DIG Into the Data on Digoxin Use In Heart Failure & Atrial Fibrillation

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Disclosure

• I have no real or perceived conflict of interest related to the content of this presentation
Learning Objectives

• Discuss the current guideline recommendations for using digoxin in patients suffering from heart failure or atrial fibrillation

• Interpret the clinical trial evidence that supports the use of digoxin in patients suffering from heart failure or atrial fibrillation

• Evaluate the morbidity and mortality data of digoxin use in heart failure and atrial fibrillation patients, and determine if the use of digoxin should be continued in these populations
In what century was the use of digitalis first described for heart failure management?

A 1600’s
B 1700’s
C 1800’s
D 1900’s
History of Digoxin

• William Withering was an English botanist, chemist, and physician:
  • First discussed the use if foxglove, digitalis purpurea, for the treatment of dropsy (edema) in 1785
  • Withering has been inappropriately given credit for the development of this treatment

• Mother Hutton was an English botanist, pharmacist, and general practitioner of medicine:
  • Discovered through experimentation that foxglove was useful in treating heart disease, kidney troubles, and dropsy

Digoxin Pharmacology

• Neurohormonal
  • Augments parasympathetic tone
    • Possibly reducing plasma norepinephrine

• Parasympathetic actions lead to electrophysiological effects
  • Slows conduction and increases the refractory period of the AV node

• Cellular actions leading to hemodynamic effects
  • Inhibits sodium-potassium ATPase, which increases intracellular calcium
    • Calcium is prevented from leaving the cell via the sodium-calcium pump while more calcium is released from the sarcoplasmic reticulum
  • = Positive inotrope (stronger contraction)
Digoxin Serum Concentrations

- Safest serum concentration range: of 0.5 to 0.9 ng/mL

- Wait at least 7 days following initiation or dose adjustment to ensure accurate serum concentrations

- Draw levels 8 – 12 hours following the dose
  - Ensures proper distribution and avoids falsely elevated concentrations

- At risk patient populations
  - Low muscle mass
  - Renal impairment

What is your personal opinion with regards to the use of digoxin in patients with heart failure?

A. It has quality data and I recommend it to my patients
B. It may have limited data, but I still use it
C. It has limited data and I avoid it except in special circumstances
D. I don’t recommend it to my patients
### ACC/AHA Clinical Practice Guideline

#### Recommendation Classification System

<table>
<thead>
<tr>
<th><strong>CLASS (STRENGTH) OF RECOMMENDATION</strong></th>
<th><strong>LEVEL (QUALITY) OF EVIDENCE</strong></th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>CLASS I (STRONG)</strong></td>
<td><strong>LEVEL A</strong></td>
</tr>
<tr>
<td>Benefit &gt;&gt; Risk</td>
<td>High-quality evidence from more than 1 RCT</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Meta analyses of high-quality RCTs</td>
</tr>
<tr>
<td>• Is recommended</td>
<td>One or more RCTs corroborated by high-quality registry studies</td>
</tr>
<tr>
<td>• Is indicated/useful/effective/beneficial</td>
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<tr>
<td>• Should be performed/administered/other</td>
<td></td>
</tr>
<tr>
<td>• Comparative-Efficacy Phrases:</td>
<td></td>
</tr>
<tr>
<td>• Treatment/strategy A is recommended/indicated in preference to treatment B</td>
<td></td>
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<tr>
<td>• Treatment A should be chosen over treatment B</td>
<td></td>
</tr>
<tr>
<td><strong>CLASS IIa (MODERATE)</strong></td>
<td><strong>LEVEL B-R</strong></td>
</tr>
<tr>
<td>Benefit &gt; Risk</td>
<td>(Randomized)</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Moderate-quality evidence from 1 or more RCTs</td>
</tr>
<tr>
<td>• Is reasonable</td>
<td>Meta analyses of moderate-quality RCTs</td>
</tr>
<tr>
<td>• Can be useful/effective/beneficial</td>
<td></td>
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<tr>
<td>• Comparative-Efficacy Phrases:</td>
<td></td>
</tr>
<tr>
<td>• Treatment/strategy A is probably recommended/indicated in preference to treatment B</td>
<td></td>
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<tr>
<td>• It is reasonable to choose treatment A over treatment B</td>
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</tr>
<tr>
<td><strong>CLASS IIb (WEAK)</strong></td>
<td><strong>LEVEL B-NR</strong></td>
</tr>
<tr>
<td>Benefit ≥ Risk</td>
<td>(Nonrandomized)</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Moderate-quality evidence from 1 or more well-designed, well-executed nonrandomized studies, observational studies, or registry studies</td>
</tr>
<tr>
<td>• May/might be reasonable</td>
<td>Meta analyses of such studies</td>
</tr>
<tr>
<td>• May/might be considered</td>
<td></td>
</tr>
<tr>
<td>• Usefulness/effectiveness is unknown/unclear/uncertain or not well established</td>
<td></td>
</tr>
<tr>
<td><strong>CLASS IIIc (NO BENEFIT)</strong></td>
<td><strong>LEVEL C-LD</strong></td>
</tr>
<tr>
<td>Benefit = Risk</td>
<td>(Limited Data)</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Randomized or nonrandomized observational or registry studies with limitations of design or execution</td>
</tr>
<tr>
<td>• Is not recommended</td>
<td>Meta analyses of such studies</td>
</tr>
<tr>
<td>• Is not indicated/useful/effective/beneficial</td>
<td></td>
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<tr>
<td>• Should not be performed/administered/other</td>
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</tr>
<tr>
<td><strong>CLASS IIIb: Harm (MODERATE)</strong></td>
<td><strong>LEVEL C-ED</strong></td>
</tr>
<tr>
<td>Risk &gt; Benefit</td>
<td>(Expert Opinion)</td>
</tr>
<tr>
<td>Suggested phrases for writing recommendations:</td>
<td>Consensus of expert opinion based on clinical experience</td>
</tr>
<tr>
<td>• Potentially harmful</td>
<td></td>
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<tr>
<td>• Causes harm</td>
<td></td>
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<tr>
<td>• Associated with excess morbidity/mortality</td>
<td></td>
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<tr>
<td>• Should not be performed/administered/other</td>
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</tbody>
</table>

CGR and LOE are determined independently (any CGR may be paired with any LOE).

A recommendation with LOE C does not imply that the recommendation is weak. Many important clinical questions addressed in guidelines do not lend themselves to clinical trials. Although these are uncommon, one may not be a very clear clinical consensus that a particular test or therapy is useful or effective.

The outcome or result of the intervention should be specified (i.e., improved clinical outcome or increased diagnostic accuracy or incremental prognostic information).

For comparative-effectiveness recommendations (COE and LOE A and B only), studies that support the use of comparative verbs should involve direct comparisons of the treatments or strategies being evaluated.

The method of assessing quality is evolving, including the application of standardized, widely used, and preferably validated evidence grading tools, and systematic reviews, the incorporation of an Evidence Review Committee.

COE indicates Classes of Recommendations; ED, expert opinion; LD, limited data; LOE, level of Evidence; NR, nonrandomized; R, randomized; and RCT, randomized controlled trial.

Digoxin HF Recommendation

- Digoxin can be beneficial in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF

A 68 year Caucasian male presents to clinic for follow-up after his 3rd admission for HFrEF this year. He remains mildly dyspneic despite his regimen of lisinopril 40 mg PO daily, furosemide 40 mg PO BID, carvedilol 12.5 mg BID, and spironolactone 25 mg daily. His labs are unremarkable and vitals show a weight of 70 kg, BP = 126/87 and HR 90. Would you prescribe digoxin to this patient at this time?

A Yes
B No
Specifics from the HF Recommendations

“Several placebo-controlled trials have shown that treatment with digoxin for 1 to 3 months can improve symptoms, HRQOL, and exercise tolerance in patients with mild to moderate HF. These benefits have been seen regardless of the underlying rhythm (normal sinus rhythm or AF), cause of HF (ischemic or nonischemic cardiomyopathy), or concomitant therapy (with or without ACE inhibitors).”

Mild to Moderate Heart Failure on a diuretic if needed (n = 300)

Captopril 25 - 50 mg TID (n = 104)

Digoxin 0.125 – 0.375 mg daily (n = 96)

Placebo (n = 100)

Primary Endpoint: Exercise tolerance
Mean follow-up: 6 months

Captopril-Digoxin Multicenter Research Group

• Exercise time compared with placebo:
  • Captopril significantly improved (82s vs 35s)
  • No improvement with digoxin (54s)

• Notable secondary outcomes
  • NYHA Classification compared with placebo
    • Captopril significantly improved (41% vs 22%)
    • No improvement with digoxin (31%)
  • Left ventricular ejection fraction compared to placebo
    • Digoxin significantly improved LVEF (4.4% vs 0.9%)
    • No improvement was seen with captopril (1.8%)

Maintenance of digoxin after an episode of heart failure

- Clinically stable outpatients with HF in sinus rhythm or AF with no history of a heart rate > 120 bpm (n = 46)
- Patients who had been clinically stable for 3 months were given digoxin or placebo
  - After 6 weeks their treatment was crossed over
- Patients completed a questionnaire and were examined by a blinded physician at each visit
  - An unblinded clinician could restart active treatment when indicated
- A third clinician analyzed records
  - 16 patients who deteriorated on placebo were classified as group 1
  - 30 patients who did not were compared as group 2

Maintenance of digoxin after an episode of heart failure

- “Our findings showed the value of maintenance digoxin but cast some doubt on that of long-term diuretics”

Heart Failure in Outpatients: Digoxin vs Placebo

- Clinically stable outpatients with HF on diuretics, but without AF (n = 25)

- Randomized, double-blind, cross-over design of digoxin versus placebo

- Utilized a clinicoradiographic scoring system to determine severity of heart failure
  - 14 patients showed improvement

- Third heart sound was the strongest correlation to digoxin response

- “These data suggest that long-term digoxin therapy is clinically beneficial in patients with heart failure unaccompanied by atrial fibrillation whose heart failure persists despite diuretic therapy and who have a third heart sound”

Controlled Trial of Dig in CHF

- Heart failure patients in sinus rhythm (n = 20)
- Randomized, cross-over design of digoxin versus placebo
  - 7 weeks of digoxin titrated to a level of 1.54 – 2.56 ng/mL
  - 7 weeks matched placebo
- 7 placebo patients required premature termination due to worsening symptoms
- Significant improvements seen in dyspnea, walking, and LVEF
- “Oral digoxin improved quality of life and functional exercise capacity in some patients with CHF in sinus rhythm”

Oral Milrinone, Dig, & Their Combination in CHF

- Patients with moderately severe HF in sinus rhythm (n = 230)
- Randomized, double-blind, placebo controlled trial designed to compare the effects of oral milrinone, digoxin, and their combination on exercise capacity over 12 weeks

- “Milrinone significantly increased exercise tolerance and reduced the frequency of worsened heart failure”
- “Milrinone or the combination of milrinone and digoxin offered no advantage over digoxin alone”

Digoxin Withdrawal Trials

- PROVED (without ACEI)
- Radiance (with ACEI)
NYHA Class II or III HF and normal sinus rhythm receiving digoxin and diuretics (n = 88)

Placebo (n = 46)

Digoxin titrated to a concentration of 0.9 – 2 ng/mL (n = 42)

Primary endpoints: 1) treadmill time; 2) distance covered in 6 min; 3) treatment failure; 4) time to treatment failure

Duration: 20 weeks
8 week baseline phase (all on digoxin) followed by a 12 week withdrawal phase

### Endpoint Placebo Digoxin p value

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Digoxin</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Exercise duration decrease (seconds)</td>
<td>96</td>
<td>4.5</td>
<td>0.003</td>
</tr>
<tr>
<td>Treatment failures*</td>
<td>39%</td>
<td>19%</td>
<td>0.0039</td>
</tr>
<tr>
<td>Distance covered in 6 mins</td>
<td>Data was not reported</td>
<td>NS</td>
<td></td>
</tr>
</tbody>
</table>

**Secondary Endpoints Reported**

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Digoxin</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>- 3</td>
<td>+ 2</td>
<td>0.016</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>+ 0.5</td>
<td>- 0.9</td>
<td>0.044</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>+ 11</td>
<td>- 0.2</td>
<td>0.003</td>
</tr>
<tr>
<td>BUN (mg/dL)</td>
<td>3</td>
<td>0.2</td>
<td>0.003</td>
</tr>
<tr>
<td>Cr (mg/dL)</td>
<td>+ 0.09</td>
<td>- 0.02</td>
<td>0.024</td>
</tr>
</tbody>
</table>

*Increased drug therapy, hospital admission for HF, ED treatment for HF, or death

Clinically stable NYHA Class II or III HF, LVEF < 35% and normal sinus rhythm receiving digoxin, diuretics, and captopril or enalapril (n = 178)

Placebo (n = 93)

Digoxin titrated to a concentration of 0.9 – 2 ng/mL (n = 85)

Primary endpoints: 1) study withdrawal due to worsening HF; 2) time to withdrawal; 3) changes in exercise tolerance, Duration: 3 months

"These findings indicate that the withdrawal of digoxin carries considerable risk for patients with chronic heart failure and impaired systolic function who have remained clinically stable while receiving digoxin and angiotensin converting enzyme inhibitors."

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Digoxin</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Number of patients with worsening HF leading to study withdrawal</td>
<td>23</td>
<td>4</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Changes in exercise tolerance (duration)</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>46 second difference</td>
<td></td>
<td>0.033</td>
</tr>
<tr>
<td>Changes in exercise distance</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>41 m difference</td>
<td></td>
<td>0.01</td>
</tr>
</tbody>
</table>

Interesting Secondary Endpoints Reported

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Placebo</th>
<th>Digoxin</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>LVEF (%)</td>
<td>- 4</td>
<td>- 1</td>
<td>0.001</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>+ 7</td>
<td>0</td>
<td>0.001</td>
</tr>
<tr>
<td>HR (bpm)</td>
<td>+ 1</td>
<td>- 1</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

Specifics from the HF Recommendations

• “In a long-term trial that primarily enrolled patients with NYHA class II or III HF, treatment with digoxin for 2 to 5 years had no effect on mortality but modestly reduced the combined risk of death and hospitalization.”

HF patients with an LVEF < 45 % and normal sinus rhythm (n = 6800)

Digoxin (n = 3397)  |  Placebo (n = 3403)

Primary endpoint: Mortality  
Average follow-up: 37 months

# DIG Trial

<table>
<thead>
<tr>
<th>Baseline characteristics</th>
<th>Digoxin</th>
<th>Placebo</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age</td>
<td>63.4</td>
<td>63.5</td>
</tr>
<tr>
<td>Ejection fraction</td>
<td>28.6</td>
<td>28.4</td>
</tr>
<tr>
<td>NYHA Class II</td>
<td>53.3</td>
<td>54.5</td>
</tr>
<tr>
<td>Previous digoxin use*</td>
<td>44.1</td>
<td>44.6</td>
</tr>
<tr>
<td>Ischemic cause of HF</td>
<td>70.8</td>
<td>70.4</td>
</tr>
<tr>
<td>Concomitant Diuretics</td>
<td>81.2</td>
<td>82.2</td>
</tr>
<tr>
<td>Concomitant ACEI</td>
<td>94.1</td>
<td>94.8</td>
</tr>
<tr>
<td>Concomitant Nitrates</td>
<td>42.1</td>
<td>43.1</td>
</tr>
<tr>
<td>Concomitant other vasodilators**</td>
<td>0.9</td>
<td>1.5</td>
</tr>
<tr>
<td>Most common daily dose of digoxin (0.25 mg)</td>
<td>70.6</td>
<td>70</td>
</tr>
</tbody>
</table>

*Patients on digoxin were randomly assigned to digoxin or placebo without a washout period

**clonidine, doxazosin, labetalol, minoxidil, prazosin, and terazosin

## DIG Trial

<table>
<thead>
<tr>
<th>Endpoint</th>
<th>Digoxin</th>
<th>Placebo</th>
<th>p value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Deaths</td>
<td>1181 (34.8%)</td>
<td>1194 (35.1%)</td>
<td>0.80</td>
</tr>
<tr>
<td>Secondary Endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Deaths from CV causes</td>
<td>1016 (29.9%)</td>
<td>1004 (29.5%)</td>
<td>0.78</td>
</tr>
<tr>
<td>Deaths from worsening HF</td>
<td>394 (11.6%)</td>
<td>449 (13.2%)</td>
<td>0.06</td>
</tr>
<tr>
<td>Hospitalizations</td>
<td>2184 (64.3%)</td>
<td>2282 (67.1%)</td>
<td>0.006</td>
</tr>
<tr>
<td>Hospitalizations for HF</td>
<td>910 (26.8%)</td>
<td>1180 (34.7%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Hospitalizations for suspected digoxin toxicity</td>
<td>67 (2%)</td>
<td>31 (0.9%)</td>
<td>&lt; 0.001</td>
</tr>
<tr>
<td>Combined Endpoints</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death due to worsening HF or hospitalization for HF</td>
<td>1041 (30.7%)</td>
<td>1291 (37.9%)</td>
<td>&lt; 0.001</td>
</tr>
</tbody>
</table>

What is your personal opinion with regards to the use of digoxin in patients with atrial fibrillation?

A. It has quality data and I recommend it to my patients
B. It may have limited data, but I still use it
C. It has limited data and I avoid it except in special circumstances
D. I don’t recommend it to my patients
In what set of circumstances would you recommend or prescribe digoxin for a patient with atrial fibrillation and rapid ventricular response?
Digoxin AF Recommendations: Special Populations

- Wolf Parkinson White and pre-excitation syndromes
  - IV amiodarone, adenosine, digoxin, or nondihydropyridine calcium channel antagonists should be avoided

- AF complicating ACS
  - Administration of amiodarone or digoxin may be considered to slow a rapid ventricular response in patients with ACS and AF associated with severe left ventricular dysfunction and HF or hemodynamic instability.

Digoxin AF Recommendations: Special Populations

- **Heart Failure**
  - In the absence of pre-exccitation, IV digoxin or amiodarone is recommended to control heart rate acutely.
  - Digoxin is effective to control resting heart rate with HFrEF.
  - A combination of digoxin and beta blocker (or a nondihydropyridine calcium channel antagonist with HFpEF) is reasonable to control resting and exercise heart rate with AF.
  - Amiodarone may be considered when resting and exercise heart rate cannot be controlled with a beta blocker (or a nondihydropyridine calcium channel antagonist with HFpEF) or digoxin, alone or in combination.

Controlling Ventricular Rate in AF

**Htn or HFpEF or no CV dz**
- Beta blocker
  - Diltiazem
  - Verapamil
- Amiodarone

**HFrEF**
- Beta blocker
  - Digoxin
- Amiodarone

- Digoxin may be combined with a beta blocker or CCB when rate control is not sufficient
- Amiodarone should be reserved for patients who do not respond or are intolerant to beta blockers and CCBs due its side effect profile

How many randomized placebo controlled trials have yielded data supporting the use of digoxin for rate control in atrial fibrillation?

A 6
B 3
C 1
D 0
Recent Systemic Reviews & Meta-Analysis

Digoxin Mortality Data
Increased All-Cause Mortality Associated With Digoxin Therapy in Patients With Atrial Fibrillation: An Updated Meta-Analysis

Population: AF

N = 408,660 from 17 studies

Observational trials

AF with HF = 14% increase in all-cause mortality (RR=1.14, 95% CI 1.04 – 1.24)

AF alone = 36% increase in all-cause mortality (RR=1.36, 95% CI 1.18 – 1.56)

Significantly higher all-cause mortality in AF patients without HF compared with those with HF (p = 0.04)

“Given other available options, digoxin should be avoided as a first-line agent for heart rate control in AF patients.”

Meta-Analysis of Digoxin Use and Risk of Mortality in Patients With Atrial Fibrillation

Population: AF

N = 318,191 from 11 studies

Observational trials

21% increased risk for mortality (HR = 1.21, 95% CI 1.12 to 1.30)

Increased mortality was seen in patients with or without HF

“The results suggest that digoxin use was associated with a greater risk for mortality in patients with AF, regardless of concomitant heart failure. A well-powered randomized trial is necessary to reveal the true effect of digoxin.”

**Digoxin Is Associated With Increased All-cause Mortality in Patients With Atrial Fibrillation Regardless of Concomitant Heart Failure: A Meta-analysis.**

<table>
<thead>
<tr>
<th>Population:</th>
<th>AF</th>
<th>N = 302,738 from 8 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>Observational trials</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Increased all-cause mortality overall (HR = 1.375, 95% CI 1.201-1.574, p = 0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AF with HF = increase in all-cause mortality (HR = 1.201, 95% CI 1.074 – 1.344, p = 0.001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>AF alone = increase in all-cause mortality (HR = 1.172, 95% CI 1.148 – 1.198, p = 0.0001)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>“Digoxin use was associated with significantly increased all-cause mortality in patients with AF regardless of concomitant HF.”</td>
</tr>
</tbody>
</table>

### Digoxin-associated mortality: a systemic review and meta-analysis of the literature

<table>
<thead>
<tr>
<th>Population:</th>
<th>N = 326,426 from 19 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>AF or HF</td>
<td>Observational and randomized controlled trials</td>
</tr>
<tr>
<td></td>
<td>21% increase in all-cause mortality (HR=1.21, 95% CI 1.07 – 1.38, p &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td>AF alone = 29% increase in all-cause mortality (HR=1.29, 95% CI 1.21 – 1.39, p &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td>HF alone = 14% increase in all-cause mortality (HR=1.14, 95% CI 1.06-1.22, p &lt; 0.01)</td>
</tr>
<tr>
<td></td>
<td>“Until proper randomized controlled trials are completed, digoxin should be used with great caution, particularly when administered for rate control in AF.”</td>
</tr>
</tbody>
</table>

Safety and efficacy of digoxin: systemic review and meta-analysis of observational and controlled trial data

<table>
<thead>
<tr>
<th>Population:</th>
<th>N = 621,845 from 52 studies</th>
</tr>
</thead>
<tbody>
<tr>
<td>All</td>
<td>Observational and randomized controlled trials analyzed separately</td>
</tr>
</tbody>
</table>

Unadjusted mortality rates from 33 observational trials showed higher mortality rates in the digoxin group (RR = 1.76; 95% CI 1.57 - 1.97; P<0.001)

Adjusted mortality data from 22 observational trials showed higher rates of death in the digoxin group (RR = 1.61, 95% CI 1.31 to 1.97, p <0.001; hazard ratio 1.17, 1.07 to 1.29, p =0.001)

In 7 HF RCTs there was no difference between digoxin mortality and placebo (RR 0.99, 95% CI 0.93 - 1.05; p = 0.75)

“Digoxin use has a neutral effect on mortality in randomized trials and reduces hospital admissions. Regardless of statistical analysis, prescription biases limit the value of observational data.”

C.A.M. Cardiology: The Digoxin Story
Future studies: 2019?

• Digitoxin to Improve Outcomes in Patients with Advanced Systolic Heart Failure (DIGIT-HF)
  • Digitoxin versus placebo in HFrEF with or without AF
    • NYHA III-IV HF, LVEF < 40%
    • NYHA II HF, LVEF < 30%
  • Primary outcome: composite of overall mortality and hospitalization for worsening HF

• Rate control Therapy Evaluation in Atrial Fibrillation (RATE-AF)
  • Digoxin versus beta-blockers for first line rate control in permanent AF patients NYHA Class I or II HF.
  • Primary outcome: patient-reported QOL
Key Takeaways

• Key Takeaway #1
  • The recommendations for the use of digoxin in HFrEF are largely based on the results of one RCT (DIG) and two digoxin withdrawal trials (PROVED & RADIANCE)

• Key Takeaway #2
  • There are no randomized control trials that support the use of digoxin in atrial fibrillation. However, there are several meta-analyses that raise mortality concerns when digoxin is used in this population

• Key Takeaway #3
  • More RCTs are needed to determine the safety of digoxin use in patients with HF and/or AF