Anticoagulants-II

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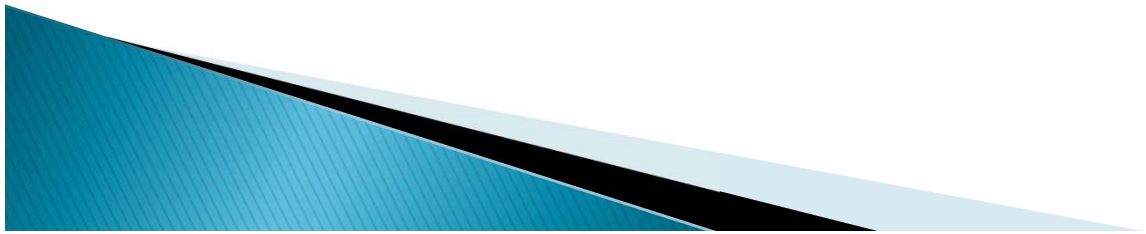
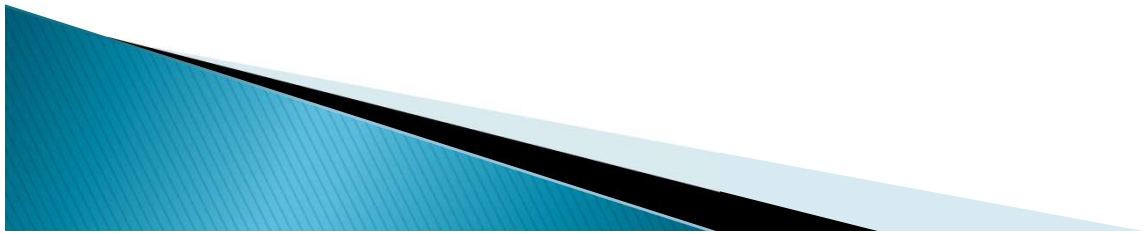
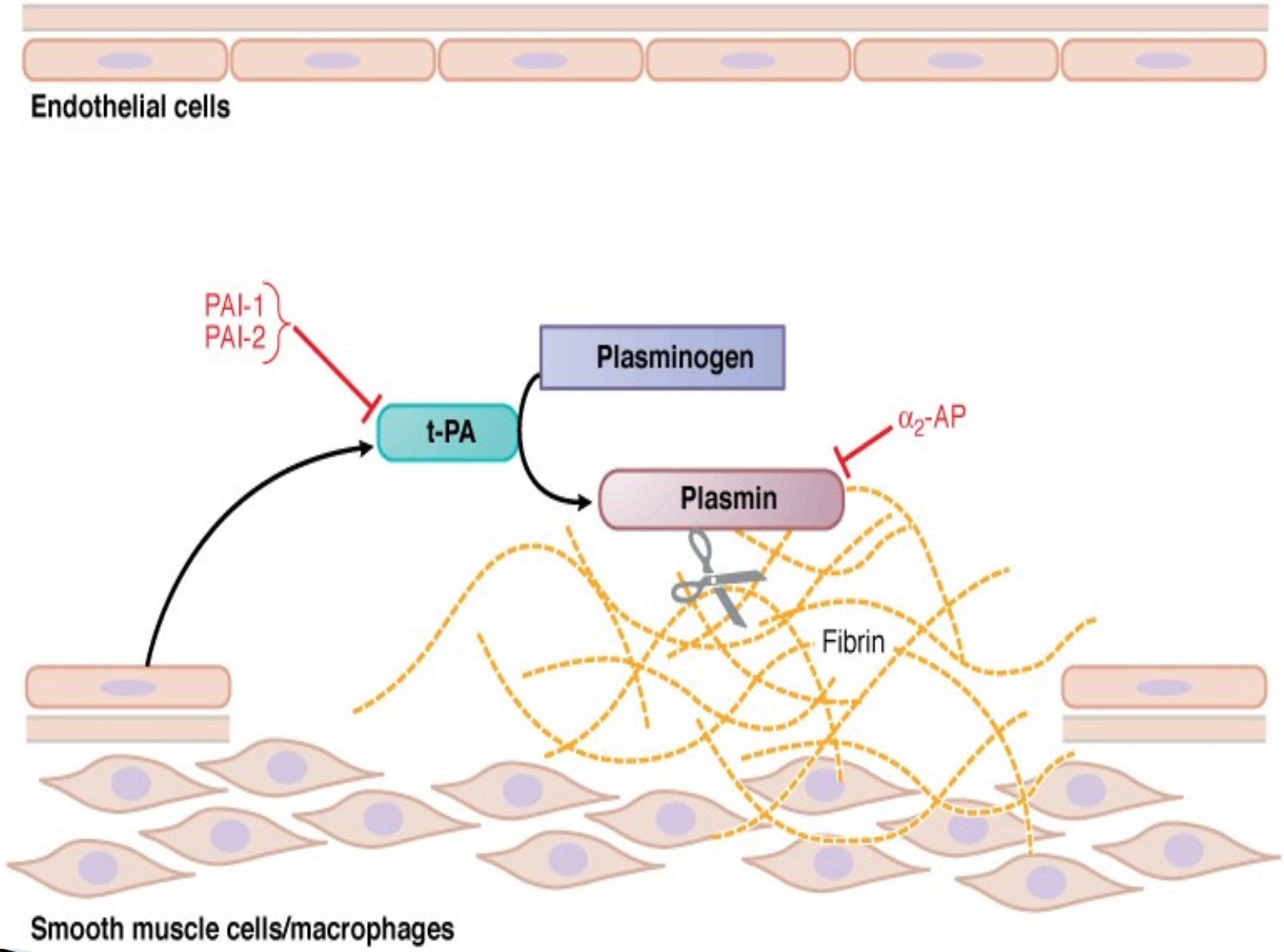
Fibrinolytics

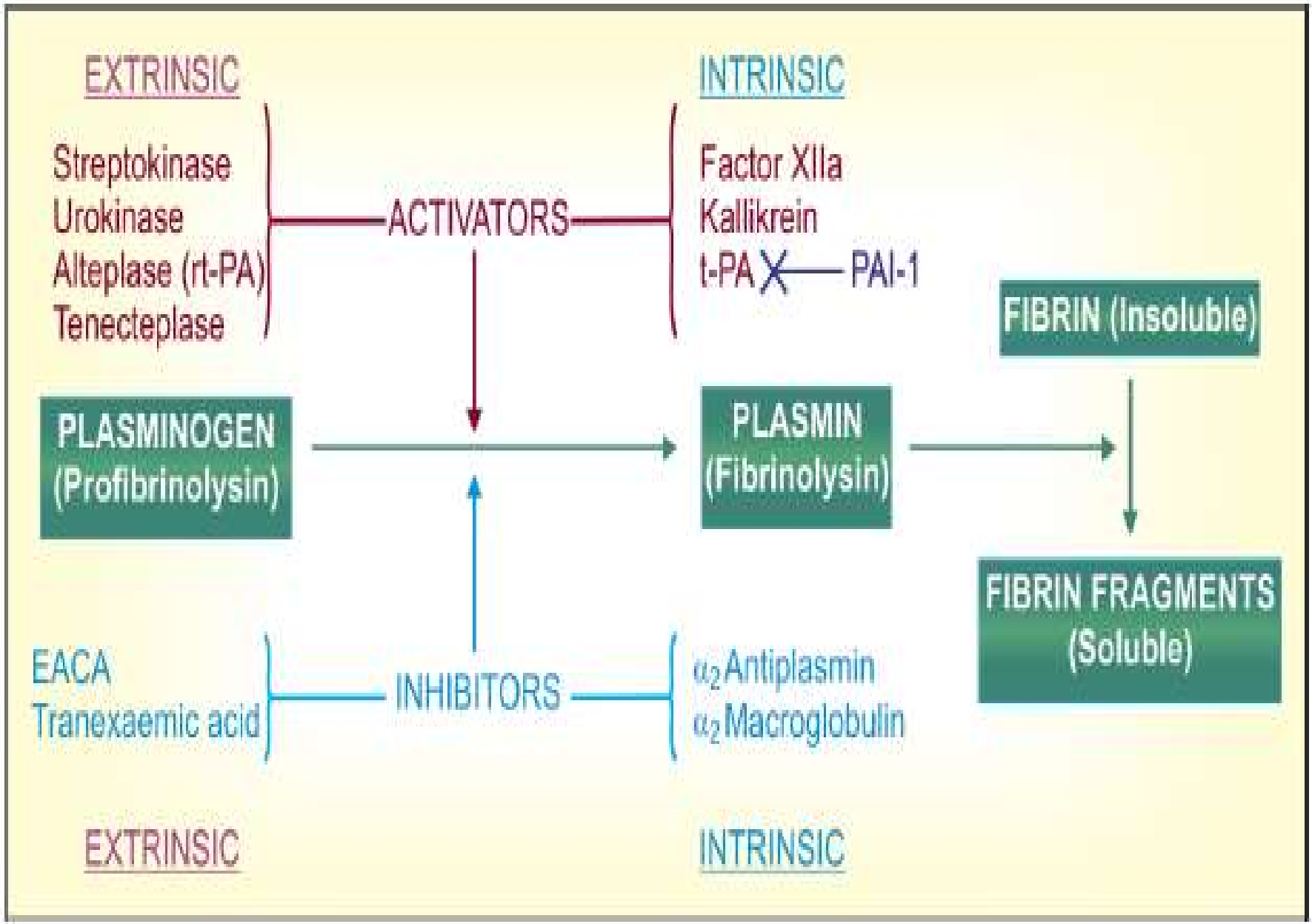
- Lyses thrombi
- Activating natural system
- Plasminogen (derived from endothelium): Two types
  - 1. fibrin specific:- activated by t-PA
  - 2. non specific
- Excessive/leaking plasmin deactivated by antiplasmin



- On overdose of fibrinolytics, excessive plasmin lead to bleeding complications
- Therapeutic but not prophylactic
- Recent and venous thrombi lysed easily




Endothelial cells
PAI-1
PAI-2
Plasminogen
t-PA
α_2-AP
Plasmin
Fibrin
Smooth muscle cells/macrophages


EXTRINSIC
INTRINSIC
Streptokinase
Urokinase
Alteplase (rt-PA)
Tenecteplase
ACTIVATORS
Factor XIIa
Kallikrein
t-PA
PAI-1
FIBRIN (Insoluble)
PLASMINOGEN (Profibrinolysin)
PLASMIN (Fibrinolysin)
FIBRIN FRAGMENTS (Soluble)
EACA
Tranexaemic acid
INHIBITORS
α2 Antiplasmin
α2 Macroglobulin
EXTRINSIC
INTRINSIC

	Streptokinase	Urokinase	Alteplase	Tenecteplase
Source	Streptococci	Cultured kidney cells	Rt-PA	Genetically
Plasma $t_{1/2}$	30-80 min	10-15 min	4-8 min	Long duration
Fibrin-specificity	Non-fibrin specific	same	moderate	Higher
Advantages	Cheaper	Same	-Higher thrombolytic efficacy over strepto. -less bleeding	-Less bleeding -Given during transportation
Disadva. / side effects	-More bleeding -Previous Streptococcal infe. -Hypersensitivity reaction -Cant be used second time	-Fever -Seldom used now	-Cost -Nonantigenic still lead to fever, nausea, hypotension	-Cost
Dose	MI: 7.5-15 lac IU IV over 1 hr DVT: 2.5 lac f/b 1lac/hr for 24 hr	2.5 lac f/b 5 lac over 1 hr	15 mg IV f/b 50 mg over 30 min f/b 35 mg over 1h	0.5 mg/kg IV single bolus infusion

Therapeutic uses

1. Acute MI :-

- All STEMI cases, selected NSTEMI
- Alternative to surgical approach
- Golden hour
- Aspirin with heparin is started concurrently
- Facilitated PCI
- Primary PCI when thrombolytic is contraindicated

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 tumour/vascular abnormality/ aneurysms
5	Active bleeding/bleeding disorders
6	Peptic ulcer, esophageal varices
7	Any wound or recent fracture or tooth extraction
8	H/o major surgery within 3 weeks
9	Uncontrolled hypertension
10	Pregnancy

2. DVT:-

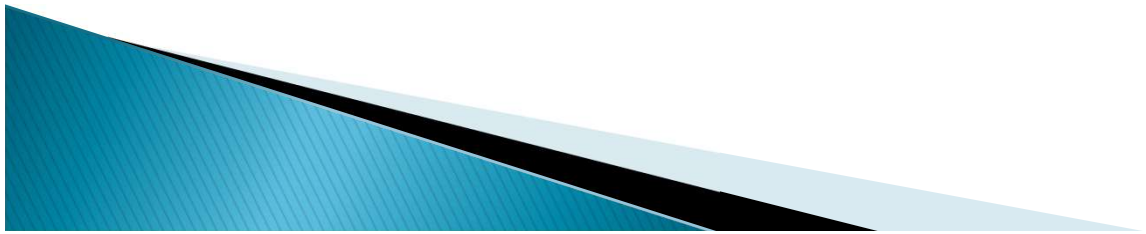
- Upto 60% treated, reduce pain and save venous valve

- Reduce risk of pulmonary embolism

3. Pulmonary embolism:-

- Life-threatening PE

- Lung functions can be preserved



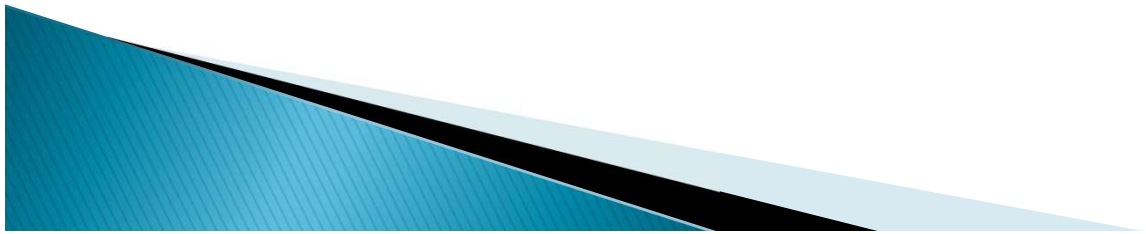
4. Stroke:-

- Controversial due to bleeding chances

- Still alteplase can be given in patients of stroke within 1-3 hr of onset

5. Peripheral arterial occlusion:-

- When surgical thrombectomy is not possible



Anti fibrinolytic therapy

- Inhibits plasminogen activation and check fibrinolysis associated bleeding

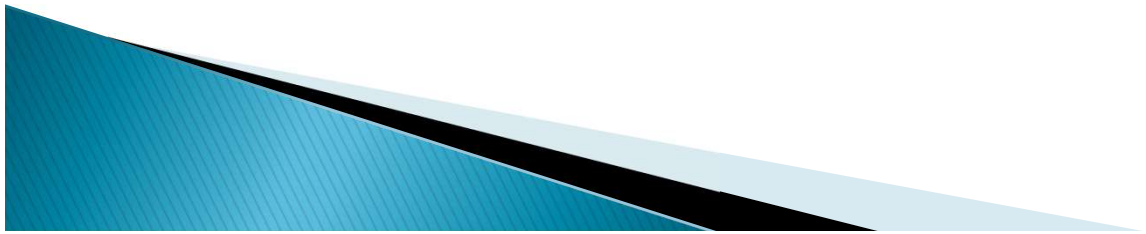
1. Epsilon amino caproic acid
2. Tranexamic acid

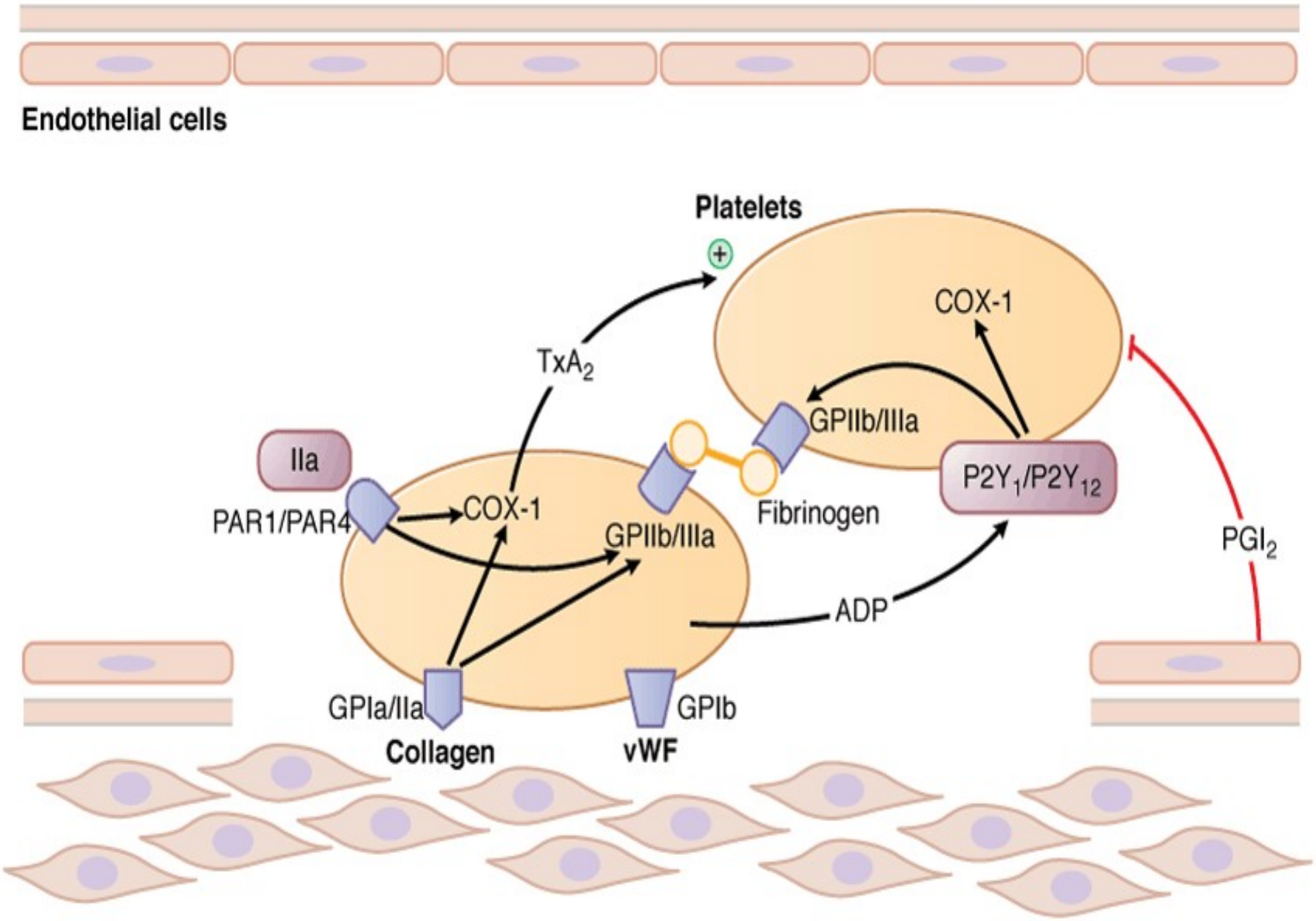
- Also can be used in :-
  -Tooth extraction in hemophiliacs,
  -Menorrhagia after use of IUCD,
  -Recurrent epistaxis

Antiplatelet drugs

- Platelet aggregators:-
  - TXA2
  - ADP
  - 5-HT

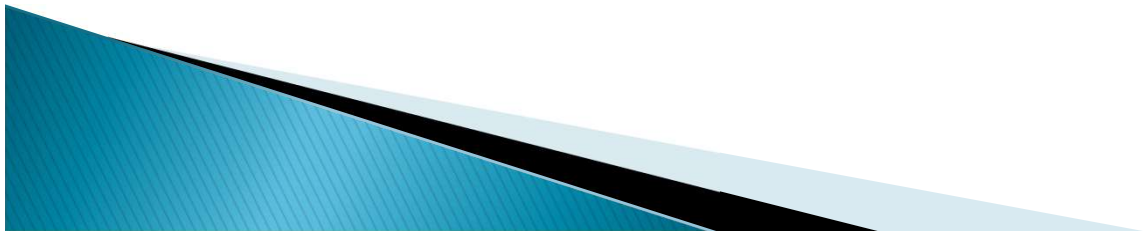
- Platelet disintegrators:-
  - PGI2
  - cAMP




Endothelial cells
Platelets
COX-1
TxA_2
GPIIb/IIIa
IIa
PAR1/PAR4
COX-1
GPIIb/IIIa
Fibrinogen
$P2Y_1/P2Y_{12}$
PGI_2
ADP
GPIa/IIa
GPIb
Collagen
vWF
Smooth muscle cells/macrophages

Antiplatelet drugs

1. Irreversible COX inhibitors:-Aspirin
2. PDE inhibitors:-Dipyridamole
3. P2Y1 and P2Y12 antagonist:- Ticlopidine, clopidogrel, prasugrel
4. GP2b/3a antagonist:- abciximab, eptifibatide, tirofiban



Aspirin

- Irreversible
- No nuclei in platelets (long duration)
- Low dose required (in portal circulation)
- Dose:- 75 to 150 mg/day, 300 mg twice/wk
- Higher doses may also suppress PGI_2

Dipyridamole

- Vasodilator for angina
- Block adenosine uptake and also PDE ⟶ more cAMP ⟶ potentiate PGI_2
- Main indication:-
  - prosthetic heart valve:- with warfarin and
  - stroke prevention in TIAs:- with aspirin
- Dose :- 150-300 mg/day

$P2Y_{1/12}$ antagonists

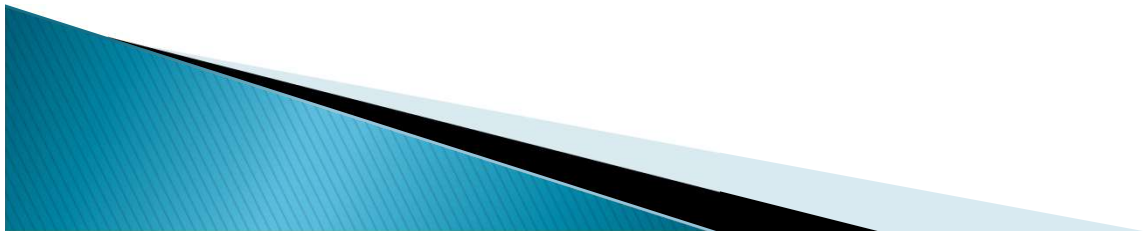
- Combination with aspirin is synergistic

Ticlopidine :- prodrug;
Irreversible inhibitor (250 mg BD);
longer duration of action (5-6 days)

- S/E:-

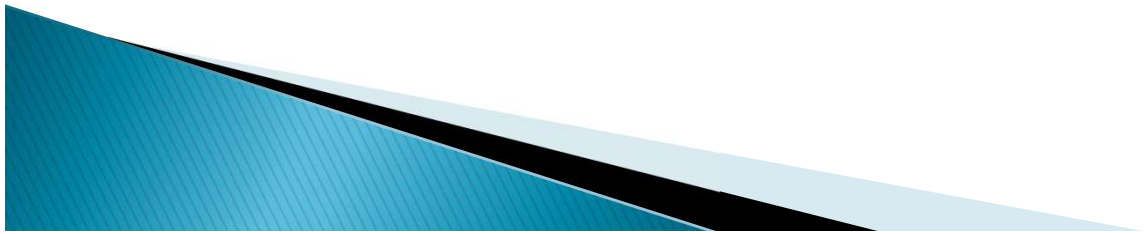
GIT:- vomiting, diarrhea, pain
Blood:- bleeding, neutropenia, thrombocytopenia, hemolysis

- Use is declined



Clopidogrel :- Prodrug
Irreversible inhibitor(75 mg OD)
Safer and better tolerated

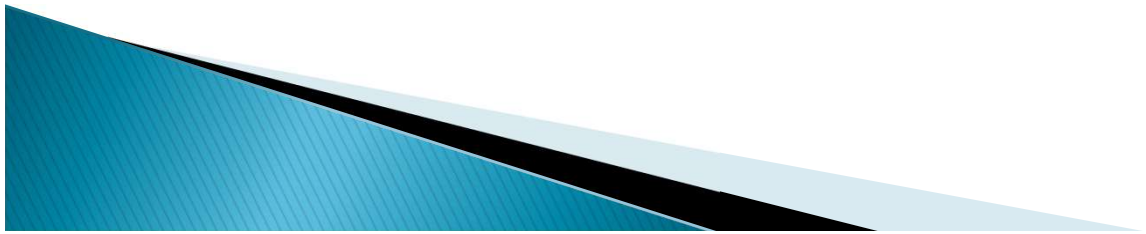
- Slow onset of action
- Metabolism:- CYP2C19 (variability, omeprazole)
- s/e:- GIT:- diarrhea, epigastric pain,
  Blood:- Less serious than ticlopidine



Prasugrel :- Prodrug

Rapid activation (10 mg OD)

- Activated by CYP2C19; No variation
- Better drug for STEMI
- s/e:- more intracranial bleeding (not given in patients with history of stroke and TIAs)

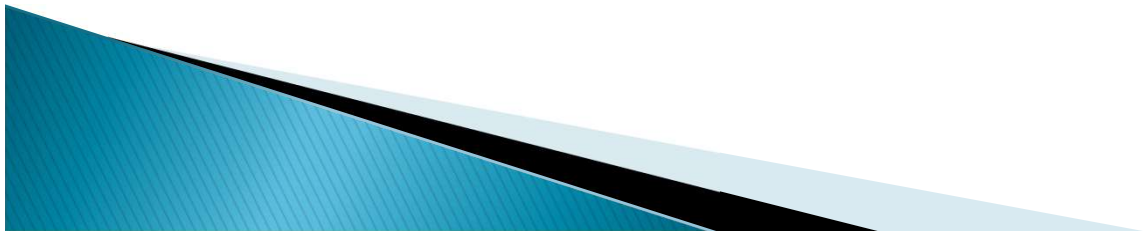


$GPII_b/III_a$ antagonist

Names	Abciximab	Eptifibatide	Tirofiban
Structure	Monoclonal antibody	Cyclic peptide	Nonpeptide
Half-life	Short half life but inhibits for longer duration (24 hr)	Longer half life(2.5 hr) but action last shorter(6-10 hr)	Similar to eptifibatide
Nature	Nonantigenic	Antigenic	
Side effects	-Haemorrhage, -Thrombocytopenia, increase on second time	-Bleeding -Thrombocytopenia -rashes -anaphylaxis	Similar
Cost	Expensive	Similar	Simliar
Therapeutic uses	Useful in both unstable angina and PCI in STEMI	Unstable angina and coronary angioplasty	similar

Vorapaxar

- PAR-1 receptor antagonist
- Prevent further activation
- Can be used as add on therapy
- s/e:- bleeding



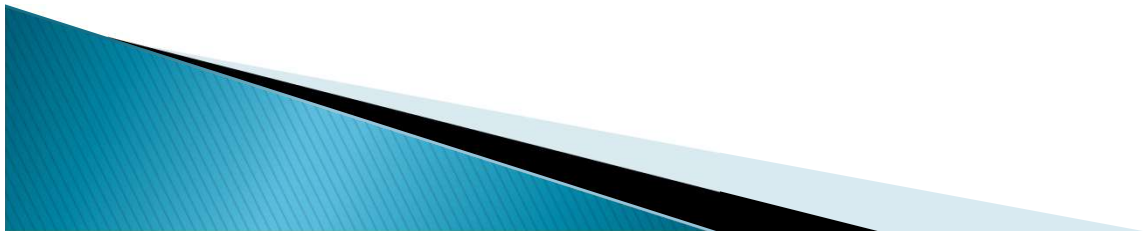
- Therapeutic uses:-combinations preferred

1. CAD (coronary artery disease)
- In post MI patients, 75 to 150 mg/day aspirin

- Not for primary prevention

- Increases chances of cerebral hemorrhage

- Clopidogrel is alternative



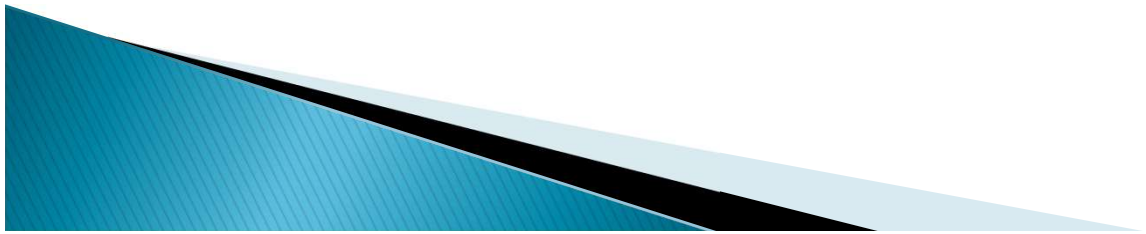
2. Acute Coronary Syndrome:-

- Unstable angina:- aspirin, with or without clopidogrel

- NSTEMI:- aspirin + clopidogrel, for 1 year

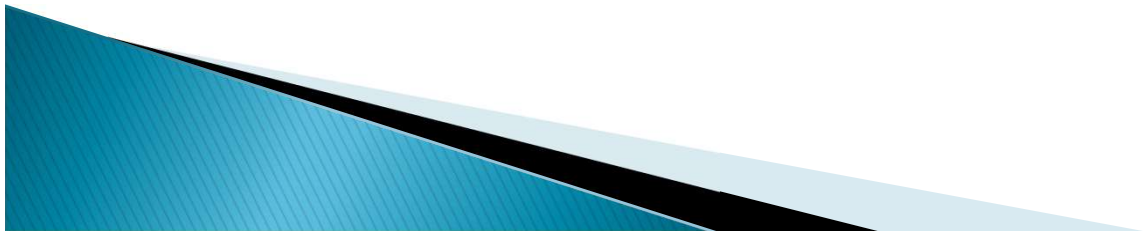
- STEMI:- PCI with or without stent, with aspirin + prasugrel.

  if high risk, aspirin + abciximab/eptifibatide/tirofiban, for 72 hr.



3. Cerebrovascular disease:-

- Do not alter the course of stroke
- Reduce incidence after TIAs or AF
- Stroke prevention :- Aspirin or clopidogrel with dipyridamole

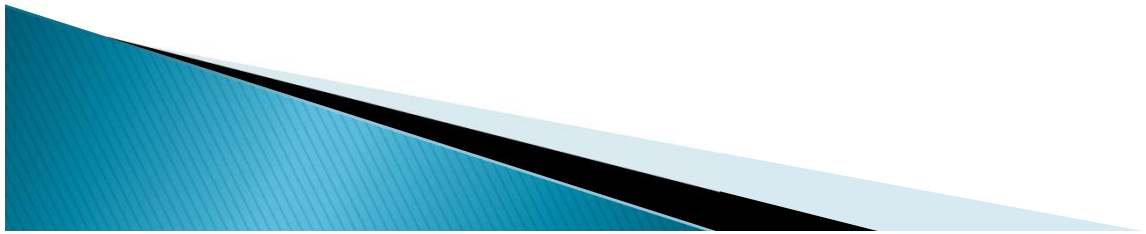


4. Prosthetic heart valve:-

- Mircothrombi and emboli forms

- Aspirin increased risk of bleeding while dipyridamole will not

- Dipyridamole with warfarin given

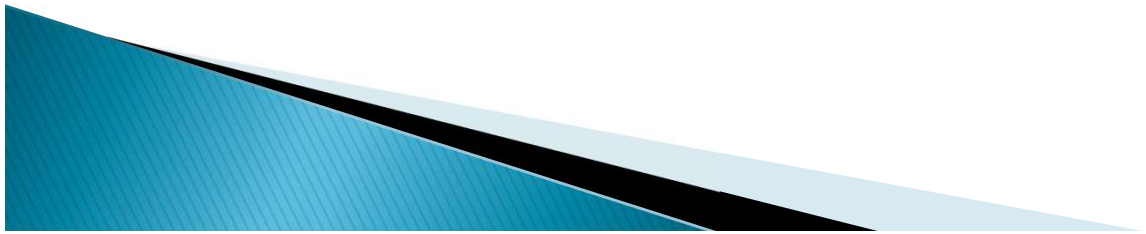


5. Venous thromboembolism:- (DVT/PE)

- Anticoagulants are preferred

6. Peripheral vascular disease:-

- Little improvement by antiplatelets



MCQs

1. All of the following are disadvantages of streptokinase over others, Except:

a) Less possibility of reuse in same patient

b) Serious side effects

c) Non-fibrin specific

d) costly

2. Which one of the following is antifibrinolytic drug?

a) Streptokinase

b) Heparin

c) Aspirin

d) Tranexamic acid

3. What is golden hour during MI attack?

a) It is hour in which you can take patient to hospital

b) It is hour just before death of the patient

c) It is hour during which you can give streptokinase for most beneficial effect

d) It is hour during which you can administer aspirin

4. Which of the following antiplatelet drug is associated with “coronary steal phenomenon”?

a) Aspirin

b) Dipyridamole

c) Clopidogrel

d) Abciximab

5. Which one of the following antiplatelet is preferred in STEMI?

a) Ticlopidine

b) Prasugrel

c) Clopidogrel

d) None of the above

Thank you