New Frontiers
The Historical Evolution of Beta-Blockers &
ACEi / ARBs / ARNI
1). MCP Bases of Transition from Disease to Health

1. Two Critical Tools – Imaging, Genetics

2. Three Behavioral Ages - Elderly, Mid Life, Children

3. Two Historical Paths – B. Blockers, ACE / ARBs / ARNI

4. Two Historical Paths – Statins / PCSK9i, SGLT2i / GLP1-RA

Cardona, July 15, 2019

No Disclosures
## Pharmacologic Properties of Common Prescribed β-Blockers

<table>
<thead>
<tr>
<th>Drug</th>
<th>β1/β2 Selectivity (Cardio-Selectivity)</th>
<th>ISA</th>
<th>Half-Life</th>
<th>Additional Properties</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Second generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Bisoprolol</td>
<td>++</td>
<td>0</td>
<td>9-12</td>
<td></td>
</tr>
<tr>
<td>Metoprolol</td>
<td>++</td>
<td>0</td>
<td>3-7</td>
<td></td>
</tr>
<tr>
<td>Atenolol</td>
<td>+</td>
<td>0</td>
<td>6-9</td>
<td></td>
</tr>
<tr>
<td><strong>Third generation</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Carvedilol</td>
<td>0</td>
<td>0</td>
<td>7-10</td>
<td>α1-receptor inhibition mediated vasodilation</td>
</tr>
<tr>
<td>Nebivolol</td>
<td>+++</td>
<td>0</td>
<td>8-27</td>
<td>L-arginine/nitric oxide mediated vasodilation</td>
</tr>
</tbody>
</table>

*P Joseph, S Yusuf et. al. J Am Coll Cardiol 2019;74:672*
## Effects of β-Blockers in Heart Failure

<table>
<thead>
<tr>
<th>Cardiac Disease</th>
<th>Effects of β-Blockers Based on RCTs</th>
<th>Recommendations</th>
</tr>
</thead>
<tbody>
<tr>
<td>Heart failure with reduced ejection fraction</td>
<td>• Reduces mortality</td>
<td>• Use widely</td>
</tr>
<tr>
<td></td>
<td>• Reduces hospitalizations</td>
<td></td>
</tr>
<tr>
<td>Heart failure with mid-range or preserved ejection</td>
<td>• Insufficient data on major adverse</td>
<td>• No data to support use without a secondary</td>
</tr>
<tr>
<td>fraction</td>
<td>cardiac outcomes</td>
<td>indication (i.e. atrial fibrillation, hypertension)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>• Large RCTs needed</td>
</tr>
</tbody>
</table>

β-Blockers and Clinical Outcomes by EF in a Patient-Level Meta-Analysis of 11 RCTs

## Effects of β-Blockers in Coronary Disease

### Post ACS

**Immediate effect:**
- Reduces mortality (pre-reperfusion era data)
- Reduces re-infarction
- Can increase risk of heart failure and cardiogenic shock (mainly observed in patients at higher risk)

**Longer-term effect:**
- Reduces mortality (pre-reperfusion era data)

**Initiate post-ACS in patients without a low blood pressure or clinical evidence of decompensated heart failure**
- Start at low doses, and titrate gradually to avoid adverse effects.
- Continue treatment for up to 3 years (or permanently if heart failure with reduced ejection fraction)
- Large contemporary RCTs in progress to study long-term effect in patients without left ventricular dysfunction

### Stable CAD (without recent ACS, and with normal left ventricular function)

**Insufficient data on major adverse cardiac outcomes**

**Use for angina**
- No data to support routine use
- Large RCTs needed

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*P Joseph, S Yusuf et. al. J Am Coll Cardiol 2019;74:672*
We analysed the use of β-blockers or calcium antagonists (baseline and annually) and outcomes in 22,006 stable CAD patients (enrolled 2009-2010) followed annually to 5 years, in the CLARIFY registry (45 countries). Primary outcome was all-cause death. Secondary outcomes were CVD death and the composite of CVD death/non-fatal MI. In this contemporary cohort of stable CAD, β-blocker use was associated with lower 5-year mortality (all cause 7% vs 10%; CV 4.5% vs 8.5%) only in patients enrolled in the year following MI. Use of calcium antagonists was of no benefit associated with...

CLARIFY (E Sorbets, KM Fox et al.), Eur Heart J 2019; 40:1399
All-cause Mortality According To β-blocker Use, Time Elapsed Since The Index MI Prior To Enrolment

CLARIFY (E Sorbets, KM Fox et. al.) Eur Heart J. 2019;40:1399
We examine the current evidence supporting β-blocker use in HFpEF, HFmEF and HFrEF, post ACS & in stable CAD. β-Blockers remain essential in HFrEF, but limited evidence supports their use in HFmEF or HFpEF. Are considered routinely following ACS, but there is a need for contemporary trials in patients without LV dysfunction, as well as in stable CAD. From a global perspective, more studies are needed to characterize the extent of β-blocker use in CAD and HF, and how evidence-based use can be improved in these conditions.
β-Blocker Use in Participants With Established CAD - the PURE Study

Among 2,588 U.S. outpatients with chronic HFrEF in the CHAMP-HF registry with complete medication data and no contraindications to medical therapy, use and dose were examined at baseline and at 12-month follow-up. Most eligible HFrEF patients did not receive target doses of medical therapy at any point during follow-up, and few patients had doses increased over time.

Molecular (M), Clinical (C), Population (P) Bases of Cardiovascular Disease and Health, 2019

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Cardona, July 15, 2019

No Disclosures
The pharmacological inhibition of the RAAS is one of the most significant advances in the treatment and prevention of HFrEF and in CAD. Recently, the addition of neprilysin inhibition to ARB or ARNI has been shown to be even more effective than ACEI inhibition alone in HFrEF. This review summarizes the major trials that have informed the clinical role of inhibition of the RAA and neprilysin pathways, as well as the limitations of these strategies.
Chronology of Landmark Trials Involving RAAS/ACEI in HFrEF & CAD

# Evidence for Use of ACEI, ARB, MCRA & ARNI in Coronary Artery Disease and Heart Failure

**Table:**

<table>
<thead>
<tr>
<th></th>
<th>Stable Atherosclerotic Vascular Disease</th>
<th>High-Risk Post-Myocardial Infarction</th>
<th>Acute Post-Myocardial Infarction</th>
<th>Heart Failure With Reduced Ejection Fraction</th>
<th>Heart Failure With Midrange Ejection Fraction</th>
<th>Heart Failure With Preserved Ejection Fraction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Angiotensin-Converting Enzyme Inhibitor</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Angiotensin Receptor Blockers</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>-</td>
</tr>
<tr>
<td>Mineralocorticoid Receptor Antagonists</td>
<td>?</td>
<td>+</td>
<td>+</td>
<td>+</td>
<td>?</td>
<td>(+)</td>
</tr>
<tr>
<td>Angiotensin Receptor-Neprilisin Inhibitors</td>
<td>?</td>
<td>To Be Determined</td>
<td>To Be Determined</td>
<td>+</td>
<td>To Be Determined</td>
<td>To Be Determined</td>
</tr>
</tbody>
</table>

**References:**

The Effects of RASI or MCRI on Mortality in Stable Vascular Disease or HFrEF

<table>
<thead>
<tr>
<th>Study ID</th>
<th>OR (95% CI)</th>
<th>% Weight</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atherosclerotic vascular disease</td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIRe</td>
<td>0.70 (0.56, 0.87)</td>
<td>2.16</td>
</tr>
<tr>
<td>Chinese Captopril</td>
<td>0.94 (0.84, 1.05)</td>
<td>14.85</td>
</tr>
<tr>
<td>EUROPA</td>
<td>0.89 (0.77, 1.02)</td>
<td>13.30</td>
</tr>
<tr>
<td>GISSI-3</td>
<td>0.88 (0.79, 0.99)</td>
<td>20.57</td>
</tr>
<tr>
<td>HOPE</td>
<td>0.83 (0.73, 0.94)</td>
<td>10.12</td>
</tr>
<tr>
<td>PEACE</td>
<td>0.88 (0.75, 1.04)</td>
<td>9.03</td>
</tr>
<tr>
<td>PROGRESS</td>
<td>0.96 (0.81, 1.13)</td>
<td>6.65</td>
</tr>
<tr>
<td>SAVE</td>
<td>0.79 (0.64, 0.96)</td>
<td>2.43</td>
</tr>
<tr>
<td>TRACE</td>
<td>0.73 (0.60, 0.88)</td>
<td>1.90</td>
</tr>
<tr>
<td>TRANSCEND</td>
<td>1.06 (0.90, 1.24)</td>
<td>6.45</td>
</tr>
<tr>
<td>Subtotal (I-squared = 54.1%, p = 0.020)</td>
<td>0.89 (0.85, 0.94)</td>
<td>87.47</td>
</tr>
<tr>
<td>Heart failure with reduced EF</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CONSENSUS</td>
<td>0.55 (0.34, 0.91)</td>
<td>0.28</td>
</tr>
<tr>
<td>RALES</td>
<td>0.56 (0.46, 0.68)</td>
<td>1.87</td>
</tr>
<tr>
<td>SOLVD-P</td>
<td>0.93 (0.79, 1.10)</td>
<td>4.60</td>
</tr>
<tr>
<td>SOLVD-T</td>
<td>0.82 (0.70, 0.97)</td>
<td>2.80</td>
</tr>
<tr>
<td>EMPHASIS-HF</td>
<td>0.78 (0.63, 0.97)</td>
<td>2.98</td>
</tr>
<tr>
<td>Subtotal (I-squared = 83.6%, p = 0.000)</td>
<td>0.81 (0.73, 0.89)</td>
<td>12.53</td>
</tr>
<tr>
<td>Overall (I-squared = 76.1%, p = 0.000)</td>
<td>0.88 (0.84, 0.92)</td>
<td>100.00</td>
</tr>
</tbody>
</table>

The Effects of RASIs on MI in Stable Vascular Disease or HFrEF

Nonfatal Myocardial Infarction

<table>
<thead>
<tr>
<th>Study</th>
<th>OR (95% CI)</th>
<th>Events, Treatment</th>
<th>Events, Control</th>
</tr>
</thead>
<tbody>
<tr>
<td>Trials without LV dysfunction or HF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>HOPE (n = 9297)</td>
<td>0.77 (0.66, 0.91)</td>
<td>273/9297</td>
<td>351/9297</td>
</tr>
<tr>
<td>EUROPA (m = 12,218)</td>
<td>0.78 (0.67, 0.90)</td>
<td>295/12218</td>
<td>378/12218</td>
</tr>
<tr>
<td>PEACE (n = 8290)</td>
<td>1.01 (0.84, 1.22)</td>
<td>222/8290</td>
<td>220/8290</td>
</tr>
<tr>
<td>Subtotal (I-squared = 64.6%, p = 0.059)</td>
<td></td>
<td>790/29805</td>
<td>949/29805</td>
</tr>
<tr>
<td>Trials with LV dysfunction or HF</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>SAVE (n = 2231)</td>
<td>0.79 (0.60, 1.03)</td>
<td>101/2231</td>
<td>127/2231</td>
</tr>
<tr>
<td>AIRE (n = 1986)</td>
<td>0.96 (0.68, 1.34)</td>
<td>68/1986</td>
<td>71/1986</td>
</tr>
<tr>
<td>TRACE (n = 1749)</td>
<td>0.76 (0.55, 1.05)</td>
<td>66/1749</td>
<td>86/1749</td>
</tr>
<tr>
<td>SOLVD-P (n = 4228)</td>
<td>0.70 (0.54, 0.89)</td>
<td>103/4228</td>
<td>147/4228</td>
</tr>
<tr>
<td>SOLVD-T (n = 2569)</td>
<td>0.79 (0.57, 1.10)</td>
<td>66/2569</td>
<td>83/2569</td>
</tr>
<tr>
<td>Subtotal (I-squared = 0.0%, p = 0.695)</td>
<td>0.78 (0.68, 0.89)</td>
<td>404/12763</td>
<td>514/12763</td>
</tr>
<tr>
<td>Overall (I-squared = 16.6%, p = 0.299)</td>
<td>0.81 (0.75, 0.88)</td>
<td>1194/42568</td>
<td>1463/42568</td>
</tr>
</tbody>
</table>

The Effects of RASI on Stroke in Vascular Disease or HFrEF

DP Leong, S Yusuf et. al. J Am Coll Cardiol 2019;74:683 - 16%
Among 2,588 U.S. outpatients with chronic HFrEF in the CHAMP-HF registry with complete medication data and no contraindications to medical therapy, use and dose were examined at baseline and at 12-month follow-up. Most eligible HFrEF patients did not receive target doses of medical therapy at any point during follow-up, and few patients had doses increased over time.
## Cardiovascular Medications in Pregnancy

### Arrhythmias
- Adenosine
- Metoprolol/propranolol
- Digoxin
- Lidocaine
- Verapamil
- Diltiazem
- Procaainamide
- Sotalol
- Flecainide
- Propafenone
- Amiodarone

*May be used only if other therapies fail.

### Hypertension
- Labetalol
- Nifedipine
- Alpha-methyldopa (oral)
- Hydralazine
- Nitroglycerin
- Nitroprusside
- Isosorbide dinitrate
- Amlodipine
- Furosemide
- Hydrochlorothiazide
- Clonidine

### Heart Failure
- Metoprolol
- Carvedilol
- Furosemide
- Bumetanide
- Dopamine
- Dobutamine
- Norepinephrine
- Hydralazine
- Nitroglycerin
- Isosorbide dinitrate
- Torsemide
- Metolazone

### Pulmonary Hypertension
- Iloprost
- Epoprostenol
- Sildenafil
- Treprostinil

### Contraindicated in Pregnancy
- Atenolol
- ACE-I class
- ARB class
- Aldosterone antagonists
- Statin class
- DOACs
- ERAs (e.g., bosantan)

*# captopril, benazepril and enalapril are considered safe during lactation.

### Anticoagulants/Antiplatelets/Thrombolytics
- **Anticoagulants**
  - Warfarin
  - Unfractionated Heparin
  - Enoxaparin
  - Fondaparinux
  - Argatroban
  - Bivalirudin

- **Antiplatelets**
  - Aspirin (low dose)
  - Clopidogrel
  - Prasugrel
  - Ticagrelor
  - Thrombolytics
  - Alteplase
  - Streptokinase

### Safety in Pregnancy
- **FDA category**
  - Considered safe
  - Limited data/to be used with caution
  - Contraindicated
  - Conflicting data/unknown

### Safety in Lactation
- **Used also for fetal treatment**
  - Considered safe
  - Limited data/to be used with caution
  - Contraindicated
  - Conflicting data/unknown

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DG Halpern, AM Valente et. al. J Am Coll Cardiol 2019;73:457
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