Evolving Antithrombotic Strategies for Patients with DM and CAD

Dominick J. Angiolillo, MD, PhD
Professor of Medicine
Medical Director - Cardiovascular Research
Program Director – Interventional Cardiology Fellowship
University of Florida College of Medicine - Jacksonville
Presenter Disclosure Information

Name: Dominick J Angiolillo

Within the past 12 months, the presenter or their spouse/partner have had a financial interest/arrangement or affiliation with the organization listed below.

Received payment as an individual for:
a) Consulting fee or honorarium from Amgen, Bayer, Chiesi, Sanofi, Eli Lilly, Daiichi-Sankyo, The Medicines Company, AstraZeneca, Merck, Abbott Vascular, Pfizer, and PLx Pharma;
b) Honorarium for participation in review activities (DSMB member) from CeloNova, Johnson & Johnson, St. Jude, and Sunovion.
c) Honorarium from the American Board of Internal Medicine (Interventional Cardiology Subspecialty Exam Writing Committee Member)

Institutional payments for:
b) Grant in gift: Spartan; Scott R. MacKenzie Foundation
c) Federal agency: NIH
Cumulative Incidence of All-Cause Mortality Through 1 Year After ACS

Estimated Growth in Type 2 Diabetes and US Population From 2000-2050

Mechanisms Involved in Platelet Dysfunction in Diabetes Mellitus

Hyperglycemia
- Increased P-selectin expression
- Osmotic effect
- Activation of PKC
- Decreased membrane fluidity by glycation of surface proteins

Deficient Insulin Action
- Impaired response to NO and PGI_2
- IRS-dependent factors: Increased intracellular Ca++

Associated Metabolic Conditions
- Obesity
- Dyslipidemia
- Inflammation

Other Cellular Abnormalities
- Increased platelet turnover
- Increased intracellular Ca++
- Upregulation of P2Y_{12} signaling
- Oxidative stress
- Increased P-selectin and GP expression

Endothelial Cells

H_2O

ACP=adenosine disphosphate; GP=glycoprotein; IRS-1=insulin receptor substrate-1; NO=nitric oxide; PGI_2=prostacyclin; PKC=protein kinase C; TF=tissue factor.

Timeline of landmark studies of antithrombotic therapy and proportion of patients with diabetes mellitus.

Capodanno D, Angiolillo DJ. Circulation. 2020; 142:2172-2188.
DON'T BRING A KNIFE TO A GUNFIGHT
Influence of Diabetes Mellitus on Clopidogrel-induced Antiplatelet Effects

Acute Phase of Treatment

Long-term Phase of Treatment

- Responders (Platelet inhibition >30%)
  - DM: 56%
  - No-DM: 78%

- Low responders (Platelet inhibition 10-29%)
  - DM: 14%
  - No-DM: 8%

- Non-responders (Platelet inhibition <10%)
  - DM: 38%
  - No-DM: 6%

24 hrs post 300 mg LD

$P = 0.04$

ADP 20μM

DM: $P = 0.002$

No DM: $P < 0.0001$

ADP 6μM

DM

No DM


Among DM patients, impaired P2Y12 inhibition mediated by clopidogrel is largely attributable to attenuation of clopidogrel's PK profile, characterized by lower plasma levels of active metabolite compared with non-DM patients and only modestly attributed to upregulation of the P2Y12 signaling pathway.
Efficacy of Potent P2Y12 inhibitors in Reducing Adverse Outcomes in Diabetes Mellitus From Large-Scale Clinical Trials

<table>
<thead>
<tr>
<th>Study</th>
<th>% of Events</th>
<th>Hazard Ratio (95% confidence interval)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard</td>
<td>New Drug/Approach</td>
</tr>
<tr>
<td>TRITON-TIMI 38</td>
<td>17.0</td>
<td>12.2</td>
</tr>
<tr>
<td>(prasugrel)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PLATO</td>
<td>16.2</td>
<td>14.1</td>
</tr>
<tr>
<td>(ticagrelor)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

CURRENT-OASIS= Clopidogrel Optimal Loading Dose Usage to Reduce Recurrent Events Optimal Antiplatelet Strategy for Interventions; PCI=percutaneous intervention; PLATO= A Study of Platelet Inhibition and Patient Outcomes; TRITON-TIMI= Trial To Assess Improvement in Therapeutic Outcomes by Optimizing Platelet inhibition With Prasugrel Thrombolysis in Myocardial Infarction.
Efficacy of Prasugrel vs Ticagrelor in ACS patients according to DM status: Insights from ISAR-REACT 5

**Primary Endpoint (Death, Myocardial Infarction, or Stroke)**

- Hazard Ratio = 0.84 [95% CI: 0.58-1.24]; p = 0.383 for Ticagrelor vs. Prasugrel in patients with DM
- Hazard Ratio = 1.70 [95% CI: 1.29-2.24]; p < 0.001 for Ticagrelor vs. Prasugrel in patients without DM
- p for interaction = 0.0035

**Treatment Effect According to Ticagrelor and Prasugrel**

<table>
<thead>
<tr>
<th>Endpoints</th>
<th>Hazard Ratio [95% Confidence Interval]</th>
<th>P_{int}</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary endpoint</td>
<td></td>
<td>0.0035</td>
</tr>
<tr>
<td>With DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td></td>
<td>0.194</td>
</tr>
<tr>
<td>With DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td></td>
<td>0.004</td>
</tr>
<tr>
<td>With DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td>0.845</td>
</tr>
<tr>
<td>With DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent Thrombosis (probable or definite)</td>
<td></td>
<td>0.079</td>
</tr>
<tr>
<td>With DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stent Thrombosis (definite)</td>
<td></td>
<td>0.058</td>
</tr>
<tr>
<td>With DM</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Without DM</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

The primary endpoint of PRU defined by VN-P2Y12 after 1 week of MD treatment was significantly lower levels with ticagrelor 90 mg bid compared with prasugrel 10 mg qd (52 [32-72] vs 83 [63-103]; LSM difference: -31; 95% CI: -57 to -4; p=0.022).
Antithrombotic strategies for patients with diabetes mellitus

- **No CVD**: Aspirin may be considered in selected candidates who are at higher risk of ischemic events but not at high risk of bleeding.

- **ACS**: DAPT with aspirin and a P2Y\(_{12}\) inhibitor (preferably prasugrel in patients managed by PCI or ticagrelor in patients invasively and non-invasively managed) is indicated for 12 months (or 6 months in patients at risk of bleeding).

- **Elective PCI**: DAPT with aspirin and clopidogrel is indicated for 6 months (or 1 to 3 months in patients at high risk of bleeding), followed by single antiplatelet therapy.

- **CCS**: Aspirin is indicated lifelong. DAPT or DPI should be considered in selected candidates who are at high risk of ischemic events but not at high risk of bleeding.

PEGASUS TIMI 54: Primary Endpoint – MACE Impact of DM status with prior MI (1-3 yrs post-MI)

CV Death, MI, Stroke (%)

Ticagrelor in Diabetic Patients
HR 0.84 (95% CI 0.72 – 0.99)
ARR 1.5%; P=0.03

Ticagrelor in Non-Diabetic Patients
HR 0.84 (95% CI 0.72 – 0.99)
ARR 1.1%; P=0.01

Benefit in Diabetic vs. Non-Diabetic Patients:
Interaction P=0.99

THEMIS: Patients with DM and CAD but no prior acute cardiovascular event (MI/CVA)

Primary Composite Endpoint
Cardiovascular Death/MI/Stroke

KM estimates at 36 months

HR 0.90 (95% CI 0.81–0.99)  
P=0.038

**THEMIS-PCI: Primary Composite Endpoint**

Cardiovascular Death/MI/Stroke

<table>
<thead>
<tr>
<th>Months from Randomization</th>
<th>Ticagrelor</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>6</td>
<td></td>
<td></td>
</tr>
<tr>
<td>12</td>
<td></td>
<td></td>
</tr>
<tr>
<td>18</td>
<td></td>
<td></td>
</tr>
<tr>
<td>24</td>
<td></td>
<td></td>
</tr>
<tr>
<td>30</td>
<td></td>
<td></td>
</tr>
<tr>
<td>36</td>
<td></td>
<td></td>
</tr>
<tr>
<td>42</td>
<td></td>
<td></td>
</tr>
<tr>
<td>48</td>
<td></td>
<td></td>
</tr>
<tr>
<td>54</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**Cumulative %**

- **Ticagrelor**: 6.5%
- **Placebo**: 7.4%

**HR 0.98 (95% CI 0.84, 1.14)**

**P=0.76**

**KM at 36 months**

**No History of PCI**

**HR 0.85 (95% CI 0.74, 0.97)**

**P=0.013**

**KM at 36 months**

**Interaction p=0.16**

**CI=Confidence Interval; CV=cardiovascular; HR=hazard ratio; KM=Kaplan-Meier; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention**

PD effects of low-dose ticagrelor vs standard dose clopidogrel in THEMIS-like patients undergoing PCI: the OPTIMUS-6 study

Primary endpoint measure of trough levels of PRU at 30 days (ticagrelor 60mg bid vs clopidogrel 75mg qd):
146 (106 to 185) vs. 60 (32 to 89); least square mean difference 91; 95% CI 42-140; p=0.001

Franchi F & Angiolillo DJ. Circulation. 2020; 142:1500-1502
Patients with DM are not only at increased risk for recurrent thrombotic/ischemic events, but also at increased risk for bleeding.
Three major uncertainties surround the use of aspirin for secondary prevention:

- Major bleeding (e.g. GI and intracranial)
- Actual risk reduction on top of – for example - statins
- Role of newer antiplatelet drugs (e.g. ticagrelor)
Landmark Trials and Ongoing Directions

*Trials of Very Short DAPT (Dropping Aspirin)*

<table>
<thead>
<tr>
<th>Trial (N)</th>
<th>DAPT duration</th>
<th>Pts</th>
<th>Design</th>
<th>Objective</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>GLOBAL LEADERS (N=15,968)</td>
<td>1 vs. 12 mo</td>
<td>PCI</td>
<td>Superiority</td>
<td>Death or MI</td>
<td>X</td>
</tr>
<tr>
<td>GLASSY (7,585)</td>
<td>1 vs 12 mo</td>
<td>PCI</td>
<td>Noninferiority</td>
<td>MACE</td>
<td>✓</td>
</tr>
<tr>
<td>STOP-DAPT 2 (N=3,045)</td>
<td>1 vs. 12 mo</td>
<td>PCI</td>
<td>Noninferiority</td>
<td>NACE</td>
<td>✓</td>
</tr>
<tr>
<td>SMART-CHOICE (N=3,000)</td>
<td>3 vs. 12 mo</td>
<td>PCI</td>
<td>Noninferiority</td>
<td>MACE</td>
<td>✓</td>
</tr>
<tr>
<td>TWILIGHT (N=9,000)</td>
<td>3 vs. 12 mo</td>
<td>PCI</td>
<td>Superiority</td>
<td>Bleeding</td>
<td>✓</td>
</tr>
<tr>
<td>TICO (N=3,000)</td>
<td>3 vs. 12 mo</td>
<td>ACS-PCI</td>
<td>Superiority</td>
<td>NACE</td>
<td>✓</td>
</tr>
<tr>
<td>STOPDAPT-2 ACS (N=3,000)</td>
<td>1 vs. 12 mo</td>
<td>ACS-PCI</td>
<td>Noninferiority</td>
<td>NACE</td>
<td>✓</td>
</tr>
<tr>
<td>WOEST (N=573)</td>
<td>0 vs. 12 mo</td>
<td>PCI (HBR)</td>
<td>Superiority</td>
<td>Bleeding</td>
<td>✓</td>
</tr>
<tr>
<td>PIONEER-AF PCI (N=2,124)</td>
<td>0 vs. 1-12 mo</td>
<td>PCI (HBR)</td>
<td>Superiority</td>
<td>Bleeding</td>
<td>✓</td>
</tr>
<tr>
<td>RE-DUAL PCI (N=2,725)</td>
<td>0 vs. 1-3 mo</td>
<td>PCI (HBR)</td>
<td>NI -&gt; Superiority</td>
<td>Bleeding</td>
<td>✓</td>
</tr>
<tr>
<td>AUGUSTUS (N=4,614)</td>
<td>0 vs. 6 mo</td>
<td>PCI (HBR)</td>
<td>Superiority</td>
<td>Bleeding</td>
<td>✓</td>
</tr>
<tr>
<td>ENTRUST-AF PCI (N=1,506)</td>
<td>0 vs. 1-12 mo</td>
<td>PCI (HBR)</td>
<td>NI -&gt; Superiority</td>
<td>Bleeding</td>
<td>✓</td>
</tr>
</tbody>
</table>

Ticagrelor With or Without Aspirin After Percutaneous Coronary Intervention in High-Risk Patients With Diabetes Mellitus

Pre-defined cohort analysis from the multicenter, double-blind, randomized TWILIGHT Trial

2,620 DM Patients adherent to 3 months of DAPT post-PCI without ischemic or bleeding events

<table>
<thead>
<tr>
<th></th>
<th>Ticagrelor + Placebo (90 mg twice daily)</th>
<th>Ticagrelor + Aspirin (90 mg twice daily) (81-100 mg daily)</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>1,319</td>
<td>1,301</td>
</tr>
</tbody>
</table>

BARC 2, 3, or 5 Bleeding 12 Months After Randomization

- 4.5% (HR: 0.65; 95% CI: 0.47-0.91; p = 0.012)
- 6.7% (HR: 0.34; 95% CI: 0.19-0.63; p = 0.001)

BARC 3 or 5 Bleeding 12 Months After Randomization

- 1.1%
- 3.1%

Ticagrelor monotherapy was not associated with an increase in ischemic events (all-cause death, MI or stroke) compared to ticagrelor plus aspirin

4.6% vs. 5.9%; HR: 0.77; 95 CI: 0.55 to 1.09; p = 0.14

Net adverse clinical events (composite of BARC 3 or 5 bleeding, death, MI, or stroke) favored ticagrelor monotherapy with a NNT of 30

5.4% vs. 8.7%; HR: 0.61; 95 CI: 0.45 to 0.82; p = 0.001

Angiolillo DJ & Mehran R. JACC 2020; 75:2403-2413
Emerging Concepts: Dual-Pathway Inhibition (DPI)

Synergy of oral anticoagulant and antiplatelet therapy

Oral anticoagulant therapy, including direct inhibitors of factor IIa and Xa, and antiplatelet agents, such as acetylsalicylic acid and P2Y$_{12}$ inhibitors, synergistically target two essential components of thrombosis: coagulation and platelet activation.

Capodanno D & Angiolillo DJ. Nat Rev Cardiol. 2018; 15:480-496
Efficacy of DPI strategy with vascular dose of rivaroxaban (2.5 mg bid) plus aspirin vs aspirin alone according to DM status

Aspirin Alone
Rivaroxaban plus Aspirin

Diabetes (N=6,922)
HR 0.74, 95% CI: 0.61-0.90, p=0.002
ARR 2.3%

No Diabetes (N=11,356)
HR 0.77, 95% CI: 0.64-0.93, p=0.005
ARR 1.4%

P value for interaction=0.77

Aspirin still remains the mainstay of treatment for long-term secondary prevention in patient with DM and CAD.

Can we be “smarter” about aspirin?
Schematic of circadian release of platelets into bloodstream from bone marrow and impact of a single daily dose of aspirin on newly generated platelets in type 2 DM

Novel, Pharmaceutical Lipid-Aspirin Complex (PL-ASA; Vazalore): Mechanism of Action

1. **Stomach**
   Capsule rapidly dissolves releasing the liquid lipid-aspirin complex

2. **Duodenum**
   a) Rising pH leads to dissociation
   b) Aspirin is now free for absorption

3. **Bidirectional Protection**
   Reassembly of the lipid-aspirin complex at low pH

---

Angiolillo DJ et al. J Thromb Thrombolysis 2019
PK/PD Comparison of ASA, EC-ASA & PL-ASA (i.e., VAZALORE): Implications for Aspirin Efficacy in Patients with Diabetes Mellitus

Bhatt DL. JACC 2017;69(6):603-612

$C_{\text{max}}$ and $T_{\text{max}}$ for serum ASA concentrations

Plain Aspirin: 1964  PL2200: 2523  EC: aspirin 456

Patients with complete antiplatelet response

Plain Aspirin: 84%  Vazalore: 92%  EC aspirin: 47%
ABCs of Treatment of Diabetic Patients and Impact on Thrombosis

A1C (blood glucose): <7%
Blood pressure: <130/80 mm Hg
Cholesterol-LDL: <70 mg/dl

Platelet Reactivity