Late Breaking Clinical Trial Vignettes

Martin C. Burke DO, FACOI
CorVita Science Foundation
&
Academic Medical Center, Amsterdam
Blood-Pressure and Cholesterol Lowering in Persons without Cardiovascular Disease

Salim Yusuf, M.B., B.S., D.Phil., Eva Lonn, M.D., Prem Pais, M.D., Jackie Bosch, Ph.D.,
Patricio López-Jaramillo, M.D., Ph.D., Jun Zhu, M.D., Denis Xavier, M.D.,
Alvaro Avezum, M.D., Ph.D., Lawrence A. Leiter, M.D., Leopoldo S. Piegas, M.D., Ph.D.,
Alexander Parkhomenko, M.D., Ph.D., Matyas Keltai, M.D., Ph.D.,
Katalin Keltai, M.D., Ph.D., Karen Sliwa, M.D., Ph.D., Irina Chazova, M.D., Ph.D.,
Ron J.G. Peters, M.D., Ph.D., Claes Held, M.D., Ph.D., Khalid Yusoff, M.D.,
Basil S. Lewis, M.D., Petr Jansky, M.D., Kamlesh Khunti, M.D., Ph.D.,
William D. Toff, M.D., Christopher M. Reid, Ph.D., John Varigos, B.Sc.,
Jose L. Accini, M.D., Robert McKelvie, M.D., Ph.D., Janice Pogue, Ph.D.,*
Hyejung Jung, M.Sc., Lisheng Liu, M.D., Rafael Diaz, M.D., Antonio Dans, M.D.,
and Gilles Dagenais, M.D., for the HOPE-3 Investigators†
HOPE-3- Background

• Investigators evaluated the effects of a MODERATE DOSE OF A POTENT STATIN VS PLACEBO, and

• A FIXED COMBINATION OF MODERATE DOSES OF AN ARB DIURETIC VS PLACEBO, and THE COMBINATION OF BOTH TREATMENTS VS DUAL PLACEBO on the prevention of major cardiovascular events.

• Both systolic blood pressure and low density lipoprotein (LDL) cholesterol show graded associations with cardiovascular disease.

• This profile accounts for two thirds of the population-attributable risk of cardiovascular disease.

NEJM 2016; 374: 2021-2031
TRIAL DESIGN AND OVERSIGHT

• The HEART OUTCOMES PREVENTION EVALUATION (HOPE)–3 trial is a multicenter, long-term, international, double-blind, randomized, placebo-controlled trial with a 2-by-2 factorial design among persons who did not have cardiovascular disease and who were at intermediate risk (defined as an annual risk of major cardiovascular events of approximately 1%).

• Conducted at 228 centers in 21 countries.

NEJM 2016; 374: 2021-2031
Figure S1: CONSORT Diagram for the Candesartan/HCTZ versus Placebo Comparison

14,682 included in Run-In

1,977 (13.5%) Excluded
- 509 (3.5%) Side effects
- 844 (5.7%) Compliance <80%
- 483 (3.3%) Unwilling to continue
- 141 (1.0%) Other reasons

12,705 Randomized (86.5%)

6,356 assigned to Candesartan/HCTZ
- 6,291 primary outcome status ascertained
  - 52 were lost to follow-up
  - 13 withdrew consent
- 6,356 were included in analysis
  - 0 were excluded from analysis

6,349 assigned to Placebo
- 6,301 primary outcome status ascertained
  - 38 were lost to follow-up
  - 10 withdrew consent
- 6,349 were included in analysis
  - 0 were excluded from analysis
Figure S2: CONSORT Diagram for the Rosuvastatin versus Placebo Comparison

14,682 included in Run-In

1,977 (13.5%) Excluded
509 (3.5%) Side effects*
844 (5.7%) Compliance <80%
483 (3.3%) Unwilling to continue
141 (1.0%) Other reasons

12,705 Randomized (86.5%)

6,361 assigned to Rosuvastatin
6,308 primary outcome status ascertained
45 were lost to follow-up
8 withdrew consent
6,361 were included in analysis
0 were excluded from analysis

6,344 assigned to Placebo
6,284 primary outcome status ascertained
45 were lost to follow-up
15 withdrew consent
6,344 were included in analysis
0 were excluded from analysis
Figure S3: CONSORT Diagram for the Double Active versus Double Placebo Comparison

14,682 Participants screened for eligibility

1,977 (13.5%) Excluded
- 509 (3.5%) Side effects*
- 844 (5.7%) Compliance <80%
- 483 (3.3%) Unwilling to continue
- 141 (1.0%) Other reasons

12,705 were randomized (86.5%)

3,180 assigned Cand/HCTZ Active Rosuvastatin Active
3,181 assigned Rosuvastatin Active Cand/HCTZ Placebo
3,176 assigned Cand/HCTZ Active Rosuvastatin Placebo
3,168 assigned Double Placebo

3,149 primary outcome status ascertained
- 27 were lost to follow up
- 4 withdrew consent

3,159 primary outcome status ascertained
- 18 were lost to follow up
- 4 withdrew consent

3,180 Included in analysis
3,181 Included in analysis
3,176 Included in analysis
3,168 Included in analysis

*Side effects: nausea, diarrhea, headache, and fatigue.
Table S1: The Heart Outcomes Prevention Evaluation (HOPE) - 3 Trial Design (N=12,705)

<table>
<thead>
<tr>
<th>Rosuvastatin</th>
<th>Candesartan/HCTZ</th>
<th>Rosuvastatin Margins</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Active</td>
<td>Placebo</td>
</tr>
<tr>
<td>Active</td>
<td>Rosuvastatin Active/ Candesartan/HCTZ Active n=3,180</td>
<td>Rosuvastatin Active/ Candesartan/HCTZ Placebo n=3,181</td>
</tr>
<tr>
<td>Placebo</td>
<td>Rosuvastatin Placebo/ Candesartan/HCTZ Active n=3,176</td>
<td>Rosuvastatin Placebo/ Candesartan/HCTZ Placebo n=3,168</td>
</tr>
<tr>
<td>Candesartan/HCTZ Margins</td>
<td>Candesartan/HCTZ Active n=6,356</td>
<td>Candesartan/HCTZ Placebo n=6,349</td>
</tr>
</tbody>
</table>

HCTZ=hydrochlorothiazide
TRIAL PROCEDURES

• Eligible persons entered a single-blind run-in phase, during which they received both active treatments for 4 weeks.

• Participants who adhered to the regimen and who did not have an unacceptable level of adverse events were randomly assigned to a fixed combination of CANDESARTAN (16 mg per day) and HYDROCHLOROTHIAZIDE (12.5 mg per day) or placebo and to ROSUVASTATIN (10 mg per day) or placebo.

NEJM 2016; 374: 2021-2031
Follow Up

• Follow-up visits occurred at 6 weeks and 6 months after randomization and every 6 months thereafter.

• Blood pressure was recorded at each visit in the first year and then annually.

• Lipid levels were measured at baseline in all participants and at 1 year, at 3 years, and at the end of the trial.
OUTCOMES

• There were two co-primary outcomes:
  1) the composite of death from cardiovascular causes, nonfatal myocardial infarction, or nonfatal stroke.
  2) the composite of these events plus resuscitated cardiac arrest, heart failure, or revascularization.

• The secondary outcome was the composite of events comprising the second co-primary outcome plus angina with evidence of ischemia.
## ADHERENCE TO TRIAL DRUGS

### Table S3: Adherence to Study Drug and Open Label Use of ARBs, ACE-Is and Thiazides in the Candesartan/HCTZ and Placebo Groups

#### A. Candesartan

<table>
<thead>
<tr>
<th>Visit</th>
<th>Eligible</th>
<th>On Study Drug</th>
<th>On Open Label</th>
<th>Other BP Lowering Drug(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Candesartan/HCTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cand/HCTZ N (%)</td>
<td>ARB N (%)</td>
<td>ACE-I N (%)</td>
</tr>
<tr>
<td>1 year</td>
<td>6314</td>
<td>5567(88.2)</td>
<td>14(0.2)</td>
<td>24(0.4)</td>
</tr>
<tr>
<td>2 years</td>
<td>6267</td>
<td>5374(85.8)</td>
<td>28(0.4)</td>
<td>41(0.7)</td>
</tr>
<tr>
<td>3 years</td>
<td>6205</td>
<td>5189(83.6)</td>
<td>45(0.7)</td>
<td>48(0.8)</td>
</tr>
<tr>
<td>4 years</td>
<td>6101</td>
<td>4967(81.4)</td>
<td>52(0.9)</td>
<td>59(1.0)</td>
</tr>
<tr>
<td>5 years</td>
<td>4854</td>
<td>3639(75.0)</td>
<td>60(1.2)</td>
<td>66(1.4)</td>
</tr>
<tr>
<td>End</td>
<td>5990</td>
<td>4599(76.8)</td>
<td>93(1.6)</td>
<td>100(1.7)</td>
</tr>
</tbody>
</table>

#### B. Placebo

<table>
<thead>
<tr>
<th>Visit</th>
<th>Eligible</th>
<th>On Study Drug</th>
<th>On Open Label</th>
<th>Other BP Lowering Drug(s)*</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Candesartan/HCTZ</td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td>Cand/HCTZ Placebo N (%)</td>
<td>ARB N (%)</td>
<td>ACE-I N (%)</td>
</tr>
<tr>
<td>1 year</td>
<td>6306</td>
<td>5545(87.9)</td>
<td>30(0.5)</td>
<td>48(0.8)</td>
</tr>
<tr>
<td>2 years</td>
<td>6262</td>
<td>5359(85.6)</td>
<td>66(1.1)</td>
<td>67(1.1)</td>
</tr>
<tr>
<td>3 years</td>
<td>6188</td>
<td>5161(83.4)</td>
<td>76(1.2)</td>
<td>82(1.3)</td>
</tr>
<tr>
<td>4 years</td>
<td>6089</td>
<td>4953(81.3)</td>
<td>106(1.7)</td>
<td>102(1.7)</td>
</tr>
<tr>
<td>5 years</td>
<td>4818</td>
<td>3588(74.5)</td>
<td>104(2.2)</td>
<td>110(2.3)</td>
</tr>
<tr>
<td>End</td>
<td>5985</td>
<td>4530(75.7)</td>
<td>146(2.4)</td>
<td>137(2.3)</td>
</tr>
</tbody>
</table>

NEJM 2016; 374: 2021-2031
BLOOD PRESSURE AND LIPID LEVELS

• On average, the mean SBP was lower by 6.2 mm Hg in the combined-therapy group than in the dual placebo group, the mean DBP was lower by 3.2 mm Hg, and the mean LDL cholesterol level was lower by 33.7 mg per deciliter.

• The difference in blood pressure was similar for participants assigned to candesartan–hydrochlorothiazide alone versus placebo.

• The difference in LDL cholesterol level was similar for participants assigned to rouvastatin alone versus placebo.

NEJM 2016; 374: 2021-2031
Table 2. Primary, Secondary, and Other Outcomes.‡

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Candesartan–Hydrochlorothiazide plus Rosuvastatin (N=3180)</th>
<th>Rosuvastatin plus Placebo (N=3181)</th>
<th>Candesartan–Hydrochlorothiazide plus Placebo (N=3176)</th>
<th>Placebo plus Placebo (N=3168)</th>
<th>Candesartan–Hydrochlorothiazide plus Rosuvastatin vs. Placebo plus Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratio (95% CI)</td>
<td>P Value</td>
<td>Hazard Ratio (95% CI)</td>
</tr>
<tr>
<td><strong>Coprimary outcomes — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>First coprimary outcome</td>
<td>113 (3.6)</td>
<td>122 (3.8) †</td>
<td>147 (4.6)</td>
<td>157 (5.0)</td>
<td>0.71 (0.56–0.90)</td>
</tr>
<tr>
<td>Second coprimary outcome</td>
<td>136 (4.3)</td>
<td>141 (4.5) †</td>
<td>176 (5.5)</td>
<td>187 (5.9)</td>
<td>0.55 (0.32–0.93)</td>
</tr>
<tr>
<td><strong>Secondary outcome — no. (%)</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from cardiovascular causes</td>
<td>75 (2.4)</td>
<td>79 (2.5)</td>
<td>80 (2.5)</td>
<td>91 (2.9)</td>
<td>0.82 (0.60–1.11)</td>
</tr>
<tr>
<td>Fatal or nonfatal myocardial infarction</td>
<td>21 (0.7)</td>
<td>24 (0.8)</td>
<td>31 (1.0)</td>
<td>38 (1.2)</td>
<td>0.55 (0.32–0.93)</td>
</tr>
<tr>
<td>Fatal or nonfatal stroke</td>
<td>31 (1.0)</td>
<td>39 (1.2)</td>
<td>44 (1.4)</td>
<td>55 (1.7)</td>
<td>0.56 (0.36–0.87)</td>
</tr>
<tr>
<td>Resuscitated cardiac arrest</td>
<td>1 (&lt;0.1)</td>
<td>3 (0.1)</td>
<td>1 (&lt;0.1)</td>
<td>3 (0.1)</td>
<td>0.33 (0.02–3.18)</td>
</tr>
<tr>
<td>Revascularization</td>
<td>27 (0.8)</td>
<td>25 (0.8)</td>
<td>37 (1.2)</td>
<td>45 (1.4)</td>
<td>0.59 (0.37–0.95)</td>
</tr>
<tr>
<td>Heart failure</td>
<td>10 (0.3)</td>
<td>11 (0.3)</td>
<td>11 (0.3)</td>
<td>18 (0.6)</td>
<td>0.55 (0.25–1.19)</td>
</tr>
<tr>
<td>Angina with objective evidence of ischemia</td>
<td>25 (0.8)</td>
<td>31 (1.0)</td>
<td>26 (0.8)</td>
<td>38 (1.2)</td>
<td>0.65 (0.38–1.08)</td>
</tr>
<tr>
<td><strong>Other outcomes</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death from any cause — no. (%)</td>
<td>163 (5.1)</td>
<td>171 (5.4)</td>
<td>179 (5.6)</td>
<td>178 (5.6)</td>
<td>0.91 (0.73–1.12)</td>
</tr>
<tr>
<td>New-onset diabetes — no./total no. (%)</td>
<td>123/2982 (4.1)</td>
<td>109/3001 (3.6)</td>
<td>113/2984 (3.8)</td>
<td>113/2999 (3.8)</td>
<td>1.06 (0.85–1.31)</td>
</tr>
<tr>
<td>Hospitalization — no. (%)***</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>For cardiovascular causes</td>
<td>141 (4.4)</td>
<td>140 (4.4)</td>
<td>178 (5.6)</td>
<td>191 (6.0)</td>
<td>0.73 (0.59–0.91)</td>
</tr>
<tr>
<td>For noncardiovascular causes</td>
<td>463 (14.6)</td>
<td>418 (13.1)</td>
<td>436 (13.7)</td>
<td>443 (14.0)</td>
<td>1.04 (0.92–1.19)</td>
</tr>
<tr>
<td><strong>First and recurrent events of the second coprimary outcome††</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of participants with ≥1 event</td>
<td>136</td>
<td>141</td>
<td>176</td>
<td>187</td>
<td></td>
</tr>
<tr>
<td>No. of participants with ≥2 events</td>
<td>29</td>
<td>39</td>
<td>30</td>
<td>59</td>
<td></td>
</tr>
<tr>
<td>No. of participants with ≥3 events</td>
<td>2</td>
<td>4</td>
<td>3</td>
<td>13</td>
<td></td>
</tr>
<tr>
<td>Total no. of events</td>
<td>169</td>
<td>184</td>
<td>211</td>
<td>262</td>
<td></td>
</tr>
</tbody>
</table>

* The first coprimary outcome was the composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke; the second coprimary outcome was the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, or revascularization; and the secondary outcome was the composite of cardiovascular death, nonfatal myocardial infarction, nonfatal stroke, resuscitated cardiac arrest, heart failure, revascularization, or angina with objective evidence of ischemia. CI denotes confidence interval.
Complications

- **No significant differences** between the combined-therapy group and the dual placebo group were seen in the rate of new-onset diabetes, renal dysfunction, syncope, liver-function abnormalities, eye problems, or cancers.

- The rates of muscle weakness or pain and of dizziness were higher in the combined-therapy group than in the dual-placebo group.

- These effects were reversible by temporary is continuation of the trial drug.

NEJM 2016; 374: 2021-2031
True Prevention

• Investigators approach of selecting persons on the basis of age and easily measured risk factors meant that neither complex screening nor blood tests are required to initiate treatment with low doses of combination therapy.

• Trial included persons of diverse racial and ethnic groups from 21 countries with broadly consistent benefits and safety.

NEJM 2016; 374: 2021-2031
CONCLUSION

• Treatment with fixed doses of rouvastatin and two antihypertensive agents was associated with a significantly lower risk of cardiovascular events than the risk with placebo among intermediate-risk persons without previous cardiovascular disease.

NEJM 2016; 374: 2021-2031
The Third DANish Study of Optimal Acute Treatment of Patients with ST-segment Elevation Myocardial Infarction: DEFERred stent implantation in connection with primary PCI: DANAMI 3-DEFER

Henning Kelbæk, MD, DMSci
Roskilde Hospital & Rigshospitalet
Zealand & Capitol Regions
Denmark

Lancet 2016; 387(10034): 2199-2206
Deferred versus conventional stent implantation in patients with ST-segment elevation myocardial infarction (DANAMI 3-DEFER): an open-label, randomised controlled trial


Summary

Background Despite successful treatment of the culprit artery lesion by primary percutaneous coronary intervention (PCI) with stent implantation, thrombotic embolisation occurs in some cases, which impairs the prognosis of patients with ST-segment elevation myocardial infarction (STEMI). We aimed to assess the clinical outcomes of deferred stent implantation versus standard PCI in patients with STEMI.

Methods We did this open-label, randomised controlled trial at four primary PCI centres in Denmark. Eligible patients (aged >18 years) had acute onset symptoms lasting 12 h or less, and ST-segment elevation of 0·1 mV or more in at least two or more contiguous electrocardiographic leads or newly developed left bundle branch block. Patients were
Aim of DANAMI-3-DEFER study

To evaluate whether the prognosis of STEMI patients treated with pPCI can be improved by deferred stent implantation

Lancet 2016; 387(10034): 2199-2206
Inclusion criteria:
• chest pain of <12 hours’ duration
• ST-segment elevation > 0·1 mV in at least 2 contiguous leads

Exclusion criteria
• Known intolerance of contrast media, anticoagulant or DAPT
• unconsciousness or cardiogenic shock
• stent thrombosis
• indication for acute CABG
• increased bleeding risk

Participants

Lancet 2016; 387(10034): 2199-2206
Flow Chart DANAMI-3

**STEMI**

- **Angiography**
  - **TIMI 0-I**
  - **TIMI 2-3**

**Randomization**

- **PCI**
  - **Postcon**
  - **Conv**
  - **Defer**

**Excluded**

*Lancet* 2016; 387(10034): 2199-2206
Primary endpoint

A composite of:

• All cause mortality
• Hospitalization for heart failure
• Re-infarction
• Target vessel revascularization
Methods

**DEFER:**
- Minimal acute manipulation to restore stable flow in IRA
- Stent implantation 48 hours later

*Conventional PCI:*
- Immediate stent implantation

Lancet 2016; 387(10034): 2199-2206
## Procedural Data

<table>
<thead>
<tr>
<th></th>
<th>Conventional (n = 612)</th>
<th>DEFER (n = 603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median stent diameter (mm)</td>
<td>3.5</td>
<td>3.5</td>
</tr>
<tr>
<td>Median stent length (mm)</td>
<td>22</td>
<td>18 *</td>
</tr>
<tr>
<td>No stenting</td>
<td>3%</td>
<td>15%*</td>
</tr>
<tr>
<td>Use of GP-inhibitor or Bivalirudin</td>
<td>92%</td>
<td>93%</td>
</tr>
<tr>
<td>Thrombus aspiration</td>
<td>58%</td>
<td>63%</td>
</tr>
</tbody>
</table>

**TIMI flow before PCI**

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>DEFER</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>38%</td>
<td>38%</td>
</tr>
<tr>
<td>2 - 3</td>
<td>62%</td>
<td>62%</td>
</tr>
</tbody>
</table>

**TIMI flow after PCI**

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>DEFER</th>
</tr>
</thead>
<tbody>
<tr>
<td>0 - 1</td>
<td>1.0%</td>
<td>1.0%</td>
</tr>
<tr>
<td>2 - 3</td>
<td>99%</td>
<td>99%</td>
</tr>
</tbody>
</table>

* P < 0.001  ** self-reported

Lancet 2016; 387(10034): 2199-2206
## Clinical Status at Discharge

<table>
<thead>
<tr>
<th></th>
<th>Conventional (n = 612)</th>
<th>DEFER (n = 603)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Killip Class II - IV at any time</td>
<td>7%</td>
<td>7%</td>
</tr>
<tr>
<td>Median LVEF</td>
<td>50%</td>
<td>50%</td>
</tr>
<tr>
<td>Medical treatment at discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Antiplaetelet drug</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Aspirin</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Clopidogrel / Prasugrel / Ticagrelor</td>
<td>99%</td>
<td>99%</td>
</tr>
<tr>
<td>Statin</td>
<td>98%</td>
<td>98%</td>
</tr>
<tr>
<td>Betablocker</td>
<td>90%</td>
<td>92%</td>
</tr>
<tr>
<td>ACE inhibitor or ARB</td>
<td>44%</td>
<td>41%</td>
</tr>
</tbody>
</table>

Lancet 2016; 387(10034): 2199-2206
Primary Endpoint

HR: 0.99 [0.75-1.29]; P=0.92

Lancet 2016; 387(10034): 2199-2206
Components of the primary endpoint

A. All cause mortality

HR: 0.83 [0.56 - 1.24]; P=0.37

B. Recurrent myocardial reinfarction

HR: 1.1 [0.69 - 1.64]; P=0.77

C. Hospitalisation for heart failure

HR: 0.82 [0.47 - 1.43]; P=0.49

D. Unplanned target vessel revascularisation

HR: 1.7 [1.04 - 2.92]; P=0.03

Lancet 2016; 387(10034): 2199-2206

Number at risk

<table>
<thead>
<tr>
<th></th>
<th>Conventional</th>
<th>Deferred</th>
</tr>
</thead>
<tbody>
<tr>
<td>All cause mortality</td>
<td>612</td>
<td>594 575 403 173 0</td>
</tr>
<tr>
<td>Recurrent myocardial reinfarction</td>
<td>612</td>
<td>586 554 379 165 0</td>
</tr>
<tr>
<td>Hospitalisation for heart failure</td>
<td>612</td>
<td>580 560 391 167 0</td>
</tr>
<tr>
<td>Unplanned target vessel revascularisation</td>
<td>612</td>
<td>587 561 387 170 0</td>
</tr>
</tbody>
</table>

Number at risk
Subgroup analysis

Lancet 2016; 387(10034): 2199-2206
## Secondary Endpoint

<table>
<thead>
<tr>
<th>Left ventricular ejection fraction (LVEF) at 18 months</th>
<th>Conventional</th>
<th>DEFER</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Median LVEF</td>
<td><strong>57%</strong></td>
<td><strong>60%</strong></td>
<td><strong>0.04</strong></td>
</tr>
<tr>
<td>Lancet 2016; 387(10034): 2199-2206</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No of patients with LVEF ≤45%</td>
<td><strong>18%</strong></td>
<td><strong>13%</strong></td>
<td><strong>0.05</strong></td>
</tr>
</tbody>
</table>

Lancet 2016; 387(10034): 2199-2206
Complications

Procedure-related MI, bleeding *, contrast-induced nephropathy or stroke occurred in

28 (5%) patients in the conventional group and

27 (4%) in the DEFER group

*Lancet 2016; 387(10034): 2199-2206

* Requiring blood transfusion or surgical intervention
Conclusions

Deferred stent implantation in patients with STEMI did not reduce the risk of death, heart failure, or reinfarction compared with standard immediate stent implantation.

Left ventricular function and target vessel revascularization is slightly better after deferred stent implantation.

Lancet 2016; 387(10034): 2199-2206
Non-invasive Lung IMPEDANCE-Guided Preemptive Treatment in Chronic Heart Failure Patients: a Randomized Controlled Trial (IMPEDANCE-HF trial)

Michael Kleiner Shochat, MD, BSc, PhD, Avraham Shotan, MD, David S Blondheim, MD, Mark Kazatsker, MD, Iris Dahan, MSIT, Aya Asif, MD, Yoseph Rozenman, MD, Ilia Kleiner, MD, Jean Marc Weinstein, MBBS, FRCP, Aaron Frimerman, MD, Lubov Vasilenko, MD, Simcha R Meisel, MD, MSc

Heart Institute, Hillel Yaffe Medical Center, Hadera, Rappaport School of Medicine, Technion, Haifa, Israel; Cardiovascular Institute, Wolfson Medical Center, Holon, Sackler Faculty of Medicine, Tel-Aviv University, Israel, Cardiology Department, Soroka University Medical Center, Beer Sheva.

American College of Cardiology. Chicago.
Late Braking Clinical Trial Session. Apr.04. 2016

Presenter - Michael Kleiner Shochat

Now Published in the Journal of Cardiac Failure 2016 On Line

Conflict of interest: Michael Kleiner Shochat is a co-founder and member of the board of directors of the RSMM Company that manufactured and supplied the devices for the study.
Study design: Randomized, single blinded, two centers.

Study population.

Efficacy endpoints.

Future Monitoring Group

HF hospitalizations = 1.2/patients year

Future Control Group

HF hospitalizations = 1.1/patients year

One year before randomization

Run in period (3m) for adjustment maximally possible guidelines recommended drug doses for CHF treatment.

Randomization

Mean age in both groups 67 y. Men – 80%. Both groups were well adjusted by baseline patient characteristics, baseline medications and parameters of physical examination.

Monitoring Group (N=128). Mean = 48 m. FU

1 y  2 y  3 y  4 y  5 y  6 y  7 y  8 y

Control Group (N=128). Mean = 39 m. FU

Primary efficacy endpoints:
1. Acute heart failure hospitalizations up to 12 months.
2. Acute heart failure hospitalizations during entire follow up

Secondary efficacy endpoints:
1. All –cause, Cardiac hospitalizations during entire follow up.
2. All-cause, Cardiac and Heart Failure mortality during entire follow up.

J. Card Failure 2016; http://dx.doi.org/10.1016/jcardfail.2016.03.015.
Strategy of drug adjustment

\[ (\Delta \text{LIR}) = \left[ \frac{\text{current LI}}{\text{BLI}} \right] - 1 \]

Baseline (dry) lung impedance (BLI). As if patient is healthy.

Target zone for adjustment treatment
-18%
-24%

Beginning Heart Failure hospitalizations
Increasing in congestions
Increased risk of Heart Failure hospitalizations

Patient’s status is very stable.
No or very small interstitial congestion.
NYHA class I – II. No need in additional treatment.

Patients became more congested but still no more complains

Hospitalizations for Heart Failure

J. Card Failure 2016; [http://dx.doi.org/10.1016/j.cardfail.2016.03.015](http://dx.doi.org/10.1016/j.cardfail.2016.03.015)
Results

Linear mixed effects regression model was used to evaluate differences between ∆LIR into and between groups.

\[ P < 0.001 \]

**Difference in pulmonary congestion between groups during follow up period**

J. Card Failure 2016; [http://dx.doi.org/10.1016/jcardfail.2016.03.015](http://dx.doi.org/10.1016/jcardfail.2016.03.015).
Results

Hospitalizations

All-cause Hospitalizations

Cardiac Hospitalizations

Heart Failure Hospitalizations

Method of statistics: Cox regression analyses

J. Card Failure 2016; http://dx.doi.org/10.1016/j.cardfail.2016.03.015.
Results

Mortality

All-cause Death

Cardiac Death

Heart Failure death

Method of statistics: Kaplan Meyer analyses

J. Card Failure 2016; http://dx.doi.org/10.1016/j.cardfail.2016.03.015.
**TABLE Drug modifications during entire follow up**

<table>
<thead>
<tr>
<th>Medications</th>
<th>Monitored Group</th>
<th>Control Group</th>
<th>p</th>
<th>Monitoring /Control group. Ratio of drug adjustment</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Rate of changes in medical therapy</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>3166 (6.2)†</td>
<td>1244 (3.0)†</td>
<td>&lt;0.05</td>
<td>2.1 times</td>
</tr>
<tr>
<td>Diuretics</td>
<td>1530 (48%)‡</td>
<td>515 (42%)‡</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>1530 (3.0)†</td>
<td>515 (1.3)†</td>
<td>&lt;0.05</td>
<td>2.3 times</td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>792 (25%)‡</td>
<td>303 (24%)‡</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Beta Blockers</td>
<td>792 (1.6)†</td>
<td>303 (0.7)†</td>
<td>&lt;0.05</td>
<td>2.3 times</td>
</tr>
<tr>
<td>ACE inh /ARB</td>
<td>410 (13%)‡</td>
<td>142 (11%)‡</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>ACE inh /ARB</td>
<td>410 (0.8)†</td>
<td>142 (0.3)†</td>
<td>&lt;0.05</td>
<td>2.7 times</td>
</tr>
<tr>
<td>Nitrates</td>
<td>166 (5%)‡</td>
<td>78 (6%)‡</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Nitrates</td>
<td>166 (0.3)†</td>
<td>78 (0.2)†</td>
<td>&lt;0.05</td>
<td>1.5 times</td>
</tr>
<tr>
<td>MRA</td>
<td>154 (5%)‡</td>
<td>144 (12%)‡</td>
<td>NS</td>
<td></td>
</tr>
<tr>
<td>MRA</td>
<td>154 (0.3)†</td>
<td>144 (0.4)†</td>
<td>NS</td>
<td>0.9 times</td>
</tr>
<tr>
<td>Digoxin</td>
<td>114 (4%)‡</td>
<td>62 (5%)‡</td>
<td>&lt;0.05</td>
<td></td>
</tr>
<tr>
<td>Digoxin</td>
<td>114 (0.2)†</td>
<td>62 (0.15)†</td>
<td>&lt;0.05</td>
<td>1.5 times</td>
</tr>
</tbody>
</table>

J. Card Failure 2016; [http://dx.doi.org/10.1016/j.cardfail.2016.03.015](http://dx.doi.org/10.1016/j.cardfail.2016.03.015).
Results

Rate of Heart Failure hospitalizations (per patient*year)

Follow up period

Lung Impedance-guided treatment group
Control group treated by clinical assessment

P < 0.001

J. Card Failure 2016; http://dx.doi.org/10.1016/j.cardfail.2016.03.015.
Data of “IMPEDANCE-HF” trial shows that Lung Impedance guided treatment in compare with treatment based on clinical assessment of HFrEF patients:

**Hospitalizations** (Primary endpoint)

1. Reduces rate of HF hospitalizations during first year by 58%.
2. Reduces rate of HF hospitalizations during 4 years by 56%.

**Hospitalizations** (Secondary endpoint)

3. Reduces rate of all-cause hospitalizations during 4 years by 39%.
4. Reduces rate of cardiac hospitalization during 4 years by 52%.
5. Reduces rate of Non-cardiac hospitalization during 4 years by 9%, \((p=0.6)\).

**Deaths** (Secondary endpoint)

7. Reduces rate of All-cause mortality during 4 years by 43%.
8. Reduces rate of Cardiac mortality during 4 years by 55%.
9. Reduces rate of Heart Failure mortality during 4 years by 62%.
10. No changes in Non-cardiac mortality during 4 years.

J. Card Failure 2016; [http://dx.doi.org/10.1016/jcardfail.2016.03.015](http://dx.doi.org/10.1016/jcardfail.2016.03.015).
Non-invasive Lung Impedance technology is enough sensitive to detect a very early stage of evolving pulmonary congestion and Lung Impedance-guided treatment is reliable for improving hospitalization and survival of Heart Failure patients.

Thank you very much for attention!

J. Card Failure 2016; http://dx.doi.org/10.1016/j.cardfail.2016.03.015.