WHAT EVIDENCE DO WE HAVE TO START EVIDENCE-BASED DRUGS IN HOSPITAL?

Dr. Nadia Giannetti
Medical Director, Heart Failure and Heart Transplant Program
Chief Division of Cardiology
McGill University Health Centre
Conflict of Interest

- Funding, honoraria or research with the following companies:
  - Novartis
  - Servier
  - Amgen
  - Pfizer
  - Boehringer Ingelheim
  - Astra
Overview

• Review the limitations of current heart failure management
• Discuss the risks and benefits of in-hospital initiation of heart failure therapy
• Review the evidence to support in-hospital initiation of heart failure therapy
The limitations of current heart failure management

- We know that medical therapy can reduce heart failure hospitalizations, CV death and total mortality in patients with heart failure.

PARADIGM-HF: Cardiovascular Death or Heart Failure Hospitalization (Primary Endpoint)

Based on results of SOLVD-Treatment, CHARM-Alternative, COPERNICUS, MERIT-HF, CIBIS II, RALES and EMPHASIS-HF.
The limitations of current heart failure management

- Despite this, we know from multiple registries that medical therapy is under prescribed
Why is there under-prescription of medical therapy?

- Multi-factorial:
  - Lack of follow-up: some patients are not seen by a physician after a heart failure presentation
    - Majority who are seen in follow-up are seen by their family MD
    - Majority wait weeks to months before they are seen in follow-up
  - Physician inertia
  - Patient preference which may be due to lack of understanding
How can we improve the use of appropriate medical therapy?

- We can start during the hospitalization period when the patient is under our care, where we can provide education.
- What evidence do we have to support this?
How important is medical therapy during a heart failure hospitalization?

Initiation, Continuation, or Withdrawal of Angiotensin-Converting Enzyme Inhibitors/Angiotensin Receptor Blockers and Outcomes in Patients Hospitalized With Heart Failure With Reduced Ejection Fraction

Lauren G. Gristrap, MD; Gregg C. Fonarow, MD; Akshay S. Desai, MD, MPH; Li Liang, PhD; Roland Matsouaka, PhD; Adam D. DeVore, MD, MHS; Eric E. Smith, MD, MPH; Paul Heidenreich, MD, MS; Adrian F. Hernandez, MD, MHS; Clyde W. Yancy, MD; Deepak L. Bhatt, MD, MPH

Background—Guidelines recommend continuation or initiation of guideline-directed medical therapy, including angiotensin-converting enzyme inhibitors/angiotensin II receptor blockers (ACEI/ARB), in hospitalized patients with heart failure with reduced ejection fraction.

Methods and Results—Using the Get With The Guidelines-Heart Failure Registry, we linked clinical data from 16,052 heart failure with reduced ejection fraction (ejection fraction ≤40%) patients with Medicare claims data. We divided ACEI/ARB-eligible patients into 4 categories based on admission and discharge ACEI/ARB use: continued (reference group), started, discontinued, or not started on therapy. A multivariable Cox proportional hazard model was used to determine the association between ACEI/ARB category and outcomes. Most, 90.5%, were discharged on ACEI/ARB (56.6% continued and 30.9% newly started). Of those discharged without ACEI/ARB, 1.9% were discontinued, and 7.5% were eligible but not started. Thirty-day mortality was 3.5% for patients continued and 4.1% for patients started on ACEI/ARB. In contrast, 30-day mortality was 8.8% for patients discontinued (adjusted hazard ratio [HRadj] 1.92; 95% CI 1.32-2.81; P<0.001) and 7.5% for patients not started (HRadj 1.50; 95% CI 1.12-2.00; P=0.006). The 30 day readmission rate was lowest among patients continued or started on therapy. One-year mortality was 28.2% for patients continued and 29.7% for patients started on ACEI/ARB compared to 41.6% for patients discontinued (HRadj 1.35; 95% CI 1.14-1.63, P<0.001) and 41.7% (HRadj 1.28; 95% CI 1.14-1.43, P<0.001) for patients not started on therapy.

Conclusions—Compared with continuation, withdrawal of ACEI/ARB during heart failure hospitalization is associated with higher rates of postdischarge mortality and readmission, even after adjustment for severity of illness. (J Am Heart Assoc. 2017;6:e004675. DOI: 10.1161/JAHA.116.004675.)
Medical therapy during hospitalization

A. 1-year mortality

B. 1-year readmission
Can we initiate novel therapy during hospitalization?: TIRATION study

**Down-titration or temporary discontinuation of sac/val is allowed in all groups at any time**

**Hospital admission for ADHF**

3 strata
- ACEi + OMT
- ARB + OMT
- OMT but no ACEi/ARB

**36 h ACEi washout**

**Any OMT as per treating physician**

**PRE-discharge initiation**
- Open-label
  - Sac/val 50 mg → 100 mg b.i.d. → 200 mg b.i.d.
  - Sac/val 100 mg → 200 mg b.i.d.
- Sac/val as per label and at investigator discretion
- OMT continued throughout the study (excluding ACEi/ARB)

**POST-discharge initiation**
- Open-label
  - Sac/val 50 mg → 100 mg b.i.d. → 200 mg b.i.d.
  - Sac/val 100 mg → 200 mg b.i.d.
- Sac/val as per label and at investigator discretion
- OMT continued throughout the study (excluding ACEi/ARB)

**Randomization to PRE- or POST-discharge**

**Patient stabilized**

**1-3 days’ screening epoch**

**Discharge**

- max. 2 weeks

**Treatment epoch**

- 10 weeks’ duration starting at randomization

**16 weeks’ follow-up epoch**

ACEi, angiotensin converting enzyme inhibitor; ADHF, acute decompensated heart failure; ARB, angiotensin receptor blocker; b.i.d., twice daily; HF, heart failure; OMT, optimal medical treatment for HF; sac/val, sacubitril/valsartan

Pascual-Figal et al. ESC Heart Failure DOI: 10.1002/ehf2.12246
Most Common Serious Adverse Events*

- Hyperkalemia
- Hypotension
- Cardiac failure
- Ventricular tachycardia
- Non-cardiac chest pain
- Pneumonia
- Respiratory tract infection
- Acute kidney injury
- Renal failure
- Pulmonary edema
- COPD

Proportion of patients (%)

- $P = 1.000$
- $P = 0.687$
- $P = 0.725$
- $P = 0.249$
- $P = 0.124$
- $P = 1.000$
- $P = 0.124$
- $P = 0.789$
- $P = 0.624$
- $P = 0.100$
- $P = 0.062$

$P$ values indicate statistical significance.

Safe to initiate therapy pre-discharge

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* ≥0.5% of patients in any group

** Fischer's Exact Test, full analysis set
Angiotensin–Neprilysin Inhibition in Acute Decompensated Heart Failure


*pTarget Dose
HF, Heart Failure. EF, Ejection Fraction

Velazquez EJ et al. nejm.org/doi/full/10.1056/NEJMoa1812851
PIONEER-HF

Key Entry Criteria

• Hospitalized for Acute Decompensated Heart Failure (ADHF)
• LVEF ≤40% within the last 6 months
• NT-proBNP ≥1600pg/mL or BNP ≥400 pg/mL*
• While hospitalized:
  • SBP ≥100 mmHg in prior 6h; no symptomatic hypotension
  • No increase in IV diuretics in prior 6h
  • No IV vasodilators in prior 6h
  • No IV inotropes in prior 24h

*At screening
A complete list of inclusion and exclusion criteria has been previously published at Velazquez et al. Am Heart J 198 (2018) 145-151
LVEF, Left Ventricular Ejection Fraction. NT-proBNP, N-terminal pro–Brain Natriuretic Peptide. BNP, Brain Natriuretic Peptide. SBP, Systolic Blood Pressure. IV, Intravenous

Velazquez EJ et al. nejm.org/doi/full/10.1056/NEJMoa1812851
PIONEER-HF

**Study Endpoints***

*Primary endpoint:*
- Time-averaged proportional change in NT-proBNP from baseline at 4 and 8 weeks

**Safety**
- Worsening renal function
- Hyperkalemia
- Symptomatic hypotension
- Angioedema

**Exploratory Clinical Outcomes**

- Serious Clinical Composite: Death, Hospitalization for HF, LVAD or listing for cardiac transplant

*More complete list of PIONEER study endpoints has been previously published at Velazquez et al. Am Heart J 198 (2018) 145. NT-proBNP N-terminal pro–Brain Natriuretic Peptide. HF, Heart Failure. LVAD, Left Ventricular Assist Device. HF, Heart Failure. Data on File: PIONEER-HF Protocol, Novartis Pharmaceutical Corp; October 2018

Velazquez EJ et al. nejm.org/doi/full/10.1056/NEJMoa1812851
# Baseline Characteristics

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<th>Sacubitril/Valsartan (n=440)</th>
<th>Enalapril (n=441)</th>
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<td>Age (years)</td>
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<td>LVEF, median (25th, 75th)</td>
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**Primary Endpoint**

**Time-average proportional change of NT-proBNP from baseline**

- **Enalapril**
- **Sacubitril/Valsartan**

HR 0.71 (95% CI 0.63, 0.80)  
P<0.001

*Percentage (%) change from baseline to mean of weeks 4 and 8*

Velazquez EJ et al. [nejm.org/doi/full/10.1056/NEJMoa1812851](https://doi.org/10.1056/NEJMoa1812851)
## PIONEER-HF

### Exploratory Clinical Endpoints

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<th>RR Sac/Val vs Enalapril (95% CI)</th>
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<td>Composite of serious clinical events *</td>
<td>41 (9.3)</td>
<td>74 (16.8)</td>
<td>0.54 (0.37 to 0.79)</td>
</tr>
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<td>Death</td>
<td>10 (2.3)</td>
<td>15 (3.4)</td>
<td>0.66 (0.30 to 1.48)</td>
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<td>Re-hospitalization for HF</td>
<td>35 (8.0)</td>
<td>61 (13.8)</td>
<td>0.56 (0.37 to 0.84)</td>
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<tr>
<td>Requirement of LVAD</td>
<td>1 (0.2)</td>
<td>1 (0.2)</td>
<td>0.99 (0.06 to 15.97)</td>
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<td>Inclusion on list for heart transplantation</td>
<td>0</td>
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*Exploratory Serious Clinical Composite endpoint consisted of death, rehospitalization for heart failure, implantation of a left ventricular device, and inclusion on the list of patients eligible for heart transplantation.

**Study Limitations**

- The study was powered for changes in NTproBNP and interpretation of secondary and exploratory endpoints should be viewed with caution.

- Safety data were collected for only 12 weeks, therefore adverse events that take longer to transpire may not have appeared in this study. Safety information should be interpreted in the context of prior trials with longer duration.

- In-hospital initiation included 2 placebo doses in the sacubitril/valsartan group and 6 hours of mandatory observation after the 3rd dose of study medication in both arms, which may have prolonged length of stay.

- The 8 week double-blind study duration could limit the ability to fully assess long-term outcomes such as death, cardiac transplantation, and LVAD implantation.
Effect of HR upon normal and Failing LV

![Graph showing the effect of heart rate on cardiac index for normal (Control) and failing left ventricle (DCM). The graph illustrates the cardiac index (L/min/m²) against heart rate (min⁻¹). The control group shows a peak cardiac index at a heart rate of 120 min⁻¹, while the failing left ventricle group shows a decrease in cardiac index at higher heart rates.](image-url)
Effect of early treatment with ivabradine combined with beta-blockers versus beta-blockers alone in patients hospitalised with heart failure and reduced left ventricular ejection fraction (ETHIC-AHF): A randomised study

Francisco J. Hidalgo *, Manuel Anguita, Juan C. Castillo, Sara Rodríguez, Laura Pardo, Enrique Durár José J. Sánchez, Carlos Ferreiro, Manuel Pan, Dolores Mesa, Mónica Delgado, Martín Ruiz

Department of Cardiology, Hospital Universitario Reina Sofía, Córdoba, Spain

During hospitalization

• Beta-blockers
  on BBs: not stop after admission, with reduction in doses if necessary (based on clinical and hemodynamic condition of patients). BBs were uptitrated every 48 h in both groups
  No BBs before admission: BBs were started at low doses (carv: 3,125 mg/12 h or 6.25 mg/12 h, bisop: 1.25 to 2.5 mg/day) once the patient was stabilized, in both groups.

• Ivabradine: added to BBs at initial dose of 5 mg bid after and uptitrated every 48 h until a dose of 7.5 mg bid based on HR

After discharge

• BBs: uptitration continued at the 14 and 28 days visits in both groups
• Ivabradine: uptitration to target dose of 7, 5 mg bid at 14 days

Effect of early treatment of ivabradine with BBs vs BB alone in patients hospitalized for WHF: randomized ETHIC study

n = 71 patients hospitalized for WHF

Effect of early treatment of ivabradine with BBs vs BB alone in patients hospitalized for WHF: randomized ETHIC study

n = 71 patients hospitalized for WHF

Better reduction in BNP

![Bar chart showing BNP levels at admission, discharge, and 4 months follow-up for ivabradine + BB and BB alone.](chart.png)

Early Co-administration of Ivabradine and β-blockers During Hospitalization is Safe and May Improve HF Parameters (effects at 12 months)

N=414 patients hospitalized due to worsening HF who were in sinus rhythm, NYHA Class II-IV, and LVEF <40%. Physicians were free to choose the strategy of co-administration of BBs and ivabradine (37.2%) or with BBs alone (62.8%).

Lopatin et al. AHA 2017 (Abstract 12310).
Early co-administration of **ivabradine** and **β**-**blockers** during hospitalization may reduce mortality

A retrospective analysis on 370 hospitalized HF patients with heart rate ≥ 70 bpm (150 BB + ivabradine, 220 BB alone) in the Optimize Heart Failure Care Program from 8 countries (2015-2016)

**Probability of survival**

HR=0.41 (95% CI, 0.29-0.57)  P<0.0001

Lopatin et al., *Int. J Cardiol.*, 2018, 260, 113-117
PRIME-HF

- Primary Endpoint: Uptake of ivabradine at 180 days post-discharge
- Secondary: QOL, HR, beta-blocker use and dose
- Ancillary Study – wearable technology
Initiation of ivabradine pre-discharge improve the likelywood to take the medication as recommended (PRIME-HF)

Six months after hospitalization, the patients whose physicians were asked to initiate ivabradine prior to discharge:
- Were far more likely to be using ivabradine (40.4 percent vs. 11.5 percent)
- Had a greater reduction in heart rate
  - 10 bpm vs. 0.7 bpm
  - average heart rate 77 bpm vs 86 bpm
- Had not reduced their dose of beta-blockers
- Did not develop abnormally low blood pressure or heart rate
Is early initiation worth it? How quickly does medical therapy work?

PARADIGM –HF trial (NEJM 2014); SHIFT Trial (LANCET 2010)
Summary

- Heart failure has a high morbidity and mortality, with a high re-admission rate
- Medical therapy can reduce all of the above with benefits achieved early on
- Medical therapy is under-utilized
- Is there another way to approach these patients?
- Is there a better window of opportunity to get patients onto GDMT?
  - In well selected patients, can initiate therapy and titration in hospital