Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome - Thrombolysis in Myocardial Infarction 51 Trial (ATLAS ACS 2 - TIMI 51):
A Randomized, Double-Blind, Placebo Controlled Study to Evaluate the Efficacy and Safety of Rivaroxaban in Subjects with Acute Coronary Syndrome

C. Michael Gibson, MS, MD
on behalf of the ATLAS ACS 2 TIMI 51 Investigators

Funded by a research grant from Johnson and Johnson and Bayer to Brigham & Women’s Hospital. Dr. Gibson has received honoraria & consulting fees from J&J and Bayer.
ATLAS ACS-TIMI 46
N = 3,491

THROMBUS
PLAQUE RUPTURE

TIMI Major Bleeding (%)

Placebo 5 mg 10 mg 15 mg 20 mg
0.1 0.7 1.5 1.8 1.8

Rivaroxaban

Death, MI, or stroke (%)

Placebo 5.5%
Rivaroxaban (combined) 3.9%

HR 0.69
(95% CI, 0.50 - 0.96)
P = 0.03

Days after randomization

TRIAL ORGANIZATION

**Trial Leadership: TIMI Study Group**

- Chairman: Eugene Braunwald
- Principal Investigator: C. Michael Gibson
- Investigator: Jessica Mega
- Statisticians: Sabina Murphy, Charles Contant

**Executive Committee**

- Jean-Pierre Bassand
- Deepak Bhatt
- Christoph Bode
- Keith Fox
- Marc Cohen
- Shinya Goto
- David Schneider
- Freek Verheugt

**Sponsors: Johnson & Johnson and Bayer Health Care**

- **J&J:** Paul Burton, Peter DiBattiste, Alexei N. Plotnikov, Linda DeCaprio, Xiang Sun
- **Bayer:** Nancy Cook Bruns, Scott Berkowitz, Frank Misselwitz

**Data Safety Monitoring Board**

- Douglas Weaver (Chair)
- Christian Hamm
- Judith S. Hochman
- Jeffrey Anderson
- Hiroyuki Daida
- Statistician: Allan Skene
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

ASA 75 to 100 mg/day

Stratified by Thienopyridine Use at MD Discretion

Placebo
n=5,176

Rivaroxaban
2.5 mg BID
n=5,174

Rivaroxaban
5.0 mg BID
n=5,176

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
## BASELINE CHARACTERISTICS

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Rivaroxaban 2.5 mg BID</th>
<th>Rivaroxaban 5.0 mg BID</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>BASELINE</strong></td>
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<tr>
<td><strong>HOSPITAL</strong></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Age, mean (SD)</td>
<td>61.5 (± 9.4)</td>
<td>61.8 (± 9.2)</td>
<td>61.9 (± 9.0)</td>
</tr>
<tr>
<td>Sex, male (%)</td>
<td>75.0</td>
<td>74.9</td>
<td>74.2</td>
</tr>
<tr>
<td>Prior MI, (%)</td>
<td>27.3</td>
<td>26.3</td>
<td>27.1</td>
</tr>
<tr>
<td>Diabetes, (%)</td>
<td>31.8</td>
<td>32.3</td>
<td>31.8</td>
</tr>
<tr>
<td>STEMI, (%)</td>
<td>50.9</td>
<td>50.3</td>
<td>49.9</td>
</tr>
<tr>
<td>NSTEMI, (%)</td>
<td>25.6</td>
<td>25.5</td>
<td>25.8</td>
</tr>
<tr>
<td>UA, (%)</td>
<td>23.6</td>
<td>24.2</td>
<td>24.3</td>
</tr>
<tr>
<td>Revasc at Index, (%)</td>
<td>60.7</td>
<td>60.4</td>
<td>60.4</td>
</tr>
<tr>
<td>ASA+Thienopyridine, (%)</td>
<td>93.1</td>
<td>93.3</td>
<td>93.3</td>
</tr>
</tbody>
</table>
The primary method of analysis was a log rank test stratified by thienopyridine use in the mITT population with confirmation in an ITT analysis.
PRIMARY EFFICACY ENDPOINT:
CV Death / MI / Stroke

Placebo
10.7%
(%)  
2 Yr KM Estimate
8.9%

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

Months After Randomization
NNT = 56

HR and 95% confidence interval estimates from Cox model stratified by thienopyridine use are provided per mITT approach; Stratified log-rank p-values are provided for both mITT and ITT approaches.
STENT THROMBOSIS
ARC Definite / Probable / Possible

**Placebo**
- 2 Yr KM Estimate: 2.9%
- HR: 0.69 (0.51-0.93)
- mITT p = 0.016
- ITT p = 0.008

**Rivaroxaban** (both doses)
- ARC Definite/probable: HR=0.65, mITT p=0.017, ITT p=0.012

**Months After Randomization**
- 0 4 8 12 16 20 24

**Estimated Cumulative Incidence (%)**
- 0 1 2 3
Efficacy Endpoints:
Low Dose 5.0 mg BID

CV Death / MI / Stroke

Placebo: HR 0.85, mITT p=0.028, ITT p=0.010
Rivaroxaban: NNT=53

Cardiovascular Death

Placebo: HR 0.94, mITT p=0.010, ITT p=0.57
Rivaroxaban: 4.1% vs 4.0%
EFFICACY ENDPOINTS:
Very Low Dose 2.5 mg BID

- CV Death / MI / Stroke
  - Rivaroxaban: HR 0.84, p=0.020
    - mITT: 4.5%, NNT = 63
  - Placebo: HR 0.68, p=0.002
    - mITT: 4.1%, NNT = 71
- Cardiovascular Death
  - Rivaroxaban: HR 0.66, p=0.007
    - mITT: 9.1%, NNT = 63
  - Placebo: HR 0.68, p=0.005
    - mITT: 2.7%, NNT = 63
- All Cause Death
  - Rivaroxaban: HR 0.68, p=0.002
    - mITT: 2.9%, NNT = 63
  - Placebo: HR 0.68, p=0.004
    - mITT: 4.5%, NNT = 63
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 0.62, mITT p<0.001, ITT p<0.001

Cardiovascular Death
- Placebo: HR 0.64, mITT p<0.001, ITT p<0.001
- Rivaroxaban 2.5 mg BID: HR 0.68, mITT p<0.001, ITT p<0.001

All Cause Death
- Placebo: HR 0.64, mITT p<0.001, ITT p<0.001
- Rivaroxaban 2.5 mg BID: HR 0.62, mITT p<0.001, ITT p<0.001

NNT = 71
NNT = 59
NNT = 56
## PRIMARY EFFICACY SUBGROUP RESULTS

### All Rivaroxaban vs. Placebo

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Pinteraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.84 (0.74 - 0.96)</td>
<td></td>
</tr>
<tr>
<td>ASA</td>
<td>0.69 (0.45 - 1.05)</td>
<td>0.34</td>
</tr>
<tr>
<td>ASA + thienopyridine</td>
<td>0.86 (0.75 - 0.98)</td>
<td></td>
</tr>
<tr>
<td>&lt;65 Years</td>
<td>0.83 (0.70 - 0.99)</td>
<td>0.94</td>
</tr>
<tr>
<td>65 Years</td>
<td>0.84 (0.70 - 1.01)</td>
<td></td>
</tr>
<tr>
<td>STEMI</td>
<td>0.85 (0.70 - 1.03)</td>
<td>0.96</td>
</tr>
<tr>
<td>NSTEMI</td>
<td>0.85 (0.68 - 1.06)</td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>0.82 (0.62 - 1.07)</td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>0.87 (0.75 - 1.01)</td>
<td>0.40</td>
</tr>
<tr>
<td>Female</td>
<td>0.77 (0.60 - 0.99)</td>
<td></td>
</tr>
<tr>
<td>Weight &lt;60 kg</td>
<td>0.83 (0.56 - 1.25)</td>
<td>0.98</td>
</tr>
<tr>
<td>Weight 60 to &lt;90 kg</td>
<td>0.85 (0.72 - 0.99)</td>
<td></td>
</tr>
<tr>
<td>Weight 90 kg</td>
<td>0.83 (0.64 - 1.08)</td>
<td></td>
</tr>
<tr>
<td>Prior MI</td>
<td>0.83 (0.68 - 1.01)</td>
<td>0.80</td>
</tr>
<tr>
<td>No Prior MI</td>
<td>0.85 (0.72 - 1.01)</td>
<td></td>
</tr>
<tr>
<td>Diabetes Mellitus</td>
<td>0.96 (0.77 - 1.20)</td>
<td>0.14</td>
</tr>
<tr>
<td>No Diabetes Mellitus</td>
<td>0.78 (0.67 - 0.92)</td>
<td></td>
</tr>
<tr>
<td>Creatinine Cl &lt;50mL/min</td>
<td>0.88 (0.62 - 1.26)</td>
<td>0.82</td>
</tr>
<tr>
<td>Creatinine Cl &gt;50mL/min</td>
<td>0.84 (0.73 - 0.96)</td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>0.57 (0.33 - 0.97)</td>
<td>0.80</td>
</tr>
<tr>
<td>South America</td>
<td>0.89 (0.59 - 1.34)</td>
<td></td>
</tr>
<tr>
<td>Western Europe</td>
<td>0.90 (0.59 - 1.37)</td>
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<tr>
<td>Eastern Europe</td>
<td>0.83 (0.69 - 1.00)</td>
<td></td>
</tr>
<tr>
<td>Asia</td>
<td>0.86 (0.63 - 1.17)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>0.92 (0.60 - 1.39)</td>
<td></td>
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</tbody>
</table>
### SAFETY ENDPOINTS

#### Treatment-Emergent Non CABG TIMI Major Bleeding*

<table>
<thead>
<tr>
<th>Analysis</th>
<th>Placebo</th>
<th>2.5 mg Rivaroxaban</th>
<th>5.0 mg Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>2 Yr KM Estimate</td>
<td>0.6%</td>
<td>1.8% (HR 3.46)</td>
<td>2.4% (HR 4.47)</td>
</tr>
</tbody>
</table>

* p<0.001

#### Liver Function Test (ALT > 3xULN) #

<table>
<thead>
<tr>
<th>ALT &gt; 3X ULN</th>
<th>Placebo</th>
<th>2.5 mg Rivaroxaban</th>
<th>5.0 mg Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.6%</td>
<td>1.3%</td>
<td>1.4%</td>
<td></td>
</tr>
</tbody>
</table>

* p=NS

There was no excess of either combined ALT > 3x ULN and Total Bilirubin > 2x ULN cases among patients treated with Rivaroxaban, or SAEs.

#### Post-Treatment CVD / MI / Stroke##

<table>
<thead>
<tr>
<th>1-10 Days After Last Dose</th>
<th>Placebo</th>
<th>2.5 mg Rivaroxaban</th>
<th>5.0 mg Rivaroxaban</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.8%</td>
<td>1.4%</td>
<td>2.2%</td>
<td></td>
</tr>
</tbody>
</table>

* p=NS

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*: First occurrence of Non-CABG TIMI major bleeding events occurred between first dose to 2 days post last dose as adjudicated by the CEC across thienopyridine use strata; Two year Kaplan-Meier estimates, HR and 95% confidence interval estimates from Cox model stratified by thienopyridine are provided; Stratified log-rank p-values are provided; #: Raw percentage of subjects with abnormal value measured between first dose to 2 days post last dose among subjects with normal baseline measurement; ##: Raw percentage.
TREATMENT-EMERGENT FATAL BLEEDS AND ICH

- Placebo
  - p=NS for Riva vs Placebo
  - p=0.009 for Riva vs Placebo
  - p=NS for Riva 5 vs Placebo
  - p=0.005 Riva 5 vs Placebo
  - p=NS for Riva 2.5 vs Placebo
  - P=0.037 for Riva 2.5 vs Placebo
  - p=0.044 for Riva 2.5 vs 5
  - p=0.005 Riva 5 vs Placebo
  - p=0.44 for Riva 2.5 vs 5

- 2.5 mg Rivaroxaban
  - p=NS for all comparisons

- 5.0 mg Rivaroxaban
  - p=NS for all comparisons
SUMMARY

• Rivaroxaban reduced the risk of cardiovascular death, myocardial infarction, or stroke in patients across the spectrum of ACS.

• Rates of major bleeding and ICH were higher with rivaroxaban; however, there was no excess risk of fatal ICH or fatal bleeding with rivaroxaban compared to placebo (particularly with 2.5 mg BID).

• One death would be prevented if 56 patients on antiplatelet therapies were treated for two years with rivaroxaban 2.5 mg BID.
CONCLUSION

- Very low dose anticoagulation with rivaroxaban (2.5 mg BID), in addition to antiplatelet therapies, represents an effective strategy to reduce cardiovascular events in patients with a recent ACS.
Rivaroxaban in Patients with a Recent Acute Coronary Syndrome

Jessica L. Mega, M.D., M.P.H., Eugene Braunwald, M.D., Stephen D. Wiviott, M.D., Jean-Pierre Bassand, M.D., Deepak L. Bhatt, M.D., M.P.H., Christoph Bode, M.D., Paul Burton, M.D., Ph.D., Marc Cohen, M.D., Nancy Cook-Bruns, M.D., Keith A.A. Fox, M.B., Ch.B., Shinya Goto, M.D., Sabina A. Murphy, M.P.H., Alexei N. Plotnikov, M.D., David Schneider, M.D., Xiang Sun, Ph.D., Freek W.A. Verheugt, M.D., and C. Michael Gibson, M.D., for the ATLAS ACS 2–TIMI 51 Investigators*