Changing Course: Anticoagulation in Secondary Prevention of Cardiovascular Disease Events
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This activity discusses an off-label use for rivaroxaban.
Platelet Amplification
Two Positive Feedback Loops

Thrombin Made on Platelet Surface

ADP Secreted by Platelet

Thrombin Most Potent Activator of Platelet

ADP Activates Platelet

“Amplification”
“Burst”
“Activation”
“Growth of Thrombus”

Antithrombins

Thienopyridines

Slide by C. Michael Gibson, M.S., M.D.
Ex vivo effects of single administration of CS-747 on washed platelet aggregation induced by ADP (A), collagen (B), and thrombin (C) in rats. CS-747 was orally administered once to rats at doses of 0.3 and 3 mg kg⁻¹. The aggregation was measured 4 h after the dosing. Results are presented as the mean±s.e.mean (n=6). **P<0.01 vs control (vehicle-treated group).

“Treatment with CS-747 (Prasugrel) inhibited ex vivo washed platelet aggregation in response to ADP but not to thrombin. This is consistent with the hypothesis that the antiaggregative action of CS-747 (Prasugrel) is due to its specific inhibition of the G_i-linked P2T receptor rather than its interference with the fibrinogen receptors.”

ACS Is Associated With Long Term Abnormalities in Coagulation

Christina Yip¹, Aruni Seneviratna², Sock Hwee Tan², Sock Cheng Poh², Zhen Long Teo³, Joshua Loh², Eng Soo Yap¹,⁴, E. Magnus Ohman⁵, C. Michael Gibson⁶, Mark Richards²,³ and Mark Chan²,³

Slide by C. Michael Gibson, M.S., M.D.
PHASE 2 STUDY DESIGN

Recent ACS Patients
Stabilized 1-7 Days Post-Index Event

MD Decision to Treat with Clopidogrel

NO

STRATUM 1
ASA Alone
N=761

PLACEBO
N=253
5 mg (77)
10 mg (98)
20 mg (78)

RIVA QD
N=254
5 mg (77)
10 mg (99)
20 mg (78)

RIVA BID
N=254
2.5 mg (77)
5 mg (77)
10 mg (97)
20 mg (80)

YES

STRATUM 2
ASA + Clop.
N=2,730

PLACEBO
N=254
5 mg (74)
10 mg (428)
15 mg (178)
20 mg (227)

RIVA QD
N=912
5 mg (78)
10 mg (430)
15 mg (178)
20 mg (226)

RIVA BID
N=911
2.5 mg (76)
5 mg (430)
7.5 mg (178)
10 mg (227)

N = 3,491
21 Doses

6 Month Bleeding / Efficacy

Aspirin 75-100 mg

Gibson CM, AHA 2008

Slide by C. Michael Gibson, M.S., M.D.
PRIMARY SAFETY ENDPOINT: CLINICALLY SIGNIFICANT BLEEDING

(= TIMI Major, TIMI Minor, Bleed Req. Med. Attn.)

Total Daily Dose:
- Rivaroxaban 20 mg
- Rivaroxaban 15 mg
- Rivaroxaban 10 mg
- Rivaroxaban 5 mg
- Placebo

Clinically Significant Bleeding (%)

Days After Start of Treatment

0 30 60 90 120 150 180

HR

15.3% 12.7% 10.9% 6.1% 3.3%

5.1 (3.4-7.4) 3.6 (2.3-5.6) 3.4 (2.3-4.9) 2.2 (1.25-3.91)

*p<0.01 for placebo Vs Riva 5mg. p<0.001 for Riva 10,15,20mg vs placebo

Slide by C. Michael Gibson, M.S., M.D.  Gibson CM, AHA 2008
SECONDARY EFFICACY ENDPOINT:
Incidence of Death / MI / Stroke

All Rivaroxaban
(n = 2331)

All Placebo
(n = 1160)

HR 0.69
(0.50-0.96)
P = 0.028

ARR = 1.6%
NNT = 63

P = 0.028

5.5%
3.9%

Death / MI / Stroke (%)

Days After Randomization

Slide by C. Michael Gibson, M.S., M.D.
Recent ACS: STEMI, NSTEMI, UA
Stabilized 1-7 Days Post-Index Event

Exclusions: increased bleeding risk, warfarin use, ICH, prior stroke if on ASA + thienopyridine

PRIMARY ENDPOINTS:
EFFICACY: CV Death, MI, Stroke (Ischemic, Hemorrhagic, or Uncertain Origin)
SAFETY: TIMI major bleeding not associated with CABG

Event driven trial with 1,002 primary efficacy events

Placebo
n=5,176

Rivaroxaban
2.5 mg BID
n=5,174

Rivaroxaban
5.0 mg BID
n=5,176

ASA 75 to 100 mg/day

Stratified by Thienopyridine Use at MD Discretion

Gibson CM, AHA 2011

Slide by C. Michael Gibson, M.S., M.D.
Months After Randomization

**PRIMARY EFFICACY ENDPOINT:**

CV Death / MI / Stroke

Rivaroxaban (both doses)

HR 0.84 (0.74-0.96)

mITT p = 0.008

ITT p = 0.002

ARR 1.8%

NNT = 56

Placebo

Rivaroxaban

Estimated Cumulative Incidence (%)

No. at Risk

Placebo  5113  4307  3470  2664  1831  1079  421

Rivaroxaban  10229  8502  6753  5137  3554  2084  831

2 Yr KM Estimate

Placebo 10.7%

Rivaroxaban 8.9%

Slide by C. Michael Gibson, M.S., M.D.
Efficacy Endpoints:
Very Low Dose 2.5 mg BID
Patients Treated with ASA + Thienopyridine

CV Death / MI / Stroke
- Placebo
  - HR 0.85
  - mITT p=0.039
  - ITT p=0.011
- Rivaroxaban 2.5 mg BID
  - NNT = 71

Cardiovascular Death
- Placebo
  - HR 0.62
  - mITT p<0.001
  - ITT p<0.001
- Rivaroxaban 2.5 mg BID
  - NNT = 59

All Cause Death
- Placebo
  - HR 0.64
  - mITT p<0.001
  - ITT p<0.001
- Rivaroxaban 2.5 mg BID
  - NNT = 56

Slide by C. Michael Gibson, M.S., M.D.
Gibson CM, AHA 2011
Objective: efficacy and safety of rivaroxaban, low-dose rivaroxaban plus ASA or ASA alone for reducing risk of MI, stroke or CV death in CAD or PAD

Rivaroxaban 2.5 mg bid ± ASA 100 mg od ± pantoprazole 40 mg od

Rivaroxaban 5.0 mg bid ± ASA 100 mg od ± pantoprazole 40 mg od

ASA 100 mg od ± pantoprazole 40 mg od

N~27,000

1:1:1

30-day run-in, ASA 100 mg

30-day washout period*

Final follow-up visit#

Final washout period visit

*Patients treated according to local standard of care

#≤30 days of the required pre-specified number of events having occurred

Slide by C. Michael Gibson, M.S., M.D.
### Primary: CV death, stroke, MI

<table>
<thead>
<tr>
<th>Outcome</th>
<th>N (%)</th>
<th>N (%)</th>
<th>N (%)</th>
<th>HR (95% CI)</th>
<th>p</th>
<th>HR (95% CI)</th>
<th>p</th>
</tr>
</thead>
<tbody>
<tr>
<td>CV death, stroke, MI</td>
<td>379 (4.1%)</td>
<td>448 (4.9%)</td>
<td>496 (5.4%)</td>
<td>0.76 (0.66-0.86)</td>
<td>&lt;0.0001</td>
<td>0.90 (0.79-1.03)</td>
<td>0.12</td>
</tr>
</tbody>
</table>
Primary: CV death, stroke, MI

Rivaroxaban + Aspirin vs. Aspirin  HR: 0.76, 95% CI 0.68-0.86, P<0.0001
Rivaroxaban vs. Aspirin    HR: 0.90, 95% CI 0.79-1.03, P= 0.12

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Year</th>
<th>Rivaroxaban + Aspirin</th>
<th>Rivaroxaban</th>
<th>Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td>9152</td>
<td>0</td>
<td>9117</td>
<td>9126</td>
<td></td>
</tr>
<tr>
<td>7904</td>
<td>1</td>
<td>7824</td>
<td>7908</td>
<td></td>
</tr>
<tr>
<td>3912</td>
<td>2</td>
<td>3862</td>
<td>3860</td>
<td></td>
</tr>
<tr>
<td>658</td>
<td>3</td>
<td>670</td>
<td>669</td>
<td></td>
</tr>
</tbody>
</table>

*Slide by C. Michael Gibson, M.S., M.D.*
## Secondary outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban + Aspirin N=9,152</th>
<th>Aspirin N=9,126</th>
<th>Rivaroxaban + Aspirin vs. Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>CHD death, IS, MI, ALI</td>
<td>329 (3.6%)</td>
<td>450 (4.9%)</td>
<td>0.72 (0.63-0.83)</td>
</tr>
<tr>
<td>CV death, IS, MI, ALI</td>
<td>389 (4.3%)</td>
<td>516 (5.7%)</td>
<td>0.74 (0.65-0.85)</td>
</tr>
<tr>
<td>Mortality</td>
<td>313 (3.4%)</td>
<td>378 (4.1%)</td>
<td>0.82 (0.71-0.96)</td>
</tr>
</tbody>
</table>

* pre-specified threshold P=0.0025

*Slide by C. Michael Gibson, M.S., M.D.*
## CAD and PAD
### Subgroups for primary outcome

<table>
<thead>
<tr>
<th>Outcome</th>
<th>R + A N=9,152</th>
<th>A N=9,126</th>
<th>Rivaroxaban + Aspirin vs. Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td>CAD</td>
<td>347 (4.2%)</td>
<td>460 (5.6%)</td>
<td>0.74 (0.65-0.86)</td>
</tr>
<tr>
<td>PAD</td>
<td>126 (5.1%)</td>
<td>174 (6.9%)</td>
<td>0.72 (0.57-0.90)</td>
</tr>
</tbody>
</table>

*Slide by C. Michael Gibson, M.S., M.D.*
### Major bleeding

<table>
<thead>
<tr>
<th>Outcome</th>
<th>R + A N=9,152</th>
<th>R N=9,117</th>
<th>A N=9,126</th>
<th>Rivaroxaban + Aspirin vs. Aspirin</th>
<th>Rivaroxaban vs. Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N (%)</td>
<td>N (%)</td>
<td>N (%)</td>
<td>HR (95% CI)</td>
<td>P</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>288 (3.1%)</td>
<td>255 (2.8%)</td>
<td>170 (1.9%)</td>
<td>1.70 (1.40-2.05)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Fatal</td>
<td>15 (0.2%)</td>
<td>14 (0.2%)</td>
<td>10 (0.1%)</td>
<td>1.49 (0.67-3.33)</td>
<td>0.32</td>
</tr>
<tr>
<td>Non-fatal ICH*</td>
<td>21 (0.2%)</td>
<td>32 (0.4%)</td>
<td>19 (0.2%)</td>
<td>1.10 (0.59-2.04)</td>
<td>0.77</td>
</tr>
<tr>
<td>Non-fatal other critical organ*</td>
<td>42 (0.5%)</td>
<td>45 (0.5%)</td>
<td>29 (0.3%)</td>
<td>1.43 (0.89-2.29)</td>
<td>0.14</td>
</tr>
</tbody>
</table>

* symptomatic

*Slide by C. Michael Gibson, M.S., M.D.*
### Net clinical benefit

<table>
<thead>
<tr>
<th>Outcome</th>
<th>R + A N=9,152</th>
<th>A N=9,126</th>
<th>Rivaroxaban + Aspirin vs. Aspirin</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td><strong>N (%)</strong></td>
<td><strong>N (%)</strong></td>
<td><strong>HR (95% CI)</strong></td>
</tr>
<tr>
<td>Net clinical benefit (Primary + Severe bleeding events)</td>
<td>431 (4.7%)</td>
<td>534 (5.9%)</td>
<td>0.80 (0.70-0.91)</td>
</tr>
</tbody>
</table>
Rivaroxaban 2.5 mg: Efficacy
Pooled Analysis of ATLAS ACS 2–TIMI 51 and COMPASS

- CV Death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rivaroxaban Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 2.5 mg BID (ATLAS ACS 2–TIMI 51)</td>
<td>94</td>
<td>5114</td>
<td>143</td>
<td>5113</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)</td>
<td>160</td>
<td>9152</td>
<td>203</td>
<td>9126</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>14266</td>
<td>14239</td>
<td>100.0%</td>
<td>0.73 [0.62, 0.87]</td>
</tr>
<tr>
<td>Total events</td>
<td>254</td>
<td>346</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.00; Chi² = 1.13, df = 1 (P = 0.29); I² = 12%
Test for overall effect: Z = 3.57 (P = 0.0004)

- All-Cause Death

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rivaroxaban Events</th>
<th>Control Events</th>
<th>Weight</th>
<th>Risk Ratio M–H, Random, 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 2.5 mg BID (ATLAS ACS 2–TIMI 51)</td>
<td>103</td>
<td>5114</td>
<td>153</td>
<td>5113</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)</td>
<td>313</td>
<td>9152</td>
<td>378</td>
<td>9126</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>14266</td>
<td>14239</td>
<td>100.0%</td>
<td>0.76 [0.63, 0.93]</td>
</tr>
<tr>
<td>Total events</td>
<td>416</td>
<td>531</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Heterogeneity: Tau² = 0.01; Chi² = 1.95, df = 1 (P = 0.16); I² = 49%
Test for overall effect: Z = 2.71 (P = 0.007)

Slide by C. Michael Gibson, M.S., M.D.
Bewildering Number of Strategies in the ACS Patient with Atrial Fibrillation

- **ASA Dose:** None Low High 2 1+8 = 9
- **ASA Duration (mos):** 1 3 6 12 4
- **Thienopyridine:** None Clop Ticlid Pras Ticag 4 1+16 = 17
- **Thienopyridine duration (mos):** 1 3 6 12 4
- **AC:** None Warf Dabi Riva Apix Edox 5 1+10 = 11
- **AC INR/Dose:** Low High 2

Permutations of Single, Dual or Triple Therapy as *Early Initial Therapy* (0,1,3,6 mos) following ACS: 9 X 17 X 11 = 1,683

Permutations of Single or Dual Therapy *Late After Early Therapy* (0,1,3,6 mos) following ACS: 1,683

Total Permutations *throughout one year*: 2.8 Million

Gibson et al. AHA 2016
Gibson CM, J Am Coll Cardiol 2016
Aspirin and DAPT Do Reduce Risk Of Stroke Among Patients With Atrial Fibrillation

- Placebo 1: 1.4% / yr
- Aspirin 1: 3.6% / yr
- DAPT 2: 2.4% / yr
- OAC 2: 1.4% / yr

Gibson et al. AHA 2016

Slide by C. Michael Gibson, M.S., M.D.
Rivaroxaban + DAPT Bleeding

**Total Daily Dose:**
- Rivaroxaban 20 mg ----
- Rivaroxaban 15 mg ----
- Rivaroxaban 10 mg ----
- Rivaroxaban 5 mg ----
- Placebo ---

**Clinically Significant Bleeding (%):**
- Rivaroxaban 20 mg: 15.3%
- Rivaroxaban 15 mg: 12.7%
- Rivaroxaban 10 mg: 10.9%
- Rivaroxaban 5 mg: 6.1%
- Placebo: 3.3%

**Fatal Bleeding:**
- 5 mg: 0.4%
- 10 mg: 0.04%
- 20 mg: ?

P = 0.018

Gibson CM, AHA 2008

STEMI cohort, p=0.044 in all ACS

**Slide by C. Michael Gibson, M.S., M.D.**
**J-ROCKET AF:**
Primary Efficacy Endpoint

### Primary Efficacy Endpoint

**Hazard Ratio (95% CI):** 0.49 (0.24-1.00)

*P* = 0.050 (two-sided test)

<table>
<thead>
<tr>
<th>Event Rate (%/year)</th>
<th>Rivaroxaban</th>
<th>Warfarin</th>
</tr>
</thead>
<tbody>
<tr>
<td>Stroke or Systemic Embolism</td>
<td>1.26</td>
<td>2.61</td>
</tr>
</tbody>
</table>

**Cumulative Event Rate**

- **Rivaroxaban 15 mg**
- **Warfarin**

**Days from Randomization**

- **Rivaroxaban:** 637, 593, 563, 542, 443, 313, 217, 156, 48, 0
- **Warfarin:** 637, 581, 547, 517, 406, 285, 212, 154, 48, 0

---

CI, confidence interval.
Per-protocol, on-treatment population
Analysis method: Cox proportional hazard model

---

Gibson et al. AHA 2016
Hori M et al. Circ J 2012; 76: 2104-2111
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
Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events

TIMI Major, TIMI Minor, or Bleeding Requiring Medical Attention (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at risk</th>
<th>Days</th>
<th>180</th>
<th>270</th>
<th>360</th>
</tr>
</thead>
<tbody>
<tr>
<td>VKA + DAPT</td>
<td>696</td>
<td>0</td>
<td>543</td>
<td>510</td>
<td>383</td>
</tr>
<tr>
<td>Riva + DAPT</td>
<td>706</td>
<td>628</td>
<td>636</td>
<td>600</td>
<td>426</td>
</tr>
<tr>
<td>Riva + P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>697</td>
<td>593</td>
<td>555</td>
<td>521</td>
<td>426</td>
</tr>
</tbody>
</table>

Riva + P2Y<sub>12</sub> v. VKA + DAPT
HR=0.59 (95% CI: 0.47-0.76)
p <0.000013
ARR=9.9
NNT=11

Riva + DAPT v. VKA + DAPT
HR=0.63 (95% CI: 0.50-0.80)
p <0.00018
ARR=8.7
NNT=12

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Clinically significant bleeding is the composite of TIMI major, TIMI minor, and BRMA. Hazard ratios as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model. Log-Rank P-values as compared to VKA group are based on the (stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA) two-sided log rank test.

Gibson et al. AHA 2016
<table>
<thead>
<tr>
<th></th>
<th>Riva + P2Y&lt;sub&gt;12&lt;/sub&gt; (N = 696)</th>
<th>Riva + DAPT (N = 706)</th>
<th>Combined Riva (N = 1402)</th>
<th>VKA + DAPT (N = 697)</th>
<th>Group 1 vs Group 3 p-value</th>
<th>Group 2 vs Group 3 p-value</th>
<th>Combined vs Group 3 p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>GUSTO classification</strong></td>
<td></td>
<td></td>
<td></td>
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<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>7 (1.0%)</td>
<td>10 (1.4%)</td>
<td>17 (1.2%)</td>
<td>20 (2.9%)</td>
<td>0.012</td>
<td>0.060</td>
<td>0.007</td>
</tr>
<tr>
<td>Moderate</td>
<td>13 (1.9%)</td>
<td>10 (1.4%)</td>
<td>23 (1.6%)</td>
<td>9 (1.3%)</td>
<td>0.388</td>
<td>0.839</td>
<td>0.539</td>
</tr>
<tr>
<td>Mild</td>
<td>193 (27.7%)</td>
<td>214 (30.3%)</td>
<td>407 (29.0%)</td>
<td>255 (36.6%)</td>
<td>&lt;0.001</td>
<td>0.013</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>BARC classification</strong></td>
<td></td>
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<td></td>
<td></td>
<td></td>
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<td></td>
</tr>
<tr>
<td>Type 0</td>
<td>9 (1.3%)</td>
<td>14 (2.0%)</td>
<td>23 (1.6%)</td>
<td>10 (1.4%)</td>
<td>0.820</td>
<td>0.428</td>
<td>0.721</td>
</tr>
<tr>
<td>Type 1 (minimal)</td>
<td>125 (18.0%)</td>
<td>153 (21.7%)</td>
<td>278 (19.8%)</td>
<td>167 (24.0%)</td>
<td>0.006</td>
<td>0.307</td>
<td>0.029</td>
</tr>
<tr>
<td>Type 2 (actionable)</td>
<td>92 (13.2%)</td>
<td>91 (12.9%)</td>
<td>183 (13.1%)</td>
<td>126 (18.1%)</td>
<td>0.013</td>
<td>0.007</td>
<td>0.002</td>
</tr>
<tr>
<td>Type 3a</td>
<td>8 (1.2%)</td>
<td>7 (1.0%)</td>
<td>15 (1.1%)</td>
<td>12 (1.7%)</td>
<td>0.369</td>
<td>0.237</td>
<td>0.212</td>
</tr>
<tr>
<td>Type 3b (&gt;5g, pressors)</td>
<td>13 (1.9%)</td>
<td>16 (2.3%)</td>
<td>29 (2.1%)</td>
<td>26 (3.7%)</td>
<td>0.035</td>
<td>0.108</td>
<td>0.025</td>
</tr>
<tr>
<td>Type 3c</td>
<td>2 (0.3%)</td>
<td>5 (0.7%)</td>
<td>7 (0.5%)</td>
<td>4 (0.6%)</td>
<td>0.687</td>
<td>&gt;0.999</td>
<td>0.760</td>
</tr>
<tr>
<td>Type 4</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>-</td>
<td>-</td>
<td>-</td>
</tr>
<tr>
<td>Type 5a</td>
<td>1 (0.1%)</td>
<td>0 (0.0%)</td>
<td>0 (0.0%)</td>
<td>1 (0.1%)</td>
<td>&gt;0.999</td>
<td>0.497</td>
<td>0.554</td>
</tr>
<tr>
<td>Type 5b (Definite Fatal)</td>
<td>1 (0.1%)</td>
<td>2 (0.3%)</td>
<td>3 (0.2%)</td>
<td>7 (1.0%)</td>
<td>0.070</td>
<td>0.106</td>
<td>0.019</td>
</tr>
</tbody>
</table>

BARC denotes Bleeding Academic Research Consortium, GUSTO Global Utilization Of Streptokinase and Tpa For Occluded Arteries
Probable fatal bleeding (type 5a) is bleeding that is clinically suspicious as the cause of death, but the bleeding is not directly observed and there is no autopsy or confirmatory imaging.
Definite fatal bleeding (type 5b) is bleeding that is directly observed (by either clinical specimen [blood, emesis, stool, etc] or imaging) or confirmed on autopsy.
Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Gibson et al. AHA 2016
Kaplan-Meier Estimates of First Occurrence of CV Death, MI or Stroke

Cardiovascular Death, Myocardial Infarction, or Stroke (%)

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. at Risk</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Riva + P2Y&lt;sub&gt;12&lt;/sub&gt;</td>
<td>694, 648, 633, 621</td>
<td>180</td>
</tr>
<tr>
<td>Riva + DAPT</td>
<td>704, 662, 640, 628</td>
<td>270</td>
</tr>
<tr>
<td>VKA + DAPT</td>
<td>695, 635, 607, 579</td>
<td>360</td>
</tr>
</tbody>
</table>

Riva + P2Y<sub>12</sub> v. VKA + DAPT
HR=1.08 (95% CI: 0.69-1.68)
p=0.750

Riva + DAPT v. VKA + DAPT
HR=0.93 (95% CI: 0.59-1.48)
p=0.765

6.5%
6.0%
5.6%

Log-Rank P-values as compared to the VKA group are based on the two-sided log rank test.

Gibson et al. AHA 2016
CV Death, MI, Ischemic Stroke, ICH or Fatal Bleed

Ischemic stroke includes ischemic stroke + ischemic stroke with hemorrhagic transformation. There were 2 strokes of uncertain cause: Riva + DAPT (n=1) & VKA (n=1).

Fatal bleed was defined as BARC Type 5B bleeds.
Hospitalization Related to Cardiovascular or Bleeding Event

Adverse events leading to hospitalization were classified by consensus panel blinded to treatment group as potentially related to either bleeding, CV or other causes.

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Rehospitalizations do not include the index event and include the first rehospitalization after the index event.

Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.

Log-Rank P-values as compared to VKA group are based on the two-sided log rank test.

<table>
<thead>
<tr>
<th></th>
<th>Cardiovascular</th>
<th></th>
<th>Bleeding</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. at risk cardiovascular</td>
<td>No. at risk bleeding</td>
<td></td>
</tr>
<tr>
<td>Riva + P2Y_{12}</td>
<td>696 632 607 586</td>
<td>Riva + P2Y_{12}</td>
<td>696 645 630 618</td>
</tr>
<tr>
<td>Riva + DAPT</td>
<td>706 627 595 576</td>
<td>Riva + DAPT</td>
<td>706 659 636 621</td>
</tr>
<tr>
<td>VKA + DAPT</td>
<td>697 609 560 517</td>
<td>VKA + DAPT</td>
<td>697 630 601 568</td>
</tr>
</tbody>
</table>

Treatment-emergent period: period starting after the first study drug administration following randomization and ending 2 days after stop of study drug.

Rehospitalizations do not include the index event and include the first rehospitalization after the index event.

Hazard ratios as compared to the VKA group are based on the Cox proportional hazards model.

Log-Rank P-values as compared to VKA group are based on the two-sided log rank test.

Gibson et al. AHA 2016
### Results of PIONEER & ReDual PCI

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Control</th>
<th>RR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>PIONEER AF-PCI (Riva combined) ¹</strong></td>
<td>127/1398 (9.08)</td>
<td>64/695 (9.21)</td>
</tr>
<tr>
<td>Rivaroxaban 15 mg QD + P2Y₁₂ inhibitor</td>
<td>63/694 (9.08)</td>
<td>64/695 (9.21)</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + P2Y₁₂ inhibitor + ASA</td>
<td>64/704 (9.09)</td>
<td>64/695 (9.21)</td>
</tr>
<tr>
<td><strong>RE-DUAL PCI (Dabi combined) ²</strong></td>
<td>239/1744 (13.70)</td>
<td>131/981 (13.35)</td>
</tr>
<tr>
<td>Dabigatran 110 mg BID + P2Y₁₂ inhibitor</td>
<td>149/981 (15.19)</td>
<td>131/981 (13.35)</td>
</tr>
<tr>
<td>Dabigatran 150 mg BID + P2Y₁₂ inhibitor</td>
<td>90/763 (11.80)</td>
<td>98/764 (12.83)</td>
</tr>
</tbody>
</table>

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2. Data on file PERFUSE Study Group
When a NOAC is used in combination with aspirin and/or clopidogrel, the lowest approved dose effective for stroke prevention tested in AF trials should be considered.\textsuperscript{c}

When rivaroxaban is used in combination with aspirin and/or clopidogrel, rivaroxaban 15 mg q.d. may be used instead of rivaroxaban 20 mg q.d.\textsuperscript{191}

The use of ticagrelor or prasugrel is not recommended as part of triple antithrombotic therapy with aspirin and OAC.

<table>
<thead>
<tr>
<th>IIa</th>
<th>C</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIb</td>
<td>B</td>
</tr>
<tr>
<td>III</td>
<td>C</td>
</tr>
</tbody>
</table>