THE SPRINT STUDY: IMPLICATIONS FOR CARDIOLOGISTS

Vasilios Papademetriou, MD
Professor of Medicine
Georgetown University
A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group

Promised to change everything know in hypertension management
Reduced all Cv events
Safe for the heart
Reasonable for the kidney
Settled the J shape curve
Applicable to high risk patients
RATES OF BP CONTROL AND MORTALITY
EDWARD D. FREIS

At Georgetown

The VA Medical Center

Author of landmark VA studies
### Severe HTN

#### Effects of Treatment on Morbidity in Hypertension

**V.A. Cooperative Study**

<table>
<thead>
<tr>
<th>Hypertensive Complications</th>
<th>Placebo (n=70)</th>
<th>Treated (n=73)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Retinopathy (Gr.III/IV)</td>
<td>7</td>
<td>0</td>
</tr>
<tr>
<td>Accelerated Hypertension</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Renal Failure</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Dissecting Aneurysm</td>
<td>3</td>
<td>0</td>
</tr>
<tr>
<td>Retinopathy With CHF</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Stroke</td>
<td>2</td>
<td>0</td>
</tr>
<tr>
<td>Sudden Death</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Drug Reaction</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td><strong>Total</strong></td>
<td>21</td>
<td>1</td>
</tr>
</tbody>
</table>


### Mild to moderate HTN

#### Effects of Treatment on Morbidity in Hypertension

**V.A. Cooperative Study**

<table>
<thead>
<tr>
<th>Hypertensive Complication</th>
<th>Placebo (n=194)</th>
<th>Treated (n=186)</th>
</tr>
</thead>
<tbody>
<tr>
<td>CVA</td>
<td>20</td>
<td>5</td>
</tr>
<tr>
<td>Coronary Artery Disease</td>
<td>13</td>
<td>11</td>
</tr>
<tr>
<td>CHF</td>
<td>11</td>
<td>0</td>
</tr>
<tr>
<td>Accelerated Hypertension</td>
<td>4</td>
<td>0</td>
</tr>
</tbody>
</table>

*Statistically Significant Benefit Derived at Diastolic BP Levels Of 105 mm Hg And Greater*

The Veterans Administration Cooperative Study on Antihypertensive Agents. Implications for Stroke Prevention

BY EDWARD D. FREIS, M.D.

Abstract:
The Veterans Administration Cooperative Study on Antihypertensive Agents. Implications for Stroke Prevention

- Hypertension and atherosclerosis are the leading causes of stroke. The risk of stroke is directly related to the height of the blood pressure.

  The Veterans Administration Cooperative Study included 523 male patients. If the results of two subgroups (115 to 129 mm Hg and 90 to 114 mm Hg initial diastolic) are combined, the total incidence of stroke was 25 in the control group and six in the treated group.

  In addition to widespread lack of awareness of the medical profession of the benefits of treatment, there also is a failure of detection of hypertension in large segments of our population. There is need for greater professional as well as public education concerning hypertension.
PRINCIPAL RESULTS OF THE HYPERTENSION OPTIMAL TREATMENT (HOT) RANDOMISED TRIAL

13,547 patients enrolled
13,133 patients randomised
12,730 patients randomised and followed up
403 patients excluded

6264 <90 mm Hg
6264 <85 mm Hg
6262 <80 mm Hg

3132 acetylsalicylic acid
3132 placebo
2133 acetylsalicylic acid
2133 placebo
2134 acetylsalicylic acid
2134 placebo
2135 acetylsalicylic acid
2135 placebo

188 died
134 died
207 died
188 lost to follow-up
157 lost to follow-up
188 lost to follow-up

Figure 1: Trial profile

Lancet 1998; 351: 1755–62
THE SHEP STUDY

4736 pts >60 yo, SBP=160-219, DBP<90

Meds: Chlorthalidone, atenolol, etc
Matching placebo

JAMA, 1991;265:3255
Odds Ratio for CV Events and Systolic BP Difference: Recent and Older Trials


**Graph:***
- **Y-axis:** Odds Ratio (experimental/reference)
- **X-axis:** Difference (reference minus experimental) in Systolic BP (mm Hg)
- **Legend:**
  - Recent trials
  - Older trials placebo
  - Older trials active
- **Statistical Test:** $P<.0001$

**Trials:**
- Recent
  - AASK L vs. H
  - ABCD/NT L vs. H
  - ALLHAT/Aml
  - ALLHAT/Lis
  - ALLHAT/Lis ≥65
  - ALLHAT/Lis Blacks
  - ANBP2
  - CONVINCE
  - DIABHYCAR
  - ELSA
  - IDNT2
  - LIFE/ALL
  - LIFE/DM
  - NICOLE
  - PREVENT
  - SCOPE
- Older
  - ALLHAT/Dox
  - ATMH
  - EWPHE
  - HEP
  - HOPE
  - HOT
  - HOT M vs. H
  - INSIGHT
  - MIDAS/NICS/VHAS
  - L vs. H
  - MRC
  - MRC2
  - PART2/SCAT
  - PATS
  - PROGRESS/Per
  - PROGRESSION/Com
  - RCT70-80
  - RENAAAL
  - SHEP
  - STONE
  - STOP 1
  - STOP2/CCBs
  - STOP2/ACEIs
  - Syst-China
  - Syst-Eur
  - UKPDS C vs. A
  - UKPDS L vs. H
CHANGE IN SYSTOLIC AND DIASTOLIC BP WITH AGE
Lower is better
Earlier is better
<140/90 in most,
<130/85
<150 in pts >60yo
# BP TARGETS

## HOW LOW TO GO?

2014 Meta-analysis of RCTs of Achieved SBP:

<table>
<thead>
<tr>
<th>Condition</th>
<th>RRR</th>
<th>NNT/5y</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Stroke</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>140-149 vs 150-159*</td>
<td>↓35%</td>
<td>52</td>
</tr>
<tr>
<td>130-139 vs 140-149**</td>
<td>↓27%</td>
<td>90</td>
</tr>
<tr>
<td>120-129 vs 130-139***</td>
<td>↓31%</td>
<td>106</td>
</tr>
<tr>
<td><strong>Coronary Heart Disease:</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>140-149 vs 150-159*</td>
<td>↓21%</td>
<td>169</td>
</tr>
<tr>
<td>130-139 vs 140-149**</td>
<td>↓23%</td>
<td>122</td>
</tr>
<tr>
<td>120-129 vs 130-139***</td>
<td>↓12% (NS)</td>
<td>---</td>
</tr>
</tbody>
</table>

*5RCTs; 12,406 pts  **13 RCTs; 79,736 pts  ***4 RCTs; 24,404 pts

*J Hypertension 2014; 32:2296*
CONCERNS ABOUT J-SHAPE CURVE

The J-Curve Hypothesis

Adapted from Hansson L. Blood Pressure 1993;2:62.
Incidence of total myocardial infarction (MI) and total stroke by diastolic blood pressure strata
INCIDENCE OF THE PRIMARY OUTCOME

**Systolic Blood Pressure, mm Hg**

- Patients with primary outcome:
  - Total patients: 234
  - 45
  - 196
  - 493
  - 596
  - 437
  - 253
  - 248

- Mean diastolic blood pressure, mm Hg:
  - Patients with primary outcome:
    - 65.7
    - 70.8
    - 74.4
    - 76.8
    - 79.6
    - 81.7
    - 83.1
    - 89.1
  - Patients without primary outcome:
    - 67.9
    - 73.5
    - 76.7
    - 78.9
    - 81.3
    - 84.6
    - 89.4

**Diastolic Blood Pressure, mm Hg**

- Patients with primary outcome:
  - Total patients: 176
  - 56
  - 389
  - 1003
  - 596
  - 174
  - 33
  - 17

- Mean systolic blood pressure, mm Hg:
  - Patients with primary outcome:
    - 124.3
    - 131.7
    - 135.1
    - 143.7
    - 160.2
    - 171.6
    - 186.0
  - Patients without primary outcome:
    - 127.0
    - 129.1
    - 131.0
    - 138.8
    - 154.2
    - 169.4
    - 187.5
THE VA STUDY
DEATH RATE BY LAST SYSTOLIC BP

Papademetriou et al 2013, AHA
DEATH RATE BY LAST DIASTOLIC BP

N=477,730

Follow up > 10 years

Papademetriou et al: AHA, 2013
Death Rate for Hypertensives
Using Last BP

Fletcher et al
>40 years after the publication of the landmark VA studies we still do not have definite treatment targets

- Indications that optimal systolic is 130-140 mmHg and diastolic 80-90 mmHg
- The Guidelines suggest higher BPs in people >60 years of age
- The threat of J shape Curve is looming!!
- SPRINT to the rescue
SYSTOLIC BLOOD PRESSURE INTERVENTION TRIAL: SPRINT

A Randomized Trial of Intensive versus Standard Blood-Pressure Control

The SPRINT Research Group*

Promised to change everything we know in hypertension management
**SPRINT Research Question**

Examine effect of more intensive high blood pressure treatment than is currently recommended

Randomized Controlled Trial

Target Systolic BP

- **Intensive Treatment**
  - Goal SBP < 120 mm Hg

- **Standard Treatment**
  - Goal SBP < 140 mm Hg

**SPRINT design details available at:**
- ClinicalTrials.gov (NCT01206062)
Methods

- Open-label RCT sponsored by NHLBI at 102 sites in the USA
- An independent data and safety monitoring board
- **INCLUSION CRITERIA**: Age >50, Systolic BP 130-180 mmHg, and increased CV risk
- **EXCLUSION CRITERIA**:
  - DM
  - Prior CVA
  - eGFR <20 or ESRD
  - ACS or revascularization within past 3 months
  - One-minute standing BP < 110 mmHg
  - LVEF <35% OR symptomatic HF within past 3 months
  - Other standard exclusions (poor prognosis from other disease, transplant patients, pregnancy, non-compliance, substance abuse, etc.)
**SPRINT: Enrollment and Follow-up Experience**

**Screened**  
(N=14,692)

**Randomized**  
(N=9,361)

- **Intensive Treatment**  
(N=4,678)
  - Consent withdrawn: 224
  - Discontinued intervention: 111
  - Lost to follow-up: 154
  - Analyzed (Intention to treat): 4,678

- **Standard Treatment**  
(N=4,683)
  - Consent withdrawn: 242
  - Discontinued intervention: 134
  - Lost to follow-up: 121
  - Analyzed (Vital status assessment: entire cohort): 4,683
**Blood Pressure Change During Follow up**

**Systolic BP During Follow-up**

- **Year 1**
  - **Mean SBP**: 136.2 mm Hg
  - **Mean SBP**: 121.4 mm Hg

**Average SBP (During Follow-up)**
- **Standard**: 134.6 mm Hg
- **Intensive**: 121.5 mm Hg

**Average number of antihypertensive medications**
- **Number of participants**
  - Standard N: 274
  - Intensive N: 286
Hazard Ratio = 0.75 (95% CI: 0.64 to 0.89)

During Trial (median follow-up = 3.26 years)
Number Needed to Treat (NNT) to prevent a primary outcome = 61

SPRINT Primary Outcome
Cumulative Hazard
Adapt from Figure 2B in the N Engl J Med manuscript

All-cause Mortality
Cumulative Hazard

Figure 2B: All-Cause Mortality Cumulative Hazards

Hazard Ratio = 0.73 (95% CI: 0.60 to 0.90)

During Trial (median follow-up = 3.26 years)
Number Needed to Treat (NNT) to Prevent a death = 90

Standard
(210 deaths)

Intensive
(155 deaths)

HR=0.73 (95% CI: 0.60 to 0.90)

Number of Participants
### Primary Outcome in the Six Pre-specified Subgroups of Interest

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>HR</th>
<th>P*</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>0.75 (0.64,0.89)</td>
<td></td>
</tr>
<tr>
<td>No Prior CKD</td>
<td>0.70 (0.56,0.87)</td>
<td>0.36</td>
</tr>
<tr>
<td>Prior CKD</td>
<td>0.82 (0.63,1.07)</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 75</td>
<td>0.80 (0.64,1.00)</td>
<td>0.32</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>0.67 (0.51,0.86)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>0.84 (0.62,1.14)</td>
<td>0.45</td>
</tr>
<tr>
<td>Male</td>
<td>0.72 (0.59,0.88)</td>
<td></td>
</tr>
<tr>
<td>African–American</td>
<td>0.77 (0.55,1.06)</td>
<td>0.83</td>
</tr>
<tr>
<td>Non African–American</td>
<td>0.74 (0.61,0.90)</td>
<td></td>
</tr>
<tr>
<td>No Prior CVD</td>
<td>0.71 (0.57,0.88)</td>
<td>0.39</td>
</tr>
<tr>
<td>Prior CVD</td>
<td>0.83 (0.62,1.09)</td>
<td></td>
</tr>
<tr>
<td>SBP ≤ 132</td>
<td>0.70 (0.51,0.95)</td>
<td>0.77</td>
</tr>
<tr>
<td>132 &lt; SBP &lt; 145</td>
<td>0.77 (0.57,1.03)</td>
<td></td>
</tr>
<tr>
<td>SBP ≥ 145</td>
<td>0.83 (0.63,1.09)</td>
<td></td>
</tr>
</tbody>
</table>

*Treatment by subgroup interaction
*Unadjusted for multiplicity
### All-cause Mortality in the Six Pre-specified Subgroups of Interest

**Figure 4: All-Cause Mortality**

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Intensive</th>
<th>Standard</th>
<th>HR</th>
<th>Int P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>155/4678 (3.31)</td>
<td>210/4683 (4.48)</td>
<td>0.73 (0.60, 0.90)</td>
<td></td>
</tr>
<tr>
<td>No Prior CKD</td>
<td>85/3348 (2.54)</td>
<td>115/3367 (3.42)</td>
<td>0.75 (0.57, 1.00)</td>
<td>0.76</td>
</tr>
<tr>
<td>Prior CKD</td>
<td>70/1330 (5.26)</td>
<td>95/1316 (7.22)</td>
<td>0.73 (0.53, 1.00)</td>
<td></td>
</tr>
<tr>
<td>Age &lt; 75</td>
<td>82/3361 (2.44)</td>
<td>104/3364 (3.09)</td>
<td>0.77 (0.58, 1.03)</td>
<td>0.58</td>
</tr>
<tr>
<td>Age ≥ 75</td>
<td>73/1317 (5.54)</td>
<td>106/1319 (8.04)</td>
<td>0.68 (0.50, 0.92)</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>46/1684 (2.73)</td>
<td>54/1648 (3.28)</td>
<td>0.85 (0.57, 1.26)</td>
<td>0.49</td>
</tr>
<tr>
<td>Male</td>
<td>109/2994 (3.64)</td>
<td>156/3035 (5.14)</td>
<td>0.71 (0.55, 0.91)</td>
<td></td>
</tr>
<tr>
<td>African-American</td>
<td>53/1454 (3.65)</td>
<td>55/1493 (3.68)</td>
<td>0.96 (0.65, 1.40)</td>
<td>0.06</td>
</tr>
<tr>
<td>Non African-American</td>
<td>102/3224 (3.16)</td>
<td>155/3190 (4.86)</td>
<td>0.64 (0.50, 0.82)</td>
<td></td>
</tr>
<tr>
<td>No Prior CVD</td>
<td>106/3738 (2.84)</td>
<td>140/3746 (3.74)</td>
<td>0.75 (0.58, 0.96)</td>
<td>0.78</td>
</tr>
<tr>
<td>Prior CVD</td>
<td>49/940 (5.21)</td>
<td>70/937 (7.47)</td>
<td>0.70 (0.48, 1.02)</td>
<td></td>
</tr>
<tr>
<td>SBP ≤ 132</td>
<td>46/1583 (2.91)</td>
<td>64/1553 (4.12)</td>
<td>0.73 (0.49, 1.07)</td>
<td>0.70</td>
</tr>
<tr>
<td>132 &lt; SBP &lt; 145</td>
<td>41/1489 (2.75)</td>
<td>63/1549 (4.07)</td>
<td>0.69 (0.46, 1.03)</td>
<td></td>
</tr>
<tr>
<td>SBP ≥ 145</td>
<td>68/1606 (4.23)</td>
<td>83/1581 (5.25)</td>
<td>0.81 (0.59, 1.13)</td>
<td></td>
</tr>
</tbody>
</table>

*\( p = 0.34 \), after Hommel adjustment for multiple comparisons
### Table 2. Primary and Secondary Outcomes and Renal Outcomes.

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Intensive Treatment</th>
<th>Standard Treatment</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>no. of patients (%)</td>
<td>% per year</td>
<td>no. of patients (%)</td>
<td>% per year</td>
</tr>
<tr>
<td>All participants</td>
<td>(N = 4678)</td>
<td>(N = 4683)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome</td>
<td>243 (5.2)</td>
<td>1.65</td>
<td>319 (6.8)</td>
<td>2.19</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>97 (2.1)</td>
<td>0.65</td>
<td>116 (2.5)</td>
<td>0.78</td>
</tr>
<tr>
<td>Acute coronary syndrome</td>
<td>40 (0.9)</td>
<td>0.27</td>
<td>40 (0.9)</td>
<td>0.27</td>
</tr>
<tr>
<td>Secondary outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td>62 (1.3)</td>
<td>0.41</td>
<td>100 (2.1)</td>
<td>0.67</td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>37 (0.8)</td>
<td>0.25</td>
<td>65 (1.4)</td>
<td>0.43</td>
</tr>
<tr>
<td>Death from any cause</td>
<td>155 (3.3)</td>
<td>1.03</td>
<td>210 (4.5)</td>
<td>1.40</td>
</tr>
<tr>
<td>Participants with CKD at baseline</td>
<td>(N = 1330)</td>
<td>(N = 1316)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Composite renal outcome</td>
<td>14 (1.1)</td>
<td>0.33</td>
<td>15 (1.1)</td>
<td>0.36</td>
</tr>
<tr>
<td>≥50% reduction in estimated GFR</td>
<td>10 (0.8)</td>
<td>0.23</td>
<td>11 (0.8)</td>
<td>0.26</td>
</tr>
<tr>
<td>Long-term dialysis</td>
<td>6 (0.5)</td>
<td>0.14</td>
<td>10 (0.8)</td>
<td>0.24</td>
</tr>
<tr>
<td>Kidney transplantation</td>
<td>0</td>
<td>0</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident albuminuria</td>
<td>49/526 (9.3)</td>
<td>3.02</td>
<td>59/500 (11.8)</td>
<td>3.90</td>
</tr>
<tr>
<td>Participants without CKD at baseline</td>
<td>(N = 3332)</td>
<td>(N = 3345)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30% reduction in estimated GFR to ≤60 ml/min (1.73 m²)</td>
<td>127 (3.8)</td>
<td>1.21</td>
<td>37 (1.1)</td>
<td>0.35</td>
</tr>
<tr>
<td>Incident albuminuria</td>
<td>110/1769 (6.2)</td>
<td>2.00</td>
<td>135/1831 (7.4)</td>
<td>2.41</td>
</tr>
</tbody>
</table>
### SPRINT: Adverse events

<table>
<thead>
<tr>
<th>Conditions of interest – SAE only, n (%)</th>
<th>Intensive treatment (N=4678)</th>
<th>Standard treatment (N=4683)</th>
<th>Hazard ratio</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAE, n (%)</td>
<td>1793 (38.3)</td>
<td>1736 (37.1)</td>
<td>1.04</td>
<td>0.25</td>
</tr>
<tr>
<td>Hypotension</td>
<td>110 (2.4)</td>
<td>66 (1.4)</td>
<td>1.67</td>
<td>0.001</td>
</tr>
<tr>
<td>Syncope</td>
<td>107 (2.3)</td>
<td>80 (1.7)</td>
<td>1.33</td>
<td>0.05</td>
</tr>
<tr>
<td>Bradycardia</td>
<td>87 (1.9)</td>
<td>73 (1.6)</td>
<td>1.19</td>
<td>0.28</td>
</tr>
<tr>
<td>Electrolyte abnormality</td>
<td>144 (3.1)</td>
<td>107 (2.3)</td>
<td>1.35</td>
<td>0.02</td>
</tr>
<tr>
<td>Injurious fall</td>
<td>105 (2.2)</td>
<td>110 (2.3)</td>
<td>0.95</td>
<td>0.71</td>
</tr>
<tr>
<td>Acute kidney injury or acute renal failure</td>
<td>193 (4.1)</td>
<td>117 (2.5)</td>
<td>1.66</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

SAE, serious adverse event
## SPRINT: Adverse renal outcomes

### Intensive treatment vs Standard treatment

<table>
<thead>
<tr>
<th></th>
<th>Intensive treatment</th>
<th>Standard treatment</th>
<th>HR (95% CI)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Participants with CKD at baseline (N=1330)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary CKD outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥50% reduction in eGFR*</td>
<td>14</td>
<td>15</td>
<td>0.89 (0.42–1.87)</td>
<td>0.76</td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>11</td>
<td>0.87 (0.36–2.07)</td>
<td>0.75</td>
</tr>
<tr>
<td>Secondary CKD outcome</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Incident albuminuria†</td>
<td>49</td>
<td>59</td>
<td>0.72 (0.48–1.07)</td>
<td>0.11</td>
</tr>
<tr>
<td><strong>Participants without CKD at baseline (N=3332)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Secondary CKD outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥30% reduction in eGFR*</td>
<td>127</td>
<td>37</td>
<td>3.49 (2.44–5.10)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Incident albuminuria†</td>
<td>110</td>
<td>135</td>
<td>0.81 (0.63–1.04)</td>
<td>0.10</td>
</tr>
</tbody>
</table>

*Confirmed on a second occasion ≥90 days apart
†Doubling of urinary albumin/creatinine ratio from <10 to >10 mg/g
KAPLAN-MEIER CURVES FOR THE PRIMARY CARDIOVASCULAR DISEASE (PANEL A) AND ALL-CAUSE MORTALITY (PANEL B) OUTCOMES.
RENAL OUTCOMES: PRIMARY END POINT

<table>
<thead>
<tr>
<th>Years Follow-up</th>
<th>Number at risk</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Standard</td>
</tr>
<tr>
<td>0</td>
<td>1316</td>
</tr>
<tr>
<td>1</td>
<td>1265</td>
</tr>
<tr>
<td>2</td>
<td>1214</td>
</tr>
<tr>
<td>3</td>
<td>854</td>
</tr>
<tr>
<td>4</td>
<td>266</td>
</tr>
<tr>
<td>5</td>
<td></td>
</tr>
</tbody>
</table>

Cumulative Hazard

0.000 0.005 0.010 0.015 0.020

0 1 2 3 4 5
Gait Speed as an Incremental Predictor of morbidity and Mortality

Gait Speed as an Incremental Predictor of Mortality and Major Morbidity in Elderly Patients Undergoing Cardiac Surgery

Jonathan Afshalo, MD, MSc,† Mark J. Eisenberg, MD, MPH,‡ Jean-François Morin, MD,§ Howard Bergman, MD,¶ Johanne Monette, MD, MSc,¶ Nicolas Noisoux, MD,# Louis P. Pernault, MD, PhD,† Karen P. Alexander, MD,‡ Yves Langlois, MD,# Nundini Dendukuri, PhD,‡ Patrick Charmoun, RRT,§ Georges Kasparian, BSc,¶ Sophie Robichaud, RRT,‡ S. Michael Gharaboulou, MD,‡ Jean-François Provost, MD, ScD‡
Montreal, Quebec, Canada; and Durham, North Carolina

Objectives  The purpose of this study was to test the value of gait speed, a clinical marker for frailty, to improve the prediction of mortality and major morbidity in elderly patients undergoing cardiac surgery.

Background  It is increasingly difficult to predict the elderly patient’s risk posed by cardiac surgery because existing risk assessment tools are incomplete.

Methods  A multicenter prospective cohort of elderly patients undergoing cardiac surgery was assembled at 4 tertiary care hospitals between 2008 and 2009. Patients were eligible if they were 70 years of age or older and were scheduled for coronary artery bypass and/or valve replacement or repair. The primary predictor was slow gait speed, defined as a time taken to walk 5 m of =6 s. The primary end point was a composite of in-hospital postoperative mortality or major morbidity.

Results  The cohort consisted of 131 patients with a mean age of 75.8 ± 4.4 years. 34% were female patients. Sixty patients (46%) were classified as slow walkers before cardiac surgery. Slow walkers were more likely to be female (44% vs. 26%, p = 0.03) and diabetics (50% vs. 28%, p = 0.01). Thirty patients (23%) experienced the primary composite end point of mortality or major morbidity after cardiac surgery. Slow gait speed was an independent predictor of the composite end point after adjusting for the Society of Thoracic Surgeons risk score (odds ratio: 2.05; 95% confidence interval: 1.23 to 3.54).

Conclusions  Gait speed is a simple and effective test that may identify a subset of vulnerable elderly patients at incrementally higher risk of mortality and major morbidity after cardiac surgery. (J Am Coll Cardiol 2010;56:1658–76)  © 2010 by the American College of Cardiology Foundation
Predicted Probability of Mortality or Major Morbidity According to Gait Speed and the STS Risk Score

Slow gait speed (solid circles) conferred a 2- to 3-fold increase in risk for any given level of Society of Thoracic Surgeons (STS) predicted mortality or major morbidity compared with normal gait speed (open circles). The adjusted odds ratio for mortality or major morbidity was 3.05 (95% confidence interval: 1.23 to 7.54).
Intensive blood pressure control, gait speed, and mobility limitation: The Systolic Blood Pressure Intervention Trial (SPRINT)
How do SPRINT results compare with ACCORD?

**ACCORD (Primary outcome: nonfatal MI nonfatal stroke, CVD death)**

- Intensive treatment: SBP <120 mmHg
- Standard treatment: SBP <140 mmHg

<table>
<thead>
<tr>
<th>Hazard ratio: 0.88  (95% CI, 0.73–1.06)</th>
<th>p=0.20</th>
</tr>
</thead>
<tbody>
<tr>
<td>Years post-randomization</td>
<td></td>
</tr>
<tr>
<td>0 1 2 3 4 5 6 7 8</td>
<td></td>
</tr>
<tr>
<td>Patients with events (%)</td>
<td></td>
</tr>
<tr>
<td>0 5 10 15 20</td>
<td></td>
</tr>
</tbody>
</table>

**SPRINT (Primary outcome: MI, non-MI ACS, stroke, heart failure, CVD death)**

- Intensive treatment: SBP <120 mmHg
- Standard treatment: SBP <140 mmHg

<table>
<thead>
<tr>
<th>Hazard ratio with intensive treatment: 0.75 (95% CI, 0.64–0.89)</th>
<th>p&lt;0.001</th>
</tr>
</thead>
<tbody>
<tr>
<td>Cumulative hazard</td>
<td></td>
</tr>
<tr>
<td>0 0.00 0.02 0.04 0.06 0.08 0.10</td>
<td></td>
</tr>
</tbody>
</table>

0 1 2 3 4 5

How do SPRINT results compare with SPS-3?

**SPS3**: No difference in CV events† in prior stroke patients with BP <130 (lower-target group) and <150 mmHg (higher-target group)¹

Hazard ratio: 0.81 (95% CI, 0.64–1.03) 

p=0.08

**SPRINT (Primary outcome: MI, non-MI ACS, stroke, heart failure, CVD death)**²

Hazard ratio with intensive treatment: 

0.75 (95% CI, 0.64–0.89) 

p<0.001

†Recurrent stroke, MI, or vascular death BUT significant benefit of lower BP target in reducing risk of intracerebral haemorrhage. Mean baseline SBP: 144 ±SD 19 mmHg (higher-target); 142 ±SD 19 mmHg (lower-target)

How do SPRINT results compare with VALUE?

**VALUE:** Primary endpoint† vs. mean SBP during the treatment period†

*Note. VALUE was not a randomized trial between target pressures*

---

**SPRINT (Primary outcome: MI, non-MI ACS, stroke, heart failure, CVD death)**

Hazard ratio with intensive treatment: 0.75 (95% CI, 0.64–0.89)  
*p*<0.001

<table>
<thead>
<tr>
<th>Years post-randomization</th>
<th>Cumulative hazard</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>0.00</td>
</tr>
<tr>
<td>1</td>
<td>0.02</td>
</tr>
<tr>
<td>2</td>
<td>0.04</td>
</tr>
<tr>
<td>3</td>
<td>0.06</td>
</tr>
<tr>
<td>4</td>
<td>0.08</td>
</tr>
<tr>
<td>5</td>
<td>0.10</td>
</tr>
</tbody>
</table>

---

†Time to first cardiac event (fatal or nonfatal MI, sudden cardiac death, death from revascularization procedures, HF requiring hospitalization, and emergency procedures to prevent MI

---

HOPE-3 evaluated antihypertensive therapy in a low-risk population

**Objective:**
- Evaluate the following in preventing major CV events in patients at low risk* (N=12,705; 21 countries):
  - LDL-C-lowering with rosvastatin 10 mg/day vs placebo
  - BP-lowering with candesartan/hydrochlorothiazide (HCTZ) 16/12.5 mg/day vs placebo
  - The combination of both vs double placebo

**Primary outcomes:**
- Composite of CV death, nonfatal MI, and nonfatal stroke
- Composite of CV death, nonfatal MI, nonfatal stroke, resuscitated cardiac arrest, heart failure, and revascularization

*No previous CVD, no strictly defined cholesterol or BP levels upon entry, and having received lifestyle advice.

CVD, cardiovascular disease; HOPE-3, Heart Outcomes Prevention Evaluation; MI, myocardial infarction
SPRINT vs ACCORD

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Event Rate per Year with Standard Treatment percent</th>
<th>Risk Ratio (95% CI)</th>
<th>P Value for Heterogeneity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Nonfatal myocardial infarction</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPRINT</td>
<td></td>
<td>0.39 (0.74–1.07)</td>
<td>0.8</td>
</tr>
<tr>
<td>ACCORD trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Stroke</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPRINT</td>
<td></td>
<td>0.75 (0.58–0.97)</td>
<td>0.1</td>
</tr>
<tr>
<td>ACCORD trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Heart failure</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPRINT</td>
<td></td>
<td>0.77 (0.62–0.95)</td>
<td>0.07</td>
</tr>
<tr>
<td>ACCORD trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Primary outcome as defined in each trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SPRINT</td>
<td></td>
<td>0.81 (0.72–0.92)</td>
<td>0.2</td>
</tr>
<tr>
<td>ACCORD trial</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Combined</td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
### INTENSIVE VS STANDARD TREATMENT OF BP IN ACCORD CKD AND NON-CKD PATIENTS

#### CKD group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate/Year (N=1000)</th>
<th>Rate/Year (N=1804)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Intensive to Standard Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td>2.70%</td>
<td>3.19%</td>
<td>0.86 (0.67, 1.11)</td>
<td></td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NonFatal MI</td>
<td>1.88%</td>
<td>1.84%</td>
<td>0.89 (0.63, 1.24)</td>
<td></td>
</tr>
<tr>
<td>Any Stroke</td>
<td>0.30%</td>
<td>0.62%</td>
<td>0.60 (0.36, 1.08)</td>
<td></td>
</tr>
<tr>
<td>NonFatal Stroke</td>
<td>0.46%</td>
<td>0.72%</td>
<td>0.64 (0.36, 1.15)</td>
<td></td>
</tr>
<tr>
<td>Death Any Cause</td>
<td>1.79%</td>
<td>2.13%</td>
<td>0.86 (0.63, 1.16)</td>
<td></td>
</tr>
<tr>
<td>CVD Death</td>
<td>0.78%</td>
<td>0.85%</td>
<td>0.93 (0.57, 1.49)</td>
<td></td>
</tr>
<tr>
<td>PO/Reu/NonFatalCHF</td>
<td>7.74%</td>
<td>7.19%</td>
<td>1.01 (0.64, 1.57)</td>
<td></td>
</tr>
<tr>
<td>Major Coronary</td>
<td>3.12%</td>
<td>3.41%</td>
<td>3.90 (0.70, 1.15)</td>
<td></td>
</tr>
<tr>
<td>Any CHF</td>
<td>1.40%</td>
<td>1.51%</td>
<td>3.92 (0.63, 1.32)</td>
<td></td>
</tr>
</tbody>
</table>

#### Non-CKD group

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Rate/Year (N=1000)</th>
<th>Rate/Year (N=1804)</th>
<th>Hazard Ratio (95% CI)</th>
<th>Intensive to Standard Hazard Ratio</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary Outcome</td>
<td></td>
<td></td>
<td>0.86 (0.67, 1.17)</td>
<td></td>
</tr>
<tr>
<td>Secondary Outcomes</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>NonFatal MI</td>
<td>0.82%</td>
<td>0.94%</td>
<td>0.97 (0.60, 1.23)</td>
<td></td>
</tr>
<tr>
<td>Any Stroke</td>
<td>0.17%</td>
<td>0.38%</td>
<td>0.45 (0.22, 0.86)</td>
<td></td>
</tr>
<tr>
<td>NonFatal Stroke</td>
<td>0.17%</td>
<td>0.34%</td>
<td>0.50 (0.25, 0.99)</td>
<td></td>
</tr>
<tr>
<td>Death Any Cause</td>
<td>0.87%</td>
<td>0.70%</td>
<td>1.41 (0.88, 2.02)</td>
<td></td>
</tr>
<tr>
<td>CVD Death</td>
<td>0.36%</td>
<td>0.30%</td>
<td>1.22 (0.68, 2.17)</td>
<td></td>
</tr>
<tr>
<td>PO/Reu/NonFatalCHF</td>
<td>3.00%</td>
<td>4.27%</td>
<td>0.00 (0.76, 1.08)</td>
<td></td>
</tr>
<tr>
<td>Major Coronary</td>
<td>1.81%</td>
<td>1.86%</td>
<td>0.96 (0.76, 1.26)</td>
<td></td>
</tr>
<tr>
<td>Any CHF</td>
<td>0.35%</td>
<td>0.36%</td>
<td>0.87 (0.50, 1.49)</td>
<td></td>
</tr>
</tbody>
</table>

Papademetriou. Tsioufis.....Doumas; AJN 2016
CHANGE IN ANY STROKE IN ACCORD CKD AND NON-CKD PATIENTS

P<0.001

Papademetriou. Tsioufis.....Doumas; AJN 2016
CHANGE IN NON-FATAL STROKE IN ACCORD CKD AND NON-CKD PATIENTS

P < 0.05

Papademetriou, Tsioufis,...Doumas; AJN 2016
Figure 2: Number of U.S. Adults Meeting SPRINT Eligibility Criteria, Overall and Among Those With Treated Hypertension

See Online Table 2 for the numbers and 95% confidence intervals in the figure. Abbreviations as in Figure 1.
MORE DATA FROM SPRINT ARE COMING

- SPRINT-MIND
  - Mini-mental test at closing---underway
- SPRINT ABPM
  - Correlation with events
  - Correlation with office BP
- Details of gait, fragility, fractures, renal function
- Visit to visit variability
- Intensive Rx in pre-diabetics
- Assessment by diastolic BP
- Renal outcomes etc
- More that 104 proposals for manuscripts
Intensive treatment of bp works and saves lives

Intensive treatment is safe and low BPs are achievable in most pts

Low BPs are well tolerated even in the very old

Effects on the kidney seem to be due to hemodynamic changes

Benefits from BP control are not drug specific

BP control should be achieved by the least intrusive means
HOW TO CONTROL BP

- Use drugs that are effective
- Use drugs that are safe and well tolerated
- Combinations with complementary mechanism of action
- Try to establish and maintain compliance
- Be aware of cost
- Expensive is not necessarily better.
- See patients frequently
- Use the SPRINT approach
Services are provided through a network of 151 Medical Centers, 300 Vet Centers, 827 Community-based Outpatient Clinics (CBOC), 135 Community Living Centers, 6 Independent Outpatient Clinics, and 103 Residential Rehabilitation Centers
Hypertension Control by Age

Mean Percent Controlled

Year-month

Fletcher, Papademetriou AHA
4,353,383 Hypertensive Patients
HOW WILL SPRINT AFFECT YOUR PRACTICE

- **In every way, it will change everything**
  - It will change practice
  - It will change targets; Treat 130 or more, target <120 systolic
  - It will change methods of measurement
  - It may decrease need for home BPs
  - It may decrease need for ABPM
  - It will need more office visits
  - It will need more lab tests
  - It will need more medicine, would it be cost-effective?

- **It will**
  - Save lives
  - Improve morbidity
  - Decrease hospitalizations and
  - May save money
PCSK9 INHIBITORS: SECOND REVOLUTION IN CV DISEASE

(The first was the revolution of statins)

Vasilios Papademetriou, MD
Professor of Medicine
Georgetown University
Almost two decades the 4S first showed that simvastatin effectively improve survival in patients with cardiovascular disease (CVD), and initiated a revolution in the treatment of atherosclerotic heart disease.

Results with other statins confirmed and enhanced these results.

Other newer and/or novel compounds were abandoned either because of lack of efficacy or unacceptable side effects.

Recently ezetimibe-in the IMPROVE-IT study- showed further improvement of outcomes when added to a statin.

Yet the incremental reduction of LDL-C was modest and additional benefits small, but the study confirmed the impression that “Lower is better”.

That’s where PCSK9 in come into play.
Recently the Food and Drug Administration (FDA) approved **alirocumab** and **evolocumab**, PCSK9 inhibitors, for the treatment of hyperlipidemia.

More specifically these to be used as an:

“adjunct to diet and maximally tolerated statin therapy for the treatment of adults with heterozygous familial hypercholesterolemia or clinical atherosclerotic cardiovascular disease, who require additional lowering of LDL [low-density lipoprotein]-cholesterol.”

A third PCSK9 inhibitor-**Bococizumab**- is under intensive investigation
Why is this so important?
Are very potent LDL reducing agents
Lower LDL to levels we have never seen before
Their mechanism of action is favorable, work well with statins and work like statins
Have the potential of eliminating CV events ??
Have the potential of eliminating atherosclerosis ??

BUT

Have issues and Limitations:
They are injectable proteins/antibodies
May cause side effects
Are expensive ( $14,000.00/year in the US)
WHAT ARE THE PCSK9 INHIBITORS

- PCSK9 is a protein
- Proprotein convertase subtilisin kexin 9 (PCSK9) is produced predominantly in the liver
- Its job is to tag the LDL receptors for destruction
- PCSK9 inhibitors prevent that by binding PCSK9
- Another small molecule the “interfering RNA (siRNA)”, can cause direct degradation of messenger RNA that leads to production of PCSK9
- It is currently under intense investigation. A single dose of siRNA resulted in 70% reduction of circulating PCSK9 and 40% reduction in LDL cholesterol
The first suggestion of a link between PCSK9 and hypercholesterolemia was published in 2003.

The progress from PCSK9 discovery to the development of targeted treatment has been unprecedented in terms of scale and speed.

PCSK9 inhibition is now considered an exciting and revolutionary approach in the reduction of residual risk of cardiovascular disease.

Can reduce LDL to its infancy levels.
Total Cholesterol Levels Increase During Development and Remain Higher Than Those in Hunter-Gatherer Populations

TC Changes During Fetal Development Through Adulthood

- **Birth**
  - Breast fed
  - Formula diet
- **Weaned**
  - High fat
  - Low fat

Distribution of Total Serum Cholesterol Levels in ~34,000 US Adults From NHANES III (1988–1994)

Cholesterol levels for modern hunter-gatherer populations range from:

- 101 mg/dL to 146 mg/dL

Exact N is not available for Hunter-gatherer data, but is likely in the hundreds.

---

LDL-C Levels Rise After Adulthood and Remain Higher Than Those in Early Development

Mean LDL-C by Age

<table>
<thead>
<tr>
<th>Age</th>
<th>Mean LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>33-34</td>
<td>49</td>
</tr>
<tr>
<td>41-42</td>
<td>28</td>
</tr>
<tr>
<td>4-5</td>
<td>48</td>
</tr>
<tr>
<td>5-9</td>
<td>83</td>
</tr>
<tr>
<td>20-39</td>
<td>113</td>
</tr>
<tr>
<td>40-59</td>
<td>124</td>
</tr>
<tr>
<td>60-74</td>
<td>123</td>
</tr>
</tbody>
</table>

Average LDL-C Levels in the US

<table>
<thead>
<tr>
<th>Years</th>
<th>LDL-C (mg/dL)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1988-1994</td>
<td>129</td>
</tr>
<tr>
<td>1999-2002</td>
<td>123</td>
</tr>
<tr>
<td>2007-2010</td>
<td>116</td>
</tr>
</tbody>
</table>

*Formula fed.  ‡Breast fed.  ∞Umbilical cord plasma concentrations

*NHANES trends in mean LDL-C serum levels of US adult respondents from 1999-2006, estimates are age adjusted to the 2000 standard US population using the direct method.  †Mean age-adjusted LDL-C levels- approx. 15,000 US adults from NHANES (1988-2010)

Why Are PSCK9 Inhibitors Important?

- Are considered a breakthrough in the management of dyslipidemias because
  - Are safe and
  - Very-very effective
SAFE BECAUSE ARE HUMANIZED MONOCLONAL ANTIBODIES

Monoclonal Antibody Evolution

- **e.g. irbritumomab**
  - Highly immunogenic
  - 100% Mouse

- **e.g. rituximab and abciximab**
  - Still immunogenic
  - ~30% Mouse

- **e.g. trastuzumab and bevacizumab**
  - Still immunogenic
  - ~5-10% Mouse

- **e.g. adalimumab and panitumumab**
  - Least immunogenic

**Categories:***
- Mouse variable
- Mouse constant
- Human variable
- Human constant

**Generations:**
- Fully Mouse (1st generation)
- Chimeric (2nd generation)
- Humanised (3rd generation)
- “Fully” Human (4th generation)
ANOTHER CAVEAT: STATINS INCREASE PCSK9 LEVELS

Effect of statin therapy on plasma proprotein convertase subtilisin kexin 9 (PCSK9) concentrations: a systematic review and meta-analysis of clinical trials

A. Sahebkar¹,², L. E. Simental-Mendia³, F. Guerrero-Romero³, J. Golledge⁴,⁵ & G. F. Watts⁶

¹ Biotechnology Research Centre, Mashhad University of Medical Sciences, Mashhad, Iran
² Metabolic Research Centre, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Australia
³ Biomedical Research Unit, Mexican Social Security Institute, Durango, Mexico
⁴ Vascular Biology Unit, Queensland Research Centre for Peripheral Vascular Disease, College of Medicine and Dentistry, James Cook University Townsville, Townsville, Queensland, Australia
⁵ Department of Vascular and Endovascular Surgery, The Townsville Hospital, Townsville, Queensland, Australia
⁶ Lipid Disorders Clinic, Cardiovascular Medicine, Royal Perth Hospital, School of Medicine and Pharmacology, University of Western Australia, Perth, Western Australia, Australia

-Meta-analysis from 15 studies with 19 treatment arms
-A total of 2691 subjects, with 1973 in the statin arm and 718 in the control arm.
-Changes in PCSK9 levels were irrespective of the type of statin

Diabetes, Obesity and Metabolism 17: 1042–1055, 2015.
### Change in PCSK9 Levels After Statin Therapy

#### Study name

<table>
<thead>
<tr>
<th>Study name</th>
<th>Difference in means</th>
<th>Statistics for each study</th>
<th>Differences in means and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>26.000</td>
<td>25.373 to 26.627</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>20.000</td>
<td>19.312 to 20.688</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>15.000</td>
<td>6.029 to 23.971</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>A</td>
<td>38.000</td>
<td>-1.742 to 77.742</td>
<td>p = 0.061</td>
</tr>
<tr>
<td>A</td>
<td>90.000</td>
<td>41.037 to 139.963</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>101.000</td>
<td>48.005 to 153.995</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>42.000</td>
<td>-85.159 to 169.509</td>
<td>p = 0.516</td>
</tr>
<tr>
<td>A</td>
<td>245.700</td>
<td>191.108 to 300.232</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>44.000</td>
<td>-10.850 to 102.860</td>
<td>p = 0.177</td>
</tr>
<tr>
<td>A</td>
<td>57.000</td>
<td>36.001 to 77.743</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>100.000</td>
<td>36.213 to 77.785</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>57.000</td>
<td>36.213 to 77.785</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>59.000</td>
<td>-25.919 to 143.919</td>
<td>p = 0.173</td>
</tr>
<tr>
<td>A</td>
<td>76.000</td>
<td>41.176 to 110.824</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>59.300</td>
<td>43.803 to 64.207</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>32.000</td>
<td>-40.810 to 110.810</td>
<td>p = 0.420</td>
</tr>
<tr>
<td>A</td>
<td>40.715</td>
<td>34.795 to 46.647</td>
<td>p = 0.000</td>
</tr>
</tbody>
</table>

#### Grouped by Type of Statin

<table>
<thead>
<tr>
<th>Group by Statin type</th>
<th>Study name</th>
<th>Difference in means</th>
<th>Statistics for each study</th>
<th>Differences in means and 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>A</td>
<td>Careskey et al., 2008</td>
<td>15.000</td>
<td>0.029 to 29.971</td>
<td>p = 0.001</td>
</tr>
<tr>
<td>A</td>
<td>Guo et al., 2013a</td>
<td>38.000</td>
<td>-1.742 to 77.742</td>
<td>p = 0.061</td>
</tr>
<tr>
<td>A</td>
<td>Guo et al., 2013b</td>
<td>90.000</td>
<td>41.037 to 139.963</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>Guo et al., 2014</td>
<td>101.000</td>
<td>48.005 to 153.995</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>Cost et al., 2010</td>
<td>42.000</td>
<td>-85.159 to 169.509</td>
<td>p = 0.516</td>
</tr>
<tr>
<td>A</td>
<td>Mayne et al., 2008</td>
<td>44.000</td>
<td>-10.850 to 102.860</td>
<td>p = 0.177</td>
</tr>
<tr>
<td>A</td>
<td>Weller et al., 2010</td>
<td>45.000</td>
<td>35.268 to 54.732</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>A</td>
<td>47.552</td>
<td>24.872 to 70.233</td>
<td>p = 0.000</td>
<td></td>
</tr>
<tr>
<td>R</td>
<td>Amin et al., 2012a</td>
<td>26.000</td>
<td>25.373 to 26.627</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>R</td>
<td>Amin et al., 2012b</td>
<td>20.000</td>
<td>10.312 to 20.688</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>R</td>
<td>Kawashiri et al., 2012</td>
<td>245.700</td>
<td>191.108 to 300.232</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>R</td>
<td>26.443</td>
<td>10.565 to 33.322</td>
<td>p = 0.000</td>
<td></td>
</tr>
<tr>
<td>S</td>
<td>Thousch et al., 2014</td>
<td>59.000</td>
<td>53.758 to 64.089</td>
<td>p = 0.000</td>
</tr>
<tr>
<td>S</td>
<td>Berthold et al., 2013</td>
<td>32.000</td>
<td>-40.810 to 110.810</td>
<td>p = 0.425</td>
</tr>
<tr>
<td>S</td>
<td>58.924</td>
<td>53.758 to 64.089</td>
<td>p = 0.000</td>
<td></td>
</tr>
</tbody>
</table>
PSCK9 INHIBITORS HAVE BEEN APPROVED FOR ASCVD AND FH

Clinical ASCVD

- Defined in 2013 ACC/AHA guidelines as one or more of the following: \(^1,2\)
  - Coronary heart disease (CHD)
    - Acute coronary syndrome
    - History of myocardial infarction (MI)
    - Stable or unstable angina (UA)
    - Coronary or other arterial revascularization
  - Stroke or transient ischemic attack
  - Peripheral arterial disease

Familial Hypercholesterolemia (FH) \(^2-4\)

- Inherited conditions characterized by elevated LDL-C and mutations in genes involved in LDL metabolism \(^3\)

Heterozygous FH

- LDL-C \(\geq 190 \text{ mg/dL}^{3,*}\)
- Identification \(^4\)
  - Elevated LDL-C with physical findings or family history
  - OR
  - DNA-based evidence

Homozygous FH

- LDL-C \(> 500 \text{ mg/dL}^{5,*}\)
- CVD diagnosis on average at 20 years \(^3\)
GUIDELINES ARE CONFUSING

>50% reduction

% LDL-C Reduction*

ACC/AHA Guidelines\(^1,2\)

ADA Recommendations\(^3\)

NLA Recommendations\(^4\)

AACE Guidelines\(^5\)

IAS Recommendations\(^6\)

ESC/EAS Guidelines\(^7,\dagger\)

ASCVD = atherosclerotic cardiovascular disease; ACC = American College of Cardiology; AHA = American Heart Association; ADA = American Diabetes Association; NLA = National Lipid Association; AACE = American Association of Clinical Endocrinologists; IAS = International Atherosclerosis Society; ESC = European Society of Cardiology; EAS = European Atherosclerosis Society.

*Percent LDL-C reduction defines treatment intensity and assesses adherence;\(^1\) \(\dagger\)also includes percent LDL-C reduction as an efficacy metric.\(^7\)
Despite Treatment Many US Adults With CHD* Are Not Achieving Prespecified LDL-C Levels

Treated Patients From NHANES

- 28% Achieving LDL-C < 70 mg/dL
- 72% Not achieving LDL-C < 70 mg/dL

NHANES = National Health and Nutrition Examination Survey

*NHANES defined CHD based on answers to questions about CHD, angina, and MI from patient surveys
HOW LDL PARTICLES ARE CLEARED

LDL Particles Are Cleared From the Plasma by Binding to LDL Receptors and Being Internalized by the Hepatocyte

1. LDL binds to LDL receptor
2. LDL/LDL receptor complex internalized by hepatocyte
3. LDL degraded in lysosome
4. LDL receptor recycled to cell surface
PSCK9 TAGS LDL-R FOR DESTRUCTION

PCSK9 Binds to the LDL Receptor and Targets the LDL Receptor for Degradation

1. PCSK9: made in hepatocyte, secreted
2. PCSK9 binds to LDL receptor
3. Internalization of entire complex
4. LDL receptor as part of entire complex is degraded
5. LDL receptor not recycled
EVOLOCUMAB BINDS TO PCSK9
PREVENTING IT FROM BINDING THE LDL RECEPTORS

LDL receptors can recycle to hepatocyte surface to clear more plasma LDL
Across Four Clinical Trials, Repatha™ Demonstrated Significant LDL-C Reduction

as an adjunct to diet in: adults with HeFH or clinical ASCVD on maximally tolerated statin therapy or patients with HoFH on other LDL-lowering therapies

**COMBINATION WITH STATIN THERAPY IN CLINICAL ASCVD**

- LAPLACE-2 (Study 1)
  - Mean Baseline LDL-C: 108 mg/dL
  - N = 296

**52-WEEK EFFICACY AND SAFETY IN CLINICAL ASCVD**

- DESCARTES (Study 2)
  - Mean Baseline LDL-C: 105 mg/dL
  - N = 139

**FAMILIAL HYPERCHOLESTEROLEMIA**

- RUTHERFORD-2 (Study 3)
  - Heterozygous
  - N = 329
- TESLA (Study 4)
  - Homozygous
  - N = 49

*Maximally tolerated includes patients who have been optimized on statins or cannot tolerate any statin type or dose.*
Repatha™ + a Statin Achieved Intensive LDL-C Reduction Up to 77% vs Placebo\(^1,2\)

**Repatha™ 140 mg Q2W + or Placebo +**

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dose</th>
<th>LDL-C Reduction</th>
<th>Treatment Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atorvastatin</td>
<td>80 mg</td>
<td>-64%</td>
<td>-63%</td>
</tr>
<tr>
<td>Rosuvastatin</td>
<td>40 mg</td>
<td>-65%</td>
<td>-66%</td>
</tr>
<tr>
<td>Simvastatin</td>
<td>40 mg</td>
<td>-64%</td>
<td>-77%</td>
</tr>
</tbody>
</table>

**Mean % Change in LDL-C From Baseline to Week 12**

- Atorvastatin 80 mg: -1%
- Rosuvastatin 40 mg: 2%
- Simvastatin 40 mg: 13%

**N = 147**

- Red: Repatha™ 140 mg Q2W + statin
- Gray: Placebo + statin

**P < 0.0001 for all arms represented**

Estimates based on a multiple imputation model that accounts for treatment adherence.\(^1\)
Repatha™ Helped Up to 90% of Patients Achieve LDL-C < 70 mg/dL

Repatha™ 140 mg Q2W +

Percent of patients achieving LDL-C < 70 mg/dL at week 12

- Atorvastatin 80 mg: 90%
- Rosuvastatin 40 mg: 88%
- Simvastatin 40 mg: 87%

N = 95

Repatha™ provided intensive, predictable LDL-C reduction regardless of statin type studied.
Intensive LDL-C Reduction With Repatha™ Was Maintained Over 52 Weeks

**Percent Change in LDL-C at Week 52: Placebo vs Repatha™**

- **Placebo QM + background therapy**:
  - Baseline: -60%
  - Week 12: -70%
  - Week 24: -65%
  - Week 36: -55%
  - Week 52: -52%

- **Repatha™ 420 mg QM + background therapy**:
  - Baseline: 0%
  - Week 12: 0%
  - Week 24: 0%
  - Week 36: 0%
  - Week 52: 2%

**Mean % Change in LDL-C From Baseline to Week 52**

- **N = 139**
- **P < 0.0001**

- Multicenter, double-blind, randomized, placebo-controlled, 52-week study of Repatha™ in 139 patients with clinical ASCVD
- In this study, Repatha™ was administered as the 420 mg once monthly dose. The 140 mg every 2 weeks or 420 mg once monthly doses yield similar reductions in LDL-C

**QM = once monthly.**

Error bars indicate 95% CI; LDL-C measured via ultracentrifugation; Estimates based on a multiple imputation model that accounts for treatment adherence.

*Atorvastatin 80 mg with or without 10 mg ezetimibe daily.*
In HeFH, Repatha™ Lowered LDL-C an Additional 61% vs Placebo When Combined With Background Therapy.¹ ²

![Bar graph showing mean % change in LDL-C from baseline to week 12.]

- Repatha™ 140 mg Q2W + background therapy* (n = 110)
- Placebo + background therapy* (n = 54)

*P < 0.0001 for treatment difference

68% of patients receiving Repatha™ + background therapy achieved LDL-C < 70 mg/dL compared with 2% of patients receiving placebo + background therapy.¹

Estimates based on a multiple imputation model that accounts for treatment adherence.¹
*Background therapy included statins with or without other lipid-lowering therapies; †baseline LDL-C 156 mg/dL.
Repatha™ Was Studied in Patients With HoFH\textsuperscript{1,2}

The safety and effectiveness of Repatha™ have not been established in pediatric patients with HoFH who are younger than 13 years old.

\textsuperscript{1}Key exclusion criteria included New York Heart Association Class III or IV heart failure or last known left ventricular ejection fraction < 30\%, uncontrolled serious cardiac arrhythmia or MI within 3 months prior to enrollment, and uncontrolled hypertension. Patients who previously received Repatha™ or any other investigational therapy to inhibit PCSK9 were also excluded;\textsuperscript{2} other lipid-lowering therapies (eg, statins, ezetimibe).
### Baseline Characteristics for Patients With HoFH

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>All patients with HoFH (n=49)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years), mean</td>
<td>31</td>
</tr>
<tr>
<td>Female (%)</td>
<td>49</td>
</tr>
<tr>
<td>Male (%)</td>
<td>51</td>
</tr>
<tr>
<td>Race: White (%)</td>
<td>90</td>
</tr>
<tr>
<td>LDL-C (mg/dL), mean</td>
<td>349</td>
</tr>
<tr>
<td>Statin (atorvastatin or rosuvastatin) (%)</td>
<td>100</td>
</tr>
<tr>
<td>Ezetimibe (%)</td>
<td>92</td>
</tr>
</tbody>
</table>
In HoFH, Repatha™ Lowered LDL-C 31% More Than Placebo When Combined With Background Therapy

- Repatha™ 420 mg QM + background therapy* (n = 33)
- Placebo + background therapy* (n = 16)

$P < 0.0001$ for treatment difference

Estimates based on a multiple imputation model that accounts for treatment adherence.
*Other lipid-lowering therapies (eg, statins, ezetimibe).
Repatha™ Had an Additional Impact on Key Lipid Parameters in Patients With HoFH

- Non-HDL-C: -20% (8% reduction)
- ApoB: -17% (4% reduction)
- TC: -17% (8% reduction)

Repatha™ 420 mg QM + background therapy* (n = 33)
Placebo + background therapy* (n = 16)

Estimates based on a multiple imputation model that accounts for treatment adherence.
*Other lipid-lowering therapies (eg, statins, ezetimibe).
STUDIES WITH ALIROCUMAB

- Long term studies and
- Studies in Familial hypercholesterolemia
Calculated LDL-C Levels over Time

ITT Analysis

- Placebo + maximally tolerated statin ± other LLT
- Alirocumab + maximally tolerated statin ± other LLT

Least-squares mean calculated LDL-C Level (mg/dL)

No. of pts with data available:
- Placebo: 780, 747, 716, 708, 694, 676, 659, 652
- Alirocumab: 1530, 1458, 1412, 1386, 1359, 1349, 1324, 1269

LONG TERM EFFICACY IN FH

Alirocumab Maintained Consistent LDL-C Reductions Over 52 Weeks

Achieved LDL-C Over Time on Background of Maximally-Tolerated Statin ± Other LLT

- Placebo: FH I, FH II
- Alirocumab: FH I, FH II

LDL-C, LS mean (SE), mmol/L

- 4.0 mmol/L
- 3.5 mmol/L
- 3.7 mmol/L
- 1.8 mmol/L
- 1.7 mmol/L

mg/dL

Week

Dose ↑ if LDL-C >70 mg/dL at W8

Intent-to-treat (ITT) Analysis
LLT = lipid-lowering therapy

Efficacy and Safety of Evolocumab in Reducing Lipids and Cardiovascular Events

Marc S. Sabatine, M.D., M.P.H., Robert P. Giugliano, M.D.,
Stephen D. Wiviott, M.D., Frederick J. Raal, M.B., B.Ch., M.Med., Ph.D.,
Dirk J. Blom, M.B., Ch.B., M.Med., Ph.D., Jennifer Robinson, M.D., M.P.H.,
Christie M. Ballantyne, M.D., Ransi Somaratne, M.D., Jason Legg, Ph.D.,
Scott M. Wasserman, M.D., Robert Scott, M.D., Michael J. Koren, M.D.,
and Evan A. Stein, M.D., Ph.D., for the Open-Label Study of Long-Term Evaluation against LDL Cholesterol (OSLER) Investigators

ABSTRACT
CHANGE IN LDL CHOLESTEROL

<table>
<thead>
<tr>
<th>No. at Risk</th>
<th>Baseline</th>
<th>4</th>
<th>12</th>
<th>24</th>
<th>36</th>
<th>48</th>
</tr>
</thead>
<tbody>
<tr>
<td>Standard therapy</td>
<td>1489</td>
<td>394</td>
<td>1388</td>
<td>1376</td>
<td>402</td>
<td>1219</td>
</tr>
<tr>
<td>Evolocumab</td>
<td>2976</td>
<td>864</td>
<td>2871</td>
<td>2828</td>
<td>841</td>
<td>2508</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Absolute reduction (mg/dl)</th>
<th>Standard therapy</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>60.4</td>
<td>73.4</td>
<td>70.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Percentage reduction</th>
<th>Standard therapy</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>45.3</td>
<td>60.9</td>
<td>58.8</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>P value</th>
<th>Standard therapy</th>
<th>Evolocumab</th>
</tr>
</thead>
<tbody>
<tr>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>
Figure 2. Cumulative Incidence of Cardiovascular Events.
Efficacy and Safety of Alirocumab in Reducing Lipids and Cardiovascular Events

Jennifer G. Robinson, M.D., M.P.H., Michel Farnier, M.D., Ph.D., Michel Krempf, M.D., Jean Bergeron, M.D., Gérald Luc, M.D., Maurizio Averna, M.D., Erik S. Stroes, M.D., Ph.D., Gisle Langslet, M.D., Frederick J. Raal, M.D., Ph.D., Mahfouz El Shahawy, M.D., Michael J. Koren, M.D., Norman E. Lepor, M.D., Christelle Lorenzato, M.Sc., Robert Pardy, M.D., Umesh Chaudhari, M.D., and John J.P. Kastelein, M.D., Ph.D., for the ODYSSEY LONG TERM Investigators*

ABSTRACT
CALCULATED LDL CHOLESTEROL LEVELS OVER TIME: ALIROCUMAB VS PLACEBO

Figure 2. Calculated LDL Cholesterol Levels over Time (Intention-to-Treat Analysis).

NEJM March 15 2015
ADVERSE AND CV EVENTS

- **Myalgia**
- **Neurogon.ev**
- **Opthal even**
- **CV event**

<table>
<thead>
<tr>
<th>Condition</th>
<th>Alirocumab</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Site inj react</td>
<td>6</td>
<td>4</td>
</tr>
<tr>
<td>Myalgia</td>
<td>5</td>
<td>3</td>
</tr>
<tr>
<td>Neurogon.ev</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Opthal even</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>CV event</td>
<td>3</td>
<td>2</td>
</tr>
</tbody>
</table>

P<0.2
<table>
<thead>
<tr>
<th>Trial name</th>
<th>Study drug</th>
<th>Patient population</th>
<th>Primary outcome</th>
<th>Follow-up</th>
</tr>
</thead>
<tbody>
<tr>
<td>FOURIERNCT</td>
<td>Evolocumab</td>
<td>n = 27,000; h/o CVD high risk of CV; LDL-C ≥70 mg/dL on statin therapy</td>
<td>Time to cardiovascular death, CV event</td>
<td>5 years</td>
</tr>
<tr>
<td>ODYSSEY OUTCOME</td>
<td>Alirocumab</td>
<td>n = 18,000; ACS &lt;52 weeks earlier; LDL-C ≥70 mg/dL or non-HDL-C ≥100 mg/dL; on statin therapy</td>
<td>Time to cardiovascular death CV event</td>
<td>64 months</td>
</tr>
<tr>
<td>SPIRE-1 NCT</td>
<td>Bococizumab</td>
<td>n = 17,000; high risk of CVD event, background lipid-lowering treatment; LDL-C 70–100 mg/dL</td>
<td>Time to composite major CV event</td>
<td>60 months</td>
</tr>
<tr>
<td>SPIRE-2 NCT</td>
<td>Bococizumab</td>
<td>n = 9000; high risk of CVD event; background lipid-lowering treatment; LDL-C ≥100 mg/dL</td>
<td>Time to composite major CV event</td>
<td>60 months</td>
</tr>
</tbody>
</table>
EFFECTS OF PCSK9 INHIBITORES IN ADULTS WITH HYPERCHOLESTEROLEMIA

Data from 22 phase 2 or 3 randomized, controlled trials (RCTs) comparing treatment using PCSK9 antibodies with no anti-PCSK9 therapy in adults with hypercholesterolemia were included.

A total of 10 159 patients were randomized to PCSK9 antibody or no antibody

TREATMENT WITH PCSK9 ANTIBODIES (N=10,159 PTS)

- LDL-C reduction: -47.5%
- All cause mortality: -55%
- CV mortality: -50%
- Myocardial Infarction: -51%
compared with no anti-PCSK9 treatment, use of PCSK9 antibodies is associated with:

- Lower odds of all-cause mortality and myocardial infarction and a statistically nonsignificant reduction in cardiovascular mortality;
- Marked reduction of LDL-C and Lp (a)
- Lower increase in the serum creatine kinase level;
- No increase in serious adverse events; and
- A marked reduction in atherogenic lipid fractions.

Improvements in clinical outcomes were consistent in multiple sensitivity analyses that used different methods of analysis.
A second revolution is happening in cardiology today. It is happening “RIGHT HERE and RIGHT NOW”.

Thank you very much!!!!!