Annual Therapeutic Refresher

Digoxin Therapy: Lest We Forget
( when and how to use it )

presented by
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Disclosures

I will be planting some wooly foxglove in my backyard this summer.
Objectives

- **overview** present status of digoxin therapy
- discuss **pathophysiologic rationale** for digoxin therapy
- **critical review** re. reasons for it's underuse and consequences
- **not to forget** when and how to use it
Section I

The Present Status of Digoxin Therapy
Recommendation: Consider digoxin in those with HFrEF and sinus rhythm who continue to have moderate / severe symptoms despite appropriate doses of GDM Therapy, to relieve symptoms and reduce hospitalizations.

In a nutshell

- Digoxin's benefit as part of the first line therapy in HFrEF is “controversial”
- you may try it out of desperation and that's OK
- but keep in mind that it's toxic too.
"How did we get there...?"

“Evidence-based drugs used in HF”. Digoxin NOT on the list! It does appear in the text as the number 8 drug, before fish oil

Comprehensive Update of the CCS Guidelines for the Management of Heart Failure 2017

“Drugs commonly used for HFREF” (Stage III CHF)

Digoxin NOT on the list! ACC/AHA/ HFSA “Focused” Update 2017

Digoxin can be beneficial (should be considered) in patients with HFrEF, unless contraindicated, to decrease hospitalizations for HF

ACCF/AHA Guideline for the Management of Heart Failure 2013 (B II a)

Digoxin may be used to reduce hospital admission in patients with sinus rhythm and symptomatic HF and an EF < 40%. Digoxin may be used in symptomatic HF and AF, to slow ventricular rate, if maximum beta-blocker dose is not tolerated

ESC HF Guideline Recommendations 2012 (B II b)

Class IIb meaning usefulness/efficacy is less well established by statistical evidence/expert opinion
Definition Update 2015

II a (MODERATE)

- recommendation is reasonable
- can be useful/effective/beneficial
- probably recommended to choose Tx A over Tx B
- it is reasonable to choose Tx A over Tx B

II b (WEAK)

- recommendation may/might be reasonable
- may/might be considered
- usefulness, effectiveness is unknown/unclear/uncertain/
- or not well established
Where were we 15 years ago... ?

Digitalis is recommended as part of the first-line therapy for patients with clinical HF and LVSD. 

ACC / AHA Guidelines 2004 (A-I)
In Other Words

once was a captain in charge of cockpits
then was escorted to zone D by it's armpits
So much of *Stats*... What were *Steths* saying?

Digitalis remains a **mainstay of the therapy** for CHF. It's effects are most prominent in HF associated with Afib and rapid HR but it is also effective in severe HF and cardiac dilatation secondary to **volume overload**, as well as in patients with a **dilated, failing ventricle secondary to hypertension**. In patients with IHD, the response of particular segments of the myocardium depends on the relative quantity of **viable muscle**.

*Eugene Braunwald* JACC 5 (5) 1985

Digitalis is **part of the first-line therapy** for patients with clinical HF and LVSD. ACEI, beta blocker, MRA therapies all have additive effect on survival **when combined** with digitalis, diuretics.

*Shahbudin Rahimtoola* Circ 109 2004

Digoxin has multiple favourable **properties** that make it ideal therapy for **worsening chronic HF**. It is the only oral inotrope known to increase forward flow without causing deleterious HR increase or BP drop.

*Mihai Gheorghiade* JACC- HF 4(5) 2016
Section II

Pathophysiologic rationale for digoxin therapy
Pathophysiology of Systolic Heart Failure
I. Principal Causes

- Ischemic damage
- Ischemic hibernation
- Chronic hypertension (increased mechanical work)
- Morbid obesity (increased mechanical work)
- Valvular disease MR, TR, AR (volume / pressure overload)
- Post myocarditis sequela
- Cardiotoxic drugs, substances, stress
- Respiratory causes
- CHD, familial etiology
Pathophysiology of Systolic Heart Failure
II. Hemodynamic consequences

- Dilated ventricle (increased ED, ES volume)
- Stretching of sarcomeres
- Myocyte hypertrophy (genes switch to “fetal” mode)
- Dilated atrium (increased atrial pressure)
- Valvular incompetence
- Reduced EF, stroke volume
Pathophysiology of Systolic Heart Failure

III. Triggered mechanisms

- **Tachycardia** to compensate for low stroke volume (NE)
- **Periph. vasoconstr.** maintain vital organ perfusion (NE, RAAS)
- **Sodium retention** for volume expansion (RAAS)
- Natriuretic peptide release to adjust filling volumes & pressures
- Altered **intracellular handling of calcium** ions
- Switch to “fetal gene mode” to stimulate growth

**Note:** Triggering is not always “appropriate”, there may be dissociation between responses!
“Tropic” Effects of Digitalis

- Firing rate decrease ( - chrono tropism )
- Conduction v. decrease ( - dromo tropism )
- Excitation v. increase ( + bathmo tropism )
- Contraction v. increase ( + ino tropism )
Digitalis: Basic Science

- Braunwald, E. Effects of digitalis on the normal and the failing heart
- JACC 5 (5) 51A-59A, 1985

**Human studies**
- higher **stroke volume** at lower end-diastolic pressure
- higher rate of change of LV pressure (\(dP/dt\))
- increased EF, faster / more extensive **fiber shortening**
- improved performance in **viable** myocardium in chronic IHD
- superior salutary effects in **chronic vol. overload** ( ! )
Actions of Cardiac Glycosides in Clinical Heart Failure


- Increases LVEF, CO. Lowers LV filling pressure
- Slows SR. Slows VR in rapid AFib. Does not drop BP
- Lowers vascular resistance, venous tone, CVP (slow / po adm.)
- Tunes up blunted baroreceptor reflex
- Reduces neurohormone levels (NE, Aldosterone, PRA)
- Diuretic effect (renal Na-K ATP'ase inhibition)
Beneficial Clinical Effects of Digitalis Therapy for Heart Failure

Rahimtoola S. The use of digitalis in heart failure.
Curr Probl Cardiol 21:751-6, 1996

- Symptom, NYHA, HF score improvement (10 RT's)
- Increased exercise time (5 RT's)
- Less worsening HF, hosp. / deaths related to HF (13 RT's)
- Reduces cost of treatment of HF (1 RT)
- Increases LVEF (6 RT's)
- Reduction of LV dimensions (2 RT's)
- Reduces LVFP, PCWP, increases CO
- Reduces elevated neurohormones (2 RT's)
- Improved renal function (1 RT)
Randomized Digoxin Discontinuation Trials

- Uretsky B. JACC 22 (4) : 955-62
- Packer M. NEJM 329 : 1-7

- PROVED and RADIANCE Trials (1993)
- Class II-III NYHA and EF < 0.35
  - PROVED diuretic + / - dig. groups (n: 88)
  - PROVED dig. STOP. group, worsening HF rate 39%
  - dig. CONT. group, worsening HF rate 19%

- RADIANCE diuretic + ACEI + / - digoxin groups (n: 178)
  - RADIANCE dig. STOP x 3 mo, worsening HF rate 24%
Digoxin Therapy: Known Merits & Rationale For It's Use

acc. to Rahimtoola S. Special Review. Circulation 2004

- Reduces, prevents sarcomere stretching
- Reduces, prevents remodelling
- Increases contractility of the viable myocardium
- Electrically stabilizes the atrium
- Stood test of time as an oral inotrope
- Easily tolerated, side effects infrequent
- Has multiple actions, all mild
- Reduces costs of treating heart failure
Section III

Digoxin Underuse
And
Probable Consequences
Reasons For Underusing Digoxin

- The "there is no evidence..." effect
- Using an old drug as first line of therapy doesn't make us (look) up to date
- If we don't use it, we don't have to learn how to use it
- Knowing how to use digoxin is no longer essential knowledge
- "Digoxin is likely to reduce frequency of hospitalization but not survival" has become more essential knowledge
- Toxicity scare (in case you didn't know that farmaki = poison)
- Emphasis on (all cause) mortality
What did the DIG study show?
(reading the fine prints)

- 6800 patients placebo vs dig
- sinus rhythm, EF < 0.45
- 65% had previous MI
- mean f/u 3 years
- relevant outcomes in 43% av. of the cohort
- benefit greater in EF < 0.25, Class III-IV
- adding digoxin had no effect on overall mortality
- adding digoxin was effective in reducing both death + hospitalization
  - (attributable to worsening HF)
- open-label digoxin adding rate 15 vs 10% (25%)
- hospitalization for suspected toxicity attributable to digoxin 1%

What do these results mean for our patients?

- I work in a busy group practice. Would I be comfortable with the outcome of losing 53% of my 800+ patients with HFrEF in the next 3 years because I chose not to treat them with digoxin?

- I work in a busy heart function clinic with 2000+ patients with HFrEF. Would I be happy with the outcome of 56% of them dying or decompensating because digoxin was not introduced early enough?
Chronology of therapeutic choices in heart failure

- Digitalis - diuretic (1980's)

- ACE-I 1990's onward
- Bbl 2000's onward
- MRA 2000's onward
- ARB mid 2000's
- NI 2002
- AR+ NI mid 2010's - ...
- SN blocker mid 2010's - ...
What is the goal of adding 1/2 dozen drugs in 25 years to treat HF?

- Try to block the presumed triggering of neurohormonal responses and its consequences, namely
  - to block vasoconstrictor release
  - to blunt HR response
Can digoxin not do this neurohormonal inhibition?

- Digoxin does it both and more gently. Moreover, it directly enhances myocyte contraction.

- But in the era of “aggressive” medical treatment, disease mechanisms are attacked on all fronts even if goals & outcomes do not always make solid pathophysiological sense.
30 years in search of better drugs for HF

- A. Let's prevent vasoconstriction - ACEI (cough)
- B. Let's try one causing less cough - ARB (inferior)
- C. Let's try a more selective one - NI (serious angioedema)
- D. Let's try A + B (not superior plus hyperkalemia)
- E. OK, Let's try B + C - ARNI (non-serious angioedema)

***********************************************************************

- A. Let's prevent tachycardia - beta blockers (side effects)
- B. Let's try one w/o side effects - SN blocker (inferior to \textit{Bb})
- C. OK, Let's try A + B then - not superior to A alone
The long journey from potion to first-line therapy

- A family receipt kept secret by an old woman in Shropshire who made cures of the dropsy after more regular practitioners had failed...It was not difficult for one conversant in these subjects to know that the active herb could be no other than the Foxglove...

  William Withering 1785
Use of digoxin in HF over the last 25 years

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Digoxin Use</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONSENSUS</td>
<td>1987</td>
<td>Sweden</td>
<td>(dig 93%)</td>
</tr>
<tr>
<td>SOLVD</td>
<td>1991</td>
<td>US</td>
<td>(dig 67%)</td>
</tr>
<tr>
<td>MERIT-HF</td>
<td>1999</td>
<td>Sweden</td>
<td>(dig 64%)</td>
</tr>
<tr>
<td>HOPE</td>
<td>2000</td>
<td>Canada</td>
<td>(??)</td>
</tr>
<tr>
<td>Val-HeFT</td>
<td>2001</td>
<td>US</td>
<td>(dig 67%)</td>
</tr>
<tr>
<td>COPERNICUS</td>
<td>2001</td>
<td>US</td>
<td>(dig 66%)</td>
</tr>
<tr>
<td>SOLVD 12-yr f/u</td>
<td>2003</td>
<td>Canada</td>
<td>(??)</td>
</tr>
<tr>
<td>COMET</td>
<td>2003</td>
<td>UK</td>
<td>(dig 59%)</td>
</tr>
<tr>
<td>CHARM</td>
<td>2003</td>
<td>US</td>
<td>(dig 42%)</td>
</tr>
<tr>
<td>PARADIGM-HF</td>
<td>2014</td>
<td>UK-US</td>
<td>(dig 30%)</td>
</tr>
</tbody>
</table>
Is Heart Failure The New Epidemic?

- More than 5.8 million prevalence
- Incidence has remained stable during the past 2 decades
- Survival estimate 10% decline each year but on the improve
- Yet 1 million hospitalizations for HF are occurring each year
  (care increasingly delivered in the OP setting not included)
- The epidemic is that of hospitalizations among survivors who
  now live longer with the disease
- HF-specific hospitalizations are a key indicator of the
  effectiveness of HF-specific treatments

The New “Epidemic” of Heart Failure

Roger, V. HF Epidemic in Olmstead County, MN, 2000-2010. JAMA Int Med 175 (6), 996-1004, 2015

- HF hospitalization annual rate increase (1980 - 2006) 1.5%
  - (CAD highest rate of comorbidity 40-50%)
- 985 pts with SHF admitted 1699 times during the 1st 2 years
- Adm. due to non-CV cause increasing (#1 respiratory)
- 5 year mortality 24% at age 60, 54% at age 80
- The rate of outpatient-diagnosed HF 32% (2000 – 2010)
- Once again, HF-specific hospitalizations are a key indicator
  - of the effectiveness of HF-specific treatments
The New “Epidemic” of Heart Failure

The reason for the “epidemic” is multifactorial

growing awareness ( admissions on the rise )
more readily / liberally diagnosed
aging population
living longer with HF
better treatment of CAD
invisible causes (statistical causes, market pressure)
In What Clinical Scenarios of HF Using Digoxin Makes Pathophysiological Sense?

- SHF / LVSD with intermittent or persistent A. Fibrillation
- SHF / LVSD with hemodynamically significant MR
- Ischemic CMP without a large scar / aneurysm
- “Idiopathic” dilated cardiomyopathy
- Advanced Hypertensive CMP / eccentric LV hypertrophy
- SHF / LVSD with undetermined etiology in the morbidly obese
- SHF / LVSD in patients on predominantly paced rhythm
- Aggravated cardiac decompensation after device therapy
- SHF / LVSD due to drug or substance effect (?)
- Total HF (R + L) due to valvulopathy with secondary PHTN
Digoxin Therapy: Lest We Forget
(when and how to use it)

- Half-life 1.5-2 days
- Check level at steady state (in 1 week av. for N renal function)
- Check K, Mg, Ca, Cr before starting
- Loading dose NOT necessary in HF (unless tachyarrhythmic)
- Has both neurohormonal and inotropic effects
- Classify per (CrCl 40-60, age 70's-80's, wt 40-60 kg)
- Choose an initial po dose 0.125 mg, 0.1875 mg, 0.25 mg
- M - F (wknd off) advisable; check level on day 8
- SDC up to 1.0-1.5 nmol/L acceptable if no suggestion of toxicity
- Adjust dose if SDC < 0.5 or > 1.5 nmol. First order kinetics
The rest of the poem

- once was a captain in charge of cockpits
- then was escorted to zone D by it's armpits
- time to remove eye shades and start to think
- before it's flushed down the toilet or sink
TAKE HOME MESSAGES

● To date digoxin remains irreplacable. Even those who do not prescribe it are not comfortable to stop it. But marketing pressures are forcing doctors to disown digoxin and that will threaten public health.

● Do not avoid using it when it makes pathophysiological sense. The only thing we have to fear is the fear of not looking “up to date”

● Think pathology and pathophysiology to avoid getting lost in the jungle

● Time spared for listening to your patients and observing their clinical progress is the best teacher on the job
Thought of the day for Lanatophobes

“Undoubtedly Evidence Based Medicine is the gold standard for modern medicine. The results, however, should be applied in patient care with careful reflection ...
... otherwise, Evidence Based Medicine may acquire the same status for the doctor as a lamp post for a drunk; it gives more support than enlightenment.

Acknowledgement

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and

Thank you ALL For Listening!