L ESSENTIEL du congrès ESC 2019

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Remerciements:
A Baumbach, D Capodanno, C Lam, E Prescott, S Silber
● Heart failure:
- DAPA HF, EVALUATE HF, PARAGON, GALACTIC.

● Secondary Prevention:
- THEMIS

● Coronary artery disease/Interventional cardiology:
- SYNTAX 10 years, DANAMI 16 years, COMPLETE, ISAR REACT 5, CLARIFY
HEART FAILURE AND CARDIOMYOPATHIES

HFrEF

DAPA-HF
EVALUATE-HF
Sodium Glucose co-transporter inhibitors

- Dapagliflozin
- Canagliflozin
- Empagliflozin

Diagram showing the transport of glucose and sodium across the tubular lumen.
Dapagliflozin in patients with HFrEF (DAPA-HF)

Median FU 18.2 months
≥844 Primary endpoints
Composite of:
• CV death
• HF hospitalization
• Urgent HF visit

HFrEF
• Symptomatic EF ≤40%
• NT-proBNP ≥600 (400 if HHF in last 12 months 900 if AF)
• No eGFR <30 or SBP <95 or T1DM

N=2373
Dapagliflozin 10 mg once daily

N=2371
Placebo

Enrolment Randomization

Visit 1 Visit 2 Visit 3 Visit 4 Visit 5 Visit 6 etc.

Day -14 Day 0 Day 14 Day 60 Day 120 Every 120 days
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mean age (yr)</td>
<td>66</td>
<td>67</td>
</tr>
<tr>
<td>Male (%)</td>
<td>76</td>
<td>77</td>
</tr>
<tr>
<td>NYHA class II/III/IV (%)</td>
<td>68/31/1</td>
<td>67/32/1</td>
</tr>
<tr>
<td>Mean LVEF (%)</td>
<td>31</td>
<td>31</td>
</tr>
<tr>
<td>Median NT pro BNP (pg/ml)</td>
<td>1428</td>
<td>1446</td>
</tr>
<tr>
<td>Mean systolic BP (mmHg)</td>
<td>122</td>
<td>122</td>
</tr>
<tr>
<td>Ischaemic aetiology (%)</td>
<td>55</td>
<td>57</td>
</tr>
<tr>
<td>Mean eGFR (ml/min/1.73m²)</td>
<td>66</td>
<td>66</td>
</tr>
<tr>
<td>Prior diagnosis T2D (%)</td>
<td>42</td>
<td>42</td>
</tr>
<tr>
<td>Any baseline T2D (%)*</td>
<td>45</td>
<td>45</td>
</tr>
</tbody>
</table>

*includes 82 dapagliflozin and 74 placebo patients with previously undiagnosed diabetes i.e. two HbA1c ≥6.5% (≥48 mmol/mol)
<table>
<thead>
<tr>
<th>Treatment (%)</th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Diuretic</td>
<td>93</td>
<td>94</td>
</tr>
<tr>
<td>ACE-inhibitor/ARB/ARNI*</td>
<td>94</td>
<td>93</td>
</tr>
<tr>
<td>ACE inhibitor</td>
<td>56</td>
<td>56</td>
</tr>
<tr>
<td>ARB</td>
<td>28</td>
<td>27</td>
</tr>
<tr>
<td>Sacubitril/valsartan</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>Beta-blocker</td>
<td>96</td>
<td>96</td>
</tr>
<tr>
<td>MRA</td>
<td>71</td>
<td>71</td>
</tr>
<tr>
<td>ICD*</td>
<td>26</td>
<td>26</td>
</tr>
<tr>
<td>CRT**</td>
<td>8</td>
<td>7</td>
</tr>
</tbody>
</table>

*ARNI = angiotensin receptor neprilysin inhibitor  
*ICD or CRT-D  **CRT-P or CRT-D  

For full details see McMurray JJV et al  
Eur J Heart Fail.2019 Jul 15. doi: 10.1002/ejhf.1548
Primary composite outcome

CV Death/HF hospitalization/Urgent HF visit

HR 0.74 (0.65,0.85)
p=0.00001
NNT=21

Number at Risk
Dapagliflozin 2373 2305 2221 2147 2002 1560 1146 612 210
Placebo 2371 2258 2163 2075 1917 1478 1096 593 210
Components of primary outcome

**Worsening HF event**
HR 0.70 (0.59, 0.83); p=0.00003

**Cardiovascular death**
HR 0.82 (0.69, 0.98); p=0.029
CV death or HF hospitalization

HR 0.75 (0.65, 0.85)
p=0.00002
Congress Highlights

Groupe hospitalier Paris Saint-Joseph

All cause death

**HR 0.83 (0.71, 0.97)**

p=0.022*

Cumulative Percentage (%)

<table>
<thead>
<tr>
<th>Months since Randomization</th>
<th>Number at Risk</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>2373 2371</td>
</tr>
<tr>
<td>3</td>
<td>2342 2330</td>
</tr>
<tr>
<td>6</td>
<td>2296 2279</td>
</tr>
<tr>
<td>9</td>
<td>2251 2231</td>
</tr>
<tr>
<td>12</td>
<td>2130 2092</td>
</tr>
<tr>
<td>15</td>
<td>1666 1638</td>
</tr>
<tr>
<td>18</td>
<td>1243 1221</td>
</tr>
<tr>
<td>21</td>
<td>672 665</td>
</tr>
<tr>
<td>24</td>
<td>233 235</td>
</tr>
</tbody>
</table>

*Nominal p value
Primary Endpoint: Prespecified Subgroups

### Overall effect
- **Age (years)**
  - ≤65: HR (95% CI) = 0.74 (0.65, 0.85)
  - >65: HR (95% CI) = 0.72 (0.60, 0.85)

### Sex
- Male: HR (95% CI) = 0.73 (0.63, 0.85)
- Female: HR (95% CI) = 0.79 (0.59, 1.06)

### Race
- White: HR (95% CI) = 0.78 (0.66, 0.91)
- Black or African: HR (95% CI) = 0.62 (0.37, 1.04)
- Asian: HR (95% CI) = 0.64 (0.48, 0.86)
- Other

### Geographic region
- Asia: HR (95% CI) = 0.65 (0.49, 0.87)
- Europe: HR (95% CI) = 0.84 (0.69, 1.01)
- North America: HR (95% CI) = 0.73 (0.51, 1.03)
- South America: HR (95% CI) = 0.64 (0.47, 0.88)

### NYHA class
- II: HR (95% CI) = 0.63 (0.52, 0.75)
- III or IV: HR (95% CI) = 0.90 (0.74, 1.09)

### LVEF
- ≤ Median: HR (95% CI) = 0.70 (0.59, 0.84)
- > Median: HR (95% CI) = 0.81 (0.65, 0.99)

### NT-proBNP
- ≤ Median: HR (95% CI) = 0.63 (0.49, 0.80)
- > Median: HR (95% CI) = 0.79 (0.68, 0.92)

### Prior hospitalization for HF
- Yes: HR (95% CI) = 0.67 (0.56, 0.80)
- No: HR (95% CI) = 0.84 (0.69, 1.01)

### MRA at baseline
- Yes: HR (95% CI) = 0.74 (0.63, 0.87)
- No: HR (95% CI) = 0.74 (0.57, 0.95)

### Type 2 diabetes at baseline
- Yes: HR (95% CI) = 0.75 (0.63, 0.90)
- No: HR (95% CI) = 0.73 (0.60, 0.88)

### Atrial fibrillation or flutter at enrollment ECG
- Yes: HR (95% CI) = 0.82 (0.63, 1.06)
- No: HR (95% CI) = 0.72 (0.61, 0.84)

### Main Etiology of HF
- Ischemic: HR (95% CI) = 0.77 (0.65, 0.92)
- Non-Ischemic/Unknown: HR (95% CI) = 0.71 (0.58, 0.87)

### BMI (kg/m²)
- <30: HR (95% CI) = 0.78 (0.66, 0.92)
- ≥30: HR (95% CI) = 0.69 (0.55, 0.86)

### Baseline eGFR (mL/min/1.73m²)
- <60: HR (95% CI) = 0.72 (0.59, 0.86)
- ≥60: HR (95% CI) = 0.76 (0.63, 0.92)
No diabetes / Diabetes subgroup
Primary Endpoint

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
<th>HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>All patients</td>
<td>386/2373</td>
<td>502/2371</td>
<td>0.74 (0.65, 0.85)</td>
</tr>
<tr>
<td>Type 2 diabetes at baseline*</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>215/1075</td>
<td>271/1064</td>
<td>0.75 (0.63, 0.90)</td>
</tr>
<tr>
<td>No</td>
<td>171/1298</td>
<td>231/1307</td>
<td>0.73 (0.60, 0.88)</td>
</tr>
</tbody>
</table>

*Defined as history of type 2 diabetes or HbA1c ≥6.5% at both enrollment and randomization visits.
**ARNI/no ARNI post hoc subgroup:**
**Primary Endpoint**

<table>
<thead>
<tr>
<th></th>
<th>Dapagliflozin (n=2373)</th>
<th>Placebo (n=2371)</th>
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<tr>
<td><strong>All patients</strong></td>
<td>386/2373</td>
<td>502/2371</td>
<td>0.74 (0.65, 0.85)</td>
</tr>
<tr>
<td><strong>Angiotensin Receptor Neprilysin Inhibitor (ARNI)</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Yes</td>
<td>41/250</td>
<td>56/258</td>
<td>0.75 (0.50, 1.13)</td>
</tr>
<tr>
<td>No</td>
<td>345/2123</td>
<td>446/2113</td>
<td>0.74 (0.65, 0.86)</td>
</tr>
</tbody>
</table>
Kansas City Cardiomyopathy Questionnaire (KCCQ)

Total Symptom Score (TSS): Change from baseline to 8 months

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Change</th>
<th>Difference</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>+6.1 ± 18.6</td>
<td>2.8 points (95% CI 1.6, 4.0)</td>
</tr>
<tr>
<td>Placebo</td>
<td>+3.3 ± 19.2</td>
<td>p&lt;0.001*</td>
</tr>
</tbody>
</table>

Increase in score indicates an improvement

*Calculated from win ratio, incorporating death. Win ratio = 1.18 (CI 1.11, 1.26). Win ratio >1 indicates superiority of dapagliflozin over placebo
Worsening renal function endpoint

Composite of: Sustained* ≥50% reduction in eGFR, end-stage renal disease (ESRD) or death from renal causes

<table>
<thead>
<tr>
<th>Treatment</th>
<th>No. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dapagliflozin</td>
<td>28 (1.2)</td>
</tr>
<tr>
<td>Placebo</td>
<td>39 (1.6)</td>
</tr>
</tbody>
</table>

Hazard ratio (95% CI)
0.71 (0.44, 1.16)
p=0.17

ESRD consisted of sustained eGFR below 15 ml/min/1.73m², sustained dialysis or kidney transplantation
*Sustained = 28 days or more
Effect of Sacubitril-Valsartan vs Enalapril on Aortic Stiffness in Patients With Heart Failure and Reduced Ejection Fraction: A Randomized Clinical Trial

Akshay S. Desai, MD, MPH; Scott D. Solomon, MD; Amil M. Shah, MD; Brian L. Claggett, PhD; James C. Fang, MD; Joseph Izzo, MD; Kevin McCague, MA; Cheryl A. Abbas, PharmD; Ricardo Rocha, MD; Gary F. Mitchell, MD; for the EVALUATE-HF Investigators
To determine whether treatment of HFrEF with sacubitril/valsartan improves central aortic stiffness and cardiac remodeling compared with enalapril.
Primary Endpoint: Change in aortic characteristic impedance $Z_c$

<table>
<thead>
<tr>
<th></th>
<th>Baseline</th>
<th>12 Weeks</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sacubitril/Valsartan</td>
<td>223.8</td>
<td>218.9</td>
</tr>
<tr>
<td>Enalapril</td>
<td>213.2</td>
<td>214.3</td>
</tr>
</tbody>
</table>

$Z_c$ (dynes-sec/cm$^5$)

-2.2 (-17.6, +13.2) $p = 0.78$

-2.9 (-13.8, +8.0)

-0.7 (-11.6, +10.1)

A. Desai, JAMA 2019
Secondary Endpoints: Change in Cardiac Structure and Function from Baseline to 12 weeks, by Treatment

**Systolic Function**
- LVEF: +1.9, +1.3, -0.3, -0.2
- GLS: -0.3, -0.2

**Cardiac Structure**
- LVEDVI: -5.2, -4.9, -3.2, -3.3
- LVESVI: -3.3, -3.2
- LAVI: -2.2

**Diastolic Function and Ventricular-Vascular Coupling**

**Implications**
Clinical benefits of sacubitril/valsartan in HFrEF are likely unrelated to changes in central aortic stiffness or pulsatile load, but might be related to effects on myocardial remodeling and wall stress.

A. Desai, JAMA 2019
HEART FAILURE AND CARDIOMYOPATHIES

HFpEF

PARAGON-HF
Angiotensin-neprilysin inhibition in heart failure with preserved ejection fraction

Primary results of the PARAGON-HF trial

Scott D. Solomon, MD, and John J.V. McMurray, MD

for the PARAGON-HF Committees, National Leaders and Investigators
Randomized, double-blind, active comparator trial testing the hypothesis that sacubitril/valsartan, compared with valsartan, would reduce the composite outcome of total HF hospitalizations and CV death.

### Primary Endpoint
Composite of total (first and recurrent) HF hospitalizations and CV death

### Secondary Endpoints:
- Improvement in NYHA functional classification at 8 months
- Changes in KCCQ clinical summary score at 8 months
- Time to first occurrence of worsening renal function
- Time to all-cause mortality

**Key Inclusion Criteria**

- ≥ 50 years of age and LVEF ≥ 45%
- Heart failure signs/symptoms (NYHA Class II–IV) requiring treatment with diuretic(s) for at least 30 days prior to enrollment
- Structural heart disease (LAE or LVH by echocardiography)
- Elevation in natriuretic peptides
  - NT-proBNP 200 pg/ml if hospitalized for HF within 9 months, and 300 pg/ml if not hospitalized; 3-fold increase for patients in AF at enrollment

**Key Exclusion Criteria**

- Any prior measurement of LVEF < 40%
- Current acute decompensated heart failure
- Alternative reason for signs and symptoms
- SBP < 110 or > 180mm Hg (or > 150mm Hg if patient not taking 3 or more antihypertensive medications)
# Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Sacubitril/valsartan</th>
<th>Valsartan</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>N = 2,407</td>
<td>N = 2,389</td>
</tr>
<tr>
<td>Age (years) – mean (SD)</td>
<td>72.7 (8.3)</td>
<td>72.8 (8.5)</td>
</tr>
<tr>
<td>Sex – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>1166 (48.4)</td>
<td>1151 (48.2)</td>
</tr>
<tr>
<td>Female</td>
<td>1241 (51.6)</td>
<td>1238 (51.8)</td>
</tr>
<tr>
<td>Race – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>82%</td>
<td>81%</td>
</tr>
<tr>
<td>Black</td>
<td>2.2%</td>
<td>2.1%</td>
</tr>
<tr>
<td>Asian</td>
<td>12%</td>
<td>13%</td>
</tr>
<tr>
<td>Region – n (%)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America*</td>
<td>12%</td>
<td>11%</td>
</tr>
<tr>
<td>Latin America</td>
<td>7.9%</td>
<td>7.5%</td>
</tr>
<tr>
<td>Western Europe</td>
<td>29%</td>
<td>29%</td>
</tr>
<tr>
<td>Central Europe</td>
<td>36%</td>
<td>36%</td>
</tr>
<tr>
<td>Asia/Pacific/other**</td>
<td>16%</td>
<td>16%</td>
</tr>
<tr>
<td>Baseline LVEF – median [IQR]</td>
<td>57 [51,62]</td>
<td>57 [50,63]</td>
</tr>
<tr>
<td>Baseline NT-proBNP (pg/mL) – median (IQR) – Sinus rhythm</td>
<td>583 [370, 1046]</td>
<td>611 [389, 1072]</td>
</tr>
<tr>
<td>Baseline NT-proBNP (pg/mL) – median (IQR) – Atrial fibrillation</td>
<td>1633 [1191, 2368]</td>
<td>1536 [1153, 2212]</td>
</tr>
</tbody>
</table>

*North America = US and Canada. **Asia/Pacific/Other includes Israel, South Africa, Australia, China, India, Japan, Rep of Korea, Philippines, Singapore, Taiwan.
## Baseline Demographics

<table>
<thead>
<tr>
<th></th>
<th>Sacubitril/valsartan N=2,407</th>
<th>Valsartan N=2,389</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NYHA class at randomization – n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Class I</td>
<td>3.0%</td>
<td>2.7%</td>
</tr>
<tr>
<td>Class II</td>
<td>78%</td>
<td>77%</td>
</tr>
<tr>
<td>Class III</td>
<td>19%</td>
<td>20%</td>
</tr>
<tr>
<td>Class IV</td>
<td>0.3%</td>
<td>0.5%</td>
</tr>
<tr>
<td><strong>BMI – mean (SD)</strong></td>
<td>30.2 (4.9)</td>
<td>30.3 (5.1)</td>
</tr>
<tr>
<td><strong>Baseline systolic/diastolic blood pressure at randomization – mean (SD)/mean(SD)</strong></td>
<td>130.5 (15.6)/74.3 (10.6)</td>
<td>130.6 (15.3)/74.3 (10.4)</td>
</tr>
<tr>
<td><strong>Medical history – n (%)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension, n (%)</td>
<td>96%</td>
<td>95%</td>
</tr>
<tr>
<td>Diabetes mellitus, n (%)</td>
<td>44%</td>
<td>43%</td>
</tr>
<tr>
<td>Atrial fibrillation at screening ECG, n (%)</td>
<td>32%</td>
<td>33%</td>
</tr>
<tr>
<td>Hospitalization for HF within 9 months</td>
<td>38%</td>
<td>39%</td>
</tr>
<tr>
<td><strong>Medications</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>Prior to randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>ACEi or ARBs</td>
<td>87%</td>
<td>87%</td>
</tr>
<tr>
<td><strong>At randomization</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diuretics</td>
<td>94%</td>
<td>95%</td>
</tr>
<tr>
<td>MRA</td>
<td>24%</td>
<td>27%*</td>
</tr>
<tr>
<td>Beta blockers</td>
<td>79%</td>
<td>79%</td>
</tr>
<tr>
<td>Calcium channel blockers</td>
<td>34%</td>
<td>34%</td>
</tr>
</tbody>
</table>
PARAGON-HF primary results
Recurrent event analysis of total HF hospitalisations and CV death*

*Semiparametric LWYY method.

Total HF hospitalisations and CV death

Valsartan (n = 2389)
1009 events, 14.6 per 100 pt-years

Sacubitril/valsartan (n = 2407)
894 events, 12.8 per 100 pt-years

Rate ratio 0.87 (95% CI 0.75, 1.01)
p = 0.059
**HF hospitalisations and CV death**

### HF hospitalisations*

- **Valsartan**: 797 events
- **Sacubitril/valsartan**: 690 events

Rate ratio 0.85 (95% CI 0.72, 1.00)  
*p = 0.056

### CV death*

- **Valsartan**: 212 patients (8.9%)
- **Sacubitril/valsartan**: 204 patients (8.5%)

Hazard ratio 0.95 (95% CI 0.79, 1.16)  
*p = 0.62

*Semiparametric LWYY method
### Secondary endpoints

<table>
<thead>
<tr>
<th></th>
<th>Sacubitril/valsartan N = 2316</th>
<th>Valsartan N = 2302</th>
<th>Effect size (95% CI)</th>
<th>Nominal P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NYHA functional classification at 8 months</strong> – Change from baseline (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Improved</td>
<td>15.0%</td>
<td>12.6%</td>
<td>OR for improvement</td>
<td>1.45 (1.13, 1.86)</td>
</tr>
<tr>
<td>Unchanged</td>
<td>76.3%</td>
<td>77.9%</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Worsened</td>
<td>8.7%</td>
<td>9.6%</td>
<td></td>
<td></td>
</tr>
<tr>
<td><strong>KCCQ clinical summary score at 8 months</strong> – Change from baseline (SE)</td>
<td>-1.6 (0.4)</td>
<td>-2.6 (0.4)</td>
<td>LSM of difference =</td>
<td>1.03 (0.00, 2.1)</td>
</tr>
<tr>
<td><strong>KCCQ responder (&gt; than 5-point improvement)</strong></td>
<td>33.0%</td>
<td>29.6%</td>
<td>OR = 1.30 (1.04, 1.61)</td>
<td>0.019</td>
</tr>
<tr>
<td><strong>Worsening Renal Function Composite of renal death, reaching ESRD, or ≥50% decline in eGFR relative to baseline.</strong></td>
<td>1.4%</td>
<td>2.7%</td>
<td>HR = 0.50 (0.33, 0.77)</td>
<td>0.002</td>
</tr>
<tr>
<td><strong>All-cause mortality (%)</strong></td>
<td>14.2%</td>
<td>14.6%</td>
<td>HR = 0.97 (0.84, 1.13)</td>
<td>0.68</td>
</tr>
</tbody>
</table>

Solomon S et al, NEJM 2019
### Pre-specified subgroups for primary endpoint

#### Evidence for overall heterogeneity

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of events /patients</th>
<th>Rate ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1903/4796</td>
<td>0.87 (0.75−1.01)</td>
</tr>
<tr>
<td><strong>Age (years)</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Less than 65 years</td>
<td>276/825</td>
<td>0.99 (0.64−1.53)</td>
</tr>
<tr>
<td>65 years or older</td>
<td>1627/3971</td>
<td>0.85 (0.73−0.99)</td>
</tr>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>980/2317</td>
<td>1.03 (0.85−1.25)</td>
</tr>
<tr>
<td>Female</td>
<td>923/2479</td>
<td>0.73 (0.59−0.90)</td>
</tr>
<tr>
<td><strong>Race</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Caucasian</td>
<td>1542/3907</td>
<td>0.83 (0.71−0.97)</td>
</tr>
<tr>
<td>Black</td>
<td>89/102</td>
<td>0.69 (0.24−1.99)</td>
</tr>
<tr>
<td>Asian</td>
<td>237/607</td>
<td>1.25 (0.87−1.79)</td>
</tr>
<tr>
<td>Other</td>
<td>35/180</td>
<td>1.03 (0.47−2.28)</td>
</tr>
<tr>
<td><strong>Region</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>North America</td>
<td>478/559</td>
<td>0.80 (0.57−1.14)</td>
</tr>
<tr>
<td>Latin America</td>
<td>83/370</td>
<td>1.33 (0.75−2.36)</td>
</tr>
<tr>
<td>Western Europe</td>
<td>544/1390</td>
<td>0.69 (0.53−0.89)</td>
</tr>
<tr>
<td>Central Europe</td>
<td>466/1715</td>
<td>0.97 (0.76−1.24)</td>
</tr>
<tr>
<td>Asia/Pacific</td>
<td>332/762</td>
<td>1.10 (0.79−1.52)</td>
</tr>
</tbody>
</table>

#### Multivariate interaction p < 0.05.

**Diabetic**
- Yes: 1041/2069, 0.89 (0.74−1.09)
- No: 862/2727, 0.84 (0.68−1.04)

**LVEF**
- at or below median (57%): 1048/2495, 0.78 (0.64−0.95)
- above median (57%): 855/2301, 1.00 (0.81−1.23)

**History of AF**
- Yes: 1140/2521, 0.83 (0.69−1.00)
- No: 763/2275, 0.94 (0.75−1.18)

**Screening NT-proBNP**
- at or below median (911 pg/mL): 708/2379, 0.85 (0.67−1.08)
- above median (911 pg/mL): 1183/2378, 0.87 (0.73−1.05)

**Screening SBP**
- at or below median (137 mmHg): 984/2450, 0.88 (0.72−1.07)
- above median (137 mmHg): 919/2344, 0.86 (0.69−1.06)

**MRA use**
- Yes: 543/1238, 0.73 (0.56−0.94)
- No: 1360/3558, 0.94 (0.79−1.12)

**Baseline eGFR**
- <60 mL/min/1.73m²: 1115/2341, 0.79 (0.66−0.95)
- ≥60 mL/min/1.73m²: 787/2454, 1.01 (0.80−1.27)

**NYHA class**
- I/II: 1402/3843, 0.90 (0.76−1.06)
- III/IV: 499/951, 0.79 (0.59−0.96)
**Significant Heterogeneity in Multivariate Analysis by Ejection Fraction and Sex**

Only interactions for sex and ejection fraction remained nominally significant

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of events/patients</th>
<th>Rate ratio (95% CI)</th>
<th>Primary endpoint</th>
<th>Multivariable interaction p-value</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Sex</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male</td>
<td>980/2317</td>
<td>1.03 (0.85–1.25)</td>
<td>P &lt; 0.006</td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>923/2479</td>
<td>0.73 (0.59–0.90)</td>
<td>P = 0.03 (categorical)</td>
<td>P = 0.002 (continuous)</td>
</tr>
<tr>
<td><strong>LVEF</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>at or below median (57%)</td>
<td>1048/2495</td>
<td>0.78 (0.64–0.95)</td>
<td></td>
<td></td>
</tr>
<tr>
<td>above median (57%)</td>
<td>855/2301</td>
<td>1.00 (0.81–1.23)</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
Treatment effect by ejection fraction quartiles

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>No. of Events/Patients</th>
<th>Rate Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Overall</td>
<td>1903/4796</td>
<td>0.87 (0.75–1.01)</td>
</tr>
<tr>
<td>EF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;=50</td>
<td>512/1208</td>
<td>0.82 (0.63–1.06)</td>
</tr>
<tr>
<td>&gt;50–57</td>
<td>536/1287</td>
<td>0.77 (0.57–1.03)</td>
</tr>
<tr>
<td>&gt;57–63</td>
<td>467/1202</td>
<td>0.91 (0.68–1.22)</td>
</tr>
<tr>
<td>&gt;63</td>
<td>388/1099</td>
<td>1.09 (0.80–1.47)</td>
</tr>
</tbody>
</table>
## Safety endpoints

<table>
<thead>
<tr>
<th>Adverse event</th>
<th>Sacubitril/Valsartan (N = 2407)</th>
<th>Valsartan (N = 2389)</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hypotension with SBP &lt; 100 mm Hg</td>
<td>15.8%</td>
<td>10.8%</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>≥ 2.0 mg/dl</td>
<td>10.8%</td>
<td>13.7%</td>
<td>0.002</td>
</tr>
<tr>
<td>≥ 2.5 mg/dl</td>
<td>4%</td>
<td>4.6%</td>
<td>0.36</td>
</tr>
<tr>
<td>≥ 3.0 mg/dl</td>
<td>1.6%</td>
<td>1.7%</td>
<td>0.79</td>
</tr>
<tr>
<td>Elevated serum creatinine</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2.0 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 2.5 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≥ 3.0 mg/dl</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Elevated serum potassium</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt; 5.5 mmol/liter</td>
<td>13.2%</td>
<td>15.3%</td>
<td>0.05</td>
</tr>
<tr>
<td>&gt; 6.0 mmol/liter</td>
<td>3.1%</td>
<td>4.3%</td>
<td>0.04</td>
</tr>
<tr>
<td>Angioedema*</td>
<td>0.6%</td>
<td>0.2%</td>
<td>0.02</td>
</tr>
</tbody>
</table>

*Adjudicated
HEART FAILURE AND CARDIOMYOPATHIES

ACUTE HEART FAILURE

GALACTIC
Methods: Design

• All other therapies including loop diuretic dose and duration, beta-blockers, aldosterone antagonists, cardiac devices, and follow-up care were according to ESC Guidelines + at the discretion of the treating physician in both groups

*stratified for site and BNP/NT-proBNP
Results: Intervention

A: Nitroglycerin

B: Hydralazine

C: Furosemide equivalent dose

D: ACEI / ARB / RNI

E: Systolic and diastolic blood pressure

F: Weight reduction

Mueller CE, Hot Line Session 3, FP 3178
Results: Primary Endpoint (Death or AHF)

Adjusted hazard ratio 1.07 95% CI (0.83-1.39)  
p=0.592
BALANCING THROMBOSIS AND BLEEDING IN SECONDARY PREVENTION

THEMIS and THEMIS-PCI
Tools for the clinician
THEMIS

Event risk is high in patients with diabetes and CAD

Themis included patients with stable CAD, diabetes and no previous MI/stroke

Ticagrelor 90/60 mg bid added to aspirin versus aspirin alone

N 19,220

Follow-up 39.9 months

Steg PG, et al. NEJM. 2019

Cardiovascular death/stroke/MI

HR 0.90 (95% CI 0.81-0.99)
P=0.04

8.5% Placebo
7.7% Ticagrelor

Major bleeding

HR 2.32 (95% CI 1.82-2.94)
P<0.001

2.2% Ticagrelor
1.0% Placebo

Steg PG, et al. NEJM. 2019
**THEMIS-PCI – Prespecified subgroup analysis**

Patients with a history of PCI – N 11,154

Conclusion

- In patients with diabetes and CAD the bleeding risk of long-term treatment with ticagrelor and aspirin outweighs the benefit
- There may be subgroups where the treatment is beneficial

Net Clinical Benefit
All cause death, MI, stroke, fatal bleed or ICH (ITT)*

History of PCI

- KM at 36 months
- Placebo
- Ticagrelor
- HR 0.85
  (95% CI 0.75, 0.95)
  p=0.005

Interaction p=0.012

No history of PCI

- KM at 36 months
- Placebo
- Ticagrelor
- HR 1.06
  (95% CI 0.93, 1.21)
  p=0.39

*Prespecified definition of net clinical benefit.
CI=confidence interval; HR=hazard ratio; ICH=intracranial hemorrhage; ITT=intention to treat; MI=myocardial infarction; PCI=percutaneous coronary intervention
LONG-TERM OUTCOMES
SYNTAXES: background

- The SYNTAX trial compared stenting with the first generation DES Taxus and CABG in patients with multivessel coronary artery disease and left main stem stenosis.
- The SYNTAX Score defined three groups of anatomic complexity with different outcomes.
- The long-term outcome (>5 year) of stent and bypass surgery is of interest.

SYNTAXES 10 yr all cause death

- 62 EU Sites
- 23 US Sites
- de novo Three-Vessel and/or Left Main Coronary Artery disease

PCI
- N=903 (100%)

CABG
- N=897 (100%)

Randomisation

PCI
- N=871 (96.5%)

5-Year Follow-up

CABG
- N=805 (89.7%)

PCI
- N=841 (93.4%)

10-Year Follow-up

CABG
- N=848 (94.7%)

Overall completeness of follow-up: 94%

Overall completeness of follow-up: 94%

PCI
- N=841 (93.4%)

CABG
- N=848 (94.7%)

SYNTAX: Left main


HR $0.90$, 95% CI (0.68-1.20), $P = 0.47$
SYNTAXES: Three-vessel disease

HR $1.41$, 95% CI (1.10-1.80), $P = 0.006$

Follow-up (years)

All-cause death (%)
**SYNTAXES: Diabetes**

**DIABETES**

HR **1.10**, 95% CI (0.80-1.52), \( P = 0.56 \)

**NO DIABETES**

HR **1.20**, 95% CI (0.96-1.51), \( P = 0.11 \)

---

**SYNTAXES: Diabetes**

### Diabetes

- **Follow-up (years)**
  - **All-cause death (%)**
    - PCI: 34.2%
    - CABG: 32.1%
  - **HR 1.10, 95% CI (0.80-1.52), P = 0.56**

### No Diabetes

- **Follow-up (years)**
  - **All-cause death (%)**
    - PCI: 24.6%
    - CABG: 20.7%
  - **HR 1.20, 95% CI (0.96-1.51), P = 0.11**
DANAMI-2 16 Years: Background

**Included**
1,572 STEMI patients

- Invasive centres: 443
  - Primary endpoint: pPCI n=223
  - Fibrinolysis n=220
- Referral hospitals: 1,129
  - Primary endpoint: pPCI n=567
  - Fibrinolysis n=562

**Primary endpoint:**
Composite of death, reinfarction, or disabling stroke at 30 days

**Graph:**
- Cumulative Event Rate (%)
- Days of Follow-up
- Fibrinolysis group
- Angioplasty group
- p=0.002

DANAMI-2: 16 years later

### COMPOSITE ENDPOINT

**Composite endpoint**

- **Fibrinolysis**: 62.3%
- **pPCI**: 58.7%
- Absolute difference: 3.6%
- Hazard ratio (95% CI): 0.86 (0.76–0.98)
- Mean gain in time to first event (95% CI): 12.3 months (5.0–19.9)

**p=0.022**

### REINFARCTION

**Mean gain in time to first event (95% CI)**

- **Fibrinolysis**: 24.5% (11.5 months (4.8–18.3))
- **pPCI**: 19.0%

**p=0.008**

---

Thrane PG, et al. EHJ. 2019
INTERVENTION FOR STEMI

Multivessel strategy
Patients undergoing primary PCI of the culprit lesion for STEMI are often found to have multivessel CAD, with 1 or more angiographically significant non-culprit lesions.

There is uncertainty about how best to manage these non-culprit lesions:
- Routinely revascularise them with PCI?
- Manage them conservatively with guideline-directed medical therapy alone?

While prior RCTs have shown non-culprit lesion PCI reduces revascularisation, none were powered to detect moderate reductions in hard clinical outcomes such as CV death or MI.

**COMPLETE Trial design**

**STEMI with Multivessel CAD and Successful PCI to the Culprit Lesion**

≥70% stenosis or 50-69% with FFR ≤0.80

**Randomisation**

Stratified to in-hospital or after discharge

**Complete Revascularisation**

N=2,000

**Culprit Lesion Only Revascularisation**

N=2,000

**Median Follow-up: 3 years**

**Co-primary Outcomes:**

1. Composite of CV death or new MI
2. Composite of CV death, new MI or ischaemia-driven revascularisation

**Key Secondary Outcome:**

CV death, new MI, IDR, unstable angina, NYHA class IV heart failure

COMPLETE: Main results

First Co-Primary Outcome: CV Death or New MI

- Hazard Ratio: 0.74
- 95% CI: 0.60 - 0.91
- P-value: 0.004
- NNT (median 3 years) = 37

2nd Co-Primary Outcome: CV Death, MI, or IDR

- Hazard Ratio: 0.51
- 95% CI: 0.43 - 0.61
- P-value: < 0.001
- NNT (median 3 years) = 13

### CV death or New MI

<table>
<thead>
<tr>
<th>Intent to perform non-culprit lesion PCI</th>
<th>Complete</th>
<th>Culprit Only</th>
<th>HR (95% CI)</th>
<th>Interaction P</th>
</tr>
</thead>
<tbody>
<tr>
<td>During initial hospitalization</td>
<td>101/1353 (2.7)</td>
<td>130/1349 (3.5)</td>
<td>0.77 (0.59-1.00)</td>
<td>0.62</td>
</tr>
<tr>
<td>After initial hospitalization</td>
<td>57/663 (2.7)</td>
<td>83/676 (3.9)</td>
<td>0.69 (0.49-0.97)</td>
<td></td>
</tr>
</tbody>
</table>

### CV death, New MI, or IDR

<table>
<thead>
<tr>
<th>Intent to perform non-culprit lesion PCI</th>
<th>Complete</th>
<th>Culprit Only</th>
<th>HR (95% CI)</th>
<th>Interaction P</th>
</tr>
</thead>
<tbody>
<tr>
<td>During initial hospitalization</td>
<td>113/1353 (3.0)</td>
<td>227/1349 (6.6)</td>
<td>0.47 (0.38-0.59)</td>
<td>0.27</td>
</tr>
<tr>
<td>After initial hospitalization</td>
<td>66/663 (3.1)</td>
<td>112/676 (5.4)</td>
<td>0.59 (0.43-0.79)</td>
<td></td>
</tr>
</tbody>
</table>

### Median Time to study NCL PCI in Complete Group

- During initial hospitalisation: 1 day (IQR 1-3)
- After Hospital discharge: 23 days (IQR 12.5-33.5)
ACUTE CORONARY SYNDROMES

ANTIPLATELET THERAPY

ISAR-REACT 5
### Antiplatelet therapy for ACS in the ESC Guidelines

#### Recommendations on P2Y$_{12}$ inhibitor selection

<table>
<thead>
<tr>
<th>Class</th>
<th>Level</th>
</tr>
</thead>
<tbody>
<tr>
<td>I</td>
<td>B</td>
</tr>
</tbody>
</table>

In patients with ACS, ticagrelor (180 mg loading dose, 90 mg twice daily) on top of aspirin\(^a\) is recommended, regardless of initial treatment strategy, including patients pre-treated with clopidogrel (which should be discontinued when ticagrelor is commenced) unless there are contraindications.

In patients with ACS undergoing PCI, prasugrel (60 mg loading dose, 10 mg daily dose) on top of aspirin is recommended for P2Y$_{12}$ inhibitor-naive patients with NSTE-ACS or initially conservatively managed STEMI if indication for PCI is established, or in STEMI patients undergoing immediate coronary catheterization\(^a\) unless there is a high risk of life-threatening bleeding or other contraindications.

---

\(^a\) Contraindications for ticagrelor: previous intracranial haemorrhage or ongoing bleeds. Contraindications for prasugrel: previous intracranial haemorrhage, previous ischaemic stroke or transient ischaemic attack, ongoing bleeds. Prasugrel is not recommended for patients ≥75 years of age or with a body weight <60 kg.

---

2017 ESC focused update on dual antiplatelet therapy in coronary artery disease developed in collaboration with EACTS. EHJ. https://doi.org/10.1093/eurheartj/ehx419.
ISAR-REACT 5

4,018 pts with invasively managed ACS (STEMI 41%, NSTEMI 46%, UA 13%)

- **Prasugrel**: N=2,006
  - Loading dose after coronary angiography in NSTE-ACS and at randomisation in STEMI with dose reduction as per IFU

- **Ticagrelor**: N=2,012
  - Loading dose at randomisation irrespective of clinical presentation

**CONTROL ARM**

**INVESTIGATIONAL ARM**

DEATH, MI OR STROKE AT 12 MONTHS (PRIMARY ENDPOINT, ITT)

- Hazard ratio 1.36 [95% CI 1.09-1.70]
- P = 0.006

Ticagrelor vs Prasugrel:
- **Ticagrelor**: 9.3%
- **Prasugrel**: 6.9%

Schüpke S, et al. NEJM. 2019
ISAR-REACT 5

4,018 pts with invasively managed ACS (STEMI 41%, NSTEMI 46%, UA 13%)

**Control Arm**
- **Prasugrel**: N=2,006
  - Loading dose after coronary angiography in NSTE-ACS and at randomisation in STEMI with dose reduction as per IFU

**Investigational Arm**
- **Ticagrelor**: N=2,012
  - Loading dose at randomisation irrespective of clinical presentation

**Patient-level randomisation**
- Open label

**BARC Type 3, 4, 5 Bleeding**
(Safety endpoint, mITT)

- **Ticagrelor**: 5.4%
- **Prasugrel**: 4.8%

Hazard ratio 1.12 [95% CI 0.83-1.51]
P = 0.46

Schüpke S, et al. NEJM. 2019
CLARITY: a prospective observational Longitudinal Registry of patients with stable coronary artery disease

32,703 patients
45 countries

2898 physicians
to consecutively enrol 10-15 patients

Enrolment: 2009 - 2010
Database locked: 2016

Yearly visit
Median follow-up: 5.0 years

Medical care at the discretion of each physician

Inclusion criteria for chronic coronary syndromes, non-mutually exclusive:

- prior myocardial infarction >3 months
- prior revascularisation >3 months
- proven symptomatic myocardial ischaemia
- angiographic coronary stenosis >50%

Exclusion criteria:

- conditions interfering with life expectancy
- advanced heart failure
According to angina and prior MI
5-year incidence of CV death or non-fatal MI

Angina: a poor prognosis only if prior MI

Adjusted* P value for interaction between angina and prior MI = 0.0016

* Multivariable analysis (Cox proportional hazards model) including: age, gender, diabetes, smoking status, history of hypertension, MI, PCI, CABS, hospitalisation for heart failure, asthma/COPD, atrial fibrillation/flutter, prior stroke, cerebrovascular disease, peripheral artery disease, current angina, blood pressure <140/90 mm Hg, geographical zones.