MHIF FEATURED STUDY:  
**ATTR CM**

**CONDITION:** Transthyretin-Mediated Amyloid Cardiomyopathy  
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**RESEARCH CONTACTS:**  
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**SPONSOR:** Ionis Pharmaceuticals

**DESCRIPTION:** A Phase 3 Global, Double-Blind, Randomized, Placebo-Controlled Study to Evaluate the Efficacy and Safety of ION-682884 in Patients with Transthyretin-Mediated Amyloid Cardiomyopathy

ION-682884 vs. placebo administered by subcutaneous injection once every 4 weeks in patients with ATTR-CM receiving available background therapy. ION-682884 is a ligand-conjugated antisense drug designed to reduce the production of transthyretin to treat all types of TTR amyloidosis.

**CRITERIA LIST/QUALIFICATIONS:**

**Inclusion**
- Amyloid deposits in cardiac or non-cardiac tissue
- Medical history of HF secondary to hereditary or wild-type ATTR-CM

**Exclusion**
- Cardiomyopathy not primarily caused by ATTR-CM
- Significant co-morbidities
- Current treatment with inotersen, patisiran, diflunisal, doxycycline, non-dihydropyridine calcium-channel blocker
A 2021 Update on Post PCI Antithrombotic Therapy

Yashasvi Chugh, MD
Interventional Cardiology Fellow
No Disclosures
BALANCING ISCHEMIA & BLEEDING
4 Clinical Scenarios

- **Triple vs Dual** Therapy for PCI in AF
- Anti-thrombotic **therapy 1 year out** from PCI in AF
- **Short DAPT** scenarios
- **Prolonged DAPT** scenarios
Major Bleeding and MI: similar association with mortality in the first year after PCI

More Severe Bleeding equates to greater Risk of Mortality
Scenario 1:

My Patient with Atrial Fibrillation had a PCI
**WOEST 2013**

**Design:** Open Label, RCT (randomized before or 4h after PCI) Netherlands, Belgium

**Duration:** 1 year follow up

**Primary Outcome:**
Any TIMI Bleeding: $P<0.0001$

**Secondary Outcome:**
Combined Death, MI, Revascularization, Stroke, Stent Thrombosis: $P=0.025$

**Limitations:** underpowered to detect differences in thrombotic events

**ACS vs SIDH:** 25% ACS patients

**Stent Type:** 30% BMS vs 70% DES (in both groups)

**ASA:** Everyone loaded with 324mg

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After WOEST 2013 we questioned the standard paradigm of Triple Therapy (1 year)
**ISAR-TRIPLE 2015**

**Design:** Open Label, RCT, 3 centers Europe

**Duration:** 9 months

**Primary Outcome (Ischemic+Bleeding Events):** Net clinical benefit (death, MI, stent thrombosis, stroke, major bleeding): no difference

**Secondary Outcome (Ischemic Events):** Cardiac death, MI, stent thrombosis, or ischemic stroke: no difference

**Limitations:** modest sample size limit power to detect rare outcomes such as stent thrombosis.

**ACS vs SIDH:** 30% ACS

**Stent Type:** 0.5% BMS

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ISAR-TRIPLE 2015, Landmark Analysis

Analysis: 6 weeks vs 6 months of Triple Therapy

Primary Outcome (Ischemic+Bleeding Events): No Difference

Secondary Outcome (Ischemic Events): No Difference

Outcome BARC 1 to 5 Bleeding: More bleeding with Triple

ISAR TRIPLE 2015 helped shed light on safety of shorter duration of triple therapy (6 weeks vs 6 months)
What evidence is there for NOACs in AF + ACS?

- **PIONEER AF-PCI³**
  - Rivaroxaban
  - N=2,124

- **RE-DUAL PCI²**
  - Dabigatran
  - N=2,725

- **AUGUSTUS ACS/PCI³**
  - Apixaban
  - N=4,614

- **ENTRUST AF-PCI⁴,⁵**
  - Edoxaban
  - N=1,508

**2016**
- ANA 2016
- Parallel assignment

**2017**
- ESC 2017
- Parallel assignment

**2018**
- ACC 2019
- 2x2 factorial

**2019**
- ESC 2019
- Parallel assignment

None of these trials were powered for efficacy
**Design:** Open Label, RCT, 26 countries

**Duration:** 12 months

**Primary Outcome:** Clinically relevant bleeding

**Secondary Outcome:** CV death, MI, Stroke

**ACS vs SIDH:** ACS 51.6% (12% STEMI)

**Stent Type:** 66% DES

**ASA:** for 3 days after PCI

**2nd Antiplatelet:** 96% Plavix

**Limitations:** Not powered for efficacy, Rivaroxaban dose approved for AF is 20mg/day or 15mg (for renal impairment) vs 15mg/10mg in trial

Safety of Rivaroxaban based group > VKA based group

Similar Efficacy
**REDUAL-PCI 2017**

**Design:** Open Label, RCT, 41 countries

**Duration:** 14 months

**Primary Outcome:** Major or CRNM bleeding through follow-up

**Secondary Outcome:** Death, MI, Stroke, Systemic Embolism, Unplanned Revascularization (no difference)

**ACS vs SIDH:** ACS 50.5% (includes STEMI)

**Stent Type:** DES 82%

**ASA:** for 5 days post PCI

**2nd Antiplatelet:** 88% Plavix

**Limitations:** Not powered for efficacy

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No difference in secondary outcomes

Favors DAT
In both these trials, unclear if the low bleeding events were attributed to the use of a DOAC over VKA or to dropping ASA? (as there was no placebo arm)
**Design:** Open Label, RCT, 33 countries, placebo controlled

**Duration:** 6 months

**Limitations:** Not powered for efficacy

**ACS vs SIDH:** ACS 38% (includes STEMI)

**Stent Type:** DES only

**ASA:** for upto 14 days post PCI

**2nd Antiplatelet:** 93% Plavix

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**Stent Thrombosis (any): no significant difference**

Primary Outcome: Major or CRNM bleeding

RANDOMIZATION 1: Comparisons are apixaban versus warfarin HR 0.69 (95% CI 0.58-0.81); p < 0.001

RANDOMIZATION 2: Comparisons are aspirin versus placebo HR 1.89 (95% CI 1.59-2.24); p < 0.001

Secondary Outcome: Death, Hospitalization

RANDOMIZATION 1: HR 0.83 (95% CI 0.74-0.93); p = 0.002

RANDOMIZATION 2: HR 1.08 (95% CI 0.96-1.21); p = NS
AUGUSTUS helps to disentangle the individual contribution of DOACs and aspirin withdrawal on the risk of bleeding
**Design:** Open Label, RCT

**Duration:** 12 months

**Primary Outcome:** Major or CRNM bleeding at 12 months \( P=0.001 \) for noninferiority

**Secondary Outcome:** composite CV death, stroke, SEE, MI or definite stent thrombosis \( (p = \text{ns}) \)

**ACS vs SIDH:** 52% ACS

**Stent Type:** DES

**ASA:** upto 5 days post PCI

**2nd Antiplatelet:** 92% Plavix

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**Meta-Analysis 2019**

### ISTH MAJOR OR CLINICALLY RELEVANT NONMAJOR BLEEDING

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAT</td>
<td></td>
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<td></td>
<td></td>
</tr>
<tr>
<td>AUGUSTUS</td>
<td>204</td>
<td>2279</td>
<td>0.56</td>
<td>[0.47, 0.65]</td>
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<tr>
<td>ENTRUST AF-PCI</td>
<td>128</td>
<td>751</td>
<td>0.85</td>
<td>[0.68, 0.93]</td>
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<tr>
<td>PIONEER AF-PCI</td>
<td>117</td>
<td>696</td>
<td>0.66</td>
<td>[0.53, 0.81]</td>
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<tr>
<td>RE-DUAL PCI</td>
<td>305</td>
<td>1744</td>
<td>0.65</td>
<td>[0.56, 0.75]</td>
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<tr>
<td>TAT</td>
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**Lower Major Bleeding with DAT**

### MYOCARDIAL INFARCTION

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
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<tbody>
<tr>
<td>DAT</td>
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</tr>
<tr>
<td>AUGUSTUS</td>
<td>84</td>
<td>2307</td>
<td>1.24</td>
<td>[0.90, 1.69]</td>
</tr>
<tr>
<td>ENTRUST AF-PCI</td>
<td>29</td>
<td>751</td>
<td>1.27</td>
<td>[0.74, 2.17]</td>
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<tr>
<td>PIONEER AF-PCI</td>
<td>19</td>
<td>694</td>
<td>0.91</td>
<td>[0.49, 1.67]</td>
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<tr>
<td>RE-DUAL PCI</td>
<td>70</td>
<td>1744</td>
<td>1.36</td>
<td>[0.89, 2.08]</td>
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<tr>
<td>TAT</td>
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</table>

**Lower ICH with NOAC based DAT**

### STENT THROMBOSIS

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Events</th>
<th>Total</th>
<th>Weight</th>
<th>Risk Ratio M-H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>DAT</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AUGUSTUS</td>
<td>21</td>
<td>2307</td>
<td>1.91</td>
<td>[0.92, 3.95]</td>
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<tr>
<td>ENTRUST AF-PCI</td>
<td>8</td>
<td>751</td>
<td>1.34</td>
<td>[0.47, 3.84]</td>
</tr>
<tr>
<td>PIONEER AF-PCI</td>
<td>5</td>
<td>694</td>
<td>1.25</td>
<td>[0.34, 4.64]</td>
</tr>
<tr>
<td>RE-DUAL PCI</td>
<td>22</td>
<td>1744</td>
<td>1.55</td>
<td>[0.69, 3.46]</td>
</tr>
<tr>
<td>TAT</td>
<td></td>
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</tr>
</tbody>
</table>

**Increased risk of MI and ST with DAT**
Scenario 2:

How do I manage my Patient with Atrial Fibrillation who had PCI >1 year ago
**OAC ALONE 2019**

**Design:** Open Label, RCT, 111 sites

**OAC (DOAC or VKA) vs OAC + single antiplatelet (ASA or Plavix) 1 year after PCI**

**Duration:** 3 years, 696 patients

**Primary Outcome:** composite of all-cause death, myocardial infarction, stroke, or systemic embolism

**Secondary Outcome:** composite of the primary end point and major bleeding

**Limitations:** Terminated early because of slow enrollment, not powered

**ACS vs SIDH:** only SIHD

**Stent Type:** 71% DES

**ASA or PLAVIX as Single APT:** 86% ASA, 14% PLAVIX

**WARFARIN or DOAC:** 75% VKA

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**Figure 4. Cumulative incidence of the primary and major secondary end points.**

A and B, Kaplan–Meier curves showing the cumulative incidence of the primary end point (a composite of all-cause death, myocardial infarction, stroke, or systemic embolism; A) and major secondary end point (a composite of primary end point or major bleeding; B). APT indicates antiplatelet therapy, and OAC, oral anticoagulation.

<table>
<thead>
<tr>
<th>End Points</th>
<th>OAC Alone (N=344)</th>
<th>Combined OAC and APT (N=346)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value for Noninferiority</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Myocardial infarction</td>
<td>8 (23/0.93)</td>
<td>4 (12/0.46)</td>
<td>2.03 (0.64–7.59)</td>
<td>0.23</td>
<td></td>
</tr>
<tr>
<td>Stent thrombosis</td>
<td>2 (0.58/0.23)</td>
<td>0 (0.00/0.0)</td>
<td>NA*</td>
<td>0.15†</td>
<td></td>
</tr>
</tbody>
</table>
Design: Open Label, RCT, Japan

Rivaroxaban vs Rivaroxaban + single antiplatelet (ASA or P2Y12) 1 year after PCI or CABG in AF patients

Duration: 24 months

Efficacy Outcome: composite of stroke, systemic embolism, myocardial infarction, unstable angina requiring revascularization, or death from any cause

Safety Outcome: safety end point was major bleeding (ISTH)

Limitations: Rivaroxaban dose based on approval in Japan (10 mg or 15 mg once daily) vs (15mg/20 mg elsewhere)

Terminated Early, Increase Mortality in DAT

ACS vs SIDH: SIHD only

Stent Type: 70% DES

ASA or PLAVIX as Single APT: ASA 70%

OAC >> OAC + APT
North American Expert Consensus, 2021
1 Major or 2 Minor

Table 3. Definition of High Bleeding Risk According to Academic Research Consortium Criteria

<table>
<thead>
<tr>
<th>Major</th>
<th>Minor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Anticipated use of long-term oral anticoagulation*</td>
<td>Age ≥75 years</td>
</tr>
<tr>
<td>Severe or end-stage CKD (eGFR &lt;30 mls/min)</td>
<td>Moderate CKD (eGFR 30 to 59 mls/min)</td>
</tr>
<tr>
<td>Hemoglobin &lt;11 g/dL</td>
<td>Hemoglobin 11 to 12.9 g/dL for men and 11 to 11.9 g/dL for women</td>
</tr>
<tr>
<td>Spontaneous bleeding requiring hospitalization or transfusion in the past 6 months or at any time, if recurrent</td>
<td>Spontaneous bleeding requiring hospitalization or transfusion within the past 12 months not meeting the major criterion</td>
</tr>
<tr>
<td>Moderate or severe baseline thrombocytopenia (platelet count ≤100,000/µL)</td>
<td>Long-term use of oral NSAIDs or steroids</td>
</tr>
<tr>
<td>Chronic bleeding diathesis</td>
<td>Any ischemic stroke at any time not meeting the major criterion</td>
</tr>
<tr>
<td>Liver cirrhosis with portal hypertension</td>
<td>—</td>
</tr>
<tr>
<td>Active malignancy (excluding non-melanoma skin cancer) within the past 12 months</td>
<td>—</td>
</tr>
<tr>
<td>Previous spontaneous ICH (at any time)</td>
<td>—</td>
</tr>
<tr>
<td>Previous traumatic ICH within the past 12 months</td>
<td>—</td>
</tr>
<tr>
<td>Presence of a bAVM</td>
<td>—</td>
</tr>
<tr>
<td>Moderate or severe ischemic stroke within the past 6 months</td>
<td>—</td>
</tr>
<tr>
<td>Non-deferrable major surgery on DAPT</td>
<td>—</td>
</tr>
<tr>
<td>Recent major surgery or major trauma within 30 days before PCI</td>
<td>—</td>
</tr>
</tbody>
</table>

Adapted from Urban et al with permission. bAVM indicates brain arteriovenous malformation; CNS, central nervous system; DAPT, dual antiplatelet treatment; ICH, intracranial hemorrhage; NSAID, nonsteroidal anti-inflammatory drug; and OAC, oral anticoagulation.

Table 4. Definition of High Thrombotic and Ischemic Risk

<table>
<thead>
<tr>
<th>High thrombotic risk (early events)</th>
<th>High ischemic risk (long-term events)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Acute coronary syndrome</td>
<td>Previous myocardial infarction</td>
</tr>
<tr>
<td>Previous stent thrombosis while on antiplatelet treatment</td>
<td>Multivessel coronary artery disease</td>
</tr>
<tr>
<td>PCI complexity</td>
<td>Polysurgical disease</td>
</tr>
<tr>
<td>3 vessels treated</td>
<td>Diabetes mellitus</td>
</tr>
<tr>
<td>≥3 stents implanted</td>
<td>Chronic kidney disease</td>
</tr>
<tr>
<td>≥3 lesions treated</td>
<td>Heart failure</td>
</tr>
<tr>
<td>Bifurcation with 2 stents implanted</td>
<td>Total stent length &gt;60 mm</td>
</tr>
<tr>
<td>Surgical bypass graft PCI</td>
<td>Chronic total occlusion PCI</td>
</tr>
<tr>
<td>Atherectomy device use</td>
<td>Left main PCI</td>
</tr>
</tbody>
</table>

PCI indicates percutaneous coronary intervention.
AF patients undergoing PCI—2021 North American Consensus

**Default strategy**
- **Peri-PCI**
  - Triple Therapy (OAC + DAPT)
- **1 month**
  - Triple Therapy up to 1 month (OAC + DAPT)
- **3 months**
  - Double Therapy up to 12 months (OAC + P2Y12 inhibitor)
- **6 months**
  - Double Therapy up to 12 months (OAC + P2Y12 inhibitor)
- **12 months**
  - OAC alone
- **>12 months**
  - OAC alone

**Patients at high ischemic/thrombotic and low bleeding risk**
- **Peri-PCI**
  - Triple Therapy (OAC + DAPT)
- **1 month**
  - Triple Therapy up to 1 month (OAC + DAPT)
- **3 months**
  - Double Therapy up to 12 months (OAC + P2Y12 inhibitor)
- **6 months**
  - Double Therapy up to 12 months (OAC + P2Y12 inhibitor)
- **12 months**
  - OAC alone
- **>12 months**
  - OAC alone

**Patients at low ischemic/thrombotic or high bleeding risk**
- **Peri-PCI**
  - Triple Therapy (OAC + DAPT)
- **1 month**
  - Double Therapy up to 6 months (OAC + P2Y12 inhibitor)
- **3 months**
  - Double Therapy up to 6 months (OAC + P2Y12 inhibitor)
- **6 months**
  - Double Therapy up to 6 months (OAC + P2Y12 inhibitor)
- **12 months**
  - OAC alone
- **>12 months**
  - OAC alone

Peri-PCI period: inpatient stay until time of discharge or a few days longer, up to 1 week post-PCI.
OAC: prefer a NOAC over VKA if no contraindications.
Clopidogrel is the P2Y12 inhibitor of choice; ticagrelor may be considered in patients at high thrombotic and acceptable bleeding risks; avoid prasugrel.
Continuation of antiplatelet therapy in adjunct to OAC beyond one-year should be considered only for select patients with high risk for ischemic recurrences and low bleeding risk.
ASA vs PLACEBO

< 30d More Bleeding but less ischemic events

>30d More Bleeding, no difference in ischemic events

Figure. The risk/benefit tradeoff of aspirin over time.
Kaplan-Meier curves comparing aspirin and placebo for fatal, intracranial, or major bleeding (severe bleeding) from randomization to 30 days (A) and from 30 days to 6 months (B) and for cardiovascular death, stent thrombosis, myocardial infarction, or stroke (severe ischemic events) from randomization to 30 days (C) and from 30 days to 6 months (D). The y axis from randomization to 30 days goes from 0% to 3% and from 30 days to 6 months from 0% to 5%, reflecting the larger absolute number of events between 30 days to 6 months than randomization to 30 days.
Choosing The Right DOAC
<table>
<thead>
<tr>
<th>Drug</th>
<th>AF+PCI Trial</th>
<th>NVAF Trial</th>
<th>VTE Trial</th>
<th>Renal Dysfunction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Apixaban</td>
<td>5mg BID or 2.5mg BID</td>
<td>5mg BID</td>
<td>10mg BIDx7d, 5mg BID</td>
<td>2.5 mg BID if 2/3 i) Age&gt;80y (ii) Cr&gt;1.5 (iii) Wt&lt;60kg ESRD+</td>
</tr>
<tr>
<td>Dabigatran</td>
<td>150mg BID and 110mg BID</td>
<td>150mg BID and 110mg BID</td>
<td>5-10d parenteral AC, then 150mg BID</td>
<td>75mg BID if CrCL15-30ml/min</td>
</tr>
<tr>
<td>Edoxaban</td>
<td>60mg Daily and 30mg daily</td>
<td>60mg Daily</td>
<td>5-10d parenteral AC, then 60mg daily</td>
<td>30mg Daily, if CrCL15-50ml/min</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>15mg Daily, 10mg if CrCl 30-50</td>
<td>20mg Daily</td>
<td>15mg BIDx21d, 20mg daily</td>
<td>15mg Daily, if CrCL15-50ml/min</td>
</tr>
</tbody>
</table>
NOAC>VKA

PLAVIX best for DAT or TAT

ASA therapy during Hospital Stay followed by DAT

Know your thrombotic and bleeding risks

OAC alone at 1 year
Scenario 3:

My patient has a NSTEMI and needs surgery for her Breast Cancer ASAP
DILEMMA

Which Stent?: BMS, DES (New Gen)

DAPT Duration?

SAPT after DAPT with ASA or P2Y12i?
Figure 2  Evolving duration of antiplatelet therapy after percutaneous coronary intervention. BARC, Bleeding Academic Research Consortium; BMS, bare metal stents; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; ESC, European Society of Cardiology; PCI, percutaneous coronary intervention; PES, paclitaxel-eluting stent; SES, sirolimus-eluting stent; ST, stent thrombosis; U.S. FDA, United States Food and Drug Administration.
ACC/AHA 2016, ESC 2017 GUIDELINES ON DAPT

Irrespective of stent type (3m prefer, can do 1m)

DILEMMA

Which Stent?: BMS, DES (New Gen)
LEADERS FREE 2015

Design: DCS (Biofreedom: Polymer Free Umirolimus coated stent) vs BMS, 1:1 randomization, double blind, High bleeding risk patients

Duration: 390 days, 2466 patients

Primary Safety Outcome: composite of cardiac death, MI, ST

Secondary Efficacy Outcome: TLR

DAPT Duration: 1 month (ASA, PLAVIX) followed by ASA

SIHD/ACS: 59% SIHD
Design: ZES (Endeavor Spirit) vs BMS, 1:1
Randomization, Single Blinded, High Bleeding Risk Patients

Duration: 12 months, 828 patients

Primary Outcome: MACE (Death, MI, TVR)

ACS vs SIDH: 35% SIHD

DAPT Duration: 1 month (ASA, P2Y12i) followed by ASA

Rate of events for primary composite endpoint of death, myocardial infarction (MI), and target vessel revascularization (TVR) (A), MI (B), TVR (C), or definite or probable stent thrombosis (D) at 12 months. BMS = bare-metal stent(s); E-ZES = zotarolimus-eluting Endeavor Sprint stent(s); HRR = high bleeding risk; HR = hazard ratio.

J Am Coll Cardiol Intv 2016;9:426–36
LEADERS FREE II 2018

Design: DCS (Biolimus, BioFreedom Stent) vs BMS (historical cohort from LEADERS FREE 2015), High bleeding risk patients

Duration: 12 months, 1,203 patients

Primary Safety Outcome: composite of cardiac death, or MI

Primary Efficacy Outcome: TLR

DAPT Duration: 1 month (ASA, PLAVIX) followed by ASA

SIHD/ACS: 44% ACS

This trial led to the FDA approval of Biolimus A9
The End of BMS? LEADERS FREE II Shows Superiority of Polymer-Free, Drug-Coated Stent

DES are recommended over bare-metal stents for any PCI irrespective of:

- Clinical presentation.
- Lesion type.
- Planned non-cardiac surgery.
- Anticipated duration of DAPT.
- Concomitant anticoagulant therapy.  

BMS < DES (New Gen)

European Heart Journal (2021) 42, 1289–1367
Design: Polymer based ZES (Resolute) vs Polymer-free DCS (Biolimus, Biofreedom), Randomized, High Bleeding Risk Patients

Duration: 1 year, 1996 patients

Primary Outcome: Cardiac Death, MI or ST

Efficacy Outcome: composite Cardiac Death, Target Vessel MI, TLR

Limitations: High Ischemic and Bleeding events (high risk population studied?)

ACS vs SIDH: 38% SIHD

DAPT Duration: 1 month (ASA, P2Y12i) followed by ASA

Complex Lesions: 80%

**Figure 1.** Kaplan-Meier Time-to-Event Curves for the Primary Outcome and its Components.

Data for patients who were lost to follow-up or withdrew from the trial before 1 year were censored at the end of follow-up. Insets show the same data on an enlarged y axis.
Design: HBR patients, Xience (Everolimus) 1m vs 12m DAPT or 3m vs 12m DAPT (Xience 28 and Xience 90 patients compared to historical control)

Primary Safety Outcome: all death or MI

Clinically Relevant Bleeding: 1 or 3m vs 12m DAPT

Limitations: excluded STEMI, LM, Grafts, CTO, ISR

ACS vs SIDH: ~35%

Complex Lesions: ~40%
ACS Patients
DAPT STEMI 2018

**Design:** RCT, STEMI only, *(Resolute Onyx, Zotarolimus eluting)* 1:1, 6m (followed by ASA) vs 12m DAPT

**Duration:** 24 months months, 870 patients

**Primary Safety Outcome:** all-cause mortality, MI, CVA, Any Revascularization, Major Bleeding

**Limitations:** low sample size, high drop out after 6 months

**P2Y12i:** Plavix 40% Ticagrelor 30% Prasugrel 30%

**Complex:** 25%, excluded LM

BMJ 2018;363:k3793 | doi: 10.1136/bmj.k3793
Design: RCT, ACS only, 6m vs 12m DAPT followed by ASA (Xience (Everolimus), Resolute Onyx (Zotarolimus), Biomatrix (Biolimus))

31 sites, South Korea

Duration: 18 months, 2,712 patients

Primary Safety Outcome: MACCE – the composite of all-cause death, MI or stroke

Secondary Endpoint: BARC 2-5 bleeding

P2Y12i: Plavix 82%

Limitations: High rates of Plavix use (even though Ticagrelor and Prasugrel are superior)

Complex: 45%
BMS Obsolete

“Simple Coronary Lesion/SIHD” in HBR 1-3 month DAPT (6 month per guidelines)

“Complex Lesions/ACS” in HBR 3-6 months DAPT (12 month per guidelines)
Short DAPT followed by P2Y12i
TWILIGHT 2019

**Design:** RCT, 1:1 double blind, ASA+Ticagrelor 3m followed by Ticagrelor monotherapy VS ASA+Ticagrelor for 12 months

**Duration:** 12 months, 7,119 patients (HBR and High Ischemic Risk)

**Primary Outcome:** BARC 2, 3, or 5 bleeding

**Limitations:** excluded STEMI, shock

**ACS vs SIDH:** ACS 64%

**DAPT Duration:** 3 vs 12 months

**Lesion Types:** Complex
STOPDAPT-2 2019

Design: RCT, 1 month DAPT followed by Clopidogrel monotherapy vs 12 month DAPT followed by ASA monotherapy (DES- Xience, Everolimus eluting)

Duration: 1 year, 3,045 patients

Primary Outcome: Death, myocardial infarction (MI), stent thrombosis, stroke, TIMI major/minor bleeding

Secondary Outcome: TIMI bleeding

ACS vs SIDH: 62% SIHD

DAPT Duration: 1 month vs 12 months

Lesion Types: ~30% complex

**TICO 2020**

**Design:** RCT, (Orsiro, Ultrathin Sirolimus eluting), ASA+Ticagrelor 3m followed by Ticagrelor monotherapy VS ASA+Ticagrelor for 12 months in ACS patients

**Duration:** 12 months, 3,056 patients

**Primary Outcome:** Composite of death, MI, ST, TVR or TIMI major bleeding (NACE)

**ACS:** 1/3rd STEMI

**Lesion Types:** Complex 15%

**Limitations:** South Korea– High rates of IC imaging used, excluded HBR patients

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**POPULATION**

2428 Men
628 Women

Adults with acute coronary syndrome treated with drug-eluting stents
Mean age: 61 years

**INTERVENTION**

3056 Patients randomized

1527

Ticagrelor monotherapy after 3 months of DAPT
100 mg aspirin once daily and 90 mg ticagrelor twice daily for 3 months, then 90 mg ticagrelor twice daily for 9 months

1529

Ticagrelor-based DAPT for 12 months
100 mg aspirin once daily and 90 mg ticagrelor twice daily maintained for 12 months

**LOCATIONS**

38 Centers in South Korea

**PRIMARY OUTCOME**

1-year net adverse clinical events, defined as a composite of major bleeding and adverse cardiac and cerebrovascular events (death, myocardial infarction, stroke, thrombosis, stent, or target-vessel revascularization)

**FINDINGS**

Net adverse clinical events at 12 months

Ticagrelor monotherapy after 3 months of DAPT
3.9% (5% of 1527 patients)

Ticagrelor-based DAPT for 12 months
5.9% (89 of 1529 patients)

The difference was significant:

absolute difference = -1.98% (95% CI, -3.50 to -0.45)

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Complex Anatomy/ACS : Ticagrelor > Plavix

Short DAPT (3m) followed by P2Y12i (HBR)
BMI: High BMI reduce P2Y12i intensity (studies out of South East Asia VS USA)

East Asian: CYP2C19 mutation, poor Clopidogrel metabolism

Studies out of Japan/Korea: IVUS/OCT use
Time for New Guidelines incorporating Short DAPT?
ESC 2020 GUIDELINES ON DAPT (SIHD)

- **LOW**
  - 6 month DAPT (irrespective of stent type)

- **HIGH**
  - 3 month DAPT (irrespective of stent type)

- **VERY HIGH**
  - 1 month DAPT (irrespective of stent type)
Scenario 4:

My patient had PCI in 2003 with a 1st Gen DES. I am hesitant to go from DAPT to SAPT.
AHA/ACC 2016 Guidelines: SIHD>6m and ACS>12m (Class 2b) if tolerating well and at low bleeding risk

- PRODIGY 2012: 6m vs 24m
- DAPT 2014: 12m vs 30m
- ARCTIC 2014: 12m vs 18-24m
- OPTIDUAL 2015: 12m vs 48m
- NIPPON 2017: 6m vs 18m

6 RCTs
Plavix 100% 1st Gen DES or BMS 50%
Plavix 65% 1st Gen DES 40%
Plavix 90% 1st Gen DES 40%
Plavix 100% 1st Gen DES 35%
Plavix 99% 2nd Gen DES 100%
Plavix 99% 2nd Gen DES 100%

PRODIGY 2012
DAPT 2014
ARCTIC 2014
OPTIDUAL 2015

6m vs 24m
12m vs 30m
12m vs 18-24m
12m vs 48m

NIPPON 2017

6m vs 18m
6m vs 24m

Plavix 100% 1st Gen DES or BMS 50%
Plavix 65% 1st Gen DES 40%
Plavix 90% 1st Gen DES 40%
Plavix 100% 1st Gen DES 35%
Plavix 99% 2nd Gen DES 100%
Meta-Analysis 2019 (<12m vs >12m DAPT after PCI)

Benefit of >12m DAPT more apparent for ACS not SIHD patients
Network Meta-analysis, 2020 (79,073 patients)

Comparison | No. of Trials (Patients)
---|---
Extended-term vs 12-month | 5 (20,351)
Mid-term [Aspirin] vs 12-month | 8 (15,020)
Mid-term [Aspirin] vs Extended term | 3 (7,099)
Short-term [Aspirin] vs 12-month | 4 (7,514)
Short-term [P2Y12 inhibitor] vs 12-month | 4 (20,088)

Figure 1. Network of DAPT interventions.
The area of the circles is based on the total number of patients for each treatment among all trials. The thickness of the lines is based on the total number of studies comparing the 2 treatments. DAPT indicates dual antiplatelet therapy.
Shared Decision Making

- DAPT Score (≥2 favors >12m DAPT)
- PRECISE DAPT Score (<25 favors prolonged DAPT)
- PCI Complexity
- Stent Type
- Bleeding Risk
Evolving Concepts

• **Genotyping** (Clopidogrel non-responders) and **Platelet Function testing** to escalate or de-escalate therapy

• **Low dose Rivaroxaban** (with 2.5mg BID + ASA: COMPASS) or (ASA+PLAVIX: ATLAS ACS 2 TIMI-51), underutilized (↓ MACE, ↑ BLEEDING)
ONGOING TRIALS

• MASTER DAPT (1 vs 6m DAPT in HBR) *Ultimaster Tansei stent* (NCT03023020)

• BIOFLOW DAPT (1m DAPT) *Orsiro stent* (NCT04137510)

• TARGET-SAFE (1 vs 6m DAPT in HBR) *FirehawkTM Stent* (NCT03287167)
Thank You

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