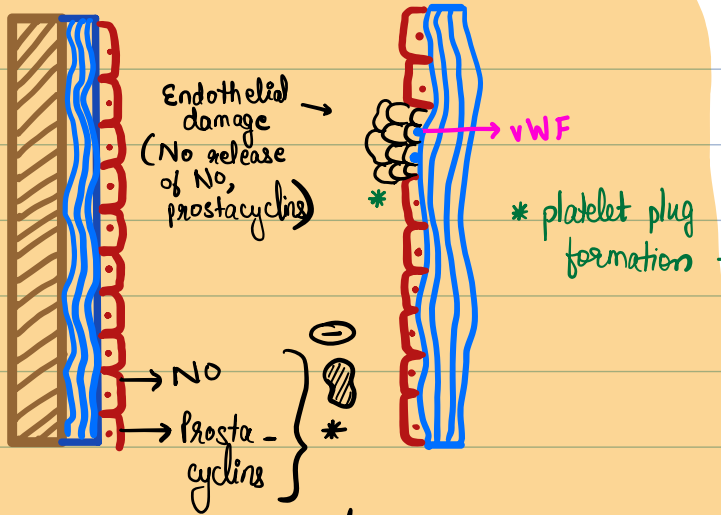


* inhibit platelets / keep them away from endothelial cells
[secreted naturally by endothelial cells]

→ Platelets have high affinity of binding to vWF

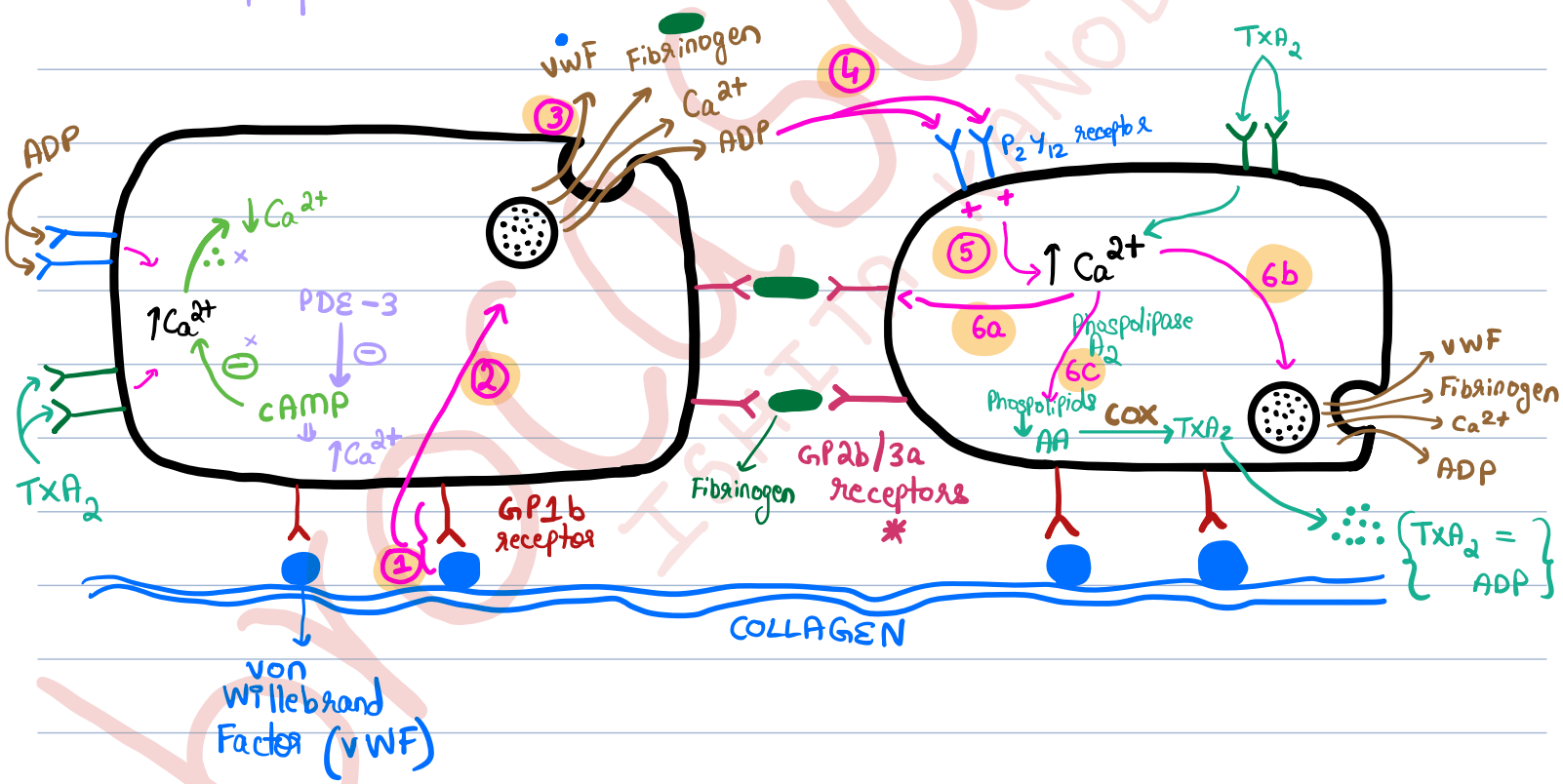
→ in injured endothelium, absence of NO & prostacyclins & presence of vWF, attracts platelets.

→ activates platelets ⇒ platelets release • ADP • TxA_2 • vWF • fibrinogen

* help in binding of a platelet to its nearby platelets (Fibrinogen helps in this bridging process)

COX = cyclooxygenase enzyme

PDE-3 = phospho diesterase



P_2Y_{12} Receptor Inhibitors:

- Clopidogrel
- Prasugrel
- Ticagrelor
- Ticlopidine

PCT

COX inhibitors:

- Acetyl salicylic acid [ASPIRIN] (ASA)

GPIIb/IIIa inhibitors:

- Abciximab
- Tirofiban
- Eptifibatide

TEA

PDE-3 inhibitors:

- Dipyridamole
- Cilostazol

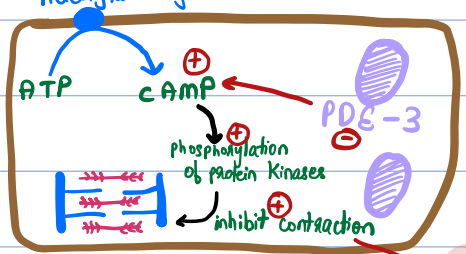
CD

antiplatelet function
vasodilatory effect

ANTIPLATELET DRUGS

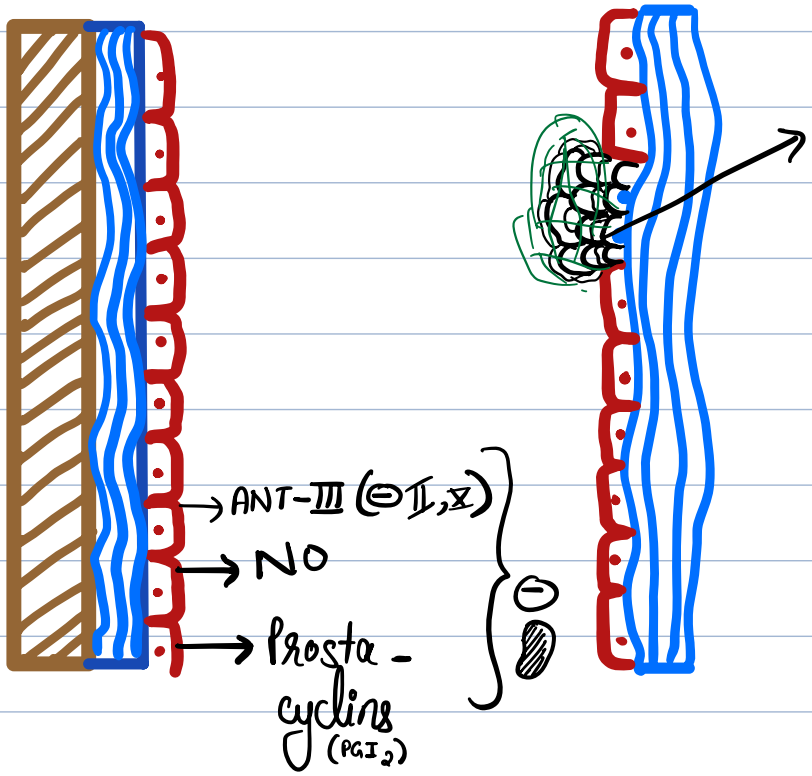
more beneficial in inhibiting arterial thrombo-emboli

do not induce lysis of a clot
⇒ they inhibit clot formation & clot propagation



VASCULAR SMOOTH MUSCLE CELL

relaxation of smooth muscle
∴ vasodilation



Platelet plug formation
↓
activation of platelets
↓
activation of coagulation proteins
↓
cascade reactions
↓
formation of fibrin mesh
↓
Stabilizes the clot & helps in increasing size of clot

EXTRINSIC PATHWAY (due to vessel injury) ⊕
Tissue factor / Factor III
VII_a ⊕

INTRINSIC PATHWAY (secondary to platelet activation) ⊕
XII → XII_a
XI_a ← XI
IX → IX_a
$VIII_a$ ⊕

COMMON PATHWAY
X → X_a
Prothrombin → (Factor II) Thrombin
Fibrinogen → Fibrin
XIII → $XIII_a$
Fibrin meshwork

Liver → Factors
GGT ⊕⊕
- II ↑
- VII ↑
- IX ↑
- X ↑

→ Protein C, S (anticlotting)

(II, VII, IX, X ↑ : pro clotting)

GGT ⊕⊕
vit. K (oxidized) → vit. K (reduced)
vit. K epoxide reductase ⊕

GGT = gamma glutamyl transferase ⇒ activates factors II, VII, IX, X

Factor X inhibitors:

Indirect Inhibition

→ by increasing AT-III (IV/SC)
(∵ inhibiting X & II)

- Unfractionated Heparin (UFH)
  - sugar moiety
  - GAG → inhibits factors II & X equally
  - very long
- Low molecular weight Heparin (LMWH)
  - GAG
  - very short
  - → inhibits X >>> II
- Fondaparinux
  - no GAG
  - → inhibits only X

Direct Inhibition

→ directly inhibit factor X (by binding to it)

[DIRECT ORAL ANTICOAGULANTS] (DOACs)

- ApiXaban
- RivaroXaban
- EdoXaban

ARE

Thrombin Inhibitors:

DIRECTLY (oral & iv)

- Dabigatran (oral)
- Argatroban } i.v.
- Bivalirudin }

BAD

Vit. K Antagonists:

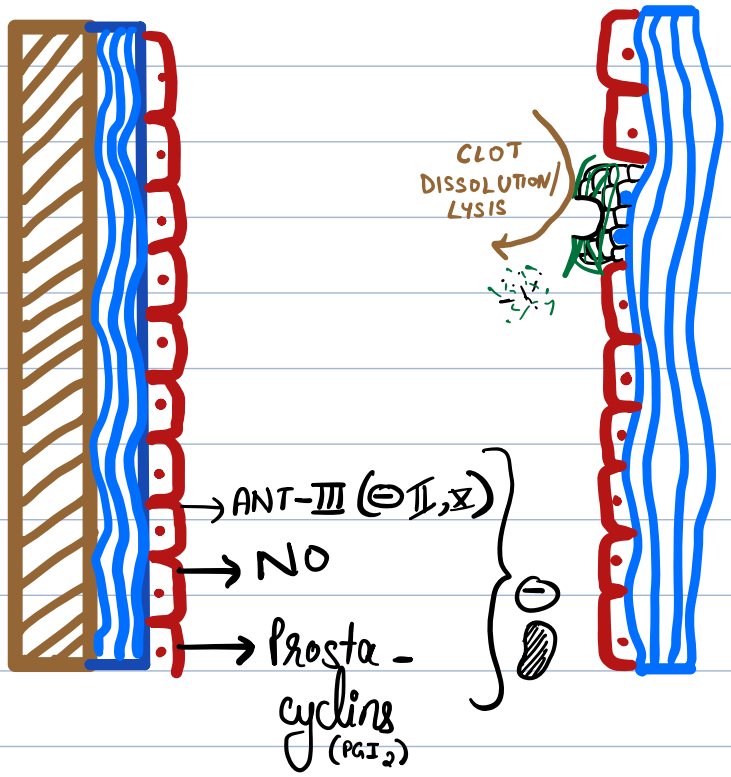
(Inhibition of vit. K epoxide reductase)

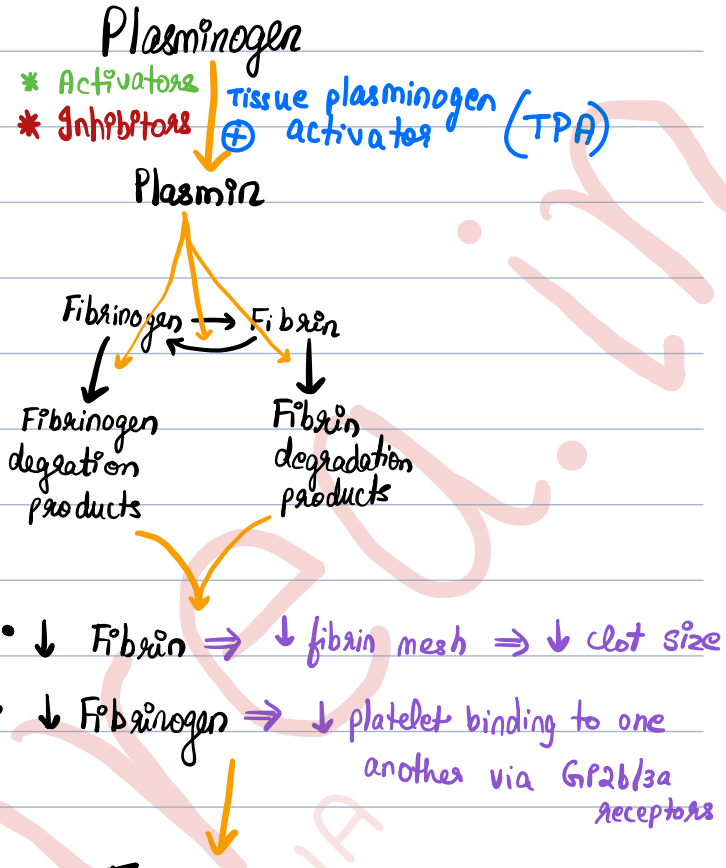
- Warfarin

ANTICOAGULANTS

→ inhibit clot formation & clot propagation

⇒ work on both, venous & arterial thromboemboli.





- ↓ Fibrin ⇒ ↓ fibrin mesh ⇒ ↓ clot size
- ↓ Fibrinogen ⇒ ↓ platelet binding to one another via GP2b/3a receptors

FIBRINOLYSIS
[Clot Busting / Clot dissolution]

TPA Stimulators: (enhance fibrinolysis)

- alteplase — true TPA ⇒ most commonly utilized
- reteplase
- tenecteplase } recombinant TPA
- Urokinase
- Streptokinase

THROMBOLYTICS

TPA * Activators:

Extrinsic	Intrinsic
• Streptokinase	• Factor XIIa
• Urokinase	• Kallikrein
• alteplase	• t-PA (rt-tPA)
• tenecteplase	

TPA * Inhibitors (Antifibrinolytics)

Extrinsic	Intrinsic
• EACA (epsilon amino-caproic acid)	• α_2 Antiplasmin
• Tranexaemic acid	• α_2 Macroglobulin

Anticoagulants

Parenteral

Indirect Thrombin Inhibitors
- Unfractionated Heparin
- Low molecular weight heparin
(Enoxaparin, Revi parin, Parnaparin
Nadroparin, Dalteparin, Ardeparin)
PANDER
- Fondaparinux
- Danaparoid

Direct Thrombin Inhibitors
- Bivalirudin
- Argatroban

Oral

vit. K Antagonists
- Bishydroxycoumarin (dicumarol)
- Warfarin
- Nicoumalone
NBW

Direct Factor Xa Inhibitors
- Rivaroxaban
- Apixaban
- Edoxaban
ARE

Direct Thrombin Inhibitor
- Dabigatranetexilat

Antiplatelet / Antithrombotics

TXA_2 Synthesis Inhibitor
- Aspirin (ASA)
[acetyl salicylic acid]

Platelet cAMP enhancer
- Dipyridamole
- Cilostazol

P_2Y_{12} receptor Blocker
- Ticlopidine
- Clopidogrel
- Prasugrel
- Ticagrelor

GP 2b/3a antagonists
- Abciximab
- Eptifibatide
- Tirofiban

	PT	aPTT
Intrinsic pathway interfered	Normal (12-14s)	Prolonged
Extrinsic pathway interfered	Prolonged	Normal (26-32s)
Common pathway interfered	Prolonged	Prolonged

Lipaemia Clearing Action of Anticoagulants (Heparin):

Heparin inj. (lower conc. of heparin required than that needed for anticoagulation)

↓

release of lipoprotein lipase from vessel wall

↓

hydrolysis of triglycerides & VLDLs to form free fatty acids (FFAs)

↓

FFAs pass into tissue & plasma looks clear

Heparin, being highly ionised, does not cross the BBB or placenta (∴ anticoagulant of choice during pregnancy)

- HEPARIN SODIUM, BEPARINE, NUPARIN 1000 & 5000 U/ml in 5ml vials for injection.
- Quick penetrating solutions (QPS) ⇒ for topical application - PHLEBOTROY QPS 1000 U/mL ; 5ml bottle ; apply on the lesion 3 times a day.

Contraindications of Heparin:

① Bleeding disorders, history of HIT (Heparin-induced thrombocytopenia)

② Severe hypertension (risk of cerebral haemorrhage), threatened abortion, piles, g.i. ulcers

③ Subacute bacterial endocarditis (risk of embolism), large malignancies (risk of bleeding in the central necrosed area of tumour), tuberculosis (risk of hemoptysis)

④ Ocular & neurosurgery, lumbar puncture

⑤ Chronic alcoholics, cirrhosis, renal failure

⑥ Aspirin (& other antiplatelet drugs) should be used cautiously during heparin therapy.

Contraindication of LMWH: Renal failure

Advantages of LMWH over UFH:

① better subcutaneous bioavailability (70-90%) than UFH (20-30%).

② Longer & more consistent monoexponential t½ ∴ once daily s.c. administration is possible

③ aPTT not prolonged ∴ laboratory monitoring is not needed

④ Risk of osteoporosis after long-term use is much lesser

Conditions in which we prefer UFH over LMWH – cardiopulmonary bypass

Indications of LMWH:

① prophylaxis of DVT & PE in high-risk patients

② treatment of established DVT

③ Unstable angina & MI (Acute Coronary Syndrome) [ACS]

④ To maintain patency of cannulae & shunts in dialysis patients

Contraindication of Fondaparinux: Renal failure

Indication of Fondaparinux: prophylaxis & treatment of DVT & PE; in ACS (when immediate intervention is not planned]

PANDER

Enoxaparin: CLEXANE 20 mg (0.2 ml) & 40 mg (0.4 ml) prefilled syringes
20-40 mg OD, s.c. (start 2 hours before surgery)

Reviparin: CLIVARINE 13.8 mg in 0.25 ml prefilled syringe [0.25 ml s.c. OD for 5-10 days]

Nadroparin: FRAXIPARINE 3075 IU & 4100 IU inj.; CARDIOPARIN 4000 or 6000 anti Xa IU inj.

Dalteparin: FRAGMIN 2500, 5000 IU prefilled syringes

Parnaparin: FLUXUM 3200 IU, 6400 IU inj.

Aadeparin: INDEPARIN 2500 IU, 5000 IU prefilled syringes.

Bivalirudin:
Indications — patients undergoing PCI for STEMI
unstable Angina & NSTEMI when early PCI is planned
- BIVAFLO, BIVASTAT, BIVASAVE 250 mg/vial inj.

Argatroban: can be given to patients of renal failure.

Vit. K Antagonists: though the synthesis of clotting factors diminishes within 2-4 hrs of warfarin administration, anticoagulant effect develops gradually over 1-3 days ∵ the levels of clotting factors already present in plasma decline according to their $t_{1/2}$.

Warfarin: UNIWARFIN 1, 2, 5 mg tabs ; WARF - 5 mg tab.

Nicoumalone: ACITROM 0.5, 1, 2, 4 mg tabs.

Contraindications of vit. K Antagonists: (same as heparin)

① Bleeding disorders, history of HIT
② Severe hypertension (risk of cerebral haemorrhage), threatened abortion, piles, g.i. ulcers
③ Subacute bacterial endocarditis (risk of embolism), large malignancies (risk of bleeding in the central necrosed area of tumour), tuberculosis (risk of hemoptysis)
④ Ocular & neurosurgery, lumbar puncture
⑤ Chronic alcoholics, cirrhosis, renal failure
⑥ Aspirin (& other antiplatelet drugs) should be used cautiously during heparin therapy.

Foetal Warfarin - Syndrome: Increased risk of birth defects due to warfarin given in early pregnancy.
→ hypoplasia of nose, eye, socket, hand bones, growth retardation.
If given later in pregnancy: can cause CNS defects, fetal haemorrhages, foetal death & accentuates neonal hypoprothrombinemia.

Drug Interactions of Anticoagulants:

Enhanced anticoagulant Action

- broad - spectrum antibiotics
- some cephalosporins (ceftriaxone, etc.)
- Aspirin
- Long-acting sulfonamides, indomethacin, phenytoin, probenecid
- allopurinol, erythromycin, chloramphenicol
- tolbutamide
- Liquid paraffin

(BLAST, SIP², ACE)

Reduced Anticoagulant Action

- Barbiturates (not BZDs)
- Oral Contraceptives.

Rivaroxaban: XARELTO 2.5 mg, 10 mg, 15 mg, 20 mg tabs.

Apixaban: ELIQUIS 2.5 mg, 5 mg tabs.

	Heparin	Warfarin
Chemistry	Mucopolysaccharide	Coumarin derivative
Source	Hog lung, pig intestine	Synthetic
Route of admin.	Parenteral (IV/SC)	Oral
Onset of action	Immediate	Delayed (1-3 days)
Activity	In vitro & in vivo	In vivo only
Mechanism	Blocks action of factor X & II	Inhibits synthesis of clotting factors
Antagonist	Protamine sulphate	Vit. K
Lab. control	aPTT / clotting time	Prothrombin time / INR
Drug interactions	—	Many
Use	To initiate therapy	For maintenance

Advantages of DOACs over Warfarin:

1. Rapid onset & offset of therapeutic effect
2. Short $t_{1/2}$
3. No laboratory monitoring required
4. Fixed dosage guidelines depending on indication
5. Antithrombotic efficacy ≥ warfarin
6. Lower risk of bleeding compared to warfarin
7. Fewer drug interactions.

Dabigatran: PRADAXA 75, 110, 150 mg caps.

Alteplase: ACTILYSE 50 mg vial with 50 mg solvent water

For MI: 15 mg I.V. bolus inj. followed by 50 mg over 30 min, then 35 mg over next 1 hour (total 100 mg in 90 min.)

For PE: 100 mg I.V infused over 2 hr.

For Ischaemic stroke: 0.9 mg/kg by I.V. infusion over 60 min, with 10% of the dose injected in the first minute.

Reteplase: RETELEX 18 mg / vial inj.

Tenecteplase: ELAXIM 30mg, 50 mg per vial inj. (Dose: 0.5mg/kg single iv bolus injection)

Contraindications for Thrombolytics:

1. H/o intracranial haemorrhage
2. H/o ischaemic stroke in past 3 months
3. H/o head injury in past 3 months
4. Intracranial tumor / vascular abnormality / aneurysms
5. Active bleeding / bleeding disorders
6. Patients receiving anticoagulants
7. Peptic ulcer, oesophageal varices
8. Any wound or recent fracture / tooth extraction
9. H/o major surgery within 3 weeks
10. Uncontrolled hypertension
11. Pregnancy

Aspirin: it acetylates COX 1 & Tx-synthase ∴ inactivating them irreversibly

↳ maximal inhibition of platelet function ⇒ 75–162 mg/day.

- ASA 50 mg tab; ASPICOT 80 mg tab; ECOSPRIN 75, 150 mg tab.
- COLSPRIN, DISPIRIN CV-100: aspirin 100 mg soluble tab.;
- Other NSAIDs ⇒ are reversible inhibitors of COX & produce short-lasting action ∴ not clinically used

Dypyridamole: Dose: 150–300 mg/day PERSANTIN 25, 100 mg tabs; THROMBONIL 75, 100 mg tabs; DYNASPRIN: dipyridamole 75 mg + aspirin 60 mg c.c. tab; CARDIWELL PLUS: dipyridamole 75 mg + aspirin 40 mg tab.

Ticlopidine: first thienopyridine drug

→ Adverse effects – neutropenia, thrombocytopenia, haemolysis, jaundice

Dose: 250 mg BD with meals

TYKLID, TICLOVAS, 250 mg tab; ASTIC ticlopidine 250 mg + aspirin 100 mg tab.

Clopidogrel: CLODREL, CLOPILET, DEPLATT 75 mg tab.

Prasugrel: recovery of platelets from prasugrel action takes longer (7 days) than with clopidogrel (5 days)

→ rapid action ∴ particularly suitable for use in STEMI

→ preferred thienopyridine in ACS to cover angioplasty with/without stent placement.

→ C/I – history of ischaemic stroke & TIAs (risk of intracranial haemorrhage)

Dose: Loading dose 60 mg, followed by 10 mg OD;

- For elderly / those < 60 kg body weight ⇒ 5 mg OD.

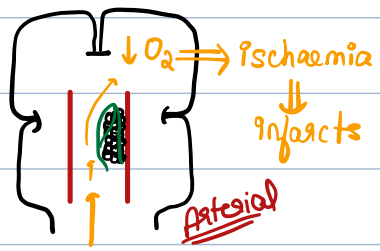
PRASULET, PRASUSAFE, PRASUREL 5 mg, 10 mg tabs.

Ticagrelor: unlike prasugrel & clopidogrel, action of ticagrelor is reversible

∴ faster onset & offset of action.

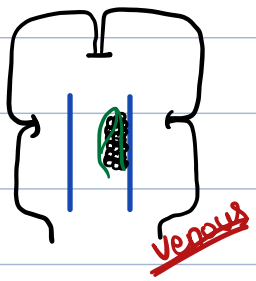
Dose: For ACS requiring urgent PCI 180 mg loading dose followed by 90 mg BD; (maybe continued for upto 12 months) BRILINTA 90 mg tab.

Neurological Indications



Acute Ischaemic Stroke

- LKW (3-4.5 hrs) ⟹ treatment
  - ↳ Thrombolytics (acutely)
  - ↳ ↓ risk of atherosclerotic CVD (later on) ⟹ further prevention
    - Aspirin +/- P_2Y_{12} receptor inhibitor



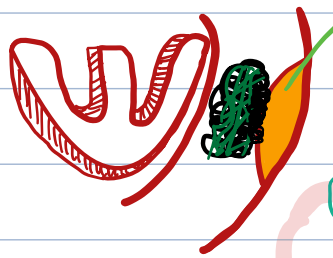
Cerebral Venous Sinus Thrombosis:

- Anticoagulants

→ Initial therapy ⟹ Heparin infusion

→ Transition into ⟹ – Xa inhibitors } DOACs
– II inhibitors }
– Warfarin ⟹ better than DOACs if patient has antiphospholipid syndrome.

Cardiac Indications:



Acute Coronary Syndrome ← Unstable angina, NSTEMI, STEMI

① + Aspirin + P_2Y_{12} receptor blocker

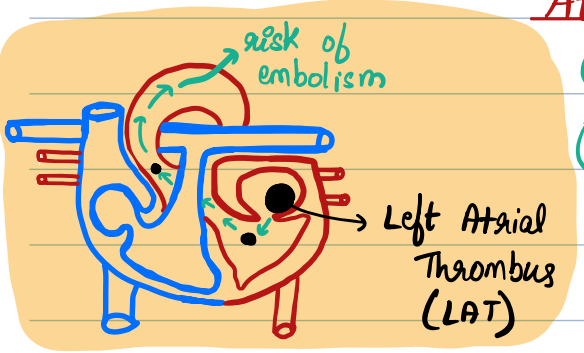
② +/- GP2b/3a inhibitor ⟹ use only prior to PCI (in very very high risk patients)

③ + Heparin (UFH) ⟹ prior to & during PCI

④ Post PCI ⟹ Aspirin + P_2Y_{12} inhibitor (12 months)
⟹ downgrade to one of the above (lifelong)

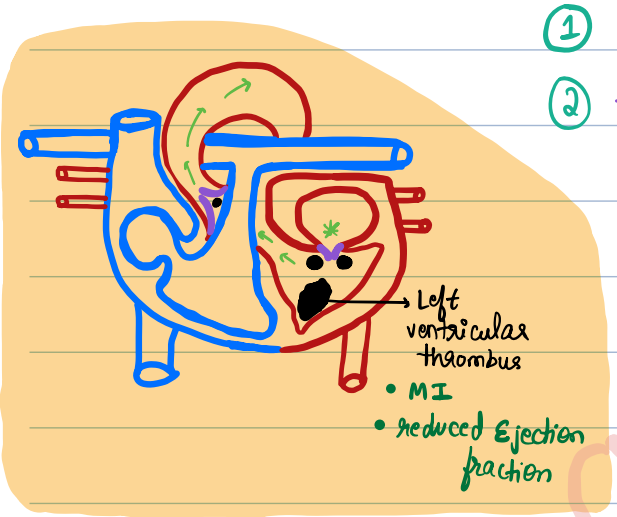
⑤ + Thrombolytics ⟹ if very far from PCI capable facility (STEMI < 12hrs onset)

Atrial Fibrillation: → Stasis of blood in atria → LAT formation



1. + Heparin (initially) (UFH / LMWH)
2. Transition to one of the following:
   - Valvular AF (Mitral stenosis / Prosthetic valve) ⇒ Warfarin
   - non-valvular AF ⇒ DOAC (or) Warfarin

Left Ventricular Thrombus



1. Heparin (initially)
2. Transition to DOAC (or) Warfarin

* Patients with mechanical prosthetic values ⇓ highly thrombogenic
1. Heparin (initially)
2. Transition to Warfarin (DOAC)

→ adding aspirin significantly reduces thromboembolic complications in patients with mechanical values

Pulmonary Indications:

Pulmonary EmbolP:

Patient is Haemodynamically unstable (Hypotension, tachycardia, hypoxic, RV dysfunction, etc.)
- Thrombolytics

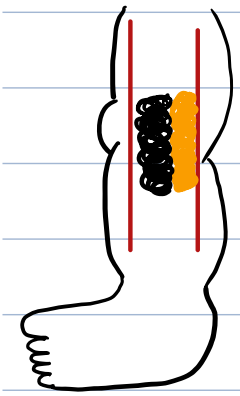
Patient is haemodynamically stable
1. Heparin (initially)
2. Transition to DOAC (or) Warfarin } [3-6 months]

Peripheral / Central Thromboemboli:

- CAD
- MI
- TIA
- CVA
- PAD

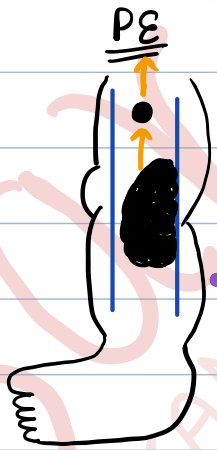
atherosclerotic plaques → rupture → platelet plug / clot formation ⇒ Aspirin (#1) &/or P_2Y_{12} inhibitor

Add on therapy: Cilostazol
antiplatelet drug with vasodilatory effect
↓
given in patients with very severe symptoms of PAD.



Acute Limb Ischaemia:

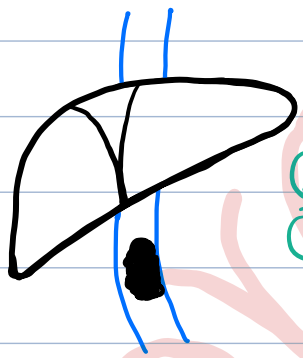
1. Catheter directed TPA
   ↳ clot busting immediately
2. Prior to intervention of choice
   ↳ Heparin



DVT:

- If ↑↑↑ Clot Burden:
  ↳ Catheter directed TPA
- No extensive clot Burden:
  1. Heparin
  2. Transition to
     - DOAc (preferred)
     - or
     - warfarin

  } 3-6 months



Mesenteric Venous Thrombosis:

1. Heparin (initial)
2. Transition to Warfarin (DOAC)

Prophylaxis - Venous Thromboembolism: [DVT / PE]

High Risk: - Post op
- Bed ridden
- Malignancy

Predisposition ← stasis of blood flow, hypercoagulability, endothelial injury (VIRCHOW'S TRIAD)

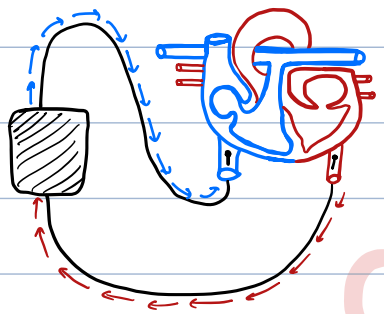
Primarily: ambulate the Patient

If ambulation is not possible → Low-dose heparin (s.c.)

(or)

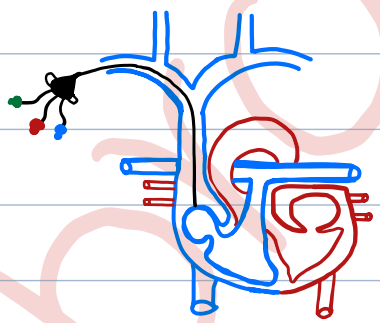
If patient is already on anticoagulant for an underlying disorder ⟹ that can serve as VTE prophylaxis

Prevention of Circuitry Clotting or Catheter Clotting:



- ECMO
- CPB

→ Heparin (UFH > LMWH)



Central Venous Catheter Clotting:

→ very low dose TPA

Adverse Effects:

① Aspirin:

→ worsening of peptic ulcer disease (PUD)

AA ⊖→ PGE_2 ⊖→ mucous secretion ⊖→ protective factor against ulcers

⊖ aspirin (cox inhibitor)

→ **Reye Syndrome:**

- < 19 years
- viral infection
- Aspirin

} TRIAD