Antiplatelet activity and the use of Cilostazol in Symptomatic ICAS

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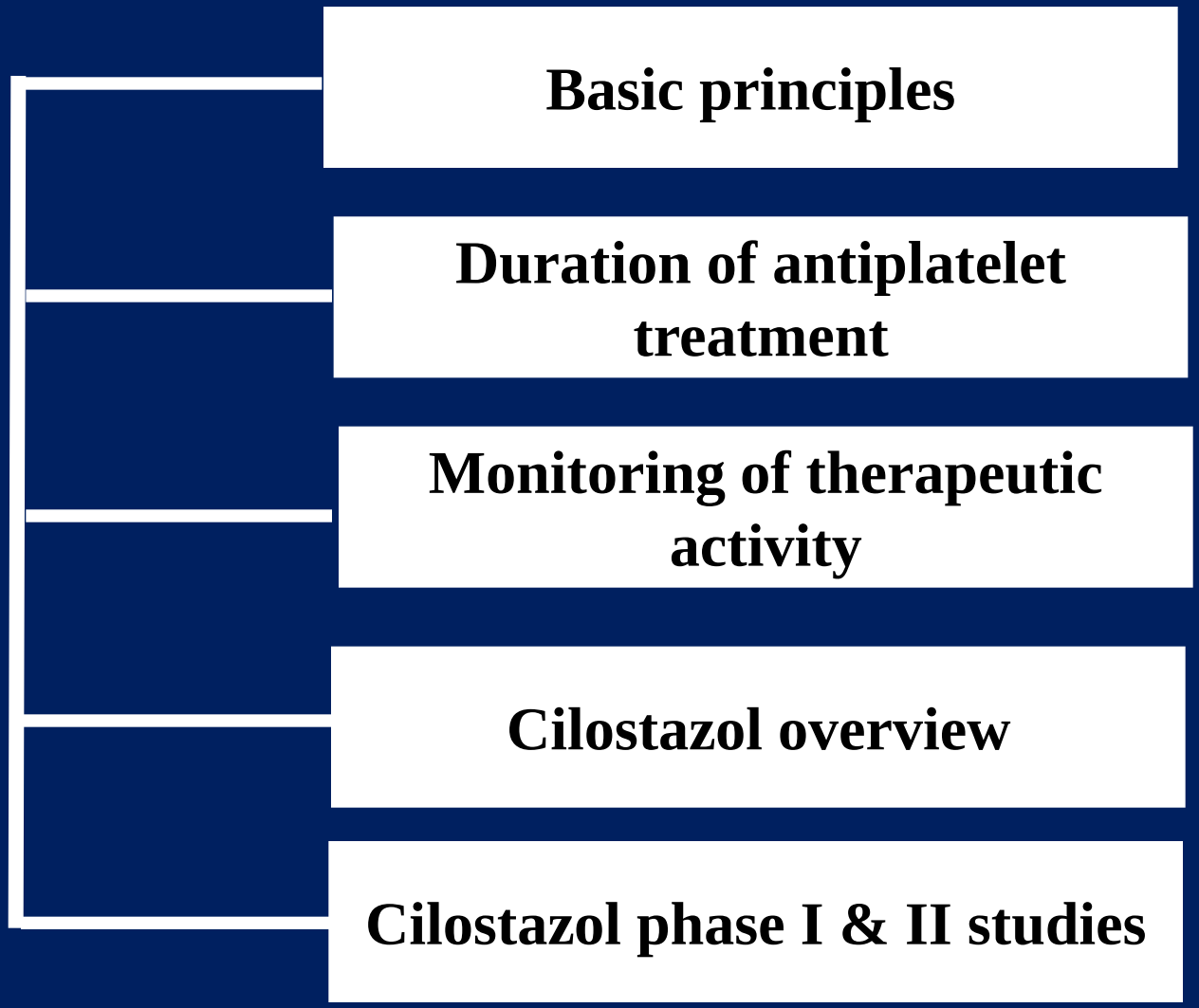
Disclosures

- Consultant –

  GE Healthcare, Microvention, Covidien – not relevant

Outline of presentation



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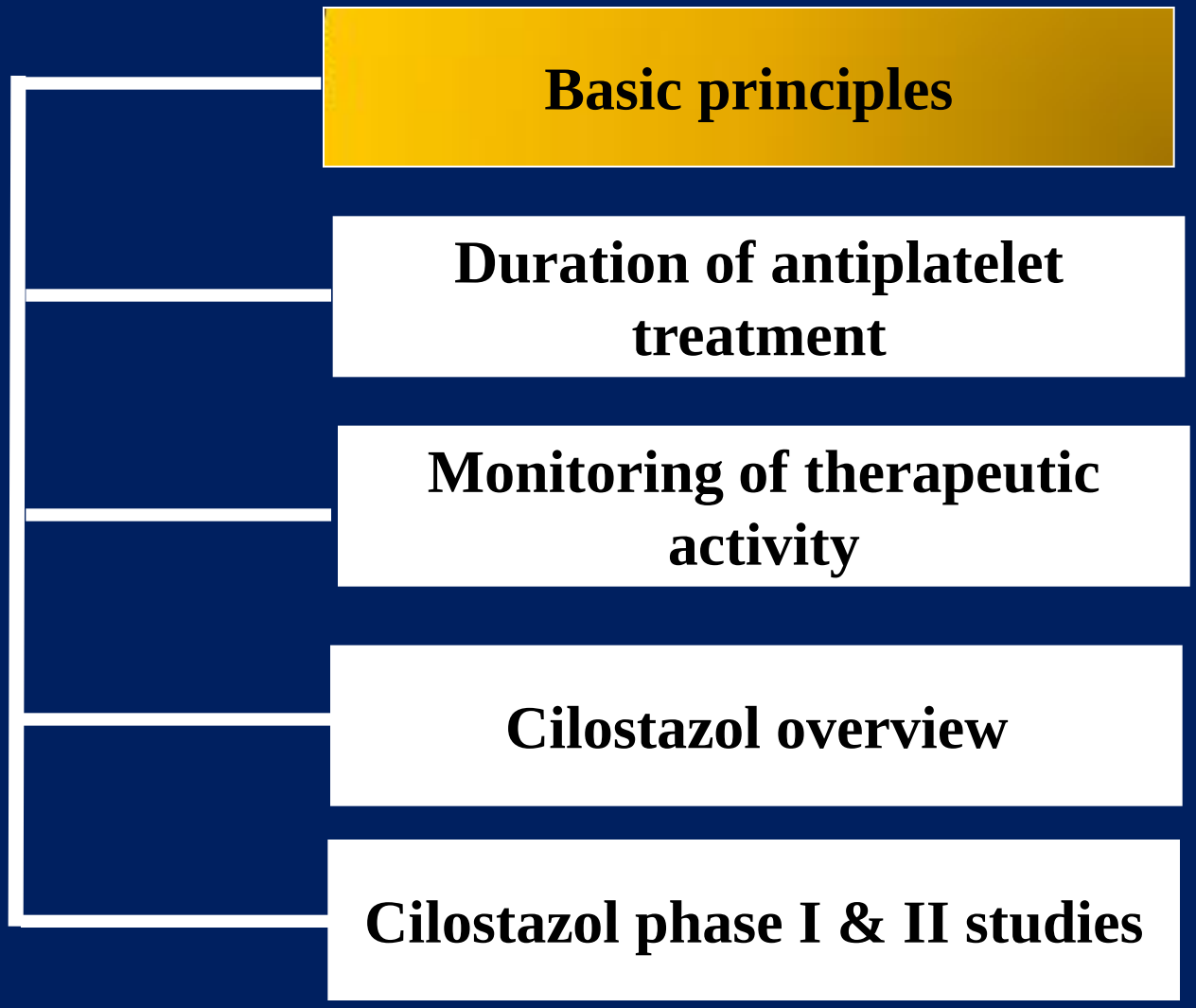
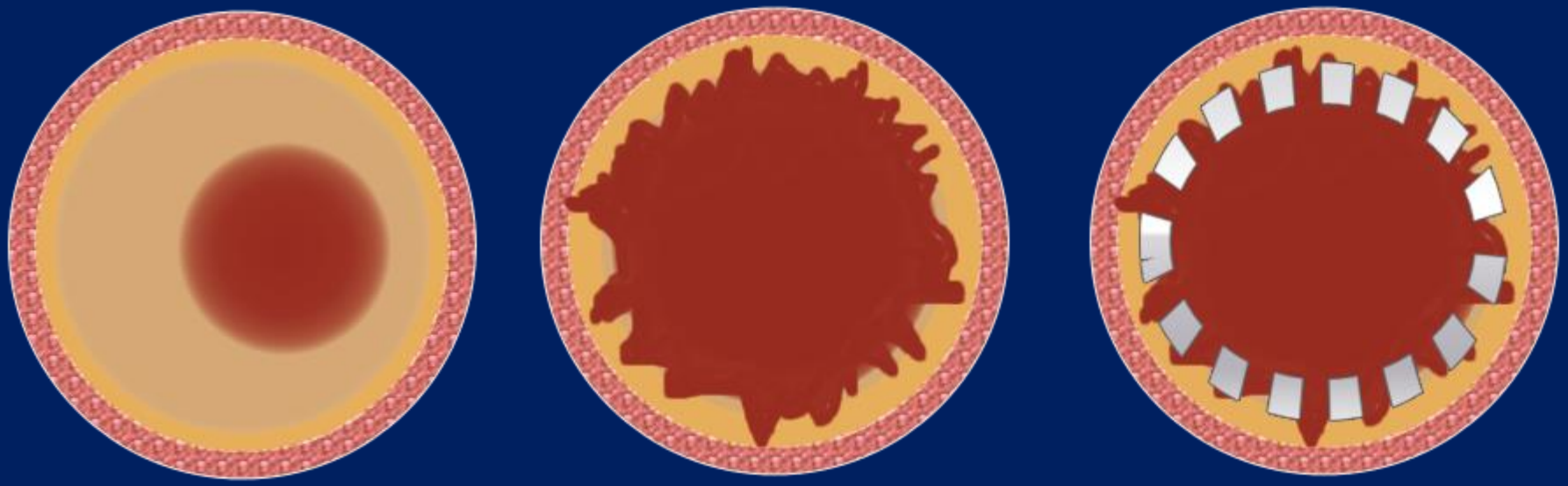


Procedure-related thromboembolic complications

Procedure	Number of patients	Thromboembolic complications	Timing
Carotid angioplasty	455	27 (5.9%)	20 (intraop) 6 (postop)
Carotid stent placement	834	73 (8.8%)	14 (intraop) **29 (postop)**

From: Qureshi: Neurosurgery, Volume 46(6).June 2000.1344-1359

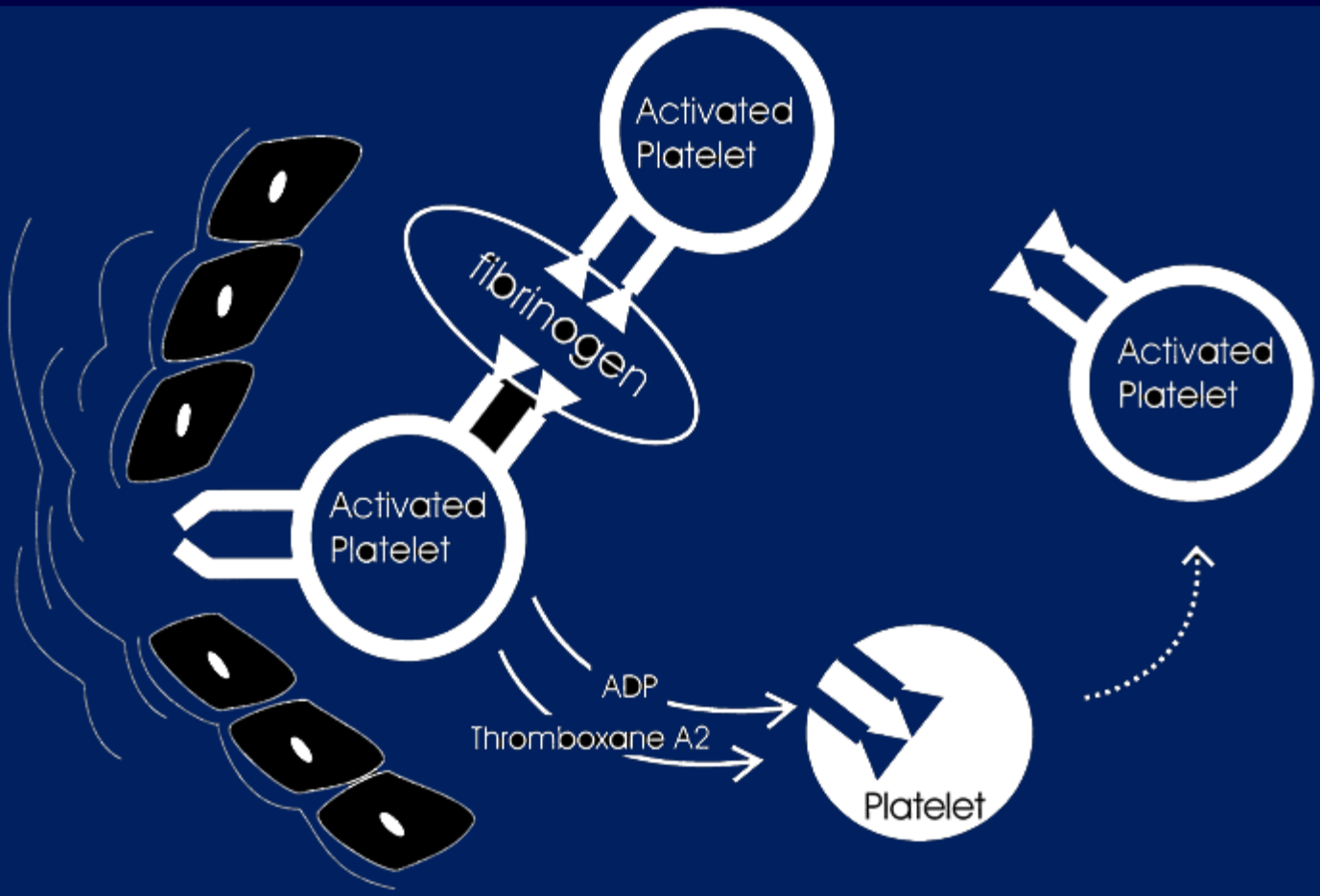
Thrombogenesis during angioplasty and stent placement



Plaque fissuring and dissections after angioplasty

Thrombogenic stent placement

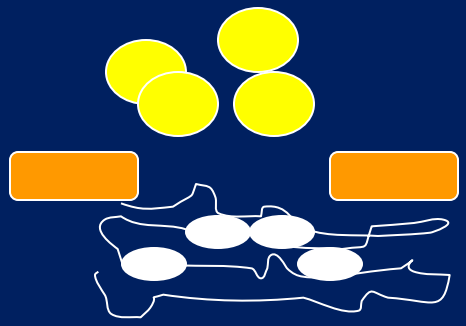
Response to intimal injury



From: Qureshi: Neurosurgery, Volume 46(6).June 2000.1344-1359

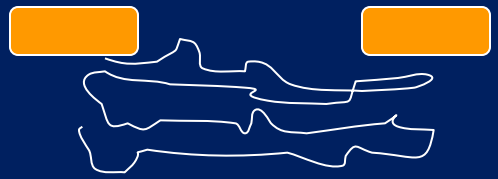
Duration of thrombogenicity after arterial injury

Immediately



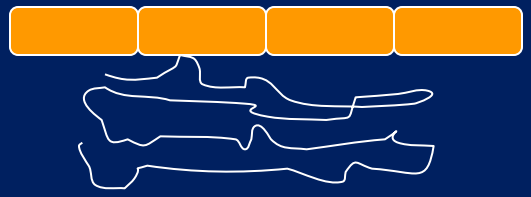
Thrombin expression

72 hours



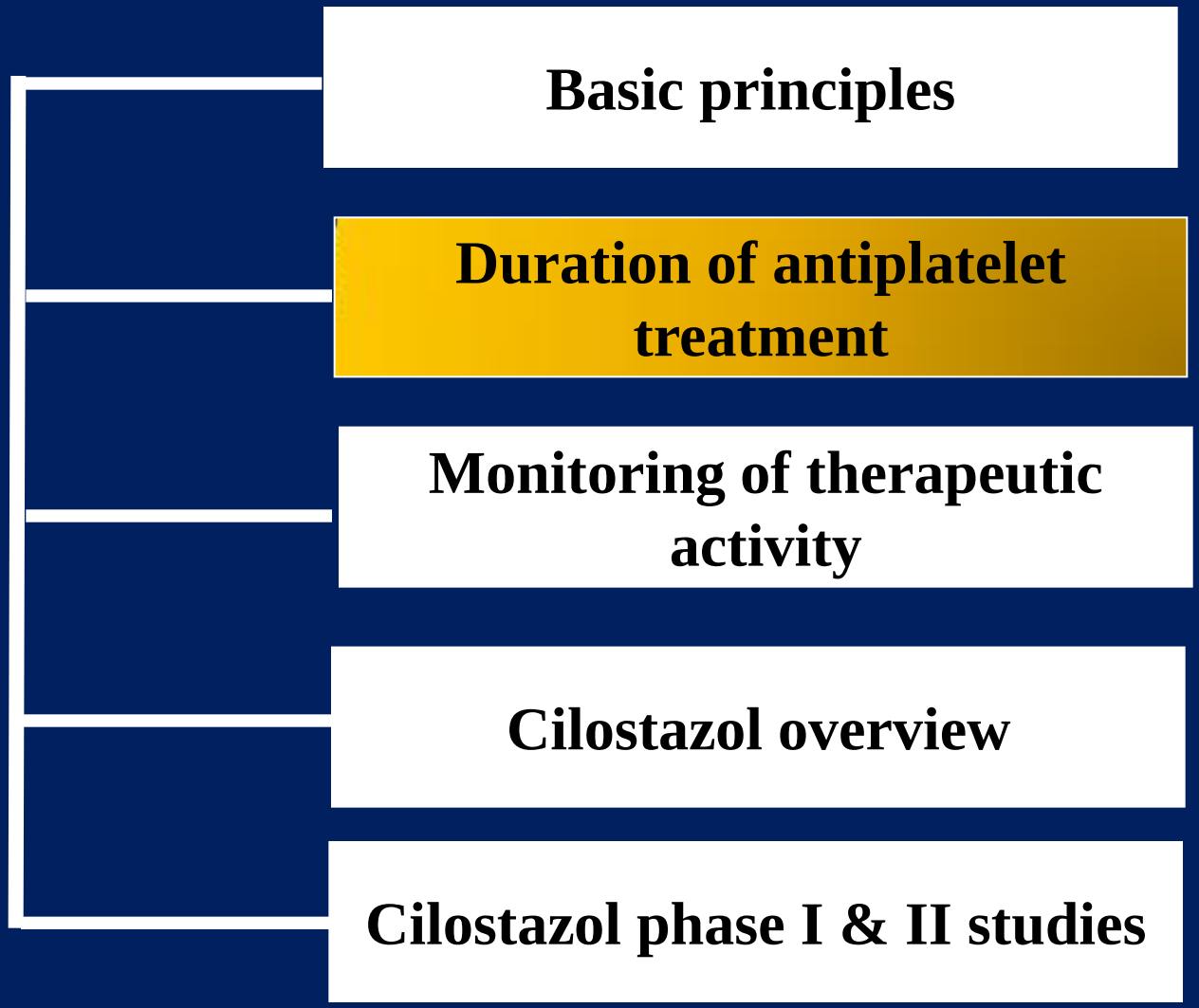
Thrombin expression ends

4 weeks



Re-endothelialization

Outline of presentation

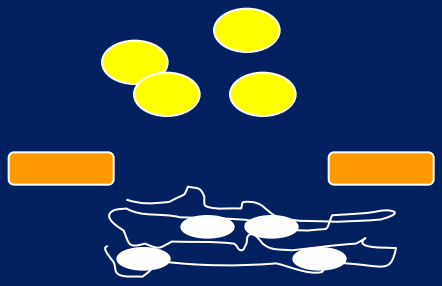


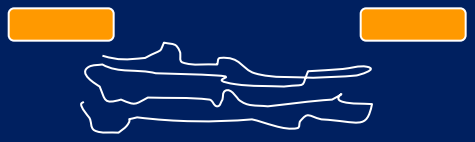
Duration of antiplatelet treatment

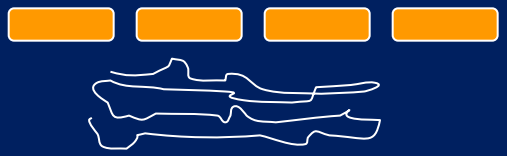
Immediately

72 hours

4 weeks







Thrombin expression

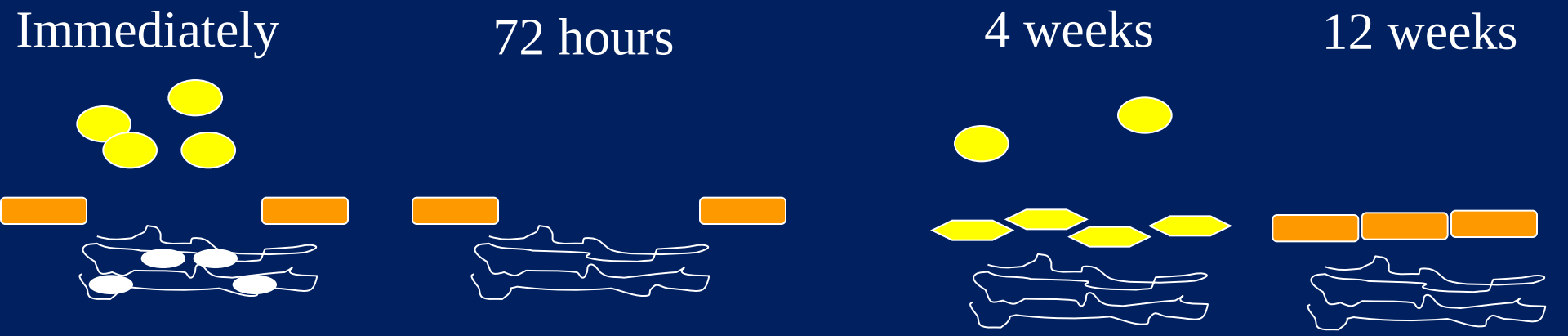
Thrombin expression ends

Re-endothel ialization

Aspirin + Clopidogrel (3 days)

Aspirin + Clopidogrel

Duration of antiplatelet treatment

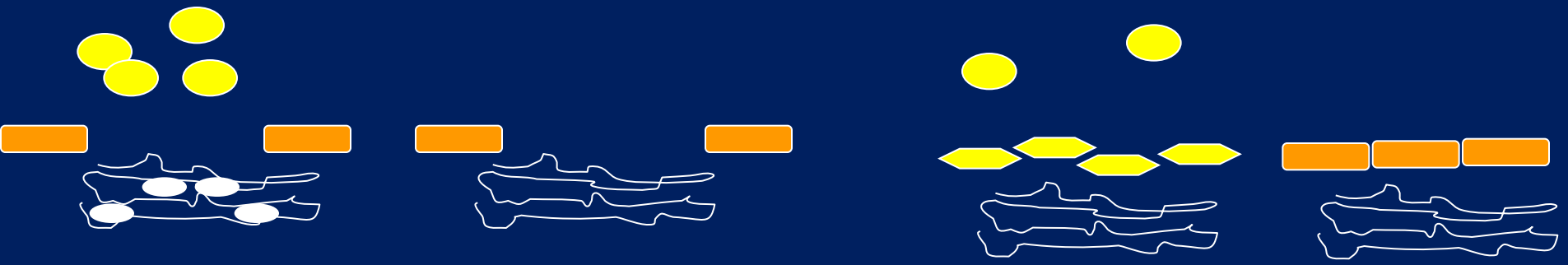


Hassan AE. J Neuroimaging. 2012 Jan;22(1):67-73

Duration of antiplatelet treatment

No major bleeding

Immediately | 72 hours | 4 weeks | 12 weeks

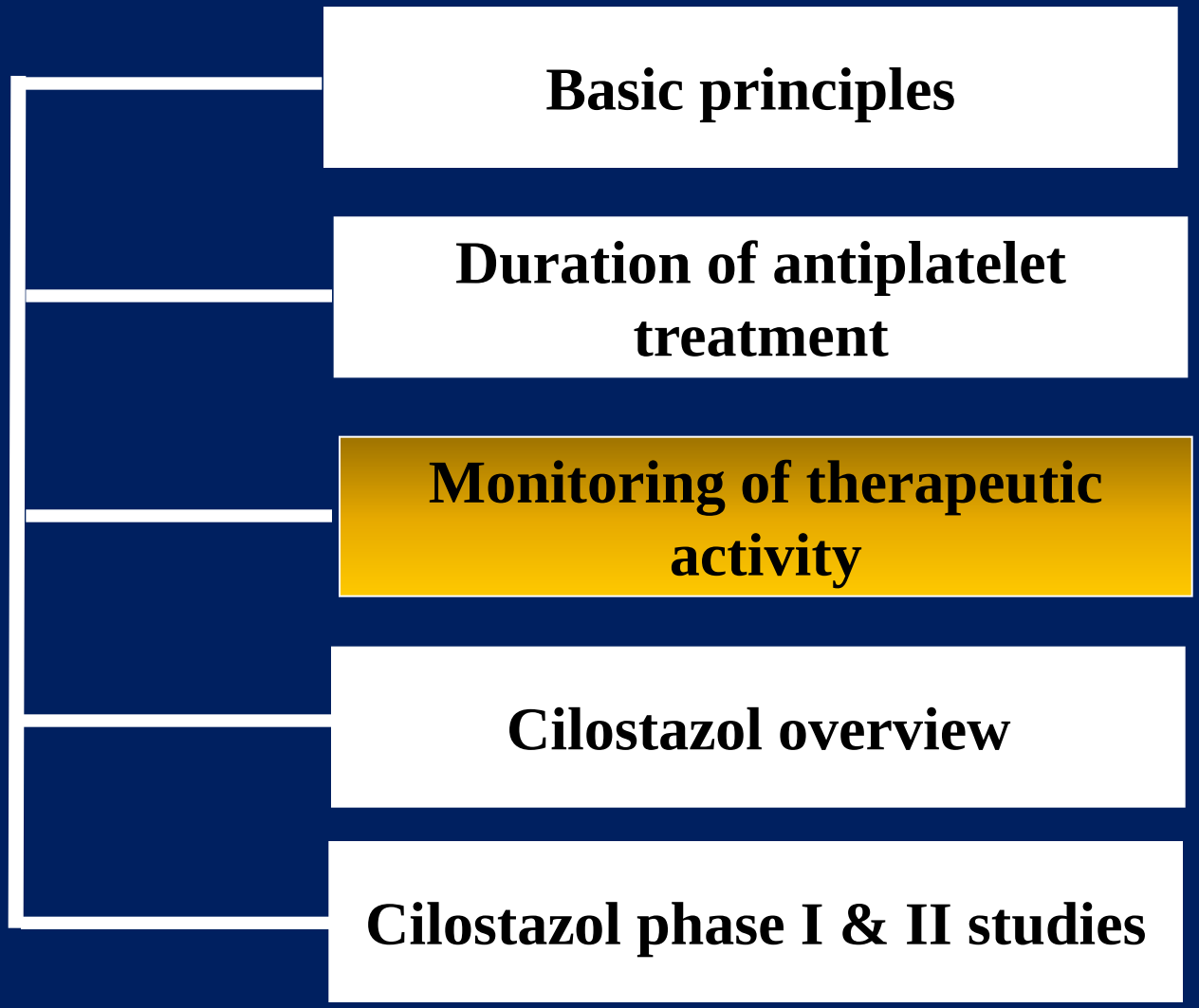


Thrombin expression | **Thrombin expression ends** | **Pseudo-endothelialization** | **Re-endothelialization**

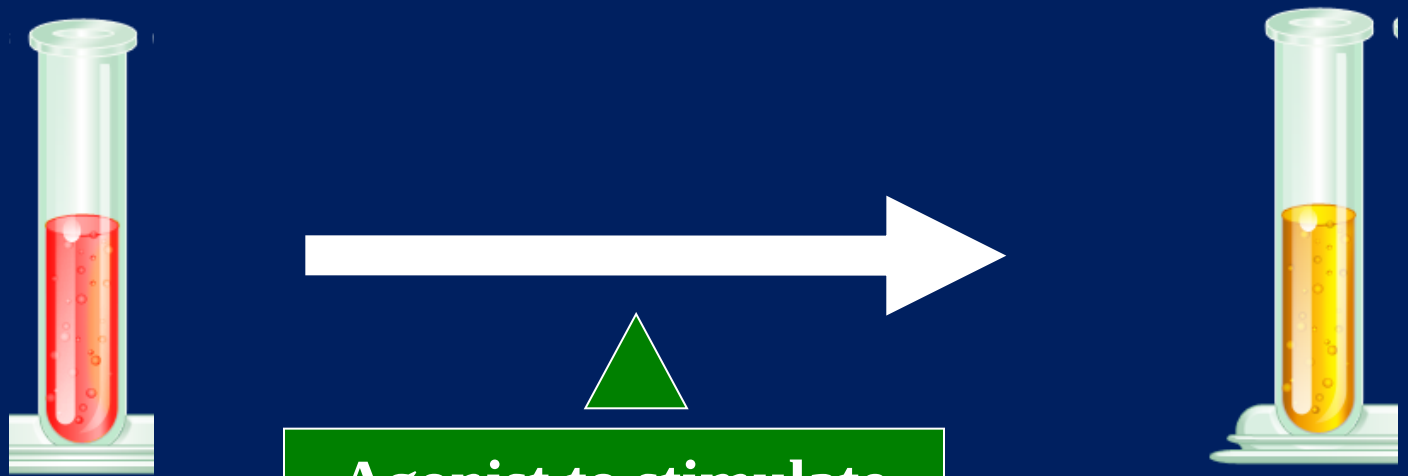
Aspirin + Clopidogrel | **Aspirin + Clopidogrel**

Hassan AE. J Neuroimaging. 2012 Jan;22(1):67-73

Outline of presentation



Monitoring antiplatelet activity



Agonist to stimulate platelet aggregation

Measure aggregation

- **ADP**
- **Collagen**
- **Arachidonic Acid**
- **Epinephrine**
- **Thrombin receptor–activating peptide**

- **Electrical impedance**
- **Light transmission**
- **Closure time**
- **Aggregation on membrane**

Monitoring antiplatelet activity

Instrument	Agonist	Response
Rapid Platelet Function Assay - VerifyNow®	Fibrinogen-coated polystyrene beads	Change in light transmittance
Plateletworks™	Collagen, ADP, and AA	Resistance to electrical current
Platelet Function Analyzer (PFA)-100®	Platelet agonist-coated membrane	Cessation of blood flow through aperture
The Model 700 Whole Blood/Optical Lumi-Aggregometer	ADP, AA, Epinephrine	Change in light transmittance +ATP assay
PAP-8E Platelet Aggregometer	ADP, AA, Epinephrine	Change in light transmittance + Ristocetin CoFactor Assay
Cone and Plate(let) analyzers - IMPACT™ and IMPACT-R™	ADP and TRAP	Platelet adhesion and aggregation on extra cellular matrix

Resistance to antiplatelet agents in patients undergoing PCI

Type	Prevalence	Clinical significance
Aspirin resistance	16%	No clear relationship
Clopidogrel resistance	15%	Related to both thrombo-embolic and bleeding events
Aspirin + Clopidogrel resistance	9%	Related to stent thrombosis

Re: Hussein HM, Emiru T, Georgiadis AL, Qureshi AI. AJNR Am J Neuroradiol. 2012 Mar 15. [Epub ahead of print]

Overcoming resistance to antiplatelet agents in patients undergoing PCI

Strategies	Clinical significance
Clopidogrel 150mg/d maintenance dose	Reduction in total major adverse cardiac
Aspirin + Clopidogrel + Cilostazol	Reduction in total major adverse cardiac

Re: Hussein HM, Emiru T, Georgiadis AL, Qureshi AI. AJNR Am J Neuroradiol. 2012 Mar 15. [Epub ahead of print]

Additional alternatives in overcoming resistance to antiplatelet agents in patients

Strategies	Clinical significance
Cilostazol (phosphodiesterase 3 inhibitor)	Reducing platelet aggregation, improved secondary stroke risk reduction, vasodilatory affect (*not to be used in CHF patients*)
Prasugrel (irreversibly binds P2Y12 ADP receptors)	Significant trend towards increased hemorrhagic complications.
Ticagrelor (reversibly binds P2Y12 ADP receptors)	Reduction in total major adverse cardiac events in acute coronary syndromes

Clopidogrel resistance and the effect of combination cilostazol in patients with ischemic stroke or carotid arterystenting using the VerifyNow P2Y12 Assay.

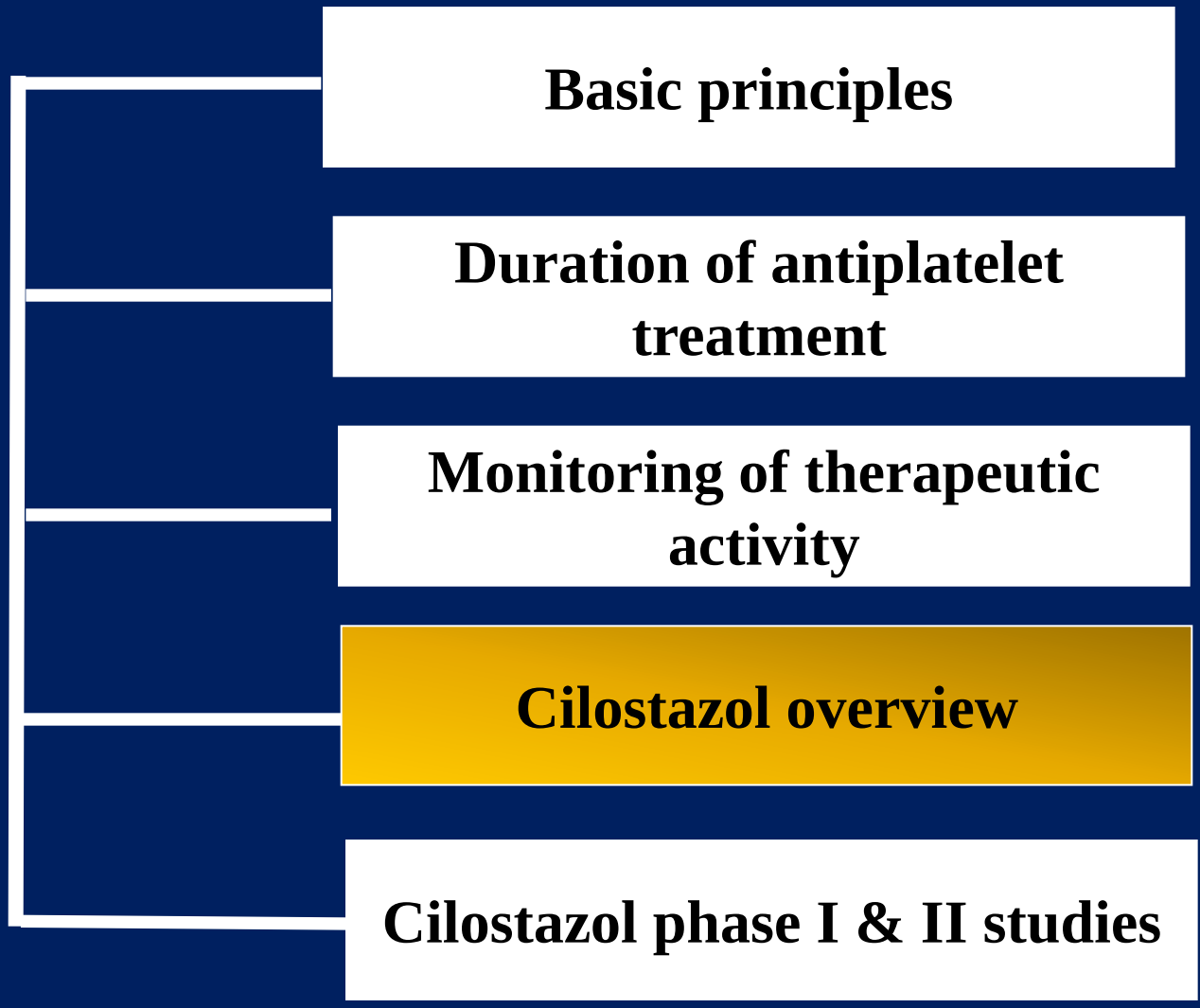
Maruyama H[1], Takeda H, Dembo T, et al.

METHODS:
Measured the ability of 20 μM ADP to aggregate platelets using the VerifyNow P2Y12 Assay.

RESULTS:
Clopidogrel resistance was identified in 18 (29%) of the 62 patients in the clopidogrel only group. None of the patients in the cilostazol combination group had % inhibition of <20%.

CONCLUSION:
Clopidogrel resistance developed in 29% of patients given clopidogrel alone. The addition of cilostazol to clopidogrel may have intensified platelet inhibition.

Outline of presentation



Pharmocokinetics

- Cilostazol, a novel antiplatelet medication unique from aspirin and clopidogrel:
  - selectively inhibits phosphodiesterase III,
  - increases intraplatelet intracellular cyclic 3’-5’- adenosine monophosphate (cAMP) levels,
  - activates protein kinase A and
  - decreases intracellular calcium levels.

Pharmocokinetics

The antiplatelet effect of Cilostazol, a prodrug, begins after it is hepatically metabolized.

It has been demonstrated to have pleitoropic effects:

– reducing smooth muscle proliferation
– reducing intimal hyperplasia
– causing vasodilation.

Current use

- Cilostazol, also known as Pletal, has been approved in the United States since 1999 for the treatment of symptomatic peripheral arterial disease.

Cardiac studies

- In the coronary circulation, cilostazol reduced the incidence of restenosis after balloon angioplasty and bare metal stent placement compared with aspirin and clopidogrel or ticlopidine, but excluded in patients with Class III or IV CHF.

Stroke secondary prevention

- The Cilostazol Stroke Prevention Study (CSP 2) demonstrated that cilostazol (200mg per day) was associated with fewer incidence of hemorrhagic events compared to aspirin (81 mg per day) for the prevention of stroke after an initial ischemic stroke (1.2% versus 0.036%) with similar risk reduction for ischemic events. .

Adverse effects

- Possible side effects of cilostazol use include headache (the most common), diarrhea, abnormal stools, increased heart rate, and palpitations.

- NOT to be used in patients with CHF.

Interactions

- Cilostazol is metabolized by CYP3A4 and CYP2C19, two isoenzymes of the cytochrome P450 system.

- Drugs that inhibit CYP3A4, such as itraconazole,erythromycin, ketoconazole, and diltiazem, are known to interact with cilostazol.

- The proton pump inhibitor omeprazole, a potent inhibitor of CYP2C19, increases exposure to the active metabolite of cilostazol.

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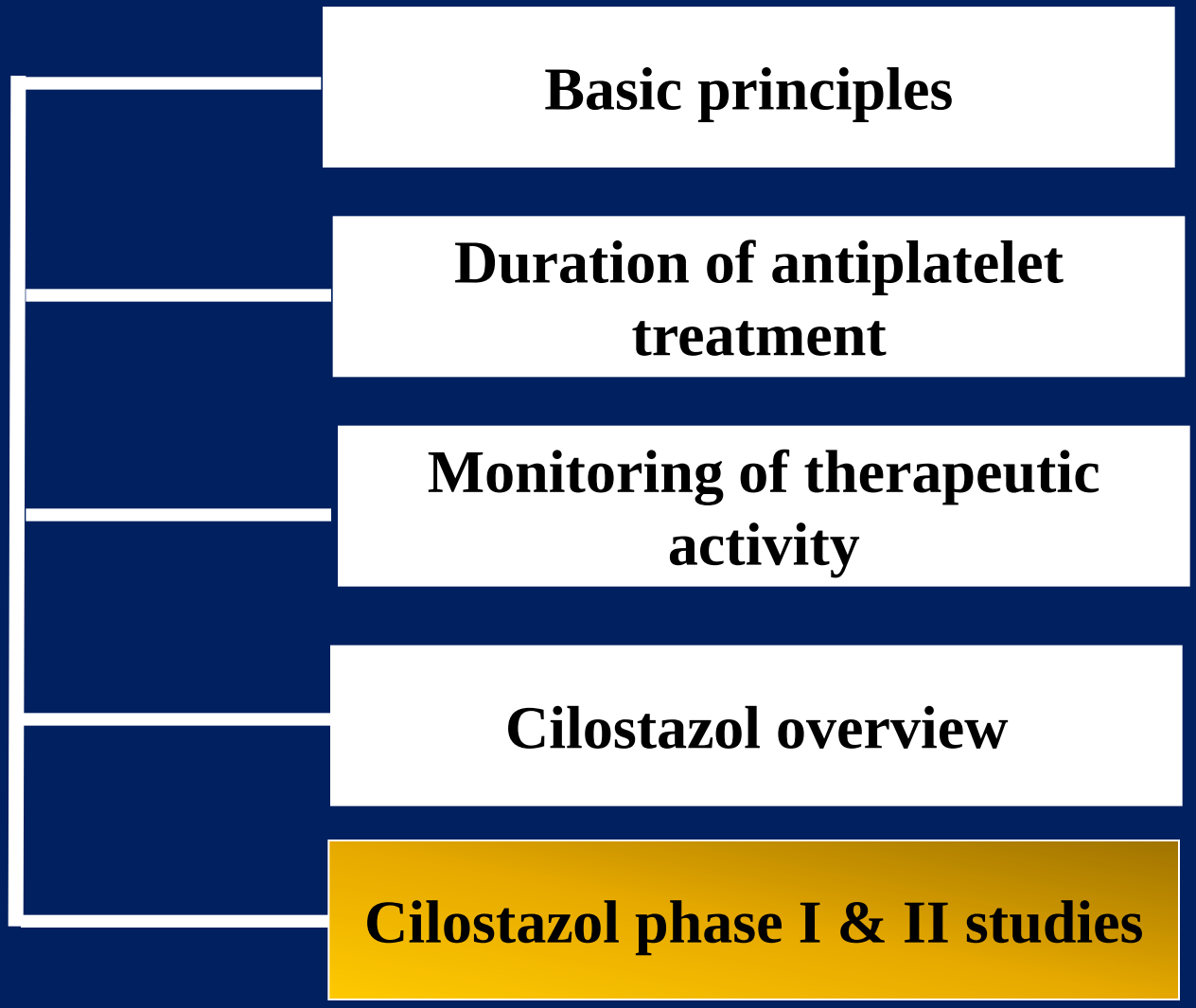

Open-label Phase I Clinical Study to Assess the Safety and Efficacy of Cilostazol in Patients Undergoing Carotid Artery Angioplasty and Stent Placement

Hassan et al. ISC Honololu, HI 2013

- We conducted a Phase I open label, non-randomized single center prospective study. All patients received Aspirin (325 mg/day) and Cilostazol (200 mg/day) for at least 3 days before extra-cranial stent placement.

- The primary efficacy end point was the 30-day composite occurrence of death, stroke, TIA, and unplanned endovascular revascularization procedure.

- The primary safety end point was bleeding (extracranial or intracranial).

Open-label Phase I Clinical Study Results

- A total of 12 patients were enrolled using the study protocol and underwent internal carotid angioplasty and stent placement.

- One patient discontinued Cilostazol after 1st dose, prior to stent placement, secondary to non-specific dizziness.

- Another patient did not follow study protocol and continued antocoagulation dose Enoxoparin as well as Aspirin and Cilostazol resulting in symptomatic intra-cerebral hemorrhage 15 hours following successful stent placement; ultimately leading to withdrawal of care and in-hospital mortality.

- None of the patients that successfully completed the study, and followed protocol had experienced any complications at one month and three month follow up.

IDEALCAST ISC Honololu, HI 2013

Impact of Pre-procedural Antiplatelet Therapy on Vascular Events After Carotid Artery Stenting: Investigation on Devices and Anti-platelet Therapy for Carotid Artery Stenting (IDEALCAST). Yamagami et al.

- A prospective, multicenter, observational study analyzed data from 934 patients underwent elective CAS for > 50 % stenosis in symptomatic or > 80% stenosis in asymptomatic carotid arteries.
- Data on pre-procedural antiplatelet drugs was obtained at patients' enrollment, and all patients were followed for 1 year after the stenting.
- The primary endpoint was the composite of death, any stroke, transient ischemic attack, myocardial infarction, and serious systemic bleeding.

IDEALCAST ISC Honololu, HI 2013

- **Results:** Of the 934 patients (818 men, 72 ± 7 years old):
  - 476 patients were treated with aspirin and clopidogrel (51.0%),
  - 162 with aspirin and cilostazol (17.3%),
  - 62 with clopidogrel and cilostazol (6.6%,),
  - 118 with asprin, clopidogrel and cilostazol (12.6%)
  - 116 with other combinations (12.4%, Other group).

IDEALCAST ISC Honololu, HI 2013

- Incidences of primary endpoint:
  - 12.6% in A+CLP,
  - **5.6% in A+CSZ,**
  - 8.1% in CLP+CSZ,
  - 14.4% in TAPT, and
  - 15.5% in Other group.
  - In multivariate analysis, combination of aspirin and cilostazol was associated with lower risk for primary endpoint compared with aspirin and clopidogrel p=0.004.

IDEALCAST ISC Honololu, HI 2013

- Combination of aspirin and cilostazol can decrease the risk of vascular events or death after CAS.
- A prospective randomized controlled trial is necessary to clarify the effect of pre-procedural antiplatelet therapy on vascular events after CAS.

Cilostazol Phase II

Specific Aims:

- We proposed to conduct a Phase II multi-center prospective randomized study to evaluate the safety, efficacy and clinical outcomes of treatment with Cilostazol and aspirin in patients who have had extracranial carotid stent placement for the duration of one month.

Significance:

- Our phase I data (under review for publication), showed the use of Cilostazol and Aspirin for carotid angioplasty and stent placement appeared to be safe.
-
- Recent studies have shown the safety of Cilostazol and aspirin in extracranial carotid stenting with significant decreased incidence of composite end point (death, stroke, hemorrhage and MI) OR 0.39 p=0.004) compared to aspirin and plavix– (Yamagami et al. IDEALCAST – ISC 2013, Honolulu, HI).

Approach

- All patients will receive aspirin (325 mg/day) and be randomized to cilostazol (200 mg/day) or clopidogrel (75mg/day) for at least 3-5 days before extracranial arterial stenting.

- The two anti-platelet drugs will be continued for 1 month after stenting and then continued on aspirin daily. Patients will have a clinic follow-up at 1 month and routine carotid ultrasound follow up at their 1 and 6 month visits.

Endpoint

- The primary efficacy end point will be the 30-day composite occurrence of death, stroke, transient ischemic attack, and unplanned or urgent surgical intervention, thrombolysis, or subsequent percutaneous revascularization.

- The primary safety end point is bleeding (extracranial or intracranial). Bleeding complications are classified as major (hemoglobin decrease >5 g/dl), minor (hemoglobin decrease 3–5 g/dl), or insignificant.

- The secondary outcome will be the restenosis rate on carotid ultrasound at six months.

Innovation:

- **Alternative, possibly safer (decreased hemorrhages and decreased re-stenosis rates), therapy to current dual antiplatelet treatment in patients undergoing extracranial carotid stent placement.**

- **(interested in other sites)**

Conclusions

- A detailed understanding of pharmacokinetics and resistance of antiplatelet medications is essential in the practice of neuro-endovascular procedures.
- Reducing platelet aggregation, improved secondary stroke risk reduction, and vasodilatory affect with Cilostazol use.
- The use of Cilostazol and Aspirin for carotid angioplasty and stent placement appears to be safe but protocol compliance needs to be emphasized.
- Further studies are required (and on going) to analyze the effectiveness and role of Cilostazol in neurointerventional procedures.

Thank You

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