ANTIPLALETELET THERAPY:
A MOVING TARGET

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FACULTY DISCUSSANT
José A. López, MD
OUTLINE OF TOPICS

• Category of antiplatelet agents (APAs)
• Major clinical trials for established APAs
• Limitations of current APAs
• Strategies for future APAs development
REALLY DUST?
PLATELET FUNCTIONS

Protein receptors:
ADP Rs: P2Y12
Thrombin Rs/PARs
Collagen Rs
TAX2 Rs

Glycoproteins:
GP IIb/IIIa
GP Ib/IX/V
GP VI

Signal pathways:
cAMP/cGMP

Coagulation:
Phospholipid surface

CATEGORY OF ANTIPLATELET AGENTS

- **Thromboxane A2 inhibitor:** Aspirin
- **P2Y12 inhibitors:**
  - Ticlopidine; Clopidogrel; Prasugrel; Ticagrelor; Cangrelor
- **GP IIb/IIIa inhibitors:**
  - Abciximab; Epitifibatide; Tirofiban
- **Thrombin activated inhibitors:**
  - PAR inhibitors (Vorapaxar & Atopaxar)
- **cAMP agonists:** Cilostazole
- **Others:** rarely used (iloprost)
“To prevent a heart attack, take one aspirin every day. Take it out for a jog, then take it to the gym, then take it for a bike ride...”
THE HISTORICAL APA: ASA

• **ISIS-2 Trial:**
  Additive benefit of thrombolysis of low dose ASA in STEMI

• **Antithrombotic Trialists:**
  Low-dose ASA reduces vascular events 1.5% per year
  Reduces stroke 0.46% per year

• **Current recs:**
  Initial loading dose: 150-300 mg followed up by 75-100 mg daily indefinitely
  No benefit for higher dose, but w/ increased GI bleeding

*ISIS-2. Lancet 1988;2:349-60*
# P2Y12 ANTAGONISTS

<table>
<thead>
<tr>
<th>Agents</th>
<th>Mechanism</th>
<th>Administration</th>
<th>Frequency of maint.</th>
<th>Approval</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ticlopidine</td>
<td>Prodrug</td>
<td>Oral</td>
<td>Daily</td>
<td>1991</td>
</tr>
<tr>
<td></td>
<td>Irreversible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>Prodrug</td>
<td>Oral</td>
<td>Daily</td>
<td>1997</td>
</tr>
<tr>
<td></td>
<td>Irreversible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>Prodrug</td>
<td>Oral</td>
<td>Daily</td>
<td>2009</td>
</tr>
<tr>
<td></td>
<td>Irreversible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>Direct-acting</td>
<td>Oral</td>
<td>Twice daily</td>
<td>2011</td>
</tr>
<tr>
<td></td>
<td>Reversible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cangrelor</td>
<td>Direct-acting</td>
<td>IV</td>
<td>Only w/ PCI</td>
<td>2015</td>
</tr>
<tr>
<td></td>
<td>Reversible</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elinogrel</td>
<td>Direct-acting</td>
<td>IV &amp; Oral</td>
<td>Twice daily</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Reversible</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
ADP RECEPTORS AND ANTAGONISTS

Extracellular

P2Y1

Gq

PLC

Ca²⁺

Platelet activation and secretion

P2Y12

Gq

Gi

PLC

cAMP

PKA

Platelet aggregation

Activation of GPIIb/IIIa

Intracellular

ADP

Antagonists

# DUAL APT: CLOPIDOGREL & ASA

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Daily Dose</th>
<th>End Point w/ Results</th>
<th>Safety (↑bleeds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CURE 2001</td>
<td>12562 w/ NSTE-ACS</td>
<td>300 mg then 75 mg</td>
<td>CV death, MI, stroke at 12 mo</td>
<td>1%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CLARITY-TIMI 28 2005</td>
<td>3491 w/ STEMI</td>
<td>300 mg then 75 mg</td>
<td>Occluded infarct-related art., death, MI at 30 d</td>
<td>0.2%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>COMMIT 2005</td>
<td>45852 w/ AMI</td>
<td>75 mg</td>
<td>Death, re-infarction, stroke (all-cause death) at 28 d</td>
<td>0.03%</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CURRENT-OASIS 7 2010</td>
<td>25086 w/ ACS</td>
<td>600/150 vs 300/75</td>
<td>CV death, MI, stroke at 30 d</td>
<td>0.5%</td>
</tr>
</tbody>
</table>

LIMITATIONS OF CLOPIDOGREL

• Modest inhibition of platelet aggregation
• A delayed onset: peak effect after 6-12 h
• Slow offset of action: 3-5 days
• Variability in response: 4-34 % of pts have an inadequate response.
• Prodrug: needs to be transformed into an active metabolite: carriers of CYP2C19*2 have worse clinical outcomes.
• Even w/ a genetic-based strategy, it has been difficult to show the ability to modulate clinical outcome.
**DUAL APT: PRASUGREL & ASA**

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Daily Dose</th>
<th>End Point w/ Results</th>
<th>Safety (↑bleeds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TRITON-TIMI 38 2007</td>
<td>13608 w/ NSTE-ACS or STEMI undergoing PCI</td>
<td>Prasugrel 60/10 vs Clopidogrel 300/75</td>
<td>CV death, MI, stroke at 450 d 9.9% vs 12.1%</td>
<td>0.6% (↑ICH)</td>
</tr>
<tr>
<td>TRILOGY ACS 2012</td>
<td>7243 w/ age &lt; 75 y/o in STEMI or UA w/o PCI</td>
<td>Prasugrel 10 vs Clopidogrel 75</td>
<td>CV death, MI, stroke at 17 mo 13.9% vs 16%</td>
<td>0%</td>
</tr>
</tbody>
</table>

- Relatively contraindicated in patients with previous stroke or TIA d/t higher risk of serious bleeding complications, including ICH.
- Benefit is limited more in pts with ST-segment elevation MI or diabetes.
- Not approved or rec’d for tx of ACS without PCI.

## DUAL APT: TICAGRELOR & ASA

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Daily Dose</th>
<th>End Point w/ Results</th>
<th>Safety (↑bleeds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PLATO 2009</td>
<td>18624 w/ NSTE-ACS or STEMI</td>
<td>Ticagrelor 180/90 BID vs clopidogrel 300/75 QD</td>
<td>CV death, MI, stroke at 12 mo 9.8% vs 11.7%</td>
<td>0.4% (combined 11%)</td>
</tr>
<tr>
<td>PEGASUS S-TIMI 54 2015</td>
<td>21162 w/ MI 1-3 yrs previously</td>
<td>Ticagrelor 90 or 60 BID vs Placebo</td>
<td>CV death, MI, stroke at 33 mo 7.85% vs 7.77% vs 9.04%</td>
<td>2.6% vs 2.3% vs 1.06%</td>
</tr>
</tbody>
</table>

- No benefit in pts enrolled in North America, likely d/t the use of higher dose of ASA: recs it to use with low dose of ASA (<150 mg daily).
- Dyspnea is 2~3-fold higher in Ticagrelor group, not a/w physical, CXR or PFT.
- Gout is 1.8-fold higher in tx group.

## INDICATIONS FOR THE APAs IN ACS

<table>
<thead>
<tr>
<th>Agents</th>
<th>Indications</th>
<th>Duration of tx (yr)</th>
<th>Recs delay for surgery</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA</td>
<td>All types of ACS</td>
<td>Indefinite</td>
<td>No Int.</td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>STEMI tx’d with thrombolysis</td>
<td>1</td>
<td>5 d</td>
</tr>
<tr>
<td></td>
<td>All types of ACS if little access to ticagrelor or prasugrel or if high risk of bleeding (including chronic tx w/ OACT)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Prasugrel</td>
<td>ACS tx’d with PCI (including primary PCI)</td>
<td>1</td>
<td>7 d</td>
</tr>
<tr>
<td></td>
<td>No previous history of stroke or TIA</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>STEMI tx’d with primary PCI</td>
<td>1</td>
<td>3-5 d</td>
</tr>
<tr>
<td></td>
<td>NSTE-ACS regardless irrespective of management (invasive or conservative)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

LIMITATIONS OF NEW P2Y12 ANTAGONISTS

• Increased bleeding
• Do not abolish the residual ischemic risk
• Cost is substantially higher than clopidogrel
• The rapidity of onset of new agents, although quicker than clopidogrel, could be insufficient in some settings such as STEMI

For pts with STEMI, particularly receiving morphine, the APE of ticagrelor and prasugrel could be delayed for several hrs.

• For some high risk pts, stent thrombosis is still an issue!
GPIIb/IIIa IN PLATELET AGGREGATION

Platelet GP IIb/IIIa Receptor in Vascular Injury: Aggregation

Fibrinogen (or von Willebrand factor)

GP IIb/IIIa Antagonists

SINGAL TRANSDUCTION VIA GPIIb/IIIa (α_{IIb}β_{3})

**AGONISTS**

Rs

Gi  Gq

Calcium flux
PKC
Decreased cAMP
Shape change, secretion

Inactive

**Fibrinogen**

PI3-Kinase

Shape change, secretion

**Inside-out**  **Outside-in**

FIBRINOGEN BINDING ON GPIIb/IIIa ($\alpha_{IIb}\beta_3$)

Fibrinogen Binding Site

KQAGDV

RGD

KGD

GPIIb ($\alpha_{IIb}$)

GPIIIa ($\beta_3$)
## PARENTERAL GPIIb/IIIa ANTAGNOISTS

<table>
<thead>
<tr>
<th>Feature</th>
<th>Abciximab</th>
<th>Eptifibatide</th>
<th>Tirofiban</th>
</tr>
</thead>
<tbody>
<tr>
<td>Structure</td>
<td>Fab fragment of chimeric McAb</td>
<td>Synthetic peptide</td>
<td>Small molecule</td>
</tr>
<tr>
<td>Mw</td>
<td>47,615 Da</td>
<td>832 Da</td>
<td>495 Da</td>
</tr>
<tr>
<td>Mechanism</td>
<td>Irreversible</td>
<td>Reversible</td>
<td>Reversible</td>
</tr>
<tr>
<td>α&lt;sub&gt;IIb&lt;/sub&gt;β&lt;sub&gt;3&lt;/sub&gt;</td>
<td>Unknown</td>
<td>KGD</td>
<td>RGD</td>
</tr>
<tr>
<td>Cross-reacting</td>
<td>α&lt;sub&gt;v&lt;/sub&gt;β&lt;sub&gt;3&lt;/sub&gt;; α&lt;sub&gt;M&lt;/sub&gt;β&lt;sub&gt;3&lt;/sub&gt;</td>
<td>No</td>
<td>No</td>
</tr>
<tr>
<td>Half-life</td>
<td>10-30 min</td>
<td>2.5 hrs</td>
<td>2 hrs</td>
</tr>
<tr>
<td>Platelet off-rate</td>
<td>Slow ~90 min</td>
<td>Rapid</td>
<td>Rapid</td>
</tr>
<tr>
<td>Efficacy</td>
<td>&gt;80% inhibition</td>
<td>40~90% on dose</td>
<td>&gt;90%</td>
</tr>
<tr>
<td>Elimination</td>
<td>Senescent plts</td>
<td>~50% renal</td>
<td>Mostly renal</td>
</tr>
<tr>
<td>FDA-approved indications</td>
<td>PCI, refractory UA</td>
<td>PCI, ACS</td>
<td>ACS</td>
</tr>
</tbody>
</table>

### EFFICACY OF GPIIb/IIIa ANTAGNOISTS

<table>
<thead>
<tr>
<th>Outcome Events Rate (%)</th>
<th>Placebo</th>
<th>Active</th>
<th>Odds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-mo composite</td>
<td>12</td>
<td>8</td>
<td>0.64</td>
<td>0.58-0.70</td>
</tr>
<tr>
<td>Abciximab</td>
<td>13</td>
<td>7</td>
<td>0.53</td>
<td>0.47-0.61</td>
</tr>
<tr>
<td>Small molecules</td>
<td>11</td>
<td>9</td>
<td>0.78</td>
<td>0.68-0.89</td>
</tr>
<tr>
<td>6-mo composite</td>
<td>25</td>
<td>21</td>
<td>0.82</td>
<td>0.75-0.89</td>
</tr>
<tr>
<td>Abciximab</td>
<td>27</td>
<td>22</td>
<td>0.83</td>
<td>0.76-0.91</td>
</tr>
<tr>
<td>Small molecules</td>
<td>18</td>
<td>14</td>
<td>0.76</td>
<td>0.60-0.96</td>
</tr>
<tr>
<td>1-yr composite</td>
<td>25</td>
<td>18</td>
<td>0.75</td>
<td>0.67-0.83</td>
</tr>
</tbody>
</table>

Pooled analysis of 10 placebo-controlled trials in PCI

Data are from Antiplatelet Trialists’ Collaboration.

Also demonstrated survival benefit.
# SAFETY OF GPIIb/IIIa ANTAGNOISTS

<table>
<thead>
<tr>
<th>Outcome Events Rate (%)</th>
<th>Placebo</th>
<th>Active</th>
<th>Adds Ratio</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major hemorrhage</td>
<td>3</td>
<td>4</td>
<td>1.29</td>
<td>1.12-1.49</td>
</tr>
<tr>
<td>Intracranial</td>
<td>0.12</td>
<td>0.12</td>
<td>--</td>
<td>--</td>
</tr>
<tr>
<td>Thrombocytopenia</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;100k</td>
<td>2</td>
<td>3</td>
<td>1.50</td>
<td>1.19-1.90</td>
</tr>
<tr>
<td>&lt;50k</td>
<td>0.2</td>
<td>0.6</td>
<td>2.39</td>
<td>1.28-4.48</td>
</tr>
</tbody>
</table>

Bleeding and thrombocytopenia are issues!
FEATURES OF GPIIb/IIIa ANTAGNOISTS

Abciximab

- Higher binding affinity to GPIIb/IIIa than soluble Fgn, and can replace bound Fgn from plts: de-thrombosis
- May affect the interaction of plts w/ endothelial cells and leukocytes
- Redistributes among plts in minutes to hours
- The continued separation of mortality events between treatment groups at 7 yrs is striking
- Trial in ischemic stroke and cancer patients as future directions?

For all three agents

- High cost
- Bleeding issues
- Trials in ACS has been disappointing
- Oral agents d/c’d b/o lack of efficacy or increased bleeding and mortality
PAR-1 ANTAGONIST

Cell Membrane

Thrombin

PAR-1 Antagonists

PAR  Coupled G-Protein

GDP

COOH

Activated G-Protein

GDP  GTP

Activated G-Protein

Cell Signaling

Shape Change  ADP Secretion  Aggregation

Plt Activation
PAR-1 ANTAGONISTS

Atopaxar
- Inhibits TRAP-induced plt activation
- Suspended d/t safety concerns: abnormal LFT and prolongs QTc

Vorapaxar
- Competitive PAR-1 antagonist, abolishing thrombin-mediated plt activation w/o affecting Fgn cleavage and fibrin formation.
- Potent plt inhibitor but leaves coagulation cascade and bleeding time intact
- Oral administration, rapidly absorbed with high bioavailability (>90%)
- Dissociation $T_{1/2}$: 20 hrs
- Plasma $T_{1/2}$: 159-311 hrs
- Two metabolites: M19 & M20, with M20 is pharmacologically equipotent
EARLY CLINICAL TRIALS OF VORAPAXAR

Phase I
- A single dose (20 mg or 40 mg orally) in volunteers results in potent inhibition (>80%) of TRAP-induced plt aggregation
- 2.5 mg daily following 1st dose achieve >80% plt inhibition
- No dose adjustment in mild to moderate hepatic impairment but should avoid in severe hepatic impairment

Phase II: TRA-PCI
- No increased bleeding based on TIMI scale used with standard APT
- No increased bleeding for pts underwent CABG
- Trend in reduction of major adverse CV events, particularly MI
- Significant reduction of fatal MI rates w/ similar TIMI bleeding events

PHASE III: TRA-CER

- Recruited 12,944 pts w/ NSE-ACS
- In combination with standard APT: ASA +/- Clopidogrel
- Vorapaxar: 40 mg then 2.5 mg daily
- Duration: one yr
- End points:
  - Primary: 0.92
  - Secondary: 0.89
  - MI: 0.88
  - Stroke: 0.93
  - Death from CV or MI: 0.90
  - Death from any causes: 1.05
  - Gusto M/S bleeding: 1.35
  - TIMI bleeding: 1.43
  - Intracranial hemorrhage: 3.39

PHASE III: TRA 2P-TIMI 50

- Recruited 29,449 pts with h/o MI, ischemic stroke and PAD
- Assess the efficacy and safety of Vorapaxar (2.5 mg QD) in the secondary prevention of atherothrombotic diz.
- End points:
  - Primary: HR 0.87
  - Secondary: HR 0.88
  - CV death or MI: HR 0.86
  - MI: HR 0.83
  - Death from other: HR 0.95
  - GUSTO bleeding: HR 1.66
  - TIMI bleeding: HR 1.46
  - TIMI major bleeding$: HR 1.46
  - Intracranial hemorrhage: HR 1.94
  - Fatal bleeding: HR 1.46

SUB-ANALYSIS OF PHASE III TRIALS

- **MI**
  In TRA-CER trial, Vorapaxar reduces type I MI by 17%, and any type by 12%
  In TRA2P-TIMI 50 trial, it obtains similar results, and a significant reduction in MI rates was also observed in diabetic pts, by 25%

- **Stent thrombosis:**
  May reduce ST occurring >1 yr after stent placement in one trial

- **Stroke**
  In stable pts w/ AVD and no h/o stroke or TIA, vorapaxar reduces the risk of stroke (HR 0.67, 95% CI 0.52-0.87)

- **PVD**
  Reduces the No. of pts needed hospitalization (2.3% vs 3.9%) and peripheral artery revascularization (18.4% vs 22.2%).

FDA approved Vorapaxar in pts with previous history of MI and in pts with PAD.
Qs REMAINED

- Definite clinical benefit: need more studies
- Its benefit with other APAs?
- Bleeding issues
- Increased risk for intracranial hemorrhage
- Recurrent ischemia
- Limited clinical indications
FUTURE DIRECTIONS
### NEW P2Y12 ANTAGONIST – IV CANGRELOLR

<table>
<thead>
<tr>
<th>Trial</th>
<th>Population</th>
<th>Daily Dose</th>
<th>End Point w/ Results</th>
<th>Safety (↑bleeds)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CHAMPION 2009</td>
<td>5362 w/ PCI</td>
<td>Cangrelor vs placebo f/u clopidogrel 600</td>
<td>Death, MI, ischemia and ST at 48 h 7.0% vs 8.0% (ST 0.6 vs 0.2, Death 0.7 vs 0.2)</td>
<td>5.5% vs 3.5%</td>
</tr>
<tr>
<td>CHAMPION PLATFORM 2009</td>
<td>8816 w/ PCI</td>
<td>Cangrelor vs clopidogrel 600</td>
<td>Death, MI, ischemia at 48h 7.5% vs 7.1%</td>
<td>3.6% vs 2.9%</td>
</tr>
<tr>
<td>CHAMPION PHOENIX 2013</td>
<td>11145 w/ urgent or elective PCI</td>
<td>Cangrelor vs clopidogrel 600</td>
<td>Death, MI, ischemia and ST at 48 h 4.7% vs 5.9%</td>
<td>Low in both groups</td>
</tr>
</tbody>
</table>

- FDA approved Cangrelor in June 2015 in pts undergoing PCI who has not been tx’d with P2Y12 inhibitor or anti GPIIb/IIIa inhibitor.
- Dyspnea is 4-fold in tx group: 1.2% vs 0.3%.
- Increased bleeding is still a potential safety issue.

PAR-1 ANTAGONIST MODIFICATION

- Vorapaxar analog (SCH 602539) with increased aqueous solubility 20-fold with comparable safety.
- In animal model, it showed additive anti-platelet effects when co-administered with the P2Y12 antagonist Cangrelor.
- Structural modifications of the vorapaxar tricyclic ring lead to the synthesis of nor-seco analogs with high ex vivo anti-platelet aggregation efficacy and an excellent pharmacokinetic profile in animals.

Bleeding risk?

OUTSIDE-IN AND INSIDE-OUT

AGONISTS

Rs

Gi Gq

Calcium flux
PKC
Decreased cAMP
Shape change, secretion

Inside-out

Talin

Outside-in

Fibrinogen

α₁₁b β₃

Gα₁₃

Inactive

PI3-Kinase

TALIN AND $\Gamma_3$ BINDING SITES ON $\beta_3$

<table>
<thead>
<tr>
<th>Binding sites:</th>
<th>Talin</th>
<th>Talin</th>
<th>Kindlins</th>
<th>c-Src</th>
</tr>
</thead>
<tbody>
<tr>
<td>$\beta_3$</td>
<td>--WKLLITIHDRKEFAKFP EEE RARAKWDTANPLYKEATSTFTNITYRGT</td>
<td>715</td>
<td>741</td>
<td>759</td>
</tr>
<tr>
<td>$\beta_1A$</td>
<td>751WKLLMIHHRERFAKFP EKE KMNAKWDTGENPILYKSAVTTVNPKYEGK</td>
<td>728</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_1D$</td>
<td>751WKLLMIHHRERFAKFP EKE KMNAKWDTGENPILYKSPINNFKNPNYGRKAGL</td>
<td>741</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_2$</td>
<td>723WKLALIHLSDLREYRRP EKE KLKSQWNND-NPLPKSATTTVMPKFAES</td>
<td>759</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_6$</td>
<td>730WKLLVFSHHRKVEAKFP EAE RSKAKWQTYGTPNPLYRGSTSKFNVTYKHSREKQKVDLSTD</td>
<td>746</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_7$</td>
<td>746YRLSVEIYDREYRSRF EKE QQQLNWKQDSNPLYKSAITTTINPRFQEADSPTL</td>
<td>759</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_5$</td>
<td>742WKLLVTHHHRERFAKFP QSE RSRARYEMASNPLYRKPISTHTVDFTPNNKNSYNGTV</td>
<td>759</td>
<td></td>
<td></td>
</tr>
<tr>
<td>$\beta_8$</td>
<td>703IQVLQWNSNKIKSSSVDYRVSAKLDKILQSVCTRAYRREKPEEEKMDISKLNAHAEHTFCNF</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Synthesized peptides:

- **mP5**: EEERAA
- **mP6**: FEEERAA
- **mP13**: KFEEERARAKWDT
- **mP6Scr**: ERAFEE

mP₆ INHIBITS OUTSIDE-IN SIGNAL

- mP₆ selectively affects the outside-in signal, but mP₁₃ affect both the inside-out and outside-in signal

Ga$_{13}$ INHIBITION AND THROMBOSIS & BLEEDING

CONCLUSIONS

• APT improves cardiovascular outcomes after ACS, particularly with the approval of new agents.

• The combination of aspirin with a potent P2Y12 antagonist (prasugrel or ticagrelor) is recommended in most pts w/ ACS.

• PAR-1 antagonist Vorapaxar is another option in pts w/ previous MI, or in pts w/ PAD in combination with cilostazole.

• Cangrelor could be used in pts undergoing PCI, but further studies needed to compare it to current anti-GPIIb/IIIa inhibitors.

• Bleeding risk remains an issue, and should be considered in the choice of agents in addition to pt factors.

• Data from trials of novel agents, strategies, combinations of drugs, will continue to emerge to help to refine personalized therapy.
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