Does COMPASS Change Practice?

C. Michael Gibson, M.S., M.D.

Professor of Medicine, Harvard Medical School
Chief, Clinical Research, Beth Israel Deaconess CV Division
Chairman, PERFUSE Study Group
Founder, Editor-In-Chief www.wikidoc.org

The World’s Open Source Textbook of Medicine
Hundreds of Million Viewers Annually
Rivaroxaban is not FDA approved in the ACS setting or in patients with atrial fibrillation undergoing stent placement. It is in many other countries. Check your local label. The use of Rivaroxaban in chronic CAD is under regulatory review and is off label at present.
Disclosure

- Dr. Gibson has received research grant support and consulting fees in the past from all major manufacturers of antiplatelets and antithrombins.

- This is an educational lecture and is not intended to be an inducement to use any drug or drug in a fashion that is inconsistent with the drug or device label. Rivaroxaban is not approved for use in acute coronary syndromes in the US, but is so in many other countries.

- The slides were prepared by C. Michael Gibson, M.S., M.D. and/or were under the editorial control of C. Michael Gibson, M.S., M.D.

Rivaroxaban is not FDA approved in the ACS setting or in patients with atrial fibrillation undergoing stent placement. It is in many other countries. Check your local label. The use of Rivaroxaban in chronic CAD is under regulatory review and is off label at present.
Platelet Amplification
Two Positive Feedback Loops

Thrombin Made on Platelet Surface
- Thrombin Most Potent Activator of Platelet
- "Amplification"
- "Burst"
- "Activation"
- "Growth of Thrombus"

ADP Secreted by Platelet
- ADP Activates Platelet
- Thienopyridines
- Antithrombins

Slide by C. Michael Gibson, M.S., M.D.
ACS: Platelet Resistance to Clopidogrel Declines Over Time


Slide by C. Michael Gibson, M.S., M.D.
**Novel Thienopyridines Do Not Block Activation by Thrombin**

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 Gᵢ-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.
Meta Analysis of Warfarin in ACS: Efficacy

Slide by C. Michael Gibson, M.S., M.D.

Rothberg et al., Ann Int Med 2005;143:241-250
U Shaped Relationship of Net Clinical Outcomes

- UFH STEMI
- Warfarin AFib
- ASA CAD
- Warfarin STEMI

PHASE 2 STUDY DESIGN

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

Aspirin 75-100 mg

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 (97)
10 mg (80)

YES

STRATUM 2
ASA + Clop.
N=2,730

PLACEBO
N=907
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)

21 Doses

N = 3,491

6 Month Bleeding / Efficacy

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 (%):**
- Rivaroxaban 20 mg: 15.3% (5.1 [3.4-7.4])
- Rivaroxaban 15 mg: 12.7% (3.6 [2.3-5.6])
- Rivaroxaban 10 mg: 10.9% (3.4 [2.3-4.9])
- Rivaroxaban 5 mg: 6.1% (2.2 [1.25-3.91])
- Placebo: 3.3%

*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

**Stratum 1: ASA Alone**

- Death / MI / Stroke (%): 11.9
- P trend = 0.01
- HR:
  - Placebo: 8.0
  - 5 mg: 7.0
  - 10 mg: 4.7
  - 20 mg: 3.0

**Stratum 2: ASA + Clop.**

- Death / MI / Stroke (%): 3.8
- P trend = 0.72
- HR:
  - Placebo: 2.7
  - 5 mg: 2.7
  - 10 mg: 2.7
  - 15 mg: 4.7
  - 20 mg: 3.0

**Gibson CM, AHA 2008**

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

Death / MI / Stroke (%)

Days After Randomization

All Placebo
(n = 1160)
P = 0.028

All Rivaroxaban
(n = 2331)

HR 0.69
(0.50-0.96)
P=0.028
ARR = 1.6%
NNT = 63

5.5%
3.9%
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

Slide by C. Michael Gibson, M.S., M.D.  Gibson CM, AHA 2011
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

No. at Risk
Placebo 5113 4307 3470 2664 1831 1079 421
Rivaroxaban 10229 8502 6753 5137 3554 2084 831

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: HR 0.64, mITT p<0.001, ITT p<0.001

NNT = 71

**Cardiovascular Death**

- Placebo: HR 0.62, mITT p<0.001
- Rivaroxaban 2.5 mg BID: HR 0.62, mITT p<0.001

NNT = 59

**All Cause Death**

- Placebo: HR 0.64, mITT p<0.001
- Rivaroxaban 2.5 mg BID: HR 0.64, mITT p<0.001

NNT = 56

---

*Slide by C. Michael Gibson, M.S., M.D.*

Gibson CM, AHA 2011
All Cause Mortality Reduced in 5 mg Arm in the Absence of Bleeding

- Rivaroxaban 5 mg PO bid: 1.8% (1.69% (100 pt-yr), n=84)
- Placebo: 2.5% (2.24% (100 pt-yr), n=117)

HR = 0.75 (0.56, 0.99)

Slide by C. Michael Gibson, M.S., M.D.
### Effects of Rivaroxaban By Type of Myocardial Infarction


<table>
<thead>
<tr>
<th>MI Type</th>
<th>Dose</th>
<th>HR (95% CI)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ALL MI</strong> (n=665)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>(n=291)</td>
<td>Pooled</td>
<td>0.82 (0.70-0.96)</td>
<td>0.01</td>
</tr>
<tr>
<td></td>
<td>2.5 mg</td>
<td>0.76 (0.54-1.07)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>0.69 (0.49-0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>STEMI</strong> (n=187)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>0.73 (0.54-0.97)</td>
<td>0.03</td>
</tr>
<tr>
<td></td>
<td>2.5 mg</td>
<td>0.76 (0.54-1.07)</td>
<td>0.11</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>0.69 (0.49-0.98)</td>
<td>0.04</td>
</tr>
<tr>
<td><strong>NSTEMI</strong> (n=291)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>Pooled</td>
<td>0.91 (0.71-1.15)</td>
<td>0.42</td>
</tr>
<tr>
<td></td>
<td>2.5 mg</td>
<td>0.92 (0.69-1.21)</td>
<td>0.54</td>
</tr>
<tr>
<td></td>
<td>5 mg</td>
<td>0.89 (0.68-1.18)</td>
<td>0.44</td>
</tr>
</tbody>
</table>

Rivaroxaban lowers MI

Rivaroxaban increases MI
Dual antiplatelet therapy with ASA + clopidogrel decreased thrombus mass by 79%.

The combination of ASA and rivaroxaban significantly inhibited thrombus mass by 86%.

Addition of the anticoagulant rivaroxaban to ASA + clopidogrel produced further improvement.

Rivaroxaban + clopidogrel + ASA inhibited stent thrombus by 98% ($P<0.001$).

Rivaroxaban dose: 1 µg/kg/min. Error bars are the standard error of the mean.

***$P<0.001$ (unpaired t-test vs representative vehicle group).

STENT THROMBOSIS
ARC Definite / Probable / Possible

Rivaroxaban (both doses)

Estimated Cumulative Incidence (%)
Placebo
Rivaroxaban (both doses)

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

2 Yr KM Estimate
Placebo: 2.9%
Rivaroxaban: 2.3%

HR 0.69 (0.51-0.93)

mITT p = 0.016
ITT p = 0.008

Slide by C. Michael Gibson, M.S., M.D.
What is The Excess Rate of TIMI Major Non-CABG Bleeding for Novel Agents?

- Rivaroxaban: 1.8% vs 0.6% over two years = 0.6% annually\(^1\)
- Ticagrelor: 2.8% vs 2.2% over one year = 0.6% annually\(^2\)
- Prasugrel: 2.4% vs 1.8% over one year = 0.6% annually\(^3\)

0.6% per year for all 3 agents (rivaroxaban, ticagrelor, prasugrel)

1. NEJM 2011; Nov 13\(^{th}\)

Slide by C. Michael Gibson, M.S., M.D.
Fatal Bleeding

Prasugrel:¹
Increase in fatal bleeding (0.4% vs 0.1%, 21 vs 5 events, p=0.002)

Ticagrelor:²
Increase in fatal ICH (Ticagrelor n = 11 vs Clopidogrel n = 1, p = 0.02)

Rivaroxaban:³
No increase in either fatal bleeding or fatal ICH

3. NEJM 2011; Nov 13th

Slide by C. Michael Gibson, M.S., M.D.
Objectives

To determine in stable CV disease, whether:

- Rivaroxaban 2.5 mg bid + aspirin 100 mg od,

OR

- Rivaroxaban 5 mg bid

Reduces CV death, stroke or myocardial infarction compared with aspirin 100 mg od

And whether:

- Pantoprazole compared with placebo reduces upper GI events (ongoing)
COMPASS design

Stable CAD or PAD
2,200 with a primary outcome event

Rivaroxaban 2.5 mg bid
+ aspirin 100 mg od

Rivaroxaban 5 mg bid

Aspirin 100 mg od

Run-in (aspirin)

Expected follow up
3-4 years
Outcomes

• **Primary**
  - CV death, stroke or myocardial infarction

• **Secondary**
  - CHD death, ischemic stroke, myocardial infarction, or acute limb ischemia,
  - CV death, ischemic stroke, myocardial infarction, or acute limb ischemia,
  - Mortality

• **Safety and net clinical benefit**
  - ISTH major bleeding (modified)
  - Primary plus fatal or critical organ bleeding
Follow up, adherence

- On February 6, 2017 the Data and Safety Monitoring Board recommended discontinuation of rivaroxaban/aspirin arms for clear evidence of efficacy (combination: $Z = -4.59$, $P < 0.00001$; rivaroxaban: $Z = -2.44$, $P = 0.01$)
- Close-out between March and June 2017
- Mean follow up 23 months
- Follow up 99.8% complete
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Rivaroxaban + aspirin N=9,152</th>
<th>Rivaroxaban N=9,117</th>
<th>Aspirin N=9,126</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, yr</td>
<td>68</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Blood pressure, mmHg</td>
<td>136/77</td>
<td>136/78</td>
<td>136/78</td>
</tr>
<tr>
<td>Total cholesterol, mmol/L</td>
<td>4.2</td>
<td>4.2</td>
<td>4.2</td>
</tr>
<tr>
<td>CAD</td>
<td>91%</td>
<td>90%</td>
<td>90%</td>
</tr>
<tr>
<td>PAD</td>
<td>27%</td>
<td>27%</td>
<td>27%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>38%</td>
<td>38%</td>
<td>38%</td>
</tr>
<tr>
<td>Lipid-lowering</td>
<td>90%</td>
<td>90%</td>
<td>89%</td>
</tr>
<tr>
<td>ACE-I or ARB</td>
<td>71%</td>
<td>72%</td>
<td>71%</td>
</tr>
</tbody>
</table>
# 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>
<tr>
<td>Rivaroxaban + aspirin vs. aspirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Rivaroxaban vs. aspirin</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

**N = 9,152**

**R**

**A**
Primary: CV death, stroke, MI

Rivaroxaban + Aspirin vs. Aspirin  HR: 0.76, 95% CI 0.66-0.86, P = <0.0001
Rivaroxaban vs. Aspirin  HR: 0.90, 95% CI 0.79-1.03, P = 0.12

<table>
<thead>
<tr>
<th></th>
<th>Year</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban + Aspirin</td>
<td>0</td>
<td>9152</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>1</td>
<td>7904</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3912</td>
</tr>
<tr>
<td>Rivaroxaban</td>
<td>3</td>
<td>658</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0</td>
<td>9117</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>7824</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3862</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>670</td>
</tr>
<tr>
<td>Aspirin</td>
<td>0</td>
<td>9126</td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>7808</td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>3860</td>
</tr>
<tr>
<td></td>
<td>3</td>
<td>669</td>
</tr>
</tbody>
</table>
## Primary components

<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>CV death</td>
<td>160 (1.7%)</td>
<td>203 (2.2%)</td>
<td>0.78 (0.64-0.96)</td>
</tr>
<tr>
<td>Stroke</td>
<td>83 (0.9%)</td>
<td>142 (1.6%)</td>
<td>0.58 (0.44-0.76)</td>
</tr>
<tr>
<td>MI</td>
<td>178 (1.9%)</td>
<td>205 (2.2%)</td>
<td>0.86 (0.70-1.05)</td>
</tr>
</tbody>
</table>
## Secondary outcomes

<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>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
<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>
# 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
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>Net clinical benefit (Primary + Severe bleeding events)</td>
<td>431 (4.7%)</td>
<td>534 (5.9%)</td>
<td>HR (95% CI)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.80 (0.70-0.91)</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>P</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.0005</td>
</tr>
</tbody>
</table>
Rivaroxaban 2.5 mg bid plus aspirin 100 mg od:

- Reduces CV death, stroke, MI
- Increases major bleeding without a significant increase in fatal, intracranial or critical organ bleeding
- Provides a net clinical benefit

No significant benefit of rivaroxaban alone
Rivaroxaban 2.5 mg: Efficacy
Pooled Analysis of ATLAS ACS 2–TIMI 51 and COMPASS

- **MI / Stroke / CV Death**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rivaroxaban Events</th>
<th>Control Events</th>
<th>Total 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>313</td>
<td>376</td>
<td>5114</td>
<td>44.8%</td>
<td>0.83 [0.72, 0.96]</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)</td>
<td>379</td>
<td>496</td>
<td>9152</td>
<td>55.2%</td>
<td>0.76 [0.67, 0.87]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>14266</strong></td>
<td><strong>14239</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td>0.79 [0.72, 0.87]</td>
</tr>
</tbody>
</table>

Total events: 692 vs. 872
Heterogeneity: Tau² = 0.00; Chi² = 0.79, df = 1 (P = 0.37); I² = 0%
Test for overall effect: Z = 4.70 (P < 0.00001)

- **MI**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rivaroxaban Events</th>
<th>Control Events</th>
<th>Total 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>205</td>
<td>229</td>
<td>5114</td>
<td>53.7%</td>
<td>0.90 [0.74, 1.08]</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)</td>
<td>178</td>
<td>205</td>
<td>9152</td>
<td>46.3%</td>
<td>0.87 [0.71, 1.06]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>14266</strong></td>
<td><strong>14239</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td>0.88 [0.77, 1.01]</td>
</tr>
</tbody>
</table>

Total events: 383 vs. 434
Heterogeneity: Tau² = 0.00; Chi² = 0.06, df = 1 (P = 0.81); I² = 0%
Test for overall effect: Z = 1.83 (P = 0.07)

- **Stroke**

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rivaroxaban Events</th>
<th>Control Events</th>
<th>Total 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>46</td>
<td>41</td>
<td>5114</td>
<td>46.9%</td>
<td>1.12 [0.74, 1.71]</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)</td>
<td>83</td>
<td>142</td>
<td>9152</td>
<td>53.1%</td>
<td>0.58 [0.45, 0.76]</td>
</tr>
<tr>
<td><strong>Total (95% CI)</strong></td>
<td><strong>14266</strong></td>
<td><strong>14239</strong></td>
<td><strong>100.0%</strong></td>
<td></td>
<td>0.79 [0.42, 1.50]</td>
</tr>
</tbody>
</table>

Total events: 129 vs. 183
Heterogeneity: Tau² = 0.18; Chi² = 6.64, df = 1 (P = 0.010); I² = 85%
Test for overall effect: Z = 0.71 (P = 0.48)
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>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>143</td>
<td>0.66 [0.51, 0.85]</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)</td>
<td>160</td>
<td>203</td>
<td>0.79 [0.64, 0.96]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>14266</td>
<td>14239</td>
<td>0.73 [0.62, 0.87]</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>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>153</td>
<td>0.67 [0.53, 0.86]</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)</td>
<td>313</td>
<td>378</td>
<td>0.83 [0.71, 0.96]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>14266</td>
<td>14239</td>
<td>0.76 [0.63, 0.93]</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)
Rivaroxaban 2.5 mg: Safety
Pooled Analysis of ATLAS ACS 2–TIMI 51 and COMPASS

• Major Bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rivaroxaban Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</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>65</td>
<td>5114</td>
<td>19</td>
<td>5113</td>
<td>43.8%</td>
<td>3.42 [2.05, 5.69]</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)</td>
<td>206</td>
<td>9152</td>
<td>116</td>
<td>9126</td>
<td>56.2%</td>
<td>1.77 [1.41, 2.22]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>271</td>
<td>14266</td>
<td>135</td>
<td>14239</td>
<td>100.0%</td>
<td>2.36 [1.24, 4.49]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.18$; $\chi^2 = 5.38$, df = 1 ($P = 0.02$); $I^2 = 81$
Test for overall effect: $Z = 2.63$ ($P = 0.009$)

• Fatal Bleeding

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rivaroxaban Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</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>6</td>
<td>5114</td>
<td>9</td>
<td>5113</td>
<td>41.5%</td>
<td>0.67 [0.24, 1.87]</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)</td>
<td>15</td>
<td>9152</td>
<td>10</td>
<td>9126</td>
<td>58.5%</td>
<td>1.50 [0.67, 3.33]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>21</td>
<td>14266</td>
<td>19</td>
<td>14239</td>
<td>100.0%</td>
<td>1.07 [0.49, 2.33]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.10$; $\chi^2 = 1.47$, df = 1 ($P = 0.23$); $I^2 = 32$
Test for overall effect: $Z = 0.17$ ($P = 0.87$)

• Intracranial Hemorrhage

<table>
<thead>
<tr>
<th>Study or Subgroup</th>
<th>Rivaroxaban Events</th>
<th>Total</th>
<th>Control Events</th>
<th>Total</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>14</td>
<td>5114</td>
<td>5</td>
<td>5113</td>
<td>40.2%</td>
<td>2.80 [1.01, 7.77]</td>
</tr>
<tr>
<td>Rivaroxaban 2.5 mg BID + ASA 100 mg QD (COMPASS)</td>
<td>21</td>
<td>9152</td>
<td>19</td>
<td>9126</td>
<td>59.8%</td>
<td>1.10 [0.59, 2.05]</td>
</tr>
<tr>
<td>Total (95% CI)</td>
<td>35</td>
<td>14266</td>
<td>24</td>
<td>14239</td>
<td>100.0%</td>
<td>1.60 [0.65, 3.93]</td>
</tr>
</tbody>
</table>

Heterogeneity: $\tau^2 = 0.25$; $\chi^2 = 2.35$, df = 1 ($P = 0.13$); $I^2 = 57$
Test for overall effect: $Z = 1.03$ ($P = 0.30$)