Objectives:

• Discuss the results of the PRECISION trial regarding cardiovascular risk of naproxen, ibuprofen, and celecoxib
• Assess the results of the FOURIER trial regarding efficacy and safety of the PCSK9 inhibitor evolocumab
• Explain the benefits of rivaroxaban over aspirin in extended treatment of VTE based on the EINSTEIN CHOICE trial
The PRECISION Trial
Prospective Randomized Evaluation of Celecoxib Integrated Safety versus Ibuprofen or Naproxen

Steven E. Nissen MD MACC

Disclosure

Study Sponsor: Pfizer
Consulting: Many pharmaceutical companies
Clinical Trials: Abbvie, Amgen, AstraZeneca, Cerenis, Eli Lilly, Esperion, Novartis, Novo Nordisk, Medtronic, The Medicines Company, and Pfizer. Companies are directed to pay any honoraria, speaking or consulting fees directly to charity so that neither income nor tax deduction is received.
Background

- Non-steroidal anti-inflammatory drugs (NSAIDs) are amongst the most widely prescribed class of drugs in the world with 100 million prescriptions in the US in 2013.

- NSAIDs inhibit cyclooxygenase (COX), which reduces pain and inflammation through inhibition of prostaglandins, but also has important vascular effects.

- The withdrawal of the selective COX-2 inhibitor, rofecoxib, raised questions about CV safety of these drugs, including the sole remaining COX-2 inhibitor in USA, celecoxib.
Objectives of the PRECISION Trial

- The primary objective was *non-inferiority* assessment of the cardiovascular risk of celecoxib vs. two widely used non-selective NSAIDs, naproxen and ibuprofen, in osteoarthritis and rheumatoid arthritis patients.

- Other objectives included comparative safety of celecoxib vs. these two NSAIDs for all-cause mortality, gastrointestinal and renal adverse events.
Osteoarthritis or rheumatoid arthritis patients with established CV disease or increased risk who required NSAIDs for ≥ 6 months for symptom relief

- Celecoxib 100 mg b.i.d
- Ibuprofen 600 mg t.i.d
- Naproxen 375 mg b.i.d

- Esomeprazole 20-40 mg

Option to increase dosage for unrelieved symptoms to the maximum approved by local regulatory authorities

Event driven trial with a minimum follow up of 18 months
## Selected Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Celecoxib N=8072</th>
<th>Ibuprofen N=8040</th>
<th>Naproxen N=7969</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>63.0</td>
<td>63.2</td>
<td>63.3</td>
</tr>
<tr>
<td>Female Gender</td>
<td>64.1%</td>
<td>64.4%</td>
<td>63.9%</td>
</tr>
<tr>
<td>White</td>
<td>75.0%</td>
<td>74.5%</td>
<td>74.4%</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>89.9%</td>
<td>89.6%</td>
<td>90.1%</td>
</tr>
<tr>
<td>Rheumatoid Arthritis</td>
<td>10.1%</td>
<td>10.4%</td>
<td>9.9%</td>
</tr>
<tr>
<td>Secondary Prevention</td>
<td>23.1%</td>
<td>22.8%</td>
<td>22.4%</td>
</tr>
<tr>
<td>Prior aspirin use</td>
<td>45.8%</td>
<td>46.2%</td>
<td>45.8%</td>
</tr>
<tr>
<td>Diabetes</td>
<td>35.2%</td>
<td>35.9%</td>
<td>34.7%</td>
</tr>
<tr>
<td>Current smoker</td>
<td>20.9%</td>
<td>20.9%</td>
<td>20.5%</td>
</tr>
<tr>
<td>Systolic BP (mm Hg)</td>
<td>125.3</td>
<td>125.4</td>
<td>125.0</td>
</tr>
</tbody>
</table>
Noninferiority Analysis for Primary APTC Endpoint

**Intention-to-Treat**

- Cele vs. Ibu, HR 0.85 (0.70-1.04), *P*<0.001*
- Cele vs. Nap, HR 0.93 (0.76-1.12), *P*<0.001*
- Ibu vs. Nap, HR 1.08 (0.90-1.31), *P*<0.02*

**On-Treatment**

- Cele vs. Ibu, HR 0.81 (0.65-1.02), *P*<0.001*
- Cele vs. Nap HR 0.90 (0.71-1.15), *P*<0.001*
- Ibu vs. Nap HR 1.12 (0.89-1.4), *P*<0.025*

*Noninferiority p values*
Time-to-Major Adverse Cardiovascular Event

Intention-to-Treat

- Cele vs. Ibu, HR 0.87 (0.75-1.01), \( P=0.06 \)
- Cele vs. Nap, HR 0.97 (0.83-1.12), \( P=0.64 \)
- Ibu vs. Nap, HR 1.11 (0.96-1.29), \( P=0.15 \)

On-Treatment

- Cele vs. Ibu, HR 0.82 (0.69-0.97)
- Cele vs. Nap, HR 0.95 (0.80-1.13)
- Ibu vs. Nap, HR 1.17 (0.99-1.38)

Ibuprofen 15% higher (borderline significant)

Patients with an Event (%)

Months Since Randomization

Intermountain Heart Institute
Intermountain Medical Center
**Time-to-Death from Cardiovascular Causes**

**Intention-to-Treat**
- Cele vs. Ibu, HR 0.84 (0.61-1.16), \( P=0.30 \)
- Cele vs. Nap, HR 0.78 (0.57-1.07), \( P=0.13 \)
- Ibu vs. Nap, HR 0.93 (0.69-1.26), \( P=0.64 \)

**On-Treatment**
- Cele vs. Ibu, HR 0.64 (0.42-0.99)
- Cele vs. Nap, HR 0.69 (0.45-1.07)
- Ibu vs. Nap, HR 1.08 (0.73-1.60)
**Time-to-Major Gastrointestinal Event**

**Intention-to-Treat**

- Cele vs. Ibu, HR 0.65 (0.50-0.85), $P=0.002$
- Cele vs. Nap, HR 0.71 (0.54-0.93), $P=0.01$
- Ibu vs. Nap, HR 0.108 (0.85-1.39), $P=0.53$

**On-Treatment**

- Cele vs. Ibu, HR 0.44 (0.32-0.61)
- Cele vs. Nap, HR 0.45 (0.33-0.63)
- Ibu vs. Nap, HR 1.03 (0.80-1.34)
Time from Randomization to Serious Renal Event

**Intention-to-Treat**

- Cele vs. Ibu, HR 0.61 (0.44-0.85), \( P=0.004 \)
- Cele vs. Nap, HR 0.79 (0.56-1.12), \( P=0.19 \)
- Ibu vs. Nap, HR 1.29 (0.95-1.76), \( P=0.10 \)

**On-Treatment**

- Cele vs. Ibu, HR 0.54 (0.37-0.80)
- Cele vs. Nap, HR 0.66 (0.44-0.97)
- Ibu vs. Nap, HR 1.21 (0.86-1.70)

Ibuprofen 64% higher

Patients with an Event (%)

Months Since Randomization
Post Hoc: Any Adjudicated CV, GI or Renal Event

Intention-to-Treat

Cele vs. Ibu, HR 0.78 (0.69-0.87), P<0.001
Cele vs. Nap, HR 0.87 (0.77-0.99), P=0.03
Ibu vs. Nap, HR 1.13 (1.01-1.26), P=0.04

On-Treatment

Cele vs. Ibu, HR 0.69 (0.61-0.79)
Cele vs. Nap, HR 0.78 (0.68-0.90)
Ibu vs. Nap, HR 1.13 (0.997-1.28)

Ibuprofen 28% higher (NNH - 59)
Naproxen 15% higher (NNH - 117)

Patients with an Event (%)

Months Since Randomization

Intermountain Heart Institute
Intermountain Medical Center
# APTC Endpoint: Aspirin Subgroup ITT Population

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Celecoxib N=8030 N</th>
<th>Ibuprofen N=7990 N</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not taking low-dose Aspirin</td>
<td>0.78 (0.58, 1.04)</td>
<td>81</td>
<td>102</td>
<td>0.40</td>
</tr>
<tr>
<td>Taking low-dose Aspirin</td>
<td>0.93 (0.71, 1.20)</td>
<td>107</td>
<td>116</td>
<td></td>
</tr>
</tbody>
</table>

Celecoxib better, Ibuprofen better

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Celecoxib N=8030 N</th>
<th>Naproxen N=7933 N</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not taking low-dose Aspirin</td>
<td>0.83 (0.61, 1.11)</td>
<td>81</td>
<td>97</td>
<td>0.29</td>
</tr>
<tr>
<td>Taking low-dose Aspirin</td>
<td>1.03 (0.79, 1.35)</td>
<td>107</td>
<td>104</td>
<td></td>
</tr>
</tbody>
</table>

Celecoxib better, Naproxen better

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR (95% CI)</th>
<th>Ibuprofen N=7990 N</th>
<th>Naproxen N=7933 N</th>
<th>Interaction P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Not taking low-dose Aspirin</td>
<td>1.06 (0.80, 1.35)</td>
<td>102</td>
<td>97</td>
<td>0.80</td>
</tr>
<tr>
<td>Taking low-dose Aspirin</td>
<td>1.40 (1.09, 1.86)</td>
<td>116</td>
<td>104</td>
<td></td>
</tr>
</tbody>
</table>

Ibuprofen better, Naproxen better

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*Intermountain Heart Institute*

*Intermountain Medical Center*
Conclusions: Celecoxib vs. Naproxen

- Numerically fewer APTC events occurred with celecoxib than naproxen, meeting all 4 noninferiority criteria ($P<0.001$).

- In ITT analyses, chronic treatment with prescription doses of naproxen, compared with celecoxib, was associated with:
  - Higher rates of gastrointestinal adverse events and a borderline significant increase in all-cause mortality.

- In the on-treatment sensitivity analysis, naproxen showed:
  - Higher rates of all-cause mortality and major gastrointestinal and renal events.
Conclusions: Celecoxib vs. Ibuprofen

- Numerically fewer APTC events occurred with celecoxib than ibuprofen, meeting all 4 noninferiority criteria ($P<0.001$)

- In ITT analyses, chronic treatment with prescription doses of ibuprofen, compared with celecoxib, was associated with:
  - Higher rates of gastrointestinal and renal adverse events

- In the on-treatment sensitivity analysis, ibuprofen showed:
  - Higher rates of MACE, cardiovascular death, all-cause mortality and major gastrointestinal and renal events.
Additional Conclusions

- These findings challenge the widely-held view that naproxen provides superior cardiovascular safety.

- Results were consistent regardless of baseline administration of aspirin. Gastrointestinal safety differences were evident despite prophylactic use of esomeprazole.

- Between drug differences should be viewed as hypothesis-generating, rather than conclusive, given multiplicity issues and the challenges of adherence and retention in the trial.

- These findings will require careful review by global health authorities to determine what changes in labeling or regulatory status of these drugs are warranted.
Brent’s Thoughts

• It is good to have a large definitive trial that evaluates the safety of several non-steroidal anti-inflammatory drugs among patients with documented or increased risk of CAD.
  - The adverse event rates were very low in all groups and did not appear to differ much from expected outcomes among similar patients not taking NSAIDS at all.

• It appears that among the three drugs tested, celexicob was a little bit safer.
An OPen-label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention PIONEER AF-PCI

C. Michael Gibson, MS, MD
on behalf of the PIONEER Investigators
AF and CAD often occur together because of the strong association of both conditions with aging and overlapping risk factors.

@ 1 Billion people in US and Europe
@ 20 Million with AF (1-2% of population)\textsuperscript{1,2}
@ 16 Million anticoagulation indicated (80%) \textsuperscript{1,2}
@ 4.8 Million have CAD as well (20%-45%) \textsuperscript{1,2}
@ 1-2 Million potential revasc (20%-25%) \textsuperscript{3,4}

24.9% of patients with AF enrolled in ARISTOTLE had prior PCI\textsuperscript{4}

1. The AFFIRM Investigators. *Am Heart J* 2002;143:991–1001;
Atrial Fibrillation (ACTIVE W)\(^1\): The combination of aspirin and clopidogrel is not as effective as \textit{warfarin} in patients with AF\(^1\)

\textit{However}

Stenting (STARS)\(^2\): The combination of \textit{aspirin and a thienopyridine} is more effective than warfarin in patients with coronary stents \(^2\)

Dose of Rivaroxaban Varies in ACS & Atrial Fibrillation Patients

ACS/Stenting
DAPT + 2.5 mg BID Riva

Atrial Fibrillation
Riva 20 mg QD

Stent + Afib

4 Fold Difference in Riva Dose Between ACS and AF


Gibson et al. AHA 2016
Is ASA Necessary In Triple Therapy? The WOEST trial

Modest-scale, open-label WOEST study (N=573) compared safety outcomes with triple therapy (VKA + clopidogrel + ASA) vs dual therapy (VKA + clopidogrel) 69% of WOEST patients had AF, included prosthetic heart valves

Safety outcomes:
- Any bleeding
- TIMI major
- TIMI major + minor

Efficacy outcomes:
- Death
- MI
- Stroke

* 23% CV Death
13.7% and 30.6%

*p<0.05.
** All-cause death (CV & non-CV death p = 0.207 & 0.069)
Gibson et al. AHA 2016
Patients With Atrial Fibrillation Undergoing Coronary Stent Placement: PIONEER AF-PCI

- 2100 patients with NVAF
- Coronary stenting
- No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

RANDOMIZE

- Rivaroxaban 15 mg qd*
  - Clopidogrel 75 mg qd†

1, 6, or 12 months – Pre randomization MD Choice

- Rivaroxaban 2.5 mg bid
  - Clopidogrel 75 mg qd†
  - Aspirin 75-100 mg qd‡

- Rivaroxaban 15mg QD
  - Aspirin 75-100 mg qd

1, 6, or 12 months – Pre randomization MD Choice

- VKA (target INR 2.0-3.0)
  - Clopidogrel 75 mg qd†
  - Aspirin 75-100 mg qd

- VKA (target INR 2.0-3.0)
  - Aspirin 75-100 mg qd

End of treatment 12 months

WOEST Like

ATLAS Like

Triple Therapy

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
Pre-Randomization Choice of Duration of DAPT & Thienopyridine: PIONEER AF-PCI

- 2100 patients with NVAF
- Coronary stenting
- No prior stroke/TIA, GI bleeding, Hb<10, CrCl<30

Randomize

XARELTO® 15 mg qd*
Clopi 95%, Ticag 4%, Prasugrel 1%

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

WOEST Like

XARELTO® 2.5 mg bid
Clopi 95%, Ticag 4%, Prasugrel 1%
Aspirin 75-100 mg qd†

ATLAS Like

XARELTO® 15mg QD
Aspirin 75-100 mg qd

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

Triple Therapy

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

VKA (target INR 2.0-3.0)
Aspirin 75-100 mg qd
TTR 65%

Gibson et al. AHA 2016
# Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Riva + P2Y$_{12}$ (N=709)</th>
<th>Riva + DAPT (N=709)</th>
<th>VKA + DAPT (N=706)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, mean ± SD</td>
<td>70.4 ± 9.1</td>
<td>70.0 ± 9.1</td>
<td>69.9 ± 8.7</td>
</tr>
<tr>
<td>Sex, female, n (%)</td>
<td>181 (25.5%)</td>
<td>174 (24.5%)</td>
<td>188 (26.6%)</td>
</tr>
<tr>
<td>Diabetes Mellitus, n (%)</td>
<td>204 (28.8%)</td>
<td>199 (28.1%)</td>
<td>221 (31.1%)</td>
</tr>
<tr>
<td>Type of Index Event, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTEMI</td>
<td>130 (18.5%)</td>
<td>129 (18.4%)</td>
<td>123 (17.8%)</td>
</tr>
<tr>
<td>STEMI</td>
<td>86 (12.3%)</td>
<td>97 (13.8%)</td>
<td>74 (10.7%)</td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>145 (20.7%)</td>
<td>148 (21.1%)</td>
<td>164 (23.7%)</td>
</tr>
<tr>
<td>Stable Angina</td>
<td>340 (48.5%)</td>
<td>329 (46.8%)</td>
<td>330 (47.8%)</td>
</tr>
<tr>
<td>Drug-eluting stent, n (%)</td>
<td>464 (65.4%)</td>
<td>471 (66.8%)</td>
<td>468 (66.5%)</td>
</tr>
<tr>
<td>Type of Atrial Fibrillation, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Persistent</td>
<td>146 (20.6%)</td>
<td>146 (20.6%)</td>
<td>149 (21.1%)</td>
</tr>
<tr>
<td>Permanent</td>
<td>262 (37.0%)</td>
<td>238 (33.6%)</td>
<td>243 (34.5%)</td>
</tr>
<tr>
<td>Paroxysmal</td>
<td>300 (42.4%)</td>
<td>325 (45.8%)</td>
<td>313 (44.4%)</td>
</tr>
</tbody>
</table>
Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events

**Graph Title:** Kaplan-Meier Estimates of First Occurrence of Clinically Significant Bleeding Events

**Graph Description:**
- **TIMI Major, TIMI Minor, or Bleeding requiring Medical Attention (%):**
  - **VKA + DAPT**: 26.7%
  - **Riva + DAPT**: 18.0%
  - **Riva + P2Y\textsubscript{12}**: 16.8%

**Legend:**
- **VKA + DAPT**
- **Riva + DAPT**
- **Riva + P2Y\textsubscript{12}**

**Statistical Results:**
- **Riva + P2Y\textsubscript{12} 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 < 0.000018
  - ARR = 8.7
  - NNT = 12

**No. at risk:**
- **VKA + DAPT:**
  - 696 → 628 → 606 → 585
  - 543 → 528
  - 389

- **Riva + DAPT:**
  - 697 → 593 → 555 → 521
  - 461
  - 329

**Days:**
- 0 → 30 → 60 → 90 → 180 → 270 → 360

**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:**
- The composite of TIMI major, TIMI minor, and BRMA.

**Hazard ratios:**
- As compared to the VKA group, based on the Cox proportional hazards model.

**Log-Rank P-values:**
- As compared to VKA group, based on the two-sided log rank test.

**References:**
- Gibson et al. AHA 2016
## Subgroup Analysis: TIMI Major, TIMI Minor, BRMA Bleeding

<table>
<thead>
<tr>
<th></th>
<th><strong>Riva + P2Y_{12}</strong></th>
<th><strong>VKA + DAPT</strong></th>
<th><strong>TIMI major, TIMI minor, BRMA</strong></th>
<th><strong>HR (95% CI)</strong></th>
<th><strong>p-value^a</strong></th>
<th><strong>p-value^b</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>109 / 696 (16.8)</td>
<td>167 / 697 (26.7)</td>
<td></td>
<td>0.59 (0.47 - 0.76)</td>
<td>&lt;0.001</td>
<td>0.447</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>80 / 517 (16.5)</td>
<td>116 / 513 (24.9)</td>
<td></td>
<td>0.63 (0.47 - 0.84)</td>
<td>0.001</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>29 / 179 (18.0)</td>
<td>51 / 184 (32.0)</td>
<td></td>
<td>0.51 (0.32 - 0.80)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td><strong>Age Group 1</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 75 years</td>
<td>60 / 445 (14.8)</td>
<td>105 / 473 (24.6)</td>
<td></td>
<td>0.56 (0.41 - 0.77)</td>
<td>&lt;0.001</td>
<td>0.712</td>
</tr>
<tr>
<td>&gt;= 75 years</td>
<td>49 / 251 (20.6)</td>
<td>62 / 224 (31.4)</td>
<td></td>
<td>0.62 (0.42 - 0.90)</td>
<td>0.011</td>
<td></td>
</tr>
<tr>
<td><strong>Age Group 2</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt; 65 years</td>
<td>22 / 184 (13)</td>
<td>35 / 179 (21.4)</td>
<td></td>
<td>0.57 (0.34 - 0.98)</td>
<td>0.039</td>
<td>0.889</td>
</tr>
<tr>
<td>&gt;= 65 years</td>
<td>87 / 512 (18.2)</td>
<td>132 / 518 (28.7)</td>
<td></td>
<td>0.60 (0.46 - 0.78)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>103 / 650 (17.0)</td>
<td>152 / 655 (26.1)</td>
<td></td>
<td>0.62 (0.48 - 0.79)</td>
<td>&lt;0.001</td>
<td>0.792</td>
</tr>
<tr>
<td>Black/African American</td>
<td>0 / 7 (0.0)</td>
<td>0 / 1 (0.0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>Asian</td>
<td>4 / 24 (18.2)</td>
<td>14 / 33 (42.6)</td>
<td></td>
<td>0.37 (0.12 - 1.13)</td>
<td>0.069</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>2 / 15 (15.2)</td>
<td>1 / 8 (14.3)</td>
<td></td>
<td>1.05 (0.10 - 11.61)</td>
<td>0.967</td>
<td></td>
</tr>
<tr>
<td><strong>Type of P2Y_{12} Inhibitor</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Clopidogrel</td>
<td>99 / 648 (16.3)</td>
<td>157 / 671 (26.1)</td>
<td></td>
<td>0.59 (0.46 - 0.76)</td>
<td>&lt;0.001</td>
<td>0.419</td>
</tr>
<tr>
<td>Prasugrel</td>
<td>5 / 12 (47.0)</td>
<td>2 / 5 (40.0)</td>
<td></td>
<td>1.16 (0.22 - 6.03)</td>
<td>0.857</td>
<td></td>
</tr>
<tr>
<td>Ticagrelor</td>
<td>5 / 36 (16.0)</td>
<td>8 / 21 (43.8)</td>
<td></td>
<td>0.33 (0.11 - 1.01)</td>
<td>0.039</td>
<td></td>
</tr>
<tr>
<td><strong>Type of Stent</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
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</tr>
<tr>
<td>Drug Eluting Stent</td>
<td>71 / 452 (16.8)</td>
<td>104 / 463 (25.2)</td>
<td></td>
<td>0.64 (0.47 - 0.86)</td>
<td>0.003</td>
<td>0.490</td>
</tr>
<tr>
<td>Bare Metal Stent</td>
<td>37 / 230 (17.3)</td>
<td>59 / 221 (29.5)</td>
<td></td>
<td>0.54 (0.36 - 0.82)</td>
<td>0.003</td>
<td></td>
</tr>
<tr>
<td>Both</td>
<td>1 / 14 (10.0)</td>
<td>4 / 11 (38.6)</td>
<td></td>
<td>0.20 (0.02 - 1.82)</td>
<td>0.115</td>
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<tr>
<td><strong>Index Event</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NSTE MI</td>
<td>27 / 130 (20.3)</td>
<td>26 / 122 (24.0)</td>
<td></td>
<td>0.94 (0.55 - 1.61)</td>
<td>0.826</td>
<td>0.181</td>
</tr>
<tr>
<td>STEMI</td>
<td>12 / 85 (14.6)</td>
<td>23 / 74 (35.9)</td>
<td></td>
<td>0.40 (0.20 - 0.80)</td>
<td>0.007</td>
<td></td>
</tr>
<tr>
<td>Unstable Angina</td>
<td>16 / 140 (12.7)</td>
<td>36 / 163 (24.2)</td>
<td></td>
<td>0.48 (0.27 - 0.87)</td>
<td>0.013</td>
<td></td>
</tr>
<tr>
<td><strong>CHADS2 Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-1</td>
<td>46 / 311 (16.1)</td>
<td>68 / 307 (24.7)</td>
<td></td>
<td>0.61 (0.42 - 0.89)</td>
<td>0.010</td>
<td>0.814</td>
</tr>
<tr>
<td>2-6</td>
<td>63 / 385 (17.4)</td>
<td>99 / 390 (28.4)</td>
<td></td>
<td>0.58 (0.42 - 0.79)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>CHA2DS2-VASC Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-3</td>
<td>49 / 309 (16.8)</td>
<td>66 / 291 (24.1)</td>
<td></td>
<td>0.66 (0.46 - 0.96)</td>
<td>0.028</td>
<td>0.457</td>
</tr>
<tr>
<td>4-7</td>
<td>60 / 387 (16.9)</td>
<td>101 / 406 (29.0)</td>
<td></td>
<td>0.55 (0.40 - 0.75)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td><strong>HAS-BLED Score</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0-2</td>
<td>25 / 192 (14.5)</td>
<td>40 / 206 (21.9)</td>
<td></td>
<td>0.61 (0.37 - 1.01)</td>
<td>0.053</td>
<td>0.548</td>
</tr>
<tr>
<td>3</td>
<td>47 / 315 (16.3)</td>
<td>78 / 302 (28.8)</td>
<td></td>
<td>0.52 (0.36 - 0.74)</td>
<td>&lt;0.001</td>
<td></td>
</tr>
<tr>
<td>4-6</td>
<td>37 / 189 (20.0)</td>
<td>49 / 199 (28.6)</td>
<td></td>
<td>0.70 (0.46 - 1.07)</td>
<td>0.101</td>
<td></td>
</tr>
</tbody>
</table>

---

Rivaroxaban Better

VKA Better---->

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

**n** = number of subjects with events, **N** = number of subjects at risk, **%** = Kaplan-Meier estimates.

Hazard ratios as compared to VKA group are based on the [stratified, only for Overall, 2.5 mg BID/15 mg QD comparing VKA] Cox proportional hazards model.

BRMA = Bleeding requiring medical attention, TIMI = Thrombolysis in myocardial infarction.

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.

**P-Value for quantitative Interaction based on the Cox proportional Hazard joint test.**

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

Cardiovascular Death, Myocardial Infarction, or Stroke (%)

No. at risk

Riva + P2Y_{12} 694 648 633 621
Riva + DAPT 704 662 640 628
VKA + DAPT 695 635 607 579

Days

Riva + P2Y_{12} 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

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

Composite of adverse CV events is composite of CV death, MI, and stroke.

Hazard ratios as compared to VKA group are based on the (stratified, only for the Overall, 2.5 mg BID/15 mg QD comparing VKA) Cox proportional hazards model.

Log-Rank P-values as compared to the VKA group are based on the (stratified, only for Overall, 2.5 mg BID/115 mg QD comparing VKA) two-sided log rank test.

6 Subjects were excluded from all efficacy analyses because of violations in Good Clinical Practice guidelines

Gibson et al. AHA 2016
All Cause Hospitalization for an Adverse Event

- **Riva + P2Y_{12}** v. **VKA + DAPT**
  - HR = 0.77 (95% CI: 0.65-0.92)
  - p = 0.005
  - ARR = 7.4
  - NNT = 14

- **Riva + DAPT** v. **VKA + DAPT**
  - HR = 0.74 (95% CI: 0.61-0.88)
  - p = 0.001
  - ARR = 10.3
  - NNT = 10

**No. at Risk**
- Riva + P2Y_{12}: 696, 609, 582, 559
- Riva + DAPT: 706, 607, 570, 548
- VKA + DAPT: 697, 592, 540, 490

**Days**
- 496
- 493
- 422

**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
Hospitalization Related to Cardiovascular or Bleeding Event

<table>
<thead>
<tr>
<th></th>
<th>Cardiovascular</th>
<th></th>
<th>Bleeding</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Riva + P2Y_{12} v. VKA + DAPT</td>
<td>HR=0.68 (95% CI: 0.54-0.85)</td>
<td>Riva + DAPT v. VKA + DAPT</td>
<td>HR=0.73 (95% CI: 0.58-0.91)</td>
</tr>
<tr>
<td></td>
<td>P&lt;0.001</td>
<td></td>
<td>p=0.005</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARR=8.1</td>
<td></td>
<td>ARR=8.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NNT=13</td>
<td></td>
<td>NNT =13</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Riva + P2Y_{12} v. VKA + DAPT</td>
<td>HR=0.61 (95% CI: 0.41-0.90)</td>
<td>Riva + DAPT v. VKA + DAPT</td>
<td>HR=0.51 (95% CI: 0.34-0.77)</td>
</tr>
<tr>
<td></td>
<td>p=0.012</td>
<td></td>
<td>p=0.001</td>
<td></td>
</tr>
<tr>
<td></td>
<td>ARR=4.0</td>
<td></td>
<td>ARR=5.1</td>
<td></td>
</tr>
<tr>
<td></td>
<td>NNT=25</td>
<td></td>
<td>NNT =20</td>
<td></td>
</tr>
</tbody>
</table>

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

- **Cardiovascular**
  - Riva + DAPT: 20.3%
  - Riva + P2Y_{12}: 10.5%
  - VKA + DAPT: 28.4%

- **Bleeding**
  - Riva + DAPT: 6.5%
  - Riva + P2Y_{12}: 5.4%

---

**Note:**
- 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
Summary

A strategy of either rivaroxaban 15 mg daily plus a P2Y\textsubscript{12} or rivaroxaban 2.5 mg BID + DAPT was associated with a reduction in clinically significant bleeding compared with conventional triple therapy of VKA + DAPT (HR = 0.59 (0.47-0.76), \( p < 0.001 \), NNT 11, and HR = 0.63 (0.50-0.80), \( p <0.001 \), NNT 12 respectively).

CV death / MI / stroke were comparable among the groups (Riva 15 mg+ P2Y\textsubscript{12} = 6.5%, Riva 2.5 mg+ DAPT = 5.6%, VKA + DAPT = 6.0%) with broad confidence intervals.

Rates of all cause death or hospitalization were reduced in the Rivaroxaban arms (Riva 15 mg + P2Y\textsubscript{12} = NNT 15, Riva 2.5 + DAPT, NNT =10)
Brent’s Thoughts

- Ever since the WOEST trial, I have stopped using triple anticoagulation therapy for my patients with both atrial fibrillation and new coronary stents.
- After the advent of DOACs, I sort of transferred the WOEST results with warfarin over to them.
- Now we have data that justifies my existing practice.
- Now we get to pick between DAPT + very low dose DOAC or Clopidogrel with normal dose DOAC.
  - We should note that all the safety data comes mainly from clopidogrel.
Long-term Comparison of Patent Foramen Ovale (PFO) Closure versus Medical Therapy after Cryptogenic Stroke:

Final Results of the RESPECT Trial

David E. Thaler, M.D., Ph.D.
Chairman of Neurology, Tufts University School of Medicine

On Behalf of RESPECT Investigators
Background

- ~25% of all ischemic strokes are “cryptogenic”\(^1\)
- 34-46% of ischemic strokes occur between 18-60 years\(^2,3\)
- PFO present in 40-50% of cryptogenic stroke patients\(^4,5\)
- Young and middle aged patients have continued exposure to PFO-related recurrence risk
- No RCT has reported long-term outcomes of PFO closure

Background

• In the ITT population, early and medium-term results in RESPECT showed point estimates in favor of closure but did not reach statistical significance
• RESPECT protocol required follow-up until an FDA regulatory decision
• Food and Drug Administration (FDA) Advisory Panel in May 2016 (data lock, August 2015)
• Following panel meeting, FDA requested an analysis of long-term outcomes using updated data – these final analyses (data lock, May 2016) of RESPECT are presented today
• Low event rates increase importance of longer follow-up
AMPLATZER™ PFO Occluder

Device Description:
- Self-expandable double disc device lined with thin polyester fabric
- Linked together by a short connecting waist
- Nitinol wire mesh
- Recapturable, repositionable
- Self-centering
- Distal and proximal radiopaque marker bands
- MR conditional
- End screw to facilitate optimal handling

Current status:
- CE-Mark in 1998; currently available in > 80 countries worldwide
RESPECT Trial

- Randomized, event-driven, open-label trial with blinded endpoint adjudication
- Patients randomized 1:1 to AMPLATZER™ PFO Occluder (device) vs. guideline-directed medical management (MM)
- 980 subjects enrolled from 2003 to 2011
- 69 sites in U.S. and Canada
Primary Endpoint

- **Composite of:**
  - Recurrent nonfatal ischemic stroke
  - Fatal ischemic stroke
  - Early post-randomization death (within 45 days)

- **Stroke definition:**
  - Acute focal neurological deficit due to cerebral ischemia with:
    - Neuroanatomically relevant infarct on imaging
    or
    - Symptoms >24 hours
Enrollment Criteria

Key Inclusion Criteria

- Cryptogenic stroke within last 9 months
- TEE-confirmed PFO
- 18-60 years
  - Patients > 60 at higher risk of recurrent stroke from non-PFO mechanisms

Key Exclusion Criteria

- Stroke due to identified cause such as:
  - Large vessel atherosclerosis (e.g., carotid stenosis)
  - Atrial fibrillation
  - Intrinsic small vessel disease (lacunar infarcts)
  - 11 other specific etiologies
- Inability to discontinue anticoagulation
Patient Flow

Enrolled

Assigned guideline-recommended medication regimen

Randomized 1:1

Device
- Implant within 21 days
- 1 month of aspirin + clopidogrel, then aspirin until 6 months
- Physician discretion thereafter

Medical Management
- Assigned guideline-recommended medication regimen

Follow-up:
- 1, 6, 12, 18, and 24 months
- Yearly after 24 months

Warfarin
Aspirin
Clopidogrel
Aspirin + dipyridamole
Aspirin + clopidogrel (eliminated in 2006)
## Baseline Characteristics Balanced Between Groups

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>AMPLATZER™ PFO Occluder (N=499)</th>
<th>Medical Management (N=481)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (yr), mean ± SD</td>
<td>48 ± 10</td>
<td>46 ± 10</td>
</tr>
<tr>
<td>Male</td>
<td>54%</td>
<td>56%</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>39%</td>
<td>41%</td>
</tr>
<tr>
<td>Family h/o CAD</td>
<td>33%</td>
<td>33%</td>
</tr>
<tr>
<td>Hypertension</td>
<td>32%</td>
<td>32%</td>
</tr>
<tr>
<td>COPD</td>
<td>0.8%</td>
<td>1.5%</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>0.6%</td>
<td>0%</td>
</tr>
<tr>
<td>History of DVT</td>
<td>4.0%</td>
<td>3.1%</td>
</tr>
<tr>
<td>Atrial septal aneurysm</td>
<td>36%</td>
<td>35%</td>
</tr>
<tr>
<td>Substantial shunt</td>
<td>50%</td>
<td>48%</td>
</tr>
</tbody>
</table>
Procedural Results and Follow-up

- Technical Success* 99.1%
- Procedural Success** 96.1%
- Mean Follow-up: 5.9 years (0-12 years)
  - Device
    - Mean 6.3 years; Total 3141 patient-years
  - Medical Management
    - Mean 5.5 years; Total 2669 patient-years

*Delivery and release of the device
**Implantation without in-hospital SAE
Antithrombotic Medication Use During Follow-up

- Device:
  - None: 6%
  - Other Therapy: 12%
  - Warfarin Alone: 79%
  - Dual Antiplatelet: 11%

- Medical Management:
  - None: 20%
  - Other Therapy: 11%
  - Warfarin Alone: 65%
  - Single Antiplatelet: 11%
RESPECT Final Results

Freedom from Recurrent Ischemic Stroke (Intention to Treat)

- **AMPLATZER™ PFO Occluder** (# strokes = 18)
- **Medical Management** (# strokes = 28)

Risk Reduction: 45%
HR: 0.55 (95% CI: 0.305, 0.999)
Log-rank 2-sided p-value = 0.046

# at Risk (KM Estimates)
- AMPLATZER: 499 (0%) 476 (1.4%) 464 (1.6%) 447 (1.6%) 421 (1.9%) 352 (2.6%) 262 (3.3%) 197 (4.5%) 128 (5.0%) 77 (5.0%) 41 (5.0%)
- MM: 481 (0%) 433 (1.8%) 394 (3.2%) 380 (3.7%) 354 (4.7%) 282 (5.0%) 218 (5.0%) 150 (6.6%) 104 (7.3%) 59 (8.5%) 31 (12.5%)

Time from Randomization (Years)
RESPECT Final Results

Freedom from Recurrent Ischemic Stroke of Unknown Mechanism (Intention to Treat)

Event-free Probability

- AMPLATZER™ PFO Occluder
  - (# strokes = 10)

- Medical Management
  - (# strokes = 23)

Risk Reduction: 62%
HR: 0.38 (95% CI: 0.18, 0.79)
Log-rank 2-sided p-value=0.007

# at Risk (KM Estimates)

<table>
<thead>
<tr>
<th></th>
<th>AMPLATZER</th>
<th>MM</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>499 (0%)</td>
<td>481 (0%)</td>
</tr>
<tr>
<td>1</td>
<td>476 (1.2%)</td>
<td>433 (1.3%)</td>
</tr>
<tr>
<td>2</td>
<td>464 (1.2%)</td>
<td>394 (2.7%)</td>
</tr>
<tr>
<td>3</td>
<td>447 (1.2%)</td>
<td>380 (3.5%)</td>
</tr>
<tr>
<td>4</td>
<td>421 (1.5%)</td>
<td>354 (4.0%)</td>
</tr>
<tr>
<td>5</td>
<td>352 (2.0%)</td>
<td>282 (4.0%)</td>
</tr>
<tr>
<td>6</td>
<td>262 (2.3%)</td>
<td>218 (4.0%)</td>
</tr>
<tr>
<td>7</td>
<td>197 (2.3%)</td>
<td>150 (5.1%)</td>
</tr>
<tr>
<td>8</td>
<td>128 (2.3%)</td>
<td>104 (5.8%)</td>
</tr>
<tr>
<td>9</td>
<td>77 (2.3%)</td>
<td>59 (7.0%)</td>
</tr>
<tr>
<td>10</td>
<td>41 (2.3%)</td>
<td>31 (11.1%)</td>
</tr>
</tbody>
</table>
RESPECT Final Results

Freedom from Recurrent Ischemic Stroke
(Intention to Treat – Patients censored at age 60 years)

Event-free Probability

- AMPLATZER™ PFO Occluder
  (# strokes = 12)
- Medical Management
  (# strokes = 25)

Risk Reduction: 58%
HR: 0.42 (95% CI: 0.21, 0.83)
Log-rank 2-sided p-value=0.010

# at Risk (KM Estimates)
AMPLATZER
475 (0%) 443 (1.3%) 418 (1.8%) 383 (1.8%) 345 (2.0%) 285 (2.6%) 203 (3.0%) 150 (3.0%) 97 (3.0%) 55 (3.0%) 29 (3.0%)

MM
463 (0%) 402 (1.8%) 353 (3.4%) 321 (3.9%) 289 (4.9%) 220 (5.2%) 159 (5.2%) 109 (6.7%) 76 (7.7%) 44 (7.7%) 22 (13.2%)
Interpretation

• These analyses support the hypothesis that PFO closure is preventing PFO-related recurrent strokes.

• PFO-closure cannot prevent strokes from non-PFO related causes.

<table>
<thead>
<tr>
<th></th>
<th>HR (95% CI)</th>
<th>Relative Risk Reducation</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ischemic stroke</td>
<td>0.55 (0.305-0.999)</td>
<td>45%</td>
<td>0.046</td>
</tr>
<tr>
<td>Stroke without known mechanism</td>
<td>0.38 (0.18-0.79)</td>
<td>62%</td>
<td>0.007</td>
</tr>
<tr>
<td>Age-censored analysis (&lt;60y)</td>
<td>0.42 (0.21-0.83)</td>
<td>58%</td>
<td>0.01</td>
</tr>
</tbody>
</table>
DSMB Adjudicated Procedure or Device Related SAEs

- No intra-procedural strokes
- No device embolization
- No device thrombosis
- No device erosion
- Major vascular complications (0.9%) and device explants (0.4%)
### Adjudicated SAEs of Interest

<table>
<thead>
<tr>
<th>Event Type</th>
<th>AMPLATZER™ PFO Occluder (N=499) [3141 Pt-Yrs]</th>
<th>Medical Management (N=481) [2669 Pt-Yrs]</th>
<th>P-value**</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Events</td>
<td>Rate*</td>
<td>Events</td>
</tr>
<tr>
<td>Atrial fibrillation</td>
<td>8</td>
<td>0.25</td>
<td>4</td>
</tr>
<tr>
<td>Major bleeding</td>
<td>18</td>
<td>0.57</td>
<td>15</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>7</td>
<td>0.22</td>
<td>11</td>
</tr>
<tr>
<td>DVT/PE</td>
<td>18</td>
<td>0.57</td>
<td>4</td>
</tr>
</tbody>
</table>

* Rate expressed as number of events per 100 patient-years
**Based on the normal approximation to a difference in Poisson rates
Conclusions

• In the RESPECT trial, PFO closure with the AMPLATZER™ PFO Occluder was more beneficial than medical management alone.

• Collaboration between a cardiologist and neurologist is important for proper patient selection.

• For patients with cryptogenic stroke and PFO, closure with the AMPLATZER™ PFO Occluder is an appropriate treatment option that reduces the risk of recurrent stroke.
The AMPLATZER™ PFO Occluder is indicated for percutaneous transcatheater closure of a patent foramen ovale (PFO) to reduce the risk of recurrent ischemic stroke in patients, predominantly between the ages of 18 and 60 years, who have had a cryptogenic stroke due to a presumed paradoxical embolism, as determined by a neurologist and cardiologist following an evaluation to exclude known causes of ischemic stroke.
Brent’s Thoughts

- Finally we have an FDA approved device for PFO closures.
- The RESPECT trial appears to confirm that at least some strokes are caused by PFO’s, and therefore, can be prevented by PFO closure.
- It emphasizes that non-PFO-related strokes remain common.
- I am not sure if I agree with the 60 year old cut-off. But I do agree that careful examination for other causes of stroke should be done in all cases.
- I look forward to subgroup analysis based on the size of PFO (substantial versus non-substantial).
- I agree with the FDA that is requiring that both a neurologist and a cardiologist approve of the procedure.
- Unfortunately, the FDA does not address TIA’s, so apparently patients with TIA’s have to wait until they have a stroke before we can act.
FOURIER Further cardiovascular Outcomes Research with PCSK9 Inhibition in subjects with Elevated Risk

MS Sabatine, RP Giugliano, AC Keech, N Honarpour, SM Wasserman, PS Sever, and TR Pedersen, for the FOURIER Steering Committee & Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 17, 2017
Background

Proprotein convertase subtilisin/kexin type 9 (PCSK9)
- Chaperones LDL-R to destruction → ↑ circulating LDL-C
- Loss-of-fxn genetic variants → ↑ LDL-R → ↓ LDL-C & ↓ risk of MI

Evolocumab
- Fully human anti-PCSK9 mAb
- ~60% ↓ LDL-C
- Safe & well-tolerated in Ph 2 & 3 studies
- Exploratory data suggested ↓ CV events

Sever P & Mackay J. Br J Cardiol 2014;21:91-3
Sabatine MS, et al. NEJM 2015;372:1500-9
In patients with established cardiovascular disease on statin therapy:

- Test whether the addition of evolocumab reduces the incidence of major cardiovascular events
- Examine the long-term safety & tolerability of evolocumab
- Investigate the efficacy and safety of achieving unprecedented low levels of LDL-C
Trial Design

27,564 high-risk, stable patients with established CV disease (prior MI, prior stroke, or symptomatic PAD)

Screening, Lipid Stabilization, and Placebo Run-in
High or moderate intensity statin therapy (± ezetimibe)

LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL

RANDOMIZED DOUBLE BLIND

Evolocumab SC
140 mg Q2W or 420 mg QM

Placebo SC
Q2W or QM

Follow-up Q 12 weeks

Endpoints

• Efficacy
  – Primary: CV death, MI, stroke, hosp. for UA, or coronary revasc
  – Key secondary: CV death, MI or stroke

• Safety
  – AEs/SAEs
  – Events of interest incl. muscle-related, new-onset diabetes, neurocognitive
  – Development of anti-evolocumab Ab (binding and neutralizing)

• TIMI Clinical Events Committee (CEC)
  – Adjudicated all efficacy endpoints & new-onset diabetes
  – Members unaware of treatment assignment & lipid levels

Follow-up

Randomized 27,564 patients

Evolocumab (N=13,784)  Placebo (N=13,780)

Follow-up median 26 months (IQR 22-30)

2907 patients experienced primary endpoint
1829 experienced key secondary endpoint

Premature perm. drug discontinuation
5.6%/yr 5.8%/yr

Withdrew consent
0.29%/yr 0.35%/yr

Lost to follow-up
5 patients 13 patients

Ascertainment for primary endpoint was complete for 99.5% of potential patient-years of follow up
### Baseline Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, years, mean (SD)</td>
<td>63 (9)</td>
</tr>
<tr>
<td>Male sex (%)</td>
<td>75</td>
</tr>
<tr>
<td><strong>Type of cardiovascular disease (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>81</td>
</tr>
<tr>
<td>Stroke (non-hemorrhagic)</td>
<td>19</td>
</tr>
<tr>
<td>Symptomatic PAD</td>
<td>13</td>
</tr>
<tr>
<td><strong>Cardiovascular risk factor (%)</strong></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>80</td>
</tr>
<tr>
<td>Diabetes mellitus</td>
<td>37</td>
</tr>
<tr>
<td>Current cigarette use</td>
<td>28</td>
</tr>
</tbody>
</table>

Median time from most recent event ~3 yrs

Pooled data; no differences between treatment arms
# Lipid Lowering Therapy & Lipid Levels at Baseline

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Statin use (%)</td>
<td></td>
</tr>
<tr>
<td>High-intensity</td>
<td>69</td>
</tr>
<tr>
<td>Moderate-intensity</td>
<td>30</td>
</tr>
<tr>
<td>Ezetimibe use (%)</td>
<td>5</td>
</tr>
<tr>
<td>Median lipid measures (IQR) – mg/dL</td>
<td></td>
</tr>
<tr>
<td>LDL-C</td>
<td>92 (80-109)</td>
</tr>
<tr>
<td>Total cholesterol</td>
<td>168 (151-189)</td>
</tr>
<tr>
<td>HDL-C</td>
<td>44 (37-53)</td>
</tr>
<tr>
<td>Triglycerides</td>
<td>133 (100-182)</td>
</tr>
</tbody>
</table>

*Per protocol, patients were to be on atorva ≥20 mg/d or equivalent.
1% were on low intensity or intensity data were missing.
Statin intensity defined per ACC/AHA 2013 Cholesterol Guidelines.

Pooled data; no differences between treatment arms
LDL Cholesterol

Placebo

59% mean reduction (95% CI 58-60), P<0.00001

Absolute reduction: 56 mg/dl (95% CI 55-57)

Evolocumab
(median 30 mg/dl, IQR 19-46 mg/dl)
**LDL Cholesterol**

- **Placebo**
  - Cohort of 11,077 patients who
    - had all measurements through 120 weeks
    - did not discontinue study drug
    - did not Δ concomitant background lipid-lowering Rx

- **Evolocumab**
  - Similar data out to 4 years in OSLER-1
    (JAMA Cardiology online)

**Graph with X-axis: Weeks (0 to 120)**

**Y-axis: LDL Cholesterol (mg/dl)**

- Placebo line: Steady at approximately 90 mg/dl for 120 weeks.
- Evolocumab line: Steady at approximately 30 mg/dl for 120 weeks.

---

*An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School*
Primary Endpoint

Hazard ratio 0.85
(95% CI, 0.79-0.92)
P<0.0001

CV Death, MI, Stroke, Hosp for UA, or Cor Revasc

Placebo

Evolocumab

14.6%
12.6%

Months from Randomization
Key Secondary Endpoint

Hazard ratio 0.80
(95% CI, 0.73-0.88)
P<0.00001

CV Death, MI, or Stroke

Months from Randomization

Placebo

Evolocumab
# Types of CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>3-yr Kaplan-Meier rate</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to acute MI</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>Death due to stroke</td>
<td>0.26</td>
<td>0.32</td>
<td>0.84 (0.49-1.42)</td>
</tr>
<tr>
<td>Other CV death</td>
<td>0.29</td>
<td>0.30</td>
<td>0.94 (0.58-1.54)</td>
</tr>
<tr>
<td>MI</td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
</tbody>
</table>

An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School
More Intensive LDL-C Lowering & CV Death

No clear benefit on CV mortality

<table>
<thead>
<tr>
<th>Trial</th>
<th>Year</th>
<th>More Intensive Rx Arm</th>
<th>Less Intensive Rx Arm</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>PROVE-IT TIMI 22</td>
<td>2004</td>
<td>27</td>
<td>36</td>
<td>0.74 (0.45-1.22)</td>
</tr>
<tr>
<td>A2Z</td>
<td>2004</td>
<td>86</td>
<td>111</td>
<td>0.76 (0.57-1.01)</td>
</tr>
<tr>
<td>TNT</td>
<td>2005</td>
<td>101</td>
<td>127</td>
<td>0.80 (0.61-1.03)</td>
</tr>
<tr>
<td>IDEAL</td>
<td>2005</td>
<td>223</td>
<td>218</td>
<td>1.03 (0.85-1.24)</td>
</tr>
<tr>
<td>SEARCH</td>
<td>2010</td>
<td>565</td>
<td>572</td>
<td>0.99 (0.88-1.11)</td>
</tr>
<tr>
<td>IMPROVE-IT</td>
<td>2015</td>
<td>538</td>
<td>537</td>
<td>1.00 (0.89-1.13)</td>
</tr>
<tr>
<td>Summary</td>
<td></td>
<td>1540</td>
<td>1601</td>
<td>0.96 (0.90-1.03)</td>
</tr>
</tbody>
</table>

NEJM 2004;350:1495-504
JAMA 2004;292:1307-16
NEJM 2005;352:1425-35
JAMA 2005;294:2437-45
Lancet 2010;376:1658-69
NEJM 2015;372:2387-97

An Academic Research Organization of Brigham and Women’s Hospital and Harvard Medical School
### Types of CV Outcomes

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Evolocumab (N=13,784)</th>
<th>Placebo (N=13,780)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>3-yr Kaplan-Meier rate</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>CVD, MI, stroke, UA, or revasc</td>
<td>12.6</td>
<td>14.6</td>
<td>0.85 (0.79-0.92)</td>
</tr>
<tr>
<td>CV death, MI, or stroke</td>
<td>7.9</td>
<td>9.9</td>
<td>0.80 (0.73-0.88)</td>
</tr>
<tr>
<td>Cardiovascular death</td>
<td>2.5</td>
<td>2.4</td>
<td>1.05 (0.88-1.25)</td>
</tr>
<tr>
<td>MI</td>
<td>4.4</td>
<td>6.3</td>
<td>0.73 (0.65-0.82)</td>
</tr>
<tr>
<td>Stroke</td>
<td>2.2</td>
<td>2.6</td>
<td>0.79 (0.66-0.95)</td>
</tr>
<tr>
<td>Hosp for unstable angina</td>
<td>2.2</td>
<td>2.3</td>
<td>0.99 (0.82-1.18)</td>
</tr>
<tr>
<td>Coronary revasc</td>
<td>7.0</td>
<td>9.2</td>
<td>0.78 (0.71-0.86)</td>
</tr>
<tr>
<td>Urgent</td>
<td>3.7</td>
<td>5.4</td>
<td>0.73 (0.64-0.83)</td>
</tr>
<tr>
<td>Elective</td>
<td>3.9</td>
<td>4.6</td>
<td>0.83 (0.73-0.95)</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>4.8</td>
<td>4.3</td>
<td>1.04 (0.91-1.19)</td>
</tr>
</tbody>
</table>
# Key Subgroups

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Patients</th>
<th>1° Endpoint HR (95% CI)</th>
<th>Key 2° Endpoint HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Overall</strong></td>
<td>27564</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Type of disease</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>MI alone</td>
<td>19113</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke alone</td>
<td>3366</td>
<td></td>
<td></td>
</tr>
<tr>
<td>PAD alone</td>
<td>1505</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Polyvascular disease</td>
<td>3563</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline LDL-C</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q1 (&lt;80 mg/dl)</td>
<td>6961</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q2 (80–&lt;92 mg/dl)</td>
<td>6886</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q3 (92–109 mg/dl)</td>
<td>6887</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Q4 (&gt;109 mg/dl)</td>
<td>6829</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Baseline statin intensity</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>High</td>
<td>19103</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Not high</td>
<td>8461</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Ezetimibe</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>1440</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No</td>
<td>26124</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Initial Dosing Regimen</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Every 2 weeks</td>
<td>24774</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Monthly</td>
<td>2790</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

All $P_{interaction}$ NS
Lower LDL-C Is Better

Patients divided by quartile of baseline LDL-C and by treatment arm

P<0.0001

Cardiovascular Death, MI or Stroke

Achieved LDL Cholesterol (mg/dl)

An Academic Research Organization of Brigham and Women's Hospital and Harvard Medical School
**Landmark Analysis**

16% RRR

HR 0.84 (95% CI 0.74-0.96)

P = 0.008

25% RRR

HR 0.75 (95% CI 0.66-0.85)

P < 0.00001

CV Death, MI, Stroke

Placebo

Evolocumab

Months from Randomization
Fatal or Nonfatal MI or Stroke

19% RRR
HR 0.81 (95% CI 0.70-0.93)
P = 0.003

33% RRR
HR 0.67 (95% CI 0.59-0.77)
P < 0.00001

Months from Randomization

An Academic Research Organization of
Brigham and Women's Hospital and Harvard Medical School
Comparison to Cholesterol Treatment Trialists Collaboration

Hazard Ratio (95% CI) per 1 mmol/L reduction in LDL-C

- Major Coronary Events:
  - CTTC Meta-analysis Year 2: 0.78 (0.70-0.86)
  - FOURIER Year 2: 0.80 (0.71-0.90)

- Stroke:
  - CTTC Meta-analysis Year 2: 0.77 (0.66-0.91)
  - FOURIER Year 2: 0.77 (0.63-0.94)

- Coronary revascularization:
  - Urgent: 0.75 (0.67-0.84)
  - Elective: 0.84 (0.73-0.98)

- Major Vascular Events:
  - CTTC Meta-analysis Year 2: 0.77 (0.73-0.82)
  - FOURIER Year 2: 0.83 (0.76-0.90)

CTTC data from *Lancet* 2010;376:1670-81
## Safety

<table>
<thead>
<tr>
<th></th>
<th>Evolocumab (N=13,769)</th>
<th>Placebo (N=13,756)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Adverse events (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any</td>
<td>77.4</td>
<td>77.4</td>
</tr>
<tr>
<td>Serious</td>
<td>24.8</td>
<td>24.7</td>
</tr>
<tr>
<td>Allergic reaction</td>
<td>3.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Injection-site reaction</td>
<td>2.1</td>
<td>1.6</td>
</tr>
<tr>
<td>Treatment-related and led to d/c of study drug</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td>Muscle-related</td>
<td>5.0</td>
<td>4.8</td>
</tr>
<tr>
<td>Cataract</td>
<td>1.7</td>
<td>1.8</td>
</tr>
<tr>
<td>Diabetes (new-onset)</td>
<td>8.1</td>
<td>7.7</td>
</tr>
<tr>
<td>Neurocognitive</td>
<td>1.6</td>
<td>1.5</td>
</tr>
<tr>
<td><strong>Laboratory results (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Binding Ab</td>
<td>0.3</td>
<td>n/a</td>
</tr>
<tr>
<td>Neutralizing Ab</td>
<td><em>none</em></td>
<td>n/a</td>
</tr>
</tbody>
</table>

New-onset diabetes assessed in patients without diabetes at baseline; adjudicated by CEC
Summary for Evolocumab

- ↓ LDL-C by 59%
  - Consistent throughout duration of trial
  - Median achieved LDL-C of 30 mg/dl (IQR 19-46 mg/dl)

- ↓ CV outcomes in patients already on statin therapy
  - 15% ↓ broad primary endpoint; 20% ↓ CV death, MI, or stroke
  - Consistent benefit, incl. in those on high-intensity statin, low LDL-C
  - 25% reduction in CV death, MI, or stroke after 1st year
  - Long-term benefits consistent w/ statins per mmol/L ↓ LDL-C

- Safe and well-tolerated
  - Similar rates of AEs, incl DM & neurocog events w/ EvoMab & pbo
  - Rates of EvoMab discontinuation low and no greater than pbo
  - No neutralizing antibodies developed
Conclusions

In patients with known cardiovascular disease:

1. PCSK9 inhibition with evolocumab significantly & safely ↓ major cardiovascular events when added to statin therapy

2. Benefit was achieved with lowering LDL cholesterol well below current targets
Brent’s Thoughts

- This study demonstrates that lipid lowering through PCSK-9 inhibition results in the expected reductions in future CV events.
- The CV event reductions correlate directly with the amount of LDL-C reduction and also with the absolute levels of on-treatment LDL-C.
- The excellent safety profile of evolocumab found in phase II trials is confirmed in this large phase III trial.
- The lack of effect on death is somewhat disappointing, but not surprising given the short 3 years of follow-up in these stable patients.
EBBINGHAUS:

A Cognitive Study of Patients Enrolled in the FOURIER Trial

RP Giugliano, F Mach, K Zavitz, AC Keech, TR Pedersen, MS Sabatine, P Sever, C Kurtz, N Honarpour, BR Ott, on behalf of the EBBINGHAUS Investigators

American College of Cardiology – 66th Annual Scientific Session
Late-Breaking Clinical Trial
March 18, 2017
Cognition and Statins

- Case series and 2 small, 6-month RCTs with statins raised concern regarding cognitive deficits

- In 2012 FDA added risk of adverse cognitive effects to label of all statins

- However analyses from large scale RCTs do not support these findings and 2014 Statin Cognitive Safety Task Force* concluded that statins are not associated with cognitive side effects.

*The National Lipid Association
Cognition and PCSK9 Inhibitors

Brain synthesizes cholesterol locally

mAb (e.g., evolocumab) are too large to cross the intact blood-brain barrier

Nevertheless meta-analysis* of adverse events from 6 trials in 9581 pts suggested an increased risk with PCSK9 inhibitors: HR 2.3 [1.1, 4.9]

- Event rates low (<1%)
- Unadjudicated, diverse AE terms reported
- Not correlated with LDL-C achieved

EBBINGHAUS: Hypothesis

The addition of evolocumab to statin therapy in patients with clinically evident cardiovascular disease does not adversely affect cognitive function.
Trial Design

Placebo SC Q2W or QM
Randomized Double Blind

Evolocumab SC
140 mg Q2W or 420 mg QM

2442 patients screened for EBBINGHAUS

1974 Enrolled (Full Analysis Pop)
Median F/U 19.8 months

Primary Analysis Cohort (N=1204)
Baseline cognitive testing on/before 1st dose of study drug and had f/u cognitive testing post dosing*

Additional 770 pts w/ baseline assessment before week 12 visit

Major Exclusions
1. Not enrolled in FOURIER
2. >12 wk FOURIER visit
3. H/O dementia, cognitive impairment or other conditions interfering with participation

* Cognitive tests performed at baseline; at 6, 12, 24 months; and end of study
Endpoints

1. Cambridge Neuropsychological Test Automated Battery (CANTAB) Assessments, a standardized, well-validated computer tablet-based testing platform. Assessed at baseline, 6, 12, 24, 48 mos and study end.
   - Primary: Spatial working memory strategy index of executive function
   - Secondary: Spatial working memory between errors
                Paired associates learning
                Reaction time
   - Exploratory: Global score (combines above 4 tests)

2. Patient survey of everyday cognition* at study end

3. Investigator report of cognitive AEs

*Memory and executive function domains

Owen 1990 PMID: 2267054; Sahakian 1988, PMID: 3382917; Owen 1996 PMID: 8714706; Kollins PMID: 21476931
Primary Endpoint
Spatial Working Memory Strategy Index

**Mean Number of boxes**

<table>
<thead>
<tr>
<th></th>
<th>Placebo</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>Baseline</td>
<td>17.8</td>
<td>17.6</td>
</tr>
<tr>
<td>Post</td>
<td>17.8</td>
<td>17.5</td>
</tr>
<tr>
<td>Change</td>
<td>-0.29</td>
<td>-0.21</td>
</tr>
</tbody>
</table>

**Non-inferiority boundary**

$P_{\text{non-inferiority}} < 0.001$

**Treatment Difference in Z score**

(Placebo minus Evolocumab)

Favors Evolocumab

Favors Placebo

$P_{NI}$ is from fixed estimate
Secondary Endpoint Results

Spatial Working Memory Between Errors Score

- **Placebo**: Baseline: 21.0, Post baseline: 20.1
- **Evolocumab**: Baseline: 20.0, Post baseline: 20.3

Trt diff of Δ in Z-scores: 0.033, \( P_{\text{superiority}} = 0.36 \)

Paired Associates Learning

- **Placebo**: Baseline: 25.2, Post baseline: 23.6
- **Evolocumab**: Baseline: 26.5, Post baseline: 24.9

Trt diff of Δ in Z-scores: 0.023, \( P_{\text{superiority}} = 0.49 \)

Median 5-Choice Reaction Time

- **Placebo**: 355, 357
- **Evolocumab**: 356, 362

Trt diff of Δ in Milliseconds: 0.073, \( P = 0.06 \)

Lower raw scores (fewer errors, faster time) are better.
Cognitive Assessments by Nadir Achieved LDL-C and Treatment (Full Pop)

**Primary CANTAB Endpoint**: Average Change from Baseline

- **Mean Δ of boxes**
  - Placebo
  - Evolocumab

- **# pts**
  - <25 mg/dL: 0, 661
  - 25-39 mg/dL: 13, 206
  - ≥ 40 mg/dL: 969, 115

**Nadir LDL-Achieved (mg/dL)**

- **P=NS across LDL values achieved and also between treatments**

**Composite Global Score**: Average Change from Baseline

- **Mean Δ -Z score**
  - <25 mg/dL
  - 25-39 mg/dL
  - ≥ 40 mg/dL

**Negative score -> improvement**

Lower scores are better

*Spatial working memory strategy index of executive function, raw score*
### Patient Self-Report: 23 Questions Regarding Everyday Cognition

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=781)</th>
<th>Evolocumab (N=800)</th>
<th>P-Value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>All Patients</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Memory</td>
<td>1.16 (0.39)</td>
<td>1.17 (0.39)</td>
<td>0.81</td>
</tr>
<tr>
<td>Executive functioning total score</td>
<td>1.11 (0.32)</td>
<td>1.12 (0.32)</td>
<td>0.28</td>
</tr>
<tr>
<td>Planning</td>
<td>1.08 (0.31)</td>
<td>1.10 (0.32)</td>
<td>0.20</td>
</tr>
<tr>
<td>Organization</td>
<td>1.09 (0.32)</td>
<td>1.10 (0.33)</td>
<td>0.57</td>
</tr>
<tr>
<td>Divided attention</td>
<td>1.15 (0.42)</td>
<td>1.16 (0.41)</td>
<td>0.54</td>
</tr>
<tr>
<td><strong>Total Score</strong></td>
<td>1.13 (0.33)</td>
<td>1.14 (0.33)</td>
<td>0.42</td>
</tr>
</tbody>
</table>

Patient self-report at end of study as compared to randomization, graded as:

1. **Better or no change**
2. Questionable / occasionally worse
3. Consistently a little worse
4. Consistently much worse

Lower scores represent better cognition.

Results shown are in the full study population.
Investigator Reported Cognitive Adverse Events

Placebo
Evolocumab

% of patients

P = 0.42
P = 0.59

Primary Cohort (N=1204)
8/618
11/586

Full Population (N=1973*)
16/990
19/983

Data shown are % of patients with at least 1 event
*1 patient who did not take study drug is excluded from the evolocumab group
Conclusions

In patients with known cardiovascular disease on background statin followed for 20 months

1. No differences btw evolocumab vs placebo
   A. A battery of cognitive tests
   B. Patient-reported everyday cognition
   C. Adverse cognitive events reported by MD

2. No evidence of differences in cognitive tests by achieved nadir LDL-C, even <25 mg/dL
Brent’s Thoughts

• This study demonstrates that, at least over the short term, aggressive LDL-C lowering does not adversely affect cognitive function.
• This safety goes all the way down to LDL-levels below 20 mg/dL.
• Although this study specifically addressed the effects of evolocumab, I believe the data probably counts for statins too.
Rivaroxaban or Aspirin for Extended Treatment of Venous Thromboembolism

EINSTEIN CHOICE

Dr. Phil Wells
on behalf of the EINSTEIN CHOICE Steering Committee and Investigators


NCT02064439
Background

- In patients without reversible risk factors, the risk of recurrent venous thromboembolism is up to 10% in the first year if anticoagulation therapy is stopped.
- Although extended anticoagulation therapy prevents recurrent venous thromboembolism, concerns about bleeding often lead to reluctance to continue treatment beyond 6 to 12 months.
- Lower dose anticoagulant therapy, or aspirin instead of an anticoagulant may reduce this bleeding risk.
- Head-to-head comparison is necessary to determine the relative efficacy and safety of these approaches.
Study Design

- Aim: Compare the efficacy and safety of once daily rivaroxaban (20 or 10 mg) with aspirin (100 mg) in VTE patients who completed 6 to 12 months of treatment and with equipoise regarding the need for extended anticoagulation.
- Randomized, double-blind, active-comparator, event-driven, superiority study.

Patients with confirmed symptomatic DVT/PE who completed 6–12 months of anticoagulation

N=3396

R

Rivaroxaban 20 mg od
Rivaroxaban 10 mg od
Aspirin 100 mg od
12-month treatment duration

1 month observation period

Outcomes

- **Efficacy outcomes:**
  - Primary: Symptomatic recurrent VTE (Non-fatal DVT or PE, fatal PE, or unexplained death where PE cannot be excluded)
  - Symptomatic recurrent VTE or MI, ischemic stroke or systemic embolism
  - Symptomatic recurrent VTE or venous thrombosis in other locations
  - Symptomatic recurrent VTE or all-cause mortality

- **Safety outcomes**
  - Principal: Major bleeding (ISTH)
  - Clinically relevant nonmajor bleeding (ISTH)
  - Nonmajor bleeding associated with study drug interruption for >14 days

Patient Flow

Randomized N=3396

1121 randomized to rivaroxaban 20 mg
- 14 Did not take study medication
  - 1107
    - 138 prematurely discontinued study treatment*
      - 8 died
      - 14 withdrew consent
      - 3 were lost to follow-up
    - 1046

1136 randomized to rivaroxaban 10 mg
- 9 Did not take study medication
  - 1127
    - 143 prematurely discontinued study treatment*
      - 2 died
      - 17 withdrew consent
      - 3 were lost to follow-up
    - 1063

1139 randomized to aspirin 100 mg
- 8 Did not take study medication
  - 1131
    - 182 prematurely discontinued study treatment*
      - 7 died
      - 16 withdrew consent
      - 4 were lost to follow-up
    - 1069

Included in ITT/safety analyses

Included in per-protocol analyses

*The other main reasons for premature discontinuation of study medication were adverse events, noncompliance with study drug, protocol violations, and efficacy or safety outcomes.
ITT (Intention to treat): all randomized patients who received at least one dose of study medication
## Clinical Characteristics

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban 20 mg (n=1107)</th>
<th>Rivaroxaban 10 mg (n=1127)</th>
<th>Aspirin 100 mg (n=1131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Male, n (%)</td>
<td>602 (54.4)</td>
<td>620 (55.0)</td>
<td>643 (56.9)</td>
</tr>
<tr>
<td>Age, (mean years±SD)</td>
<td>57.9±14.7</td>
<td>58.8±14.7</td>
<td>58.8±14.7</td>
</tr>
<tr>
<td>Body mass index, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 kg/m²</td>
<td>712 (64.3)</td>
<td>751 (66.6)</td>
<td>756 (66.8)</td>
</tr>
<tr>
<td>≥30 kg/m²</td>
<td>394 (35.6)</td>
<td>376 (33.4)</td>
<td>375 (33.2)</td>
</tr>
<tr>
<td>Creatinine clearance, n (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30 ml/min</td>
<td>1 (0.1)</td>
<td>2 (0.2)</td>
<td>1 (0.1)</td>
</tr>
<tr>
<td>30--&lt;50 ml/min</td>
<td>40 (3.6)</td>
<td>49 (4.3)</td>
<td>63 (5.6)</td>
</tr>
<tr>
<td>50--&lt;80 ml/min</td>
<td>279 (25.2)</td>
<td>302 (26.8)</td>
<td>277 (24.5)</td>
</tr>
<tr>
<td>≥80 ml/min</td>
<td>787 (71.1)</td>
<td>774 (68.7)</td>
<td>790 (69.8)</td>
</tr>
</tbody>
</table>

*Differences in baseline characteristics were not significant; SD, standard deviation
## Clinical Characteristics

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban 20 mg (n=1107)</th>
<th>Rivaroxaban 10 mg (n=1127)</th>
<th>Aspirin 100 mg (n=1131)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Index event, n (%)</td>
<td>DVT 565 (51.0)</td>
<td>565 (50.1)</td>
<td>577 (51.0)</td>
</tr>
<tr>
<td></td>
<td>PE 381 (34.4)</td>
<td>381 (33.8)</td>
<td>366 (32.4)</td>
</tr>
<tr>
<td></td>
<td>Both 155 (14.0)</td>
<td>179 (15.9)</td>
<td>181 (16.0)</td>
</tr>
<tr>
<td></td>
<td>Asymptomatic or unconfirmed 6 (0.5)</td>
<td>2 (0.2)</td>
<td>7 (0.6)</td>
</tr>
<tr>
<td>Classification of index VTE, n (%)</td>
<td>Unprovoked 441 (39.8)</td>
<td>480 (42.6)</td>
<td>468 (41.4)</td>
</tr>
<tr>
<td></td>
<td>Provoked 666 (60.2)</td>
<td>647 (57.4)</td>
<td>663 (58.6)</td>
</tr>
<tr>
<td>History of prior VTE, n (%)</td>
<td>198 (17.9)</td>
<td>197 (17.5)</td>
<td>194 (17.2)</td>
</tr>
<tr>
<td>Known thrombophilia, n (%)</td>
<td>79 (7.1)</td>
<td>74 (6.6)</td>
<td>70 (6.2)</td>
</tr>
<tr>
<td>Active cancer, n (%)</td>
<td>25 (2.3)</td>
<td>27 (2.4)</td>
<td>37 (3.3)</td>
</tr>
<tr>
<td>Study drug duration (median days, IQR)</td>
<td>349 (189-362)</td>
<td>353 (190-362)</td>
<td>350 (186-362)</td>
</tr>
</tbody>
</table>

*Differences in baseline characteristics were not significant; DVT, deep vein thrombosis; PE, pulmonary embolism; VTE, venous thromboembolism; IQR, interquartile range*
Major Bleeding – Cumulative Incidence

<table>
<thead>
<tr>
<th>Number of patients at risk</th>
<th>Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rivaroxaban 20 mg</td>
<td>1107</td>
</tr>
<tr>
<td>Rivaroxaban 10 mg</td>
<td>1126</td>
</tr>
<tr>
<td>Aspirin</td>
<td>1131</td>
</tr>
</tbody>
</table>

Treatment-emergent major bleeding: onset during study treatment up to 2 days after stop of study treatment
## Recurrent VTE—According to Risk Profile and Duration of Anticoagulation Prior to Randomization

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rivaroxaban 20 mg</th>
<th>Rivaroxaban 10 mg</th>
<th>Aspirin 100 mg</th>
</tr>
</thead>
<tbody>
<tr>
<td>Recurrent VTE, all patients, n/N (%)</td>
<td>17/1107 (1.5)</td>
<td>13/1127 (1.2)</td>
<td>50/1131 (4.4)</td>
</tr>
<tr>
<td>Risk profile index event, n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unprovoked</td>
<td>8/441 (1.8)</td>
<td>7/480 (1.5)</td>
<td>26/468 (5.6)</td>
</tr>
<tr>
<td>Provoked</td>
<td>9/666 (1.4)</td>
<td>6/647 (0.9)</td>
<td>24/663 (3.6)</td>
</tr>
<tr>
<td>History of prior VTE, n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>3/198 (1.5)</td>
<td>2/197 (1.0)</td>
<td>17/194 (8.8)</td>
</tr>
<tr>
<td>No</td>
<td>14/909 (1.5)</td>
<td>11/930 (1.2)</td>
<td>33/937 (3.5)</td>
</tr>
<tr>
<td>Duration of anticoagulation prior to randomization, n/N (%)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;9 months</td>
<td>12/774 (1.6)</td>
<td>7/782 (0.9)</td>
<td>35/793 (4.4)</td>
</tr>
<tr>
<td>≥9 months</td>
<td>5/333 (1.5)</td>
<td>6/345 (1.7)</td>
<td>15/338 (4.4)</td>
</tr>
</tbody>
</table>

VTE Venous thromboembolism

Einstein Choice

Intermountain Heart Institute
Intermountain Medical Center
Summary and Conclusions

In patients with symptomatic VTE who completed 6 to 12 months of treatment and with equipoise regarding the need for extended anticoagulation:

- Both rivaroxaban regimens (20 or 10 mg once daily) are superior to aspirin for the primary and other efficacy outcomes and are associated with similar rates of bleeding.
- Compared with aspirin, numbers needed to treat with rivaroxaban 20 or 10 mg for one year to prevent one VTE without an increase in bleeding are 33 and 30, respectively.
- Consistent results in subgroups of patients.

Rivaroxaban 10 mg once daily provides an additional option for extended VTE treatment:

- Patients requiring full-dose anticoagulant therapy were excluded and may need extended treatment with the 20 mg once daily rivaroxaban regimen.

*Number needed to treat (NNT) compared with aspirin for primary efficacy outcome up to 1 year.
Brent’s Thoughts

- This study demonstrates that for both provoked and non-provoked VTE events, long-term recurrent remain significant and can be reduced by 75% with just 10 mg/day of rivaroxiban compared with aspirin (a proven active comparator).

- This efficacy can be obtained with similar bleeding risks to aspirin.

- This is the second NOAC that has shown studies that demonstrate similar efficacy and more safety with the lower doses of the drug.
Anti-Inflammatory Therapy with Canakinumab for Atherosclerotic Disease

CANTOS
Canakinumab Anti-inflammatory Thrombosis Outcomes Study

Paul M Ridker, MD, MPH
Eugene Braunwald Professor of Medicine
Brigham and Women’s Hospital,
Harvard Medical School, Boston MA, USA

on behalf of the worldwide investigators and participants in the
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

Ridker ACC 2017
Low Grade Systemic Inflammation *Precedes* By Many Years the Onset of Vascular Events

The New England Journal of Medicine

INFLAMMATION, ASPIRIN, AND THE RISK OF CARDIOVASCULAR DISEASE IN APPARENTLY HEALTHY MEN

Paul M. Ridker, M.D., Mary Cushman, M.D., Mark J. Stampfer, M.D., Russell P. Tracy, Ph.D., and Charles H. Hennekens, M.D.

---

![Graph showing relative risk of myocardial infarction with placebo and aspirin across quartiles of plasma C-reactive protein.](image)

![Bar graph showing relative risk of myocardial infarction per quartile of plasma C-reactive protein level.](image)

---

Ridker ESC 2017
Clinical Impact of Inflammation on Atherosclerosis

- Plasma levels of inflammatory biomarkers including hsCRP and IL-6 robustly predict first and recurrent cardiovascular events, independent of lipid levels.
- Statins are both lipid lowering and anti-inflammatory, and the greatest benefits of statin therapy accrue to those who not only lower LDLC, but who also lower hsCRP.
- In primary prevention, the JUPITER trial demonstrated that those with elevated hsCRP but low levels of LDLC markedly benefit from statin therapy.
- In secondary prevention, clinicians now distinguish between those with “residual cholesterol risk” and those with “residual inflammatory risk”

Ridker PM. JACC 2016;67:712-23
Residual Inflammatory Risk: Addressing the Obverse Side of the Atherosclerosis Prevention Coin

Ridker PM. Eur Heart J 2016;37:1720-22

Known Cardiovascular Disease
LDL 150 mg/dL (3.8 mmol/L)
hsCRP 4.5 mg/L

High Intensity Statin

“Residual Cholesterol Risk”
LDL 110 mg/dL (2.8 mmol/L)
hsCRP 1.8 mg/L

Additional LDL Reduction

IMPROVE-IT: Ezetimibe 6% RRR
FOURIER/SPIRE: PCSK9 Inhibition q2 weeks 15% RRR

“Residual Inflammatory Risk”
LDL 70 mg/dL (1.8 mmol/L)
hsCRP 3.8 mg/L

Additional Inflammation Reduction

No Prior Proof of Concept

Ridker ESC 2017
Can Inflammation Reduction, in the Absence of Lipid Lowering, Reduce Cardiovascular Event Rates?

Ridker ESC 2017
From CRP to IL-6 to IL-1: Moving Upstream to Identify Novel Targets for Atheroprotection

Canakinumab (Novartis)

- high-affinity human monoclonal anti-human interleukin-1β (IL-1β) antibody currently indicated for the treatment of IL-1β driven inflammatory diseases (Cryopyrin-Associated Period Syndrome [CAPS], Muckle-Wells Syndrome)
- designed to bind to human IL-1β and functionally neutralize the bioactivity of this pro-inflammatory cytokine
- long half-life (4-8 weeks) with CRP and IL-6 reduction for up to 3 months
Effects of Interleukin-1β Inhibition With Canakinumab on Hemoglobin A1c, Lipids, C-Reactive Protein, Interleukin-6, and Fibrinogen

A Phase IIb Randomized, Placebo-Controlled Trial

![Graph showing the effects of Canakinumab dose on various parameters.]

Fibrinogen, Interleukin-6, C-reactive Protein

Ridker PM, et al; Circulation 2012; 126:2739-2748

Ridker ESC 2017
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

Stable CAD (post MI) On Statin, ACE/ARB, BB, ASA Persistent Elevation of hsCRP (≥ 2 mg/L)

N = 10,061 39 Countries April 2011 - June 2017 1490 Primary Events

Randomized Canakinumab 50 mg SC q 3 months
Randomized Canakinumab 150 mg SC q 3 months
Randomized Canakinumab 300 mg SC q 3 months
Randomized Placebo SC q 3 months

Primary CV Endpoint: Nonfatal MI, Nonfatal Stroke, Cardiovascular Death (MACE)

Key Secondary CV Endpoint: MACE + Unstable Angina Requiring Unplanned Revascularization (MACE+)

Critical Non-Cardiovascular Safety Endpoints: Cancer and Cancer Mortality, Infection and Infection Mortality

Ridker ESC 2017
Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

39 countries > 1000 investigators

17482 Screened

10105 Entered Into Randomization Process

10061 Successfully Randomized

3344 placebo
18.1% discontinued study drug
3335 known final vital status
9 unknown final vital status

2170 canakinumab 50mg
16.7% discontinued study drug
2161 known final vital status
9 unknown final vital status

2284 canakinumab 150mg
19.2% discontinued study drug
2279 known final vital status
5 unknown final vital status

2263 canakinumab 300mg
20.1% discontinued study drug
2259 known final vital status
4 unknown final vital status

7377 Excluded Prior to Entering Randomization Process
146 refused consent
71 child-bearing potential
44 age out of range
251 no documented MI
3390 hsCRP < 2 mg/L
728 exclusionary concomitant disease
1873 tuberculosis risk factors
104 infectious disease
76 immunocompromised state
27 life threatening condition
574 withdrew consent
137 site closure
81 physician decision
49 unable to contact
7 adverse event
11 died
139 other reasons

44 Failed Randomization Process
41 Invalid randomization
3 major GCP violations

Ridker ESC 2017
# CANTOS - Baseline Clinical Characteristics

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Placebo (N=3347)</th>
<th>50 mg (N=2170)</th>
<th>150 mg (N=2284)</th>
<th>300 mg (N=2263)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>61.1</td>
<td>61.1</td>
<td>61.2</td>
<td>61.1</td>
</tr>
<tr>
<td>Female (%)</td>
<td>25.9</td>
<td>24.9</td>
<td>25.2</td>
<td>26.8</td>
</tr>
<tr>
<td>Current smoker (%)</td>
<td>22.9</td>
<td>24.5</td>
<td>23.4</td>
<td>23.7</td>
</tr>
<tr>
<td>Diabetes (%)</td>
<td>39.9</td>
<td>39.4</td>
<td>41.8</td>
<td>39.2</td>
</tr>
<tr>
<td>Lipid lowering therapy (%)</td>
<td>93.7</td>
<td>94.0</td>
<td>92.7</td>
<td>93.5</td>
</tr>
<tr>
<td>Renin-angiotensin inhibitors (%)</td>
<td>79.8</td>
<td>79.3</td>
<td>79.8</td>
<td>79.6</td>
</tr>
<tr>
<td>Prior Revascularization (%)</td>
<td>79.6</td>
<td>80.9</td>
<td>82.2</td>
<td>80.7</td>
</tr>
<tr>
<td>LDL cholesterol (mg/dL)</td>
<td>82.8</td>
<td>81.2</td>
<td>82.4</td>
<td>83.5</td>
</tr>
<tr>
<td>HDL cholesterol (mg/dL)</td>
<td>44.5</td>
<td>43.7</td>
<td>43.7</td>
<td>44.0</td>
</tr>
<tr>
<td>Triglycerides (mg/dL)</td>
<td>139</td>
<td>139</td>
<td>139</td>
<td>138</td>
</tr>
<tr>
<td>hsCRP (mg/L)</td>
<td>4.1</td>
<td>4.1</td>
<td>4.2</td>
<td>4.1</td>
</tr>
</tbody>
</table>

Ridker ESC 2017
CANTOS: Dose-Dependent Effects on Inflammatory Biomarkers and Lipids (48 Months)

- Placebo SC q 3 mth
- Canakinumab 50mg SC q 3 mth
- Canakinumab 150mg SC q 3 mth
- Canakinumab 300mg SC q 3 mth

Ridker ESC 2017
CANTOS: Primary Clinical Outcome Effects on MACE and MACE +

<table>
<thead>
<tr>
<th></th>
<th>Placebo (N=3347)</th>
<th>50 mg (N=2170)</th>
<th>150 mg (N=2284)</th>
<th>300 mg (N=2263)</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR (per 100 person years)</td>
<td>4.5 1.0 (referent)</td>
<td>4.1 0.93 (referent)</td>
<td>3.9 0.85 (referent)</td>
<td>3.9 0.86 (referent)</td>
<td>0.020</td>
</tr>
<tr>
<td>HR</td>
<td>1.0 (referent)</td>
<td>0.80-1.07</td>
<td>0.74-0.98</td>
<td>0.75-0.99</td>
<td></td>
</tr>
<tr>
<td>95%CI</td>
<td>(referent)</td>
<td>0.30</td>
<td>0.021*</td>
<td>0.031</td>
<td></td>
</tr>
<tr>
<td><strong>Secondary Endpoint</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>IR (per 100 person years)</td>
<td>5.1 1.00 (referent)</td>
<td>4.6 0.90 (referent)</td>
<td>4.3 0.83 (referent)</td>
<td>4.3 0.83 (referent)</td>
<td>0.003</td>
</tr>
<tr>
<td>HR</td>
<td>1.00 (referent)</td>
<td>0.78-1.03</td>
<td>0.73-0.95</td>
<td>0.72-0.94</td>
<td></td>
</tr>
<tr>
<td>95%CI</td>
<td>(referent)</td>
<td>0.11</td>
<td>0.005*</td>
<td>0.004</td>
<td></td>
</tr>
<tr>
<td>P</td>
<td>(referent)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

*Statistically significant, adjusted for multiplicity, in accordance with the pre-specified closed-testing procedures

Ridker ESC 2017

Intermountain Heart Institute
Intermountain Medical Center
CANTOS: Primary Cardiovascular Endpoint (MACE)

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints.

HR 0.85
95%CI 0.76-0.96
P = 0.007

39% reduction in hsCRP
No change in LDLC
15% reduction in MACE

Ridker ESC 2017
CANTOS: Key Secondary Cardiovascular Endpoint (MACE+)

- Placebo SC q 3 months
- Canakinumab 150/300 SC q 3 months

HR 0.83
95% CI 0.74-0.92
P = 0.0006

The 150mg group met multiplicity adjusted thresholds for formal statistical significance for both the primary and secondary cardiovascular endpoints

39% reduction in hsCRP
No change in LDLC
17% reduction in MACE+

Ridker ESC 2017
<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo (N=3347)</th>
<th>50 mg (N=2170)</th>
<th>150 mg (N=2284)</th>
<th>300 mg (N=2263)</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary</td>
<td>1.00</td>
<td>0.93</td>
<td>0.85</td>
<td>0.86</td>
<td>0.020</td>
</tr>
<tr>
<td>Secondary</td>
<td>1.00</td>
<td>0.90</td>
<td>0.83</td>
<td>0.83</td>
<td>0.002</td>
</tr>
<tr>
<td>Myocardial Infarction</td>
<td>1.00</td>
<td>0.94</td>
<td>0.76</td>
<td>0.84</td>
<td>0.028</td>
</tr>
<tr>
<td>Urgent Revascularization</td>
<td>1.00</td>
<td>0.70</td>
<td>0.64</td>
<td>0.58</td>
<td>0.005</td>
</tr>
<tr>
<td>Any Coronary Revascularization</td>
<td>1.00</td>
<td>0.72</td>
<td>0.68</td>
<td>0.70</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Stroke</td>
<td>1.00</td>
<td>1.01</td>
<td>0.98</td>
<td>0.80</td>
<td>0.17</td>
</tr>
<tr>
<td>Cardiac Arrest</td>
<td>1.00</td>
<td>0.72</td>
<td>0.63</td>
<td>0.46</td>
<td>0.035</td>
</tr>
<tr>
<td>CV Death</td>
<td>1.00</td>
<td>0.89</td>
<td>0.90</td>
<td>0.94</td>
<td>0.62</td>
</tr>
<tr>
<td>All Cause Mortality</td>
<td>1.00</td>
<td>0.94</td>
<td>0.92</td>
<td>0.94</td>
<td>0.39</td>
</tr>
</tbody>
</table>

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CANTOS: Consistency of Effect Across All Patient Groups

<table>
<thead>
<tr>
<th>Group</th>
<th>MACE</th>
<th>MACE +</th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age &lt; 60 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Age ≥ 60 yrs</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No diabetes</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non Smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Smoker</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI &lt; 30 kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI ≥ 30 kg/m²</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL &lt; 80 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>LDL ≥ 80 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP &lt; 4 mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>hsCRP ≥ 4 mg/L</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDLC &gt; 45 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>HDLC ≤ 45 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG &lt; 150 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TG ≥ 150 mg/dL</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

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CANTOS: Greater Risk Reduction Among Those With Greater hsCRP Reduction (MACE+)

HR 0.73
95%CI 0.63-0.83
P=0.0001
for those with reductions in hsCRP ≥ median at 3-months (1.8 mg/L)

Ridker ESC 2017
## CANTOS: Additional Outcomes (per 100 person years of exposure)

<table>
<thead>
<tr>
<th>Adverse Event</th>
<th>Placebo (N=3347)</th>
<th>50 mg (N=2170)</th>
<th>150 mg (N=2284)</th>
<th>300 mg (N=2263)</th>
<th>P-trend</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any SAE</td>
<td>12.0</td>
<td>11.4</td>
<td>11.7</td>
<td>12.3</td>
<td>0.43</td>
</tr>
<tr>
<td>Leukopenia</td>
<td>0.24</td>
<td>0.30</td>
<td>0.37</td>
<td>0.52</td>
<td>0.002</td>
</tr>
<tr>
<td>Any infection</td>
<td>2.86</td>
<td>3.03</td>
<td>3.13</td>
<td>3.25</td>
<td>0.12</td>
</tr>
<tr>
<td>Fatal infection</td>
<td>0.18</td>
<td>0.31</td>
<td>0.28</td>
<td>0.34</td>
<td>0.09/0.02*</td>
</tr>
<tr>
<td>Injection site reaction</td>
<td>0.23</td>
<td>0.27</td>
<td>0.28</td>
<td>0.30</td>
<td>0.49</td>
</tr>
<tr>
<td>Any Malignancy</td>
<td>1.88</td>
<td>1.85</td>
<td>1.69</td>
<td>1.72</td>
<td>0.31</td>
</tr>
<tr>
<td>Fatal Malignancy</td>
<td>0.64</td>
<td>0.55</td>
<td>0.50</td>
<td>0.31</td>
<td>0.0007</td>
</tr>
<tr>
<td>Arthritis</td>
<td>3.32</td>
<td>2.15</td>
<td>2.17</td>
<td>2.47</td>
<td>0.002</td>
</tr>
<tr>
<td>Osteoarthritis</td>
<td>1.67</td>
<td>1.21</td>
<td>1.12</td>
<td>1.30</td>
<td>0.04</td>
</tr>
<tr>
<td>Gout</td>
<td>0.80</td>
<td>0.43</td>
<td>0.35</td>
<td>0.37</td>
<td>0.0001</td>
</tr>
<tr>
<td>ALT &gt; 3x normal</td>
<td>1.4</td>
<td>1.9</td>
<td>1.9</td>
<td>2.0</td>
<td>0.19</td>
</tr>
<tr>
<td>Bilirubin &gt; 2x normal</td>
<td>0.8</td>
<td>1.0</td>
<td>0.7</td>
<td>0.7</td>
<td>0.34</td>
</tr>
</tbody>
</table>

* P-value for combined canakinumab doses vs placebo

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Sub-clinical chronic inflammation increases cancer risk (hsCRP is also a risk factor for certain cancers, in particular lung cancer)

Inflammation in the tumor micro-environment impacts upon tumor initiation, progression, invasiveness, and metastatic progression


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Chronic Inflammation, Tumor Progression, and IL-1 Inhibition

Ron Apte, et al;
Cancer Metastasis Rev.
2006;25:387-408.

The involvement of IL-1 in tumorigenesis, tumor invasiveness, metastasis and tumor-host interactions
Ron N. Apte · Shadar Dotan · Moshe Elkasbi · Malka R. White · Eli Reich · Yaron Carmi · Xiaping Song · Tatiana Dvozkin · Yakov Krelin · Elena Voronov

Anne Lewis, et al;
J Transl Med.

Interleukin-1 and cancer progression: the emerging role of interleukin-1 receptor antagonist as a novel therapeutic agent in cancer treatment
Anne M Lewis1,2, Sheelu Varghese1,3, Hui Xu1 and H Richard Alexander*1,3

Charles A. Dinarello.
Cancer Metastasis Rev

Why not treat human cancer with interleukin-1 blockade?
Charles A. Dinarello

Ridker ESC 2017
CANTOS and Incident Cancer
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study

1. The atherosclerosis patients enrolled in CANTOS were at unusually high risk for certain inflammatory cancers, in particular lung cancer.

2. This is due to several issues including older age, a high prevalence of current and past smoking, and the enrollment only of those with elevated hsCRP (elevated hsCRP levels are an independent risk marker for lung cancer).

3. The randomized design of CANTOS ensures that prevalent cancers undiagnosed at trial entry as well as measured and unmeasured cancer risk factors are equally distributed among treatment groups.

4. A Cancer Adjudication Committee of oncologists was established at trial initiation.
CANTOS: Additional Non-Cardiovascular Clinical Benefits

Cancer Mortality

- Placebo: HR = 1.0 (95% CI: referent, referent)
- Canakinumab 50 mg: HR = 0.86 (0.59-1.24), P = 0.42
- Canakinumab 150 mg: HR = 0.78 (0.54-1.13), P = 0.19
- Canakinumab 300 mg: HR = 0.49 (0.31-0.75), P = 0.0009

P-trend across groups = 0.0007

Canakinumab 300 mg
51% reduction in death from any cancer
P = 0.0009

Ridker ESC 2017
CANTOS: Additional Non-Cardiovascular Clinical Benefits
Incident Lung Cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>HR</th>
<th>(95%CI)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0</td>
<td>(referent)</td>
<td>1.0</td>
</tr>
<tr>
<td>Canakinumab 50 mg</td>
<td>0.77</td>
<td>(0.49-1.20)</td>
<td>0.25</td>
</tr>
<tr>
<td>Canakinumab 150 mg</td>
<td>0.61</td>
<td>(0.39-0.97)</td>
<td>0.034</td>
</tr>
<tr>
<td>Canakinumab 300 mg</td>
<td>0.33</td>
<td>(0.18-0.59)</td>
<td>0.00008</td>
</tr>
</tbody>
</table>

P-trend across groups = 0.0003

Canakinumab 300 mg
67% reduction in incident lung cancer
P = 0.00008

Ridker ESC 2017
CANTOS: Additional Non-Cardiovascular Clinical Benefits
Fatal Lung Cancer

<table>
<thead>
<tr>
<th>Group</th>
<th>HR</th>
<th>95% CI</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Placebo</td>
<td>1.0</td>
<td>referent</td>
<td>referent</td>
</tr>
<tr>
<td>Canakinumab 50 mg</td>
<td>0.71</td>
<td>0.40-1.26</td>
<td>0.24</td>
</tr>
<tr>
<td>Canakinumab 150 mg</td>
<td>0.64</td>
<td>0.36-1.14</td>
<td>0.13</td>
</tr>
<tr>
<td>Canakinumab 300 mg</td>
<td>0.23</td>
<td>0.10-0.54</td>
<td>0.0002</td>
</tr>
</tbody>
</table>

P-trend across groups = 0.0002

Cumulative Incidence (%)

Follow-up Years

Canakinumab 300 mg
77% reduction in fatal lung cancer
P = 0.0002

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Conclusions:
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

1. CANTOS was designed to directly test the inflammatory hypothesis of atherothrombosis.

2. As shown in these data, inhibition of IL-1β with SC canakinumab given once every three months among patients with a prior myocardial infarction substantially lowered the inflammatory biomarkers hsCRP and IL-6 while having no beneficial impact on atherogenic lipids.

3. Concordantly, while the 50 mg dose of canakinumab did not have cardiovascular efficacy compared to placebo during an average follow-up period of 3.7 years, hazard reductions of 15% for the primary endpoint of MACE (P=0.007) and 17% for the secondary endpoint of MACE+ (P=0.006) were observed for the combined 150mg and 300mg doses groups. The 150mg group met all pre-specified multiplicity adjusted thresholds for statistical significance for both the primary and secondary cardiovascular outcomes.
Conclusions:
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

4. In exploratory analyses, relative hazard reductions of 27% (P<0.001) were observed among those with the lowest levels of on-treatment hsCRP measured at 3 months. Thus, “lower is better” appears to be true for inflammation as well as LDL-C.

5. Given mild neutropenia and an increase in risk of fatal infection, patients being considered for treatment with canakinumab will require monitoring for early signs and symptoms of infection in a manner similar to that currently done for individuals taking other biologic anti-inflammatory agents.

6. Placebo event rates in CANTOS were high, approaching 25% at five years. These data thus affirm that statin-treated patients with “residual inflammatory risk” as assessed by baseline hsCRP ≥2 mg/L have future event rates as high, if not higher, than statin-treated patients with “residual cholesterol risk”. These two patient groups differ substantially and require different personalized approaches to treatment.

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Conclusions:
The Canakinumab Anti-Inflammatory Thrombosis Outcomes Study (CANTOS)

7. Inflammation is also a determinant of invasiveness, progression, and metastasis for certain cancers. In exploratory analyses within CANTOS, those allocated to canakinumab had large dose-dependent relative risk reductions in deaths due to cancer (P=0.0007), incident lung cancers (P<0.0001), and fatal lung cancer (P=0.0002) such that those in the canakinumab 300mg group had a 50 percent reduction in cancer fatality (P=0.0009). Replication of these data is required.

8. In conclusion, these randomized placebo-controlled trial data demonstrate that targeting the IL-1β to IL-6 pathway of innate immunity with canakinumab reduces cardiovascular event rates and potentially reduces rates of incident lung cancer and lung cancer mortality. These data provide proof that inflammation inhibition, in the absence of lipid lowering, can improve atherothrombotic outcomes and potentially alter the progression of some fatal cancers.
Brent’s Thoughts

• This study is important because it demonstrates quite definitively that inflammation associated with atherosclerosis can be a therapeutic target independent of other CV risk factors.

• This particular drug adds on a modest additional benefit to standard therapy
  - But it is very expensive – whether Novartis can come up with a cost-effective business model remains to be seen.

• The shot is only required every three months which is good.

• I expect many more anti-inflammatory drugs will be tested soon.
  - Methotrexate – is underway
  - Colchicinet – small studies have been done
Thank You