Managing Atrial Fibrillation and ACS/PCI
Applying New Evidence to Clinical Practice

Dual Anti-Thrombotic Therapy in
Acute Coronary Syndromes (ACS) and Afib + PCI/ACS Patients

Robert C. Welsh, MD, FRCPC
Professor of Medicine, University of Alberta
Zone Clinical Department Head, Cardiac Sciences
Robert C. Welsh, MD, FRCPC

Faculty Disclosure (12 months):

- **Research and Clinical Trials:** Abbott Vascular, Astra Zeneca, Bayer, BMS, Boehringer Ingelheim, CIHR, CSL Behring LLC, Edwards Lifesciences, Eli Lilly, Jansen, Johnson and Johnson, Pfizer, Population Health Research Institute, University of Alberta Hospital Foundation

- **Consulting Fees/Honoraria:** Amgen, Astra Zeneca, Bayer, Bristol Myers-Squibb/Pfizer, Canadian Cardiovascular Society

- **Other:** University of Alberta (employee), Alberta Health Services (Clinical privileges) and President, The Canadian Centre for Clinicians and Scientists
Objectives

1. Briefly outline the dual antithrombotic therapy strategy in ACS and CAD
2. Discuss current evidence for Atrial Fibrillation patients with ACS/PCI
   – Discuss potential pragmatic strategies to manage these patients
Aspirin was established more than a quarter century ago as an evidence based therapy to reduce recurrent cardiovascular events in patients with coronary artery disease based upon limited data by contemporary standards. Subsequent clinical investigation has focused on the addition of antithrombotic agents on top of baseline aspirin therapy in the acute and chronic setting to reduce patient’s risk of further ischemic events; at the cost of increased bleeding complications.

The current armamentarium of potent and predictable antiplatelet and antithrombotic agents has ushered in a new era where clinicians and scientists are contemplating withdrawal of previously established agents to minimize bleeding risk while sustaining efficacy; indeed subtraction may lead to the next advance in the treatment of acute and chronic ischemic vascular disease.
Traditional treatment of ACS
Pathways For Thrombus Formation

Two pathways connecting tissue injury, coagulation, and platelet response.

Platelet Pathway

- Collagen
- ADP
- TXA

Platelet activation
Platelet aggregation

Coagulation Pathway

- Tissue Factor
- Plasma Clotting cascade
- Prothrombin

Thrombin

- Fibrinogen → Fibrin

Dual Anti-Platelet Therapy
ASA + Clopidogrel/Prasugrel or Ticagrelor

Oral Antithrombotic

THROMBUS
Pathways For Thrombus Formation

Two pathways connecting tissue injury, coagulation, and platelet response.

Platelet Pathway

- Collagen
- TXA$_2$
- ADP

Platelet activation

- Platelet aggregation

Coagulation Pathway

- Tissue Factor
- Plasma Clotting cascade
- Prothrombin

- Thrombin

- Fibrinogen
- Fibrin

Single Effective Predictable
Anti-platelet

Effective Predictable
Anti-coagulant

A critical reappraisal of aspirin for secondary prevention in patients with ischemic heart disease

Welsh et al, AHJ 2016.
Novel strategies to improve secondary prevention following ACS

**Diagnosis**
- Dual pathway
- Rivaroxaban + ADP R antagonist
- GEMINI ACS

**One month**
- DAPT
- Ticagrelor monotherapy

**Twelve months**
- Global Leaders
- COMPASS
- Dual Pathway or OAC

**Acute Coronary Syndromes**

**Atrial Fibrillation**

**OAC**

Welsh et al, AHJ 2016.
Study Design

Recent ACS
Stabilised >48 hours and ≤10 days from hospitalisation for index event

ASA

Stratify by MD decision to use either clopidogrel or ticagrelor

Clopidogrel (n=1500)

Ticagrelor (n=1500)

R

Clopidogrel
75 mg od
ASA
Rivaroxaban
2.5 mg bid

Ticagrelor
90 mg bid
ASA
Rivaroxaban
2.5 mg bid

Minimum 180; Maximum 360, Day F/U

Primary endpoint: TIMI clinically significant bleeding
Exploratory efficacy endpoint: Composite of CV death, MI, ischaemic stroke or stent thrombosis

R=Randomisation; F/U=Follow up.

ClinicalTrials.gov Identifier: NCT02293395.
Available at: https://clinicaltrials.gov/ct2/show/NCT02293395 (accessed October 2016).
75 year old man – Chest Discomfort
Onset at 6:35 am Calls EMS – at 7:55
Denies past medical history/medical therapy

Triaged directly to cath lab
Primary PCI - DES in LAD
ASA 160 mg/Ticagrelor 180 mg
Enoxaparin 0.5mg/kg

Review of electronic records: Past untreated hypertension and Diabetes Mellitus (HBA1C=7.2), past ECG’s=Atrial Fibrillation,
75 year old man – Chest Discomfort Onset at 6:35 am Calls EMS – at 7:55

What anti-thrombotic strategy do you apply to manage this patient?

Triaged directly to cath lab
Primary PCI - DES in LAD
ASA 160 mg/Ticagrelor 180 mg
Enoxaparin 0.5mg/kg

Review of electronic records: Past untreated hypertension and Diabetes Mellitus (HBA1C=7.2), past ECG’s=Atrial Fibrillation,
The Overlap of AF and CAD

AF
AF + CAD
PCI
ACS

Atrial Fibrillation
Coronary Artery Disease
Up to 30% of AF patients

Up to 21% of ACS patients have AF

Percutaneous Coronary Intervention
Acute Coronary Syndrome
Combination Anti-thrombotic Therapy
Stroke and Bleeding in Perspective
(Danish Registry – 82,000)

HR of nonfatal (n = 9785) and fatal (n = 3537) ischemic stroke

- Warfarin monotherapy: 1.83 (1.73-1.94)
- Aspirin monotherapy: 1.86 (1.52-2.27)
- Clopidogrel monotherapy: 1.56 (1.17-2.10)
- Aspirin + clopidogrel: 1.27 (1.14-1.40)
- Warfarin + aspirin: 0.70 (0.35-1.40)
- Warfarin + clopidogrel: 1.45 (0.84-2.52)
- Triple therapy

HR of nonfatal (n = 12191) and fatal (n = 1381) bleeding

- Warfarin monotherapy: 0.93 (0.88-0.98)
- Aspirin monotherapy: 1.06 (0.87-1.29)
- Clopidogrel monotherapy: 1.66 (1.34-2.04)
- Aspirin + clopidogrel: 1.83 (1.72-1.96)
- Warfarin + aspirin: 3.08 (2.32-3.91)
- Warfarin + clopidogrel: 3.70 (2.89-4.76)
- Triple therapy

Less intensive antiplatelet therapy may be effective in combination with an anticoagulant

**Primary Endpoint (Any Bleeding)**

Atrial Fib. - VKA + ASA + Clopidogrel
Atrial Fib. - VKA + Clopidogrel

Death/MI/Stroke/Target Vessel Revascularization/Stent Thrombosis Triple 17.6% vs. Double 11.1% (HR 0.60 (0.38-0.94), p<0.025)

~25% had an ACS at baseline
ISAR-TRIPLE Trial: Afib + PCI

Cardiac death, myocardial infarction, stent thrombosis or ischemic stroke

Post-hoc landmark analysis of any BARC Bleeding before and after 6 weeks (6w)

HR 0.93 (0.43 - 2.05), p=0.87

HR 0.68 (0.47 - 0.98), p=0.04
2016 Focused Update of the Canadian Cardiovascular Society Guidelines for the Management of Atrial Fibrillation

For patients with AF in association with NSTEACS or STEMI

Age < 65 and CHADS$_2$ = 0

No PCI

ASA + Ticagrelor or Clopidogrel for 12 months

ASA alone after 12 months

Age ≥ 65 or CHADS$_2$ ≥ 1

No PCI

OAC$^*$ + Clopidogrel for 12 months

OAC$^*$ alone after 12 months

PCI

ASA + Ticagrelor or Prasugrel or Clopidogrel for 12 months

ASA alone after 12 months

OAC$^*$ + Clopidogrel + ASA for 3 to 6 months

OAC$^*$ + Clopidogrel through to 12 months

Evidence Free Zone

$^*$ A NOAC is preferred over warfarin for non-valvular AF
Canadian Patterns of Practice

DAPT following PCI AND surviving to hospital discharge - December 2011-May 2013

- 2034 AMI
- 86% Double therapy
- 14% Triple therapy
- 28% New Antiplatelet
- 26% New Antiplatelet
- 50% NOAC

Sra et al; American Heart Journal, Volume 180, 2016, 82–89
Numerous Strategies for the AF Patient Undergoing PCI

Numerous Strategies!
~2.8 million permutations/year

Thienopyridine
Choice + Duration

ASA
Dose + Duration

OAC
Choice + Dose

Gibson CM, J Am Coll Cardiol 2016
### Current Trials - Afib + ACS/PCI

<table>
<thead>
<tr>
<th>Study</th>
<th>Anti-thrombotic strategies</th>
<th>Specific Details</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>RE-DUAL PCI</strong></td>
<td>Dabigitran 150 + P2Y12 inhibitor</td>
<td>Complex patients ASA continued for 1 month in Dabigitran arms</td>
</tr>
<tr>
<td></td>
<td>Dabigitran 110 + P2Y12 inhibitor</td>
<td>P2Y12 inhibitor = clopidogrel or ticagrelor</td>
</tr>
<tr>
<td></td>
<td>Warfarin + P2Y12 inhibitor + ASA</td>
<td></td>
</tr>
<tr>
<td><strong>PIONEER AF-PCI</strong></td>
<td>Rivaroxaban 15 mg + clopidogrel for 12 months</td>
<td>Duration of DAPT left at discretion of site investigator</td>
</tr>
<tr>
<td></td>
<td>Rivaroxaban 2.5 mg bid + DAPT for 1, 6, or 12 months followed by rivaroxaban 15 mg and ASA</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Warfarin + DAPT for 1, 6, or 12 months followed by warfarin and ASA</td>
<td></td>
</tr>
<tr>
<td><strong>AUGUSTUS</strong></td>
<td>Apixaban (afib dose) vs warfarin</td>
<td>2X2 factorial design</td>
</tr>
<tr>
<td></td>
<td>ASA vs placebo</td>
<td>All patients on a P2Y2 inhibitor for 6 months</td>
</tr>
<tr>
<td><strong>ENTRUST-AF-PCI</strong></td>
<td>Edoxaban 60 mg/day + P2Y12 inhibitor vs. Warfarin P2Y12 inhibitor with ASA 1-12 months</td>
<td>12 months duration</td>
</tr>
<tr>
<td></td>
<td></td>
<td>ASA duration chosen by patient presentation</td>
</tr>
</tbody>
</table>
Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI

- Primary endpoint: TIMI major + minor + bleeding requiring medical attention
- Secondary endpoint: CV death, MI, and stroke (Ischemic, Hemorrhagic, or Uncertain Origin)

*Rivaroxaban dosed at 10 mg once daily in patients with CrCl of 30 to <50 mL/min.
†Alternative P2Y12 inhibitors: 10 mg once-daily prasugrel or 90 mg twice-daily ticagrelor.
‡Low-dose aspirin (75-100 mg/d). ∆ Open label VKA


Gibson et al. AHA 2016
Stent Thrombosis Reduction with Oral Anticoagulation

ARC Definite/probable/ possible

- Placebo (n=2724)
- Rivaroxaban combined (n=4261)

RR 0.69 (0.51-0.93)
*Modified ITT p=0.016
ITT p=0.008

ARC Definite/probable: HR=0.65, mITT p=0.017, ITT p=0.012

Existing Evidence with Reduced Dose Rivaroxaban 15 mg OD ROCKET AF in moderate renal impairment

Primary efficacy endpoint: Stroke or SE

<table>
<thead>
<tr>
<th>Event rate (%/year)</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE</td>
<td>2.32</td>
<td>2.77</td>
</tr>
</tbody>
</table>

HR 0.84 (95% CI 0.57–1.23)

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>1,434</td>
<td>1,439</td>
</tr>
<tr>
<td></td>
<td>1,226</td>
<td>1,261</td>
</tr>
<tr>
<td></td>
<td>1,103</td>
<td>1,140</td>
</tr>
<tr>
<td></td>
<td>1,027</td>
<td>1,052</td>
</tr>
<tr>
<td></td>
<td>806</td>
<td>832</td>
</tr>
<tr>
<td></td>
<td>621</td>
<td>656</td>
</tr>
<tr>
<td></td>
<td>442</td>
<td>455</td>
</tr>
<tr>
<td></td>
<td>275</td>
<td>272</td>
</tr>
</tbody>
</table>

Per-protocol on-treatment population

Existing Evidence with Reduced Dose Rivaroxaban 15 mg OD
J-ROCKET AF

<table>
<thead>
<tr>
<th>Event rate (%/year)</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke/SE</td>
<td>1.26</td>
<td>2.61</td>
</tr>
</tbody>
</table>

HR=0.49 (95% CI 0.24–1.00)

\(p=0.050\) (two-sided test)

Per-protocol population on-treatment; Analysis method: Cox proportional hazard model
Hori M et al, Circ J 2012;76:2104–2111
Baseline Demographics

Patients enrolled

Age 70 (+/- 9) years (mean)
Female sex 25%
CrCl 78 (ml/min) (mean)
CHA\textsubscript{2}DS\textsubscript{2}-VASC 3.8 (mean)

Afib paroxysmal – 44%
Afib permanent – 35%
Afib persistent – 21%
HAS-BLED 3.0 (mean)

*Values calculated from data in published manuscript (not explicitly stated)
Pre-Randomization Choice of Duration of DAPT & Thienopyridine: PIONEER AF-PCI

- 2124 patients with NVAF
- Coronary stenting
- No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

Group 1: Rivaroxaban 15 mg qd*
Clopi 95%, Ticag 4%, Prasugrel 1%

1 mo: 16%
6 mos: 35%
12 mos: 49%

Group 2: Rivaroxaban 2.5 mg bid
Clopi 95%, Ticag 4%, Prasugrel 1%
Aspirin 75-100 mg qd

1 mo: 16%
6 mos: 35%
12 mos: 49%

Group 3: VKA (target INR 2.0-3.0)
Clopi 95%, Ticag 4%, Prasugrel 1%
Aspirin 75-100 mg qd

VKA TTR ~65%
Primary Outcome
Rivaroxaban Strategies were Associated With Improved Safety

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=0.59; (95% CI 0.47–0.76); p<0.001
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.63 (95% CI 0.50–0.80); p<0.001

All subgroups analyzed were consistent with overall results

Primary Safety Endpoint
Reduced with Rivaroxaban Strategies vs VKA

Both rivaroxaban strategies associated with significant reduction in incidence of clinically significant bleeding vs the VKA plus DAPT strategy

*p=0.002 vs Group 3; **p<0.001 vs Group 3; #composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention

Bleeding with Rivaroxaban 15 mg Strategy vs VKA plus DAPT - Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>0.56</td>
<td>0.41–0.77</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>≥75 years</td>
<td>0.62</td>
<td>0.42–0.90</td>
<td></td>
<td>0.011</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.63</td>
<td>0.47–0.84</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>Female</td>
<td>0.51</td>
<td>0.32–0.80</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td><strong>Type of stent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-eluting</td>
<td>0.64</td>
<td>0.47–0.86</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Bare metal</td>
<td>0.54</td>
<td>0.36–0.82</td>
<td></td>
<td>0.003</td>
</tr>
<tr>
<td>Both</td>
<td>0.20</td>
<td>0.02–1.82</td>
<td></td>
<td>0.115</td>
</tr>
<tr>
<td><strong>Type of P2Y₁₂ inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0.59</td>
<td>0.46–0.76</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>1.16</td>
<td>0.22–6.03</td>
<td></td>
<td>0.857</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>0.33</td>
<td>0.11–1.01</td>
<td></td>
<td>0.039</td>
</tr>
</tbody>
</table>

*Composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention


No significant p-value for interaction
Bleeding with Rivaroxaban 2.5 mg Strategy vs VKA plus DAPT - Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR</th>
<th>95% CI</th>
<th>HR (95% CI)</th>
<th>p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;75 years</td>
<td>0.60</td>
<td>0.45–0.82</td>
<td></td>
<td>0.001</td>
</tr>
<tr>
<td>≥75 years</td>
<td>0.66</td>
<td>0.46–0.96</td>
<td></td>
<td>0.03</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.71</td>
<td>0.54–0.93</td>
<td></td>
<td>0.012</td>
</tr>
<tr>
<td>Female</td>
<td>0.47</td>
<td>0.29–0.76</td>
<td></td>
<td>0.002</td>
</tr>
<tr>
<td><strong>Intended DAPT duration</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1 month</td>
<td>0.68</td>
<td>0.38–1.23</td>
<td></td>
<td>0.198</td>
</tr>
<tr>
<td>6 months</td>
<td>0.51</td>
<td>0.34–0.75</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>12 months</td>
<td>0.74</td>
<td>0.52–1.04</td>
<td></td>
<td>0.081</td>
</tr>
<tr>
<td><strong>Type of stent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Drug-eluting</td>
<td>0.76</td>
<td>0.57–1.01</td>
<td></td>
<td>0.057</td>
</tr>
<tr>
<td>Bare metal</td>
<td>0.45</td>
<td>0.29–0.70</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Both</td>
<td>0.35</td>
<td>0.06–1.92</td>
<td></td>
<td>0.207</td>
</tr>
<tr>
<td><strong>Type of P2Y₁₂ inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>0.62</td>
<td>0.48–0.79</td>
<td></td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>0.88</td>
<td>0.16–4.81</td>
<td></td>
<td>0.881</td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>0.59</td>
<td>0.23–1.53</td>
<td></td>
<td>0.273</td>
</tr>
</tbody>
</table>

*Composite of TIMI major bleeding, TIMI minor bleeding and bleeding requiring medical attention


No significant p-value for interaction
Efficacy Composite

Rivaroxaban 15 mg OD plus single antiplatelet vs VKA plus DAPT: HR=1.08; (95% CI 0.69–1.68); p=0.750
Rivaroxaban 2.5 mg BID plus DAPT vs VKA plus DAPT: HR=0.93 (95% CI 0.59–1.48); p=0.765

All subgroups analyzed were consistent with overall results

*Trial not powered to definitively demonstrate either superiority or non-inferiority for efficacy endpoints

Incidence of major adverse CV events was comparable between all three treatment strategies; however, the trial was not powered for efficacy.

*Composite of CV death, MI and stroke
Health Economics
Time to All Cause Death or First Rehospitalization

Gibson CM et al, Circulation 2016; doi:10.1161/CIRCULATIONAHA.116.025783
Re-hospitalization Due to CV Events and Bleeding

Adverse events leading to hospitalization were classified by consensus panel blinded to treatment group as potentially related to either bleeding, CV or other causes; Rehospitalizations do not include the index event and include the first rehospitalization after the index event.

Gibson CM et al, Circulation 2016; doi:10.1161/CIRCULATIONAHA.116.025783
A NOAC is preferred over warfarin for non-valvular AF.

CCS = Canadian Cardiovascular Society.

2016 CCS Atrial Fibrillation Guidelines: Patients with AF/ACS

For patients with AF in association with NSTEACS or STEMI

Age < 65 and CHADS$_2$ = 0

No PCI

ASA + Ticagrelor or Clopidogrel for 12 months

ASA alone after 12 months

PCI

ASA + Ticagrelor or Prasugrel or Clopidogrel for 12 months

ASA alone after 12 months

Age ≥ 65 or CHADS$_2$ ≥ 1

No PCI

OAC* + Clopidogrel for 12 months

OAC* alone after 12 months

PCI

OAC* + Clopidogrel + ASA for 3 to 6 months

OAC* + Clopidogrel through to 12 months

OAC* alone after 12 months

*A NOAC is preferred over warfarin for non-valvular AF.
NSTEACS = Non-ST elevation acute coronary syndromes.
Summary

For Afib + ACS/PCI patients

• Currently pragmatic strategies are applied to individual patient management balancing the risk for ischemic and hemorrhagic complications

• The PIONEER AF-PCI strategies enhance safety compared to triple therapy (ASA, clopidogrel, warfarin) and represents the new standard of care in this high risk patient population

• Research with the other NOAC agents continues
Managing Atrial Fibrillation and ACS/PCI
Applying New Evidence to Clinical Practice

• The PIONEER AF-PCI strategies apply to a large proportion of Afib and ACS/PCI patients
  – In Canada, Rivaroxaban 15mg and a P2Y12 inhibitor
  – Holds true for:
    • higher bleed risk patients
    • with BMS or DES
    • elective PCI and PCI with ACS
    • Clopidogrel - ticagrelor? Prasugrel???
Managing Atrial Fibrillation and ACS/PCI
Applying New Evidence to Clinical Practice

• Patient populations with special consideration for applying the PIONEER AF-PCI strategies
  1. Prior Stroke/high CHADS$_2$ score patients
  2. Extensive stenting (>100mm) or high stent thrombosis techniques
  3. Both 1 & 2
Managing Atrial Fibrillation and ACS/PCI
Applying New Evidence to Clinical Practice

Robert C. Welsh, MD, FRCPC
Professor of Medicine, University of Alberta
Zone Clinical Department Head, Cardiac Sciences