Innovating hypertension management beyond current therapies: What are the opportunities?

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London, United Kingdom

Presented - August 30, 2014
Innovations in Hypertension Therapies

• New drugs
• Renovascular Intervention
• Device-based therapies
# New Drugs for Hypertension

<table>
<thead>
<tr>
<th>Drug</th>
<th>Preclinical stage</th>
<th>Phase 1-3</th>
<th>Pharmaceutical industry</th>
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<td>Dual vasopeptidase inhibitor</td>
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<tr>
<td>Dual nephrilysin-ACE inhibitor</td>
<td>Ilepatril (AVE7688)</td>
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<td>Dual ARNI</td>
<td>LCZ696</td>
<td>Phase 3</td>
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<td>Aldosterone-synthase inhibitor</td>
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<td>Novel dual ARB and partial PPAR-γ agonist</td>
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<td>AGE breaker</td>
<td>Alagebrum (ALT-711)</td>
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<td>Synvista Therapeutics</td>
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A new drug class – angiotensin receptor neprilysin inhibitor (ARNI)

ARNI

Angiotensin receptor blocker

Neprilysin inhibitor

A single compound that can deliver concomitant inhibition of neprilysin and blockade of the AT₁ receptor
Physiological actions of natriuretic peptides

Why is a NEP inhibitor alone not an effective antihypertensive?
LCZ696: a first-in-class ARNI

- **LCZ696** is a new compound. The structure comprises molecular moieties of the neprilysin inhibitor pro-drug **AHU377** and the AT$_1$ receptor blocker valsartan in their anion forms$^1$

- **AHU377** is rapidly converted to **LBQ657** (active, highly selective NEPi) by nonspecific esterases (ester hydrolysis)

- LCZ696 is the first in a **new class** of compounds called **angiotensin receptor neprilysin inhibitors** (ARNIs)$^{1,2}$

LCZ696 versus Valsartan on mean seated SBP and DBP

Mean change from baseline in msBP at Week 8 (mmHg)

SBP reduction (placebo-subtracted)

<table>
<thead>
<tr>
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<th>AHU 200</th>
<th>Val 80</th>
<th>LCZ 100</th>
<th>Val 160</th>
<th>LCZ 200</th>
<th>Val 320</th>
<th>LCZ 400</th>
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DBP reduction (placebo-subtracted)

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<td>DBP (mmHg)</td>
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<tr>
<td>p</td>
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LCZ696 provides significantly greater reductions from baseline in Pulse Pressure than valsartan

Mean change from baseline in mean ambulatory PP (mmHg)

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<thead>
<tr>
<th></th>
<th>Val 80</th>
<th>Val 160</th>
<th>Val 320</th>
<th>LCZ 100</th>
<th>LCZ 200</th>
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<td>54</td>
<td>48</td>
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<td>-1.38</td>
<td>-0.88</td>
<td>-0.80</td>
<td>-2.36</td>
<td>-3.37</td>
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p=0.42  
p=0.0356  
p=0.0009

Potential of the ARNI

- More BP lowering than RAAS blockade alone or any other BP monotherapy
- Especially potent effects on SBP and pulse pressure – ideal for systolic hypertension
- Excellent tolerability profile
- Potential for metabolic neutrality
- Potential potent combinations with CCB or thiazide diuretic when more BP lowering is required
- Natriuresis – Applications in heart failure – data on pivotal trial to be presented at this meeting
Atherosclerotic Renovascular Disease
To stent or not to stent…?

Recommended Indications:
• Flash pulmonary oedema with bilateral renal artery stenosis
• Critical stenosis when RAS blockade is desirable

But, what about?
• Renal ischaemia and declining renal function?
• Poorly controlled BP?
Revascularization versus Medical Therapy for Renal-Artery Stenosis

The ASTRAL Investigators*

ABSTRACT

In a randomized, unblinded trial, we assigned 806 patients with atherosclerotic renovascular disease either to undergo revascularization in addition to receiving medical therapy or to receive medical therapy alone. The primary outcome was renal function, as measured by the reciprocal of the serum creatinine level (a measure that has a linear relationship with creatinine clearance). Secondary outcomes were blood pressure, the time to renal and major cardiovascular events, and mortality. The median follow-up was 34 months.
“We found substantial risks but no evidence of a worthwhile clinical benefit from revascularization in patients with atherosclerotic renovascular disease”

ASTRAL Investigators NEJM 2009;361:1953-62
Stenting and Medical Therapy for Atherosclerotic Renal-Artery Stenosis

Christopher J. Cooper, M.D., Timothy P. Murphy, M.D., Donald E. Cutlip, M.D., Kenneth Jamerson, M.D., William Henrich, M.D., Diane M. Reid, M.D., David J. Cohen, M.D., Alan H. Matsumoto, M.D., Michael Steffes, M.D., Michael R. Jaff, D.O., Martin R. Prince, M.D., Ph.D., Eldrin F. Lewis, M.D., Katherine R. Tuttle, M.D., Joseph I. Shapiro, M.D., M.P.H., John H. Rundback, M.D., Joseph M. Massaro, Ph.D., Ralph B. D’Agostino, Sr., Ph.D., and Lance D. Dworkin, M.D., for the CORAL Investigators

Primary end point: death from cardiovascular or renal causes, stroke, myocardial infarction, hospitalization for congestive heart failure, progressive renal insufficiency, or permanent renal-replacement therapy

CORAL Study Primary Outcome

CONCLUSIONS

Renal-artery stenting did not confer a significant benefit with respect to the prevention of clinical events when added to comprehensive, multifactorial medical therapy in people with atherosclerotic renal-artery stenosis and hypertension or chronic kidney disease. (Funded by the National Heart, Lung and Blood Institute and others; ClinicalTrials.gov number, NCT00081731.)
Device Based Therapies for Hypertension

- Renal Denervation – catheter based
- Renal Denervation – Highly focused Ultrasound
- Carotid Baroreceptor Stimulation
- Peripheral nerve stimulation
- Arteriovenous fistula
- Carotid body resection
Catheter-based renal sympathetic denervation for resistant hypertension: a multicentre safety and proof-of-principle cohort study

Henry Krum, Markus Schlaich, Rob Whitbourn, Paul A Sobotka, Jerzy Sadowski, Krzysztof Bartus, Boguslaw Kapelak, Anthony Walton, Horst Sievert, Suku Thambir, William T Abraham, Murray Esler

Baseline office BP: 177/101
Mean 4.7 BP drugs

Renal sympathetic denervation in patients with treatment-resistant hypertension (The Symplicity HTN-2 Trial): a randomised controlled trial

Symplicity HTN-2 Investigators*

• **Purpose**: To demonstrate the effectiveness of catheter-based renal denervation for reducing blood pressure in patients with uncontrolled hypertension in a prospective, randomized, controlled, clinical trial

• **Patients**: 106 patients randomized 1:1 to treatment with renal denervation vs. control

• **Clinical Sites**: 24 centers in Europe, Australia, & New Zealand

• **Time**: Enrollment took place from June 2009 to January 2010

Symplicity HTN-2 Investigators, Lancet 2012
Symplicity HTN-2 Primary End-Point

Symplicity HTN-2 Investigators, Lancet 2012
Symplicity HTN-2 Extended Follow Up (36m)

- **6 mo** (n = 84)
  - Systolic: -28.3 ± 25.2 (-33.8, -22.9)
  - Diastolic: -10.4 ± 11.6 (-12.9, -7.8)

- **12 mo** (n = 80)
  - Systolic: -26.3 ± 27.3 (-32.4, -20.2)
  - Diastolic: -9.9 ± 11.3 (-12.4, -7.3)

- **18 mo** (n = 74)
  - Systolic: -30.7 ± 28.8 (-37.3, -24.0)
  - Diastolic: -11.8 ± 12.7 (-14.7, -8.8)

- **24 mo** (n = 69)
  - Systolic: -30.3 ± 25.5 (-36.4, -24.1)
  - Diastolic: -11.3 ± 11.0 (-13.9, -8.6)

- **30 mo** (n = 69)
  - Systolic: -33.6 ± 27.9 (-40.3, -26.9)
  - Diastolic: -12.6 ± 12.7 (-15.6, -9.5)

- **36 mo** (n = 40)
  - Systolic: -32.7 ± 24.1 (-40.4, -24.9)
  - Diastolic: -13.6 ± 12.1 (-17.4, -9.7)

Renal Denervation – So far, So Good….

- Seemingly excellent and durable BP responses in pretty much everybody
- Safe procedure
- Simple to perform
- Explosion in development of devices and studies
- Feeding frenzy amongst cardiologists – sudden huge interest in patients with hypertension!
A Controlled Trial of Renal Denervation for Resistant Hypertension

Deepak L. Bhatt, M.D., M.P.H., David E. Kandzari, M.D., William W. O’Neill, M.D., Ralph D’Agostino, Ph.D., John M. Flack, M.D., M.P.H., Barry T. Katzen, M.D., Martin B. Leon, M.D., Minglei Liu, Ph.D., Laura Mauri, M.D., Manuela Negoita, M.D., Sidney A. Cohen, M.D., Ph.D., Suzanne Oparil, M.D., Krishna Rocha-Singh, M.D., Raymond R. Townsend, M.D., and George L. Bakris, M.D., for the SYMPPLICITY HTN-3 Investigators*
SYMPPLICITY HTN-3 Trial Design

Screening Visit 1
- Office SBP ≥160 mm Hg
- Full doses ≥3 meds
- No med changes in past 2 weeks
- No planned med changes for 6 M

Screening Visit 2
- Office SBP ≥160 mm Hg
- 24-h ABPM SBP ≥135 mm Hg
- Documented med adherence

Sham Procedure
- Renal angiogram; Eligible subjects randomized

Primary endpoint
- Home BP & HTN med confirmation

2 weeks
- Home BP & HTN med confirmation

1 M 3 M 6 M
- Home BP & HTN med confirmation

12-60 M

• Patients, BP assessors, and study personnel all blinded to treatment status
• No changes in medications for 6 M

Primary Efficacy Endpoint – Office Systolic BP

Conclusions – ACC Presentation

- In a prospective, multicenter, randomized, blinded, sham controlled trial of patients with uncontrolled resistant hypertension, percutaneous renal denervation was safe but not associated with significant additional reductions in office or ambulatory blood pressure.

- These results underscore the importance of blinding and sham controls in evaluations of new devices.
Reflections

- Surprising result in view of consistent data from observational studies and registry data
- But…these are not RCTs – Symplicity HTN-3 result is Unequivocal
- Clear and equivalent response in the Sham operated group
- Placebo effect? – Unlikely: Placebo effect is unusual with ABPM
- Does renal denervation prompt people to start taking their medication?
- Still a major problem that the magnitude of “denervation” cannot be measured
Catheter-Based Renal Denervation for Resistant Hypertension
12-Month Results of the EnligHTN I First-in-Human Study Using a Multielectrode Ablation System

Seated Clinic BP

<table>
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<tr>
<th>Month</th>
<th>Systolic BP</th>
<th>Diastolic BP</th>
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<tbody>
<tr>
<td>1</td>
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<td>-10</td>
</tr>
<tr>
<td>3</td>
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24hr ABPM

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Papademetriou V, et al. Hypertension 2014
Renal Denervation with Catheter-based Ultrasound (Recor Medical)
Noninvasive Renal Sympathetic Denervation by Extracorporeal High-Intensity Focused Ultrasound in a Pre-Clinical Canine Model

Wang Q, et al. JACC 2013
Ateriovenous Anastomosis (Rox Coupler)

- **Right Atrial Pressure**
  - ANP release → vasodilatation
  - Bainbridge reflex → ↑ heart rate
  - peripheral sympatho-inhibition

- **Cardiac Output**
  - ↑ venous oxygenation & pulmonary blood flow
  - Activation of pulmonary arterial mechanoreceptors
  - Venous baroreceptor activation

- **Systemic Vascular Resistance**
  - ↑ arterial compliance
  - ↓ reflected pulse wave
  - ↓ effective arterial volume
  - ↑ tissue oxygen delivery
  - ↓ chemoreceptor activity
  - ↓ sympatho-excitation due to cerebral / renal hypoperfusion
  - ↓ sodium and water retention

Burchell AE et al. Hypertension 2014
Conclusions

• Development of drug and device-based therapies for hypertension remains vigorous
• We have very effective therapies for the majority
• The unmet need is in the control of systolic hypertension in ageing populations and in stratified areas, e.g. true resistant hypertension, hyperaldosteronism, and in improving target organ protection for the heart (HFPEF), the Brain (stroke, dementia), and the kidney
• All studies need appropriate controls