General Medicine Update - Ambulatory

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Framing it Up

• Ambulatory-focused articles
  • Relevant to GIM
  • Plausibly practice changing
  • Culled from all original research published in
    • NEJM, AIM, JAMA, BMJ, Lancet
    • Plus selected other sources
    • October 2015 through September 2016
My Own Take

• I will offer what I see as important
• I am not a domain expert
• You should read these for yourself
  • Consider your experience, your patients
  • Perhaps consult with domain experts you trust
Few men have virtue to withstand the highest bidder.
Audience Response

• For my hypertensive patients I:
  A. Aim for a blood pressure of 140/90 or less
  B. Aim for a systolic BP of 135-140
  C. Aim for a systolic BP of 120 or less
  D. Have different targets depending on risks such as Age, Diabetes, etc
  E. Do something else
Blood Pressure Targets

• Two Articles from the Systolic Blood Pressure Intervention Trial (SPRINT)
  • A Randomized Trial of Intensive versus Standard Blood-Pressure Control
    • The SPRINT research group
    • NEJM 11/26/15
  • Intensive vs Standard Blood Pressure Control and Cardiovascular Disease Outcomes in Adults Aged 75+ years.
    • Williamson et al
    • JAMA 6/28/16

• Sponsored by the NIH
Blood Pressure Targets

• Study Questions
  • Is a target BP of 120 superior to target BP of 140 (actually 135-139) in a high-risk, non-diabetic group?
  • And specifically in an older group?

• Background
  • Target SBP < 140 remains the general standard for treatment
  • Benefit has only been proven for SBP target of 150
  • Observational studies suggest lower is better.
  • Trials of tighter control in diabetes and stroke have not shown benefit
  • Lower blood pressure comes at a price
Design – Unblinded RCT

• 9300 patients throughout US
  • Age at least 50, SBP 130-180
  • No cerebrovascular disease or Diabetes
  • Increased risk: 1 or more of
    • CV disease, GFR 20-60, Framingham 15%+, age 75+

• Received
  • Increased medication as needed to achieve SBP <120, OR
  • BP titrated to 135-139
    • Medication reduced if SBP < 130 once or 135 twice

• Followed 5 years (planned) for MI, ACS, CVA, CHF, CV Death.
  • Expected reduction from 2.2% to 1.75% per year.
  • Stopped after about 3 years
## Results – Baseline

<table>
<thead>
<tr>
<th></th>
<th>&lt;120</th>
<th>135-140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>68</td>
<td>68</td>
</tr>
<tr>
<td>Female</td>
<td>36%</td>
<td>35%</td>
</tr>
<tr>
<td>Black</td>
<td>31%</td>
<td>32%</td>
</tr>
<tr>
<td>Framingham Risk</td>
<td>61%</td>
<td>61%</td>
</tr>
<tr>
<td>15%+</td>
<td></td>
<td></td>
</tr>
<tr>
<td>CKD</td>
<td>28%</td>
<td>28%</td>
</tr>
<tr>
<td>Statin</td>
<td>42%</td>
<td>45%</td>
</tr>
</tbody>
</table>
# Results – Process

<table>
<thead>
<tr>
<th></th>
<th>&lt;120</th>
<th>135-140</th>
</tr>
</thead>
<tbody>
<tr>
<td>Achieved Blood Pressure</td>
<td>121</td>
<td>136</td>
</tr>
<tr>
<td>Number of Medications</td>
<td>2.8</td>
<td>1.8</td>
</tr>
</tbody>
</table>
Results – Outcomes

NNT = 90
1 Death over 3 years

Composite Death

<120 135-140

*
Cautions

• Intensive treatment group had more syncope, AKI, etc
• Open label
  • Potential for other differences in care
• Lack of statin treatment
• Controls were not really “Usual Care”
  • Aggressive down-titration of medications
• Does not apply to those with Diabetes or cerebrovascular disease
Conclusions

• SBP of 120 is a very aggressive goal
  • Accompanied by important, predictable side effects

• Substantial survival benefit
  • But likely over-stated in comparison to true usual care

• Serious concern about achieving 120 in non-research context
  • I struggle to get to 140

• I am not adopting this broadly
  • I see it as close to a toss-up
  • But see below...
The Senior SPRINT

• A sub-study of SPRINT
• Analyzed just the 2600 subjects age 75+
  • About 1/3 “frail” but not in residential care
NNT’s Over 3 years

• For Death
  • Older – 41
  • Younger – 160 (est)

• For Vascular Composite
  • Older - 27
  • Younger – 110 (est)
Conclusions

• A target SBP of 120 is superior to a target of 135-139 in this setting
• The benefit accrues mostly to older patients
• I am beginning to offer this to my older patients
• I am concerned about
  • Whether it is better than true “usual care”
  • “Creep” to excluded patients
    • Especially lower risk, and those with DM or Stroke
  • Side effects and other penalties
James Madison

If Tyranny and Oppression come to this land, it will be in the guise of fighting a foreign enemy.
When dealing with a healthy patient with a skin abscess, I:

A. Drain it
B. Drain it, pack it
C. Drain it, pack it, and usually prescribe an antibiotic
D. Something else
TMP/Sulfa for Skin Abscess

• Trimethoprim-Sulfamethoxazole versus Placebo for Uncomplicated Skin Abscess
  • DA Talan et al
  • NEJM 3/3/16
  • Supported by the NIH
Skin Abscess

• Study Question
  • Does TMP/Sulfa improve cure rates for drained skin abscesses?

• Background
  • I&D is generally regarded as curative for uncomplicated skin abscess
  • IDSA recommends antibiotic only for special cases
    • SIRS, immunosuppression, etc.
  • Practicing clinicians often prescribe antibiotics anyway
Design – Blinded RCT

• 1250 US patients with skin abscess
  • Age 12+
  • Purulent abscess at least 2 cm
  • Planned outpatient care

• Received I&D plus
  • TMP/Sulfa, 4 Single Strength bid for 7 days OR
  • Placebo

• Followed for clinical cure at 7-14 days

• Sought improvement from 90% to 97.5% cure
# Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>TMP/Sulfa</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35</td>
<td>35</td>
</tr>
<tr>
<td>Female</td>
<td>41</td>
<td>42</td>
</tr>
<tr>
<td>Diabetes</td>
<td>11</td>
<td>11</td>
</tr>
<tr>
<td>MRSA</td>
<td>47</td>
<td>43</td>
</tr>
</tbody>
</table>
Cautions

• Those who failed follow-up were deemed treatment failure
  • I suspect they were cured
  • Would have made TMP/Sulfa look even better if presumed cured

• Somewhat small study
  • Will miss rare but serious side effect difference
    • E.g., Stevens-Johnson syndrome
Conclusions

• TMP-Sulfa improves cure and recurrent skin abscess compared to drainage alone
  • NNT around 12

• Antibiotic stewardship and potential side effects are serious balancing concerns

• Is this permission?
  • Less guilt when I use it
  • Perhaps will aim it at less robust patients
    • (Evidence-free medicine)
It's no exaggeration to say that the undecideds could go one way or another.
Abraham Lincoln

Give me six hours
to chop down a tree
and I will spend the first four
sharpening the axe.
Audience Response

For my diabetic patients, my best chance to reduce early mortality is to use:

A. Insulin
B. Metformin
C. SGLT2 inhibitors
D. GLP-1 analogues
E. I don’t know anymore
Diabetes Treatment – Two Articles

• Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes
  • B Zinman et al
  • NEJM 11/26/15
  • Re-Review*

• Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes
  • SP Marso et al
  • July 28, 2016

• Both largely funded, designed, conducted, analyzed, written by the makers of the drugs
Diabetes Treatment

• Study Question
  • Is either Empagliflozin (SGLT2 inhibitor) or Liraglutide (GLP-1 analogue) better than other treatments for Type 2 diabetes?
  • Both studies designed as non-inferiority

• Background
  • Empagliflozin causes the kidneys to leak glucose
  • Liraglutide stimulates islet cells to release insulin
  • Both reduce A1C
  • Both thought to have potential important side effects
  • These studies were done to assess risk, not benefit
Design – Blinded RCT’s

• 7000 patients (Empagliflozin) and 9300 patients (Liraglutide) worldwide with DM type 2
  • Liraglutide
    • A1C 7+, Age 50+ with CV disease or 60+ with risk
  • Empagliflozin
    • A1C 7-10, Age 18+ with CV disease

• Received
  • Active Drug
    • Empagliflozin 10 or 25 mg daily
    • Liraglutide 1.8 mg SC daily
  • Or Placebo
    • Also usual care

• Followed 3-4 years for CV death, MI, stroke
• Sought non-inferiority
Results – Baseline, Liraglutide

<table>
<thead>
<tr>
<th></th>
<th>Liraglutide</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age</strong></td>
<td>64</td>
<td>64</td>
</tr>
<tr>
<td><strong>ACE-I</strong></td>
<td>52</td>
<td>50</td>
</tr>
<tr>
<td><strong>Statin</strong></td>
<td>73</td>
<td>71</td>
</tr>
</tbody>
</table>
Results – Outcomes, Liraglutide

- Composite
  - Liraglutide: 13
  - Placebo: 6
  - NNT = 71

- Death
  - Liraglutide: 8
  - Placebo: 8

* indicates statistical significance.
Results – Baseline, Empagliflozin

<table>
<thead>
<tr>
<th></th>
<th>Empagliflozin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63</td>
<td>63</td>
</tr>
<tr>
<td>ACE-I</td>
<td>81</td>
<td>80</td>
</tr>
<tr>
<td>Statin</td>
<td>78</td>
<td>76</td>
</tr>
</tbody>
</table>
Results – Outcomes, Empagliflozin

NNT = 38

Composite

Empagliflozin
Placebo

All Death

Empagliflozin
Placebo
Cautions

• Liraglutide did not work in North America
  • Few African Americans or Hispanic Americans

• Not treated to US Standards
  • Underuse of statins, ACE-inhibitors, metformin
  • Especially given high baseline risk

• Unexpected effect
  • Not previously noted with other SGLT2 or GLP-1 drugs
  • Not previously noted with anything for DM-2

• Are these “too good to be true?”
Conclusions

• I still don’t entirely believe it
• But these two drugs have a better case for mortality benefit than anything else
  • Including metformin
• I will begin trying low-dose Empagliflozin
  • Type 2 patients with CV disease
    • Especially if intolerant to metformin
  • Not A1C driven
  • Not dose-dependent – will use 10 mg
  • EXPENSIVE
• Liraglutide an option but less convenient (injectable) and less persuasive
• I am prepared to be proven wrong on this
Things don't turn up in this world until somebody turns them up.

James Garfield
Audience Response

My patients at risk for HIV are:

A. Asking me about PrEP
B. Teaching me about PrEP
C. Having trouble staying on their PrEP
Pre-Exposure Prophylaxis

• On-Demand Preexposure Prophylaxis in Men at High Risk for HIV-1 Infection
  • JM Molina et al
  • NEJM 12/3/2015
  • Supported by several public agencies and private foundations
Pre-Exposure Prophylaxis

• Study Question
  • Does on-demand PrEP reduce HIV transmission among men or transgender women who have anal receptive sex with men?

• Background
  • Daily anti-retroviral PrEP is effective HIV prevention
  • Adherence is important issue with daily PrEP
  • CDC guideline recommends daily PrEP as an option, but against intermittent PrEP
Design – Blinded RCT

- 414 MSM in France and Canada
  - HIV negative
  - 2+ unprotected anal sex partners in prior 6 months
- Received
  - Tonofovir 300/Emtricitabine 200 OR
  - Placebo
  - 2 tabs 2-24 hours pre-, plus 1 tab 24 and 48 hours post-exposure
- Followed 2 years for new HIV-1 infection
- Sought reduction from 3% per year to 1.5% per year
- Analyzed early due to positive pilot result from elsewhere
# Results – Baseline Characteristics

<table>
<thead>
<tr>
<th></th>
<th>PrEP</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>35</td>
<td>34</td>
</tr>
<tr>
<td>Non-White</td>
<td>6</td>
<td>11</td>
</tr>
<tr>
<td>Median partners prior 2 months</td>
<td>8</td>
<td>8</td>
</tr>
<tr>
<td>Pills taken per month</td>
<td>15</td>
<td>15</td>
</tr>
</tbody>
</table>
Results – Outcomes

HIV Infection

- **PrEP**
- **Placebo**
Additionally

• NNT 12 for a year
• Of the 3 new cases on PrEP
  • 1 converted before receiving medication
  • 2 never took any medication
Cautions

• Requires accurately anticipating exposure
• Adherence still an issue
Conclusions

• Daily PrEP is better researched
• I will offer this to HIV negative MSM who won’t use daily PrEP
No tendency is quite so strong in human nature as the desire to lay down rules of conduct for other people.
Golf is a game in which one endeavors to control a ball with implements ill adapted for the purpose.
Final Words

• I intend to
  • Offer an SBP target of 120 to my older hypertensives
  • Use TMP/Sulfa more comfortably in my skin abscess patients
  • Add low-dose empagliflozin in my high-risk diabetics
  • Offer on-demand PrEP to high risk men

• You will make your own decisions
Barack Obama

That's the good thing about being president, I can do whatever I want.