The Role of Combination Antiplatelet and Anticoagulation Therapy in Diabetes and Cardiovascular Disease: COMPASS Diabetes

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Disclosures

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This presentation may discuss off label and investigational uses of drugs.

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Impact of Prior Ischemic Events or Stable Atherosclerosis on CV Events at 4 Years

*All event rates adjusted for age and sex.

Impact of Polyvascular Disease on CV Events at 4 years

*All event rates adjusted for age and sex.

Impact of Diabetes on CV Events at 4 years

*All event rates adjusted for age and sex.

Adjusted Cumulative Incidence of Cardiovascular Death, MI or Stroke (%)

- Diabetes (Known Atherothrombosis, Prior Ischemic Event)
- Diabetes (Known Atherothrombosis)
- Diabetes (Overall)
- Diabetes (Known Atherothrombosis, No Prior Ischemic Event)
- No Diabetes (Overall)
- Diabetes (Risk Factors Only)

Dual Pathway Inhibition: Antiplatelet plus Anticoagulant
Stable CAD or PAD
27,395 participants randomized


Rivaroxaban 2.5 mg bid + Aspirin 100
Rivoxaban 5 mg bid
Aspirin 100 mg od

Expected mean follow up: 3-4 years

*excluding patients enrolled 4-14 days post CABG

COMPASS Trial Primary outcome

Rivaroxaban + aspirin vs. placebo plus aspirin
Hazard ratio, 0.76 (95% CI, 0.66-0.86)
P<0.001

Rivaroxaban alone vs. placebo plus aspirin
Hazard ratio, 0.90 (95% CI, 0.79-1.03)
P=0.12

COMPASS Diabetes Analysis

Effects in patients with diabetes at baseline (N=6,922) versus without diabetes (N=11,356)

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Patients randomized to rivaroxaban plus aspirin (N=9,126) versus placebo plus aspirin (N=9,126)

• 1° efficacy: CV death, MI, stroke
• 2° efficacy:
  - All-cause mortality
  - CV death, MI, stroke, MALE, including amputation
• 1° safety: modified ISTH criteria - major bleeding
• Prespecified net clinical benefit: CV death, MI, stroke, fatal bleeding, symptomatic bleeding into a critical organ

CV Death, Myocardial Infarction, or Stroke

Diabetes (N=6,922)
- Aspirin Alone
- Rivaroxaban plus Aspirin

No Diabetes (N=11,356)
- Aspirin Alone
- Rivaroxaban plus Aspirin

HR 0.77, 95% CI: 0.64-0.93, p=0.005
ARR 1.4%

Diabetes
HR 0.74, 95% CI: 0.61-0.90, p=0.002
ARR 2.3%

Aspirin Alone
Rivaroxaban plus Aspirin

Diabetes (N=6,922)

Aspirin Alone
Rivaroxaban plus Aspirin

No Diabetes (N=11,356)

P value for interaction=0.82

Diabetes
HR 0.81, 95% CI: 0.65-1.00, p=0.05
ARR 1.9%

No Diabetes
HR 0.84, 95% CI: 0.68-1.03, p=0.09
ARR 0.6%

CV Death, Myocardial Infarction, Stroke, MALE, or Major Vascular Amputation

Diabetes (N=6,922)
- Aspirin Alone
- Rivaroxaban plus Aspirin
No Diabetes (N=11,356)
- Aspirin Alone
- Rivaroxaban plus Aspirin

P value for interaction=0.88

Diabetes
HR 0.73, 95% CI: 0.61-0.88, p=0.0007
ARR 2.7%

No Diabetes
HR 0.74, 95% CI: 0.62-0.89, p=0.001
ARR 1.7%

### Safety Outcomes

<table>
<thead>
<tr>
<th></th>
<th>Rivaroxaban plus Aspirin</th>
<th>Aspirin Alone</th>
<th>Hazard Ratio (95% CI)</th>
<th>P value</th>
<th>P value for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Major bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes at baseline</td>
<td>178/5704 (3.1) 4.4</td>
<td>105/5652 (1.9) 3.2</td>
<td>1.69 (1.33-2.15)</td>
<td>&lt;0.0001</td>
<td></td>
</tr>
<tr>
<td>Diabetes at baseline</td>
<td>110/3448 (3.2) 4.5</td>
<td>65/3474 (1.9) 3.4</td>
<td>1.70 (1.25-2.31)</td>
<td>0.0006</td>
<td></td>
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<tr>
<td><strong>Intracranial bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes at baseline</td>
<td>17/5704 (0.3) 0.4</td>
<td>17/5652 (0.3) 0.7</td>
<td>0.99 (0.51-1.95)</td>
<td>0.98</td>
<td></td>
</tr>
<tr>
<td>Diabetes at baseline</td>
<td>11/3448 (0.3) 0.4</td>
<td>7/3474 (0.2) 0.4</td>
<td>1.57 (0.61-4.05)</td>
<td>0.35</td>
<td></td>
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<tr>
<td><strong>Fatal bleeding</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes at baseline</td>
<td>10/5704 (0.2) 0.4</td>
<td>7/5652 (0.1) 0.2</td>
<td>1.43 (0.55-3.77)</td>
<td>0.46</td>
<td></td>
</tr>
<tr>
<td>Diabetes at baseline</td>
<td>5/3448 (0.1) 0.2</td>
<td>3/3474 (&lt;0.1) 0.2</td>
<td>1.66 (0.40-6.93)</td>
<td>0.48</td>
<td></td>
</tr>
</tbody>
</table>

CV Death, MI, Stroke, Fatal Bleeding, or Symptomatic Bleeding into Critical Organ

Cumulative Hazard

Diabetes (N=6,922)
- Aspirin Alone
- Rivaroxaban plus Aspirin
No Diabetes (N=11,356)
- Aspirin Alone
- Rivaroxaban plus Aspirin

P value for interaction=0.78

Diabetes
HR 0.78, 95% CI: 0.65-0.94, p=0.02
ARR 2.7%

No Diabetes
HR 0.81, 95% CI: 0.68-0.97, p=0.01
ARR 1.0%

## Benefits in Diabetes +/- Prior Ischemic Events or Revascularization: CV Death/MI/Stroke

<table>
<thead>
<tr>
<th>Prior ischemic events, revasc</th>
<th>Rivaroxaban plus Aspirin</th>
<th>Aspirin Alone</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of first events/patients (%)</td>
<td>Kaplan-Meier risk at 36 months</td>
</tr>
<tr>
<td>No</td>
<td>18/416 (4.3)</td>
<td>11.0</td>
</tr>
<tr>
<td>Yes</td>
<td>161/3032 (5.3)</td>
<td>8.3</td>
</tr>
<tr>
<td>No</td>
<td>58/978 (5.9)</td>
<td>10.0</td>
</tr>
<tr>
<td>Yes</td>
<td>121/2470 (4.9)</td>
<td>7.9</td>
</tr>
<tr>
<td>Prior ischemic events</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>42/937 (4.5)</td>
<td>8.8</td>
</tr>
<tr>
<td>Yes</td>
<td>137/2511 (5.5)</td>
<td>8.3</td>
</tr>
<tr>
<td>Prior revasc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>58/978 (5.9)</td>
<td>10.0</td>
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<td>Yes</td>
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</table>
Limitations

Diabetes subgroup not specifically powered for efficacy or safety

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Early stopping of the trial further limits the power of subgroup analysis

• Though the independent DSMB felt the trial needed to be stopped due to overwhelming efficacy, including a reduction in all-cause mortality

Conclusions

Low-dose rivaroxaban + aspirin reduced major CV events in stable atherosclerosis, irrespective of the presence or absence of diabetes, though absolute risk reductions were numerically larger with diabetes, including for all-cause mortality.
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The net clinical benefit when examining irreversible outcomes appeared numerically greater in those with diabetes.

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As in the overall trial, there was a significant increase in major bleeding, but not in fatal or intracranial bleeding.

The net clinical benefit when examining irreversible outcomes appeared numerically greater in those with diabetes.

Use of dual pathway inhibition with low-dose rivaroxaban + aspirin is particularly attractive in high-risk patients, such as those with diabetes.
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Thank You!

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