A Phenotypic Approach to HFrEF Medicines

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Chair holder, University of Montreal Fondation Marcelle et Jean Coutu, Cal et Janine Moisan for better practices in advanced heart failure

IN-PERSON **15-minute plenary lecture**
DATE: Friday, May 13; TIME: 10:25 a.m

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Disclosures

- Speaker bureau/adboard
  - Abbott, Akcea, Alnylam, Astra-Zeneca, Bayer Boehringer-Ingelheim, Novartis, Pfizer, Sanofi.
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- Stock holder:
  - none

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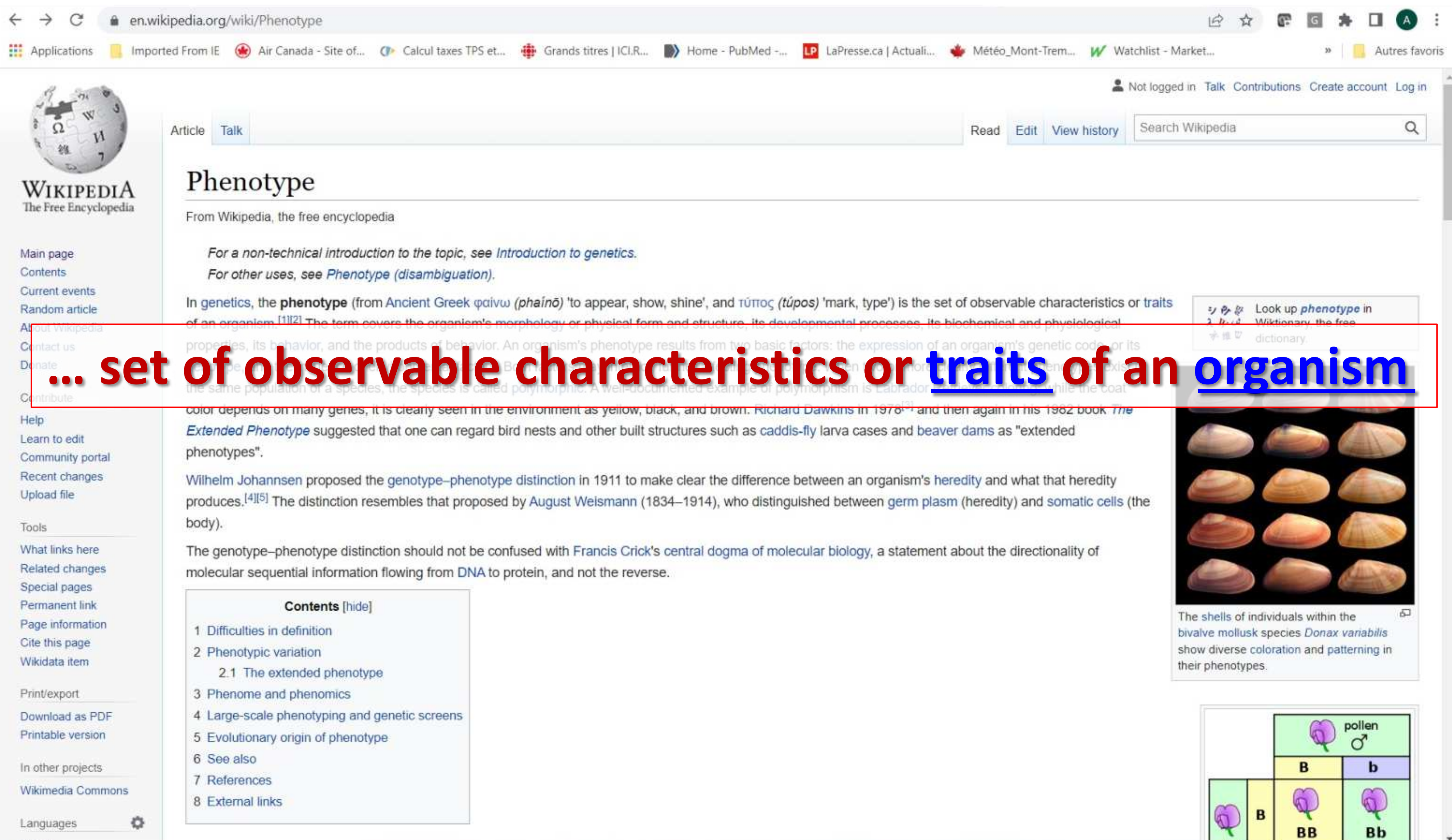
A Phenotypic Approach to HFrEF Medicines



en.wikipedia.org/wiki/Phenotype

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Phenotype

From Wikipedia, the free encyclopedia

For a non-technical introduction to the topic, see Introduction to genetics.
For other uses, see Phenotype (disambiguation).

In genetics, the **phenotype** (from Ancient Greek φαίνω *(phaínō)* 'to appear, show, shine', and τύπος *(túpos)* 'mark, type') is the set of observable characteristics or traits …

… *Extended Phenotype* suggested that one can regard bird nests and other built structures such as caddis-fly larva cases and beaver dams as "extended phenotypes".

Wilhelm Johannsen proposed the genotype–phenotype distinction in 1911 to make clear the difference between an organism's heredity and what that heredity produces.[4][5] The distinction resembles that proposed by August Weismann (1834–1914), who distinguished between germ plasm (heredity) and somatic cells (the body).

The genotype–phenotype distinction should not be confused with Francis Crick's central dogma of molecular biology, a statement about the directionality of molecular sequential information flowing from DNA to protein, and not the reverse.

Contents [hide]

Look up *phenotype* in Wiktionary, the free dictionary.

The shells of individuals within the bivalve mollusk species *Donax variabilis* show diverse coloration and patterning in their phenotypes.

… set of observable characteristics or traits of an organism

Drugs layering or personalized drug therapy?

- Traditionally, HF guidelines → stepwise Rx initiation / uptitration,
  - timing of discovery rather than efficacy or safety or the of treatment benefit.
- Most trials conducted in “stable” ambulatory patients → deferring initiation
- SGLT2i & ARNI → early risk ↓< 30 days
  - Complete optimization may take up to one year
- Up-titrate to their maximum dosage or combine them based of their pharmacodynamic actions ?
- New approach: to start early with all 4 pillars.
- Patient characteristics → prioritize & up-titrate drugs early.

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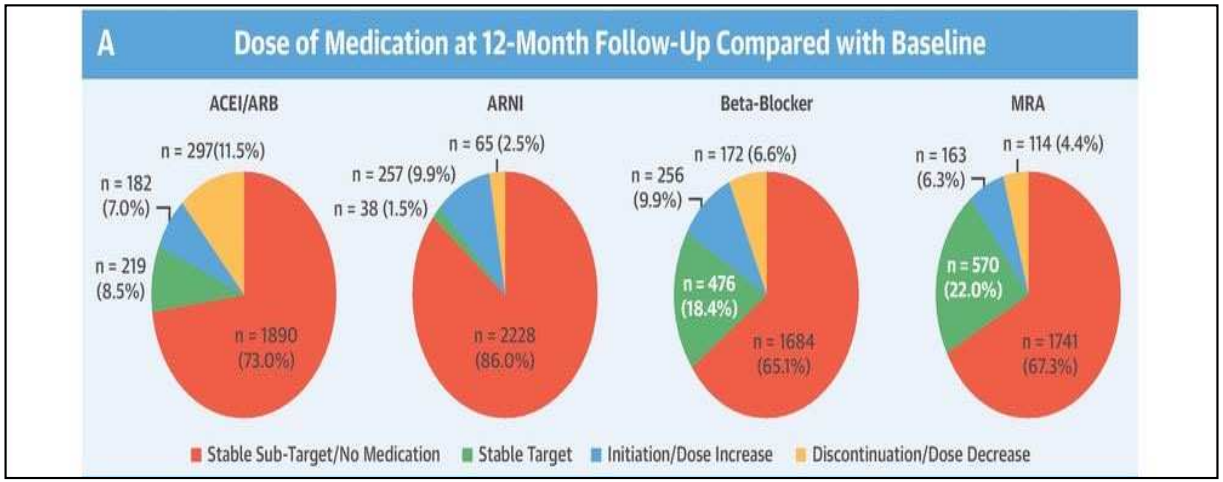
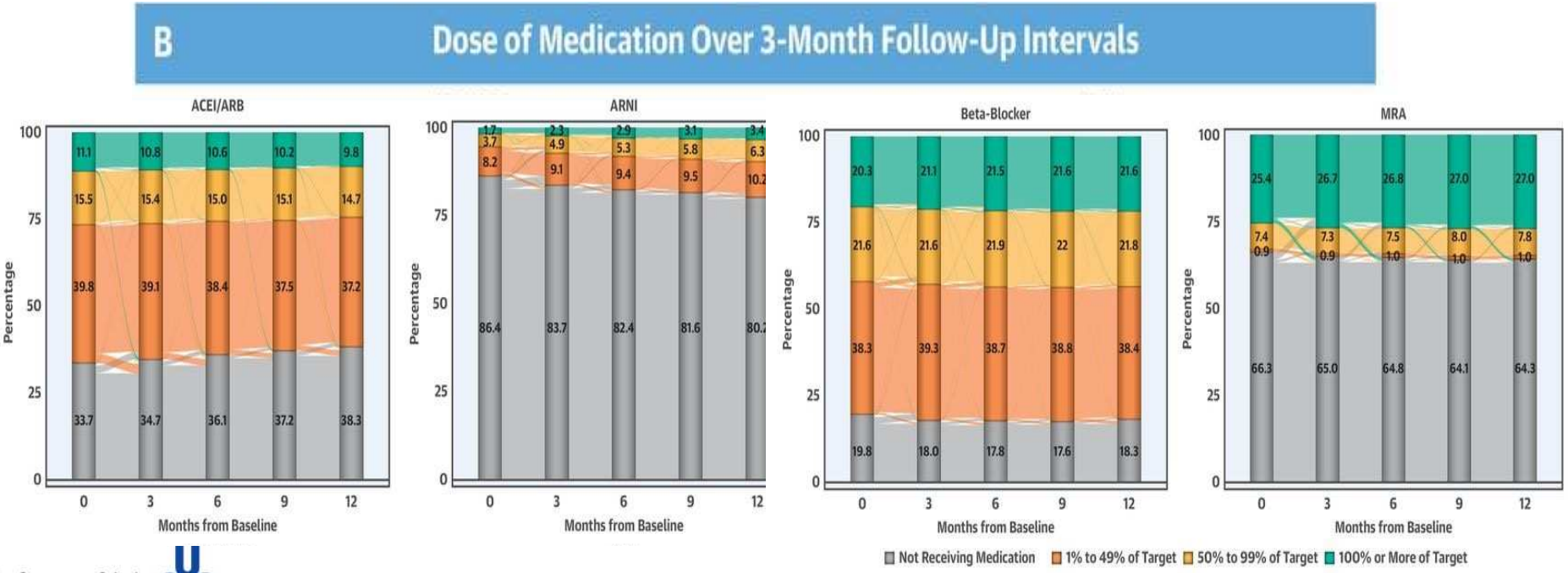
What is really happening in practice



< 1% of patients received triple therapy @ **target doses**



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Greene, S.J. et al. J Am Coll Cardiol. 2019;73(19):2365–83.

Controversy

- Whether drug initiation should start before full up-titration of pre-existing medications or whether all recommended drugs should be started together ?
- ATLAS: high dose vs low dose ACEi : no difference in mortality
- No large, RCT of high- vs low-dose for beta-blockers/ MRAs
- BIOSTAT-CHF & ASIAN-HF registries:
  - 6,787 patients with HFrEF.
  - 14% received ≥ 50% of target dose of ACE/ARB or BB
  - Nonuse/ lower doses associated with ↑ burden comorbidities (ie CKD)
  - Higher dose had modest benefit

(BIOlogy Study to TAilored Treatment in Chronic Heart Failure) study
ASIAN-HF (Asian Sudden Cardiac Death in Heart Failure)

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- Packer M, et al. Circulation. 1999;100:2312–2318.
- Ouwerkerk W, et al.. Eur J Heart Fail. 2020;22:1472–1482.

Target doses are not based on physiology..

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@home…

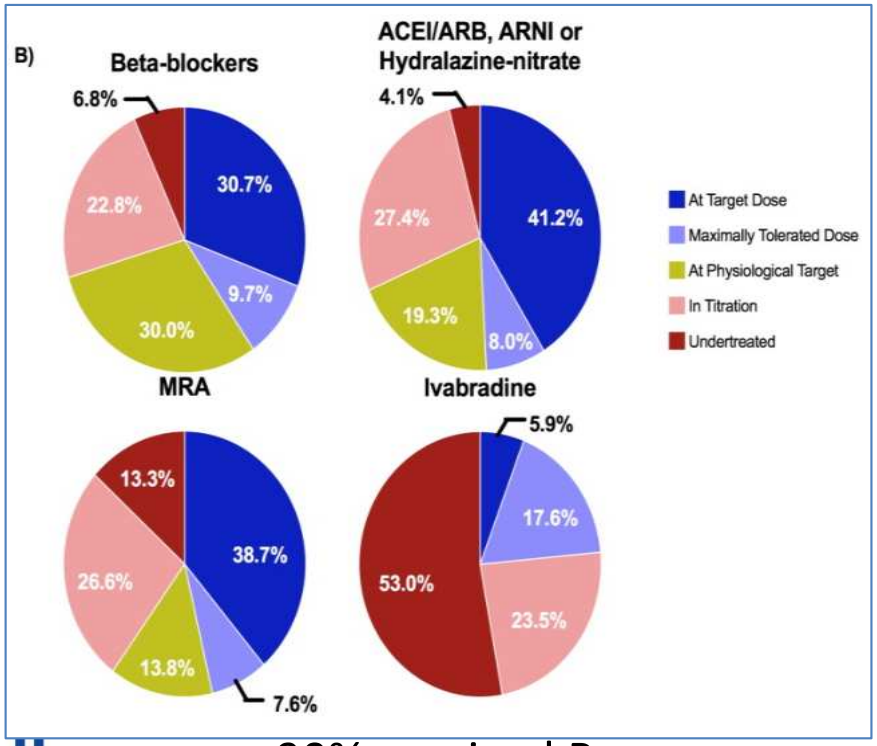
Limits:

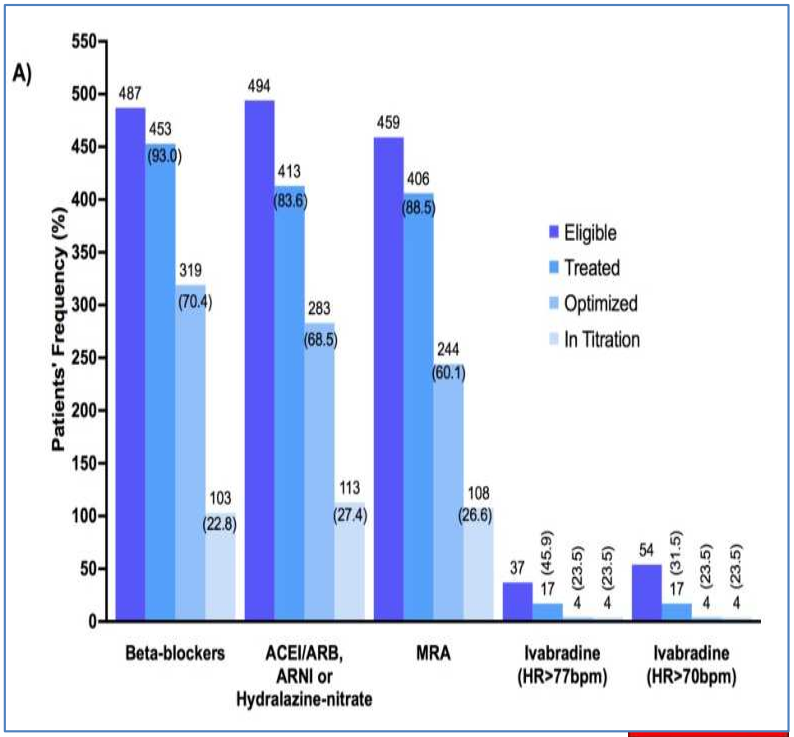
- BP
- HR
- K+
- creatinine

Care Gaps in Adherence to Heart Failure Guidelines

Clinical Inertia or Physiological Limitations?

Marilyne Jarjour, MSc,[a] Christine Henri, MD,[a] Simon de Denus, BPharm, PhD,[a] Annik Fortier, MSc,[b] Nadia Bouabdallaoui, MD, PhD(c),[a] Anil Nigam, MD,[a] Eileen O'Meara, MD,[a] Charaf Ahnadi, PhD,[c] Michel White, MD,[a] Patrick Garceau, MD,[a] Normand Racine, MD,[a] Marie-Claude Parent, MD,[a] Mark Liszkowski, MD,[a] Geneviève Giraldeau, MD,[a] Jean-Lucien Rouleau, MD,[a] Anique Ducharme, MD, MSc[a]





≈90% received Rx

22.8 - 27.4% remained *in-titration*

Jarjour M et al. JACC:HF 2020 Sep;8(9):725-738

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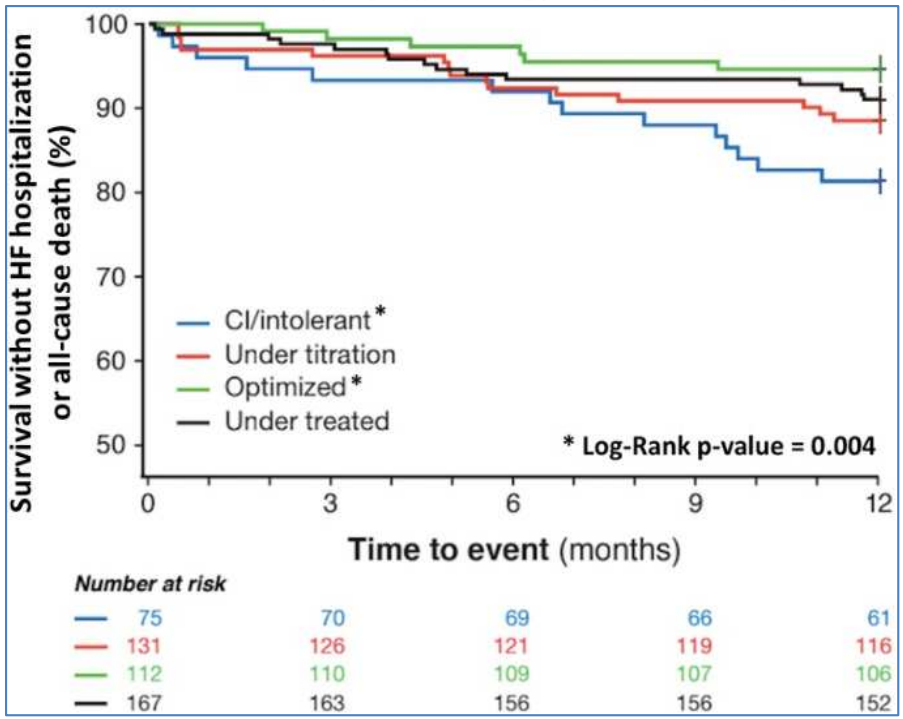
Is optimization important ?

n= 511 patients HFrEF :

Figure 1. Kaplan-Meier curves Survival free of HF hospitalization (%)

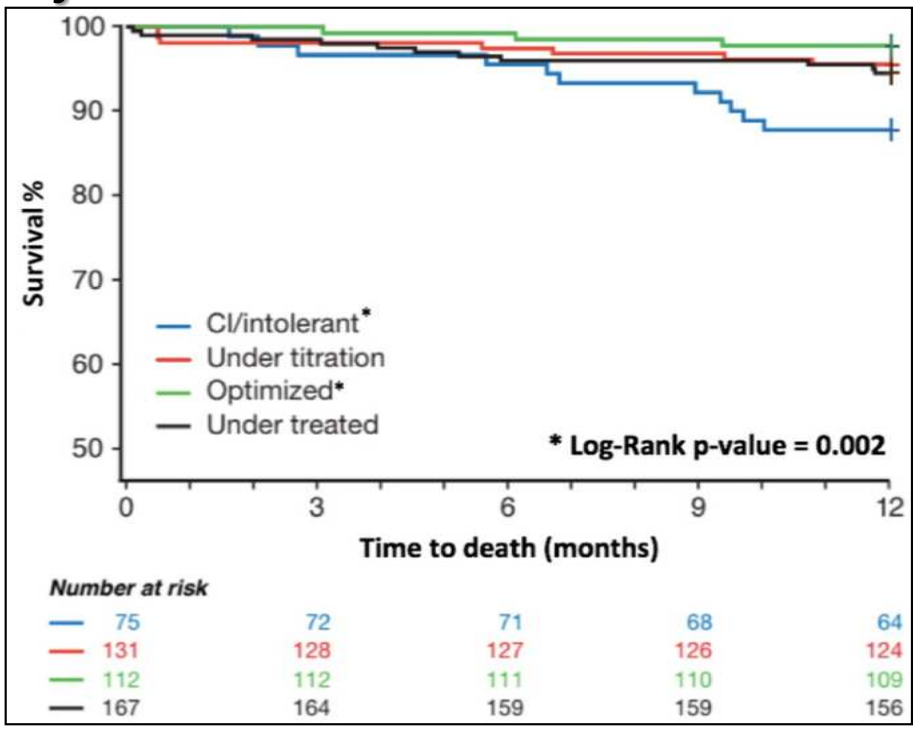


Optimized: 6 (5.4%); In titration: 15 (11.5%)

Undertreated: 15 (9.0%); Intolerant/C.I.: 14 (18.7%)

- Intolerant/C.I. vs Opt HR=3.71; 95% CI 1.43-9.66; p=0.01
- Intolerant/C.I. vs Under HR=2.17; 95% CI 1.05-4.50; p=0.04

Figure 2. Kaplan-Meier curves for time to all-cause death.



Optimized: 3 (2.7%); In titration: 7 (5.3%);

Undertreated: 11 (6.6%); Intolerant/C.I.: 11 (14.7%)

- Intolerant/C.I. vs Optimized: HR = 5.77; 95% CI 1.61-20.68; p=0.01
- Intolerant/C.I. vs In titration: HR = 2.84; 95% CI 1.10-7.33; p=0.03

Jarjour M et al. HFA-ESC 2020

New recommendation

- We recommend that in the absence of contraindications, patients with HFrEF be treated with combination therapy including 1 evidence-based medication from each of the following categories:
  a. ARNI (or ACEI/ARB);
  b. Beta-blocker;
  c. MRA;
  d. SGLT2 inhibitor.

  Strong Recommendation, Moderate-Quality Evidence

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Cumulative impact of evidence-based HFrEF medical therapies on all-cause mortality

	Relative Risk	Two-year Mortality
None	---	35.0%
ARNI (vs. imputed placebo)	↓ 28%	25.2%
BB	↓ 35%	16.4%
MRA	↓ 30%	11.5%
SGLT2i	↓ 17%	9.5%

Cumulative risk reduction in mortality if all evidence-based medical therapies are used:
RRR 72.9%, ARR: 25.5%, NNT=3.9

ARNI, angiotensin-receptor-neprilysin inhibitor; ARR, absolute risk reduction, BB, beta-blocker; EF, ejection fraction; MRA, mineralocorticoid receptor antagonist; NNT, number needed to be treated to prevent prespecified outcomes within 1 year; RRR, relative risk reduction; SGLT2i, sodium-glucose cotransporter 2 inhibitor
Updated from Fonarow GC et al. Am Heart J 2011;161(6):1024-1030 and Fonarow GC et al. Lancet 2008;372(9645):1195-1196.

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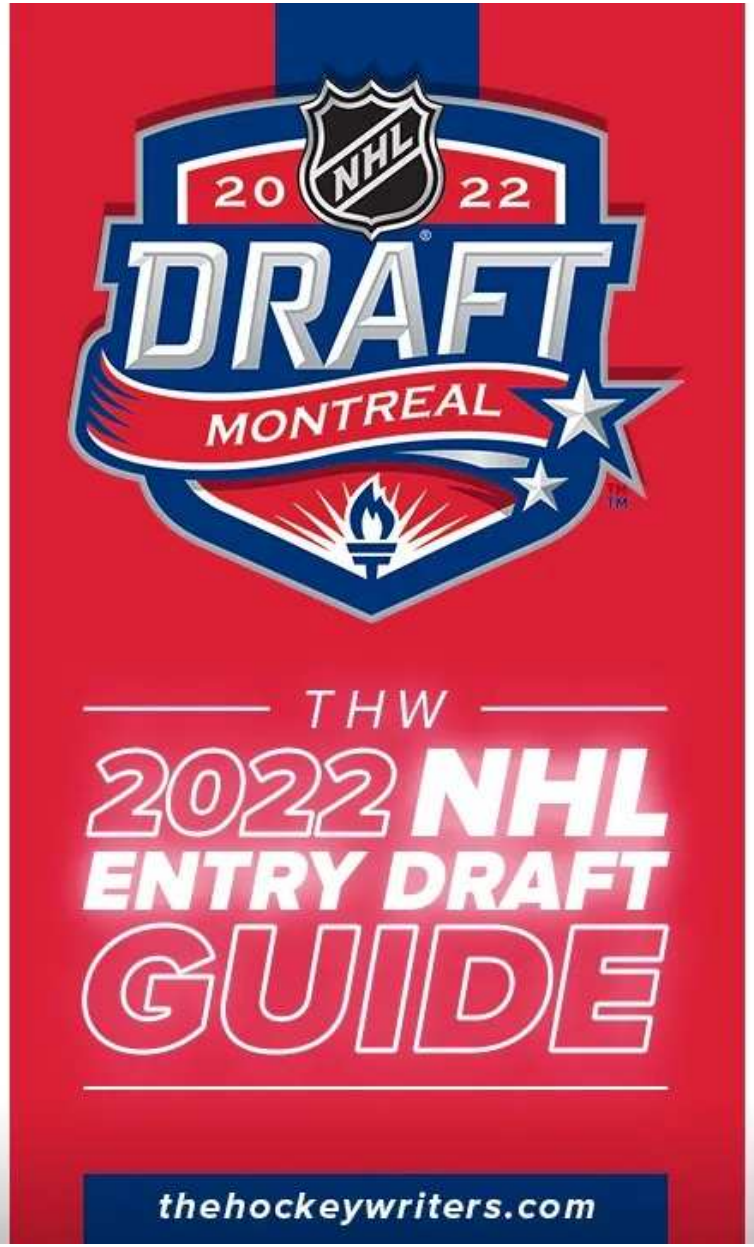
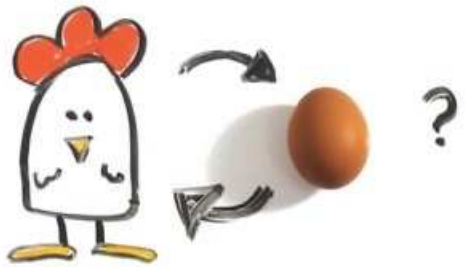
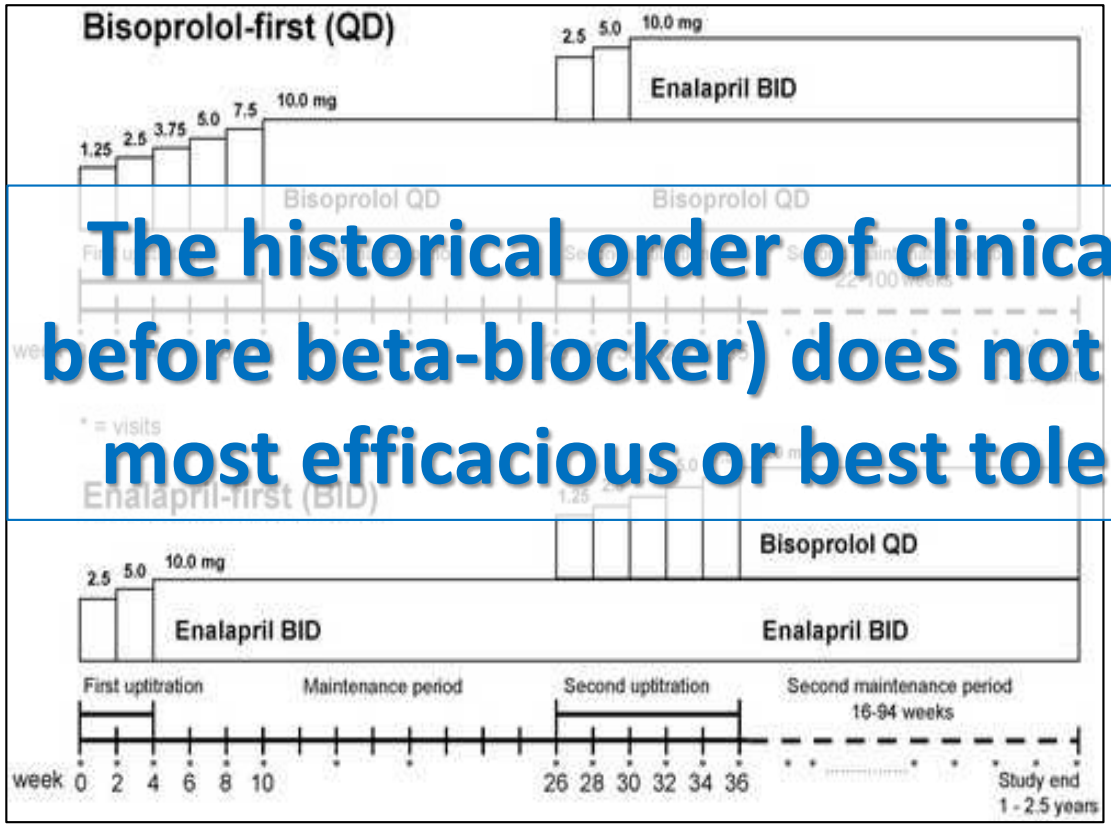
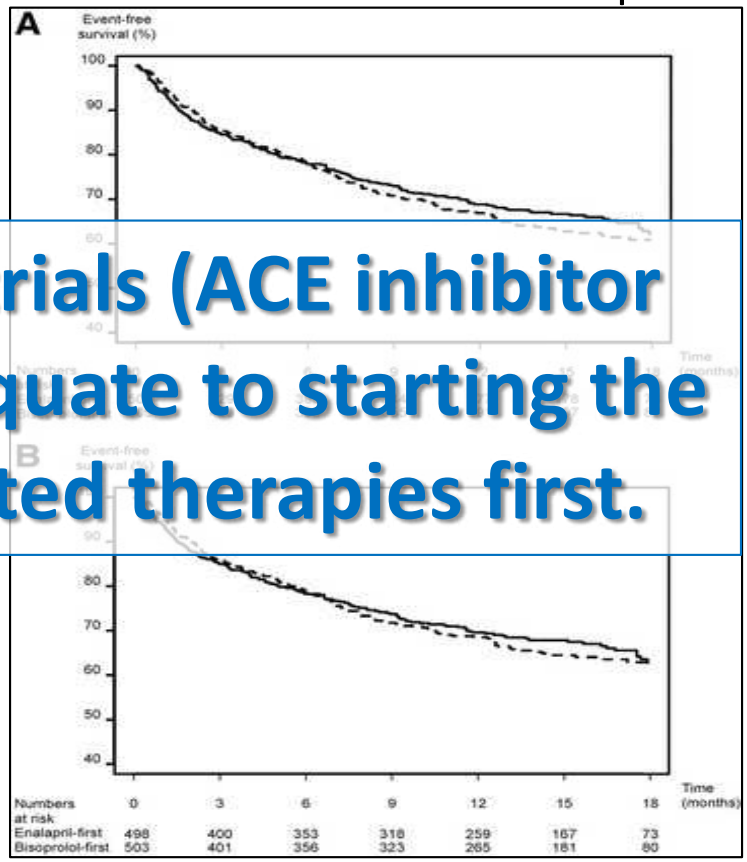
Order of initiation: B-blockers or RASi first ?



Which should come first ?







The historical order of clinical trials (ACE inhibitor before beta-blocker) does not equate to starting the most efficacious or best tolerated therapies first.

> 50% patients did not tolerate full doses of either drug when given in combination. The last doses of Rx (E or B) were higher according to which was prescribed first.

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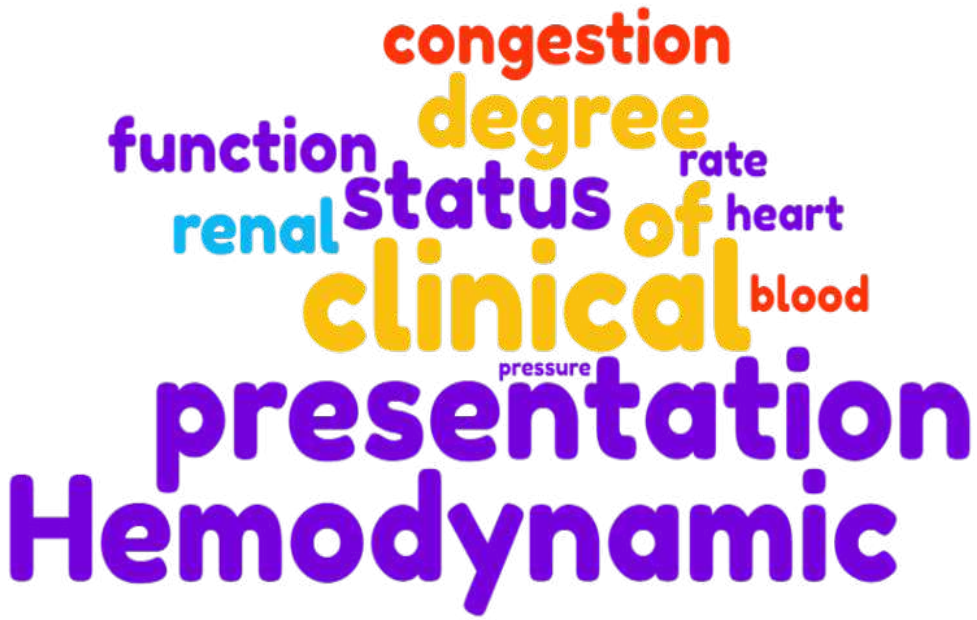
R. Willenheimer, et al. Circulation 112 (16): 2426-2435.

Variety of patients & tailored strategies



Important phenotypes for HF drugs:

- **heart rate,**
- **blood pressure,**
- **renal function, and**
- **their combinations.**

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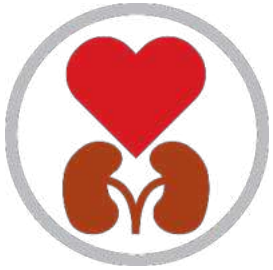
Phenotypes

T2DM



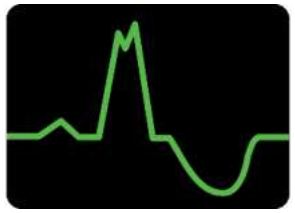
CRS/Stalled

Wet
Hypertensive

Elderly

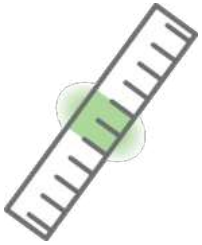
Afib

High
Heart Rate



LBBB

HFpEF



HFmrEF

De novo

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Courtesy: Shelley Zieroth

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No guidance on the optimal timing and sequence for the layering of HF medications

- Optimal timing ?
- Sequence for the layering ?
- Sequential treatment according to the size of treatment effects of drugs, specific cardiac diseases, and patient wishes.
  - B-Blockers & HR 61 ?
  - Pre-existing conditions: Db +ARB
- Clinical circumstances:
  - de novo HF
  - In-hospital or post-acute phase
  - Cardiorenal syndrome
  - etc

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Tolerance In Heart Failure Phenotypes

- Staged/slow initiation of drugs with hemodynamic effects : ↓ side effects (↓ BP, ↓ HR), which limit adherence to GDMT over time.
  - simultaneous addition of RAASi + βB: untoward effects BP, renal function & K+
- This approach contradicts the call for more rapid escalation of therapies to reach recommended doses within weeks of discharge.
- Some drugs facilitate the use of others,
  - sacubitril/valsartan & dapagliflozin + MRA → beneficial effects on renal function and hyperkalemia.
  - Ivabradine + β -blockers: additive effects on heart rate ↓; ivabradine may facilitate the up-titration of β-B.
- The timing, order, and sequence in which HF medications should be started has never been systematically investigated.

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Khattab M, et al. J Family Med Prim Care. 2020;9:3065–3069.
Desai AS, et al. JAMA Cardiol. 2017;2:79–85.
Bocchi EA, et al. Cardiology. 2015;131:218–224.
Fonarow GC, et al. J Am Coll Cardiol. 2007;50:768–777.
Shen L, et al. J Am Coll Cardiol HF. 2021;9:254–264.

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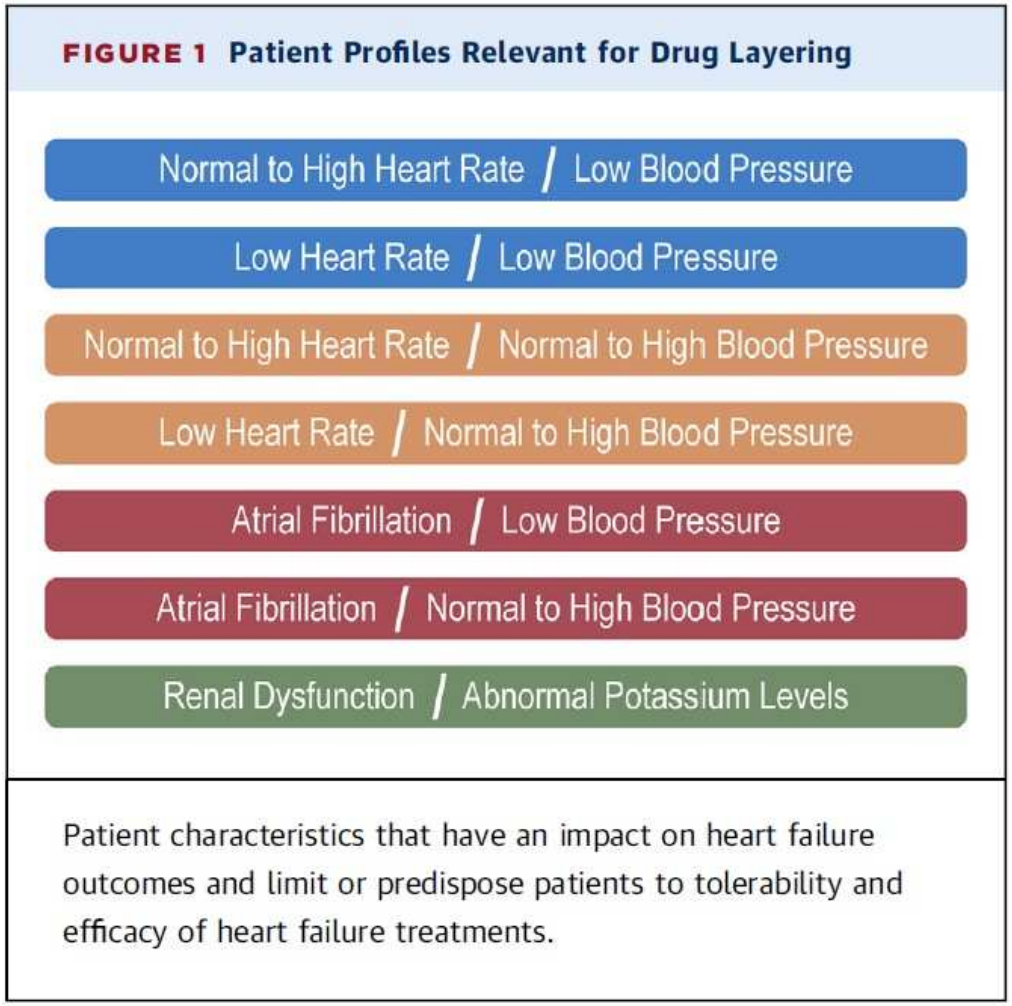
New Therapeutic Algorithm According To Patient Phenotype



- 7 phenotypes for personalized implementation and up-titration of meds.
- 4 classes of drugs
  - MRA, ARNI, β-blockers, SGLT2i
  - With lifesaving effects demonstrated in large RCT in broad groups of patients
  - should be started in eligible patients.

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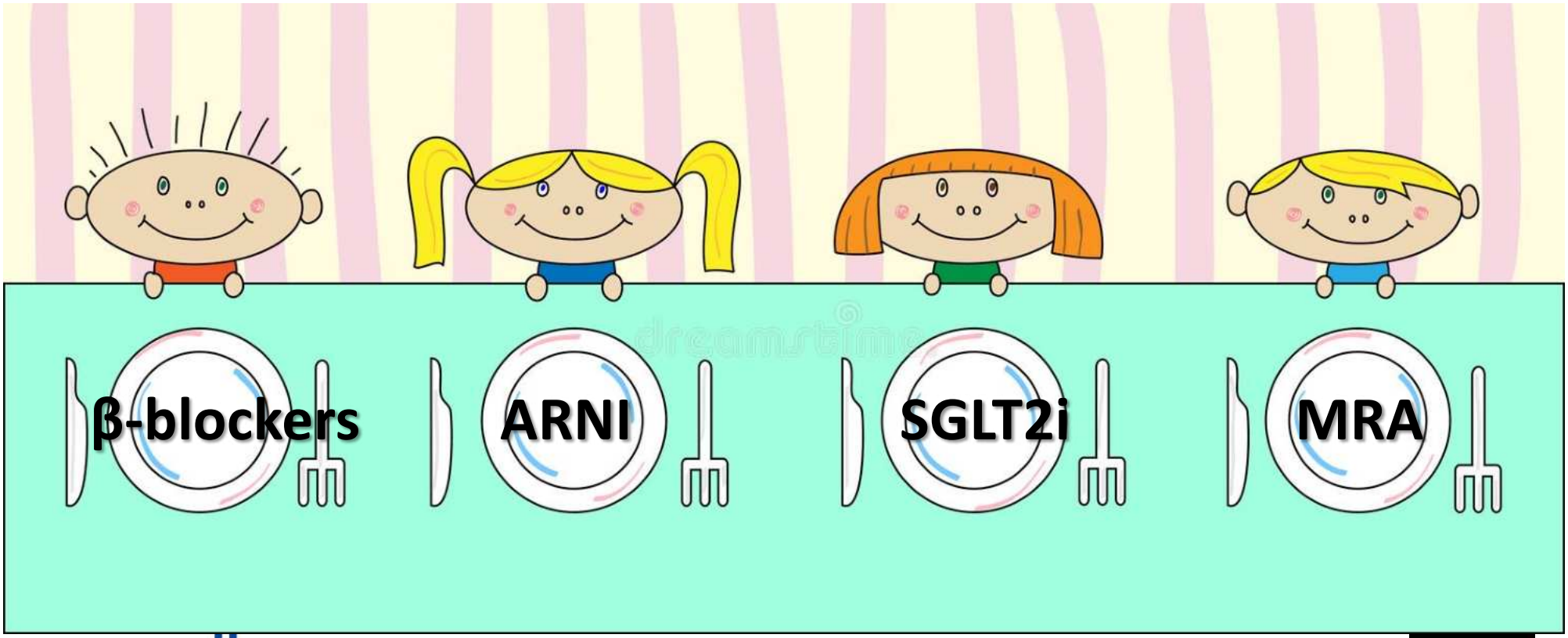
Rosano et al. Drug Layering in Heart Failure. J A C C : HF 2021



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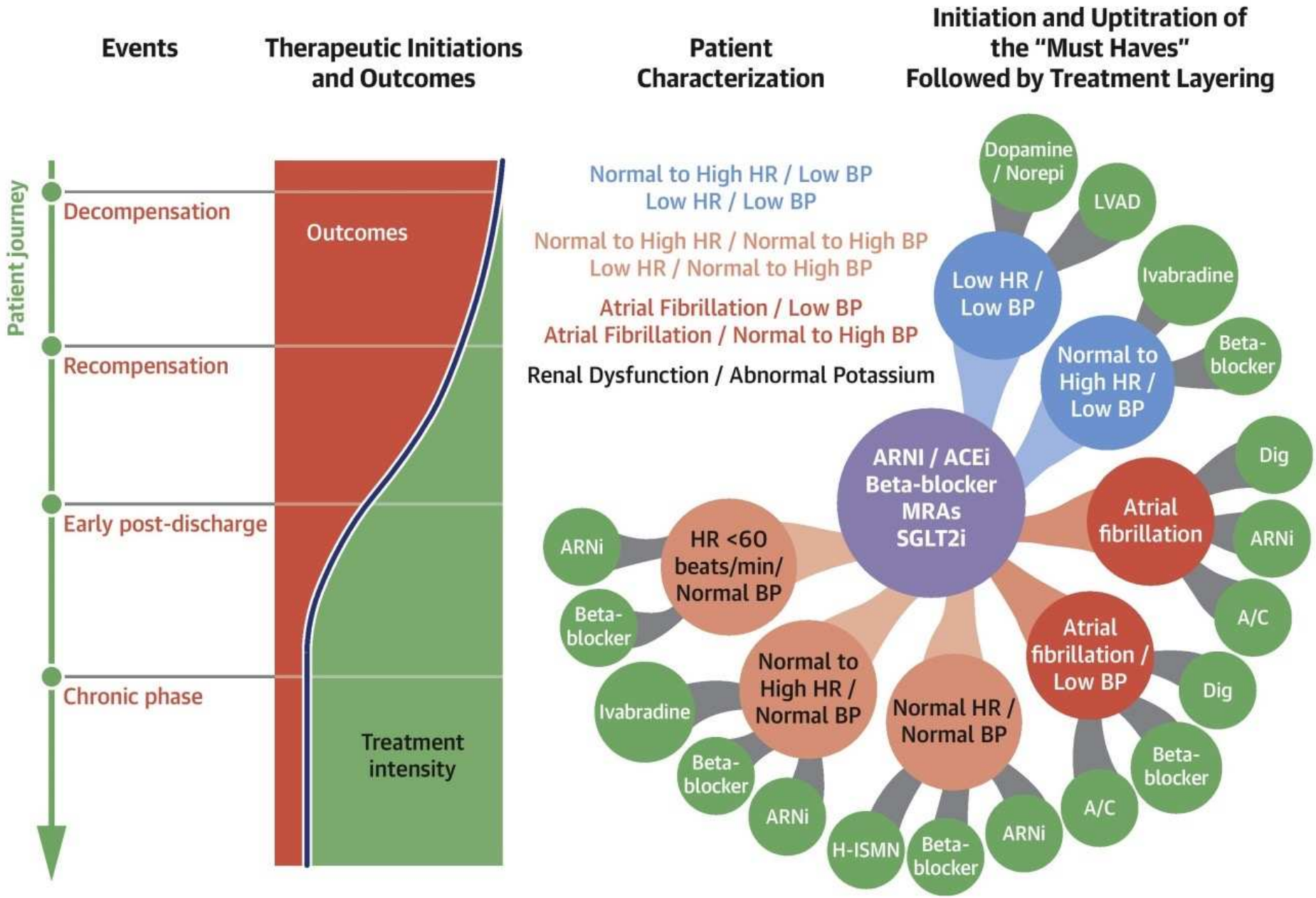
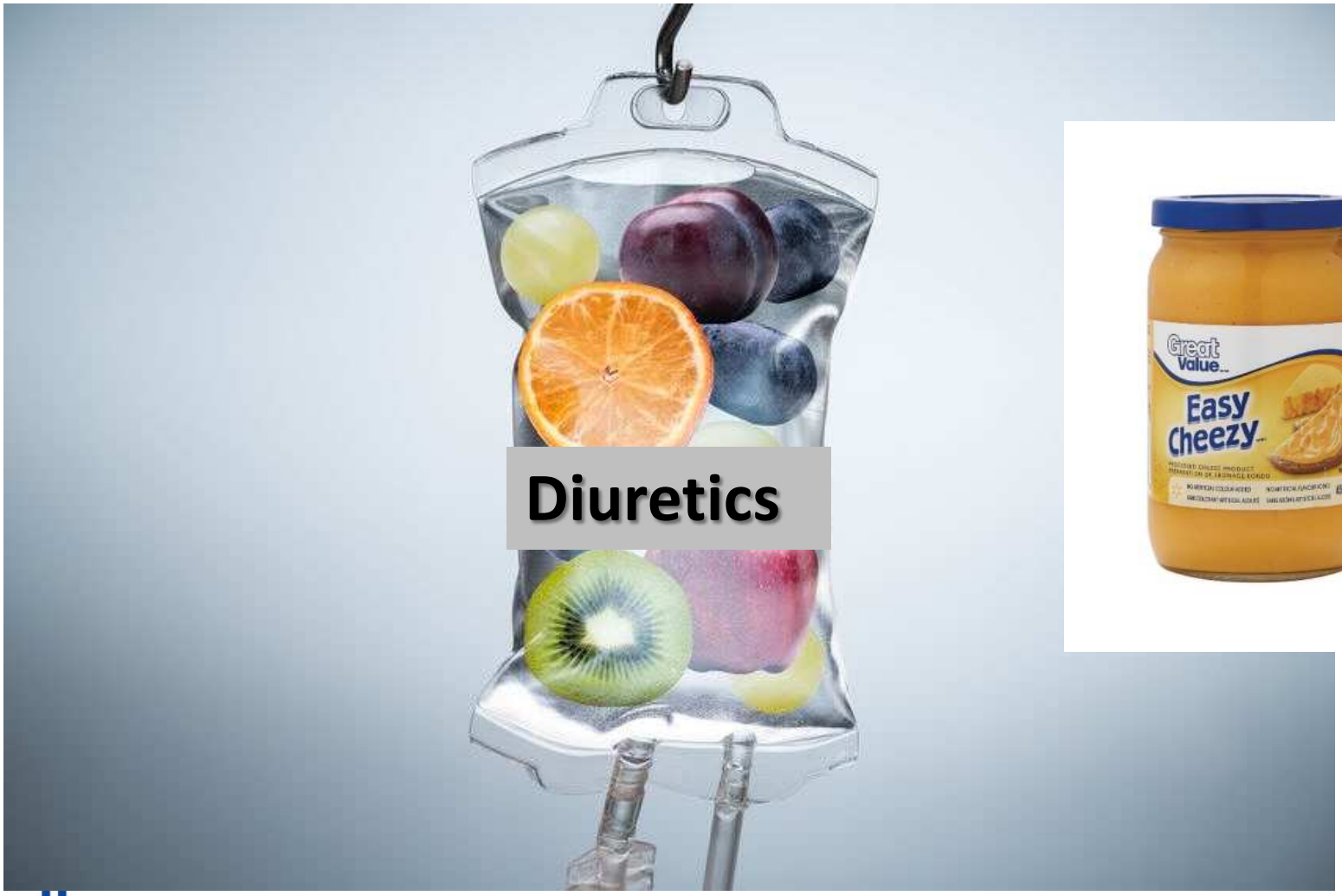
CENTRAL ILLUSTRATION: Treatment Layering According to Patient Characterization Alone: Patient Journey



Rosano, G.M.C. et al. J Am Coll Cardiol HF. 2021;9(11):775–783.

Wet & warm



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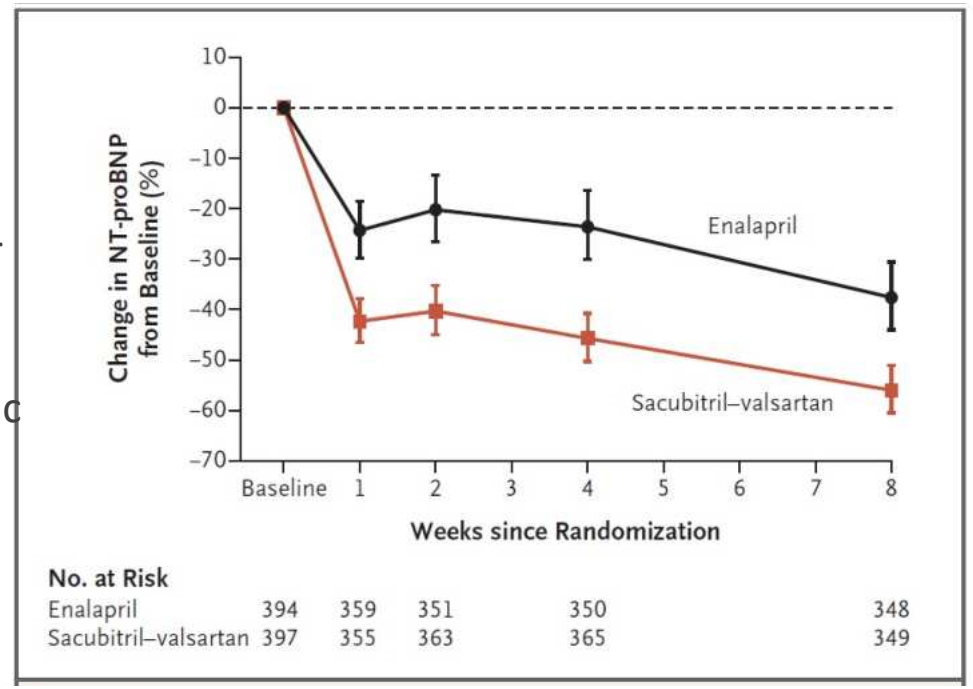
PIONEER HF: Primary Endpoint

Time-averaged proportional change of NT-proBNP from baseline

- Hospitalized for Acute Decompensated HF
- LVEF ≤40% within the last 6 months
- NT-proBNP ≥1600pg/mL / 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

ENDPOINT: Δ NT-proBNP
Follow-up: 8 weeks



Velazquez EJ et al. N Engl J Med. 2019 Feb 7;380(6):539-548

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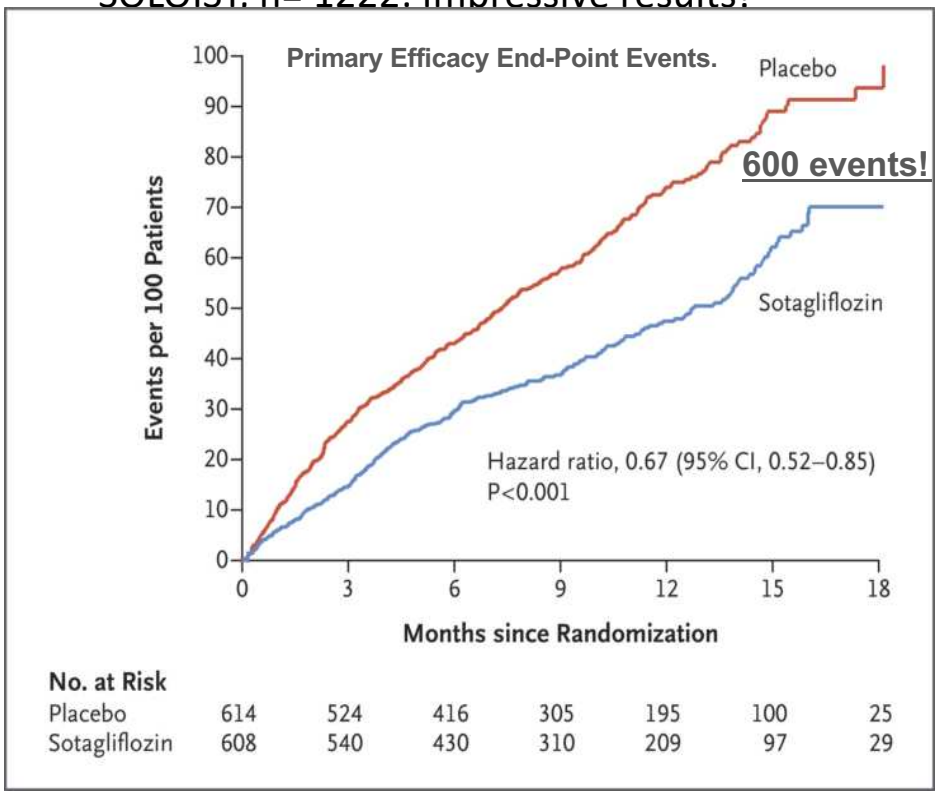
SOLOIST WHF Trial: Hosp + Vulnerable

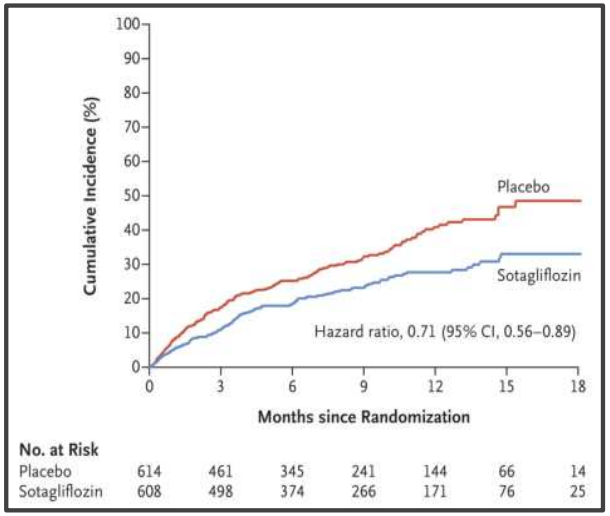
SOLOIST, n= 1222: Impressive results!



- **But keep in mind:**
  - Altered primary endpoint
  - 50% initiated after discharge
  - Stopped early
  - Events were not adjudicated

Reduces by ~30%

First Occurrence of Either Death from Cardiovascular Causes or Hospitalization for Heart Failure.



Bhatt DL et al. N Engl J Med 2021;384:117-128

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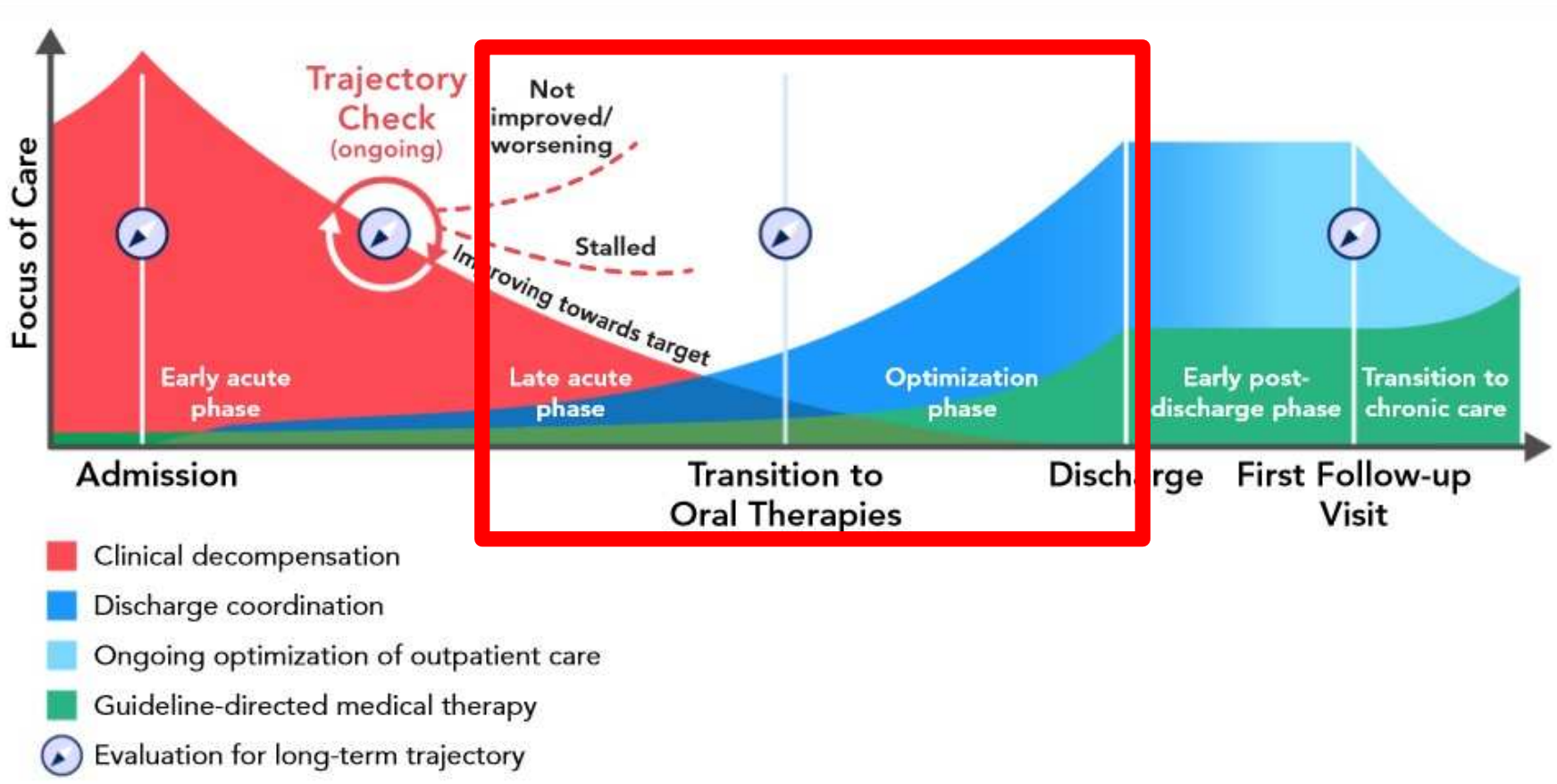
Clinical Course of Heart Failure



2019 ACC Expert Consensus Decision Pathway J Am Coll Cardiol. 2019 Oct, 74 (15) 1966-2011

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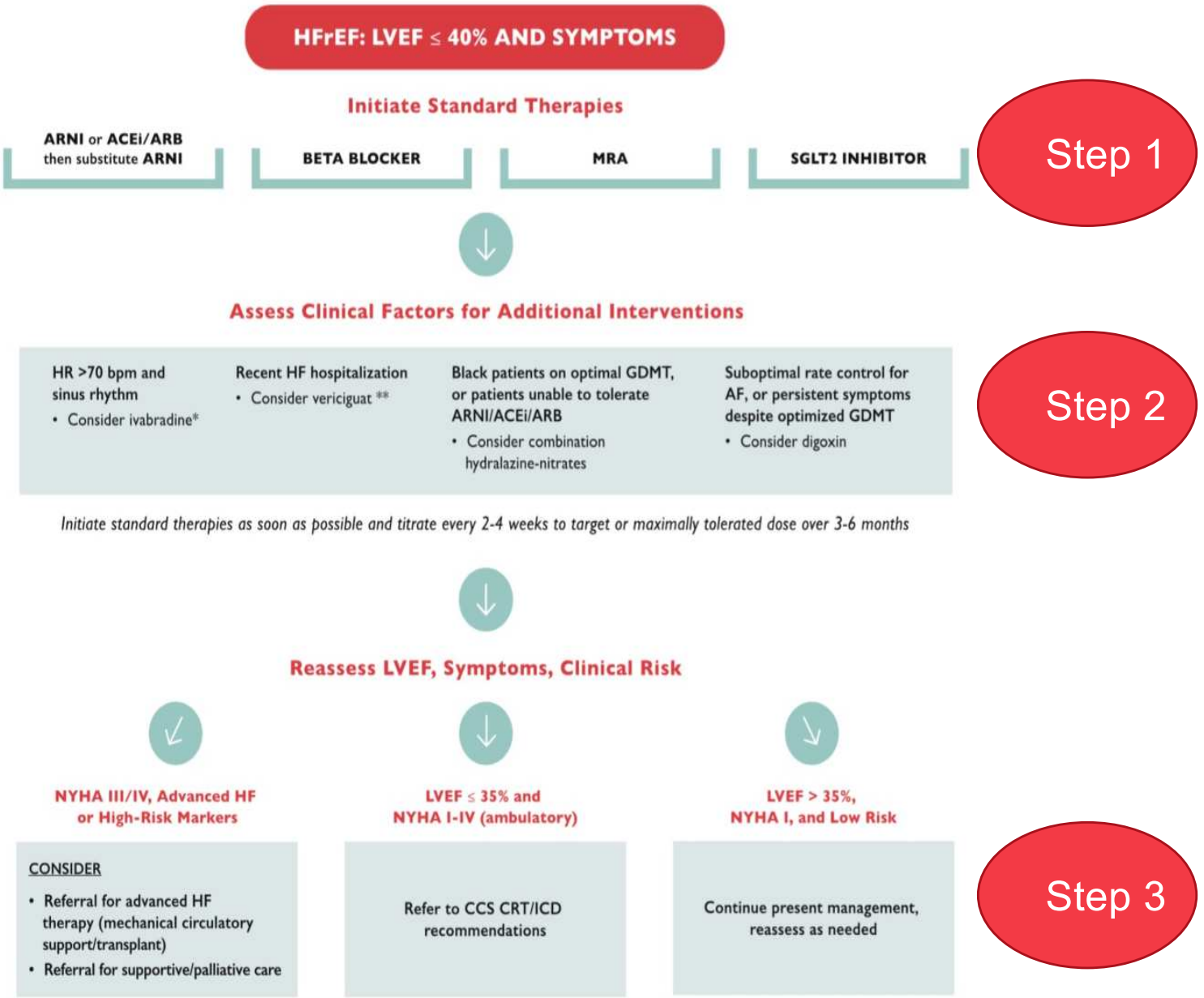
How best to prescribe?



Canadian Cardiovascular Society

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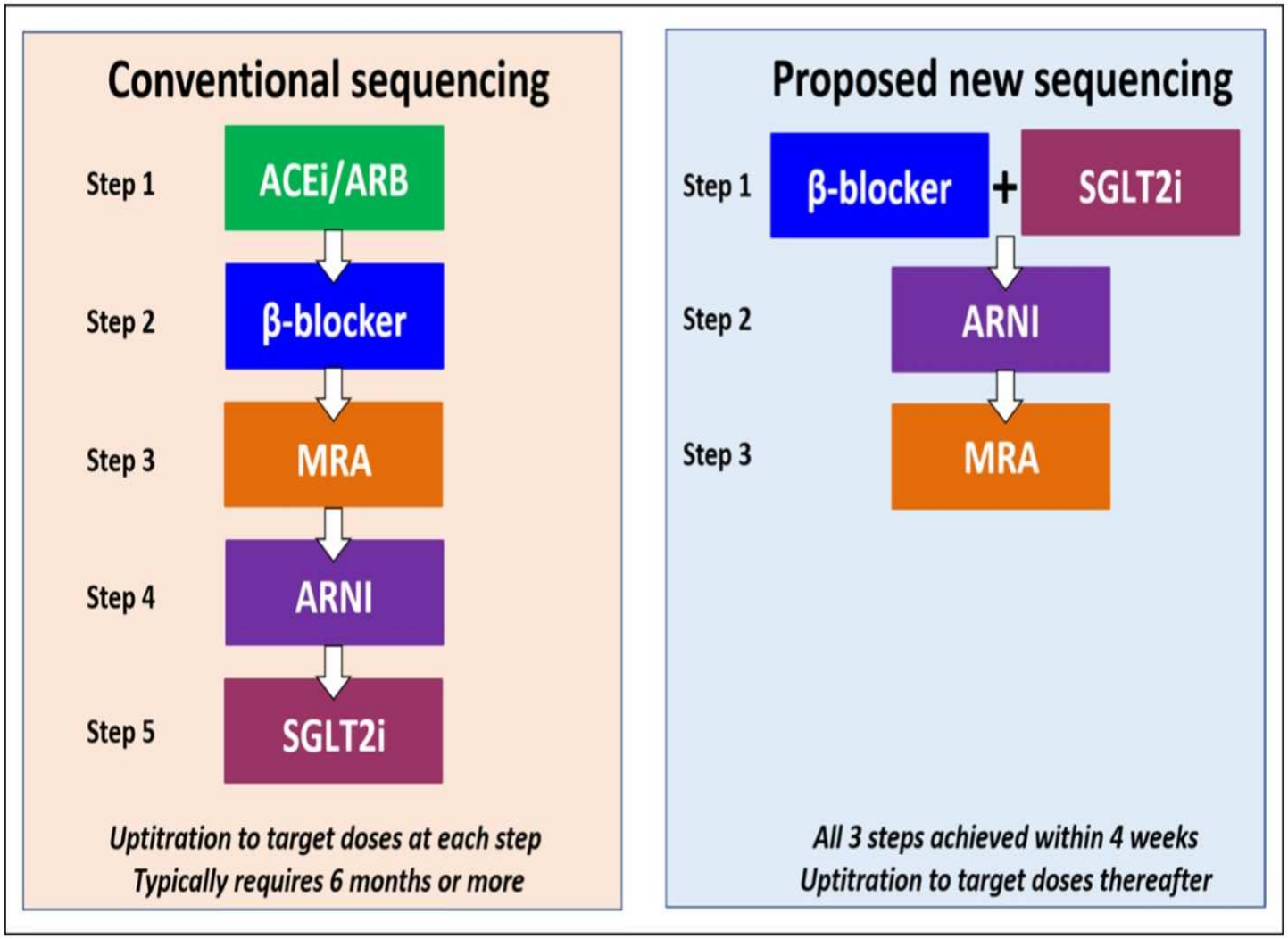
What people are talking about: how best to prescribe?



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McMurray and Packer, Circulation 2021

CONCLUSIONS

- Implementation of meds for HFrEF is challenging because patient characteristics, including their physiological parameters and comorbidities, limit up-titration of lifesaving medications.
- Phenotyping may provide tailored therapy while using all drug classes proven effective in improving prognosis.
- These 4 classes of drugs should be started ASAP according to tolerability.
- A therapeutic algorithm should allowed flexibly and take into consideration that clinical phenotypes may change over time.
- Guidelines for HFrEF enable rapid implementation of all HF medications.

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Take home message

- The goal is for patients to receive as many disease-modifying treatments as soon as possible because studies have shown an incremental progressive benefit of intensive combination treatments

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