Unmet needs in Chronic Heart Failure

Dubrovnik, September 27 2013

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Unmet needs in chronic HF

- Prevention of HF
- Comorbidities
- HF with preserved LV Ejection Fraction
- Appropriate use of drugs
- Appropriate use of devices
- Cardiac Valve dysfunction in elderly
- Prognostic modelling
- HF patient journey, Remote monitoring
The new “Heart Failure Paradox”

- “Striking improvements in the prognosis of individual cardiac conditions (ACS, severe hypertension, valvular and congenital heart disease) but growing prevalence of heart failure”.

Braunwald E. JACC Heart Failure 2013: 1: 1-20
US: Discharges from HF hospitalization

Braunwald E. JACC Heart Failure 2013: 1: 1-20
US: Projected and actual burden of heart failure

- Actual burden
- Projected burden assuming stable incidence of 10/1000 person-years in persons > 65 years

- 670,000 new HF cases in 2007
- 348,000 new HF cases in 2000

Year:
- 1960
- 1980
- 2000
- 2020
- 2040

Persons (x10,000): 0, 10, 20, 30, 40, 50, 60, 70, 80, 90, 100

Mean age at death with Heart Failure as underlying cause

- Men
- Women
- Total
1-year all-cause mortality

Worsening HF: 27.7%
De Novo HF: 19.2%
Chronic HF: 5.9%
Hospitalized HF patients: in-hospital and 1-year all-cause mortality

- In-hospital mortality (p=0.41)
  - Total n. 1855: 24%
  - Worsening n. 1058: 28%
  - De Novo n. 797: 19%

- 1 year mortality (p<.0001)
  - Total n. 1855: 6.4%
  - Worsening n. 1058: 6.0%
  - De Novo n. 797: 6.9%

Acute HF: causes of 1-year mortality

- Total mortality (p<.0001)
- CV death (p<.0001)
- HF death (p<.0001)

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ESC Heart Failure Guide Lines (2008)

Gaps in evidence: comorbidities

Does any specific treatment of these co-morbidities reduce morbidity and mortality in HF patients?

- diabetes
- COPD
- renal dysfunction
- anaemia
- depression
- disordered breathing during sleep
Prevalence of diabetes in Heart Failure

- Chronic Heart Failure: 20-30%
- Acute Heart Failure: 30-40%
Prevalence of diabetes in heart failure according to left ventricular EF

<table>
<thead>
<tr>
<th>Study</th>
<th>Reduced LVEF</th>
<th>Preserved LVEF</th>
</tr>
</thead>
<tbody>
<tr>
<td>ADHERE</td>
<td>40%</td>
<td>45%</td>
</tr>
<tr>
<td>EURO HF Survey</td>
<td>28%</td>
<td>26%</td>
</tr>
<tr>
<td>CHARM</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>GISSI-HF</td>
<td>27%</td>
<td>28%</td>
</tr>
<tr>
<td>I-PRESERVE</td>
<td>-</td>
<td>28%</td>
</tr>
</tbody>
</table>
Treatment of Diabetes in Heart Failure

Treatment of Heart Failure in Diabetes
Treatment of diabetes in Heart Failure

- **METFORMIN**: first-line, insulin sensitizer. Still inconsistent results in HF.
- **SULFONYLUREAS**: not attractive as insulin-releasing agent. Should only be considered if metformin is contraindicated or in association.
- **Thiazolidinediones**: not recommended
- **Incretin modulators α-glucosidase inhibitors**: not tested in heart failure
- **Insulin**: Prescribed in Diabetes type II when oral treatment fails, and in acute conditions. **Caution recommended** (hypoglycemia)
Acute HF: in-hospital mortality by glycemia and diabetes

<table>
<thead>
<tr>
<th>Glycemia at admittance (mg/dL)</th>
<th>n. 354</th>
<th>n. 83</th>
<th>n. 325</th>
<th>n. 109</th>
<th>n. 232</th>
<th>n. 199</th>
<th>n. 116</th>
<th>n. 315</th>
</tr>
</thead>
<tbody>
<tr>
<td>≤106</td>
<td>3.7</td>
<td>8.4</td>
<td>5.2</td>
<td>5.5</td>
<td>10.8</td>
<td>3.5</td>
<td>7.8</td>
<td>8.3</td>
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<tr>
<td>107-136</td>
<td></td>
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<tr>
<td>137-195</td>
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<td>&gt;195</td>
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</tbody>
</table>
# DPP-4 inhibitors in cardiovascular outcome trials

*(Clinicaltrials.gov)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug/ Expected end</th>
<th>No. of pts</th>
<th>Design</th>
<th>Population</th>
<th>Primary outcome: Time to any event in composite</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAVOR</td>
<td>Saxagliptin (2013)</td>
<td>16500</td>
<td>Superiority vs placebo</td>
<td>• Age &gt; 40 years&lt;br&gt;• High CV risk&lt;br&gt;• Atherosclerotic disease&lt;br&gt;• Risk factors</td>
<td>CV death, non-fatal MI, stroke</td>
</tr>
<tr>
<td>TECOS</td>
<td>Sitagliptin (2014)</td>
<td>14000</td>
<td>NI* vs placebo</td>
<td>• Age ≥ 50 years&lt;br&gt;• History of CV disease</td>
<td>CV death, non-fatal MI, stroke, angina requiring hospitalisation</td>
</tr>
<tr>
<td>EXAMINE</td>
<td>Alogliptin (2015)</td>
<td>5 400</td>
<td>NI vs placebo (if NI met, then test for superiority)</td>
<td>• Age ≥ 18 years&lt;br&gt;• Acute coronary syndrome within previous 15–90 days</td>
<td>CV death, non-fatal MI, stroke</td>
</tr>
<tr>
<td>CAROLINA</td>
<td>Linagliptin vs Glimeperide (2018)</td>
<td>6 000</td>
<td>NI vs glimepiride (if NI met, then test for superiority)</td>
<td>• Age &gt; 40 &lt; 85 years&lt;br&gt;• Pre-existing CV disease OR&lt;br&gt;• Specified diabetes end organ damage OR&lt;br&gt;• age &gt; 70 years OR&lt;br&gt;• ≥ 2 risk factors</td>
<td>CV death, non-fatal MI, stroke, angina requiring hospitalization</td>
</tr>
</tbody>
</table>
GLP-1 receptor agonists in cardiovascular outcome trials *(Clinicaltrials.gov)*

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug/ Expected end</th>
<th>No. of pts</th>
<th>Design</th>
<th>Population</th>
<th>Primary outcome: Time to any event in composite</th>
</tr>
</thead>
<tbody>
<tr>
<td>ELIXA</td>
<td>Lixisenatide 1/day (2014)</td>
<td>6000</td>
<td>Superiority vs placebo</td>
<td>≥ 30 years HbA1c &gt;5.5 &lt; 11% &lt; 180 days after ACS event</td>
<td>CV death, non-fatal MI, stroke, hospitalization for unstable angina</td>
</tr>
<tr>
<td>LEADER</td>
<td>Liraglutide 1/day (2016)</td>
<td>9341</td>
<td>Superiority vs placebo</td>
<td>&gt; 50 years with CV, PAD or RI &gt;60 years with CV risk factors HbA1c ≥ 7 % Drug-naïve or any combination</td>
<td>CV death, non-fatal MI, stroke</td>
</tr>
<tr>
<td>EXSCEL</td>
<td>Exenatide 1/weekly (2017)</td>
<td>9500</td>
<td>Superiority vs placebo</td>
<td>≥ 18 years HbA1c &gt;7 &lt; 10% On ≤ 3 oral agents &lt; 60% prior CV event</td>
<td>CV death, non-fatal MI, stroke</td>
</tr>
</tbody>
</table>
### Other antidiabetis agents in cardiovascular outcome trials (Clinicaltrials.gov)

<table>
<thead>
<tr>
<th>Study</th>
<th>Drug</th>
<th>Population</th>
</tr>
</thead>
<tbody>
<tr>
<td>ACE</td>
<td>Acarbose vs. usual care</td>
<td>T2D at high CV risk</td>
</tr>
<tr>
<td>ALLECARDIO</td>
<td>Aleglitazar vs. placebo</td>
<td>T2D, recent ACS</td>
</tr>
<tr>
<td>CANVAS</td>
<td>Canagliflozin vs. placebo</td>
<td>T2D at high CV risk</td>
</tr>
<tr>
<td>DECLARE – TIMI 58</td>
<td>Dapagliflozin vs. placebo</td>
<td>T2D at high CV risk</td>
</tr>
<tr>
<td>IRIS</td>
<td>Pioglitazone vs. placebo</td>
<td>Insulin resistant, non diabetic, recent stroke or TIA</td>
</tr>
<tr>
<td>LOOKAHEAD</td>
<td>Intensive lifestyle vs. diabetes support and education</td>
<td>T2D</td>
</tr>
</tbody>
</table>
Treatment of Heart Failure in Diabetics

- **Diuretics**: Increase insulin-resistance
- **RAAS Axis**
  - Anti-renin (*Alkiskiren*): neutral or detrimental
  - Anti-angiotensine, Anti-aldosterone: beneficial
- **Beta-blockade**: beneficial (?)
- **Statines**: neutral

All by subgroup analyses of trials
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HF with preserved LVEF in summary

- Multi-factorial disease, related to an abnormal response of both heart and vessels to common CV risk factors (age, hypertension, obesity, physical inactivity) and comorbidities (COPD, diabetes, chronic kidney disease, anemia) lasting decades in vulnerable subjects
HFpEF: an inflammatory disease?

- Two hypotheses
  - HFpEF simply reflects the *cumulative expression* of risk factors/comorbidities,
  - *or*
  - all are united by a common thread consisting in a *systemic inflammatory state*, leading to endothelial dysfunction and driving the clinical syndrome

(Paulus WJ, Tschope C, doi.10.1016/j.jacc.2013.02.092)
HF with preserved LV Ejection Fraction

• Needs:
  - Understanding (research)
  - Prevention (control of risk factors and comorbidities)
  - Therapy (no specific therapy available)
Unmet needs in chronic HF

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• Appropriate use of devices
• Cardiac Valve dysfunction in elderly
• Prognostic modelling
• HF patient journey, Remote monitoring
Aim: To evaluate how recommendations of European guidelines regarding pharmacological and non-pharmacological treatments for HF are adopted in clinical practice
ESCRегистries 2013 - Rate of use and reasons for non use of recommended treatments in HF patients with reduced EF

**ACE-I/ARB**
- ARB: 1033 pts (68.8%)
- ACE-I: 3295 pts (21.6%)
- Contraindicated: n. 94 (2.0%)
- Severe renal dysfunction: n. 61 (64.9%)
- Symptomatic hypotension: n. 13 (13.8%)
- Hyperkalemia: n. 8 (8.5%)
- Other: n. 12 (12.8%)
- Not tolerated: n. 123 (2.6%)
- Worsening renal function: n. 22 (17.9%)
- Symptomatic hypotension: n. 83 (67.5%)
- Hyperkalemia: n. 6 (4.9%)
- Angioedema: n. 2 (1.6%)
- Other: n. 10 (8.1%)
- Real undertreatment: n. 155 (3.2%)

**Betablockers**
- YES: 4439 pts (92.7%)
- NO: 353 pts (7.3%)
- Contraindicated: n. 78 (1.6%)
- Asthma/COPD: n. 28 (35.9%)
- Bradyarrhythmia: n. 11 (14.1%)
- Symptomatic hypotension: n. 11 (14.1%)
- PAD: n. 3 (3.8%)
- Other: n. 25 (32.1%)
- Not tolerated: n. 165 (3.4%)
- Bronchospasm: n. 39 (23.6%)
- Symptomatic hypotension: n. 46 (27.9%)
- Bradyarrhythmia: n. 22 (13.3%)
- Worsening HF: n. 36 (21.8%)
- Other: n. 22 (13.3%)
- Real undertreatment: n. 110 (2.3%)

**MRAs**
- YES: 3209 pts (67.0%)
- NO: 1583 pts (33.0%)
- Contraindicated: n. 268 (5.6%)
- Hyperkalemia: n. 94 (35.1%)
- Renal dysfunction: n. 153 (57.1%)
- Other: n. 21 (7.8%)
- Not tolerated: n. 147 (3.1%)
- Hyperkalemia: n. 53 (36.1%)
- Worsening renal function: n. 34 (23.1%)
- Gynecomastia: n. 34 (23.1%)
- Other: n. 26 (17.7%)
- Not indicated: n. 908 (18.9%)
- Real undertreatment: n. 260 (5.4%)
<table>
<thead>
<tr>
<th>Treatment</th>
<th>At target n. (%)</th>
<th>Not at target n. (%) and Reason for not at target, n. (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>ACE-I</strong></td>
<td>1380 (29%)</td>
<td>3330 (70.7) Still in uptitration 866 (26.0) Symptomatic hypotension 264 (7.9) Worsening renal function 958 (28.8) Other/Unknown</td>
</tr>
<tr>
<td>(4710 pts)</td>
<td></td>
<td>1123 (33.7) Still in uptitration 866 (26.0) Symptomatic hypotension 264 (7.9) Worsening renal function 958 (28.8) Other/Unknown</td>
</tr>
<tr>
<td><strong>ARBs</strong></td>
<td>362 (24%)</td>
<td>1138 (75.9) Still in uptitration 295 (25.9) Symptomatic hypotension 115 (10.1) Worsening renal function 333 (29.3) Other/Unknown</td>
</tr>
<tr>
<td>(1500 pts)</td>
<td></td>
<td>369 (32.4) Still in uptitration 295 (25.9) Symptomatic hypotension 115 (10.1) Worsening renal function 333 (29.3) Other/Unknown</td>
</tr>
<tr>
<td><strong>Betablockers</strong></td>
<td>1130 (17%)</td>
<td>5338 (82.5) Still in uptitration 904 (16.9) Symptomatic hypotension 586 (11.0) Bradyarrhythmia 1557 (29.2) Other/Unknown</td>
</tr>
<tr>
<td>(6468 pts)</td>
<td></td>
<td>1871 (35.1) Still in uptitration 904 (16.9) Symptomatic hypotension 586 (11.0) Bradyarrhythmia 1557 (29.2) Other/Unknown</td>
</tr>
<tr>
<td><strong>MRAs</strong></td>
<td>1290 (30%)</td>
<td>2936 (69.5) Still in uptitration 350 (11.9) Hyperkalemia 1378 (46.9) Other/Unknown</td>
</tr>
<tr>
<td>(4226 pts)</td>
<td></td>
<td>864 (29.4) Still in uptitration 350 (11.9) Hyperkalemia 1378 (46.9) Other/Unknown</td>
</tr>
</tbody>
</table>

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ESC-HF Registry, 2013 - Rate of implantation of devices and reasons for non implantation

**ICD (7401 pts)**
- Already implanted (n. 1745)
- Not indicated (n. 4597)
- Indicated (n. 731)
- Unknown (n. 328)

23.6% Already implanted
62.1% Not indicated

**CRT (7401 pts)**
- Already implanted (n. 942)
- Not indicated (n. 5678)
- Indicated (n. 450)
- Unknown (n. 331)

76.7% Already implanted

**323/731=44% Indicated but not planned**

- Planned (n. 408)
- Not planned (n. 323)
  - 5.5%
  - 4.4%
  - 9.9%

**Reasons**
- 161 pts Uncertainty in the indication
- 81 pts Patient refusal
- 51 pts Logistic/cost issue
- 30 pts Unknown

**178/450=40% Indicated but not planned**

- Planned (n. 272)
- Not planned (n. 178)
  - 3.7%
  - 2.4%
  - 6.1%

**Reasons**
- 85 pts Uncertainty in the indication
- 36 pts Patient refusal
- 34 pts Logistic/cost issue
- 23 pts Unknown
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TransCatheter Valve Treatment, Pilot

- 12 Countries participating

- Patients:  - TAVI : 5140
             - Mitral : 769
TCVT Pilot Registry
Haemodynamic Changes after TAVI

AVA

<table>
<thead>
<tr>
<th>cm²</th>
<th>Pre</th>
<th>Post</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>0.68</td>
<td>1.81</td>
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</table>

LV/Ao GRADIENT

<table>
<thead>
<tr>
<th>mmHg</th>
<th>Pre</th>
<th>Post</th>
</tr>
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<tbody>
<tr>
<td></td>
<td>49.1</td>
<td>11.2</td>
</tr>
<tr>
<td>Complication</td>
<td>Femoral</td>
<td>Apical</td>
</tr>
<tr>
<td>------------------------------</td>
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<td>--------</td>
</tr>
<tr>
<td>Death (Total 7.4%)</td>
<td>5.9</td>
<td>12.8</td>
</tr>
<tr>
<td>Stroke (Total 1.8%)</td>
<td>1.9</td>
<td>1.6</td>
</tr>
<tr>
<td>MI (Total 0.9%)</td>
<td>0.9</td>
<td>0.7</td>
</tr>
<tr>
<td>PM implantation</td>
<td>15.5</td>
<td>4.5</td>
</tr>
<tr>
<td>Haemodialysis</td>
<td>1.2</td>
<td>2.4</td>
</tr>
<tr>
<td>Transfusion(s)</td>
<td>15</td>
<td>20.8</td>
</tr>
<tr>
<td>New onset AF</td>
<td>5.1</td>
<td>9</td>
</tr>
<tr>
<td>Hosp. stay &gt;10 days</td>
<td>22</td>
<td>43.8</td>
</tr>
</tbody>
</table>
At 1 month follow-up, 81.7% of the patients were in NYHA class I-II.
Mitral Regurgitation and Severity & LVEF

PRE
- SEVERE: 83.6%
- MODERATE: 14.6%
- MILD: 1.83%

POST
- SEVERE: 10.1%
- MODERATE: 28.8%
- MILD: 67.7%

LVEF
- PRE: 39.6%
- POST: 37.8%
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Prognostic Modelling in Chronic Heart Failure
2012 ESC Heart Failure Guidelines PROGNOSTICATION

a list of 57 variables shown to be predictive of outcome
• **20 different risk models** developed for patients with heart failure.

• Only 5 with external validation, showing poor-to-modest discrimination (c-statistic, 0.56–0.79), being lower in more recent cohorts, and overall showing inconsistent performance.
Prognostic scores are not used in clinical practice. WHY?

- Non representative of real world (selected or undefined populations: age, comorbidities, HF severity, “once forever” assessment)
- Trials are disease-specific, but multimorbidity is the norm ≥65 years (2/3 of chronic HF pts)
- No sequential data and time-related analyses
- Not useful for decision making
- Lack of personalized therapy (same for all)
Predictive Models in Heart Failure. Who Cares?

• Currently, *time to-event nature of the data* are not taken into account.

• **Models** considering the inception point of patient observation and *updated* according to changes in the patient’s condition are needed.

• The new data electronic fabric will enable development of algorithms that can make predictions in real time about near-term and long-term prognosis and enable evaluation of the comparative effectiveness of choices about diagnosis, prevention, and treatment.
Predictive Models in Heart Failure. Who Cares?

• Califf’s dream:

  “personal mobile devices will record and feed physiological data to electronic health records.

  New data electronic fabric will enable development of algorithms that can make predictions in real time about nearterm and long-term prognosis and enable evaluation of the comparative effectiveness of choices about diagnosis, prevention, and treatment”
HF prognostic modelling in clinical practice
The ESC programme (EORP)

• All variables showed as independent prognostic indicators in large MM RCTs are included in the ongoing Long-term Heart Failure Registry for:
  - comparing the prognostic power of available risk scores in the same population
  - searching for new scores and algorithms
  - taking advantage from the large numbers available to test the validity of new scores in the overall populations and selected groups
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