Preventing Cardiovascular Events in High-Risk Diabetes Patients with CAD: New Insights and Developments

A compilation of key content from the Primetime Symposium at the 2020 15th Annual CMHC Live Online

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Impact of Prior Ischemic Events, Stable Atherosclerosis, Polyvascular Disease and Diabetes on CV Events at 4 years

*All event rates adjusted for age and sex.

Diabetes Increases Risk in Patients with Prior Ischemic Events;
Diabetes and Polyvascular Disease:
Insights from LEADER

THEMIS Trial - Primary Composite Endpoint

**Cardiovascular death/MI/stroke**

- KM estimates at 36 months
- Ticagrelor: 7.6%
- Placebo: 6.9%
- HR 0.90 (95% CI 0.81–0.99)
- P = 0.038

**Cardiovascular death/MI/stroke – on treatment**

- KM estimates at 36 months
- Ticagrelor: 6.4%
- Placebo: 5.2%
- HR 0.81 (95% CI 0.71–0.92)
- P = 0.001

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**THEMIS TRIAL**

**Benefit of Ticagrelor vs Placebo**
as a Function of Time between PCI and randomization

![Graph showing the benefit of Ticagrelor vs Placebo over time]

**Limb Outcomes by Type with Ticagrelor versus Placebo**

<table>
<thead>
<tr>
<th>Event</th>
<th>Ticagrelor (HR)</th>
<th>Placebo (HR)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Limb Ischemic Event</td>
<td>0.77 (0.61–0.96)</td>
<td>0.79 (0.62–0.99)</td>
<td>0.022</td>
</tr>
<tr>
<td>Peripheral Revascularization</td>
<td>1.59%</td>
<td>1.51%</td>
<td></td>
</tr>
<tr>
<td>Acute Limb Ischemia</td>
<td>1.30%</td>
<td>1.23%</td>
<td></td>
</tr>
<tr>
<td>Major Amputation</td>
<td>2%</td>
<td>2%</td>
<td></td>
</tr>
</tbody>
</table>

Dotted lines signify 95% confidence interval; HR=hazard ratio; PCI=percutaneous coronary intervention.


Bonaca MP, Bhatt DL, Steg PG, et al. ESC LBS 2020
Breaking Update: US FDA Approval

Ticagrelor approved by FDA June 1, 2020 “to reduce the risk of a first MI or stroke in patients with coronary artery disease at high risk for such events”

<table>
<thead>
<tr>
<th>Agent</th>
<th>ACS + PCI</th>
<th>ACS (Medical)</th>
<th>Prior MI</th>
<th>CAD (No Event)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clopidogrel</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
<td>✔</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>✔</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

DAPT Algorithm

- In ACS, at least 12 months of DAPT if no bleeding
- If high bleeding risk post PCI, can abbreviate DAPT at 3 months
  - At that point ticagrelor (preferred) or clopidogrel monotherapy is an option in select patients
- If post-MI, diabetes, complex stenting/disease, consider longer
  - Ticagrelor US label updated based on THEMIS, THEMIS PCI for CAD
Diabetes (without MI or stroke) is a high risk condition

**Known Atherothrombosis Increases CV Risk in Patients with T2DM**

REACH registry: Diabetes + known atherothrombosis with no prior MI confers greater risk than diabetes alone¹

4-year hazard rates in patients with diabetes + known atherothrombosis + no prior MI:
- CV death, MI or stroke: 14.8% (95% CI 13.3–16.2)
- CV death: 7.7% (95% CI 6.6–8.87)
- MI: 4.1% (95% CI 3.2–4.9)
- Stroke: 4.6% (95% CI 3.7–5.5)

N=19,699

**Diabetes without prior MI is a high-risk condition**

Cumulative incidence of CV death, MI, stroke

Three year Cox adjusted for gender, age [linear], previous AF and previous HF:
- THEMIS-like: 0.130; 95% CI (0.123, 0.138)
- MI-population: 0.131; 95% CI (0.128, 0.134)

CV outcomes in THEMIS-like type 2 diabetes patients in Sweden: a nationwide observational study


Hasvold LP et al ESC 2019
Antiplatelet Therapy in Diabetes and CAD

- Diabetes (without MI or stroke) is a high risk condition
- Patients with CAD should receive antiplatelet therapy (Aspirin)
- Aspirin (and clopidogrel) have certain limitations in patients with diabetes

Value of BID dosing of Aspirin in Patients with Diabetes

The ANDAMAN trial

To compare in diabetic patients with acute coronary syndrome
- aspirin protect® twice a day (100 mg in the morning and 100 mg in the evening)
- aspirin protect® 100 mg once per day

• Diabetes (without MI or stroke) is a high risk condition
• Patients with CAD should receive antiplatelet therapy (Aspirin)
• *Aspirin (and clopidogrel) have certain limitations in patients with diabetes*

CAPRIE: Superior Efficacy of Clopidogrel versus ASA


Diabetes (without MI or stroke) is a high risk condition
Patients with CAD should receive antiplatelet therapy (Aspirin)
Aspirin (and clopidogrel) have certain limitations in patients with diabetes

**Acute phase of treatment**

<table>
<thead>
<tr>
<th></th>
<th>Diabetics</th>
<th>No-DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Responders (Platelet inhibition &gt;30%)</td>
<td>38%</td>
<td>56%</td>
</tr>
<tr>
<td>Low responders (Platelet inhibition 10-29%)</td>
<td>14%</td>
<td>8%</td>
</tr>
<tr>
<td>Non responders (Platelet inhibition &lt;10%)</td>
<td>6%</td>
<td>6%</td>
</tr>
</tbody>
</table>

24 hrs post 300 mg LD

p=0.04

**Long-term phase of treatment**

<table>
<thead>
<tr>
<th></th>
<th>DM</th>
<th>No-DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet aggregation (%) ADP 20µM</td>
<td>70</td>
<td>65</td>
</tr>
<tr>
<td>p=0.002</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th></th>
<th>DM</th>
<th>No-DM</th>
</tr>
</thead>
<tbody>
<tr>
<td>Platelet aggregation (%) ADP 6µM</td>
<td>80</td>
<td>70</td>
</tr>
<tr>
<td>p&lt;0.0001</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>


Angiolillo DJ et al. J Am Coll Cardiol 2006; 48: 298-304
PLATO and PEGASUS-TIMI 54 Trial Diabetes Subgroup Results are Consistent With Ticagrelor Benefits in the Overall Trial Populations

- Diabetes (without MI or stroke) is a high risk condition

- Patients with CAD should receive antiplatelet therapy

- Antiplatelet monotherapy commonly uses aspirin in this population

- Aspirin (and clopidogrel) have certain limitations in patients with diabetes

- In select populations, there is evidence of a benefit of DAPT with aspirin and ticagrelor (and the benefit is consistent for diabetics and non diabetics)
Limited and inconsistent evidence for clopidogrel benefit in CAD patients with T2DM

Can we do better in patients with diabetes and stable CAD?

Clopidogrel in diabetes subgroups

- **CHARISMA** (CV disease or risk factors):
  - No clear benefit of clopidogrel in the overall diabetes population
  - Paradoxical trend towards harm in patients with diabetic nephropathy and in those with diabetes and multiple risk factors but no established CV disease

- **CAPRIE** (prior stroke, MI or PAD):
  - **12.5% RRR** (ARR 2.1%) with clopidogrel vs ASA for CV death, MI, ischaemic stroke or rehospitalization for ischaemia or bleeding in diabetes subgroup

- **CURE** (NSTE-ACS):
  - **16% RRR** (ARR 2.5%) with clopidogrel + ASA vs ASA alone for CV death, MI or stroke in diabetes subgroup

CHARISMA trial outcomes stratified by diabetes status

CV Prevention in pts with CAD and type 2 diabetes and without prior stroke or MI

Type 2 diabetes and high CV risk CV
- Treated ≥ 6 months
- Established CAD
- No history of MI or stroke

Established CAD defined as:
- History of PCI
- History of CABG
- At least 1 stenosis ≥ 50% on coronary angiogram

The initial dose of ticagrelor was 90 mg bid and was then changed to 60 mg bid due to emerging data on ticagrelor tolerability from PEGASUS-TIMI 54

* Added to optimal background therapy including low dose ASA

Event-driven study (750), Mean Follow-up ~3 years (n=20,000)

Primary outcome: CV death, MI, Stroke
Secondary outcomes: Components of primary outcome, All cause death, other composites
Primary Safety outcome: Major bleeding (TIMI – PLATO – BARC)

http://clinicaltrials.gov ID:NCT01991795

# THEMIS-PCI

## Primary and Secondary Efficacy Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ticagrelor (n=5658)</th>
<th>Placebo (n=5696)</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death</td>
<td>174 (3.1)</td>
<td>183 (3.3)</td>
<td>0.96 (0.78-1.18)</td>
<td>0.68</td>
</tr>
<tr>
<td>All-cause death&lt;sup&gt;2&lt;/sup&gt;</td>
<td>282 (5.1)</td>
<td>223 (3.8)</td>
<td>0.88 (0.75-1.03)</td>
<td>0.11</td>
</tr>
<tr>
<td>MI</td>
<td>171 (3.1)</td>
<td>216 (3.9)</td>
<td>0.80 (0.65-0.97)</td>
<td>0.027</td>
</tr>
<tr>
<td>Stroke</td>
<td>96 (1.7)</td>
<td>131 (2.3)</td>
<td>0.74 (0.57-0.96)</td>
<td>0.024</td>
</tr>
<tr>
<td>ALI and major amputation of vascular cause</td>
<td>7 (0.1)</td>
<td>15 (0.3)</td>
<td>0.47 (0.19-1.15)</td>
<td>0.099</td>
</tr>
<tr>
<td>Composite of all-cause death, MI, or stroke</td>
<td>494 (8.9)</td>
<td>603 (10.8)</td>
<td>0.82 (0.73-0.93)</td>
<td>0.0014</td>
</tr>
</tbody>
</table>

<sup>1</sup> Among patients receiving ASA 75–150 mg QD unless contraindicated or not tolerated.

<sup>2</sup> Includes deaths based on publicly available vital status data in patients who have withdrawn consent.

**All-cause death:** Acute kidney injury, CV = cardiovascular, HR = hazard ratio, MI = myocardial infarction, PCI = percutaneous coronary intervention.

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## Bleeding Endpoints

### THEMIS-PCI Safety Population

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Ticagrelor</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>TIMI major bleeding</td>
<td>History of PCI</td>
<td>5536</td>
</tr>
<tr>
<td>No history of PCI</td>
<td>4026</td>
<td>95 (2.4%)</td>
</tr>
<tr>
<td>BARC type 2, 3, 4 or 5</td>
<td>History of PCI</td>
<td>5536</td>
</tr>
<tr>
<td>No history of PCI</td>
<td>4026</td>
<td>453 (11.3%)</td>
</tr>
<tr>
<td>Fatal bleeding (BARC type 5)</td>
<td>History of PCI</td>
<td>5536</td>
</tr>
<tr>
<td>No history of PCI</td>
<td>4026</td>
<td>11 (0.3%)</td>
</tr>
<tr>
<td>Intracranial hemorrhage</td>
<td>History of PCI</td>
<td>5536</td>
</tr>
<tr>
<td>No history of PCI</td>
<td>4026</td>
<td>37 (0.9%)</td>
</tr>
</tbody>
</table>

Hazard ratios and p-values are calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as the only explanatory variable.

BARC= Bleeding Academic Research Consortium; Circumference of lesions; PCI=percutaneous coronary intervention; TIMI=thrombolysis in myocardial infarction.

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**References:**
### Primary and Secondary Efficacy Endpoints
**On treatment : THEMIS**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Ticagrelor (N=9562)</th>
<th>Placebo (N=9531)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CV death/ MI/stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of PCI</td>
<td>5536</td>
<td>5564</td>
</tr>
<tr>
<td>No history of PCI</td>
<td>4026</td>
<td>3967</td>
</tr>
<tr>
<td><strong>All-cause death/ MI/ stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of PCI</td>
<td>5536</td>
<td>5564</td>
</tr>
<tr>
<td>No history of PCI</td>
<td>4026</td>
<td>3967</td>
</tr>
<tr>
<td><strong>All-cause death/ MI/ stroke/ ALI/ major</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>amputation of vascular etiology</td>
<td>History of PCI</td>
<td>5536</td>
</tr>
<tr>
<td>No history of PCI</td>
<td>4026</td>
<td>3967</td>
</tr>
<tr>
<td><strong>MI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of PCI</td>
<td>5536</td>
<td>5564</td>
</tr>
<tr>
<td>No history of PCI</td>
<td>4026</td>
<td>3967</td>
</tr>
<tr>
<td><strong>STEMI</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of PCI</td>
<td>5536</td>
<td>5564</td>
</tr>
<tr>
<td>No history of PCI</td>
<td>4026</td>
<td>3967</td>
</tr>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>History of PCI</td>
<td>5536</td>
<td>5564</td>
</tr>
<tr>
<td>No history of PCI</td>
<td>4026</td>
<td>3967</td>
</tr>
</tbody>
</table>

Hazard ratios and P-values calculated for ticagrelor vs placebo from a Cox proportional hazards model with treatment as the only explanatory variable. Includes events with onset date at or after randomization day up to 7 days after the last dose; only patients who look at least 1 dose of study drug are included. The number of first events for the components are the actual number of first events for each component and do not add up to the number of events in the composite endpoint.

- ALI acute limb ischemia; CI=confidence interval; CV=cardiovascular; MI=myocardial infarction; PCI=percutaneous coronary intervention; STEMI=ST-segment elevation MI
In patients with stable CAD and diabetes, but without a prior history of MI or stroke, compared with aspirin alone, combination of ticagrelor plus aspirin reduced the primary endpoint of CV death, MI, or stroke.

This benefit was achieved at the expense of increased major bleeding.

In patients with prior PCI, ticagrelor was as effective but safety was better, and ticagrelor produced a significant net clinical benefit.

This long-term DAPT may be beneficial in patients with diabetes and CAD, with a prior history of PCI, at low risk of bleeding but with a high risk of ischemic events.
Ticagrelor is a P2Y12 platelet inhibitor indicated to reduce the risk of cardiovascular (CV) death, myocardial infarction (MI), and stroke in patients with acute coronary syndrome (ACS) or a history of MI. For at least the first 12 months following ACS, it is superior to clopidogrel. Ticagrelor also reduces the risk of stent thrombosis in patients who have been stented for treatment of ACS.

Ticagrelor is indicated to reduce the risk of a first MI or stroke in patients with coronary artery disease (CAD) at high risk for such events. While use is not limited to this setting, the efficacy of ticagrelor was established in a population with type 2 diabetes mellitus (T2DM).
What did THEMIS and THEMIS-PCI tell us?

19,220

- stable CAD
- T2DM
- prior MI or stroke

39.9 months

Ticagrelor + Aspirin
(vs Placebo + Aspirin)

Cardiovascular events\textsuperscript{a}
\[ \text{HR (95\% CI)} = 0.90 \ (0.81, 0.99) \]
\[ P = 0.04 \]

Major bleeding events\textsuperscript{b}
\[ \text{HR (95\% CI)} = 2.32 \ (1.82, 2.94) \]
\[ P < 0.001 \]

More favourable net clinical benefit among those with prior PCI

Cardiovascular events\textsuperscript{a}
\[ \text{HR (95\% CI)} = 0.85 \ (0.74, 0.97) \]
\[ P = 0.013 \]

Major bleeding events\textsuperscript{b}
\[ \text{HR (95\% CI)} = 2.03 \ (1.48, 2.76) \]
\[ P < 0.0001 \]

\textsuperscript{a} cardiovascular death, myocardial infarction, and stroke.\textsuperscript{b} TIMI-defined major bleeding.

CAD, coronary artery disease; MI, myocardial infarction; PCI, percutaneous coronary intervention; T2DM, type 2 diabetes mellitus.

In High-Risk PCI Patients Who Completed 3 Months of DAPT:

- Ticagrelor monotherapy was associated with a lower incidence of clinically-relevant bleeding vs. ticagrelor + aspirin, with no difference in ischemic adverse events.
Clinical Advances in the Management of Residual CV Risk

Known Cardiovascular Disease

- Plant-Based Diet; High Intensity Statin

<table>
<thead>
<tr>
<th>Biologic Issue</th>
<th>Residual Cholesterol Risk</th>
<th>Residual Inflammatory Risk</th>
<th>Residual Thrombotic Risk</th>
<th>Residual Triglyceride Risk</th>
<th>Residual Lp(a) Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>Critical Biomarker</td>
<td>LDL-C ≥100mg/dL</td>
<td>hsCRP ≥2mg/L</td>
<td>No simple biomarker</td>
<td>TG ≥100mg/dL</td>
<td>Lp(a) ≥50mg/dL</td>
</tr>
<tr>
<td>Potential Intervention</td>
<td>Targeted LDL / Apo B Reduction</td>
<td>Targeted Inflammation Reduction</td>
<td>Targeted Antithrombotic Reduction</td>
<td>Targeted Triglyceride Reduction</td>
<td>Targeted Lp(a) Reduction</td>
</tr>
<tr>
<td>Randomized Trial Evidence</td>
<td>IMPROVE-IT FOURIER, SPIRE, ODYSSEY</td>
<td>CANTOS, COLCOT LoDoCo2 CLEAR-Synergy</td>
<td>CHARISMA, PEGASUS COMPASS, THEMIS THEMIS-PCI</td>
<td>REDUCE-IT STRENGTH PROMINENT</td>
<td>Planned</td>
</tr>
</tbody>
</table>

**COMPASS:** CV Death, MI, or Stroke

- **Diabetes (N=6,922):**
  - Aspirin Alone
  - Rivaroxaban plus Aspirin
- **No Diabetes (N=11,356):**
  - Aspirin Alone
  - Rivaroxaban plus Aspirin

**Diabetes**
- HR 0.74, 95% CI: 0.61-0.90,
- P=0.002
- ARR 2.3%

**No Diabetes**
- HR 0.77, 95% CI: 0.64-0.93,
- P=0.005
- ARR 1.4%

**P value for interaction=0.77**

FOURIER: Clinical Outcomes by Baseline LDL-C

CVD, MI, stroke, UA, or cor revasc

All Patients
Baseline LDL-C <70 mg/dL (<1.8 mmol/L)
Baseline LDL-C ≥70 mg/dL (≥1.8 mmol/L)

CVD, MI, or stroke

All Patients
Baseline LDL-C <70 mg/dL (<1.8 mmol/L)
Baseline LDL-C ≥70 mg/dL (≥1.8 mmol/L)

REDUCE-IT: Study Design and Primary Endpoint

- Age ≥45 years with established CVD (2° Prevention Cohort) or ≥50 years with diabetes with ≥1 additional risk factor for CVD (1° Prevention Cohort)

- Fasting TG levels ≥135 mg/dL and <500 mg/dL

- LDL-C >40 mg/dL and ≤100 mg/dL and on stable statin therapy (± ezetimibe) for ≥4 weeks prior to qualifying measurements for randomization

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## Potential Benefits of Proven Secondary Prevention Therapies

<table>
<thead>
<tr>
<th>RRR/RRI</th>
<th>Rivaroxaban 2.5 mg BID + ASA(^1)</th>
<th>Lipid lowering (1 mmol/L)(^2,3)</th>
<th>BP lowering (10 mmHg)(^4)</th>
<th>ACEi(^5)</th>
<th>SGLT2 inhibitor (empagliflozin)(^6)</th>
<th>PCSK9 inhibitor (alirocumab)(^7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MACE</td>
<td>-24%</td>
<td>-21%</td>
<td>-20%</td>
<td>-18%</td>
<td>-14%</td>
<td>-14%</td>
</tr>
<tr>
<td>All-cause mortality</td>
<td>-18%</td>
<td>-9%</td>
<td>-13%</td>
<td>-14%</td>
<td>-32%</td>
<td>-15%</td>
</tr>
<tr>
<td>Stroke</td>
<td>-42%</td>
<td>-15%</td>
<td>-27%</td>
<td>-23%</td>
<td>+18%</td>
<td>-27%</td>
</tr>
<tr>
<td>MI</td>
<td>-14%*</td>
<td>-24%</td>
<td>-17%</td>
<td>-18%</td>
<td>-13%</td>
<td>-14%</td>
</tr>
</tbody>
</table>

*Not statistically significant.

Challenges in Prioritizing Secondary Prevention Strategies

Difficult to ascertain comparative benefit given

- Different patient population with varying trial designs, end points, and durations of follow up
- Studies to date have evaluated these agents individually and have not investigated whether combinations of these new prevention drugs could provide synergistic benefits
- Clinical trials commonly just add a new medication to the existing standard of care regimen
  - it is possible that the new drug could obviate the need for prior agents considered standard

Estimates do not consider

- the differences between efficacy measured in the trials vs. the effectiveness of these new drugs in community practice
- the potential adverse events associated with the widespread use of the novel therapy (e.g. bleeding events)
- the individual patient’s underlying risk and comorbidities
- the cost of the new drug!

Patients with DM, and especially with CAD, remain at high risk of a subsequent event. We now have evidence for benefit of DAPT with ticagrelor in patients with DM and CAD without prior CV event. The risks of bleeding with antiplatelets can be minimized with appropriate strategies. We are now blessed with MULTIPLE evidence-based strategies to decrease CV events in our high-risk patients with DM. Appropriate choices in a given patient will depend on degree of abnormality in the risk factor (if measurable), physician comfort with the intervention, cost/access, and patient preferences.