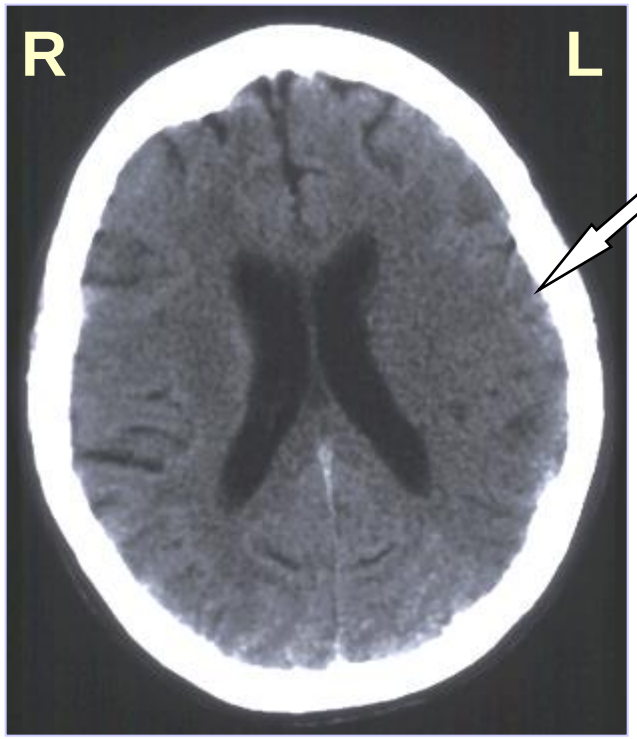
- Posterior cerebral artery:
  - Hemianopia.
  - Cognitive: memory loss/confusion.

Investigation

- CT
  - Non- contrast CT Head remains the gold standard as it is superior for showing haemorrhage.
  - CT with contrast may help identify aneurysms, AVMs, or tumors but is not required to determine whether or not the patient is a tPa lysis candidate.
- MRI
  - Superior for showing underlying structural lesions.
  - Contraindications.

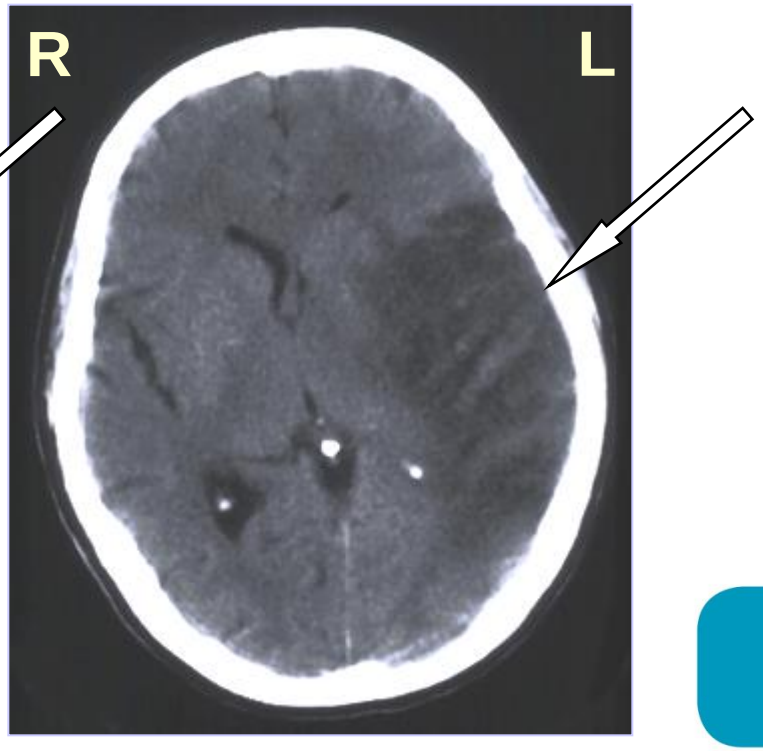
Investigation

Acute Infarction (4 hours)



Subtle blurring of gray-white junction & sulcal effacement

Subacute Infarction (4 days)



Obvious dark changes & "mass effect" (e.g. ventricle compression)

Why Treat – Nice Guidelines

- Early treatment saves brain …..
- Evaluation by stroke physician – thrombolysis or prompt referral to vascular surgeon for consideration of carotid endarterectomy within 14 days.
- Best Medical Therapy;
  - Risk factor optimisation.
  - Antiplatelets - Aspirin 300mg for 14 days followed by Clopidogrel 75mg for life.
  - Lipid lowering therapy - statins.

PHASE 1 – Immediate patient assessment indicates that this patient has the symptoms suggestive of a stroke & where the FAST test is positive for suspected stroke.

Times of **Symptom onset**	date ____/____/____	time ____:____hrs	Time difference ____:____ hrs
and **Arrival**	date ____/____/____	time ____:____hrs	

CONTRA INDICATIONS *Circle Yes, No or Not known as appropriate*

• History suggestive of subarachnoid haemorrhage	Yes	No	Not known
• Seizure at stroke onset	Yes	No	Not known
• BP > 185 mmHg systolic (or diastolic > 110 mmHg)	Yes	No	Not known
• BM < 2.8 or > 22 mmol/l	Yes	No	Not known
• Platelet count < 100,000	Yes	No	Not known
• If on Warfarin, INR >1.3	Yes	No	Not known
[contact Haematology bleep for urgent processing: **SJH** – ext 53353 / page 3729; **RIE** – bleep 6550; **WGH** – in hours ext 31482, out of hours page 8477**]**			
• Bacterial Endocarditis / Pericarditis	Yes	No	Not known
• Treated with LMW Heparin within last 48 hours & APTT is still raised	Yes	No	Not known
• NIH Stroke Scale <5 [*very minor neurological deficit*] or > 25	Yes	No	Not known
• Neurological symptoms very rapidly improving	Yes	No	Not known
or History of:			
⇒ Previous stroke **plus** Diabetes	Yes	No	Not known
⇒ Another stroke or head injury in last 3 months	Yes	No	Not known
⇒ GI, urinary or menstrual bleeding in last 21 days	Yes	No	Not known
⇒ Surgery or significant trauma in last 14 days	Yes	No	Not known
⇒ Arterial puncture at non-compressible site in last 10 days	Yes	No	Not known
⇒ Severe liver disease (hepatic failure, cirrhosis, varices etc)	Yes	No	Not known
⇒ Possibility of pregnancy	Yes	No	Not known

If there are any circles in the 'Yes' column, please discuss urgently with Stroke Consultant.

The time since onset was <3hr, and a possible contraindication was present, so discussed (telemedicine or face-to-face*) **with Stroke Consultant,** Dr. …… , who agreed the patient was eligible for Thrombolysis.

This ICP was initiated at …… : ….. Signed …… [* please delete as appropriate]

CONDITIONS *Circle Y or N as appropriate*

1. Intracerebral haemorrhage (ICA) or structural lesion must be excluded:
   Any evidence of structural lesion or ICH on CT scan? Y N initial
2. Patient must be in agreed venue for thrombolysis delivery Y N initial
3. Consent must be obtained (or assent from next of kin if unable to communicate) Y N initial
   [discussion of risk and benefit must have taken place, and be documented.]

CONCLUSION of CONTRAINDICATIONS &CONDITIONS: Is patient to receive Thrombolysis? Y N

Signed	print	designation
	date	time

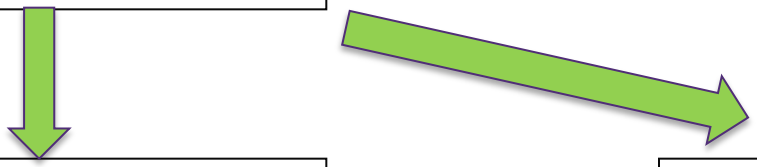
How does this affect the Vascular Surgeon?

Stroke

East Lancashire Hospitals NHS
NHS Trust

Safe | Personal | Effective

Stroke

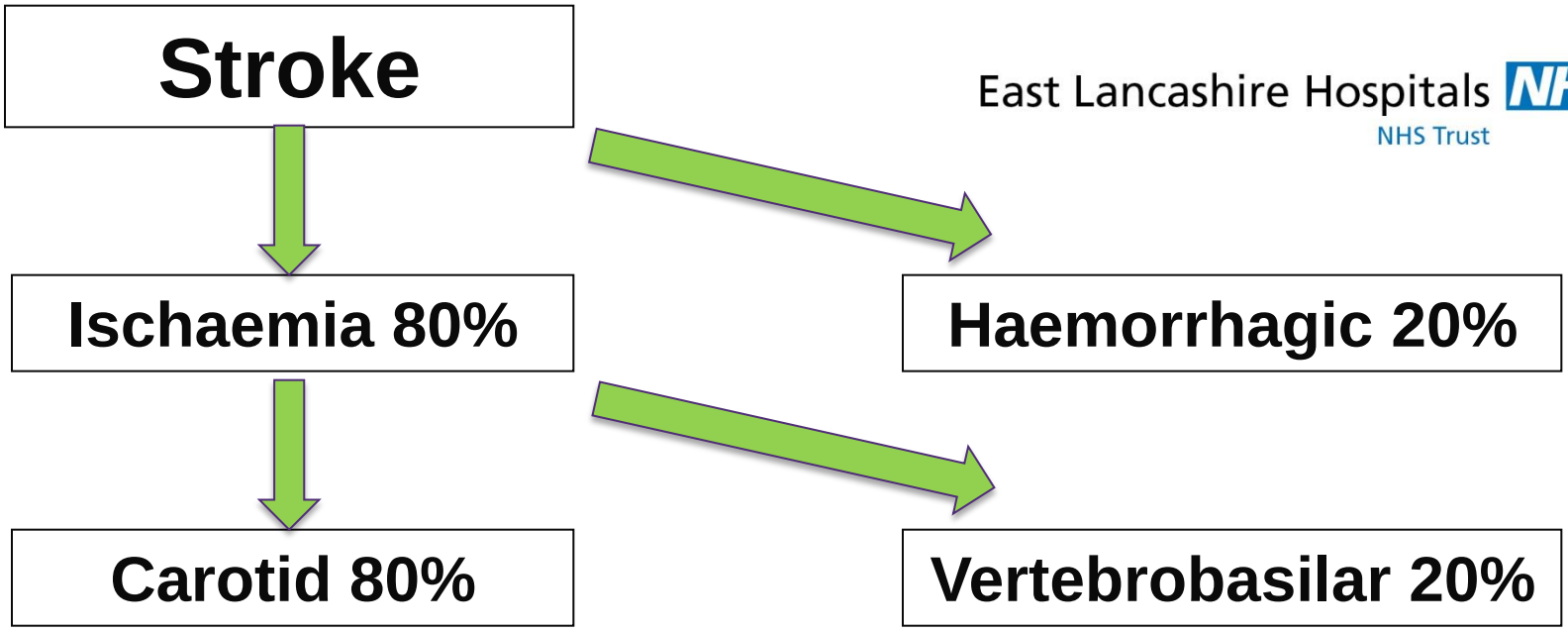


Ischaemia 80%

Haemorrhagic 20%

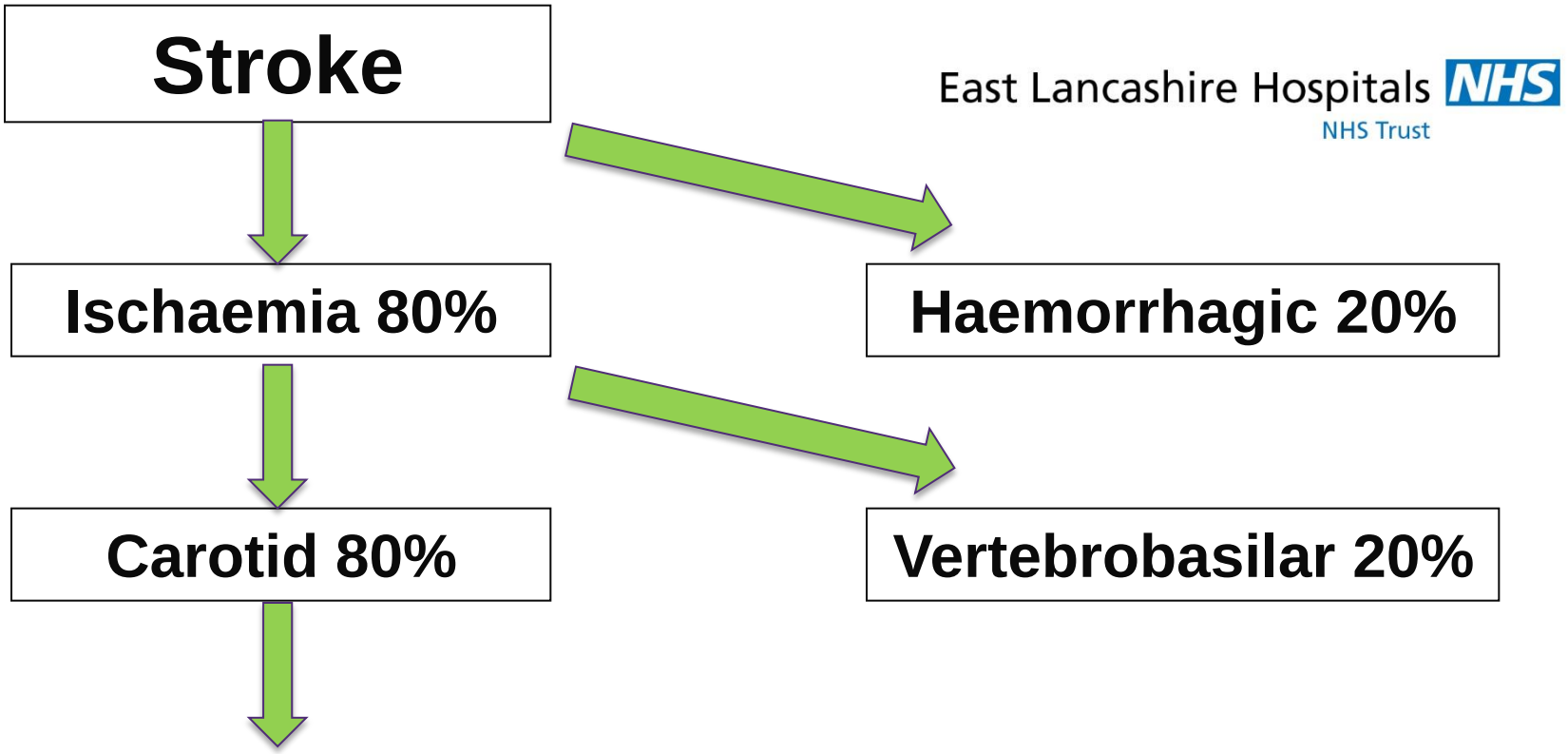
East Lancashire Hospitals NHS
NHS Trust

Safe | Personal | Effective


Stroke
Ischaemia 80%
Haemorrhagic 20%
Carotid 80%
Vertebrobasilar 20%

Stroke

- **Ischaemia 80%**
  - **Carotid 80%**
    - **Thromboembolism of ICA / middle cerebral artery 50%**
    - **Small vessel occlusion of end-arteries 25%**
    - **Cardiogenic embolism 15%**
    - **Haematological disorders 5%**
    - **Miscellaneous – tumours, arteritis 5%**
  - **Vertebrobasilar 20%**
- **Haemorrhagic 20%**



East Lancashire Hospitals NHS
NHS Trust

Thromboembolism of ICA / middle cerebral artery 50%

Small vessel occlusion of end-arteries 25%

Cardiogenic embolism 15%

Haematological disorders 5%

Miscellaneous – tumours, arteritis 5%

Safe | Personal | Effective

East Lancashire Hospitals NHS
NHS Trust

Carotid Referral to Vascular Surgery

- Symptomatology.

- Surgical Consideration.

Safe | Personal | Effective

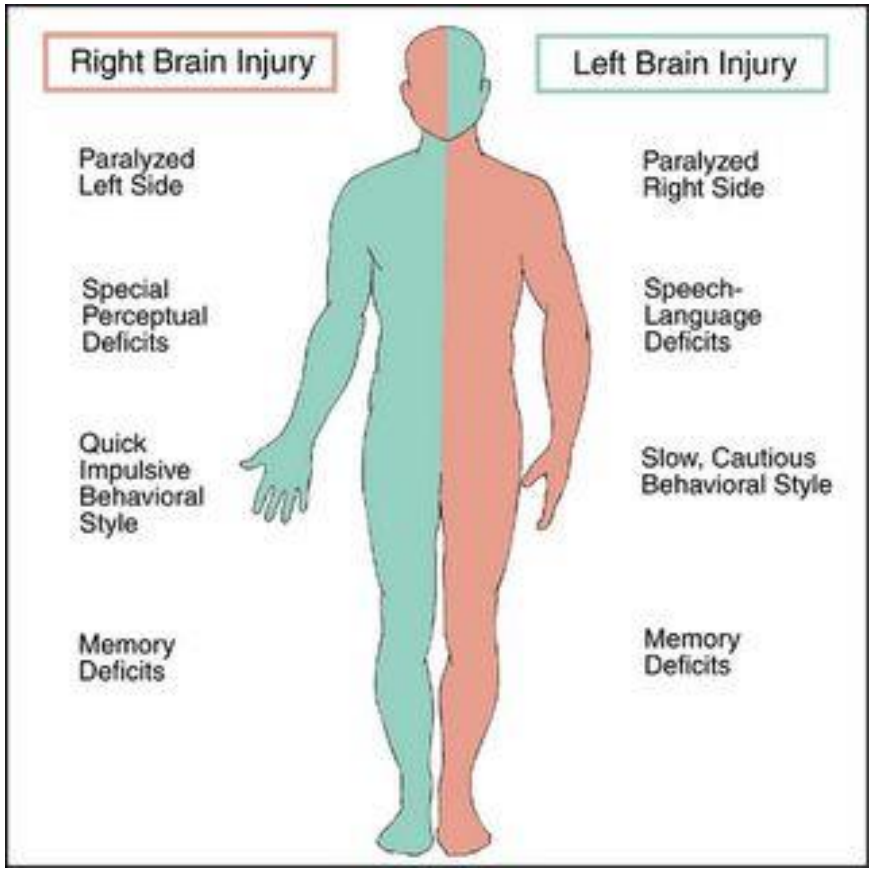
East Lancashire Hospitals NHS
NHS Trust

Carotid Referral to Vascular Surgery

- Symptomatology.

- Surgical Consideration.

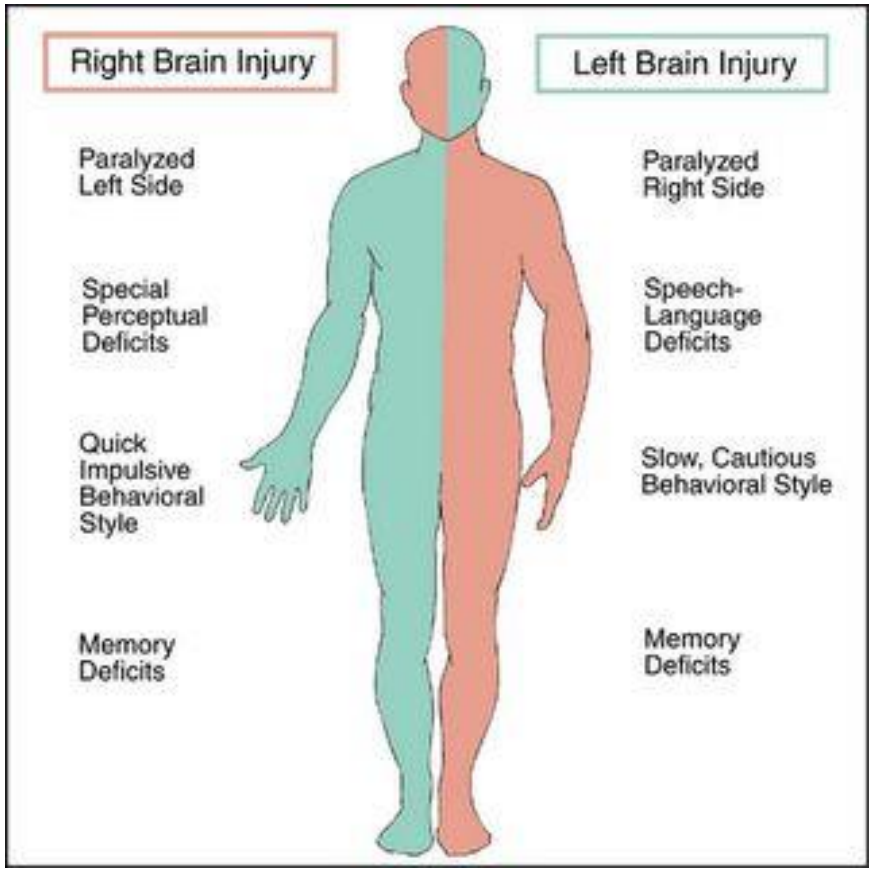
Symptomatology



Symptomatology

Left facial weakness

Right amaurosis fugax



Right facial weakness

Left amaurosis fugax

East Lancashire Hospitals NHS
NHS Trust

Carotid Referral to Vascular Surgery

- Symptomatology.

- Surgical Consideration.

Safe | Personal | Effective

Carotid Duplex

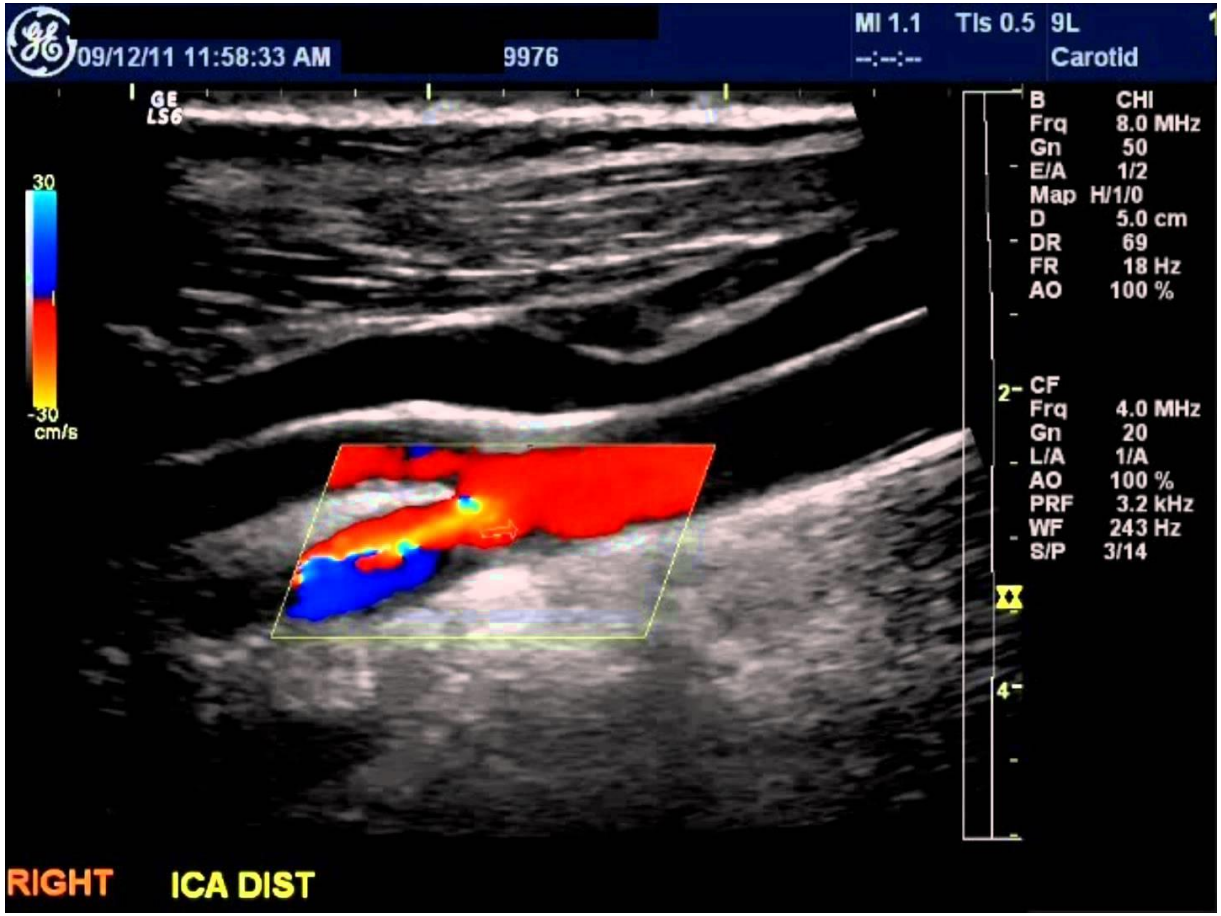


Table 10.6 • Carotid Endarterectomy Trialists Collaboration: 5-year risk of any stroke (including 30-day stroke/death) from the combined VA, ECST and NASCET trials

Trial	Stenosis	*n*	30-day CEA risk	5-year risk		ARR	RRR	NNT	Strokes prevented per 1000 CEAs
				Surgery	Medical				
CETC	<30%	1746	No data	18.36%	15.71%	– 2.6%	N/b	N/b	None at 5 years
CETC	30–49%	1429	6.7%	22.80%	25.45%	+ 2.6%	10%	38	26 at 5 years
CETC	50–69%	1549	8.4%	20.00%	27.77%	+ 7.8%	28%	13	78 at 5 years
CETC	70–99%	1095	6.2%	17.13%	32.71%	+ 15.6%	48%	6	156 at 5 years
CETC	String	262	5.4%	22.40%	22.30%	– 0.1%	N/b	N/b	None at 5 years

ARR, absolute risk reduction; N/b, no benefit conferred by CEA; NNT, number needed to treat; RRR, relative risk reduction; strokes prevented per 1000 CEAs, number of strokes prevented at 5 years by performing 1000 CEAs.
Data derived from the CETC[36–38] with all pre-randomisation angiograms remeasured using NASCET method.

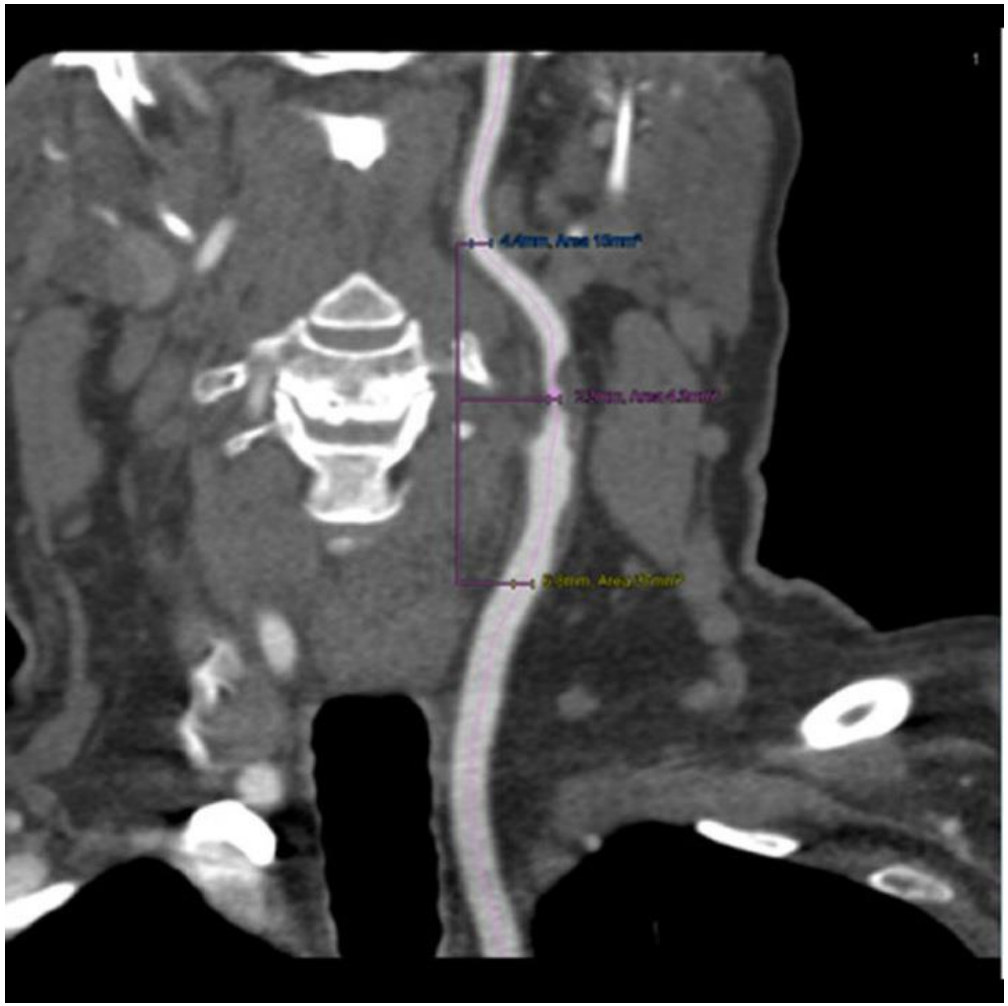
Table 10.6 • Carotid Endarterectomy Trialists Collaboration: 5-year risk of any stroke (including 30-day stroke/death) from the combined VA, ECST and NASCET trials

Trial	Stenosis	*n*	30-day CEA risk	5-year risk		ARR	RRR	NNT	Strokes prevented per 1000 CEAs
				Surgery	Medical				
CETC	<30%	1746	No data	18.36%	15.71%	– 2.6%	N/b	N/b	None at 5 years
CETC	30–49%	1429	6.7%	22.80%	25.45%	+ 2.6%	10%	38	26 at 5 years
CETC	50–69%	1549	8.4%	20.00%	27.77%	+ 7.8%	28%	13	78 at 5 years
CETC	70–99%	1095	6.2%	17.13%	32.71%	+ 15.6%	48%	6	156 at 5 years
CETC	String	262	5.4%	22.40%	22.30%	– 0.1%	N/b	N/b	None at 5 years

ARR, absolute risk reduction; N/b, no benefit conferred by CEA; NNT, number needed to treat; RRR, relative risk reduction; strokes prevented per 1000 CEAs, number of strokes prevented at 5 years by performing 1000 CEAs.
Data derived from the CETC[36–38] with all pre-randomisation angiograms remeasured using NASCET method.

East Lancashire Hospitals NHS
NHS Trust

CT Angiogram



Safe | Personal | Effective

Consent

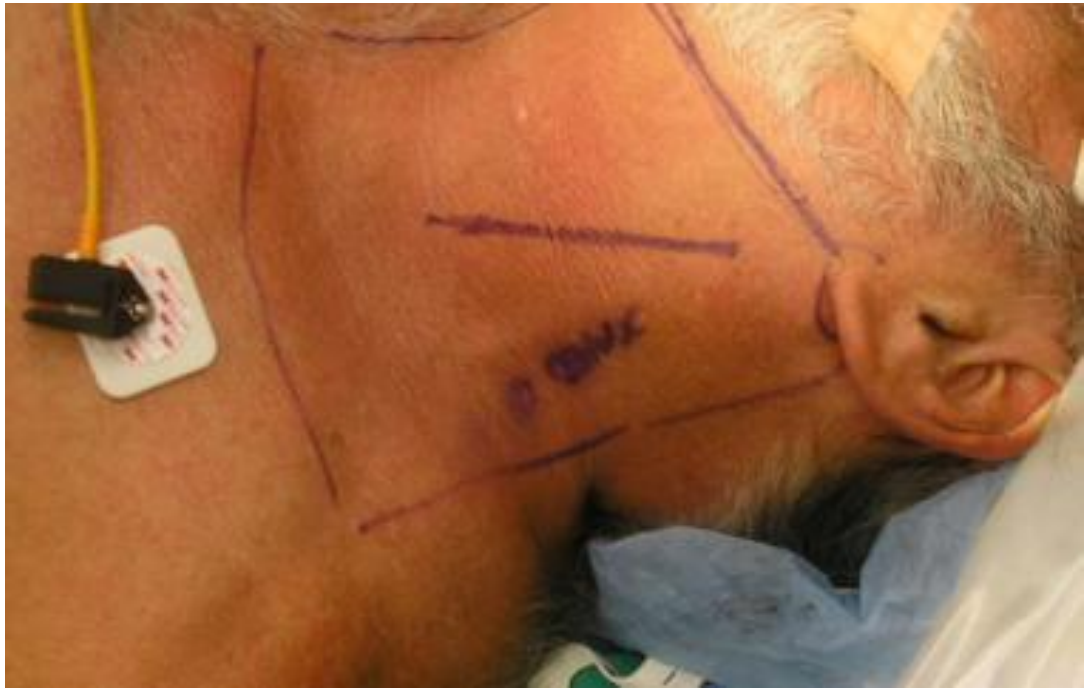
- General Local Complications;
  - Pain, Bruising, Bleeding, Wound infection.
- Systemic Complications;
  - Cardiovascular, Respiratory, Thromboembolic.
- Procedural Specific Complications;
  - Stroke.
  - Nerve injury.
  - Scar.
  - Numbness.
  - Patch infection.

East Lancashire Hospitals NHS
NHS Trust

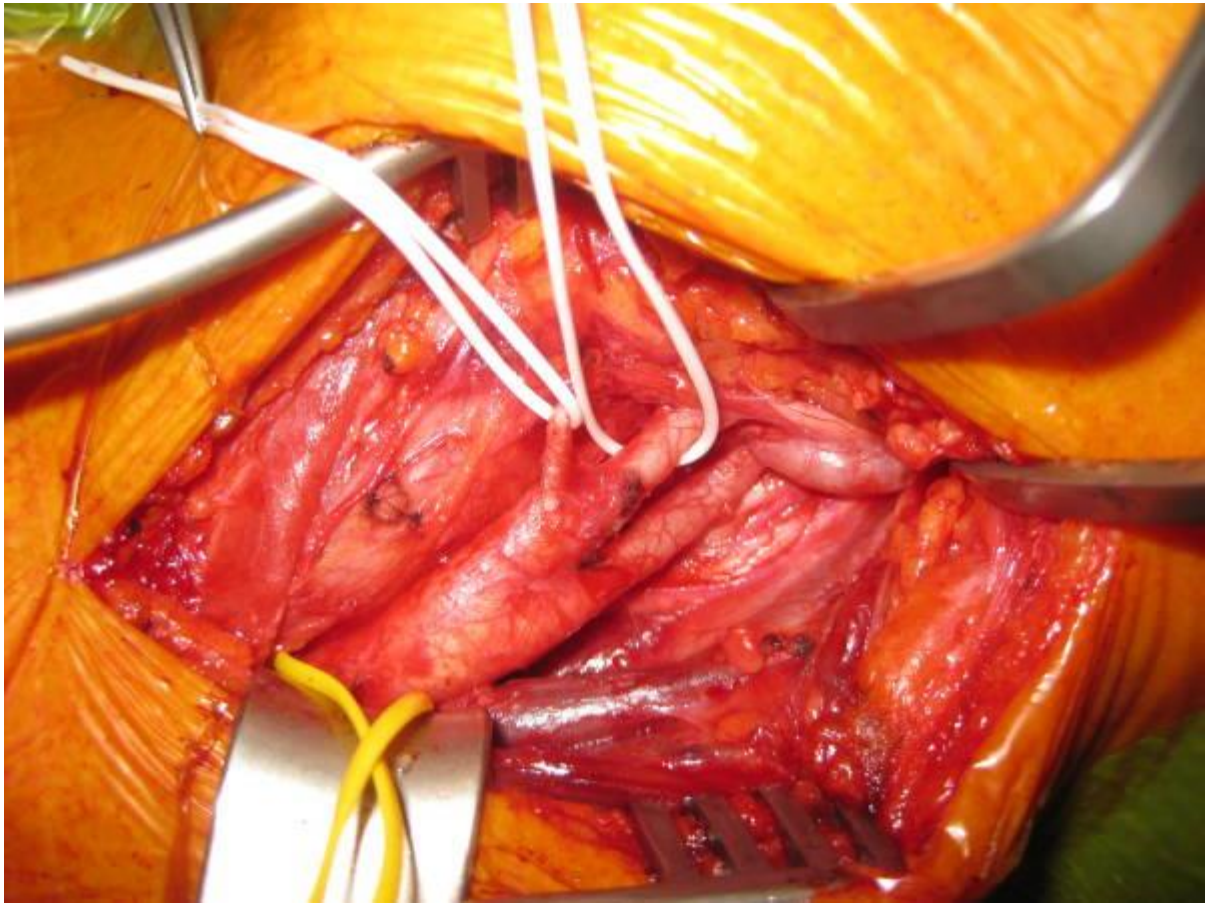
Carotid Endarterectomy

Safe | Personal | Effective

Patient Positioning

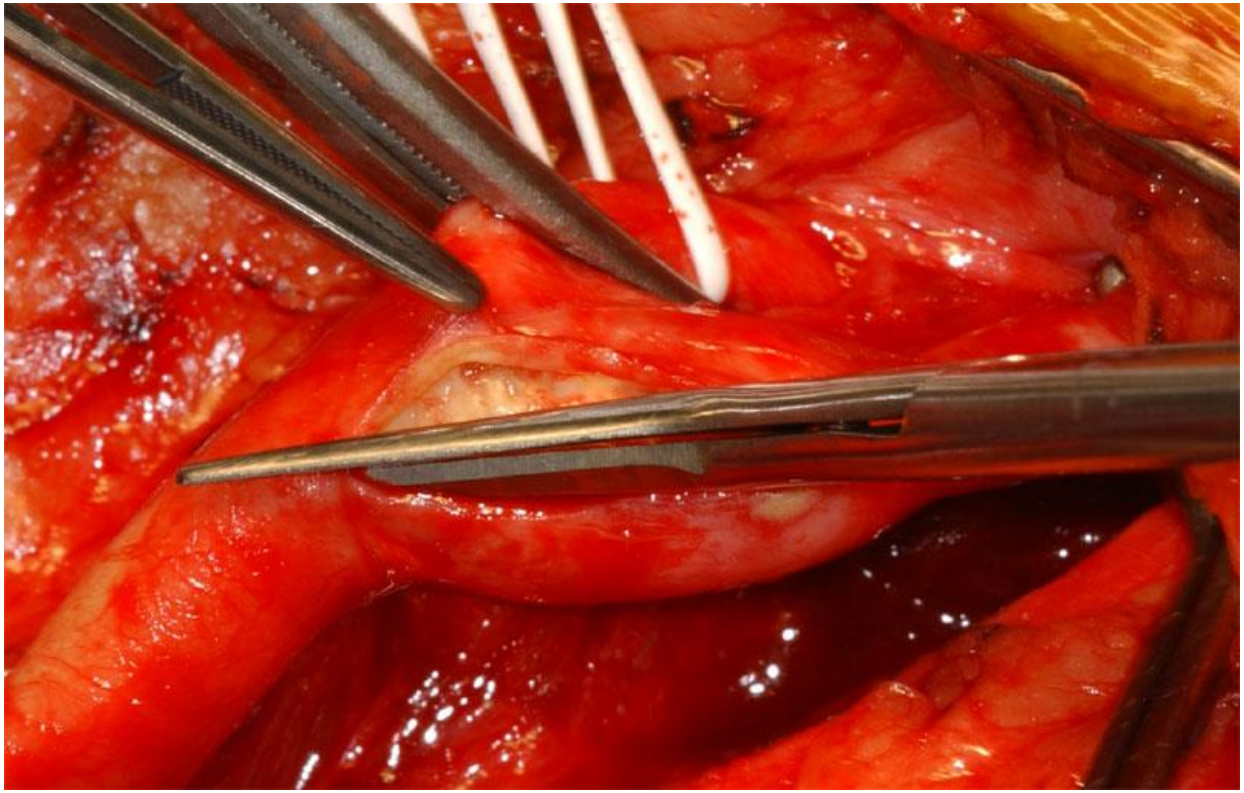


Control of Carotid Vessels

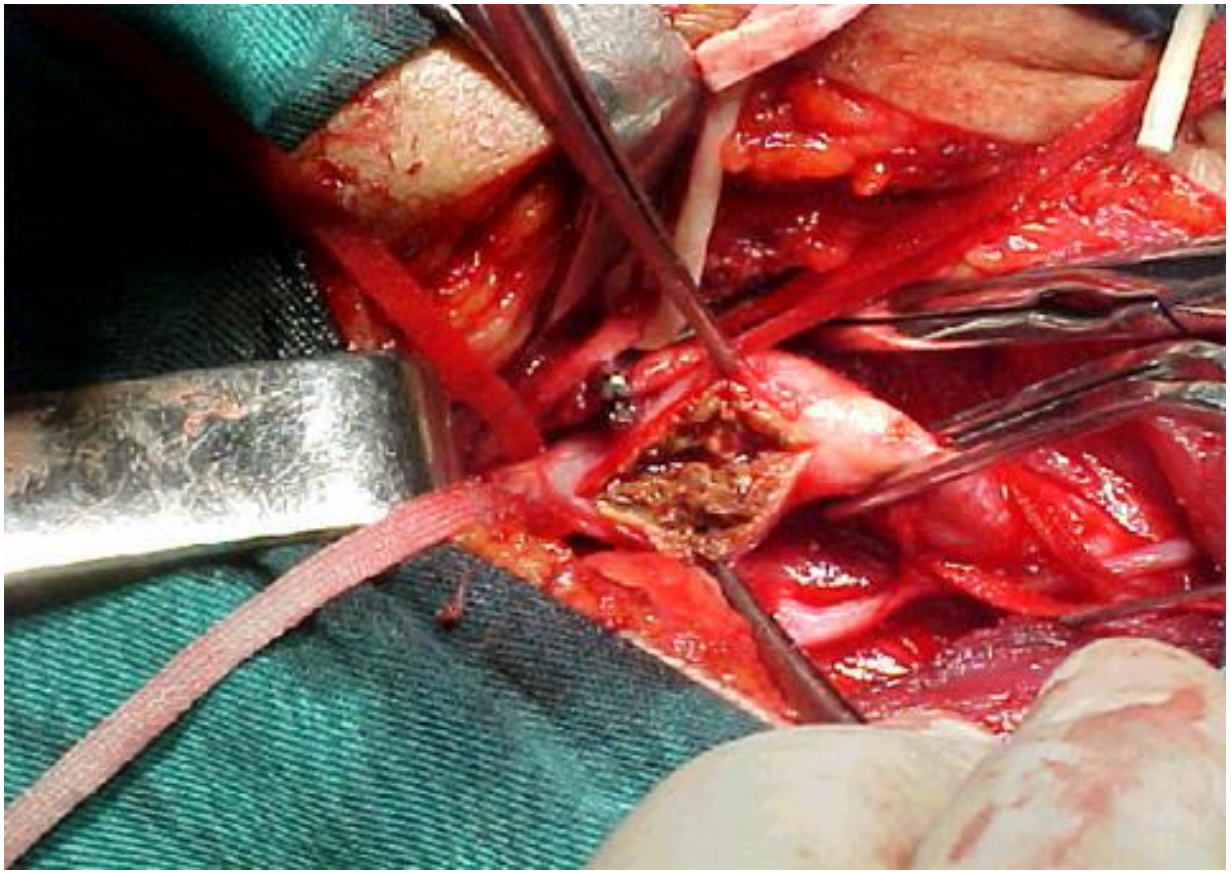


Vessel Clamping

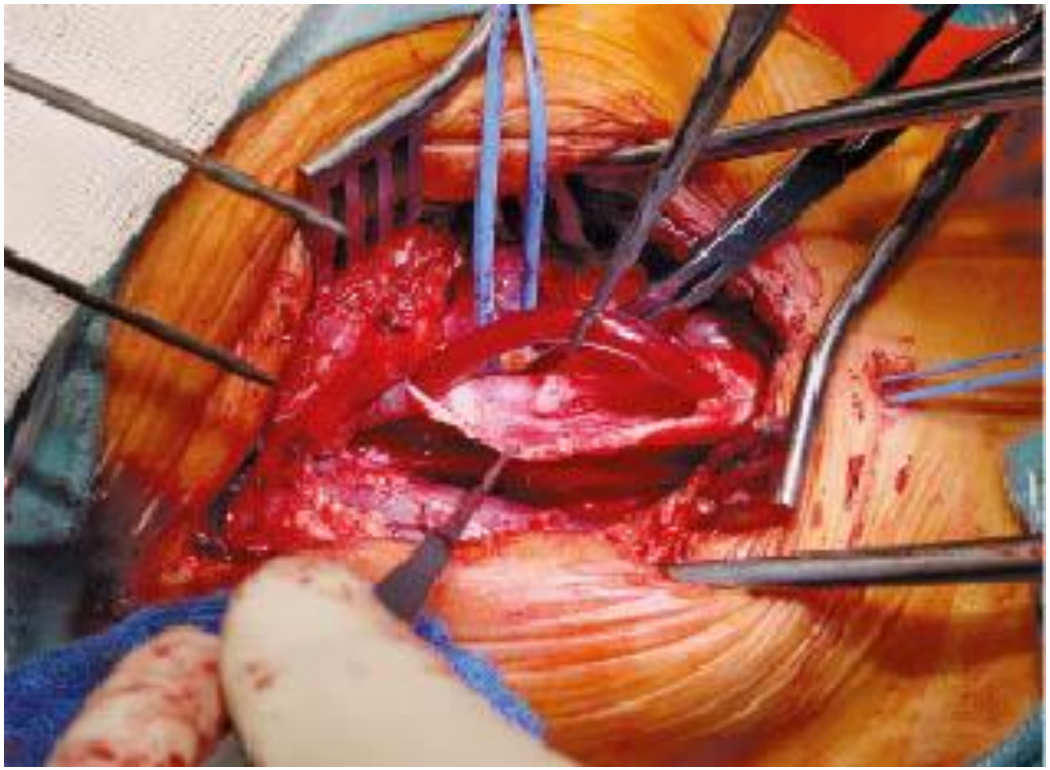
Arteriotomy



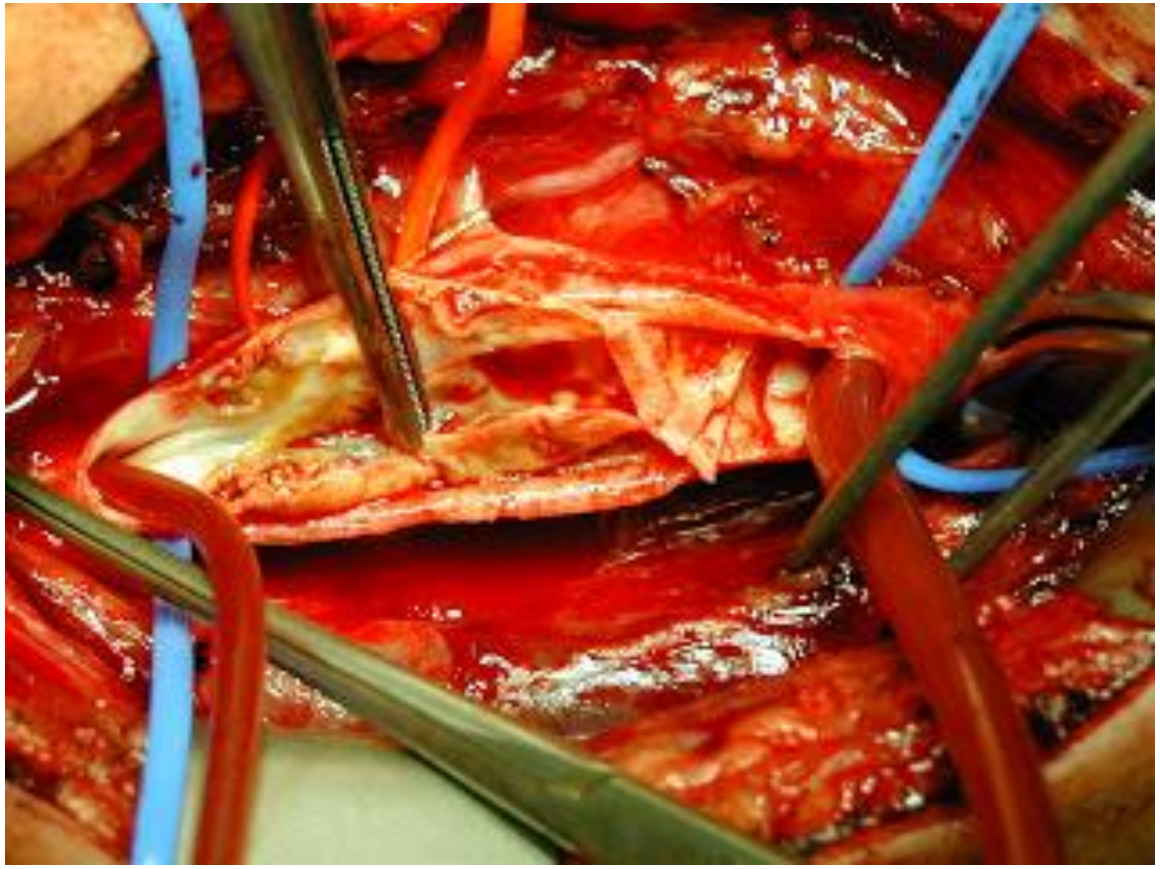
Arteriotomy



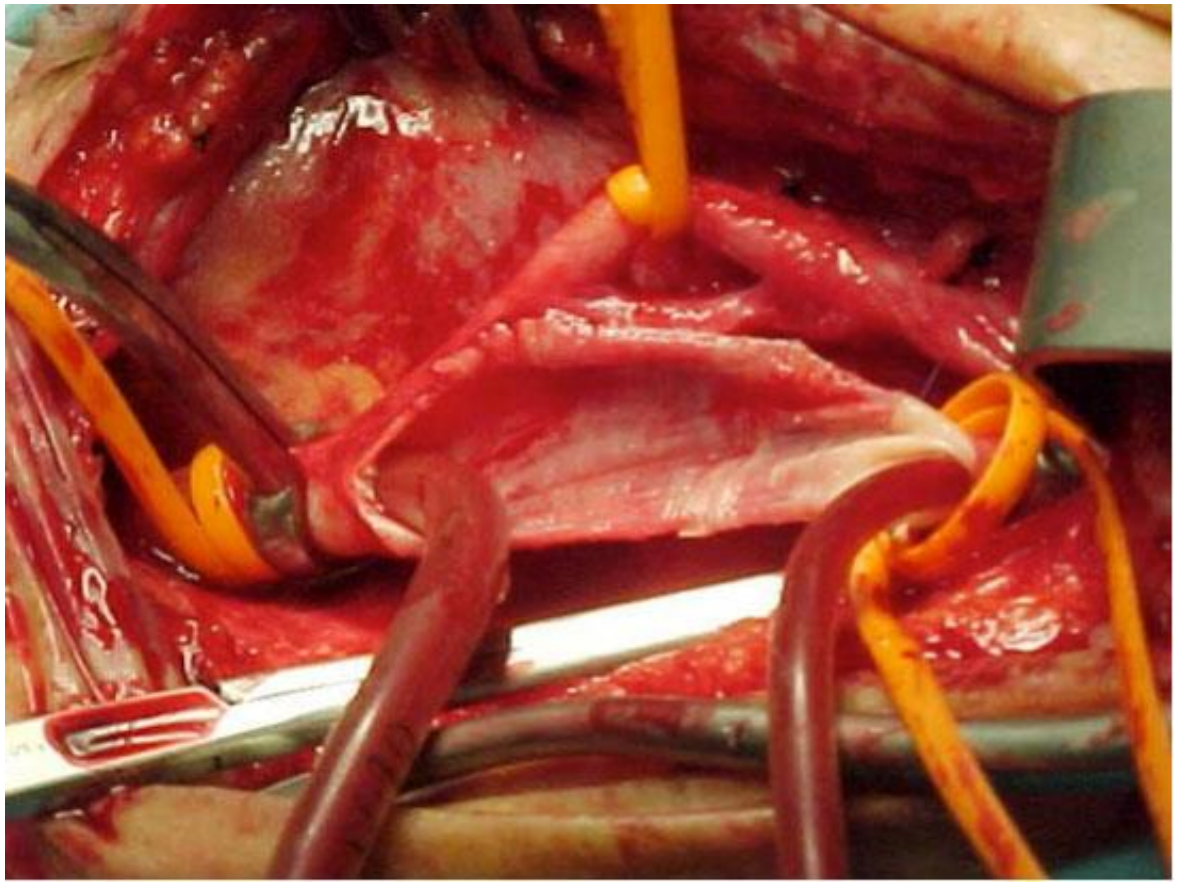
Shunt Insertion



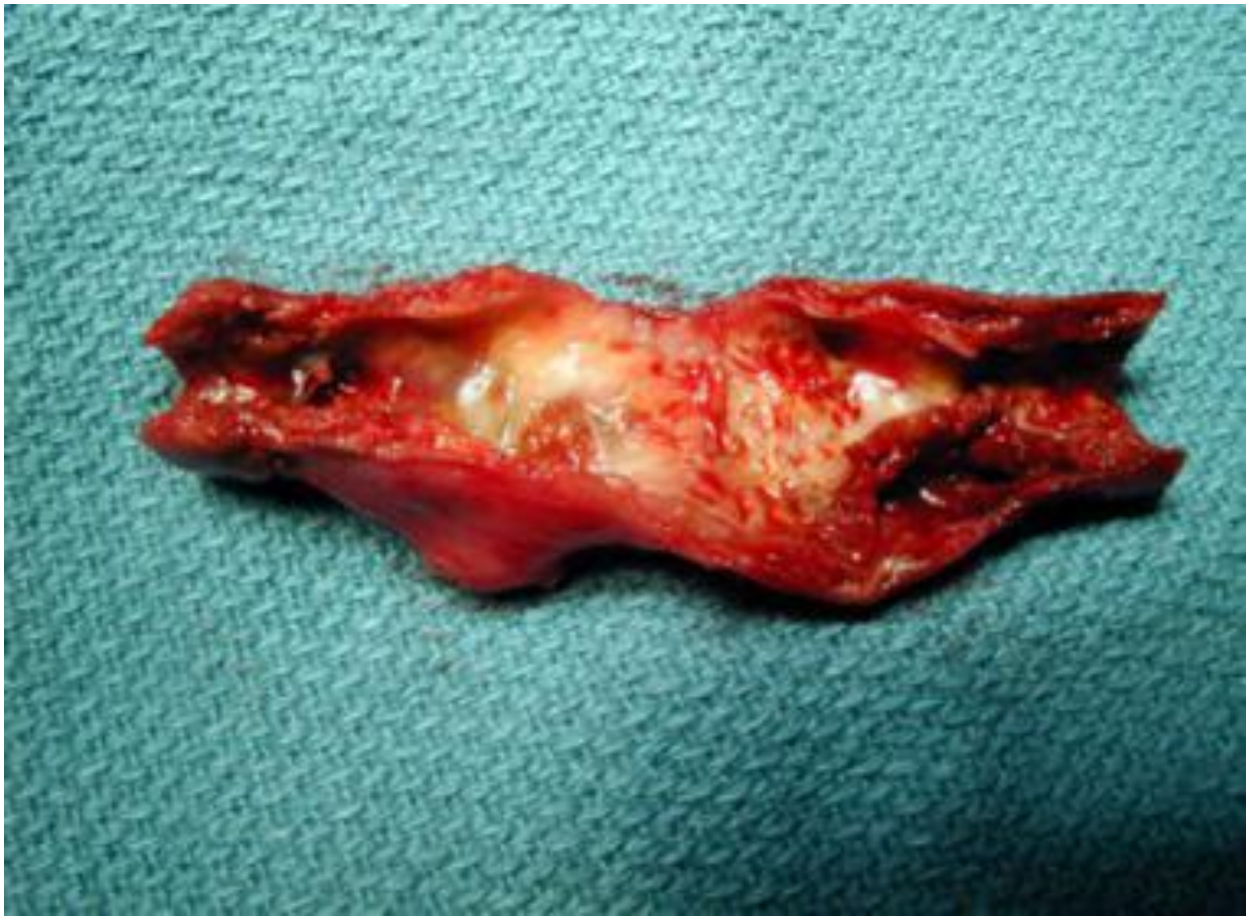
Endarterectomy



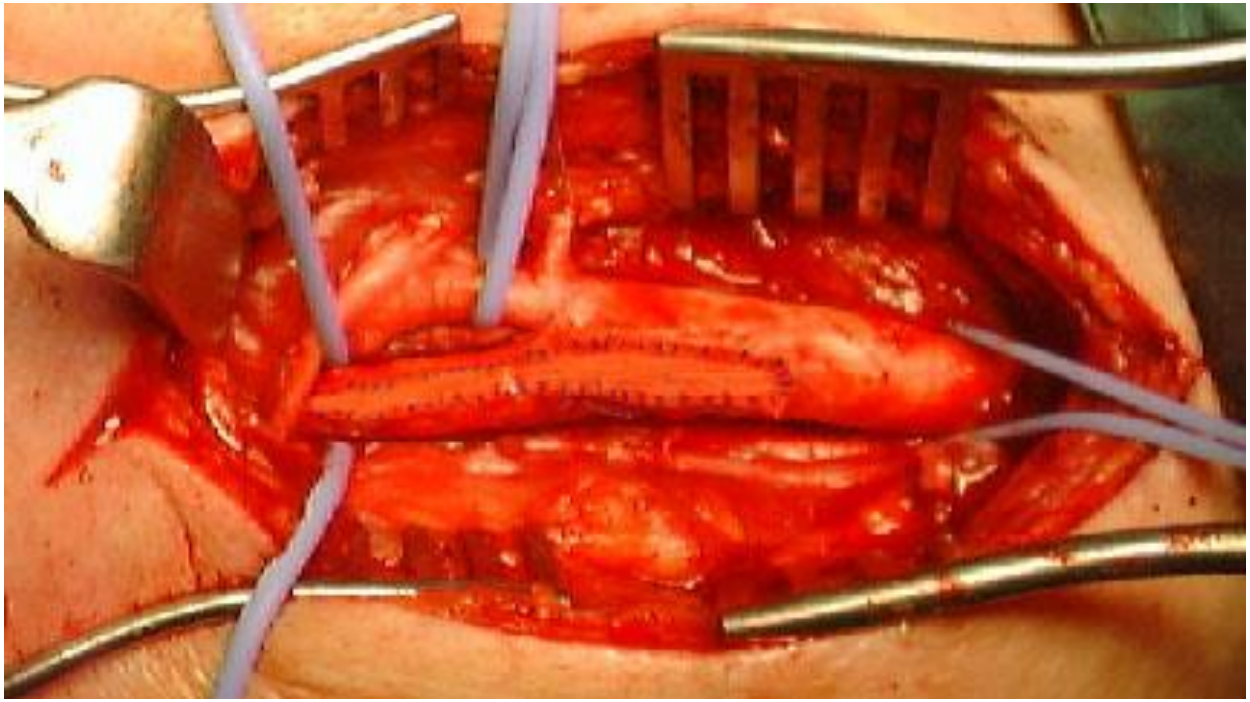
Completed Endarterectomy



Carotid Plaque



Patch Angioplasty

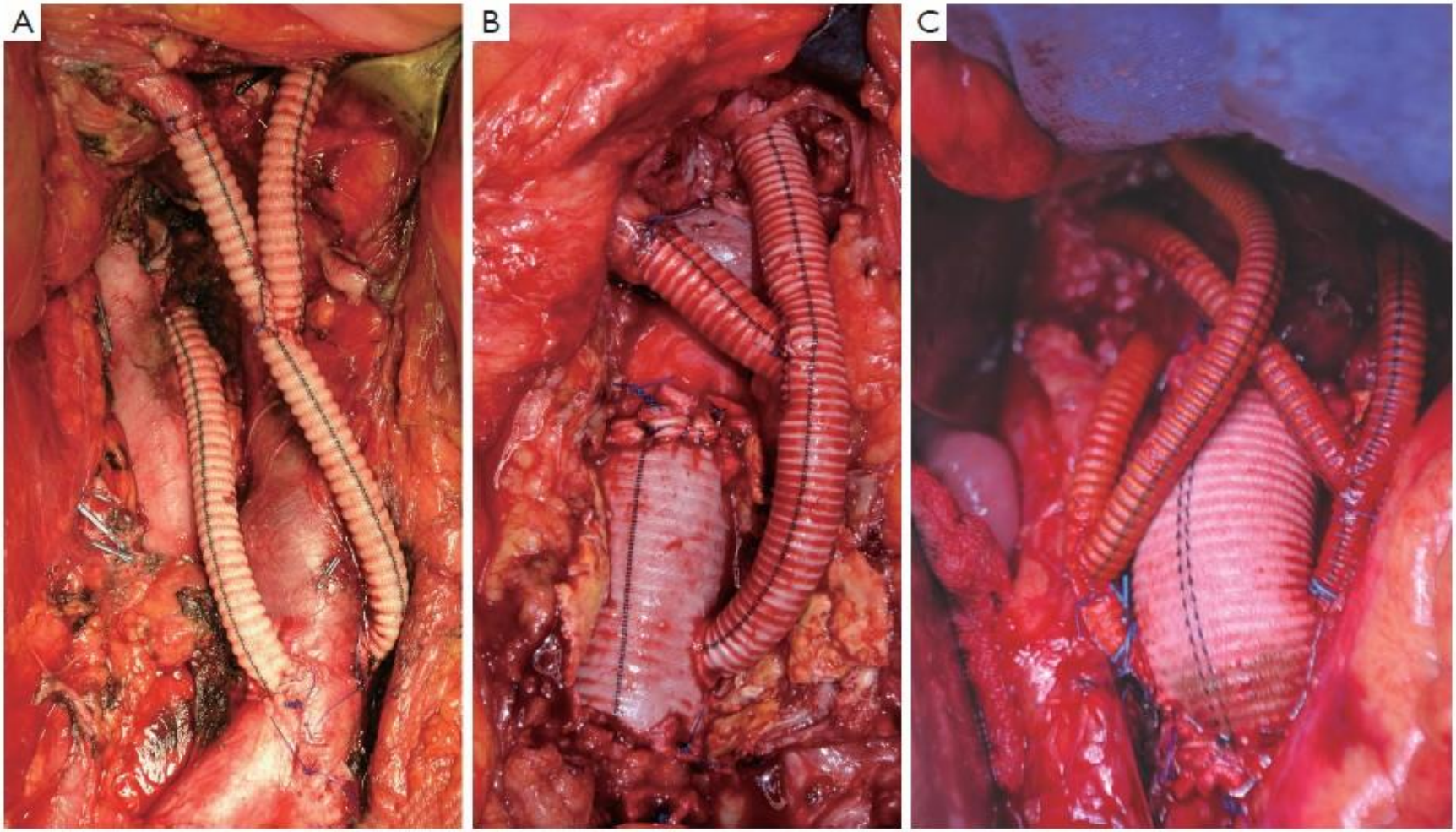


Post-procedural care

- Strict blood pressure monitoring.
- Neurovascular assessment.
- Restoration of best medical therapy.
- Most patients discharged days 1-2.
- Review 3 months with carotid duplex.

East Lancashire Hospitals NHS
NHS Trust

Aortic Aneurysm Disease



Definition

- Arteriomegaly - Diffuse enlargement of an artery but not enough to meet criteria for an aneurysm.

- Ectasia - Diffuse dilatation of an artery with increase in diameter < 50% - Aorta 2cm to 3cm.

- Aneurysm - Increase in diameter of 50% (1.5x) its normal diameter – Aorta > 3cm.

Aetiology

- Aortic aneurysmal disease is a degenerative process associated with;
  - Atherosclerosis.
  - Cystic Medial Necrosis.
  - Dissection.
  - Ehlers-Danlos Syndrome.
  - Syphilis.

- Main risk factors;
  - Smoking.
  - Male gender.
  - Hypertension.

Aetiology

- Elastin degradation due to matrix metalloproteinases (2, 9 and 12) in the aortic media;
  - Increase in the collagenase and elastase activity.
  - Decrease in collagen and elastin in arterial wall.
  - Elastin becomes fragmented leading to arterial elongation and dilatation.

- Law of Laplace - Luminal dilation results in increased wall tension and a cycle of progressive dilation and increased tension.

Epidemiology

- 30-60 cases per 1000.
- Increasing incidence over past 3 decades.
- 7-8% of patients > 65 years of age.

Incidence of AAA

Autopsy	1.5-3.0%
Ultrasound Screening	3.2%
Patients with coronary artery disease	5.0%
Patients with peripheral arterial disease	10.0%
Patients with femoral / popliteal aneurysms	50.0%

Epidemiology

- 30-60 cases per 1000.
- Increasing incidence over past 3 decades.
- 7-8% of patients > 65 years of age.

Incidence of AAA

Autopsy	1.5-3.0%
Ultrasound Screening	3.2%
Patients with coronary artery disease	5.0%
Patients with peripheral arterial disease	10.0%
Patients with femoral / popliteal aneurysms	50.0%

Approximately 10% of patients with AAA will have a popliteal aneurysm

Clinical Presentation

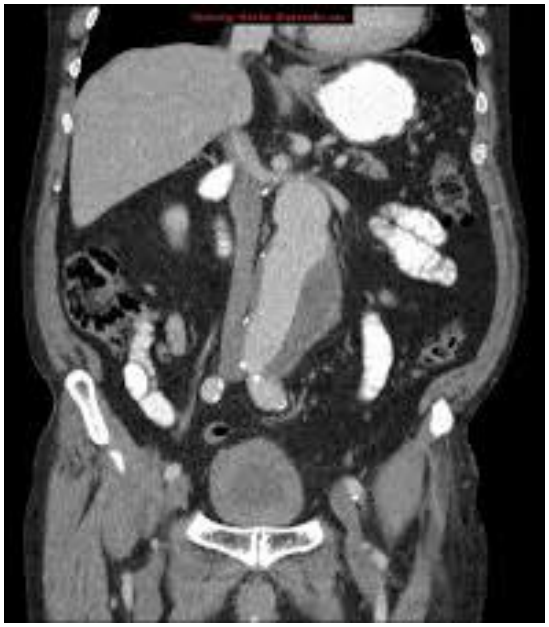
- Asymptomatic – 75%.

- Symptomatic – 25%:
  - Pain.
  - Collapse.
  - Pain / Fever / Weight loss and raised inflammatory markers suggests an inflammatory aneurysm (up to 10%).

Investigation

Ultrasound

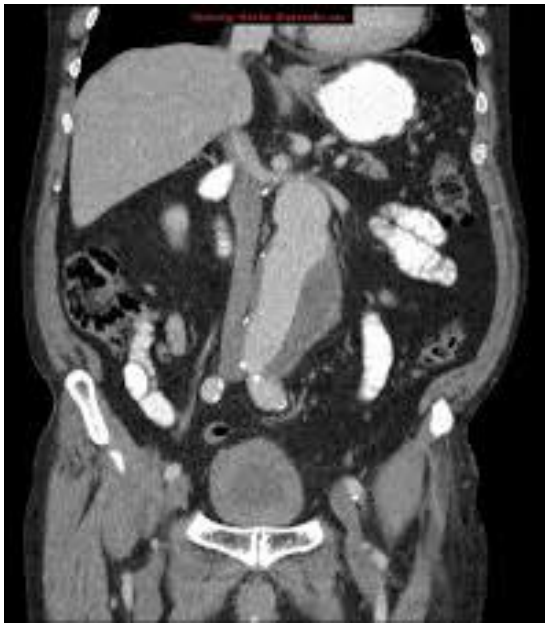
CT scan



Investigation

Ultrasound

CT scan



Beware of FAST Scans from the ED

AAA - Why Treat ??

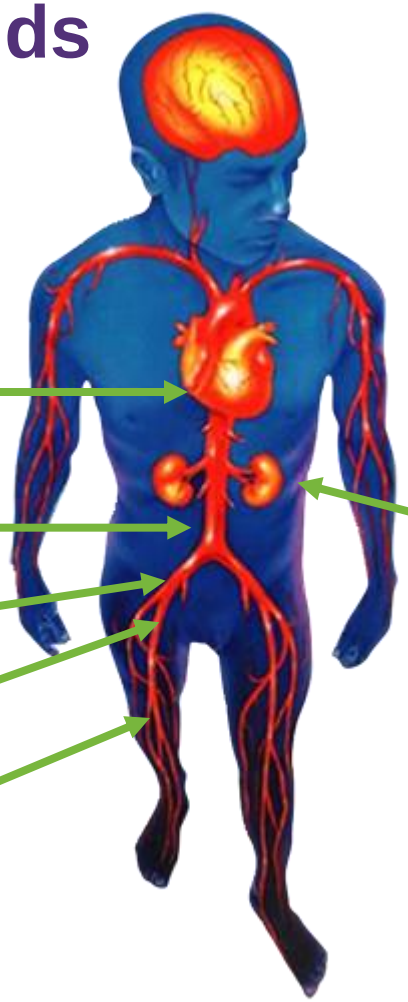
- Risk of AAA rupture;
  - Below 5cm <2%
  - 5cm to 5.9cm 5%
  - 6cm to 6.9cm 6.6%
  - 7cm to 7.9cm 20%
  - Greater than 8cm 30-50%

- UK Small Aneurysm Trial;
  - Multicentre RCT across 93 UK hospitals.
  - 1276 patients between 60-76 with AAA between 4.0 and 5.5cm.
  - Safe to monitor AAA up to 5.5cm unless tender or growth rates >1cm per year.

Lancet 1998; 352: 1649-55.

East Lancashire Hospitals NHS
NHS Trust

Aneurysm Thresholds



Thoracic Aorta 6cm

Abdominal Aorta 5cm

Iliac 4cm

Femoral 3cm

Popliteal 2cm

2cm Visceral Aneurysms
- Splenic
- Hepatic
- Renal

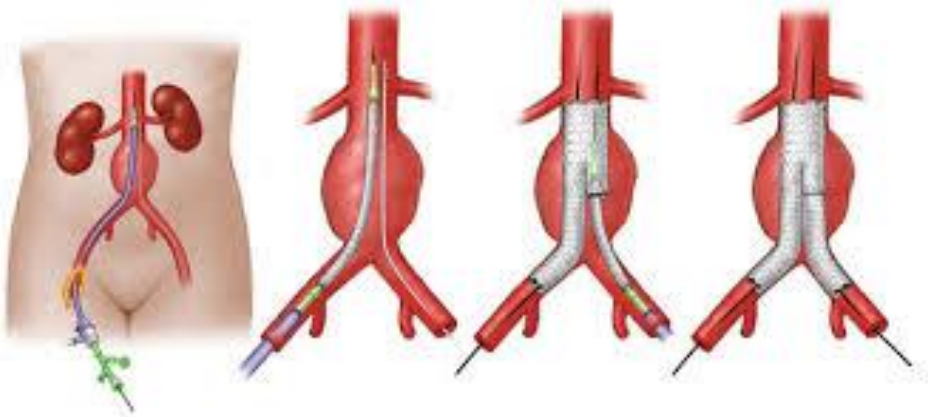
Safe | Personal | Effective

Consent

- General Local Complications;
  - Pain, Bruising, Bleeding, Wound infection.
- Systemic Complications;
  - Cardiovascular, Respiratory, Thromboembolic.
  - Renal.
- Procedural Specific Complications;
  - Graft sepsis.
  - Graft occlusion and distal ischaemia.
  - Intra-abdominal adhesions.
  - Bowel ischaemia.

Treatment

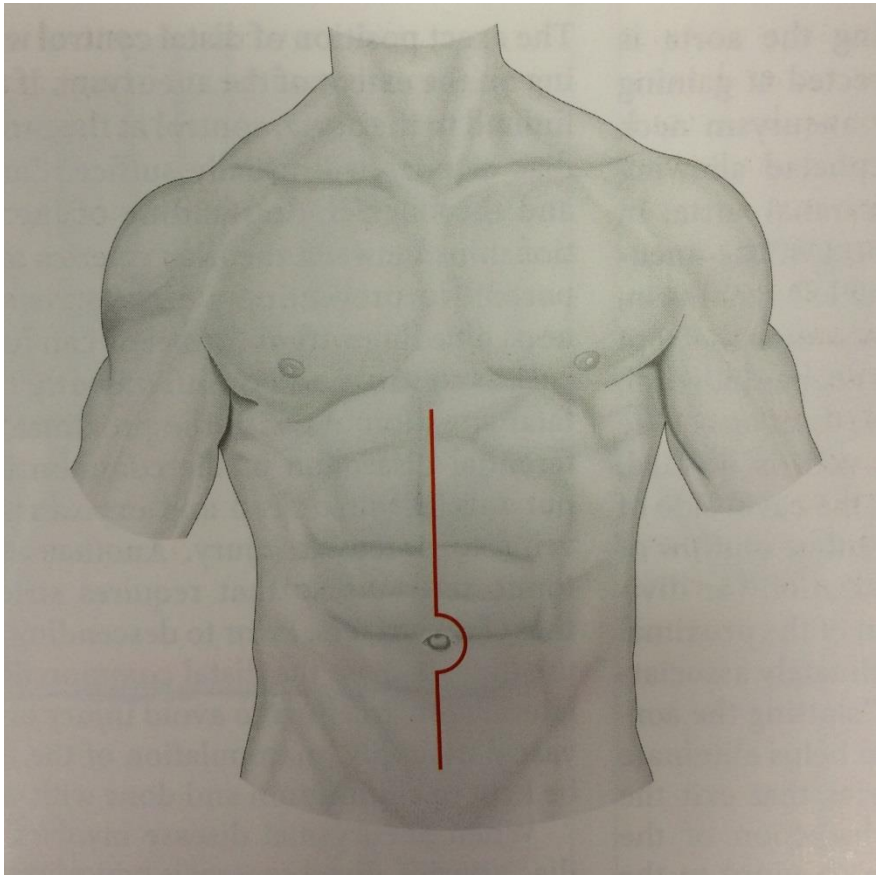
- Endovascular Repair:
  - Repair through an incision in the groin with expandable prosthesis under fluoroscopic guidance
  - Requires both surgical and radiological assistance
  - Significantly reduced morbidity.
  - Long term result unknown
  - Hospital stay 2 days, Recovery time 1-2 weeks



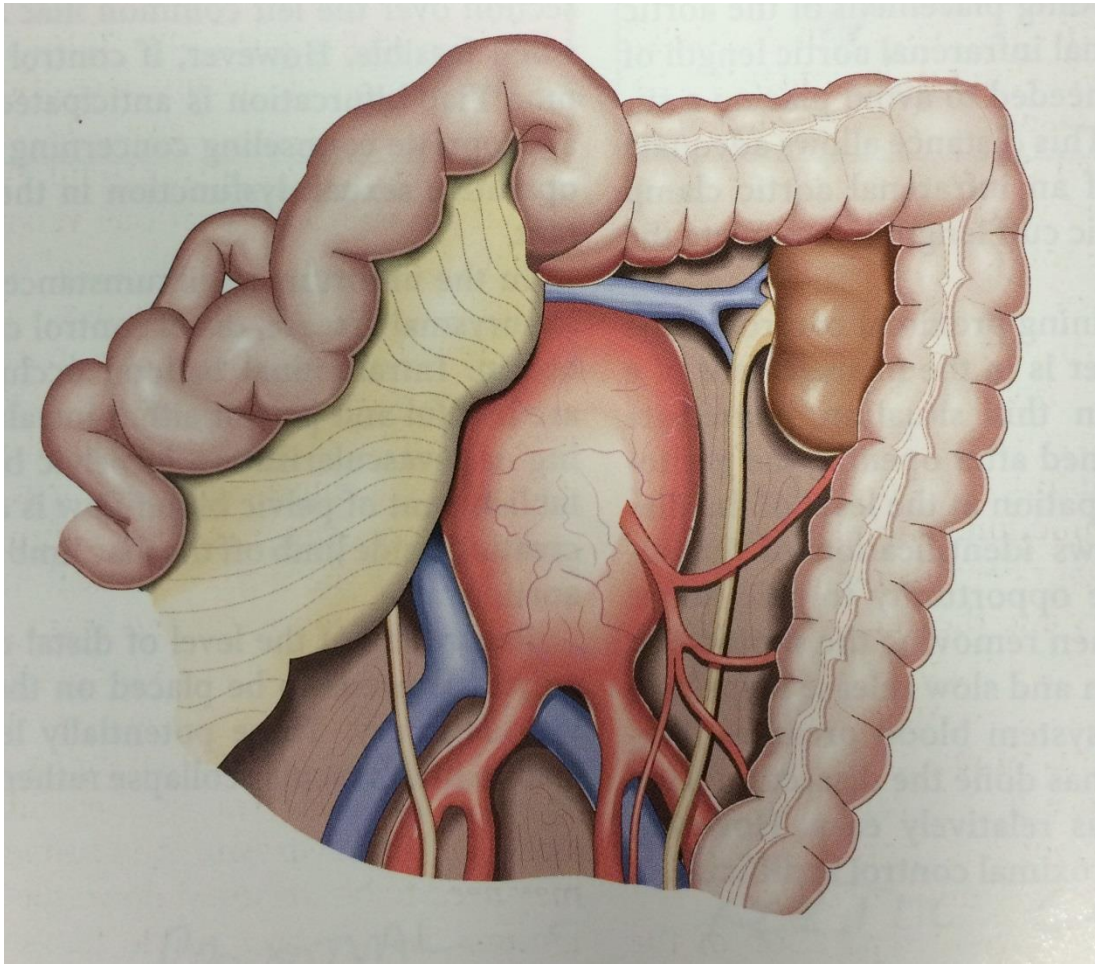
Treatment

- Standard Surgical Repair:
  - Replace diseased aorta with artificial artery.
  - Requires 7 day hospital stay.
  - Recovery time 3-6 months.
  - Proven method with good long term results.

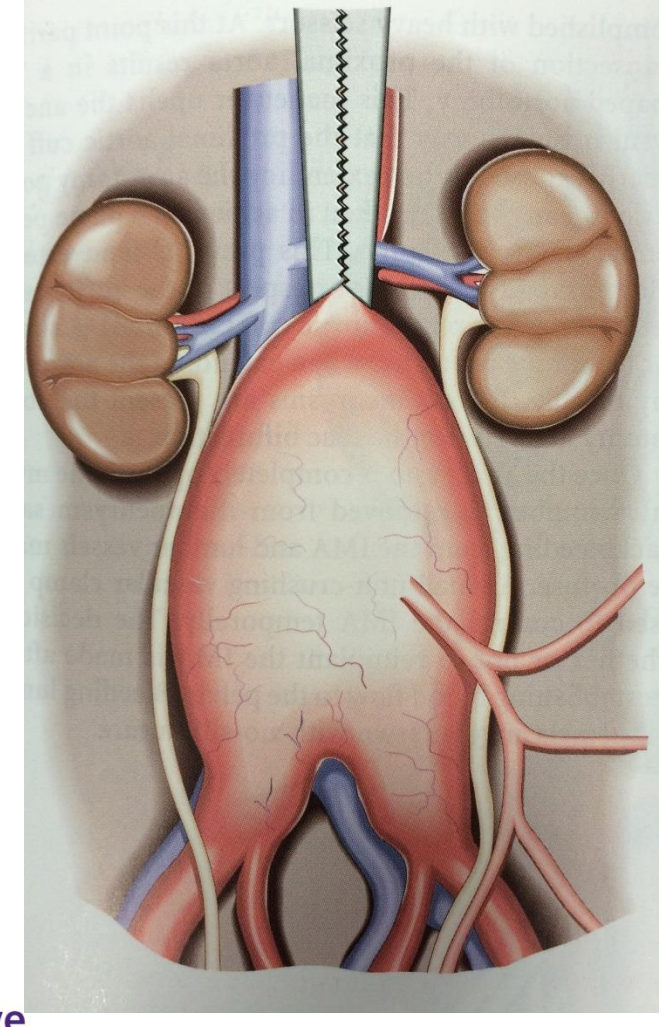
1 – Patient Positioning



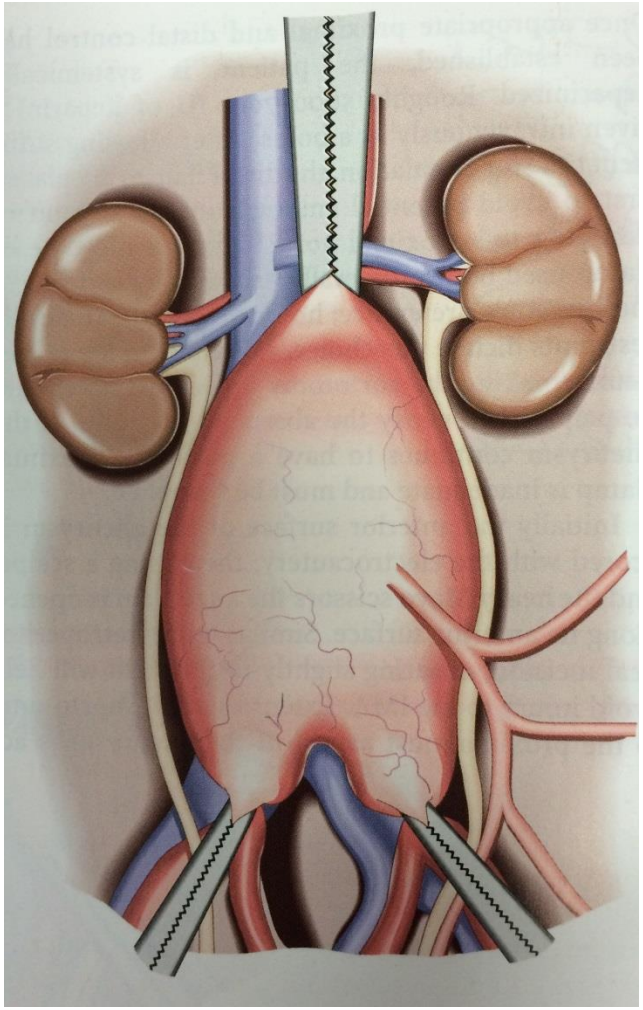
2 – Dissection down onto aorta



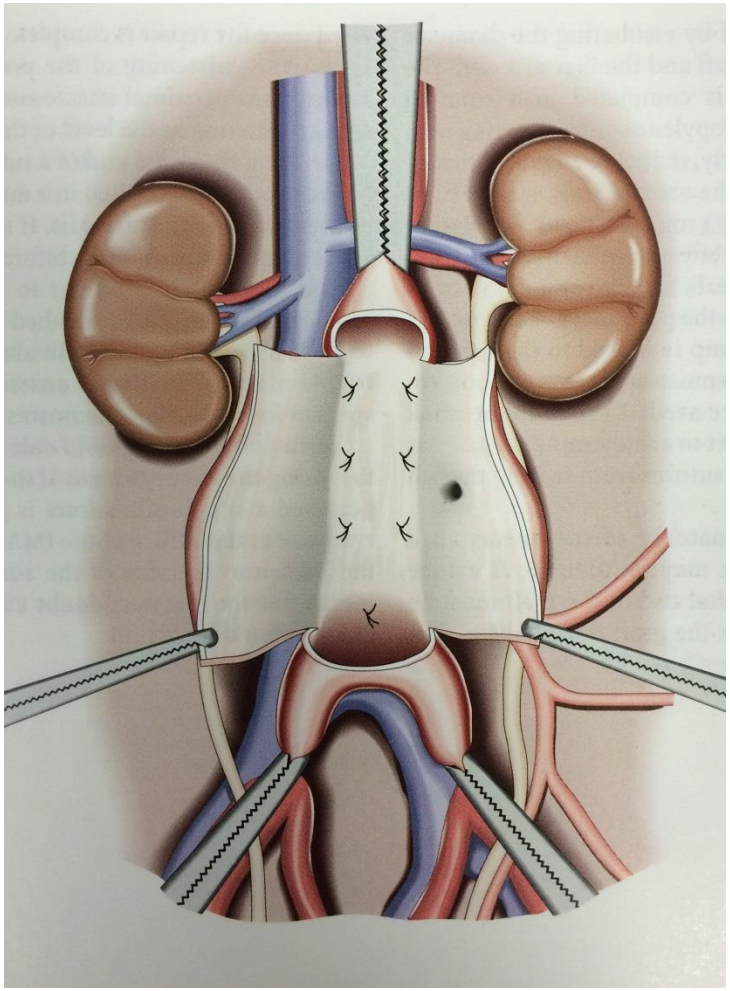
3 – Control of proximal aorta



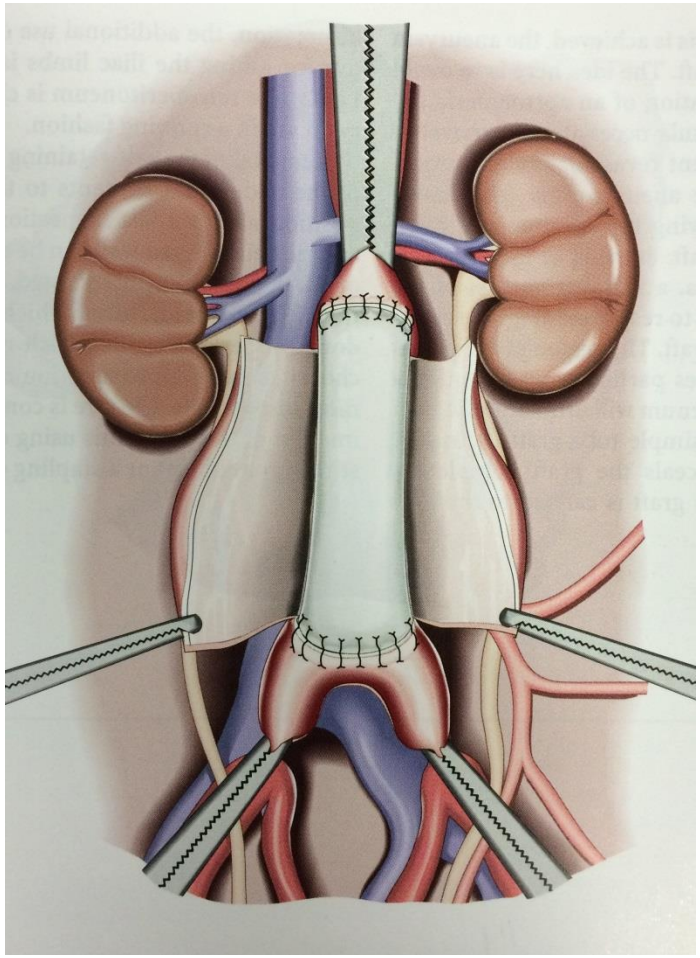
4 – Clamping of distal vessels



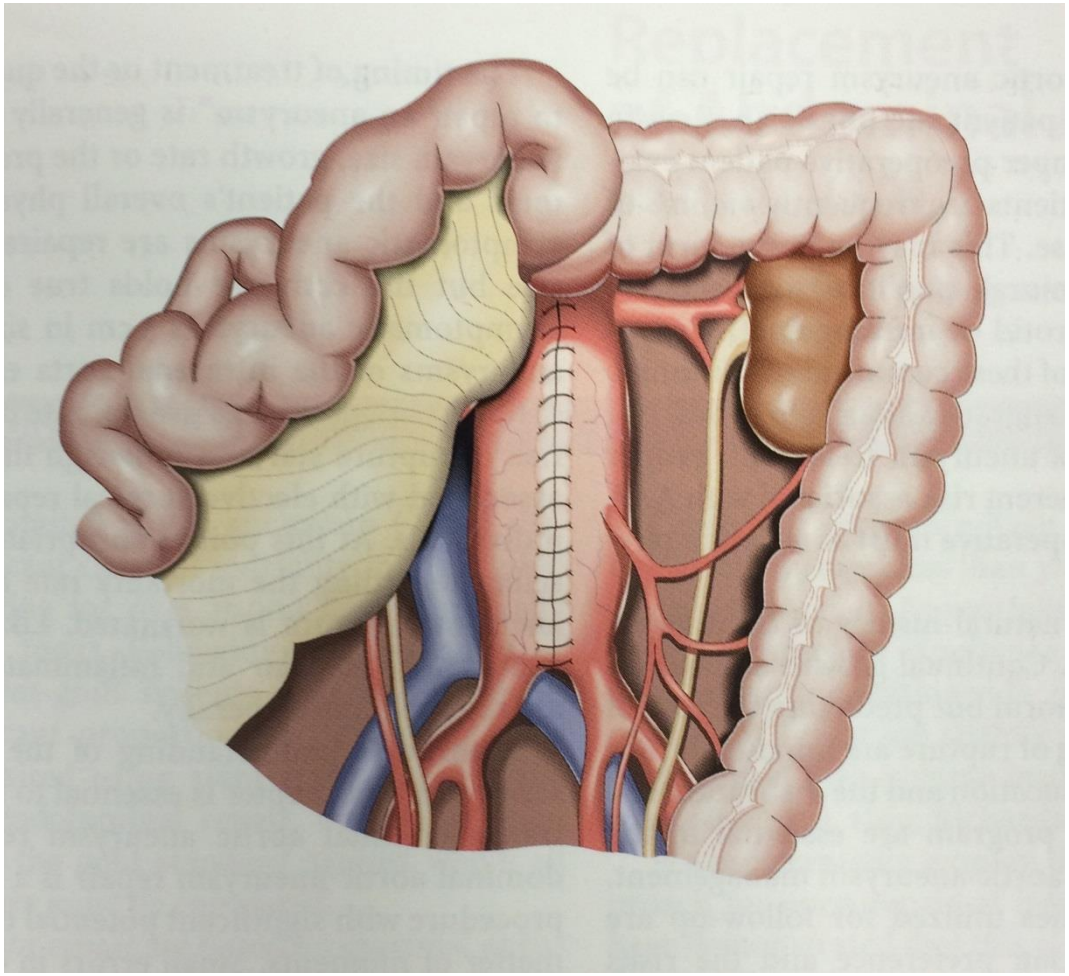
5 – Arteriotomy



6 – Graft suturing



7 – Aneurysmal sac closure



Post-procedural care

- Open AAA repair;
  - Usually POCU / HDU / ICU.
  - Clinical observations.
  - Restart medications – BMT and LMWH.
  - Slow restoration of diet.
  - Out-to-sit, slowly mobilise.
  - Ward transfer and hospital stay 5-10 day

- EVAR;
  - Ward transfer.
  - Restoration of normal diet.
  - Clinical observations / Restart medications.
  - Mobilise and Home day 1-2.

Questions ?