Role of the Platelet in Type 2 Diabetes: Therapeutic Options

Presented as a Live Webinar
Wednesday, October 13, 2021
1:00 p.m. – 2:00 p.m. ET

On-demand Activity
Recording of live webinar
Available after October 20, 2021

This webinar is not accredited for continuing education.

FACULTY
Andrew S. Bzowyckyj, Pharm.D., BCPS, CDCES
Associate Professor of Pharmacy Practice
Pacific University Oregon School of Pharmacy
Hillsboro, Oregon

View faculty bio at https://www.ashpadvantage.com/t2d/platelet/

WEBINAR INFORMATION
Visit https://www.ashpadvantage.com/t2d/platelet/ to find
• Webinar registration link
• Group viewing information and technical requirements

Any referenced figures, tables and graphs are copyrighted works of their respective owners; used with permission.
Role of the Platelet in Type 2 Diabetes: Therapeutic Options

Andrew S. Bzowyckyj, Pharm.D., BCPS, CDCES
Associate Professor of Pharmacy Practice
Pacific University Oregon School of Pharmacy
Hillsboro, Oregon

Provided by ASHP
Sponsored by AstraZeneca Pharmaceuticals

Relevant Financial Relationship Disclosure

The following person in control of this activity’s content has relevant financial relationships:

Andrew Bzowyckyj – Sanofi: consultant

All other persons in control of content do not have any relevant financial relationships with an ineligible company.

As defined by the Standards of Integrity and Independence in Accredited Continuing Education definition of ineligible company. All relevant financial relationships have been mitigated prior to this activity.
Learning Objectives

At the conclusion of this activity, participants should be able to

- Describe the impact of concurrent coronary artery disease (CAD) and type 2 diabetes (T2D)
- Summarize the mechanisms involved in altered platelet function in people with CAD and T2D
- Use guideline recommendations to assess the need for antiplatelet therapy for primary and secondary prevention of CV events in people with T2D

Understanding the Impact of Concurrent CAD and T2D
Role of the Platelet in Type 2 Diabetes: Therapeutic Options

T2D Is Associated with an Elevated CV Risk

• Diabetes is a growing healthcare concern worldwide1
  – T2D is strongly associated with microvascular and macrovascular complications2
    • Among U.S. adults in 20162
      – 16 million emergency department visits with diabetes as any listed diagnosis
      – 7.8 million hospital discharges with diabetes as any listed diagnosis
        • 1.7 million for major cardiovascular diseases (including ischemic heart disease and stroke)
        • 130,000 for a lower-extremity amputation
    • Leading cause of end-stage kidney disease and new cases of blindness among adults2

• Diabetes is associated with an increased risk of CV events
  – People with diabetes have approximately a 2-fold increase in the risk for CV events compared with people without diabetes3
  – Ischemic heart disease is the most common vascular cause of death in people with diabetes4


Comprehensive CV Risk Factor Management for People with Diabetes

**Lifestyle Modifications**
- Assess weight at every visit
  - Lifestyle modifications → medical therapy → surgical therapy
- Individualized nutrition therapy
- Moderate-intensity aerobic physical activity (and resistance training when not contraindicated)
- Smoking cessation

**Lipids**
- Periodic assessment of lipid panel, including LDL-C, HDL-C, and TG
- Statins as first-line pharmacologic therapy (may need fibrate if initial TG>500 mg/dL)

**Blood Pressure**
- Assess at every visit
  - Lifestyle modifications → medical therapy (particularly ACE inhibitor or ARB if albuminuria or CAD are present)

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; CV = cardiovascular; HDL-C = high-density lipoprotein cholesterol; LDL-C = low-density lipoprotein cholesterol; TG = triglycerides.

A Close Link Between Diabetes and CVD

28% of people with T2D have CAD
Up to 30% have HF

>50% of deaths among people with T2D are attributable to CVD

People with T2D are 2-4× more likely to develop CVD than people without diabetes

CAD = coronary artery disease; CVD = cardiovascular disease; HF = heart failure; T2D = type 2 diabetes.


T2D Confers High Risk of CV Events

Ischemic heart disease is the most common vascular cause of death in people with diabetes

>20% of deaths caused by ischemic heart disease


© 2021 American Society of Health-System Pharmacists, Inc. All rights reserved.
People with T2D and Known Atherothrombosis Have an Increased Risk of CV Events

![Graph showing the increased risk of CV events for people with T2D and known atherothrombosis.]

4-year hazard rates in people 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)

REACH registry: Diabetes + known atherothrombosis with no prior MI confers greater risk for CV events than diabetes alone.


People with CAD and T2D, With or Without Prior MI or Stroke, Are at Higher Risk of a CV Event Compared with People with T2D Alone

ATHENA CVD: A Swedish nationwide observational study investigating the impact of prior acute cardiac event or stroke vs. CAD on CV outcomes in people with T2D

**CV Event (MI, Stroke, or CV death)**

- **Group 1:** People with T2D and CAD with a history of MI or stroke (n=27,999; Mean age=74.0 yr)
  - 2-year adjusted cumulative incidence: 9.94%

- **Group 2:** People with T2D and CAD without MI or stroke (n=66,005; Mean age=72.8 yr)
  - 2-year adjusted cumulative incidence: 6.26%

- **Group 3:** People with T2D without CAD, MI, or stroke (n=237,266; Mean age=68.4 yr)
  - 2-year adjusted cumulative incidence: 4.55%

*The greater risk observed for people in Group 2 compared with people in Group 3 was primarily driven by incident MI (2.94% vs. 1.45%)*

Jernberg T et al. Poster presented at: ESC Congress, August 25-29, 2018; Munich, Germany.
Which of the following is the leading vascular cause of death for persons with diabetes?

a. Cancer  
b. Cerebrovascular disease  
c. Chronic heart failure  
d. Ischemic heart disease

The Role of Platelet Dysfunction in T2D and Selected Mechanisms of Disease in People with CAD and T2D
The Central Role of Platelets in Thrombus Formation

- **Adhesion**: Plaque rupture leads to platelet adhesion to the exposed endothelium.
- **Activation**: Activated platelets change shape and lead to initial thrombus formation.
- **Aggregation**: Activated platelets aggregate at the active lesion site, leading to growth of thrombus.

Pathophysiology of Increased Thrombotic Risk Across the CAD Spectrum Associated with T2D

- **High platelet turnover and reactivity**
- **Endothelial dysfunction**
- **Inflammation**

For illustrative purposes only.
Numerous Mechanisms Are Involved in Altered Platelet Function in People with CAD and T2D

Decreased membrane fluidity by glycation of surface proteins

HYPERGLYCEMIA

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

H2O

PLATELETS

ENDOTHELIAL CELLS

ADP=adenosine diphosphate; GP=glycoprotein; IRS=insulin receptor substrate; NO=nitric oxide; NOS=reactive nitrogen species; PGI2=prostacyclin; PKC=protein kinase C; ROS=reactive oxygen species; TF=tissue factor. Ferreiro JL, Angiolillo DJ. Circulation. 2011;123(7):798-813.

Role of the Platelet in Type 2 Diabetes: Therapeutic Options

© 2021 American Society of Health-System Pharmacists, Inc. All rights reserved.
Numerous Mechanisms Are Involved in Altered Platelet Function in People with CAD and T2D (continued)

**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 PGI₂
- IRS-dependent factors: increased intracellular Ca²⁺
- Degranulation

**ASSOCIATED METABOLIC CONDITIONS**
- Obesity
- Dyslipidemia
- Inflammation

**PLATELETS**
- H₂O
- IRS-1
- PKC
- ROS/NOS
- ADP
- TF

**ENDOTHELIAL CELLS**

ADP=adenosine diphosphate; GP=glycoprotein; IRS-1=insulin receptor substrate-1; NO=nitric oxide; NOS=reactive nitrogen species; PGI₂=prostacyclin; PKC=protein kinase C; ROS=reactive oxygen species; TF=tissue factor. Ferreiro JL, Angiolillo DJ. Circulation. 2011;123(7):798–813.
Platelet Dysfunction is a Key Contributor to the “Prothrombotic State” in CAD with T2D and is Associated with Higher CV Risk and Poor Outcomes\textsuperscript{1,2}

- Increased platelet turnover and reactivity
- Increased intracellular Ca\textsuperscript{2+}
- Upregulation of P2Y\textsubscript{12} signaling
- Increased oxidative stress
- Increased P-selectin and GP expression
- Deficient insulin action (i.e., impaired response to NO and PGI\textsubscript{2})

ENDOTHELIAL DYSFUNCTION

- Normal vessel
- Atherothrombosis

Endothelial Dysfunction

ADP = adenosine diphosphate; Ca = calcium; CAD = coronary artery disease; CV = cardiovascular; GP = glycoprotein; NO = nitric oxide; NOS = reactive nitrogen species; PG = prostaglandin; ROS = reactive oxygen species; T2D = type 2 diabetes.


Endothelial Dysfunction is a Characteristic Feature in People with CAD and T2D that May Result in a Prothrombotic State\textsuperscript{1,2}

- Increased production of TF
- Decreased NO and PGI\textsubscript{2} production
- Increased oxidative stress

ENDOTHELIAL DYSFUNCTION

- Normal vessel
- Atherothrombosis

Platelet activation

CAD = coronary artery disease; NO = nitric oxide; NOS = reactive nitrogen species; PG = prostaglandin; ROS = reactive oxygen species; T2D = type 2 diabetes; TF = tissue factor.

Systemic Inflammation May Contribute to the Prothrombotic State in CAD with T2D via Increased Platelet Reactivity\textsuperscript{1,2}

\textbf{Ca} = calcium; CAD = coronary artery disease; IRS\textsuperscript{1} = insulin-receptor substrate\textsuperscript{1}; NOS = reactive nitrogen species; ROS = reactive oxygen species; T2D = type 2 diabetes.


Which of the following mechanisms of altered platelet function is correctly paired with its underlying cause?

- a. Impaired response to nitric oxide - hyperglycemia
- b. Upregulation of P2Y\textsubscript{12} signaling - deficient insulin action
- c. Release of platelet activating factors – systemic inflammation
- d. Activation of PKC – endothelial dysfunction
Guideline Recommendations and the Role of Antiplatelet Agents for Primary and Secondary CV Prevention in People with T2D

Antiplatelet Agents: Primary CV Prevention Recommendations

Primary CV prevention strategy in people with diabetes

Consider aspirin therapy (75–162 mg/day) in people at increased CV risk after a comprehensive discussion with the patient about risks & benefits

Includes most men and women with diabetes aged ≥50 years* who have at least 1 additional major risk factor (family history of premature ASCVD, HTN, dyslipidemia, smoking, or CKD/albuninuria) and are not at increased risk of bleeding (e.g., older age, anemia, renal disease)

*For people over the age of 70 years (with or without diabetes), the balance appears to have a greater risk than benefit. Thus, for primary CV prevention, the use of aspirin needs to be carefully considered and may generally not be recommended.

ASCVD = atherosclerotic cardiovascular disease; CKD = chronic kidney disease; CV = cardiovascular; HTN = hypertension.

Current State of Oral Antiplatelet Agents for People with T2D at High Risk of a CV Event

• Studies investigating the primary prevention of CV events in people with T2D using low-dose ASA have provided inconclusive results.1-2
• Guideline recommendations to use ASA for primary prevention in people with T2D and a high risk of a CV event lack clear evidential support
  – ADA: “May be considered”; Level of evidence A3
  – ACC/AHA: Weak recommendation (COR IIb); Level of evidence A4
  – ESC/EASD: Weak recommendation (COR IIb); Level of evidence A5
• Biochemical ASA resistance?
  – Varies from 5%–57% depending on the study methods6
  – Limitations of evidence: small sample sizes, variable platelet function tests, variable dosing regimens, nonadherence in studies6

2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease

• Assessment of ASCVD risk is the foundation of primary prevention.
• For those 20–39 years old, it is reasonable to measure traditional CV risk factors every 4–6 years to identify major factors (e.g., tobacco use, dyslipidemia, family history of premature ASCVD, chronic inflammatory diseases, hypertension, or T2D) that provide a rationale for optimizing lifestyle and tracking risk factor progression and need for treatment.

<p>| Recommendations for Aspirin Use |
|-------------------------------|-------------------|</p>
<table>
<thead>
<tr>
<th>COR</th>
<th>LOE</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>A</td>
<td>1. Low-dose aspirin (75–100 mg orally daily) might be considered for the primary prevention of ASCVD among select adults 40 to 70 years of age who are at higher ASCVD risk but not at increased bleeding risk.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>B-R</td>
<td>2. Low-dose aspirin (75–100 mg orally daily) should not be administered on a routine basis for the primary prevention of ASCVD among adults &gt;70 years of age.</td>
</tr>
<tr>
<td>III: Harm</td>
<td>C-LD</td>
<td>3. Low-dose aspirin (75–100 mg orally daily) should not be administered for the primary prevention of ASCVD among adults of any age who are at increased risk of bleeding.</td>
</tr>
</tbody>
</table>

ACC = American College of Cardiology; AHA = American Heart Association; ASCVD = atherosclerotic cardiovascular disease; COR = class of recommendation; CV = cardiovascular; LOE = level of evidence. 
Effects of Aspirin for Primary Prevention in Persons with Diabetes (ASCEND)

People with diabetes ≥40 years of age without known CVD (N = 15,480)

<table>
<thead>
<tr>
<th>Randomized</th>
<th>Placebo (N = 7,740)</th>
</tr>
</thead>
<tbody>
<tr>
<td>ASA 100 mg/day (N = 7,740)</td>
<td></td>
</tr>
</tbody>
</table>

Duration of follow-up: mean 7.4 years

First Serious Vascular Event

- ASA was associated with:
  - Risk of serious vascular events<sup>a</sup> vs. placebo (<i>P</i> = 0.01)
    - NNT = 91
  - Risk of major bleeding events<sup>b</sup> vs. placebo (<i>P</i> = 0.003)

- **Primary efficacy outcome:** first serious vascular event (MI, stroke, TIA, or death from any vascular cause, excluding any confirmed intracranial hemorrhage [ICH])
- **Primary safety outcome:** first major bleeding event (ICH, sight-threatening bleeding event in the eye, gastrointestinal bleeding, or other serious bleeding)

No. at Risk

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>ASA</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>7,740</td>
<td>7,740</td>
</tr>
<tr>
<td>Follow-up (Years)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>7,740</td>
<td>7,740</td>
</tr>
<tr>
<td>1</td>
<td>7,618</td>
<td>7,555</td>
</tr>
<tr>
<td>2</td>
<td>7,486</td>
<td>7,489</td>
</tr>
<tr>
<td>3</td>
<td>7,342</td>
<td>7,346</td>
</tr>
<tr>
<td>4</td>
<td>7,188</td>
<td>7,188</td>
</tr>
<tr>
<td>5</td>
<td>7,001</td>
<td>7,004</td>
</tr>
<tr>
<td>6</td>
<td>6,825</td>
<td>6,825</td>
</tr>
<tr>
<td>7</td>
<td>5,771</td>
<td>5,771</td>
</tr>
<tr>
<td>8</td>
<td>4,625</td>
<td>4,625</td>
</tr>
<tr>
<td>9</td>
<td>3,966</td>
<td>3,966</td>
</tr>
<tr>
<td>10</td>
<td>2,222</td>
<td>2,222</td>
</tr>
<tr>
<td>11</td>
<td>1,428</td>
<td>1,428</td>
</tr>
</tbody>
</table>

ASA = aspirin; CVD = cardiovascular disease; MI = myocardial infarction; NNH = number needed to harm; NNT = number needed to treat; TIA = transient ischemic attack.


---

Risk Factors for Bleeding with Aspirin

- Higher aspirin doses
- Longer duration of use
- History of GI ulcers or upper GI pain
- Bleeding disorders
- Renal failure
- Severe liver disease
- Thrombocytopenia
- Concurrent anticoagulation or NSAID use
- Older age
- Uncontrolled hypertension (risk of intracranial hemorrhage)


© 2021 American Society of Health-System Pharmacists, Inc. All rights reserved.
Which of these patients with diabetes is MOST qualified for aspirin therapy for primary CV prevention based solely on the information provided?

a. 34-year-old female with A1C 8.3% and BP 126/74  
b. 48-year-old male who smokes 1 ppd and has albuminuria  
c. 52-year-old male with an A1C 6.3% on chronic NSAIDs  
d. 72-year-old female with an A1C 7.5% and BP 146/84

---

**Antiplatelet Agents: Secondary CV Prevention Recommendations**

- **Secondary CV prevention strategy in people with diabetes and history of ASCVD**
  - Use aspirin therapy 75–162 mg/day [Level of Evidence A] (or clopidogrel 75 mg/day if documented aspirin allergy) [Level of Evidence B]
  - DAPT (with low-dose aspirin and a P2Y12 inhibitor) is reasonable for 1 year after an acute coronary syndrome and may have benefits beyond this period [Level of Evidence A]
  - Long-term treatment with DAPT should be considered for patients with PCI, high ischemic risk, and low bleeding risk to prevent major adverse CV events [Level of Evidence A]

DAPT with Clopidogrel + ASA in Patients at High Risk for Cardiovascular Events: CHARISMA

Individuals were eligible if they were 245 years of age and had one of the following conditions: multiple atherothrombotic risk factors, documented coronary disease, documented cerebrovascular disease, or documented symptomatic PAD.

Median follow-up = 28 months

People with an established atherothrombotic disease or at high risk for CV disease saw no significant benefit associated with ASA + clopidogrel compared with ASA + placebo.

Overall rate of bleeding was not significantly greater with ASA + clopidogrel than with ASA + placebo, except for increase in rate of moderate bleeding (2.1% vs. 1.3%; RR = 1.62 (1.27-2.08)).

ASA = aspirin; CV = cardiovascular; CVO = cerebrovascular disease; DAPT = dual antiplatelet therapy; HR = hazard ratio; MI = myocardial infarction; MRF = multiple risk factors; PAD = peripheral artery disease; PCI = percutaneous coronary intervention; TIA = transient ischemic attack.


DAPT with Ticagrelor + ASA in Patients with Stable Coronary Artery Disease and Diabetes: THEMIS1

**Asahi**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Ticagrelor + ASA* (n = 9,562)</th>
<th>ASA + Placebo* (n = 9,533)</th>
</tr>
</thead>
<tbody>
<tr>
<td>n (%)</td>
<td>Event rate per 100 patient years</td>
<td>Event rate per 100 patient years</td>
</tr>
<tr>
<td>Primary safety endpoint</td>
<td>206 (2.2)</td>
<td>0.89</td>
</tr>
</tbody>
</table>

*Intracranial bleeding, clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥ 5 g/dL, fatal bleeding

*All patients received ASA 75–150 mg daily unless contraindicated or not tolerated.

ASA = aspirin; CI = confidence interval; CV = cardiovascular; HR = hazard ratio; K-M = Kaplan-Meier; TIMI = thrombolysis in myocardial infarction.

DAPT with Ticagrelor + ASA in High-Risk Patients (Post-MI) with Diabetes: PEGASUS-TIMI-54 Subgroup Analysis

Efficacy of Pooled Ticagrelor in Patients with Prior MI by DM Status at 3 Years

People with diabetes were at higher risk of MACE than people without diabetes.
The RRR in MACE was consistent for the pooled data of ASA + ticagrelor vs. ASA + placebo in people with and without diabetes.

Which most accurately describes the current evidence for long-term (>12 mo) DAPT in decreasing the risk of MI, stroke, or CV death vs. placebo in diabetes?

- Clopidogrel + ASA decreased risk at 28 mo with no increased bleeding risk
- Clopidogrel + ASA decreased risk at 28 mo with an increased bleeding risk
- Ticagrelor + ASA decreased risk at 36 mo with no increased bleeding risk
- Ticagrelor + ASA decreased risk at 36 mo with an increased bleeding risk
Key Takeaways

• As the prevalence of T2D increases in the US and globally, so will CAD as a complication
• People with concomitant CAD and T2D are at higher risk of experiencing a CV event regardless of having a prior MI/stroke
• Current recommendations include lifestyle and pharmacologic approaches in people with T2D at risk of CV events, but an unmet clinical need still exists
• Platelet dysfunction, including platelet hyper-reactivity, is a key driver of thrombotic risk in people with CAD and T2D
• The role of ASA for primary prevention remains controversial, and there is a need to identify people at high risk who may derive the most benefit

Questions and Answers