Heart Failure: Guiding-therapy

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Disclosures

• Available online:
  • [www.vigour.ualberta.ca](http://www.vigour.ualberta.ca)

• Involved in GUIDE-IT and PROACT-3,4
Learning Objectives

1. Understand the importance of following biomarkers in heart failure in the chronic environment;

2. Recognize the need for advanced biomarker-guided treatment strategies
Biomarkers that “guide” therapy

- Troponin
- Hemoglobin
- Hba1c
- LDL
- Urea/creatinine
- ECG
- Ejection fraction

- ACS
- Anemia
- Diabetes
- CV prevention
- HD, ACE inhibitor
- Chest pain
- Heart failure
What is a biomarker?

• “If it costs less than 20 bucks, it’s a lab test. If it costs more than 20 bucks, it’s a biomarker.”
  • Michael Felker, 2013

• Types of biomarkers
Biomarkers Augment Clinical Judgment

WARNING
USING WHILE STUPID CAN CAUSE SERIOUS INJURY
But what does it mean...

• A biomarker has no innate therapeutic value—it’s what you do with the information

• Hypothesis of all biomarker trials can only be tested if clinicians act on out of range biomarker values even in the setting of apparent clinical stability
Future state of care

Info from e-systems
- Clinic letters
- Pharmacy
- Socioeconomic status
- Labs, ECG, Radiology
- Pollution/particulate
- Activity from iphone
- Ambient temperature
- NHL or FIFA activity

New info from seeing patient
- Hx
- Physical
- Vitals
- ECG
- Radiology
- Biomarkers

MD
RN
Pharm
Tech
Key blood biomarkers in HF

Now:
- Troponin
- Hemoglobin
- Creatinine
- Potassium
- Sodium
- BNP/NT-proBNP

Newer:
- ST2
- MR-proANP
- Procalcitonin
- Galectin-3
- N-GAL
- MR-proADM

Not yet known:
- WS4
- Apelin
- Urinary cGMP
- ?panels
Biomarker axes

**Neurohormonal**
- Angiotensin II
- Aldosterone
- Arginine vasopressin
- Norepinephrine
- Renin
- Endothelin

**Oxidative stress**
- Oxidized LDL
- Myeloperoxidase

**Inflammation**
- C-reactive protein
- sST2
- Tumor necrosis factor
- Cytokines, adipokines

**Renal dysfunction**
- Creatinine
- Cystatin C
- NGAL

**Matrix and cellular remodeling**
- Galectin-3
- MMPs and TIMPs

**Myocardial stress and injury**
- Natriuretic peptides
- Cardiac troponins
How we often feel with biomarkers
How we should feel about biomarkers

Measurement (lab)
- Precision:
  - Closeness of two or more measurements to each other
- Accuracy:
  - Closeness of a measured value to a standard or known value
- Biologic variation understood

Methods (evaluation)
- Statistics clear and robust
- Varying across and within patient groups

Mechanism
- Represent pathophysiologic process (static or dynamic)

Management
- Added value
- Inform decision on diagnosis or treatment

Biologic variation understood
## Paris Criteria

### Improved Diagnosis and Prognostication

<table>
<thead>
<tr>
<th>Tier 1</th>
<th>Tier 2</th>
<th>Tier 3</th>
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</thead>
<tbody>
<tr>
<td>• Satisfies criteria for tiers 2 and 3</td>
<td>• Satisfies criteria for tier 3</td>
<td>• Follows STARD statement</td>
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<tr>
<td>• Interaction testing of subgroups</td>
<td>• Compares multiple biomarkers concomitantly</td>
<td>• Pathophysiological link to heart failure</td>
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<td>• Influence of therapeutics on predictive abilities</td>
<td>• Validates results in a representative cohort</td>
<td>• Confirms association with well-defined outcomes in a representative cohort of patients with heart failure after controlling for clinical factors and natriuretic peptides</td>
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### Tailoring Therapeutics

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<td>• Randomized, controlled trial in which biomarker levels determine therapeutic choices</td>
<td>• Satisfies criteria for tier 3</td>
<td>• Shows differential effect of treatment based on biomarker levels in a retrospective analysis of randomized, controlled trials</td>
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Ahmed, JACC-HF 2014
Lessons learned from Biomarker trials

• Pick the correct marker

• Target the appropriate population

• Set the target level
What NP target/level?

NT-proBNP or BNP

Fixed target

% reduction target

Troughton, STARS-BNP, UPSTEP <75, UPSTEP >75, TIME-CHF <75y, TIME-CHF >75y, BATTLESCARRED, PROTECT, Berger, GUIDE-IT

STARBRITE, SIGNAL-HF
Chronic HF Rx Guided by NT-proBNP

Cardiovascular events
- Event free (%) over time after randomisation (days)
- NT-proBNP vs Clinical
- P = 0.034

Heart failure or death
- Event free (%) over time after randomisation (days)
- NT-proBNP vs Clinical
- N = 69
- P = 0.049

Troughton, Lancet 2000
Chronic HF Rx Guided by NT-proBNP

Log rank $P = .03$

PROTECT trial

Januzzi, JACC 2011
PROTECT: Primary Endpoint

Number of events vs Total CV Events

- **100 events**
- **58 events**

- SOC
- NT-proBNP

*P = .009*

Januzzi, JACC 2011
BNP guided HF Rx: STARS-BNP

Event free survival %

- Clinical group
- BNP group

$P < .01$

Treatment modifications (n)

- Diuretics
- ACEI
- BB
- Spiro
- Other

Jourdain, JACC 2007
TIME: Positive?

499 patients
>60 years
ejection fraction ≤45%
NYHA II or greater
prior hospitalization for HF < 1 year
NT-proBNP > 2x ULN
Can’t stop TIME
NTproBNP vs. Disease Management vs. Usual Care

% Pts on “optimal therapy”

Hosp free Survival

BM = biomarker, MC = multidisciplinary, UC = Usual Care

Berger JACC 2010
Many trials since

- 11 RCT
- N=2431 patients
- Most > 12 months
NP Guided-Rx Trials

**All-cause Mortality**

![Graphs showing survival rates for NP-guided and Clinically guided treatments for <75 y and >75 y age groups.](image)

- **<75 y**
  - NP-guided: HR = 0.62 [0.45–0.85]; P = 0.004
  - Clinically guided:...

- **>75**
  - NP-guided:...
  - Clinically guided: HR = 0.98 [0.75–1.3]; P = 0.96
What to do if NP out of range

- Up-titr ate or add (ACE)-inhibitor or ARB or ARNI or BB or Hyd/N or spiro
- ?go above target dose
- ?Add thiazide, CRT
- ?Af rate control
- ?cardiac rehab
- ?Increase/decrease loop diuretic dosage
- Intensified or repeated heart failure education regarding diet, sodium restriction, etc.
GUIDE-IT Study Design

- Multicenter, prospective, RCT
- NIH sponsored (PI: Michael Felker, DCRI)
- 1100 subjects
- 12-24 months of follow-up
- CVC + 6 Canadian sites = 138 pts of 894 pts

Randomized 1:1 to either:
- **Biomarker Guided Arm:**
  - Treatment Titrated to Achieve Target NT-proBNP < 1000 pg/mL
- **Usual Care:**
  - Treatment titrated based on guidelines
DCRI announces halt to GUIDE-IT trial

September 23, 2016 – The trial was a comparison of biomarker-guided therapy and usual care for high-risk heart failure patients.

The DCRI announced today that it was terminating the Guiding Evidence-Based Therapy Using Biomarker Intensified Treatment (GUIDE-IT) trial due to a lack of difference in the primary outcome between the treatment groups.
GUIDE-IT Results
Summary

• Use all available knowledge

• Be prepared to step out of your comfort zone

• Test, Test, and re-test ideas for clinical practice
Acknowledgements