Articles that Changed our Practice in 2019

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No relevant disclosures
Topic Overview

Bugs and Drugs Round-Up

DOACs, DOACs and more DOACs (aka another bad year for Bayer)

SGLT2s and GLP1s—just add them to the H2O

Will iron heal that broken heart?

Inpatient delirium – still no quick fixes

Public Service Announcement: E-cigarettes
Case

Mr. Paul P. Tation is a 70 yo man who presents to the ER with fevers, rigors and right knee pain.

PMH is significant for T2DM, CKD3, Afib on apixaban, and a right TKA in 2012.

He is admitted for right knee septic arthritis with blood cultures positive for MSSA. He is started on cefazolin and orthopedics takes him to the OR for washout. Operative cultures grow MSSA.

He does well post-operatively without any complications.

Bugs and Drugs

What antibiotic treatment plan do you recommend?
Oral Antibiotics – Bone and Joint Infections

Current IDSA guidelines

• Vertebal osteomyelitis:
  • 6 weeks IV antibiotics or highly bioavailable antimicrobial therapy (strong, low)

• Prosthetic joint infections:
  • Staph: 2-6 weeks IV antibiotics + rifampin followed by rifampin + oral antibiotic for total of 3 months in total joint infections infection except 6 months in TKA (A-I)
  • Other organisms: 4-6 weeks IV antibiotics or highly bioavailable antimicrobial therapy (B-II)
Oral versus intravenous antibiotics for bone and joint infections: the OVIVA non-inferiority RCT

Matthew Scarborough, Ho Kwong Li, Ines Rombach, Rhea Zambellas, A Sarah Walker, Martin McNally, Bridget Atkins, Michelle Kümin, Benjamin A Lipsky, Harriet Hughes, Deepa Bose, Simon Warren, Damien Mack, Jonathan Folb, Elinor Moore, Neil Jenkins, Susan Hopkins, R Andrew Seaton, Carolyn Hemsley, Jonathan Sandoe, Ila Aggarwal, Simon Ellis, Rebecca Sutherland, Claudia Geue, Nicola McMeekin, Claire Scarborough, John Paul, Graham Cooke, Jennifer Bostock, Elham Khatamzas, Nick Wong, Andrew Brent, Jose Lomas, Philippa Matthews, Tri Wangrangsimakul, Roger Gundle, Mark Rogers, Adrian Taylor, Guy E Thwaites and Philip Bejon on behalf of the OVIVA study
Oral vs IV Antibiotics for Bone and Joint Infections (OVIVA)

Design
Randomized, open label, non-inferiority trial with intention to treat analysis

Population
1054 adult patients in the U.K. at 26 different hospitals, with acute or chronic bone or joint infections (including prosthetic joints and other hardware)

Intervention
Randomized to oral or IV antibiotic therapy
- Within 7 days after surgical intervention or start of antibiotic therapy
- Antibiotic determined by Infectious Diseases specialist

Outcome
Treatment failure within 1 year
Oral Antibiotics for Bone and Joint Infections

Isolated Bacteria in Positive Cultures

- S. Aureus
- Coag Neg Staph
- Strep
- Pseudomonas
- Other GNRs
Outcomes: Oral Antibiotics for Bone and Joint Infections

- No difference in treatment failure between the groups at one year

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Oral Group</th>
<th>Intravenous Group</th>
<th>Risk Difference (90% CI; 95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Intention-to-treat population</td>
<td>70.0/527</td>
<td>77.3/527</td>
<td>-1.4 (-4.9 to 2.2; -5.6 to 2.9)</td>
</tr>
<tr>
<td>Modified intention-to-treat population</td>
<td>67/509</td>
<td>74/506</td>
<td>-1.5 (-5.0 to 2.1; -5.7 to 2.8)</td>
</tr>
<tr>
<td>Per-protocol population</td>
<td>61/466</td>
<td>69/443</td>
<td>-2.5 (-6.3 to 1.3; -7.0 to 2.1)</td>
</tr>
<tr>
<td>Worst-case sensitivity analysis</td>
<td>85/527</td>
<td>74/527</td>
<td>2.1 (-1.5 to 5.7; -2.2 to 6.4)</td>
</tr>
</tbody>
</table>

**Figure 3. Differences in Risk According to the Analysis Performed.**
Choosing Wisely: Decreased Antibiotic Duration

Table. Infections for Which Short-Course Therapy Has Been Shown to Be Equivalent in Efficacy to Longer Therapy

<table>
<thead>
<tr>
<th>Disease</th>
<th>Treatment, Days</th>
</tr>
</thead>
<tbody>
<tr>
<td>Community-acquired pneumonia(^1)(^-)(^3)</td>
<td>Short</td>
</tr>
<tr>
<td>Nosocomial pneumonia(^6)(^,)(^7)</td>
<td>≤ 8</td>
</tr>
<tr>
<td>Pyelonephritis(^10)</td>
<td>5-7</td>
</tr>
<tr>
<td>Intraabdominal infection(^11)</td>
<td>4</td>
</tr>
<tr>
<td>Acute exacerbation of chronic bronchitis and COPD(^12)</td>
<td>≤ 5</td>
</tr>
<tr>
<td>Acute bacterial sinusitis(^13)</td>
<td>5</td>
</tr>
<tr>
<td>Cellulitis(^14)</td>
<td>5-6</td>
</tr>
<tr>
<td>Chronic osteomyelitis(^15)</td>
<td>42</td>
</tr>
</tbody>
</table>

Abbreviation: COPD, chronic obstructive pulmonary disease.

Duration of antibiotic therapy was too long in 67.8% of patients

- No difference in C. *diff*, hospital readmission, or death

Each excess day of antibiotic treatment corresponded with a 5% increase in patient reported adverse events
Diagnosis and Treatment of Adults with Community-acquired Pneumonia. An Official Clinical Practice Guideline of the American Thoracic Society and Infectious Diseases Society of America

Published, 10/1/2019

Published: 01 October 2019
IDSA/ATS CAP Guideline Updates: Differences between 2007 and 2019

• **Diagnosis:**
  - PSI > CURB 65
  - Don’t use procalcitonin to guide antibiotic initiation
  - Obtain cultures if severe CAP and/or empiric coverage for MRSA and P. aeruginosa

• **Standard empiric therapy for outpatient CAP:**
  - Macrolide monotherapy only if local pneumococcal resistance < 25% (for healthy patients)

• **Standard empiric therapy for severe CAP:**
  - β-lactam + macrolide > β-lactam + FQ
  - Do not include empiric anaerobic coverage for aspiration PNA

• **HCAP removed. Empiric MRSA and P. aeruginosa coverage:**
  - Based on individual risk factors and severity of PNA

• Steroids not recommended, can consider in refractory septic shock

• Routine follow up chest imaging not recommended
Bugs and Drugs – Take Homes

• Oral antibiotics may be reasonable for select patients with bone and joint infections under the guidance of an Infectious Disease specialist.

• Be mindful of antibiotic duration for pneumonia:
  • CAP: 3-5 days
  • Nosocomial: ≤8 days

• New IDSA/ATS Community Acquired Pneumonia guidelines
Case

Mr. Tation (history of T2DM, CKD3, Afib on apixaban) fully recovers from his septic knee infection.

One year later, he unfortunately develops escalating chest pain and is admitted to the hospital with NSTEMI.

He successfully undergoes PCI with a DES to his RCA.

He is quite worried about risk of bleeding as he has already noticed excess bruising on the apixaban.

DOACs

Given his history of afib and PCI with DES, what anti-thrombotic therapy would you recommend at hospital discharge?
Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation

Renato D. Lopes, M.D., Ph.D., Gretchen Heizer, M.S., Ronald Aronson, M.D., Amit N. Vora, M.D., M.P.H., Tyler Massaro, Ph.D., Roxana Mehran, M.D., Shaun G. Goodman, M.D., Stephan Windecker, M.D., Harald Darius, M.D., Jia Li, Ph.D., Oleg Averkov, M.D., Ph.D., M. Cecilia Bahit, M.D., Otavio Berwanger, M.D., Ph.D., Andrzej Budaj, M.D., Ph.D., Ziad Hijazi, M.D., Ph.D., Alexander Parkhomenko, M.D., Ph.D., Peter Sinnaeve, M.D., Ph.D., Robert F. Storey, M.D., Holger Thiele, M.D., Dragos Vinereanu, M.D., Ph.D., Christopher B. Granger, M.D., and John H. Alexander, M.D., M.H.S., for the AUGUSTUS Investigators*
DOACs – Atrial fibrillation and PCI/ACS: AUGUSTUS

**Question**
Safety and efficacy of apixaban vs warfarin and aspirin vs placebo in patients with afib with recent ACS or PCI

**Design**
Prospective 2x2 factorial randomized controlled trial

**Population**
4614 adults with afib on longterm AC with ACS or PCI and planned for 6 mo use of P2Y\textsubscript{12} inhibitor

**Intervention**
Randomized to either apixaban or warfarin and either low dose aspirin or placebo (all got P2Y\textsubscript{12} inhibitor) x 6 months

**Outcomes**
- **Primary:** Major and nonmajor but relevant bleeding
- **Secondary:** Composite death or hospitalization and composite of death or ischemic events (stroke, MI, stent thrombosis) or urgent revascularization
DOACs – Atrial fibrillation and PCI/ACS: AUGUSTUS

Primary Outcome

Major and Nonmajor Relevant Bleeding

Apixiban vs Warfarin: HR 0.69 (0.58-0.81) P<0.001
Aspirin vs Placebo: HR 1.89 (1.59-2.24) P<0.001

Bleeding Event Rate per 100 patient-years:

Apixiban + clopidogrel: 16.8
Warfarin + clopidogrel: 26.7
Apixiban + clopidogrel + aspirin: 33.6
Warfarin + clopidogrel + aspirin: 49.1
## Secondary Outcomes

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Apixiban % Event rate per 100 pt-yr</th>
<th>Warfarin % Event rate per 100 pt-yr</th>
<th>HR (95% CI)</th>
<th>P value for superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or hospitalization</td>
<td>23.5% 57.2</td>
<td>27.4% 69.2</td>
<td>0.83 (0.74-0.93)</td>
<td>0.002</td>
</tr>
<tr>
<td>Death or ischemic event</td>
<td>6.7% 14.3</td>
<td>7.1% 15.3</td>
<td>0.93 (0.75-1.16)</td>
<td>NS</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Outcome</th>
<th>Aspirin % Event rate per 100 pt-yr</th>
<th>Placebo % Event rate per 100 pt-yr</th>
<th>HR (95% CI)</th>
<th>P value for superiority</th>
</tr>
</thead>
<tbody>
<tr>
<td>Death or Hospitalization</td>
<td>26.2% 65.7</td>
<td>24.7% 60.6</td>
<td>1.08 (0.96-1.21)</td>
<td>NS</td>
</tr>
<tr>
<td>Death or ischemic event</td>
<td>6.5% 13.9</td>
<td>7.3% 15.7</td>
<td>0.89 (0.71-1.11)</td>
<td>NT</td>
</tr>
</tbody>
</table>
Case

Mr. Tation (history of T2DM, CKD3, Afib on apixaban, NSTEMI s/p PCI with DES) was grateful to take only two blood thinning agents (apixiban and clopidogrel) after his PCI. He has no further chest pain and resumes his active lifestyle.

At his one-year post PCI visit, he asks, "so how long do I need to continue the clopidogrel anyway?"

DOACs

What is appropriate antithrombotic therapy for patients with atrial fibrillation and stable CAD?
DOACs – Atrial fibrillation and Stable CAD

Antithrombotic Therapy for Atrial Fibrillation with Stable Coronary Disease

Satoshi Yasuda, M.D., Ph.D., Koichi Kaikita, M.D., Ph.D., Masaharu Akao, M.D., Ph.D., Junya Ako, M.D., Ph.D., Tetsuya Matoba, M.D., Ph.D., Masato Nakamura, M.D., Ph.D., Katsumi Miyachi, M.D., Ph.D., Nobuhisa Hagiwara, M.D., Ph.D., Kazuo Kimura, M.D., Ph.D., Atushi Hirayama, M.D., Ph.D., Kunihiro Matsui, M.D., M.P.H., and Hisao Ogawa, M.D., Ph.D., for the AFIRE Investigators*
DOACs – Atrial fibrillation and Stable CAD: AFIRE

Question
Is rivaroxaban monotherapy noninferior to rivaroxaban plus antiplatelet in patients with atrial fibrillation and stable CAD >1 year after revascularization or not requiring revascularization?

Design
Multicenter, randomized, open label, parallel-group trial

Population
Japanese adults with atrial fibrillation (CHADS\textsubscript{2} score >1) and angiographically confirmed CAD (>50% stenosis) with or without stenting or history of CABG >1 year prior to enrollment.

Intervention/Control
Rivaroxaban monotherapy
vs. rivaroxaban and antiplatelet (aspirin or clopidogrel) combination therapy

Outcomes
Primary: composite stroke, embolism, MI, unstable angina needing revasc, or death
Safety: major bleeding per ISTH criteria
DOACs – Atrial fibrillation and Stable CAD: AFIRE Results

Primary Outcome: Composite CVD events and all-cause mortality:
Rivaroxaban monotherapy better
HR 0.72 (0.55-0.95)
P<0.001 noninferiority

Safety Outcome: Major Bleeding
Rivaroxaban Monotherapy better
HR 0.59 (0.39-0.89)
P=0.01 superiority
DOACs – Atrial fibrillation and Stable CAD: AFIRE Results

- Main driver of primary efficacy endpoint was CV and non-CV mortality*
- Hemorrhagic stroke also significantly less in rivaroxaban monotherapy group
- Trend toward less ischemic stroke, less unstable angina

### Table 2. Primary and Secondary Efficacy and Safety End Points.

<table>
<thead>
<tr>
<th>End Point</th>
<th>Rivaroxaban Monotherapy (N=1107)</th>
<th>Combination Therapy (N=1108)</th>
<th>Hazard Ratio (95% CI)</th>
<th>P Value†</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary efficacy end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular events or death from any cause</td>
<td>89 (4.14)</td>
<td>121 (5.75)</td>
<td>0.72 (0.55–0.95)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td><strong>Secondary efficacy end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Cardiovascular events</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Ischemic stroke</td>
<td>21 (0.96)</td>
<td>28 (1.31)</td>
<td>0.73 (0.42–1.29)</td>
<td></td>
</tr>
<tr>
<td>Hemorrhagic stroke</td>
<td>4 (0.18)</td>
<td>13 (0.60)</td>
<td>0.30 (0.10–0.92)</td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>13 (0.59)</td>
<td>8 (0.37)</td>
<td>1.60 (0.67–3.87)</td>
<td></td>
</tr>
<tr>
<td>Unstable angina requiring revascularization</td>
<td>13 (0.59)</td>
<td>18 (0.84)</td>
<td>0.71 (0.35–1.44)</td>
<td></td>
</tr>
<tr>
<td>Systemic embolism</td>
<td>2 (0.09)</td>
<td>1 (0.05)</td>
<td>1.97 (0.18–21.73)</td>
<td></td>
</tr>
<tr>
<td>Death</td>
<td>41 (1.85)</td>
<td>73 (3.37)</td>
<td>0.55 (0.38–0.81)</td>
<td></td>
</tr>
<tr>
<td>Cardiovascular</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Noncardiovascular</td>
<td>26 (1.17)</td>
<td>43 (1.99)</td>
<td>0.59 (0.36–0.96)</td>
<td></td>
</tr>
<tr>
<td>Ischemic cardiovascular events or death‡</td>
<td>114 (5.37)</td>
<td>141 (6.77)</td>
<td>0.80 (0.62–1.02)</td>
<td></td>
</tr>
<tr>
<td><strong>Primary safety end point</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding‡</td>
<td>35 (1.62)</td>
<td>58 (2.76)</td>
<td>0.59 (0.39–0.89)</td>
<td>0.01</td>
</tr>
<tr>
<td><strong>Secondary safety end points</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Any bleeding</td>
<td>146 (7.22)</td>
<td>238 (12.71)</td>
<td>0.58 (0.47–0.71)</td>
<td></td>
</tr>
<tr>
<td>Nonmajor bleeding</td>
<td>121 (5.89)</td>
<td>198 (10.31)</td>
<td>0.58 (0.46–0.72)</td>
<td></td>
</tr>
</tbody>
</table>

*The primary and secondary efficacy analyses were performed in the modified intention-to-treat population, which included all the patients who had undergone randomization after the exclusion of patients who had technical reasons for not participating in the trial. The primary and secondary safety analyses were performed in the population that included all the patients who had undergone randomization and received at least one dose of a trial drug during the follow-up period (1099 patients in the monotherapy group and 1099 in the combination-therapy group). The 95% confidence intervals have not been adjusted for multiple comparisons.
†In the primary efficacy analysis, the P value for noninferiority was calculated at a one-sided alpha level of 0.025 with a noninferiority margin of 0.46. Since noninferiority was shown for the primary efficacy end point, a closed testing procedure was conducted to determine superiority for the primary safety end point.
‡The category of ischemic cardiovascular events or death is a composite of death from any cause, myocardial infarction, unstable angina requiring revascularization, stroke, transient ischemic attack, systemic arterial embolism, venous thromboembolism, revascularization, or stent thrombosis.
§The category of net adverse clinical events is a composite of death from any cause, myocardial infarction, stroke, or major bleeding.
¶Major and nonmajor bleeding events were classified according to the criteria of the International Society on Thrombosis and Hemostasis.
DOACs – Round 1 Take Homes

• For patients with atrial fibrillation and PCI/ACS, apixaban plus clopidogrel appears safer and noninferior to triple antithrombotic therapy or warfarin plus clopidogrel. (AUGUSTUS)
• For patients with atrial fibrillation and stable CAD, rivaroxaban monotherapy appears noninferior to DOAC + antiplatelet therapy (AFIRE)
Design: prospective cohort

Population:

3007 patients with Afib on apixaban, dabigatran, or rivaroxaban

Intervention:

DOAC stopped 1-2* days pre-procedure and resumed 1-2 days post-procedure
Perioperative Management of Afib Patients on DOACs: Comparison

**Safety Hypothesis:**
- Major bleeding (< 2%)
- Arterial thromboembolism (< 1.5%)

**Secondary Safety Outcomes:**
- Clinically relevant nonmajor bleeding
- Minor bleeding
- Death
- VTE
- Catheter associated venous or arterial thrombosis
Perioperative Management of Afib Patients on DOACs: Outcomes

**Table 3. Primary Study Outcomes**

<table>
<thead>
<tr>
<th>Outcome</th>
<th>DOAC Cohort</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Apixaban (n = 1257)</td>
<td>Dabigatran Etexilate (n = 668)</td>
<td>Rivaroxaban (n = 1082)</td>
<td></td>
</tr>
<tr>
<td>Primary</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Major bleeding(^a)</td>
<td>17 (1.35)</td>
<td>6 (0.90)</td>
<td>20 (1.85)</td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>0-2.00</td>
<td>0-1.73</td>
<td>0-2.65</td>
<td></td>
</tr>
<tr>
<td>1-Sided 95% CI</td>
<td>.051</td>
<td>.02</td>
<td>.36</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Arterial thromboembolism(^b,c)</td>
<td>2 (0.16)</td>
<td>4 (0.60)</td>
<td>4 (0.37)</td>
<td></td>
</tr>
<tr>
<td>No. (%)</td>
<td>0-0.48</td>
<td>0-1.33</td>
<td>0-0.82</td>
<td></td>
</tr>
<tr>
<td>1-Sided 95% CI</td>
<td>&lt;.001</td>
<td>.03</td>
<td>.001</td>
<td></td>
</tr>
<tr>
<td>P value</td>
<td></td>
<td></td>
<td></td>
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</tr>
</tbody>
</table>
Discontinuation of DOACs 1-2 days prior to surgery with resumption 1-2 days post procedure is likely safe for patients with Afib and a lower to moderate risk CHADS2 score.
Case

After discussing anti-thrombotic therapy with Mr Tation, you review his other recent labs:

HbA1c 8.1
eGFR 48 mL/min/1.73m²
Albumin to creatinine ratio 100 mg/g

He is currently taking metformin 1000 mg bid and lisinopril 20 mg bid.

What is the next most appropriate agent to add to his diabetes regimen to improve his CV and CKD outcomes?
Canagliflozin and Renal Outcomes in Type 2 Diabetes and Nephropathy

SGLT2s: CREEDENCE trial

Question
What is the effect of canagliflozin in adults with T2DM and albuminuric CKD?

Population
Adults with T2DM, A1c 6.5-12.0, eGFR 30-90 ml/min, and urine albumin to creatinine ratio 300-5000 mg/g, already receiving ACEI or ARB.

Intervention
canagliflozin 100 mg daily vs placebo

Outcomes: (stratified by eGFR category: 30-45, 45-60, or 60-90 ml/min)
Primary: composite including renal replacement therapy, doubling of serum creatinine, or death from renal or CV disease
Secondary: heart failure admits, CVD deaths, MI, CVA, all cause mortality, others

Perkovic NEJM June 2019
Composite renal outcome (B):
- doubling of serum creatinine
- eGFR <15 ml/min
- renal replacement therapy
- renal death

HR 0.66 (0.51-0.81)
ARR: 3.2% or 13 events per 1000 pt-years
(Event rate: 6.9% canagliflozin vs 10.1% placebo)

No excess fractures or amputations
### SGLT2s: CREDEENCE trial

Canagliflozin was helpful throughout included eGFR range and regardless of baseline albuminuria.

<table>
<thead>
<tr>
<th>Subgroup</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>Canagliflozin</th>
<th>Placebo</th>
<th>Hazard Ratio (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Primary composite outcome of ESKD, doubling of serum creatinine, or renal or CV death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Screening estimated GFR</td>
<td>no. of patients/total no.</td>
<td>events/1000 patient-yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 to &lt;45 ml/min/1.73 m²</td>
<td>119/657</td>
<td>153/656</td>
<td>72.2</td>
<td>95.4</td>
<td>0.75 (0.59–0.95)</td>
</tr>
<tr>
<td>45 to &lt;60 ml/min/1.73 m²</td>
<td>56/640</td>
<td>102/639</td>
<td>33.4</td>
<td>63.1</td>
<td>0.52 (0.38–0.72)</td>
</tr>
<tr>
<td>60 to &lt;90 ml/min/1.73 m²</td>
<td>70/905</td>
<td>85/904</td>
<td>29.9</td>
<td>36.5</td>
<td>0.82 (0.60–1.12)</td>
</tr>
<tr>
<td>Baseline UACR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.49</td>
</tr>
<tr>
<td>≤1000</td>
<td>69/1185</td>
<td>88/1163</td>
<td>22.0</td>
<td>28.8</td>
<td>0.76 (0.55–1.04)</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>176/1017</td>
<td>252/1036</td>
<td>69.6</td>
<td>100.8</td>
<td>0.67 (0.55–0.81)</td>
</tr>
<tr>
<td><strong>Renal-specific composite outcome of ESKD, doubling of serum creatinine, or renal death</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.18</td>
</tr>
<tr>
<td>Screening estimated GFR</td>
<td>no. of patients/total no.</td>
<td>events/1000 patient-yr</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>30 to &lt;45 ml/min/1.73 m²</td>
<td>85/657</td>
<td>115/656</td>
<td>51.6</td>
<td>71.7</td>
<td>0.71 (0.53–0.94)</td>
</tr>
<tr>
<td>45 to &lt;60 ml/min/1.73 m²</td>
<td>33/640</td>
<td>66/639</td>
<td>19.7</td>
<td>40.8</td>
<td>0.47 (0.31–0.72)</td>
</tr>
<tr>
<td>60 to &lt;90 ml/min/1.73 m²</td>
<td>35/905</td>
<td>43/904</td>
<td>14.9</td>
<td>18.5</td>
<td>0.81 (0.52–1.26)</td>
</tr>
<tr>
<td>Baseline UACR</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td>0.16</td>
</tr>
<tr>
<td>≤1000</td>
<td>29/1185</td>
<td>31/1163</td>
<td>9.2</td>
<td>10.2</td>
<td>0.90 (0.54–1.50)</td>
</tr>
<tr>
<td>&gt;1000</td>
<td>124/1017</td>
<td>193/1036</td>
<td>49.1</td>
<td>77.2</td>
<td>0.61 (0.49–0.76)</td>
</tr>
</tbody>
</table>

Perkovic NEJM June 2019
SGLT2s: Serious adverse outcomes

**55 unique cases** (3 fatal) of Fournier Gangrene reported since SGLT2s have been marketed starting March 2013 through end of January 2019.

By comparison, FDA has identified 19 cases of FG associated with other diabetes meds since 1984.

For context: FDA estimates 1.7 million patients were prescribed an SGLT2 inhibitor in 2017.

**Take Homes:**
- This outcome is exceedingly rare
- Avoid prescribing SGLT2s for pts with hx of severe GU/anorectal infections
- Counsel patients to examine skin daily and seek urgent attention for any rash/swelling/pain that develops in the genital/perineal area
GLP1s: Oral semaglutide – PIONEER 3

- **Design**: Phase 3a randomized, double blind, double dummy, parallel group, controlled trial.
- **Population**: 1864 adults T2DM uncontrolled with metformin +/- sulfonylurea
- **Interventions**: oral semaglutide 3 mg, 7 mg, or 14 mg daily
- **Control**: sitagliptin 100 mg daily
- **Outcomes**: A1c and weight change

May 2019
### GLP1s: Oral semaglutide – PIONEER 3

**Outcomes**
- A1c lowering from baseline
  - Sitagliptin: -0.8%
  - Semaglutide 3 mg: -0.6%
  - Semaglutide 7 mg: -1.0%
  - Semaglutide 14 mg: -1.3%

**Conclusion:**
Oral semaglutide 7 and 14 mg doses superior to sitagliptin for A1c lowering and weight loss

<table>
<thead>
<tr>
<th>Outcome (compared to sitagliptin at 26 weeks)</th>
<th>A1c change (%)</th>
<th>Weight Change (kg)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Semaglutide 3 mg</td>
<td>0.2 (0.1-0.3)</td>
<td>-0.6 (N/A)</td>
</tr>
<tr>
<td>Semaglutide 7 mg</td>
<td>-0.3 (-0.4 to -0.1)</td>
<td>-1.6 (-2.0 to -1.1)</td>
</tr>
<tr>
<td>Semaglutide 14 mg</td>
<td>-0.5 (-0.6 to -0.4)</td>
<td>-2.5 (-3.0 to -2.0)</td>
</tr>
</tbody>
</table>
Design: randomized, double blind, placebo controlled trial
Population: 3183 adults
Interventions: semaglutide 14 mg daily
Control: placebo
Outcomes: composite fatal and nonfatal CVD and stroke (MACE)
GLP1s: Oral semaglutide – PIONEER 6

MACE
HR 0.79
(0.57-1.11)
P<0.001
noninferiority

CV Deaths
HR 0.49
(0.27-0.92)

Conclusion: oral semaglutide trended but not stat sig for decreased MACE
Diabetes Take Homes

• Canagliflozin (SGLT2) improved renal outcomes in patients with T2DM and diabetic kidney disease (eGFR ≥30)
  • Fournier Gangrene exceedingly rare adverse event with SGLT2s
• Oral semaglutide (GLP1) superior to sitagliptin (DPP4) for A1c lowering and weight loss; FDA approved as of 9/2019
• Oral semaglutide not inferior to placebo for major adverse CV events
Case

After a particularly salty Thanksgiving dinner, Mr. Tation develops shortness of breath and swollen feet. He is admitted with a new diagnosis of heart failure and started on IV diuretics.

TTE during admit shows EF 35%

Hospital team notes his Hg is 10. Follow-up iron studies show ferritin 150 ng/mL and total iron saturation 10%.
Iron Supplementation and Heart Failure

American College of Cardiology (January 2019):
• Iron deficiency (with or without anemia)
  • Independent risk factor for worse functional capacity and survival
• Guidelines:
  • European guidelines recommend treatment with IV ferric carboxymaltose in symptomatic heart failure patients with iron deficiency (Class IIa)
  • US guidelines recommend IV iron for patients with heart failure and iron deficiency (Class IIb)
Iron Supplementation and Cardiovascular Outcomes in Heart Failure

August 2019

Iron Supplementation Improves Cardiovascular Outcomes in Patients with Heart Failure

Xiang Zhou, MD, PhD, Weiting Xu, MD, Youjia Xu, MD, Zhiyuan Qian, MD

*a Department of Cardiology, The Second Affiliated Hospital of Soochow University, Suzhou, China; b Department of Orthopedics, The Second Affiliated Hospital of Soochow University, Suzhou, China; c Department of Neurosurgery, The Second Affiliated Hospital of Soochow University, Suzhou, China.*
Iron Supplementation and Cardiovascular Outcomes in Heart Failure

Design/Population
   meta-analysis of 10 RCTs, 1404 patient with systolic heart failure and iron deficiency

Intervention/Comparison
   Iron supplementation (iron sucrose or ferric carboxymaltose) vs placebo

Outcomes
   • Objective: All cause mortality, hospitalization for worsening heart failure, LVEF
   • Subjective: NYHA class, 6 minute walk test, patient global assessment, and several HF and quality of life patient questionnaires
Outcomes: Iron Supplementation and Heart Failure

No difference in mortality
Heart Failure and IV Iron – Take Homes

Iron supplementation (IV) in patients with iron deficiency and systolic heart failure may:
- Reduce heart failure hospitalization
- Increase cardiac function
- Improve exercise capacity and quality of life

Unfortunately, no clear mortality benefit – additional large trial pending
Case

During his HF admission, Mr. Tation is noted to have increasing confusion, especially at night.

The nurse calls the covering resident at 11 PM reporting Mr. T almost fell while trying to get out of bed to “let the dog out.”

The nurse is requesting a medication to help treat his delirium and sundowning.

Delirium

Do you prescribe an antipsychotic?
If so, which one? Dose?
Antipsychotics for Treating Delirium in Hospitalized Adults

Annals of Internal Medicine

Antipsychotics for Treating Delirium in Hospitalized Adults
A Systematic Review

Roozbeh Nikooie, MD; Karin J. Neufeld, MD, MPH; Esther S. Oh, MD, PhD; Lisa M. Wilson, ScM; Allen Zhang, BS; Karen A. Robinson, PhD*; and Dale M. Needham, MD, PhD*
Antipsychotics for Treating Delirium in Hospitalized Adults

Design/Population
Meta-analysis of 16 RCTs and 10 prospective observational studies of 5607 hospitalized, delirious adult patients

Intervention
Antipsychotics vs placebo

Outcomes
• Delirium severity (DRS-R-98)
• Delirium duration
• Mortality
• Hospital LOS
• Cognitive functioning

• Inappropriate continuation of antipsychotics
• Adverse neurologic events
• Adverse cardiac events
Outcomes: Antipsychotics for the Treatment of Delirium

Figure 7. Effect of second-generation antipsychotics versus placebo on mortality*

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention</th>
<th>Inpatient population</th>
<th>Incidence, n/N</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td>Intervention</td>
</tr>
<tr>
<td>Short-term mortality</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Tahir, 2010</td>
<td>Quetiapine</td>
<td>Non-critically ill</td>
<td>4/21</td>
</tr>
<tr>
<td>Girard, 2010</td>
<td>Ziprasidone</td>
<td>Critically ill</td>
<td>4/30</td>
</tr>
<tr>
<td>Devlin, 2010</td>
<td>Quetiapine</td>
<td>Critically ill</td>
<td>2/18</td>
</tr>
<tr>
<td>Agar, 2017</td>
<td>Risperidone</td>
<td>Hospice/palliative care</td>
<td>16/82</td>
</tr>
<tr>
<td>Girard, 2018</td>
<td>Ziprasidone</td>
<td>Critically ill</td>
<td>53/190</td>
</tr>
<tr>
<td>Overall</td>
<td></td>
<td></td>
<td>1.09 (0.83, 1.45)</td>
</tr>
</tbody>
</table>

NOTE: Weights are from random effects analysis

CI = confidence interval; IV = intravenous; N = total arm population; n = incidence within arm; NG = nasogastric tube; RR = relative risk.

*Only RCTs included in the meta-analysis.
Outcomes: Antipsychotics for the Treatment of Delirium

Second generation antipsychotics vs haloperidol on delirium duration

**Figure 5. Effect of second-generation antipsychotics versus haloperidol on delirium duration**

<table>
<thead>
<tr>
<th>Author, year</th>
<th>Intervention</th>
<th>Inpatient population</th>
<th>Outcome</th>
<th>Participant, N</th>
<th>Mean difference (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jain, 2017</td>
<td>Olanzapine</td>
<td>Non-critically #</td>
<td>Days until MDAS score &lt;10</td>
<td>47 53</td>
<td>0.20 (-0.05, 0.45)</td>
</tr>
<tr>
<td>Lim, 2007</td>
<td>Olanzapine</td>
<td>General</td>
<td>Time to recovery</td>
<td>31 31</td>
<td>0.08 (-0.31, 0.47)</td>
</tr>
<tr>
<td>Maneeton, 2013</td>
<td>Quetiapine</td>
<td>Hyperactive delirium</td>
<td>Time to first remission, days</td>
<td>24 28</td>
<td>0.80 (0.24, 1.36)</td>
</tr>
<tr>
<td>Han, 2004</td>
<td>Risperidone</td>
<td>With and without critical illness</td>
<td>Period of time until MDAS &lt;13</td>
<td>12 12</td>
<td>-0.05 (-1.45, 1.35)</td>
</tr>
</tbody>
</table>

**Overall (I-squared = 37.8%, p = 0.185)**: 0.24 (0.04, 0.43)
Antipsychotics and Delirium – Take Homes

Evidence currently does not support the use of antipsychotics to prevent or treat delirium in hospitalized patients.

The best treatment is prevention, followed by non-pharmacologic interventions.
E-cigarettes (Vaping): Harms

Pulmonary Illness Related to E-Cigarette Use in Illinois and Wisconsin — Preliminary Report

Case cluster: 53 patients between April and August 2019 who reported use of e-cigarette device within 90 days of respiratory symptom onset accompanied by bilateral pulmonary infiltrates not attributable to other causes (infection, cardiac, rheumatologic, or neoplastic)

Patient characteristics:
- 83% male, 82% white
- Median age 19 (range 16-53)
- 80% used THC product (but brands/products used were diverse)
- 98% respiratory symptoms, 81% gastrointestinal symptoms, 100% constitutional symptoms
- 95% hospitalized, 87% supplemental oxygen, 58% ICU care, 32% intubated, 1 death

Conclusion: Emerging cases of severe respiratory illness related to diverse e-cigarette exposure; exact mechanism unknown and likely a spectrum
E-cigarettes (Vaping): Harms

CDC Statement 10/15/2019: “Multistate outbreak of lung injury associated with use of e-cigarette products”

- 1479 lung injury cases associated with use of e-cigarette products have been reported from 49 states and D.C.
- 33 deaths confirmed in 24 states
- THC present in most samples tested by FDA to date; findings suggest THC products obtained off the street/from informal sources/illicit dealers are linked to the most cases

CDC Recommendations

- Do not use vaping products that contain THC
- Since specific causes are unknown, safest course is to avoid all vaping products

For clinicians: do not recommend vaping to patients
Review – Take Homes

**Oral antibiotics** may be reasonable for the management of **bone/joint infections** in select patients as guided by infectious disease specialists.

We need to **be more conscientious about antibiotic duration**, particularly on discharge.

Updated community acquired pneumonia management guidelines from IDSA/ATS

**Dual therapy with apixipan and clopidogrel** was noninferior to dual therapy with warfarin and clopidogrel and triple therapy for patients with **atrial fibrillation and ACS/PCI**.

**Monotherapy with rivaroxaban** was noninferior to dual therapy with rivoroxaban and aspirin in patients with **atrial fibrillation and stable CAD**.

**DOACs** can be **safely held perioperatively (without heparin bridging)**, but further study needed to evaluate best timeline and higher risk patient groups.
**Review – Take Homes**

**Canagliflozin** improved **renal outcomes** in patients with T2DM and diabetic kidney disease with macroalbuminurina

**Oral semaglutide** is superior to sitagliptin for A1c lowering and weight loss; and is noninferior compared to placebo for major adverse cardiovascular events

**IV iron supplementation** in HFrEF patients with iron deficiency **may reduce HF associated hospitalization** and improve quality of life

Unfortunately, we **still do not have good pharmacologic treatments** for delirium

**Discourage patients from using e-cigarettes (vaping),** especially with THC products
Questions?
Thank you for your attention
References

Infectious Disease

Anticoagulation
References

Diabetes


Heart Failure


Delirium

References

• E-cigarettes