Cardiology Mythbusters: Vol 2
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Objectives

- Discuss the risks and benefits of utilizing intravenous amiodarone for the management of atrial fibrillation.
- Discuss the differences in efficacy between thiazide-type and thiazide diuretics for the management of hypertension.
- Discuss the evidence surrounding the use of anticoagulation in patients with peripheral arterial disease.
- Given a patient with a CHA2DS2-VASc score of 0, discuss the appropriateness of therapy for stroke prevention.

IV to PO Efficacy

<table>
<thead>
<tr>
<th>Study Groups</th>
<th>Treatment</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>72 patients with recent-onset sustained atrial tachyarrhythmia</td>
<td>PO amiodarone 25.7 mg/kg vs. IV amiodarone 3-5 mg/kg bolus then 10-15 mg/kg over 24 h</td>
<td>No difference in conversion to SR between PO and IV (64% vs. 68%, respectively; p=NS)</td>
</tr>
<tr>
<td>223 patients with symptomatic atrial fibrillation on digoxin</td>
<td>PO amiodarone 600 mg in 3 divided doses vs. IV amiodarone 9 mg/kg over 20 minutes then 1000 mg over 24 h</td>
<td>No difference in conversion to SR (p=NS); Longer time to cardioversion with PO (20h vs. 12h; p&lt;0.001)</td>
</tr>
</tbody>
</table>

- Rate-controlling effects of IV amiodarone have been reported as quickly as within 30 minutes of administration

IV, intravenous; PO, oral; SR, sinus rhythm

**IV VS. PO AMIODARONE: COMPARING RISKS**

**Amiodarone Cardiac Toxicities**

**Acute**
- Bradycardia
- Heart Block
- ?Hypotension

**Chronic**
- Bradycardia
- Heart Block
- QTc Prolongation*

*Rarely clinically meaningful

**Polysorbate 80**

<table>
<thead>
<tr>
<th>Author</th>
<th>Study Groups</th>
<th>Results</th>
</tr>
</thead>
<tbody>
<tr>
<td>Gough WB et al.</td>
<td>IV amiodarone in ethanol vs. polysorbate 80</td>
<td>80% drop in mean arterial pressure with polysorbate 80, no effect with ethanol group</td>
</tr>
<tr>
<td>Munoz A et al.</td>
<td>IV amiodarone 5 mg/kg with or without polysorbate 80</td>
<td>Polysorbate 80 had a significantly greater reduction in blood pressure (29.2 mmHg; p&lt;0.001) compared to control group (8.8 mmHg)</td>
</tr>
</tbody>
</table>

**Acute Hepatotoxicity with Amiodarone**

<table>
<thead>
<tr>
<th>Author (year)</th>
<th>Case</th>
<th>Result</th>
</tr>
</thead>
<tbody>
<tr>
<td>Rhodes A et al.</td>
<td>72yoM with acute hepatic impairment within 24 hours of IV amiodarone for VT</td>
<td>Resolution of transaminitis after withdrawing IV amio. Treated with PO without further hepatic impairment</td>
</tr>
<tr>
<td>Ratz Bravo AE et al.</td>
<td>Cases of elevated transaminases &gt; 500x ULN in 3 post-cardiac surgery patients</td>
<td>Cessation of IV amiodarone resolved transaminitis despite continuation of PO therapy</td>
</tr>
<tr>
<td>Lahbabi M et al.</td>
<td>29yoF with transaminis &gt; 1000x after IV amiodarone load for AF with RVR</td>
<td>IV formulation changed to PO load, followed by resolution of transaminis</td>
</tr>
</tbody>
</table>

AF, atrial fibrillation; RVR, rapid ventricular response; ULN, upper limit of normal; VT, ventricular tachycardia


Hepatotoxicity with Polysorbate 80

E-ferol Syndrome

- Seen with IV vitamin E formulation with polysorbate 80
- Causes hepatomegaly, jaundice, renal failure
- Clinical features similar to IV amiodarone

Take Home Points

- Amiodarone is highly effective but confusion exists around choosing IV vs. PO therapy
- IV and PO formulations are similar in efficacy
- Polysorbate 80 is the etiology of several acute toxicities associated with IV amiodarone
- Hypotension and acute liver toxicity

THIAZIDE VS. THIAZIDE – LIKE DIURETICS FOR TREATMENT OF HYPERTENSION

Seventh Joint National Committee
- Initial drug choice is thiazide-type diuretic for most
- No preference for specific agent(s)

Eighth Joint National Committee
- General nonblack population: initial treatment should include a thiazide-type diuretic, CCB, ACEI, or ARB
- General black population: initial treatment should include a thiazide-type diuretic or CCB
- No preference for specific agent(s)

2017 High Blood Pressure Clinical Practice Guideline
- First-line agents include thiazide diuretics, CCBs, and ACEI or ARBs
- Black adults with HTN (without HF or CKD) initial treatment should include a thiazide-type diuretic or CCB
- Chlorthalidone is preferred on the basis of prolonged half-life and proven trial reduction of CVD

ACEI, angiotensin converting enzyme inhibitor; ARB, angiotensin II receptor blocker; CCB, calcium channel blocker; CKD, chronic kidney disease; CVD, cardiovascular disease; HF, heart failure; HTN, hypertension

Agents

<table>
<thead>
<tr>
<th>Agent</th>
<th>Starting dose (mg)</th>
<th>Typical max dose (mg/d)</th>
<th>Half-life (hrs)</th>
<th>30 d supply (on $4 list*)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chlorothiazide</td>
<td>125</td>
<td>500</td>
<td>1.5</td>
<td>$7.55 – 20.77 (no)</td>
</tr>
<tr>
<td>Hydrochlorothiazide</td>
<td>12.5-25</td>
<td>25</td>
<td>2.5</td>
<td>$2.53 – 12.60 (yes)</td>
</tr>
</tbody>
</table>

Thiazide-like

| Chlorothalidone | 12.5               | 25-50                   | 47             | $36.21 – 44.66 (no)      |
| Indapamide      | 1.25               | 2.5-5                   | 14             | $42.63 – 46.48 (yes)    |

* Walmart 4 prescriptions; accessed on April 2, 2018

Clinical Trial Data

Adverse Effects

- Hydrochlorothiazide associated with increase risk of non-melanoma skin and lip cancer
- Metabolic effects
  - Chlorthalidone associated with higher uric acid levels but NOT risk of gout
  - Hyponatremia and hypokalemia more common with chlorthalidone
- Metabolic effects of HCTZ and indapamide appear similar

- Longer half-life duration of action
- Improved blood lowering effect
- Similar adverse effect profile
- Greater reduction in clinical events
- More commonly available in combination products

**Why Consider It?**

- Aspirin
- Clopidogrel
- Aspirin + clopidogrel
- Vorapaxar
- Ticagrelor

Warfarin Antiplatelet Vascular Evaluation Trial

<table>
<thead>
<tr>
<th></th>
<th>Warfarin + antiplatelet (n = 1080)</th>
<th>Antiplatelet alone (n = 1081)</th>
</tr>
</thead>
<tbody>
<tr>
<td>MI, stroke, or CV death</td>
<td>12.2%</td>
<td>13.3%</td>
</tr>
<tr>
<td>RR</td>
<td>0.92 (95% CI, 0.73 – 1.16; p=0.48)</td>
<td></td>
</tr>
<tr>
<td>MI, stroke, severe ischemia of the peripheral/coronary arteries leading to urgent intervention, or CV death</td>
<td>15.9%</td>
<td>17.4%</td>
</tr>
<tr>
<td>RR</td>
<td>0.91 (95% CI, 0.74 – 1.12; p=0.37)</td>
<td></td>
</tr>
<tr>
<td>Life-threatening bleed</td>
<td>4%</td>
<td>1.2%</td>
</tr>
<tr>
<td>RR</td>
<td>3.41 (95% CI, 1.84 – 6.35; p&lt;0.001)</td>
<td></td>
</tr>
</tbody>
</table>

CL: confidence interval; CV: cardiovascular; MI: myocardial infarction; RR: relative risk


Cardiovascular Outcomes for People using Anticoagulation Strategies

Lower risk of stroke, MI, or CV death
HR 0.72 (95% CI, 0.57 – 0.90; p=0.0047)

Lower risk of major limb events
HR 0.54 (95% CI, 0.35 – 0.82; p=0.0037)

Increased risk of major bleeding
HR 1.61 (95% CI, 1.12 – 2.31; p=0.0089)

Rivaroxaban 2.5 mg BID + ASA 100 mg/d vs. ASA 100 mg/d

HR, hazard ratio

Cardiovascular Outcomes for People using Anticoagulation Strategies

Lower risk of major limb events
HR 0.67 (95% CI, 0.45 – 1; p=0.05)

No difference in the risk of stroke, MI, or CV death
HR 0.86 (95% CI, 0.69 – 1.08; p=0.29)

Increased risk of major bleeding
HR 1.68, 95% CI 1.17–2.40; p=0.0043

Rivaroxaban 5 mg BID vs. ASA 100 mg/d

HR, hazard ratio

What’s Next?
CV Risk Reduction

- Aspirin 81 mg or clopidogrel 75 mg daily
- Statin therapy
- Control blood pressure
- Smoking cessation

2016 AHA/ACC Lower Extremity PAD Guideline: Anticoagulation should not be used to reduce the risk of cardiovascular ischemic events in patients with PAD (Class III Level A)

LOW CHA₂DS₂-VASC SCORES: IS ANTIITHROMBOTIC THERAPY NECESSARY?

Case

KJ is a 62 year-old female with a PMH of gastroesophageal reflux disease, osteoarthritis, and hyperlipidemia. Her current medications include omeprazole 40 mg daily, naproxen 500 mg q12h PRN, and pravastatin 40 mg daily. She presents with a new diagnosis of AF.

Risk Stratification Systems

C: congestive heart failure
H: hypertension
A2: ≥ 75 years
D: diabetes
S2: stroke or TIA
V: vascular disease
A: age 65 – 74 years
Sc: ex category female

C: congestive heart failure
H: hypertension
A2: ≥ 75 years
D: diabetes
S2: stroke or TIA
V: vascular disease
A: age 65 – 74 years
Sc: ex category female
### Guideline Recommendations for AF Stroke Prevention

<table>
<thead>
<tr>
<th>Risk Score</th>
<th>ACCP 2012 (CHADS₂)</th>
<th>ACC/AHA/HRS 2014 (CHA₂DS₂-VASc)</th>
<th>ESC 2016 (CHA₂DS₂-VASc)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>No antithrombotic therapy or aspirin</td>
<td>It is reasonable to omit therapy</td>
<td>No antithrombotic therapy</td>
</tr>
<tr>
<td>1</td>
<td>OAC (preferred) or DAPT</td>
<td>OAC or no antithrombotic therapy or aspirin</td>
<td>Consider OAC (patient-specific risk)</td>
</tr>
<tr>
<td>≥2</td>
<td>OAC</td>
<td>OAC</td>
<td>OAC</td>
</tr>
</tbody>
</table>

ACC/AHA/HRS, American College of Cardiology/American Heart Association/Hospital Rhythm Society; ACCP, American College of Chest Physicians; ESC, European Society of Cardiology; DAPT, dual antiplatelet therapy; OAC, oral anticoagulant

### Prevalence of Antithrombotic Therapy in Low-Risk Patients

- NCDR PINNACLE Registry
  - Percent of patients with CHA₂DS₂-VASc 0 (n = 12,348) on antithrombotic therapy: >60%

NCDR PINNACLE, National Cardiovascular Data Registry Practice Innovation and Clinical Excellence

### Annual Stroke Risk

<table>
<thead>
<tr>
<th>CHADS₂</th>
<th>Adjusted stroke rate (% per year)</th>
</tr>
</thead>
<tbody>
<tr>
<td>0</td>
<td>1.9</td>
</tr>
<tr>
<td>1</td>
<td>2.8</td>
</tr>
<tr>
<td>2</td>
<td>4</td>
</tr>
<tr>
<td>3</td>
<td>5.9</td>
</tr>
<tr>
<td>4</td>
<td>8.5</td>
</tr>
<tr>
<td>5</td>
<td>12.5</td>
</tr>
<tr>
<td>6</td>
<td>18.2</td>
</tr>
</tbody>
</table>

Circulation. January 2014;139(2):e531S–e575S

### Net Clinical Benefit of Antithrombotic Therapy

- **Objective:** Determine the NCB of no antithrombotic therapy, aspirin or warfarin in AF patients with none or one stroke risk factor
- **Population:** Danish registry data of patients with nonvalvular AF from 1998 to 2012
  - 49,916 patients with either 0 or 1 stroke risk factor
- **Outcomes:** ischemic stroke, intracranial bleeding, major extracranial bleeding (including gastrointestinal bleeding), MI, death

NCB, net clinical benefit

Thromb Haemost. 2015;114(4):826-834.
**Female sex as a risk factor: Mikkelsen et al. study**

- **Objective:** Determine risk of stroke associated with female sex in patients with nonvalvular AF
- **Population:** Danish registry data of patients with nonvalvular AF from 1997 to 2008
  - Subdivided the population into three age intervals: < 65, 65–74 and ≥ 75 years
- **Outcomes:** stroke rates

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**Mikkelsen et al. Results**

- HR 0.86 (95% CI 0.76-0.98)
- HR 0.98 (95% CI 0.90-1.07)
- HR 1.10 (95% CI 1.05-1.15)

**What about CHA₂DS₂-VASc of 1?**

Treat the Patient, Not the Number: Stroke Prevention in Atrial Fibrillation with Low CHA₂DS₂-VASc Scores

[http://blogs.pharmacy.umaryland.edu/atrium/](http://blogs.pharmacy.umaryland.edu/atrium/)
Summary

• Utilization of CHA$_2$DS$_2$-VASc allows for the identification of patients with AF that are truly at low-risk for stroke
  – Reported rates < 1%
• Data suggests that female sex does not increase the risk for stroke in the absence of other risk factors
  – Low risk = CHA$_2$DS$_2$-VASc scores 0 for males, 1 for females
• Patients with low CHA$_2$DS$_2$-VASc scores have not shown to benefit from antithrombotic therapy