

**HFrEF:**  
**So Many Medications...**  
**So Much Expense...**  
**How to Prioritize**

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# Disclosures

- Presenter has no financial or professional disclosure

# Objectives:

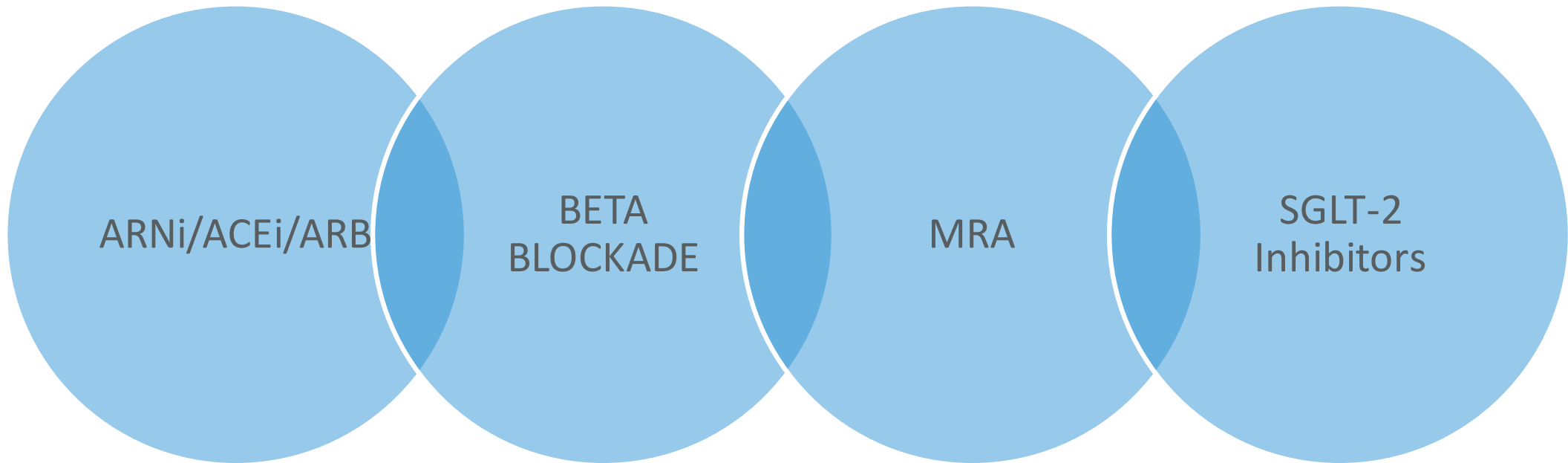
- Implement medication therapies for those with heart failure with reduced ejection fraction (HFrEF) in order to achieve maximal benefit.
- Create systems within your clinic or facility to utilize the multidisciplinary team in order to optimize individual regimens.
- Identify resources available to improve your patient's access to medications

# Optimal HFrEF Regimens

What should we be working towards?



# 2022 ACC/AHA/HFSA Heart failure Treatment Guidelines: Optimal GDMT



For all medication classes above:

| COR | LOE | Value    |
|-----|-----|----------|
| 1   | A   | High (A) |

# Guidelines: Class IA GDMT

|                   | Agents   | Target Dose                              |
|-------------------|--|--|
| ARNI              | Sacubitril-Valsartan                             | 97-103mg BID                             |
| ACEi              | Enalapril<br>Lisinopril<br>Ramipril              | 10-20mg BID<br>40mg daily<br>10mg daily  |
| ARB               | Losartan<br>Valsartan<br>Candesartan             | 150mg daily<br>160mg BID<br>32mg daily   |
| Beta-blocker      | Carvedilol<br>Metoprolol succinate<br>Bisoprolol | 25-50mg BID<br>200mg daily<br>10mg daily |
| MRA               | Spirolactone<br>Eplerenone                       | 25mg daily<br>50mg daily                 |
| SGLT-2 inhibitors | Dapagliflozin<br>Empagliflozin                   | 10mg daily<br>10 mg daily                |

# Renin-Angiotensin System Blockade

## Angiotensin Receptor – Neprilysin Inhibitors (ARNi)

- First line therapy for those with HFrEF
- De-novo initiation or as escalation of therapy

## Angiotensin-Converting Enzyme Inhibitors (ACEi)

- First line in those who do not tolerate ARNI or if cost is a limitation
- Do not use if history of angioedema

## Angiotensin-II Receptor Blockers (ARB)

- Agents of choice when ARNI and ACEi cough or angioedema develop

# ARNi – Not just for your outpatients

## PIONEER-HF

- Question: is ARNi initiation in-hospital safe/effective vs ACEi?
- At 4- and 8-week evaluation:
  - ARNi showed significantly lower NT-pro BNP vs ACEi
  - ARNi < HF rehospitalization  
0.56(0.37-0.84)
  - ARNi < composite of serious clinical events  
0.54(0.37-0.79)

## TRANSITION Trial

- Question: is it safe to initiate ARNi in-hospital vs as outpatient?
- By 10 weeks post-discharge:
  - No difference in tolerability
  - No difference in rate of achieving 97/103 dose

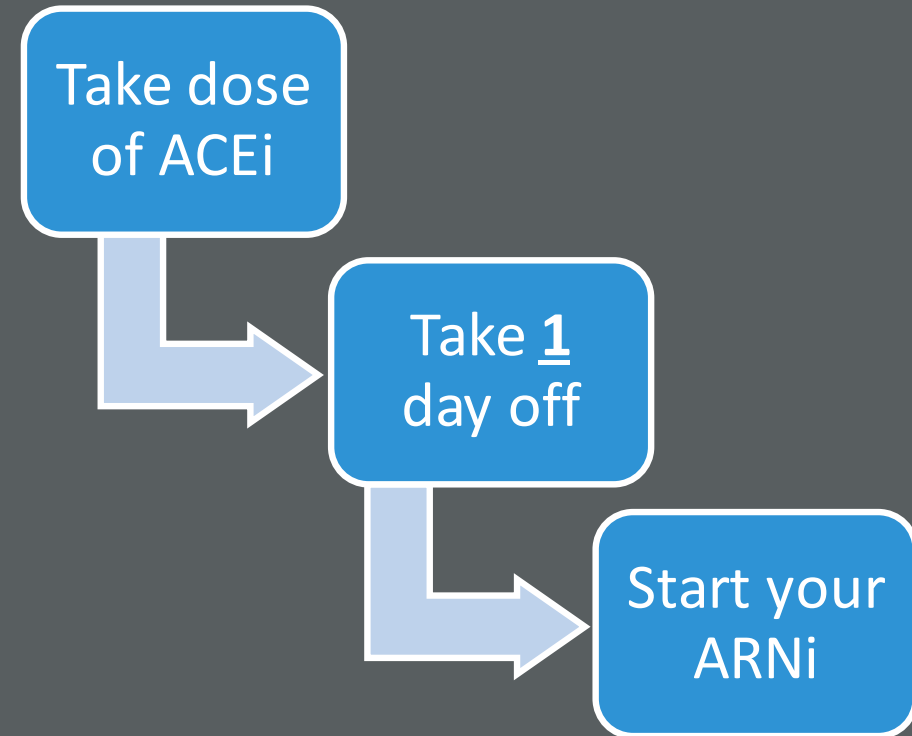


# Transitioning: ACEi → ARNi

## Cost:

- Drug cost ARNi \$\$\$ vs \$ with ACEi
- US incremental cost-effectiveness ratio (ICER) \$45,017
  - QALY Threshold in US: \$50,000-\$100,000
  - Similar results found throughout Europe & Asia

## Logistics: 36 hr washout



# RAS Blockade: Nuances & Pearls

## ARNi

- Diuretic effect
- More hypotension
- May cause SrCr increase
- May increase uric acid
- Bradykinin cough possible

## ACEi

- Bradykinin cough possible
- May cause SrCr increase
- Daily dosing possible

## ARB

- May cause SrCr increase
- No effect on bradykinin
- Daily dosing possible, but BID dosing recommended
- Many recent drug shortages

# Beta Blockade (BB)

## Benefits:

- Decreased myocardial oxygen demand
  - Less myocardial remodeling
  - Reduced catecholamine-induced myocardial necrosis
- Protects against arrhythmias
- Reduced risk of death or hospitalizations

## Not a class effect!

- Differences in:
  - Receptor specificity
  - Duration of action
- Agents:
  - Carvedilol
  - Bisoprolol
  - Metoprolol Succinate

# BB titration: tricky but important

- **MOCHA Trial**: Significant, dose-related improvements in LV function & mortality (linear relationship)
  - Linear effect also seen with dizziness & bradycardia
- **CIBIS-II subgroup analysis**: Relative to doses  $\leq 3.75$ mg/day, doses  $\geq 5$ mg/day resulted in
  - Fewer all-cause or CV deaths, sudden death (10mg), and all-cause or CV hospitalizations
    - Higher doses did NOT see more med discontinuation

# Beta-blocker: Nuances & Pearls

Small changes, made frequently

Take at bedtime to minimize sleepiness

Carvedilol may have more BP effects

Exercise intolerance is temporary

Target doses save lives

Don't crush or quarter metoprolol succinate

# Mineralocorticoid Receptor Antagonists (MRA): The Forgotten Stars

Pathophysiologic benefits:

- Mild diuresis
- Block aldosterone-induced inflammation & injury
- Lower incidence of sudden cardiac death
- Decreased myocardial remodeling & fibrosis

| Trial       | Drug           | NNT* |
|-------------|----------------|------|
| RALES       | Spirolonactone | 9    |
| EPHESUS     | Eplerenone     | 30   |
| EMPHASIS-HF | Eplerenone     | 19   |

\*To prevent 1 death or hospitalization

# MRA's: Nuances and Pearls

## For most, starting dose is target dose

- Half-dose recommended when SrCr >1.8 to control for possible hyperkalemia

## Monitor potassium closely

- Potentially mitigated with concomitant SGLT-2 use
- Consider potassium binding agents

## Blood pressure minimally affected in HF trials

- RALES (NS  $\Delta$ ), EPHESUS ( $\uparrow$  5/3 mmHg vs  $\uparrow$  8/4 mmHg w/placebo), EMPHASIS-HF ( $\downarrow$  2.5 mmHg vs  $\downarrow$  0.3 mmHg)

## Spironolactone stimulates prolactin release

- Gynecomastia
- Abnormal menstrual cycles
- Infertility

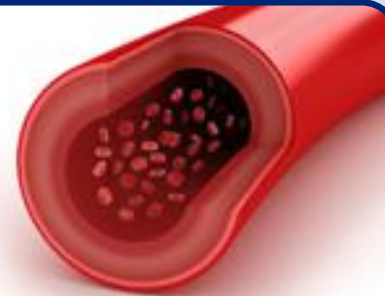
# SGLT-2 Inhibitors: Not just diabetic drugs



Improved energy metabolism  
Decreased NLRP3 Inflammation  
Improved cardiac remodeling  
Decreased ischemic & reperfusion injury  
Less oxidative stress  
Less epicardial fat mass



Increased natriuresis/diuresis  
Decreased blood glucose  
Decreased hyperuricemia  
Improved energy metabolism  
Inhibited  $\text{Na}^+/\text{H}^+$  exchange



Decreased Inflammation  
Decreased blood pressure  
Increased pro-vascular progenitor cells  
Improved vascular function



Increased weight loss  
Inhibited SNS  
Increased Erythropoietin

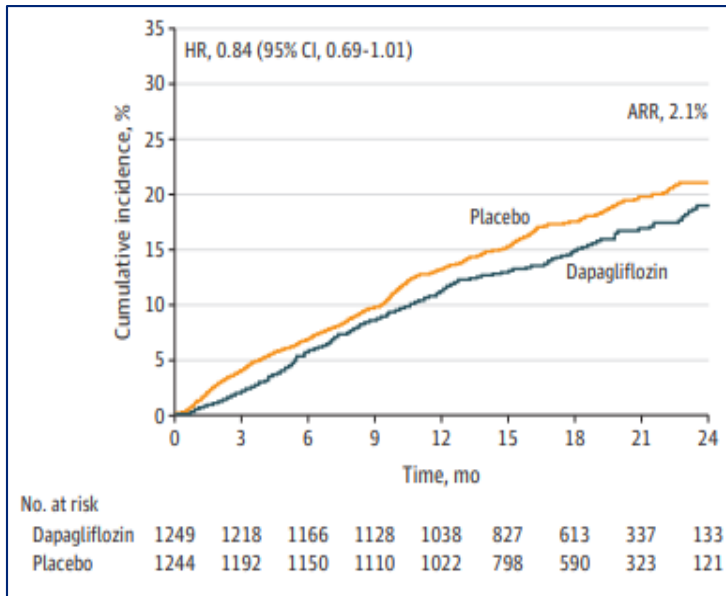


# SGLT-2 inhibitors – Sooner is better

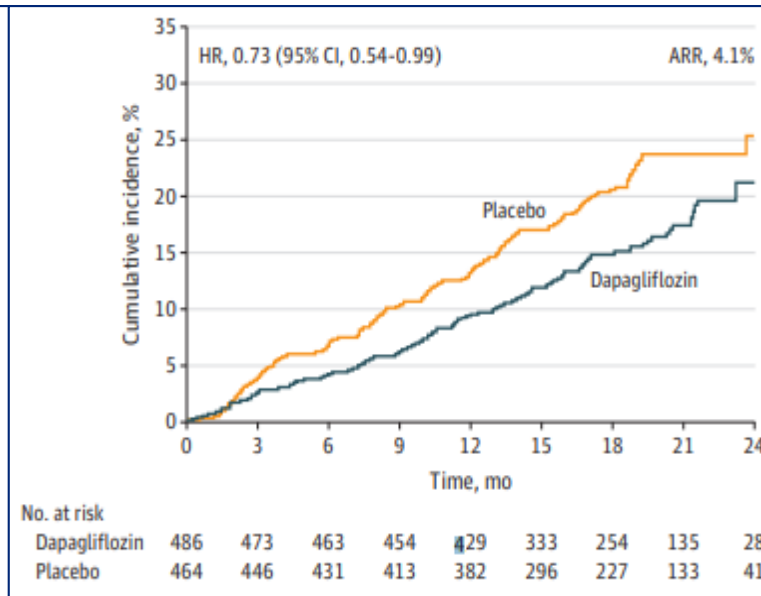
## DAPA-HF

- Composite death or worsening HF – significantly better @28 days
  - Benefit stronger in those with prior hospitalizations

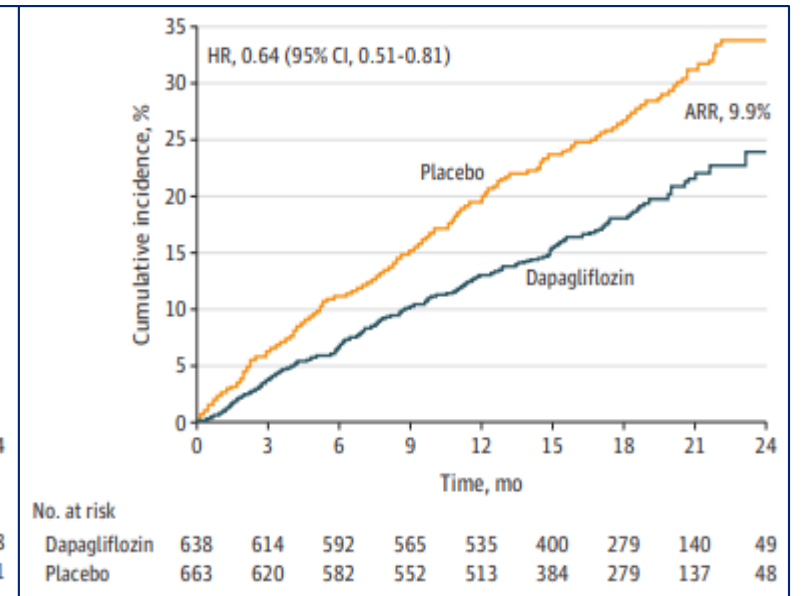
Never hospitalized



Hospitalized  $\geq 12$  months ago



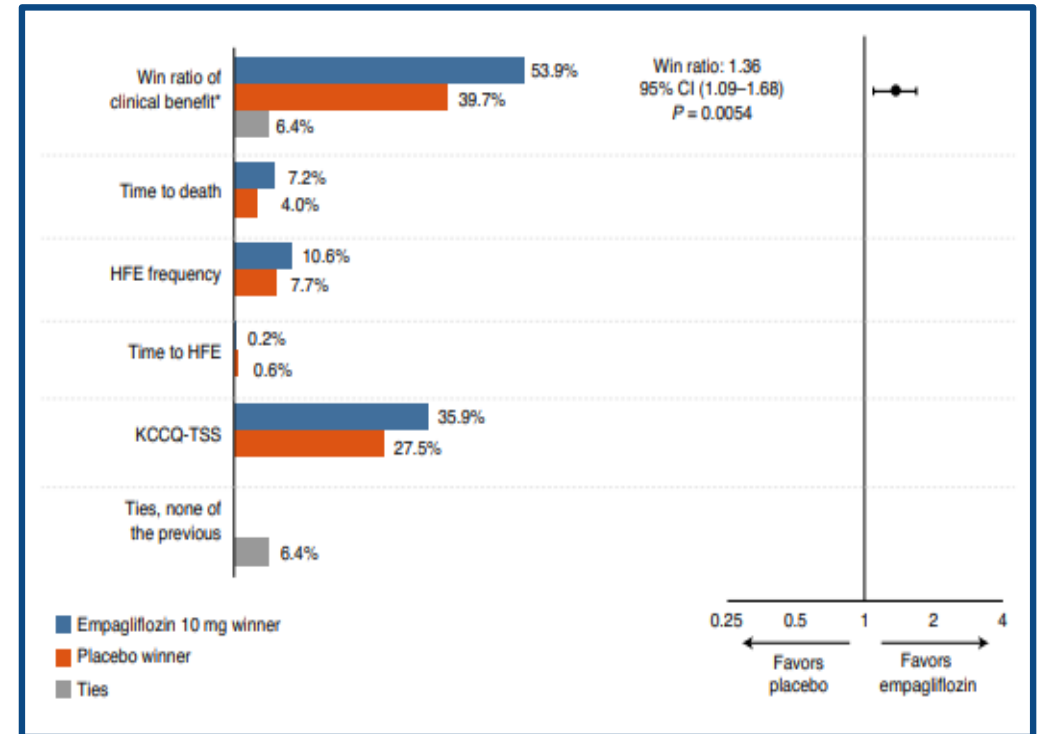
Hospitalized  $\leq 12$  months ago



# SGLT-2 inhibitors: start in the hospital

## EMPULSE Trial

- Hospitalized for de novo or decompensated HF
- Empagliflozin showed:
  - Longer time to death
  - Longer time to HF exacerbation
  - More improvement in KCCQ-TSS
- Safety:
  - No ketoacidosis
  - No difference in blood pressure
  - Less acute renal failure
  - No difference in UTI
  - Greater increase in Hg/HCT



# SGLT-2 inhibitors: Nuances and Pearls

Diuretic properties – consider adjusting other diuretics

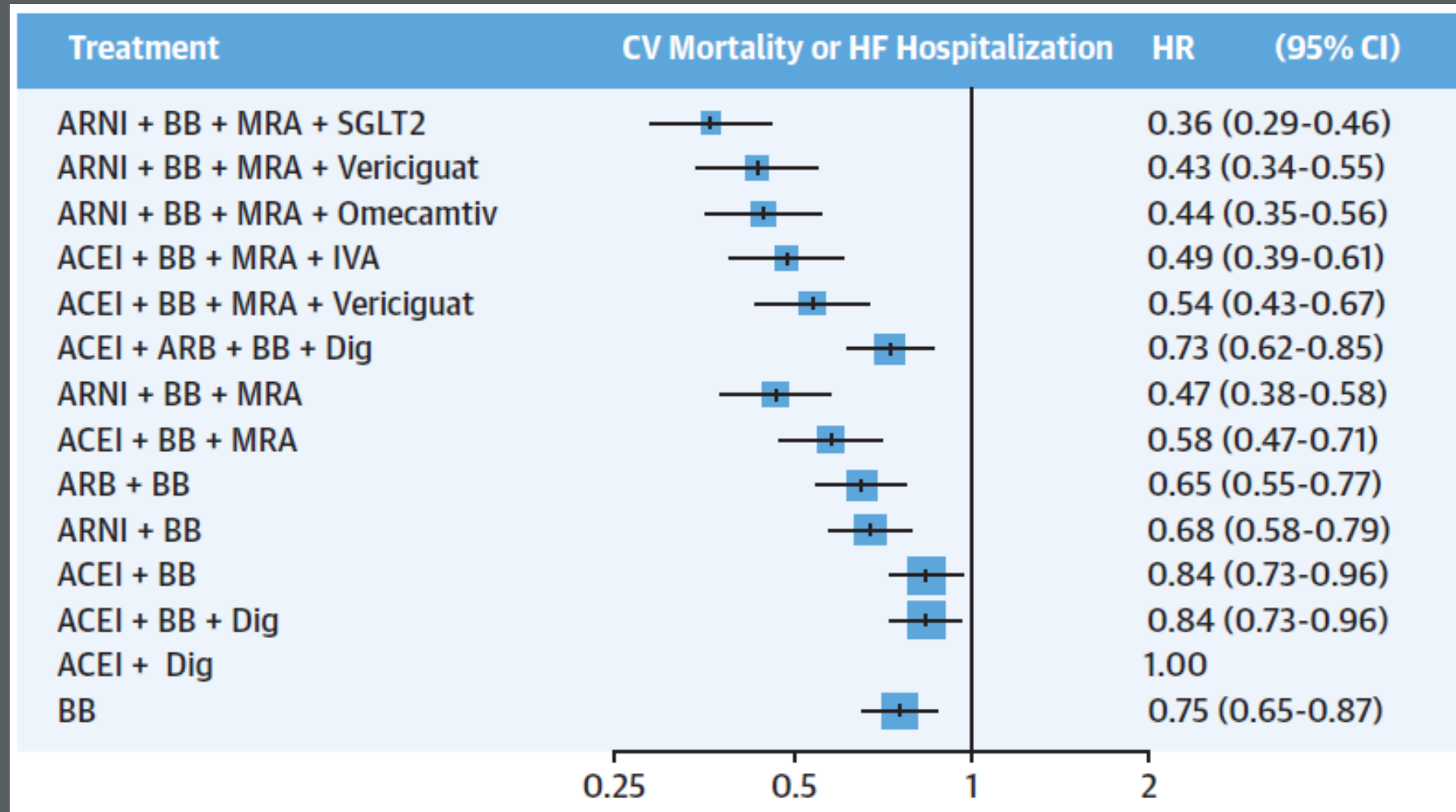
Mitigates adverse effects from other agents: hyperkalemia, hyperuricemia

Genitourinary infections – counsel about hygiene & symptom surveillance

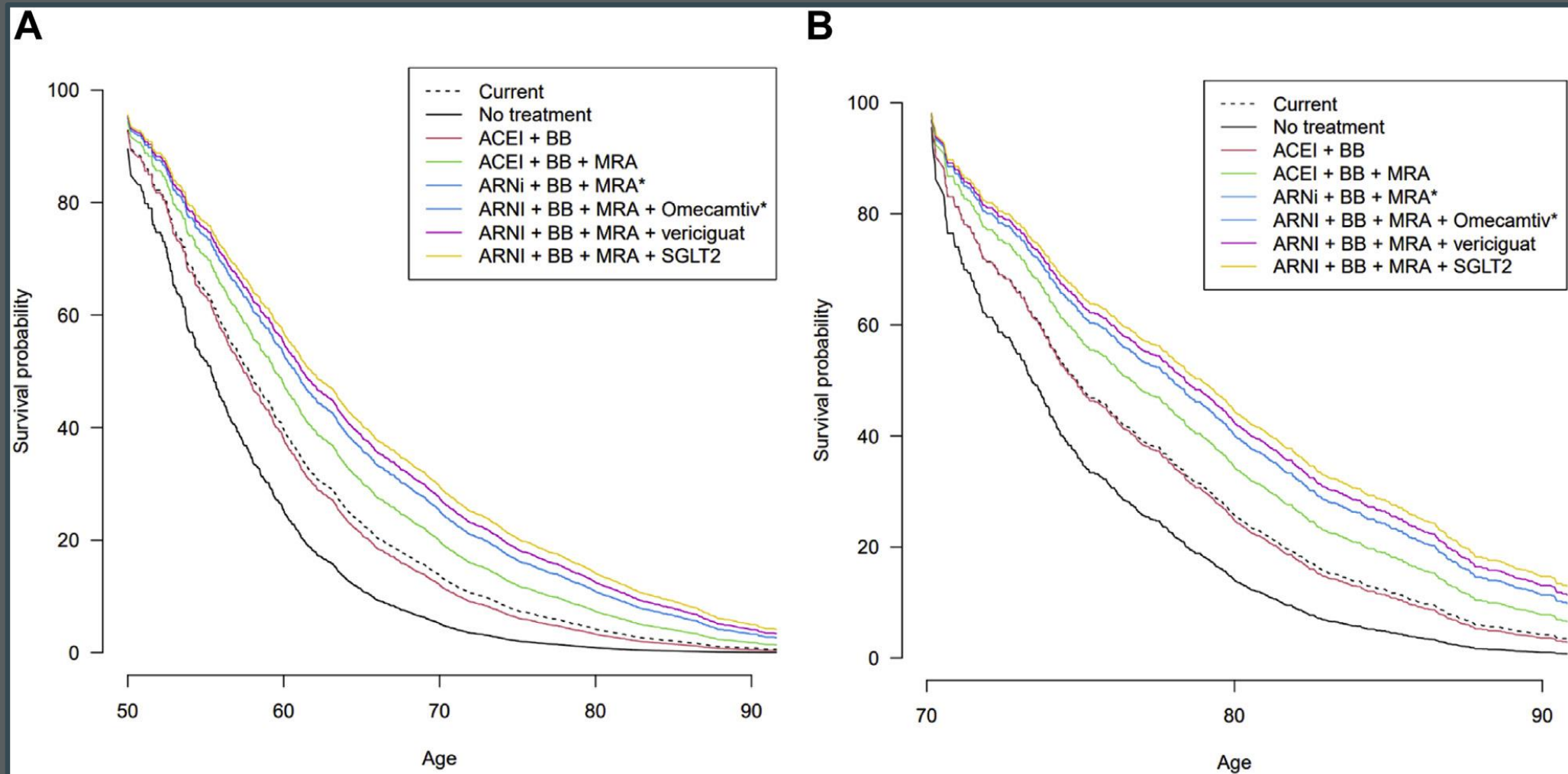
Benefits seen early after initiation, especially in those with recent hospitalizations

Euglycemic DKA not reported in non-diabetics. Hold in DM for major surgeries or when ill

# The Power of Combination Therapy:



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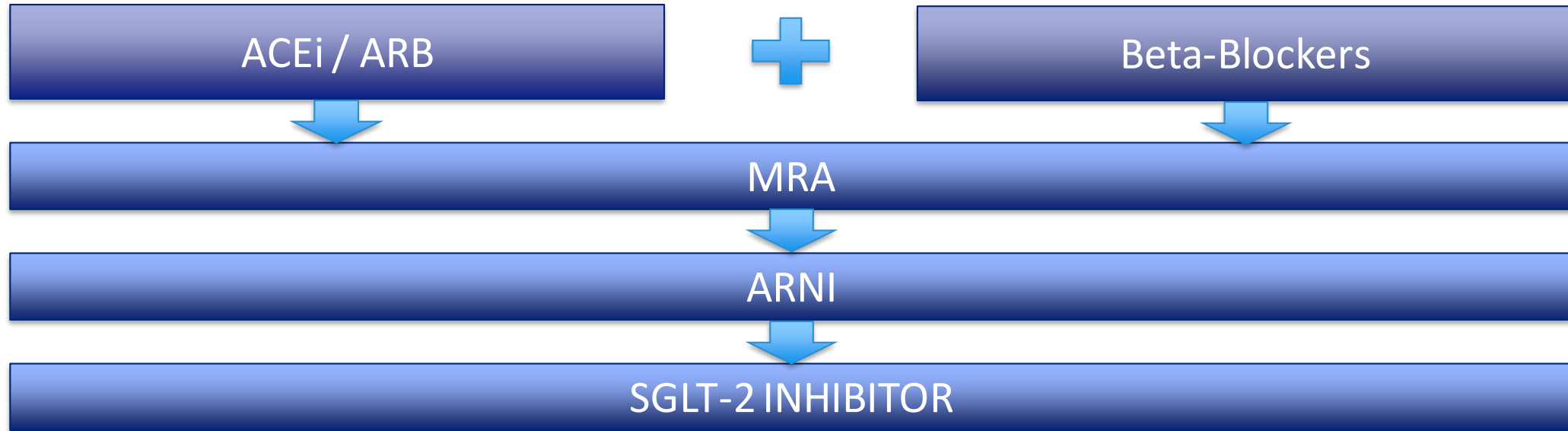


# The art of medication titration

How do we get them all started?



# Conventional GDMT Titration



## General titration approach:

- Initiate patients on 1-2 agents, titrating doses every 2 weeks as tolerated until at goal dose
- Once ACEi/ARB and BB at goal, initiate MRA
- If still symptomatic, switch ACEi/ARB to ARNI
- Consider adding SGLT-2 Inhibitor

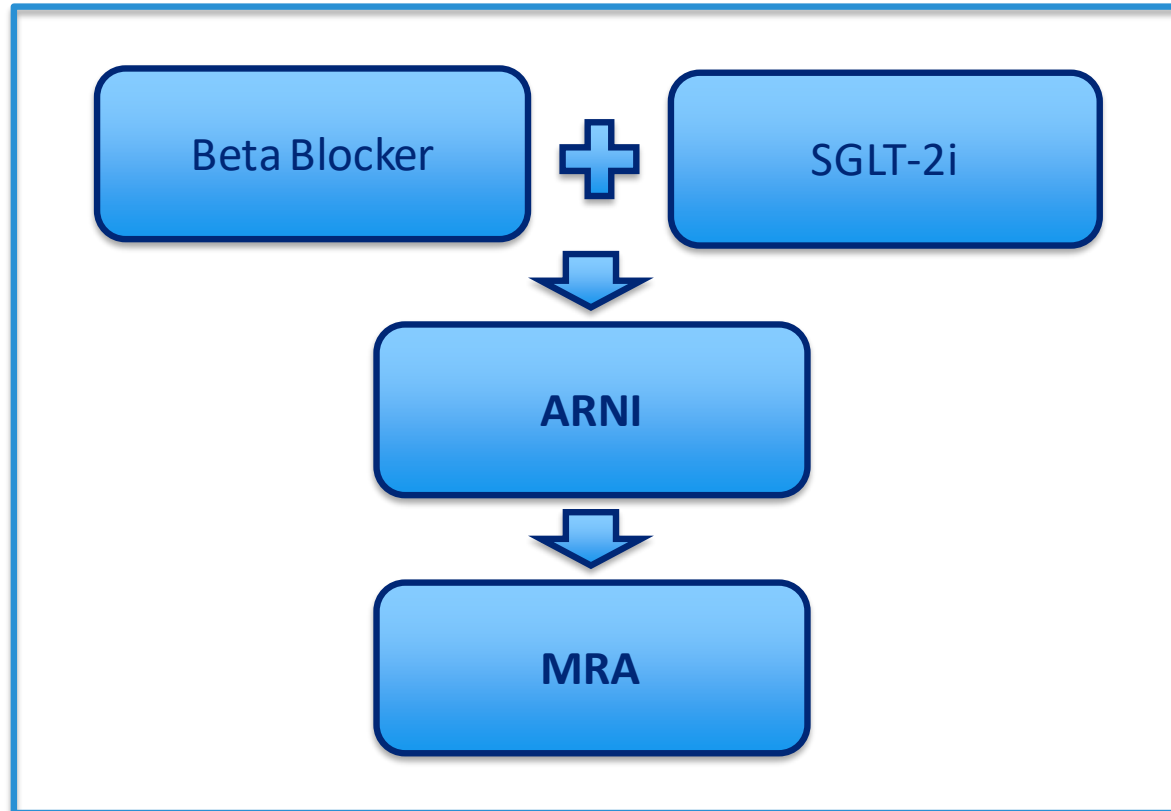
# Accelerated Titration – Hospital Setting

| Early Relative Risk Reduction             |            |                  | Initiation and optimization of medication dosing |                 |                 |                 |  |
|---|------------|------------------|--|-----------------|-----------------|-----------------|--|
| Outcomes                                  | Change (%) | Drug Class       | Day 1  | Day 7-14        | Day 14-28       | Day 21-42       | > Day 42                               |
| CV Death or HF hospital                   | -42        | ARNI             | Initiate (low dose)                              | Continue        | Titrate as able | Titrate as able | Maintain or titrate all 4 classes      |
| Death                                     | -25        | B-Blocker        | Initiate (low dose)                              | Titrate as able | Titrate as able | Titrate as able | Consider EP device<br>MVR if indicated |
| CV Death or HF hospital                   | -37        | MRA              | Initiate (low dose)                              | Continue        | Titrate as able | Continue        | Add-on therapies if refractory         |
| CV Death, ER visit for HF, or HF hospital | -58        | SGLT-2 Inhibitor | Initiate   | Continue        | Continue        | Continue        | Manage comorbidities                   |



# Accelerated Titration – Clinic Setting

Achieve in 3 weeks:



Titrate to your patient:

- Volume overloaded: SGLT-2i, ARNI, MRA
- Dry: consider lower doses SGLT-2 & MRA
- h/o arrhythmias: BB, MRA
- Chronic kidney disease: start lower dose MRA

# Identifying Barriers to Care

## Psychosocial Barriers

- Financial burden of therapy
- Food insecurity
- Housing insecurity
- Intimate partner or elder abuse
- Language barriers
- Low health literacy
- Low social support
- Transport limitations

## Medical Barriers

- Cognitive impairment
- Depression
- Substance use disorders
- Frailty

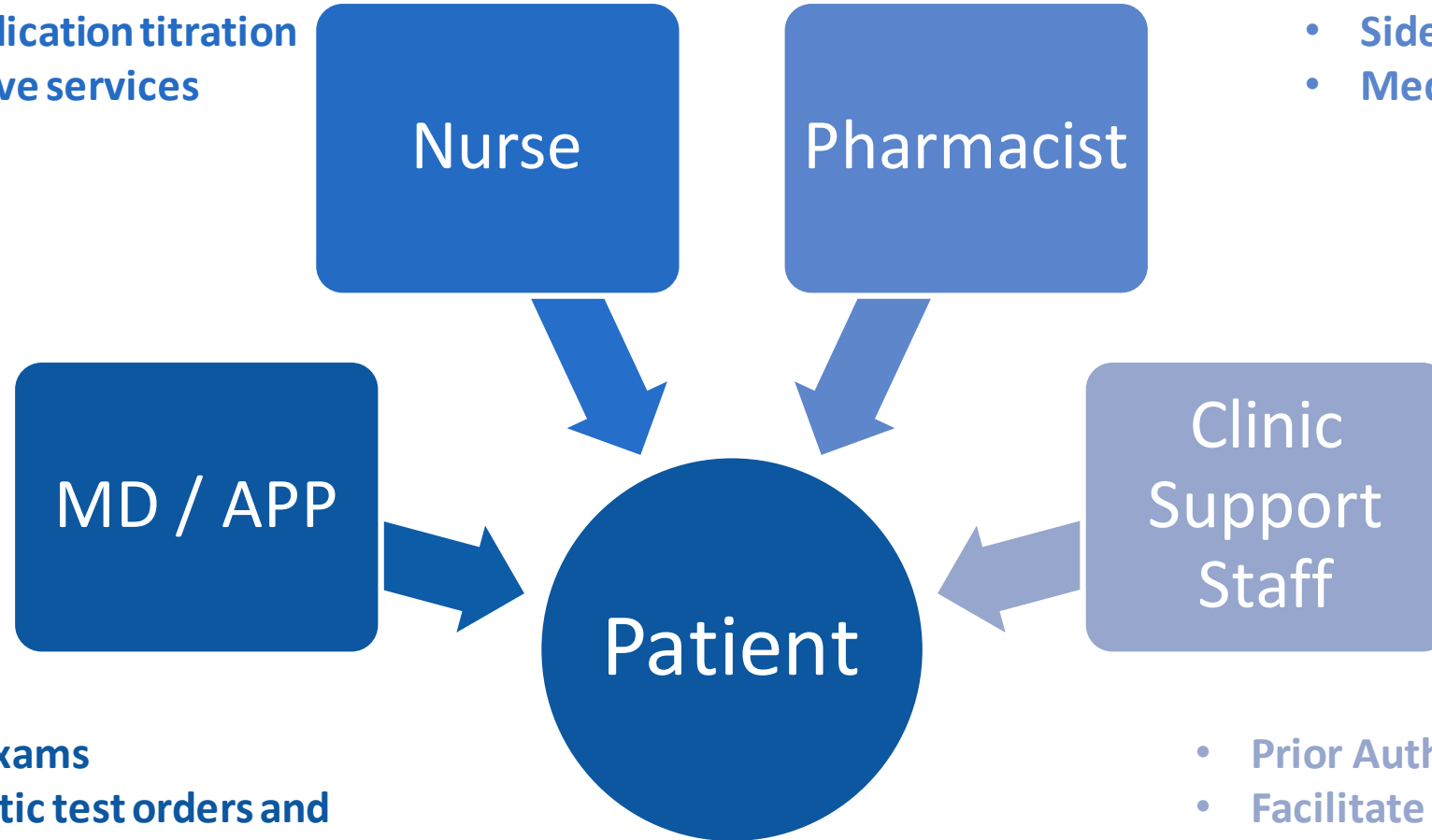
Caring for those with heart failure only STARTS with good medications

# Limited office time: How is this achieved?



- Disease state education
- Periodic symptom assessment
- Protocolized medication titration
- Arrange supportive services

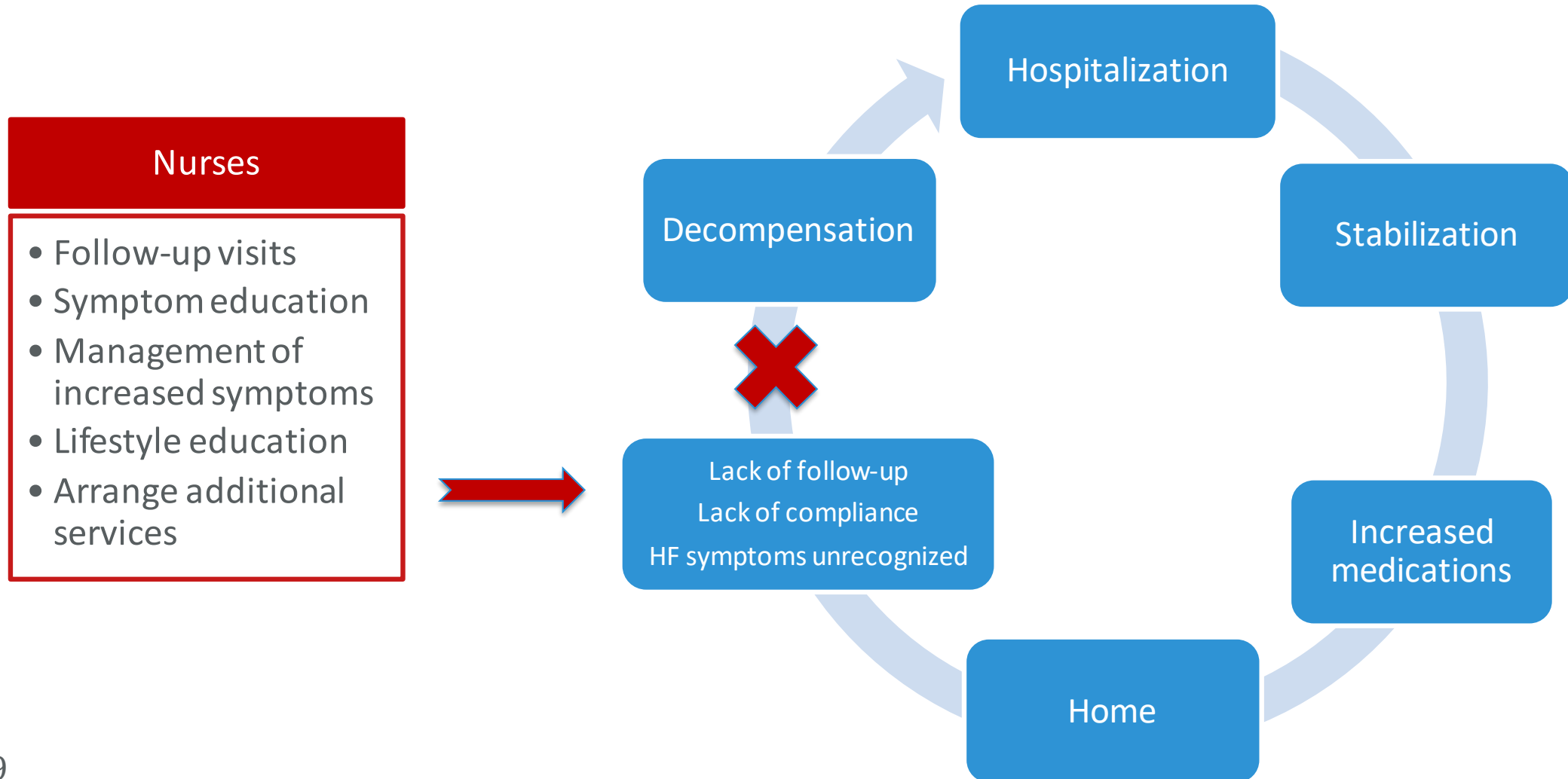
- Medication Access
- Dose titration clinics
- Side effect management
- Medication education



- Office Exams
- Diagnostic test orders and interpretation
- Prescribing
- Coordination with care team

- Prior Authorizations
- Facilitate refills
- Assistance program applications
- Triage/escalate care

# Role of the Heart Failure Nurse



# Nurse-driven protocols

Compared to usual care, patients managed via nurse-led titration (NLT):

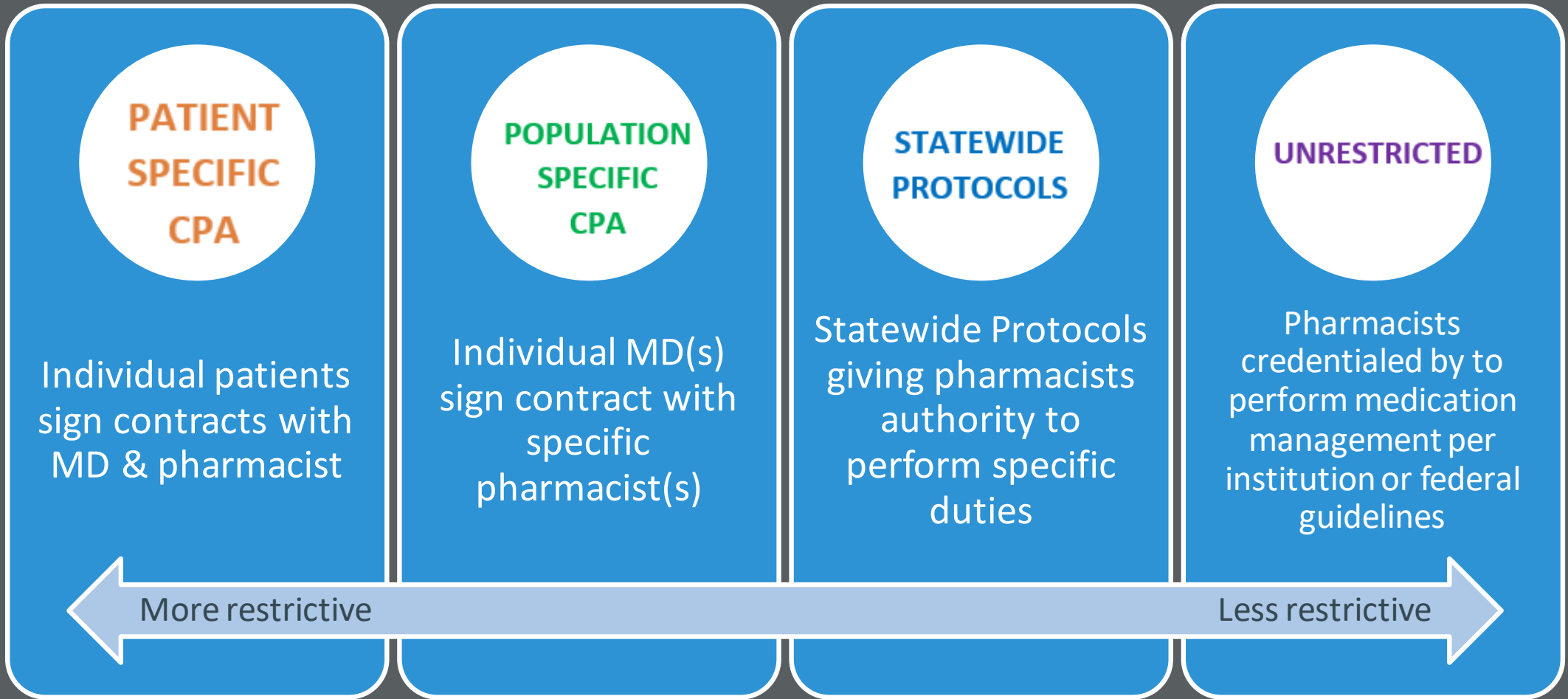
- Achieved target dose BB in half the time
- Had fewer hospitalizations
  - All-cause hospitalizations: RR 0.80 (0.72 – 0.88)
  - HF hospitalizations: RR 0.51 (0.36 – 0.72)
- Lower all-cause mortality: RR 0.66 (0.48 – 0.92)
- Improved all-cause event-free survival: RR 0.6 (0.46 – 0.77)

# Pharmacists: no longer hiding behind the counter

## Unique training with a different focus

- Medication reconciliation
- Patient-tailored medication selection
- ID drug-drug, drug-disease, drug-lab interaction
- Patient and medical staff medication education
- Medication monitoring and adjustment
- Side effect identification and management
- Improving access and affordability of medications
- Treatment protocol development

# Pharmacist Prescribing





# Office Support Staff – Our Everyday Heroes

Triage patient  
communications

Arrange refills

Prior  
Authorizations

Assist in  
medication  
reconciliation

Complete  
applications for  
services/meds

Aid in coordination  
of care with other  
providers

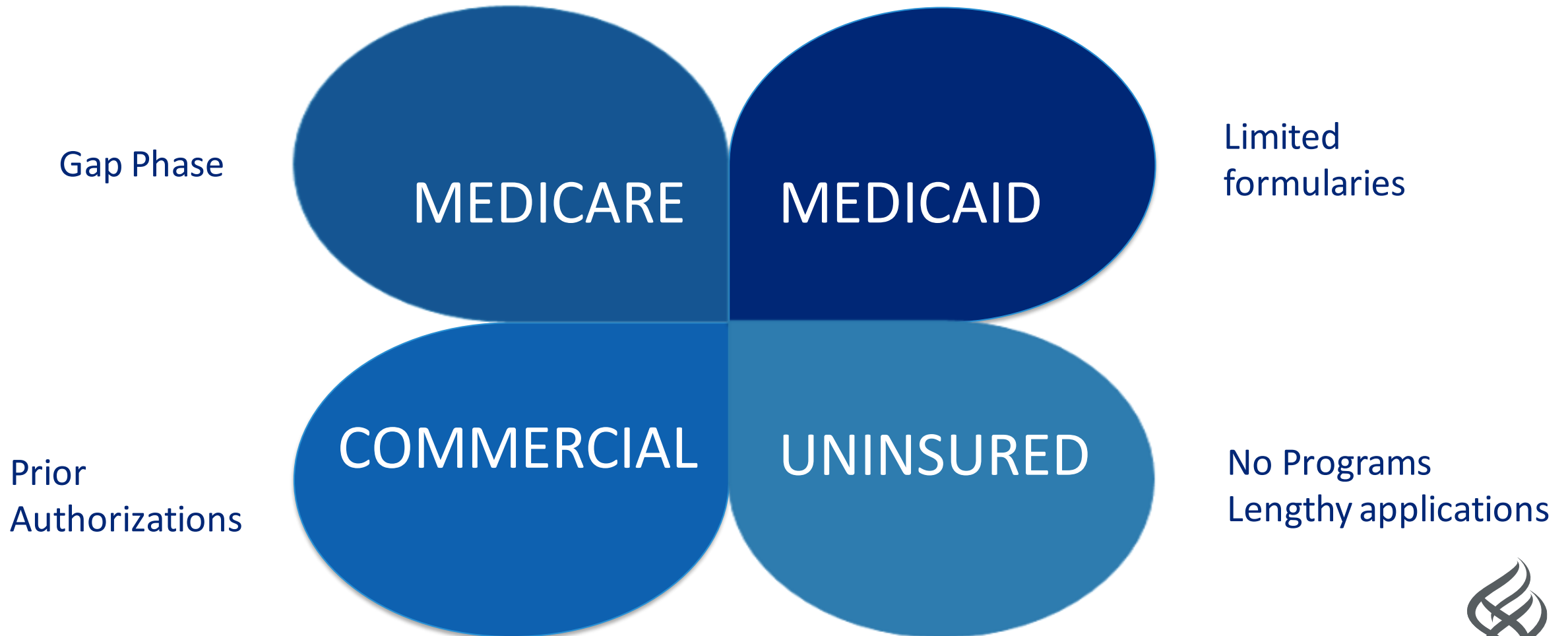
Contact patients to  
maintain  
healthcare  
engagement

# Oh but the costs...

Understanding the costs and finding support where available



# Hurdles to Medication Access



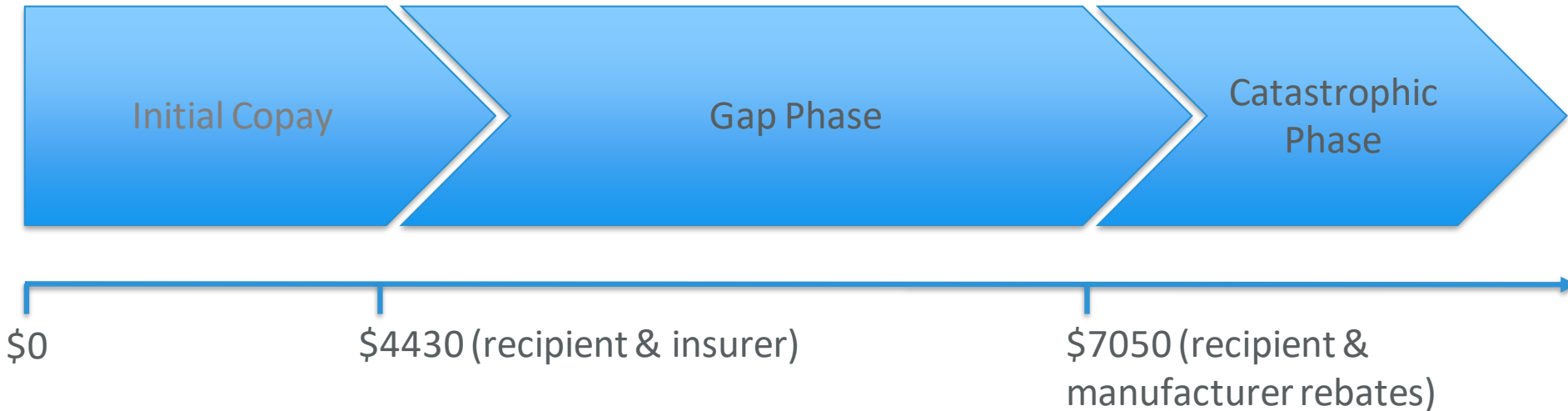
# Prior Authorizations (PA)

- Intended to improve prescribing appropriateness to decrease overall healthcare costs
  - Requirements often unknown
  - Process varies by payor
  - Cost considerations are a primary qualifier for the PA process
    - Guideline directed first-line therapies often require a PA
- ~300 million PA requests are generated annually in the US
  - In 2019, the administrative costs related to PA completion was \$528 million
  - ~36% of these prescriptions will never be filled by patients

## Ways to decrease PA barriers:

- Decrease volume required by insurers
- Publish requirements
- Automated or electronic PA process

# Medicare Part D



Complicated structure intended to minimize costs

- Initial fixed copays, which also often include an annual deductible (\$480 in 2022)
- Gap phase (“donut hole”) – copays increase to 25% of the drug + dispensing cost
  - Generic and brand name drugs accrue “out-of-pocket” amounts differently
- Catastrophic phase – copays drop to 5% of the drug + dispensing cost

# Medicare Part D – Decreasing costs in the coverage gap

1. Change to generic medications
2. Choose a Part D plan that has additional gap coverage
3. Manufacturer Assistance Programs
4. State Pharmaceutical Assistance Programs
5. Apply for Extra Help

# Medication Assistance Programs

## Copay cards

- Available only for brand name drugs (including Entresto, Farxiga, Jardiance)
- Only those with commercial insurance qualify
- Not a substitute for insurance

## Manufacturer Assistance Programs

- Requires annual re-application
- Specific, variable enrollment criteria
- Open to those without insurance or unaffordable copays

## 3<sup>rd</sup> Party Grants

- Requires annual re-application
- Specific, variable enrollment criteria
- Open to those with unaffordable copays

# 340B Drug Pricing Programs

## Facilities that qualify:

- Disproportionate share hospital
- Sole community hospital
- Rural referral center
- Children's hospital
- Free-standing cancer hospital

## What it does:

- Enables facility to acquire medications from manufacturer at a greatly reduced cost

## How this helps patients:

- Facility able to provide medications to their outpatients at a very reduced cost



# Take Home Points

Four-drug therapy initiated early and titrated frequently reduces heart failure morbidity and mortality

Healthcare is a team sport: engage each member of the team to provide more efficient and effective care

Medication costs are a frequent limitation to optimal heart failure care. Know how to identify and overcome barriers to access.

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