“Caridology Pearls for the Hospitalist”

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Stanford University School of Medicine
October 17, 2015

Disclosures

I have nothing to disclose
Goals of This Talk

• Focus on real-life clinical scenarios you will encounter
• Separate myths from reality
• Discuss new heart failure drugs you will be seeing

A Common Scenario…

• 75 y.o. woman with DM well-controlled on metformin
• Admitted with chest pain, EKG changes, +troponin
  • Chest pain resolves with antiplatelets, anticoagulants, nitrates
  • Scheduled for coronary angiogram the next day
• Cr at admission: 1.0 mg/dl
• Glucose at admission: 100 mg/dl
• How do you manage her diabetes?
How Do You Manage Her Diabetes?

1) Continue metformin + ISS if needed
2) D/C metformin, switch to sulfonylurea
3) D/C metformin, switch to ISS
4) D/C metformin, switch to long-acting insulin + ISS
How Big a Problem is This?

- Phenformin: A real issue → sunk the drug → withdrawn almost everywhere in 1970s.
- Metformin: A real issue too?
- Meta-analysis (2003): All trials/observational studies comparing metformin with other treatments
  - What is the incidence of lactic acidosis?
    - Patient years:
      - Metformin: 36,893
      - Non-metformin: 30,109
  - Incidence of lactic acidosis:
    - 0 in entire cohort
    - [95% CI] = 0-0.008% annual rate
  - Average blood lactate levels: Unchanged.


Why Exactly Are We Worried?

- Reason for stopping metformin: Risk of lactic acidosis
- Let’s think this through logically…
  - Let’s assume that metformin-induced lactic acidosis is even a real entity (more to come on that…)
  - Primary risk factor: Advanced kidney dysfunction
  - What timeframe do we typically hold metformin for a contrast procedure?
  - What timeframe does contrast nephropathy occur in?
Why Exactly Are We Worried?

• We stop metformin for the following hypothetical scenario…
  • Contrast dye $\rightarrow$ Renal failure (itself rare)
  • Renal failure $\rightarrow$ Risk factor for metformin-associated lactic acidosis
  • Except… It’s not even clear that metformin really causes lactic acidosis, and…
  • The timeframe of when we stop the metformin is out of synchrony with when we would expect the renal failure.

• Does this make *any* sense???

Calling the Practice What it Is

• Superstition (definition):
  • “A belief or notion, not based on reason or knowledge, of the ominous significance of a particular thing.”
  • “A custom or act based on such a thing.”

• Holding metformin before contrast procedures = Flat Earth Society membership
  • Both seemed to make sense at one point…
  • But we should know better now!
A Very Common Scenario

- 71 y.o. woman with h/o HTN, DM, A-fib
- At baseline takes warfarin for stroke prophylaxis
  - No history of major bleeding
- Admitted to you with NSTEMI
  - Taken to cath lab → high grade lesion → successful DES placement.
  - What do you do with her anticoagulation/antiplatelet therapy?

Which of These is the Best Option?

1) Aspirin + Clopidogrel
2) Aspirin + Warfarin
3) Clopidogrel + Warfarin
4) Aspirin + Clopidogrel + Warfarin
5) Take your pick – there’s no evidence!
Which of These is the Best Option?

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5) Take your pick – there’s no evidence!

A Quick Aside About
Trial Names & Karma…
DINAMIT Trial: ICDs Post-MI

Adapted from Hohnloser et al. NEJM. 2004;351:2481-8.

DEFINITE Trial: ICDs in Nonischemic Heart Failure

Adapted from Kadish et al. NEJM. 2004;350:2151-8.
DEFINITE Trial: ICDs in Nonischemic Heart Failure

Adapted from Kadish et al. NEJM. 2004;350:2151-8.

BEST Trial: Bucindolol for Heart Failure

Adapted from NEJM. 2001;344:1659-67.
“What is the optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary stenting?”

“What is the Optimal antiplatelet and anticoagulant therapy in patients with oral anticoagulation and coronary Stenting?”
“WOEST” Trial Name Ever?

- Question 1: Have you ever seen a worse acronym for a Cardiology trial?
- Question 2: How has this issue not been more studied?
- 573 patients receiving chronic warfarin undergoing PCI
  - 28% having ACS at the time of enrollment
  - All loaded with clopidogrel; clopidogrel continued for minimum of 1 year (DES) or 1 month (BMS)
- Randomized to:
  - Aspirin + Clopidogrel + Warfarin
  - Clopidogrel + Warfarin
- Primary endpoint: Bleeding episode within 1 year
- Secondary endpoint: Composite of death, MI, stroke, target-vessel revascularization, stent thrombosis


Primary Endpoint: Bleeding

### Primary Endpoint: Bleeding

<table>
<thead>
<tr>
<th></th>
<th>Double therapy (n=279)</th>
<th>Triple therapy (n=284)</th>
<th>Hazard ratio (95% CI)</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Any bleeding event</td>
<td>54 (19.4%)</td>
<td>126 (44.4%)</td>
<td>0.36 (0.26-0.50)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>TIMI bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major</td>
<td>9 (3.2%)</td>
<td>16 (5.6%)</td>
<td>0.55 (0.25-1.27)</td>
<td>0.459</td>
</tr>
<tr>
<td>Major and minor</td>
<td>39 (14.0%)</td>
<td>89 (31.3%)</td>
<td>0.40 (0.27-0.58)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>GUSTO bleeding</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Severe</td>
<td>4 (1.4%)</td>
<td>10 (3.5%)</td>
<td>0.40 (0.12-1.27)</td>
<td>0.119</td>
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<tr>
<td>Severe and moderate</td>
<td>15 (5.4%)</td>
<td>35 (12.3%)</td>
<td>0.42 (0.23-0.75)</td>
<td>0.003</td>
</tr>
<tr>
<td>BARC bleeding</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>3</td>
<td>18 (6.5%)</td>
<td>36 (12.7%)</td>
<td>0.48 (0.28-0.86)</td>
<td>0.011</td>
</tr>
<tr>
<td>3c</td>
<td>3 (1.1%)</td>
<td>3 (1.1%)</td>
<td>1.00 (0.20-4.90)</td>
<td>0.996</td>
</tr>
<tr>
<td>3b</td>
<td>6 (2.2%)</td>
<td>14 (5.0%)</td>
<td>0.43 (0.17-1.01)</td>
<td>0.074</td>
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<tr>
<td>3a</td>
<td>9 (3.2%)</td>
<td>19 (6.7%)</td>
<td>0.47 (0.21-1.05)</td>
<td>0.054</td>
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<tr>
<td>2</td>
<td>23 (8.2%)</td>
<td>59 (20.8%)</td>
<td>0.36 (0.23-0.59)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>2+3</td>
<td>40 (14.3%)</td>
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<td>&lt;0.0001</td>
</tr>
<tr>
<td>1</td>
<td>18 (6.5%)</td>
<td>47 (16.5%)</td>
<td>0.38 (0.17-0.84)</td>
<td>0.004</td>
</tr>
<tr>
<td>Any blood transfusion</td>
<td>11 (3.9%)</td>
<td>27 (9.5%)</td>
<td>0.39* (0.17-0.84)</td>
<td>0.011</td>
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<td>Combined secondary endpoint</td>
<td>31 (11.1%)</td>
<td>50 (17.6%)</td>
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<td>0.025</td>
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<td>Death</td>
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<td>All-cause</td>
<td>7 (2.5%)</td>
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A Syncope Admission

- 72 y.o. woman with h/o HTN controlled on HCTZ
  - Recent bronchitis, on day 3 of 5 of azithromycin
  - Had emotional argument with her daughter, felt flushed, syncope x 10 sec
  - Had been having recent diarrhea, ? Dehydrated
- Vital signs at admission: Mild + orthostatic HR/BP
- EKG: Borderline LVH, otherwise unremarkable
- Labs: Negative troponin, K 3.1, otherwise unremarkable
- Plan:
  - Admit for telemetry
  - Serial troponins
  - IVF
  - Potassium repletion
  - Echo planned for next day
- Nurse calls you for a telemetry finding…
  - Patient has still been having some continued dizziness, unsure if symptoms changed during episode
Telemetry

What is the Best Next Action?

1) Yawn & go back to sleep
2) Amiodarone gt 1 mg/min
3) Lidocaine gt 1 mg/min
4) Magnesium IV, check QTc on 12-lead EKG
5) No medications but check early troponin, plan EP consultation next day
What is the Best Next Action?

1) **Yawn & go back to sleep**
2) Amiodarone gtt 1 mg/min
3) Lidocaine gtt 1 mg/min
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5) No medications but check early troponin, plan EP consultation next day

Recognizing Noise

- *Extremely* common finding on telemetry monitors
- Ways to definitively know you’re looking at noise
  - Patient’s normal QRS coming through at normal rate
  - Sat monitor going through at normal rate & intensity
Look at the QRS Complexes

Look at the O₂ Sat Monitor
Question on I/O Goals

You have been signed out a patient who was admitted with massive volume overload because he hasn’t been taking his home furosemide & he has been using organic sea salt to flavor all of his meals. The I/O goal you have been signed out is 1.5-2 liters negative.

The nurse calls you before giving the evening IV furosemide because the patient is already 3L negative after the morning dose. A PM metabolic panel shows a normal K & stable Cr of 1.8.

What Do You Do?

1) Hold the PM dose of diuretics
2) Hold the PM dose of diuretics & give back 1L of normal saline
3) Give half the dose of diuretics that was given in the AM
4) High-five the nurse & ask that the dose be given as originally ordered
What Do You Do?

1) Hold the PM dose of diuretics
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3) Give half the dose of diuretics that was given in the AM
4) **High-five the nurse & ask that the dose be given as originally ordered**

A Few Thoughts About I/O Goals

- They don’t actually make any sense!
- Typical goals: “1500-2000 cc negative”
  - Are you going to give fluid back if the patient diureses ‘too much’?
  - If the patient diureses ‘too much’ does it mean the renal function is likely to be worse the next morning… or better?
A Few Thoughts About I/O Goals

• Let’s think about a few scenarios:
  • Scenario 1: Patient has 30 kg of extra fluid due to diet/medication nonadherence.
  • Scenario 2: Patient was diuresing well on a given inpatient regimen → stopped doing so.
• What should the response be?
  • Scenario 1: Your goal is to diurese the patient. If that’s 4-5 liters & you can keep up with electrolytes, celebrate!
  • Scenario 2: If not meeting goal → knee-jerk response is more diuretics.
    • What if it’s because you’ve gotten all you can?
    • What if it’s because the patient has developed low-output?

I/O Goals: Just Say No!
Hyponatremia
(or How I Learned to Stop Worrying and Love the Physiology)

Hyponatremia Question 1

Too much ADH is the cause of most cases of the following types of hyponatremia:

1) Hypovolemic
2) Euvolemic
3) Hypervolemic
4) Hypovolemic & Euvolemic
5) Euvolemic & Hypervolemic
6) Hypovolemic & Hypervolemic
7) Hypovolemic, Euvolemic, and Hypervolemic
Hyponatremia Question 1

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7) **Hypovolemic, Euvolemic, and Hypervolemic**

Hyponatremia Question 2

Which patient with a Na 118 is most likely to have a faster rise in serum sodium than you had intended?

1) Hypovolemic hyponatremia patient receiving NS
2) Euvolemic hyponatremia patient receiving hypertonic saline
3) Hypervolemic hyponatremia patient receiving tolvaptan (vasopressin antagonist)
Hyponatremia Question 2

Which patient with a Na 118 is most likely to have a faster rise in serum sodium than you had intended?

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Hyponatremia Made Easy

• Remember: The body wants to maintain normal osmolality at (almost) all costs.

• When it doesn’t, it’s due to one of the following reasons:
  • Need for perfusion $>$ need for normal osmolality $\rightarrow$ 'appropriate' ADH secretion
    • Hypovolemic & hypervolemic hyponatremia both occur for this reason.
    • Think evolution, diarrhea, and tigers.
  • Inappropriate ADH secretion (euvolemic)
  • Inability of kidneys to dilute urine enough
    • ESRD
    • Meds (e.g. thiazide diuretics)
    • Overwhelmingly dilute po intake (e.g. psychogenic polydipsia)
Hence… You Know How to Correct!

- **Hypovolemia:**
  - Mechanism of correction is shutting off ADH secretion by restoring hypothalamic perfusion = NS
  - Timing/degree of the change is unpredictable

- **Euvolemia:**
  - Mechanism of correction is osmolality in > osmolality out → 3% saline, Na tabs, H₂O restriction or ‘vaptan’
  - *Only* time calculations make sense. Even then, can often empirically choose a standard dose of 3% saline.

- **Hypervolemia:**
  - Mechanism of correction is attacking ADH problem:
    - Fixing underlying condition → less ADH secretion
    - ‘Vaptan’ → Block ADH activity
    - Practically speaking → you should be so lucky to have to worry about ‘over-correction’
  - Don’t forget diuretics as cause (particularly thiazides)
  - Can try H₂O restriction – but this rarely works

What Not to Waste Your Time With

- Comparing serum to urine osmolality
  - Main reason to check urine osmolality – Is it *maximally* dilute (e.g. 50-100 mOsm/kg)?

- Calculating rate of correction of normal saline
  - Probably not worth doing even with 3% saline

- Thinking you will achieve much with H₂O restriction

- Worrying about over-correction in hypervolemic hyponatremia
Another Common Scenario

- 68 y.o. man admitted with volume overload due to heart failure
- Known dilated cardiomyopathy, LVEF 30%
- Labs at admission:
  - NT-BNP: 4000
  - K: 4.2
  - Cr: 1.1
- TTE this admission: Unchanged from baseline
- Diuresed, planned discharge meds:
  - Carvedilol
  - Enalapril
  - Spironolactone
  - Furosemide
- A know-it-all medical student asks about adding digoxin...

What Do You Tell the Med Student?

1) “You’re right. I’ll start it.”
2) “No thanks. Unlike the other discharge meds, digoxin has no mortality advantage.”
3) “Digoxin is actually associated with harm. I like this patient. No thank you.”
What Do You Tell the Med Student?

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Another Clinical Dilemma

• 78 y.o. man with ischemic cardiomyopathy admitted with volume overload heart failure
  • Anterior infarct 8 years ago → stent
    • No angina since then
  • Stress imaging study:
    • LVEF 38% (at baseline)
    • No evidence of ischemia
  • Admitted 6 months ago for similar reasons
• You diurese, he feels better, ready to discharge
  • “Doc – I hate taking all these pills. You’ve got to throw at least one of them away.”
Which Medication to Stop?

1) Beta-blocker
2) ACE-inhibitor
3) Aldosterone antagonist
4) Aspirin
5) Statin
6) Digoxin
7) Loop diuretic
Digoxin

- Evidence of use for > 2000 years

- William Withering (1785) published paper re: digitalis plant & treatment of ‘dropsy’
  - “I soon found Foxglove to be a powerful diuretic – but then and for a considerable time afterwards I gave it in doses very much too large…”

- To use or not to use…

Digoxin – DIG Trial (1997)

- 6800 patients with EF ≤ 45%
- Digoxin vs. placebo
  - Most patients on diuretics & ACE-inhibitors
  - All patients in sinus rhythm
- Outcomes:
  - Primary: All-cause mortality
  - Secondary: CV death, worsened HF & hospitalizations
All-Cause Mortality

Adapted from NEJM. 1997;336:525-33.

Death or HF Hospitalization

Adapted from NEJM. 1997;336:525-33.
DIG Trial: Post-hoc Analysis of Mortality vs. 1-month Digoxin Levels


Cochrane Review: Risk of Clinical Deterioration

A Story From Last Night…

- I was nervously thinking about this talk…
A Story From Last Night…

- I was nervously thinking about this talk…
  - Will they like it?

- Will my jokes fall flat?
A Story From Last Night…

• I was nervously thinking about this talk…
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• I developed a tension headache.

A Story From Last Night…

• I was nervously thinking about this talk…
  • Will they like it?
  • Will my jokes fall flat?
• I developed a tension headache.
• I took 600 mg of ibuprofen.
A Story From Last Night…

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  • Note: I never thought I was going to live longer by taking the ibuprofen.

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• Should I have been denied the opportunity to take the ibuprofen??
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- Should I have been denied the opportunity to take the ibuprofen???
- Why do we hold digoxin to such a higher standard?

GISSI-HF Trial

- 4574 patients with HF (ischemic or nonischemic)
  - NYHA Class II-IV
  - EF ≤40% or EF >40% but HF hospitalization in past 12 months
- Randomized: Rosuvastatin 10 mg daily vs. placebo
- Primary endpoints:
  - Survival
  - Mortality or CV hospitalization

GISSI-HF: Mortality


GISSI-HF: Mortality or CV Hospitalization

A Mental Exercise

- You’re a highly-paid executive at a big pharmaceutical company which makes an on-patent statin.
A Mental Exercise

• You’re a highly-paid executive at a big pharmaceutical company which makes an on-patent statin.

• You have been tasked with designing a heart failure clinical trial to test your statin’s efficacy.

• You are very motivated to get a positive result.
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- What type of study would you pitch?

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- What type of study would you pitch?
  - Large
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  • Placebo-controlled (not versus alternative lipid-lowering agent!)

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  • Only patients with ischemic cardiomyopathy
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  • Primary endpoint: Vascular events!

• Only one problem…
A Mental Exercise

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  - You are very motivated to get a positive result.
- What type of study would you pitch?
  - Large
  - Placebo-controlled (not versus alternative lipid-lowering agent!)
  - Only patients with ischemic cardiomyopathy
  - Primary endpoint: Vascular events!
- Only one problem…
  - No way this would ever be considered ethical…
CORONA

- 5011 patients ≥ 60 years
- All with ischemic, systolic HF
  - NYHA II: EF ≤ 35%
  - NYHA III-IV: EF ≤ 40%
- Rosuvastatin 10 mg daily vs. placebo
- Primary endpoint: A vascular endpoint (!)
  - CV death, nonfatal MI, nonfatal stroke

CORONA: Primary Endpoint

Adapted from Kjekshus et al. NEJM. 2007;357:2248-61.
**CORONA: All-Cause Mortality**

Adapted from Kjekshus et al. NEJM. 2007;357:2248-61.

**So What to Do With Statins in HF?**

- Not exactly clear…

- My advice:
  - For nonischemic heart failure → forget it!
  - For ischemic heart failure…
    - If angina, PVD, etc. → still use
    - If a patient is already on & tolerating well → leave on (unless patient feels strongly about minimizing meds)
  - Otherwise → consider not using
    - Polypharmacy issues are real!
    - Let’s focus on what makes a real difference…
Tempo of Heart Failure Pharmacologic Trials

- 1980s-early 2000s: Everything works!
  - Hydral/nitrates, ACE inhibitors, ARBs, aldosterone antagonists, digoxin
Tempo of Heart Failure Pharmacologic Trials

• 1980s-early 2000s: Everything works!
  • Hydral/nitrates, ACE inhibitors, ARBs, aldosterone antagonists, digoxin

• Mid 2000s-early 2010s: Nothing works!
  • Vasopressin antagonists, statins, direct renin inhibitors, ESAs, adenosine antagonists, natriuretic peptides, neprilysin/ACE inhibitors, TNF inhibitors, sildenafil, all HFpEF studies

• Recently: (Finally) positive results again!
## Major Heart Failure Clinical Trials

- Hydralazine/nitrates
- Digoxin
- ACE-Inhibitors
- Angiotensin receptor blockers
- Beta-blockers
- Aldosterone antagonists

### Pre-2000

- Vasopressin antagonists
- Direct renin inhibitors
- Statins
- Adenosine antagonists
- Natriuretic peptides
- Neprilysin inhibitor/ACEi combination
- TNF-α Inhibitors
- Sildenafil
- Erythropoeisis-stimulating Agents

### Post-2000

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**So Is There Any Hope For New Drugs?**
So Is There Any Hope For New Drugs?

YES!

Neprilysin Inhibitors

- Neprilysin: Enzyme which degrades natriuretic peptides & angiotensin II
  - Natriuretic peptide breakdown: Bad
  - Angiotensin II breakdown: Good

- OVERTURE Trial
  - Omipatrilat – combined neprilysin & ACE inhibition
  - 5770 patients, NYHA Class II-IV
  - Randomized: Omipatrilat vs. Enalapril
  - Primary endpoint: Death or HF hospitalization requiring IV diuretics

- Angioedema:
  - Omipatrilat: 24 patients (0.8%)  
  - Enalapril: 14 patients (0.5%)  
  - Later studies showed >3x risk of angioedema w/omipatrilat

OVERTURE: Primary Endpoint


OVERTURE: Survival

PARADIGM-HF: Finally Success?

- LCZ696 (Neprilysin inhibitor sacubitril with valsartan) vs. Enalapril 10 bid
- Double-blind, randomized trial of 8442 patients
  - LVEF ≤ 40%
  - NYHA II-IV
- Primary end-point: Time to CV death or HF hospitalization
  - Did not require IV diuretic therapy as in OVERTURE – as this was speculated to have led to fewer endpoints (differences in practice patterns around the world)
- Stopped early after median follow-up of 27 months
  - Approved by FDA on July 7, 2015


Results

Breakdown of Outcomes

Table 2. Primary and Secondary Outcomes. a

<table>
<thead>
<tr>
<th>Outcome</th>
<th>LCZ696 (N=4187)</th>
<th>Enalapril (N=4212)</th>
<th>Hazard Ratio or Difference (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary composite outcome — no. (%)</td>
<td>934 (21.8)</td>
<td>1117 (26.5)</td>
<td>0.80 (0.73–0.87)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Death from cardiovascular causes or first hospitalization for worsening heart failure</td>
<td>558 (13.3)</td>
<td>693 (16.5)</td>
<td>0.80 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>First hospitalization for worsening heart failure</td>
<td>537 (12.8)</td>
<td>658 (15.6)</td>
<td>0.79 (0.71–0.89)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Secondary outcomes — vs. (%)</td>
<td>711 (17.0)</td>
<td>833 (19.8)</td>
<td>0.84 (0.76–0.93)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Change in HCCQ clinical summary score at 8 mo 1 —</td>
<td>-2.99±6.16</td>
<td>-4.63±6.16</td>
<td>1.64 (0.63–2.65)</td>
<td>0.001</td>
</tr>
<tr>
<td>New-onset atrial fibrillation</td>
<td>84 (1.1)</td>
<td>83 (1.3)</td>
<td>0.97 (0.72–1.31)</td>
<td>0.83</td>
</tr>
<tr>
<td>Decline in renal function</td>
<td>94 (2.2)</td>
<td>108 (2.6)</td>
<td>0.86 (0.65–1.13)</td>
<td>0.28</td>
</tr>
</tbody>
</table>


Ivabradine

- Ivabradine: Inhibitor of I, current of S-A node
- No direct effect on myocardial contractility or intracardiac conduction
- SHIFT
  - 6558 patients in SR, resting HR ≥ 70, EF ≤ 35%, and HF hospitalization within past 12 months.
  - Stable standard medical therapy for ≥ 4 weeks
  - Randomized: Ivabradine or placebo x mean 23 months
  - Primary endpoint: CV Death or HF hospitalization
  - Main side-effects:
    - Symptomatic bradycardia: 5% vs. 1%
    - Visual side-effects (phosphenes): 3% vs. 1%
- Approved by FDA on April 15, 2015

SHIFT: HR During Study


SHIFT: Primary Endpoint

Serelaxin

- Serelaxin: Recombinant human relaxin-2
  - Regulates maternal adaptations in pregnancy
  - Vasodilation, increased renal blood flow

- RELAX-AHF Study
  - 1161 patients admitted to hospital for AHF
  - Randomized to 48h infusion of serelaxin vs. placebo
  - Primary endpoints:
    - Dyspnea improvement in visual analog scale between Day 0-5
    - Proportion of patients with moderate or marked dyspnea improvement by standardized scale during first 24h
  - Secondary endpoints:
    - Cardiovascular death or readmission to hospital for HF or renal failure up to day 60
    - Days alive out of the hospital up to day 60

Primary Endpoints: A Mixed Bag


CV Death or Readmission for HF or Renal Failure Up to Day 60

CV & All-Cause Mortality at 180 Days – Not a Secondary Endpoint


Serelaxin Approval Decision
Serelaxin Approval Decision

European Medicines Agency → FDA → thumbs down

Serelaxin Approval Decision

European Medicines Agency → FDA → thumbs down
Serelaxin Approval Decision

- Ongoing: RELAX-AHF-2
  - 6375 patients, similarly designed trial except...
  - Primary endpoint: Time to CV Death
  - Results expected in 2016

Summary

- Common sense – time for a renaissance!
  - Keep the metformin going
  - Hyponatremia: Stop the calculations!
  - Abandon I/O goals
  - Look for clues to telemetry noise!

- Impactful clinical trials we sometimes forget
  - Avoid triple anticoagulation
  - Use digoxin more
  - Use statins less

- Look out for the new HF drugs
  - They’re coming…
One Final Thought On Questioning Orthodoxy…

“When you find yourself in the majority, it is time to pause and reflect.”

-Mark Twain