Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes

ClinicalTrials.gov
A service of the U.S. National Institutes of Health

Systolic Blood Pressure Intervention Trial (SPRINT)

This study is ongoing, but not recruiting participants.

Sponsor:
Wake Forest Baptist Health

Collaborators:
National Heart, Lung, and Blood Institute (NHLBI)
National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK)
National Institute of Neurological Disorders and Stroke (NINDS)
National Institute on Aging (NIA)

Information provided by (Responsible Party):
David Reboussin, Wake Forest University Baptist Medical Center
Preparing to present at grand rounds:
  How and why

Conflict: sumsearch.org
Slide deck:
  http://wichita.kumc.edu/im
  (Intranet > scholarly activity)
What’s new

More collaboration tools
  • DropBox, Google Drive
Cited reference searching
When evidence is sparse
  • Diamond’s judicial analogies
Meta-analyses with medical students
What are physicians any good for?

- Direct patient care (solution shop)
  - Dx of the conundrum patient
  - Rx of the complex patient
- Indirect patient care
  - Leadership (including teamwork & QI)
  - *Assimilating and promoting new knowledge*
Someone needs to interpret new information

Rxes with harm > benefit that we accepted

• Bloodletting (through 1800s)
• Flecainide (1980s)
• Estrogen replacement therapy (1980s-1990s)
• Opioids for chronic benign pain (1990s-2000s)
• Extremely tight glycemic control (2000s)
• What is next - orthopedics, cannabis?
Impact of good searching

• Physician provided unsolicited searches of the primary treatment for all patients in a random sample

• Blinded judges assessed 14% of all the patients had their care improved

• Number needed to search for inpatients
  • 8

J Gen Intern Med 2004 PMID: 15109337
Collaborative development: team science

- Lit search
  - NCBI public collection
- Slide deck
  - Google Drive

http://wichita.kumc.edu/internal-medicine/research.html
http://sumsearch.org/searching
Toss paper copies of articles

+ Me =
Collaborative development: team science

- Use DropBox or Drive to share PDFs
- Digitize your library
Schedule of emails for preparation

• 3 months
  • Pick topic (exact clinical question(s) not yet needed)

• 2 months
  • Lit search posted at MyNCBI

• 6 weeks
  • Clinical question(s) slide using pico format

• 1 month
  • Send first draft of PPT with clinical recommendations for review

• 2 weeks
  • Revisions

• 1 week
  • Practice & anticipate questions
3 months, email will request:

**Pick a topic**
Picking a topic: uncertainty

• Avoid a topic that is well covered in UpToDate and Dynamed, unless
  • New information or
  • Not commonly recognized locally

• Better, a topic:
  • UpToDate and Dynamed contradict, or
  • One of these two resources do not address
Picking a topic: examples

• "Inflammatory bowel disease"
  • R3s: more narrow
    • "Seroologic diagnosis of rheumatoid arthritis"
  • R2s: yet more narrow
    • "Should we anticoagulate patients with distal DVT"

• If the disease is rare or has recent systematic reviews, dx or rx in general is ok
  • "Treatment options for dermatomyositis"
Picking a topic: “double-dip”

• Coordinate grand rounds with
  • ACP Presentation
  • Journal Club
  • Research or QI publishing

• Hypothetical example, anti-coag QI team:
  • Journal club: RELY trial
  • Grand rounds: “When to anticoagulate with non-VKAs”
  • Meeting abstract: QI project or case; living meta-analysis
Meta-analysis?

Students can help

• Informally
  or
• Formally with academic credit
  • PVMD 977: Clinical and Population-Based Research with Dr Ablah

If a resident is interested
• Tell me your proposed topic ASAP

If a student is interested
• Contact myself or Dr Ablah as soon as possible
Opportunities to present

KUMC-KC resident/fellows research day
• Submit Feb thru April
• Event is in May

KUSM-W research forum
• Event is in April

Kansas ACP
• Event is October
10 weeks, email will request:

**INITIAL LIT SEARCH**
Lit searching

1. Pimp your browser
2. Save citations at a MyNCBI account
   • http://sumsearch.org/searching
Searching: different strategies for different settings

* Consider adding additional searches when
  a. Evidence too new to be in textbook/guideline
  b. Evidence too obscure to be in textbook/guideline
  c. Textbook/guideline seems incorrect
Lit searching: 6S

Examples of resources:

- Computerized decision support systems
- Evidence-based clinical practice guidelines
- Evidence-based textbooks
- DARE; health-evidence.ca
- Evidence-based abstraction journals
- Systematic reviews (e.g., Cochrane Library)
- Evidence-based abstraction journals
- Original articles published in journals

6S - PMID: 19779069
MEDLINE last - PMID: 17082828
Overview of the 6S

1. Search Smart Medicine / UpToDate
   • Add 3-5 key citations to your MyNCBI
2. Search systematic reviews/guidelines/studies at PubMed and/or SUMSearch.org
   • Add 3-5 key citations to your MyNCBI
3. Manual search of PubMed for key topics
   • Add 3-5 key citations to your MyNCBI

Ask me for help if other databases needed

Conclusion: PEXIVAS will inform the future standard of care for patients with severe AAV. The cooperation between investigators, funding agencies, and industry provides a model for conducting studies in rare diseases.

Impact/quality: Governmental/foundation support *

2. Changes in proteinase 3 anti-neutrophil cytoplasm autoantibody levels in early systemic granulomatosis with polyangiitis (Wegener's) may reflect treatment rather than disease activity. Clin Exp Rheumatol 2013 Jan-Feb;31:1 Suppl 75. PMID: 23380137. Cite

Conclusion: The predictive value for relapses of PR3-ANCA determinations confirm and extend previous reports. Although all relapses were related to PR3-ANCA increases, reduction or absence thereof did not always prevent relapse.
PubMed with MyNCBI

Instructions for MyNCBI at:
http://sumsearch.org/searching
Dear resident:

Per [http://gopubmed.com](http://gopubmed.com), suggested search terms:

- megestrol acetate AND (weight loss OR cachexia)

Additional citations to consider based on impact and relatedness ([http://sumsearch.org/2d/](http://sumsearch.org/2d/))

- Megestrol acetate for treatment of anorexia-cachexia syndrome. Cochrane Database. 2013. PMID: 23543530
- Interventions for fatigue and weight loss in adults with advanced progressive illness. Cochrane Database. 2012. PMID: 22258985
Cited reference search

• Identify your most important article
• If more than a year old, find everyone who cited it
• Search your title at
  • Google Scholar
  • Web of Science (database at http://library.kumc.edu/)

Any new studies?

How are experts currently interpreting your study?
ASSESSING EVIDENCE
Assessment: Good guidelines

- Transparent process
- Conflicts of interest
- Systematic review based
- Guideline developers diverse
- Structured assessment of evidence
- External review

IOM criteria. JAMA 2013 PMID 23299601.
Assessment: original studies

• Small study effect
  • Most common cause of overturned meta-analyses?
    BMJ 2001. PMID: 11451790

• Unplanned analyses: ~50% of RCTs
  • BMJ 2013. PMID: 23851720

• Selective reporting bias: >50% of RCTs
  • PMID: 15161896

• ‘Spinning’: ~20% of industry RCTs
  • NEJM 2008. PMID: 18199864

• Publication bias: ~30% of industry RCTs
  • NEJM 2008. PMID: 18199864
Assessment: original studies

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  - Most common cause of overturned meta-analyses?
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  - NEJM 2008. PMID: 18199864
- Publication bias: ~30% of industry RCTs
  - NEJM 2008. PMID: 18199864

Avoid unregistered trials!
### RCTs: Cochrane risk of bias tool

<table>
<thead>
<tr>
<th>Selection</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Random sequence generation</td>
<td>X</td>
</tr>
<tr>
<td>2. Allocation concealment</td>
<td>X</td>
</tr>
<tr>
<td><strong>Blinding</strong></td>
<td></td>
</tr>
<tr>
<td>3. Blinding of participants and personnel</td>
<td>X</td>
</tr>
<tr>
<td>4. Blinding of outcome assessment</td>
<td>X</td>
</tr>
<tr>
<td><strong>Follow-up</strong></td>
<td></td>
</tr>
<tr>
<td>5. Participants: ‘Incomplete outcome data’</td>
<td>X</td>
</tr>
<tr>
<td>6. Outcomes: ‘Selective reporting’</td>
<td>X</td>
</tr>
</tbody>
</table>

### DTAs: QUADAS-2 risk of bias tool

<table>
<thead>
<tr>
<th>Selection</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Consecutive or random sample of patients</td>
<td>X</td>
</tr>
<tr>
<td>2. Case-control design avoided</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Index test</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>3. Blinded interpreted</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Reference standard</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>5. Blinded interpreted</td>
<td>X</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Flow and timing</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>6. Appropriate time between tests</td>
<td>X</td>
</tr>
<tr>
<td>6. Did everyone get all tests</td>
<td>X</td>
</tr>
</tbody>
</table>

[http://www.bris.ac.uk/quadas/quadas-2/](http://www.bris.ac.uk/quadas/quadas-2/)
Rosuvastatin to prevent vascular events in men and women with elevated C-reactive protein.


Collaborators (1332)
Center for Cardiovascular Disease Prevention, Brigham and Women's Hospital, Harvard Medical School, Boston, MA 02215, USA. pridker@partners.org

Abstract
BACKGROUND: Increased levels of the inflammatory biomarker high-sensitivity C-reactive protein predict cardiovascular events. Since statins lower levels of high-sensitivity C-reactive protein as well as cholesterol, we hypothesized that people with elevated high-sensitivity C-reactive protein levels but without hypercholesterolemia might benefit from statin treatment.

CONCLUSIONS: In this trial of apparently healthy persons without hyperlipidemia but with elevated high-sensitivity C-reactive protein levels, rosuvastatin significantly reduced the incidence of major cardiovascular events. (ClinicalTrials.gov number, NCT00239681.)

2008 Massachusetts Medical Society

Expanding the orbit of primary prevention—moving beyond JUPITER

Hlatky MA.


Rosuvastatin in patients with elevated C-reactive protein.

[ACP Journal Club. Rosuvastatin prevented major cardiovascular events in persons with elevated C-reactive protein. [Ann Intern Med. 2009]]

[Comment from the lipidologist's viewpoint. [Praxis (Bern 1994). 2009]]
GRADE: collections of studies

http://www.gradeworkinggroup.org/

- Used by UpToDate and some guidelines
  Adds many factors including:
  - Cochrane or QUADAS for each study and...
  - Total patients in all studies (> 2000/arm is ok)
  - Directness of outcome
  - Selective reporting
  - Consistency of results (heterogeneity)
  - Publication bias
GRADE: example

- Good: provides structure
- Bad: can be arbitrary; however, gives transparency
But when no trials exist...

<table>
<thead>
<tr>
<th>Class</th>
<th>Judicial Analogy</th>
</tr>
</thead>
<tbody>
<tr>
<td>★★★★★</td>
<td>Beyond a reasonable doubt</td>
</tr>
<tr>
<td>★★★★</td>
<td>Clear and convincing evidence</td>
</tr>
<tr>
<td>★★★</td>
<td>Preponderance of the evidence</td>
</tr>
<tr>
<td>★★</td>
<td>Reasonable suspicion</td>
</tr>
<tr>
<td>★</td>
<td>Insufficient evidence</td>
</tr>
</tbody>
</table>

When accepting lesser standards, consider chance of adverse effects

6 weeks, email will request:

**CLINICAL QUESTION(S)**
6 weeks - Choosing bullets

Provide **one** (R2s) or up to **five** (R3s) proposed bullets

- Be specific in your bullets. Do not say
  - Understand treatment

- Instead
  - What is the most sensitive dx test for __?  
  - What is the most effective rx for _____?

- Use PICO format if able
  - In patients with **Problem** is **Intervention** a more effective treatment than **Comparison** for preventing **Outcome**?
  - In patients with **Problem** is **Intervention** a more accurate test than **Comparison** for detecting **Outcome**?
1 month, email will request:

**FIRST DRAFT OF SLIDE DECK**
4 weeks – first draft

• < 60 slides
• Avoid prose -> structured text or figures
• Be succinct! See links is at
  
  http://wichita.kumc.edu/internal-medicine/research.html

  o "Don't do this"
  o 5 tips
Introductory slides

Minimize, if addressed at all:
  • Epi/Path/Econ
Unless
  • Subtle topic; audience needs background
  • Affects conclusions

Rationale
  • Audience can remember 7±2 items
    • (Miller, 1956. PMID: 13310704)
Introductory slides: tell a story instead
Bullet Points

- Too
- Many
- Bullet
- Points
- Can Really
- Distract
- From Your
- Message
- Only
- Bullet
- Key Points
- As Too Many
- Bullet
- Points
- Prevent
- Your
- Message
- From
- Making
- An Impact
- In Fact
- The Term
- Bullet
- Points
- Comes From
- Audiences
- Firing
- A Gun
- At The
- Annoying Presenter

Chronic Venous Insufficiency

- Ulcers occur in about 1% of patients with chronic venous insufficiency
- Ulcers occur more commonly in men than in women
- Ulcers are more common with advancing age, especially after age 60
- Ulcers tend to be chronic and recurrent in most patients
Ulcers in Chronic Venous Insufficiency

- 1% prevalence
- Men > Women
- Increase with age
- Chronic and recurrent

Better!

After composing at slide, cut content by half - twice
ANSWERING A CLINICAL QUESTION
NASH Trial

• Pioglitazone, Vitamin E, or Placebo for Nonalcoholic Steatohepatitis.

  ClinicalTrials.gov number:NCT00063622

• Randomized controlled trial

• Funding and support:
  • NIH and Takeda pharmaceuticals
  • 2 of 16 authors have conflict of interest with Takeda
NASH Trial

• Patients: Adults with nonalcoholic steatohepatitis and without diabetes

• Intervention: pioglitazone 30 mg daily

• Comparison: Placebo

• Outcome: Liver histology at two years

Note: Outcome is definition of outcome, not the actual results.
<table>
<thead>
<tr>
<th>Characteristic</th>
<th>RFA (n = 215)</th>
<th>AADs (n = 295)</th>
<th>P†</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (y)</td>
<td>47.2 ± 16.3</td>
<td>61.6 ± 17.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>No. of women/men</td>
<td>115/110</td>
<td>110/185</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Comorbid conditions</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>23 (11)</td>
<td>106 (36)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Diabetes</td>
<td>12 (6)</td>
<td>28 (9)</td>
<td>.121</td>
</tr>
<tr>
<td>CAD</td>
<td>13 (6)</td>
<td>38 (13)</td>
<td>.010</td>
</tr>
<tr>
<td>AF</td>
<td>12 (5)</td>
<td>45 (15)</td>
<td>&lt; .002</td>
</tr>
<tr>
<td>DCM</td>
<td>68 (32)</td>
<td>85 (29)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Sleep apnea</td>
<td>1 (0.4)</td>
<td>14 (5)</td>
<td>.074</td>
</tr>
<tr>
<td>History of syncope</td>
<td>15 (7)</td>
<td>13 (4)</td>
<td>.223</td>
</tr>
<tr>
<td>Symptoms</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Shortness of breath</td>
<td>32 (15)</td>
<td>43 (15)</td>
<td>.903</td>
</tr>
<tr>
<td>Dizziness</td>
<td>19 (9)</td>
<td>22 (7)</td>
<td>.645</td>
</tr>
<tr>
<td>Palpitations</td>
<td>58 (27)</td>
<td>59 (20)</td>
<td>.100</td>
</tr>
<tr>
<td>Chest discomfort</td>
<td>27 (13)</td>
<td>17 (6)</td>
<td>.010</td>
</tr>
<tr>
<td>PVC frequency (n/24 h)</td>
<td>23,554 ± 18,448</td>
<td>17,259 ± 14,512</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>PVC burden (%)</td>
<td>18.4 ± 15.2</td>
<td>12.1 ± 12.8</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>NSVT (runs/24 h)</td>
<td>275 ± 51</td>
<td>112 ± 43</td>
<td>.014</td>
</tr>
<tr>
<td>PVC origins</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RVOT</td>
<td>74 (34)</td>
<td>33 (11)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>RV non-OT</td>
<td>22 (10)</td>
<td>39 (13)</td>
<td>.109</td>
</tr>
<tr>
<td>LVOT</td>
<td>47 (22)</td>
<td>39 (13)</td>
<td>.143</td>
</tr>
<tr>
<td>LV non-OT</td>
<td>51 (24)</td>
<td>106 (36)</td>
<td>&lt; .001</td>
</tr>
<tr>
<td>Multiform PVC</td>
<td>9 (4)</td>
<td>18 (6)</td>
<td>.202</td>
</tr>
<tr>
<td>PVC QRS duration (ms)</td>
<td>148 ± 21</td>
<td>150 ± 19</td>
<td>.311</td>
</tr>
<tr>
<td>PVC coupling interval (ms)</td>
<td>488 ± 95</td>
<td>494 ± 104</td>
<td>.545</td>
</tr>
<tr>
<td>LVEF (%)</td>
<td>53.0 ± 11.9</td>
<td>52.1 ± 8.5</td>
<td>.210</td>
</tr>
<tr>
<td>LVESD (mm)</td>
<td>37.5 ± 8.7</td>
<td>37.2 ± 9.5</td>
<td>.723</td>
</tr>
<tr>
<td>LVEDD (mm)</td>
<td>53.9 ± 7.0</td>
<td>52.4 ± 6.7</td>
<td>.301</td>
</tr>
<tr>
<td>Baseline Characteristic</td>
<td>Ablation</td>
<td>Drugs</td>
<td>P-value</td>
</tr>
<tr>
<td>-------------------------</td>
<td>----------</td>
<td>-------</td>
<td>---------</td>
</tr>
<tr>
<td>Age (y)</td>
<td>47</td>
<td>62</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>DCM (%)</td>
<td>32</td>
<td>29</td>
<td>&lt;0.001</td>
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<td>23,554</td>
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<td>&lt;0.001</td>
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<tr>
<td>LVEF (%)</td>
<td>53.0</td>
<td>52.1</td>
<td>0.210</td>
</tr>
</tbody>
</table>

Better!
Updated meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Experimental Events</th>
<th>Control Events</th>
<th>Risk Ratio</th>
<th>RR</th>
<th>95%-CI</th>
<th>W(random)</th>
</tr>
</thead>
<tbody>
<tr>
<td>cofactor = Primary prevention</td>
<td>16</td>
<td>38</td>
<td>0.42</td>
<td>[0.24; 0.73]</td>
<td>21.4%</td>
<td></td>
</tr>
<tr>
<td>COPPS</td>
<td>5</td>
<td>14</td>
<td>0.49</td>
<td>[0.19; 1.26]</td>
<td>7.1%</td>
<td></td>
</tr>
<tr>
<td>Finkelstein</td>
<td>227</td>
<td>244</td>
<td>0.44</td>
<td>[0.27; 0.70]</td>
<td>28.5%</td>
<td></td>
</tr>
<tr>
<td>cofactor = Secondary prevention</td>
<td>20</td>
<td>45</td>
<td>0.44</td>
<td>[0.28; 0.71]</td>
<td>29.9%</td>
<td></td>
</tr>
<tr>
<td>ICAP</td>
<td>12</td>
<td>34</td>
<td>0.35</td>
<td>[0.20; 0.61]</td>
<td>20.9%</td>
<td></td>
</tr>
<tr>
<td>COPP</td>
<td></td>
<td></td>
<td>0.35</td>
<td>[0.16; 0.77]</td>
<td>10.4%</td>
<td></td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td>0.45</td>
<td>[0.31; 0.64]</td>
<td>71.5%</td>
<td></td>
</tr>
</tbody>
</table>

Experimental effect rate (EER): 14%
Control effect rate (CER): 31%
Risk ratio (RR): 0.44
### Treatment of PVC cardiomyopathy

**Paul Ndunda, 2014**

<table>
<thead>
<tr>
<th>Study</th>
<th>P</th>
<th>I</th>
<th>C (n)</th>
<th>O</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Bogun 2007 Case series</td>
<td>33 patients with LVEF &lt;50, Frequent PVCs</td>
<td>RFA</td>
<td>Usual care</td>
<td>PVC burden, LVEF, LVEDD, LVESD</td>
<td>↓ PVC burden ↑ LVEF &amp; ↓ LV size</td>
</tr>
<tr>
<td>Penela 2013 Case series</td>
<td>80 patients with LVEF 50%, frequent, symptomatic PVCs</td>
<td>RFA</td>
<td>None</td>
<td>PVC burden, LVEF, LVEDD, LVESD, bnp &amp; NYHA class</td>
<td>↓ PVC burden ↑ LVEF &amp; ↓ LV size ↑ NYHA ↓ BNP</td>
</tr>
<tr>
<td>Zhong 2014 Non-randomized</td>
<td>510 patients with frequent PVCs</td>
<td>AADs</td>
<td>RFA</td>
<td>PVC frequency, LVEF, LVEDD, LVESD</td>
<td>↓ PVC frequency ↑ LVEF &amp; ↓ LV size only in RFA group</td>
</tr>
<tr>
<td>CHF-STAT 1995 RCT</td>
<td>674 Patients with CHF, LVEF &lt;40, asymptomatic PVC &gt;10/h</td>
<td>Amiodaron</td>
<td>Placebo</td>
<td>Overall mortality, Sudden cardiac death, LVEF</td>
<td>↑ LVEF No mortality benefit.</td>
</tr>
</tbody>
</table>
- Chart junk reduced
- Convey information in the axes
  - Values sorted by the causal variables
  - If no causation, sort by date/size/quality else alphabetize
- Any further changes?
- ...
Correlation between O-ring temperature and damage severity in prior Shuttle launches

R2 = -0.65; p = 0.001

Projected temperature at launch: 26° to 29°
Your conclusion

Actionable bullets
Make the audience better for having attending
Fielding questions

Don't speculate an answer that might be wrong.

Consider:

• "Sorry, I do not know the answer."

• Redirect to a question that is more important. "I do not know the answer to that, but I can tell you..."
Good luck

- Less breadth, more quality
- Actionable conclusions
- Nobody will complain if short
- Repurpose as other scholarly activity
- You will become a better doc/consultant