PHARMACY VISION 2020

CSHP SEMINAR 20 • OCTOBER 21-25

Disneyland RESORT

Translating guidelines: Tricks and Tips to Optimize Drug Therapies for Heart Failure with Reduced Ejection Fraction

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DISCLOSURE

No potential conflict of interest

Learning Objectives

- Examine the new American College of Cardiology heart failure guidance to identify gaps in clinical practice.
- Evaluate real-world and trial data in translation of guidelines.
- Identify challenges associated with dose up-titration of heart failure medications.
- Design individualized strategies to optimize drug therapy in heart failure patients.

CASE 1

MJ is a 55 Y/O WM who presents to the HF clinic with a new diagnosis of heart failure with reduced ejection fraction (HFrEF), ejection fraction (EF) 30%, and NYHA class II.

Medications	PMH
Enalapril 5mg twice daily Carvedilol 12.5mg twice daily Furosemide 60mg daily Rosuvastatin 5mg daily	Diabetes Osteoporosis CAD HLD
Vitals	**Labs**
BP 138/77 mmHg HR 70 bpm	Scr 2.0mg/dl (bumped from 1.7mg/dl) BUN 25mg/dl K 5.2 mEq/L

What should be the next step?

ACEi/ARB in Renal Impairment

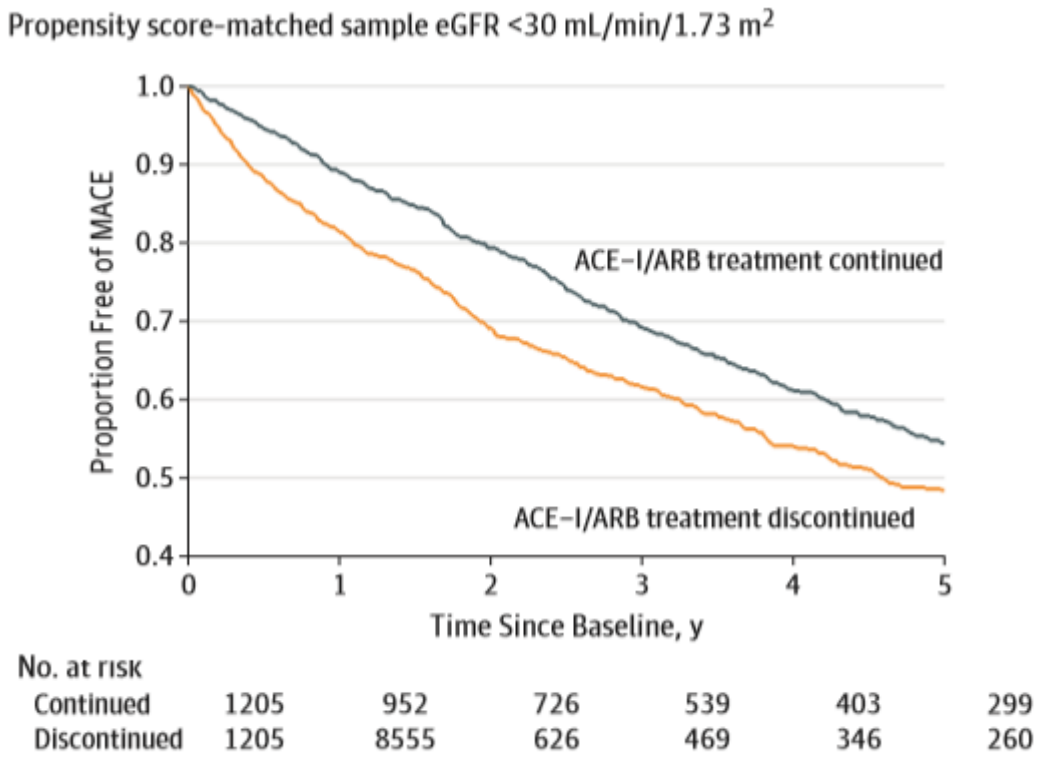
Generally considered safe when:

- SCr <3.0 mg/dL
- Renal impairment (eGFR 30-60 mL/min/1.73m^2)

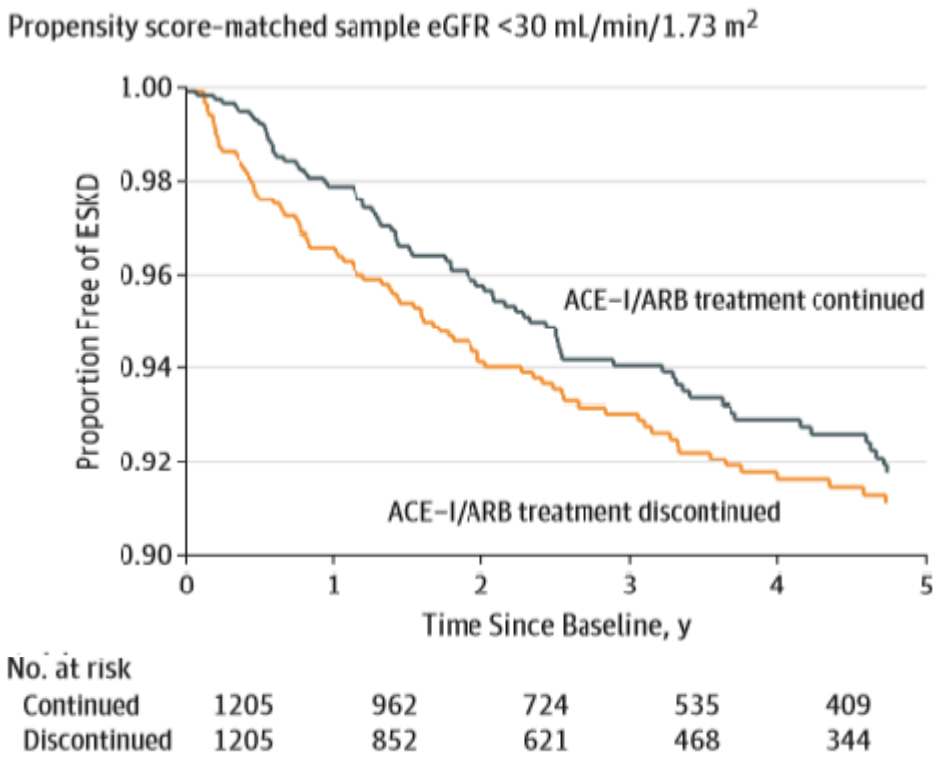
Should we stop ACEi/ARB in CKD stage 4 and 5?

CONTINUING ACEi/ARB IN SEVERE RENAL DYSFUNCTION

Cumulative Incidence of Major Adverse Cardiovascular Events (MACE)



Cumulative Incidence of End-stage Kidney Disease (ESKD)



Qiao Y, Shin J, Chen TK, et al. JAMA INTERN MED.2020.

CONSIDERATIONS WITH RENAL DYSFUNCTION

- A fall in eGFR (and rise in creatinine) is very common after initiation of RAAS inhibitors but usually stabilizes.
- The initial rise in creatinine is usually not due to intrinsic kidney injury but to a change in hemodynamics.
- A moderate, asymptomatic decline in renal function is not an indication to stop RAAS inhibitors.
- A progressive fall in eGFR on RAAS inhibition suggests careful search for potentially reversible causes of renal decline.

RECOMMENDATIONS FOR RAAS INHIBITORS

Change in renal function compared with baseline	HFrEF
Increase in serum creatinine by <30%	Continue unless symptomatic hypotension.
Increase in serum creatinine 30% - 50%	Consider reducing dose or temporary withdrawal.*
Increase in serum creatinine > 50%	Temporarily stop RAAS inhibitor *
Severe renal dysfunction, for example, eGFR < 20	Stop RAAS inhibitor if symptomatic uremia irrespective of baseline function

*Reinitiate and/or re-titrate when renal function improved in patients with HFrEF

Clark AL, et al. Heart. 2019.

SACUBITRIL/VALSARTAN: PLACE IN THERAPY

HFrEF Stage C Treatment

↓

ACEi/ARBs and beta blockers with diuretic as needed

↓

For patients stable on ACEi/ARB, NYHA class II-III

↓

Switch

↓

ARNI*

ARNI*

Prior to initiation:
- 36 hours wash out period with ACEi
- Adequate blood pressure
- eGFR ≥ 30 ml/min/1.73m^2

↓

Starting dose based on prior dose of ACEi/ARB:
- 24/26 mg or 49/51 mg twice daily
- Target dose: 97/103 mg twice daily

↓

- In 2-4 weeks, assess tolerability
- Increase dose to target
- Monitor: blood pressure, electrolytes, and renal function both after initiation and during titration

Yancy et al. JACC. 2017.

*angiotensin receptor neprilysin inhibitor (ARNI)

COMMON CLINICAL SCENARIOS

Scenario 1: *When to initiate ARNI?*

In persistently symptomatic patients who tolerate an ACEi or ARB, switching to an ARNI

Scenario 2: *Initiation of an ARNI de novo without prior exposure to ACEi or ARB*

"Accept the uncertainty about effectiveness and safety as well as potentially greater out-of-pocket costs, de novo initiation of ARNI with close follow-up and serial assessments (blood pressure, electrolytes, and renal function) might be considered"

Scenario 3: *Is use of aldosterone antagonist mandatory prior to using ARNI?*

Not mandatory prior to changing a patient to ARNI

Yancy et al. JACC .2017

ALDOSTERONE ANTAGONISTS (AA)

HFrEF Stage C Treatment

ACEi/ARBs and beta blockers with diuretic as needed

NYHA class II-IV
- eGFR ≥ 30
  - Men: SCr ≤ 2.5 mg/dL
  - Women: SCr ≤ 2.0 mg/dL
- K < 5.0 mEq/L

Add

AA

AA

Select initial dose

- Titrate doses every 2 weeks until maximum tolerated or target dose is achieved
- Monitoring: electrolytes (especially potassium) and renal function in **2-3 days** and 7 days after initiation/titration
- Then, check monthly for 3 months and every 3 months afterwards

Yancy et al. JACC.2017

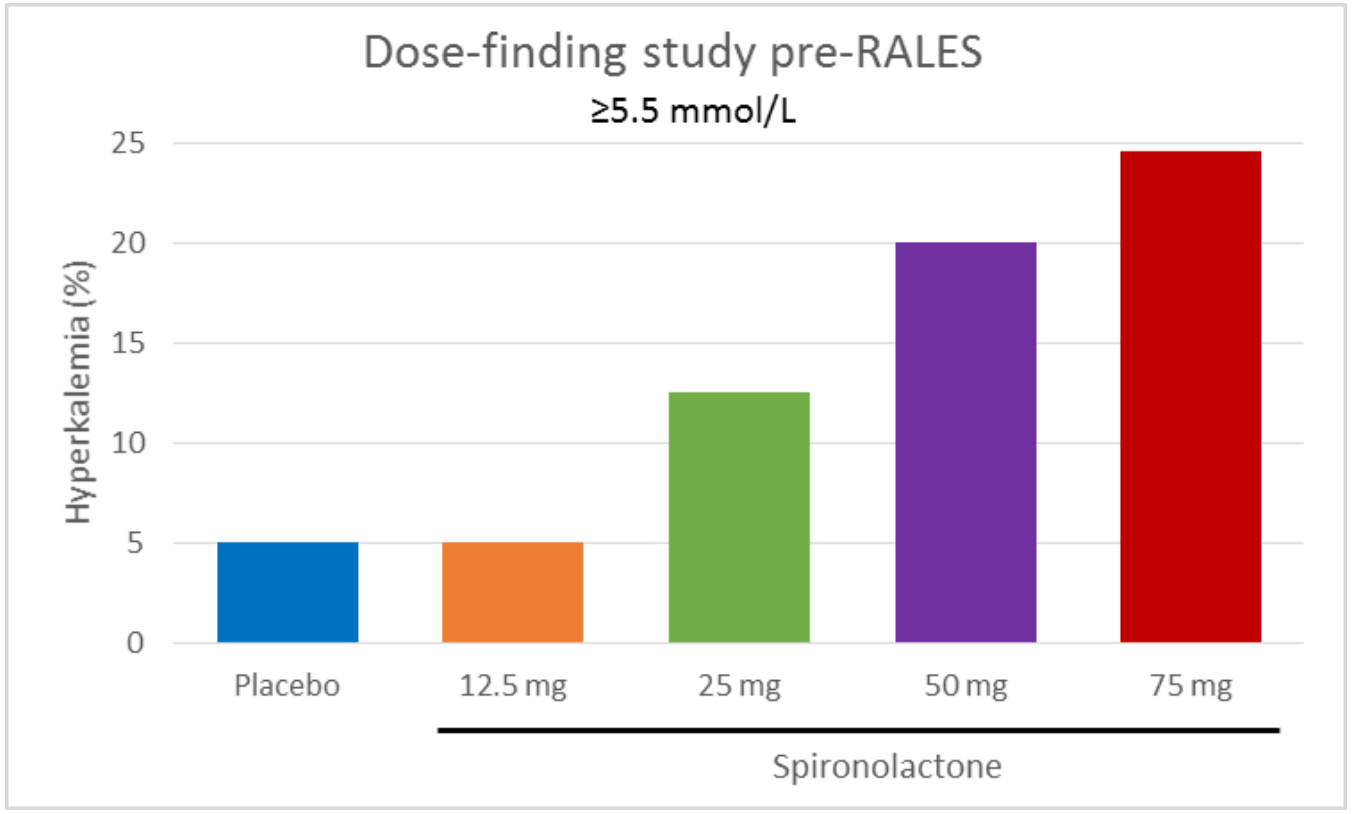
ALDOSTERONE ANTAGONIST MONITORING

Appropriate follow-up laboratory testing across all time periods occurred in 25.2% of patients with inpatient initiation compared with 2.8% of patients begun as an outpatient. Patients with chronic kidney disease had higher rates of both hyperkalemia and acute kidney failure in the early (1.3% and 2.7%, respectively) and extended (5.6% and 9.8%, respectively) post-initiation periods compared with those without chronic kidney disease.

Cooper BL, Hammill BG et al.Circ Cardiovasc Qual Outcomes. 2017

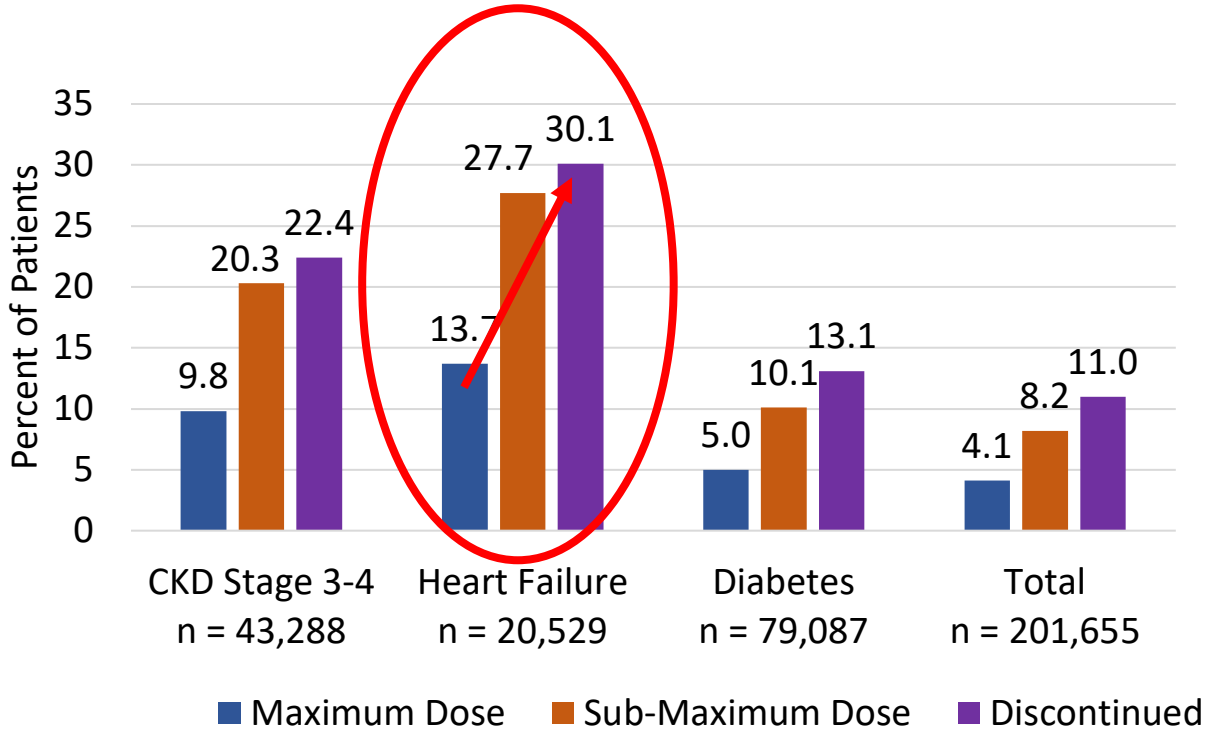
Optimal Dosing of AA Limited by Hyperkalemia

Randomized Aldactone Evaluation Study (RALES)



The Rales Investigators. Am J Cardiol. 1996.

Mortality by Prior RAAS Inhibitor Dose



Epstein M, Reaven NL. Am J Manag Care. 2015.

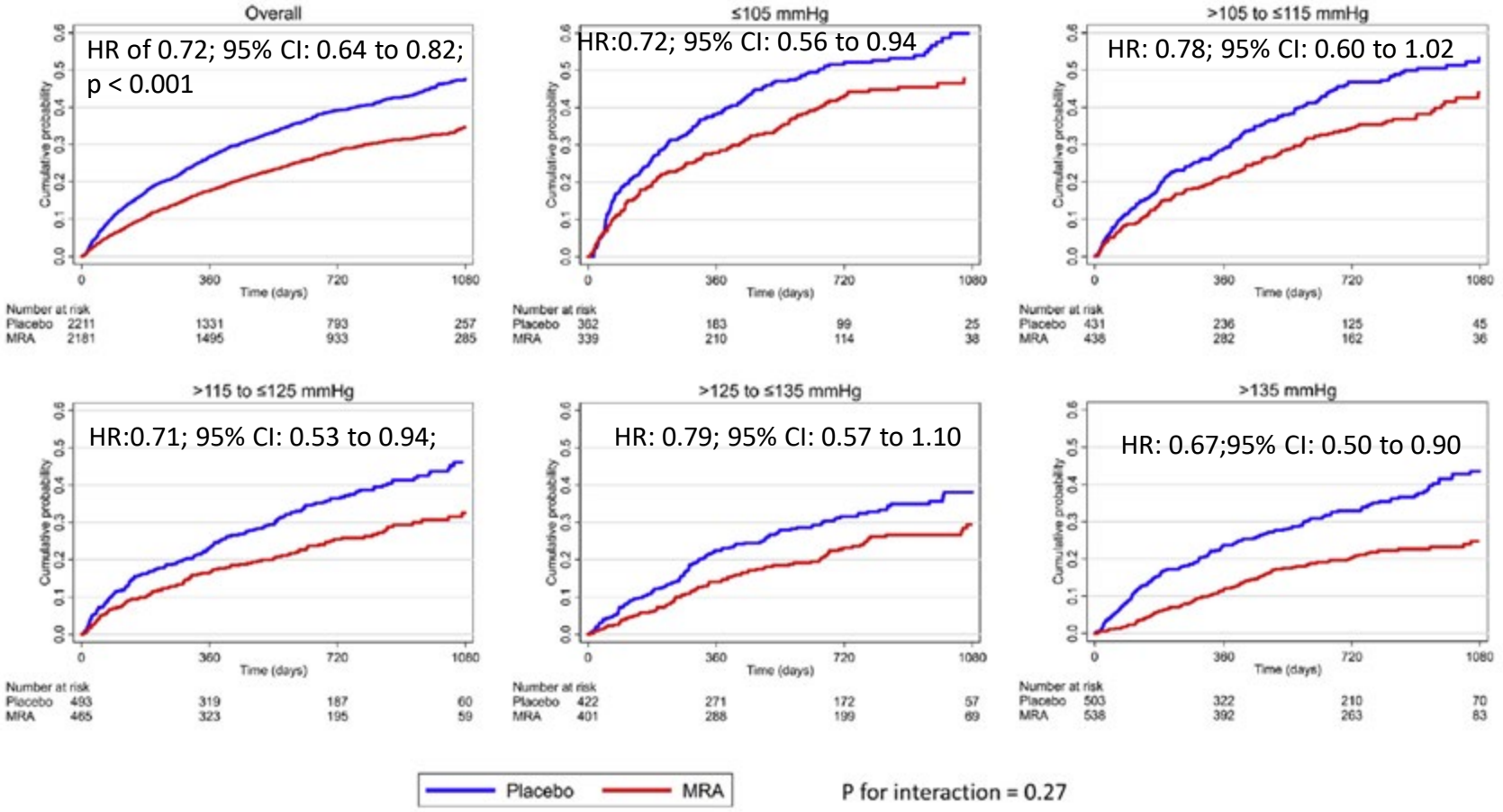
Strategies to Manage Hyperkalemia

Hyperkalemia

- Discontinue potassium supplements
- Evaluate concomitant use of potassium-sparing diuretics
- Other drugs that can increase potassium
- Dietary restrictions (salt substitutes)
- Patient education
- Potassium binders

- Monitoring: electrolytes (especially potassium) and renal function in **2-3 days** and 7 days after initiation/titration
- Then, check monthly for 3 months and every 3 months afterwards

BASELINE SBP: EFFECT OF AA TREATMENT ON OUTCOMES



Serenelli et al. JAAC HF 2020

CLINICAL SCENARIOS

Scenario 1: *When to initiate aldosterone antagonists?*

In patients who are already receiving beta blockers and ACEI/ARB/ARNI who do not have contraindications.

Scenario 2: *Is it mandatory to be on target or max tolerated doses of beta blockers and ACEI/ARB prior to initiating aldosterone antagonists?*

In practice we would like to optimize beta blockers and ACEI/ARBs first. However, in patients with persistent hypokalemia, earlier addition of an aldosterone antagonists may be considered.

Yancy et al. JACC. 2018.

Back to the Patient

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What is the best option for this patient?

A. Add Spironolactone

B. Decrease enalapril

C. Increase carvedilol

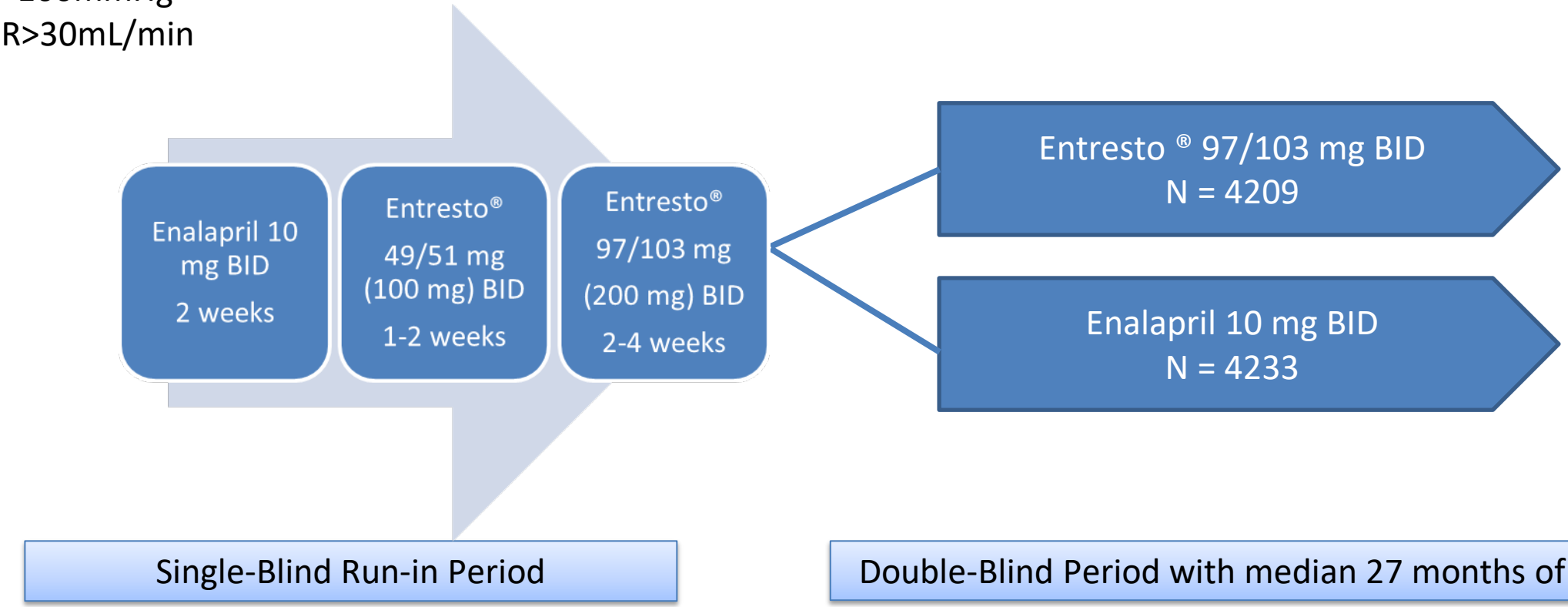
D. Add Sacubitril/Valsartan

How to Successfully Switch From ACEI or ARB to Sacubitril/Valsartan

- Identify the appropriate sacubitril/valsartan patient population in clinical practice
- Mitigate/manage side effects that occur during treatment initiation or up-titration
- Recognize how intolerance effects outcomes

PARADIGM-HF: Study Design

SBP>100mmHg
eGFR>30mL/min



McMurray et al. N Engl J Med.2014.

Pre-study Medication Daily Doses Required at Screening

Minimum Pre-study Medication Daily Doses Required at Screening	
ACEi	Daily Dose
Lisinopril	10mg
Enalapril	10mg
Ramipril	5mg
Captopril	100mg
ARB	
Candesartan	16mg
Valsartan	160mg
Losartan	50mg

McMurray et al. N Engl J Med.2014.

Reasons and Characteristics of Run-in Dropouts

Dropout Reason	Enalapril	Sacubitril/Valsartan
Hypotension	24.7%	29.8%
Renal Dysfunction	30.6%	31.6%
Hyperkalemia	29.4%	22.5%
Cough	8.3%	2.7%
Angioedema	2.5%	1.8%
Other	17.3%	23.9%

Screening Characteristics	All-Cause Dropout	Randomized
Age (yr)	64.8 ± 11.8	63.8 ± 11.4
SBP (mmHg)	125 ± 17	128 ± 17
eGFR (ml/min/m2)	64 ± 23	68 ± 19
Ischemic Cardiomyopathy	63.7%	59.5%

P<0.001 for all comparisons

Desal AS et al. Circ Heart Fail. 2016.

Prescribing Appropriately in Renal Dysfunction

eGFR>30<60
(no dose adjustment)

eGFR<30
Start at 24/26mg

Select Patient Characteristics	PARADIGM-HF	FDA	ACC/AHA/HFSA Guideline
Ejection Fraction	LVEF ≤ 35%	HFrEF	HFrEF
Renal Function	eGFR > 30ml/min/m2 Mean eGFR 68 ml/min/m2	Start at 24/26mg if eGFR <30ml/minm2	No guidance
NYHA Function Class	II : 72% III : 23%	NYHA Class II - IV	NYHA Class II - III
Blood Pressure	SBP > 100 mmHg Run-in Phase x2	No guidance	No guidance
Previous ACEi or ARB	Tolerate Moderate ACEi or ARB doses	Start at 24/26mg if no ACEi/ARB or low doses	Tolerant of ACEi or ARB

McMurray et al. N Engl J Med.2014, Entresto Package labelling Norvatis 2017 , Yancy et al. JACC.2017.

DOES CKD PREDICT RENAL TOLERABILITY OF ARNI?

	No CKD eGFR > 60 ml/min/m2	CKD eGFR 30 – 59 ml/min/m2
N (%)	5,654 (67%)	2,745 (33%)
eGFR ml/min/m2 at Screening, Mean ± SD	81 ± 14	49 ±8
Serum Creatinine at Screening, Median (IQR)	0.97 (0.85 – 1.09)	1.37 (1.26 – 1.54)
Serum creatinine > 2.5 mg/dL at follow-up, n (%)	1.3%	9.0%

CKD predicts a higher likelihood of Worsening Renal Function.

Does this differ between ACEi and ARNI?

Damman K et al. JACC: HF. 2018.

DOES CKD PREDICT RENAL TOLERABILITY OF ARNI?

- No difference between ACEI and ARNI in:
  - > 50% decrease in eGFR (p=0.23)
  - > 30ml/min/m^2 change in eGFR to < 60 ml/min/m^2 (p=0.54)
  - Progression to ESRD (p=0.11)

- No difference between ACEI and ARNI across any outcomes when analyzed by CKD at baseline

Damman K et al. JACC: HF. 2018.

DOES CKD PREDICT RENAL TOLERABILITY OF ARNI?

Summary

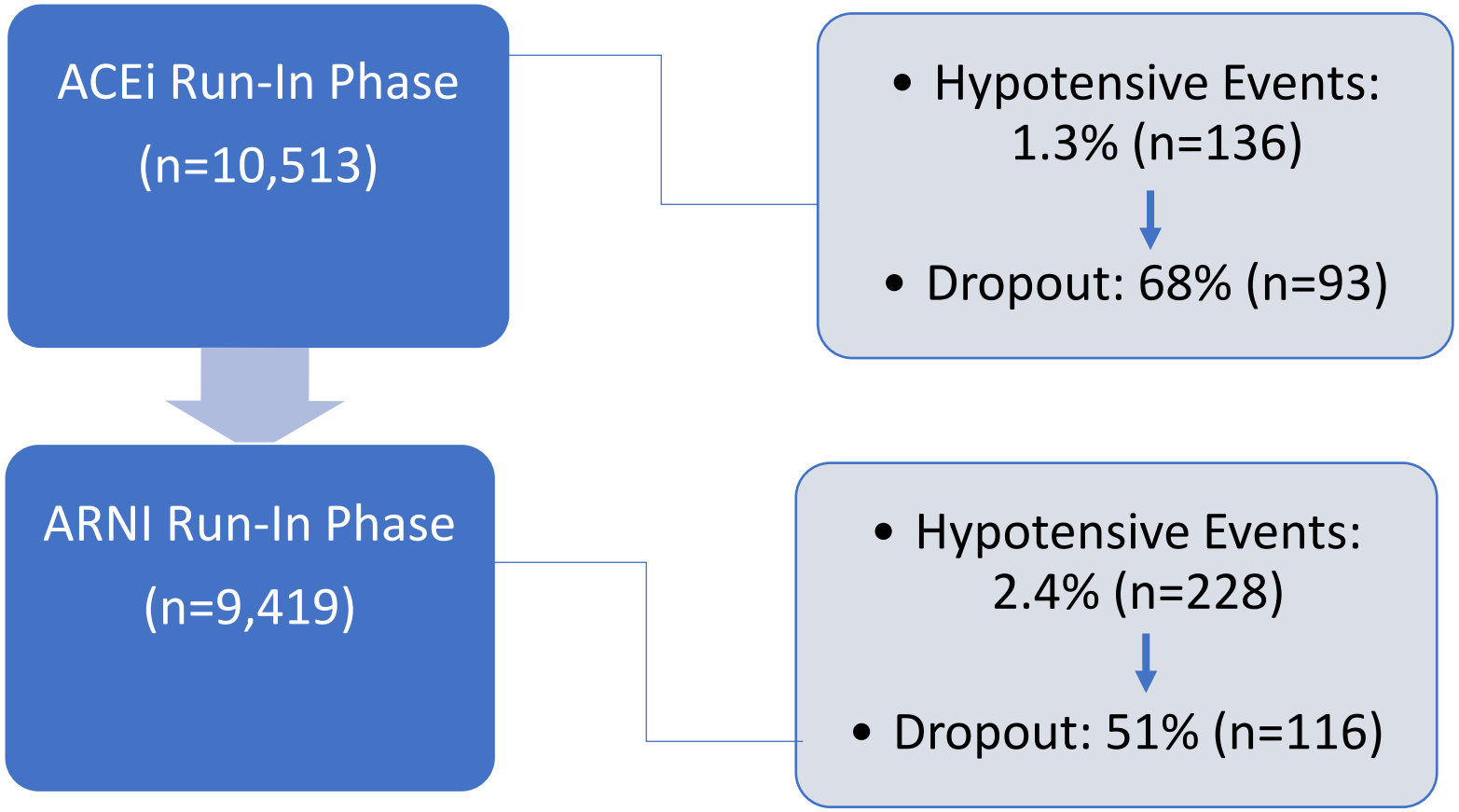
- eGFR < 60 associated with higher dropout in Run-in phase
- CKD predicted higher rates of worsening renal function(WRF) events in Trial phase
- If tolerated Run-in phase, no difference in WRF events between ACEi or ARNI

Damman K et al. JACC: HF. 2018.

Impact of SBP on the Safety and Tolerability of Initiating and Up-titrating Sacubitril/Valsartan

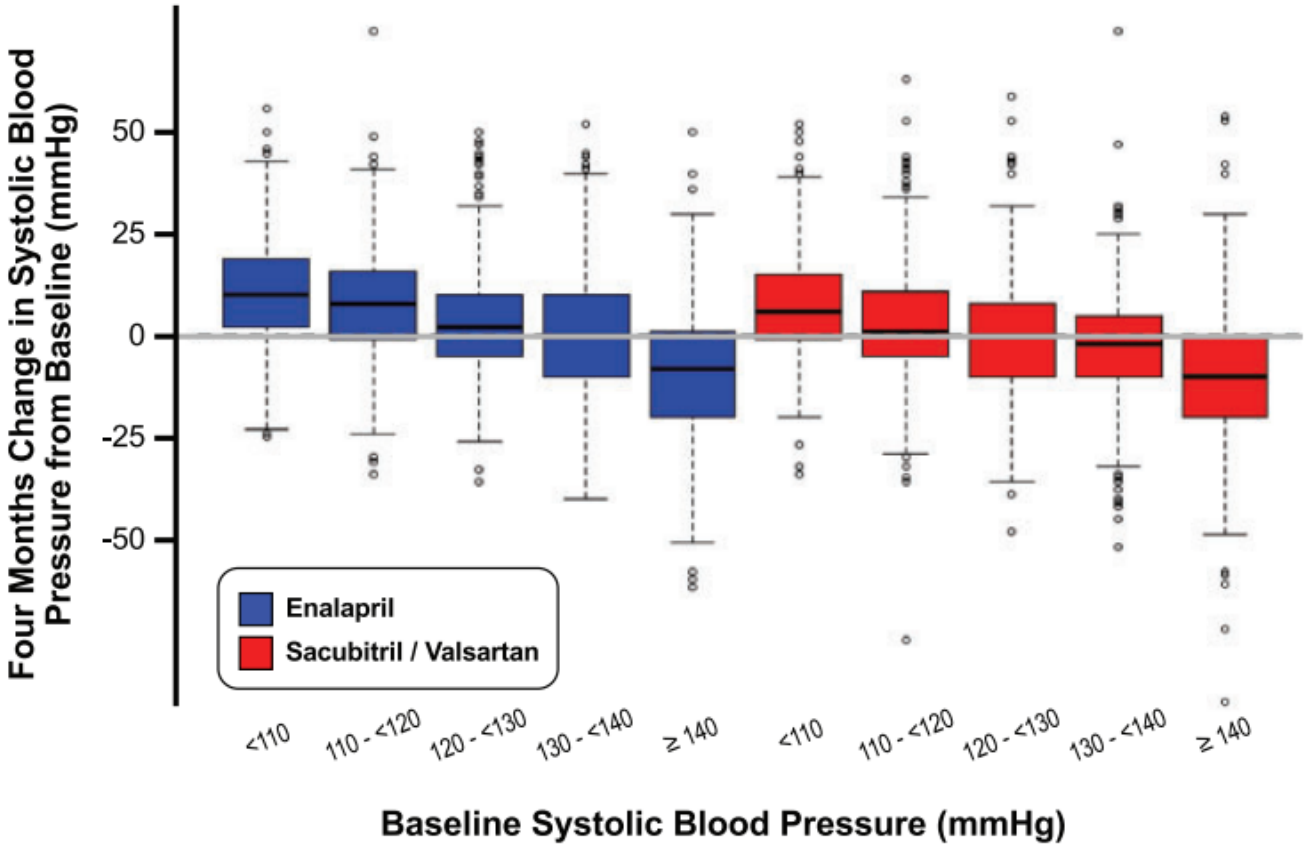
Does baseline BP predict BP tolerability of ARNI?

Hypotension Episodes in Run-in Phases



Vardeny O et al. Circ Heart Failure. 2018.

MEAN BASELINE SBP



Bohm M et al Euro Heart J. 2017.

BASELINE SBP AND ADVERSE EVENTS(AE)

Mean ± SD Baseline SBP: No Hypotension AE: 128 ±17 vs Hypotension AE: 122 ± 15 ($p<0.001$)

AE	SBP <110 mmHg		SBP 110 – 119 mmHg		SBP 120 – 129 mmHg		SBP 130 – 139 mmHg	
	ACEi	ARNI	ACEi	ARNI	ACEi	ARNI	ACEi	ARNI
Symptomatic Hypotension	13.7%	25.5%	10.7%	14.4%	8.5%	11.4%	6.7%	9.0%
Symptomatic Hypotension with SBP < 90 mmHg	2.8%	7.1%	1.9%	2.5%	1.0%	1.4%	0.7%	1.2%
Serum Creatinine >2.5mg/dL	4.6%	3.8%	5.0%	2.5%	4.5%	4.0%	3.5%	2.3%
Serum Potassium > 5.5mEq/L	16.3%	13.7%	15.5%	15.4%	19.7%	19.5%	18.2%	16.1%

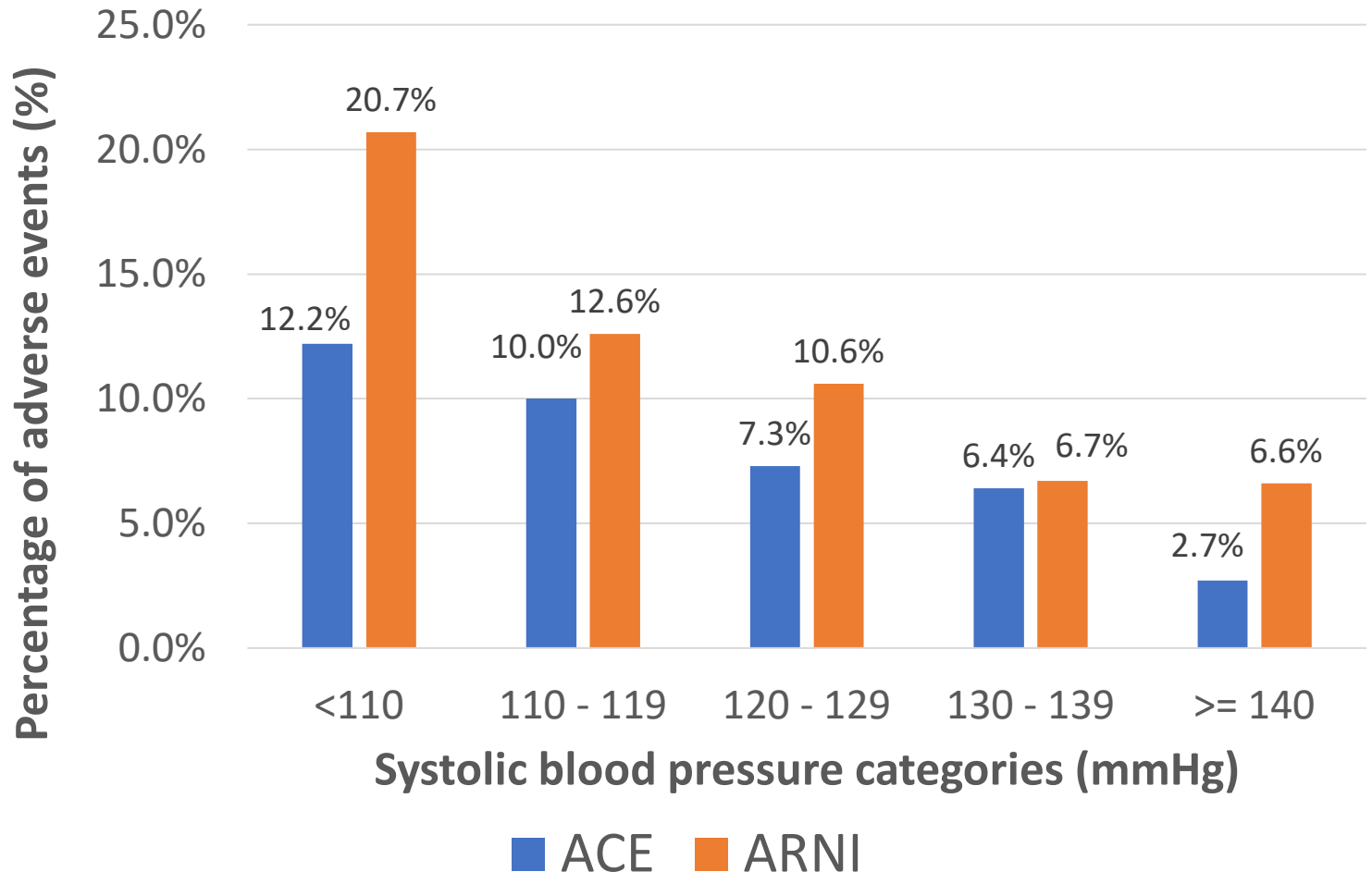
Vardeny O et al. Circ Hear Failure 2018; Bohm M et al. Euro Heart J. 2017

Actions Taken in response to Hypotension

	ACEi	ARNI	P Value
Symptomatic Hypotensive Event (%)	9.2%	14.0%	<0.001
Action by Investigator			
None	36%	34%	0.63
Dose Adjustment / Temporary Hold	52%	54%	0.42
Change Other Medications	12%	13%	0.83
Permanent Discontinuation	3.3%	2.2%	0.27
Hospitalization	7.4%	5.6%	0.23

Vardeny O et al. Circ Heart Failure. 2018.

Dose Reduction for Intolerance by Baseline SBP



Bohm M et al Euro Heart J. 2017.

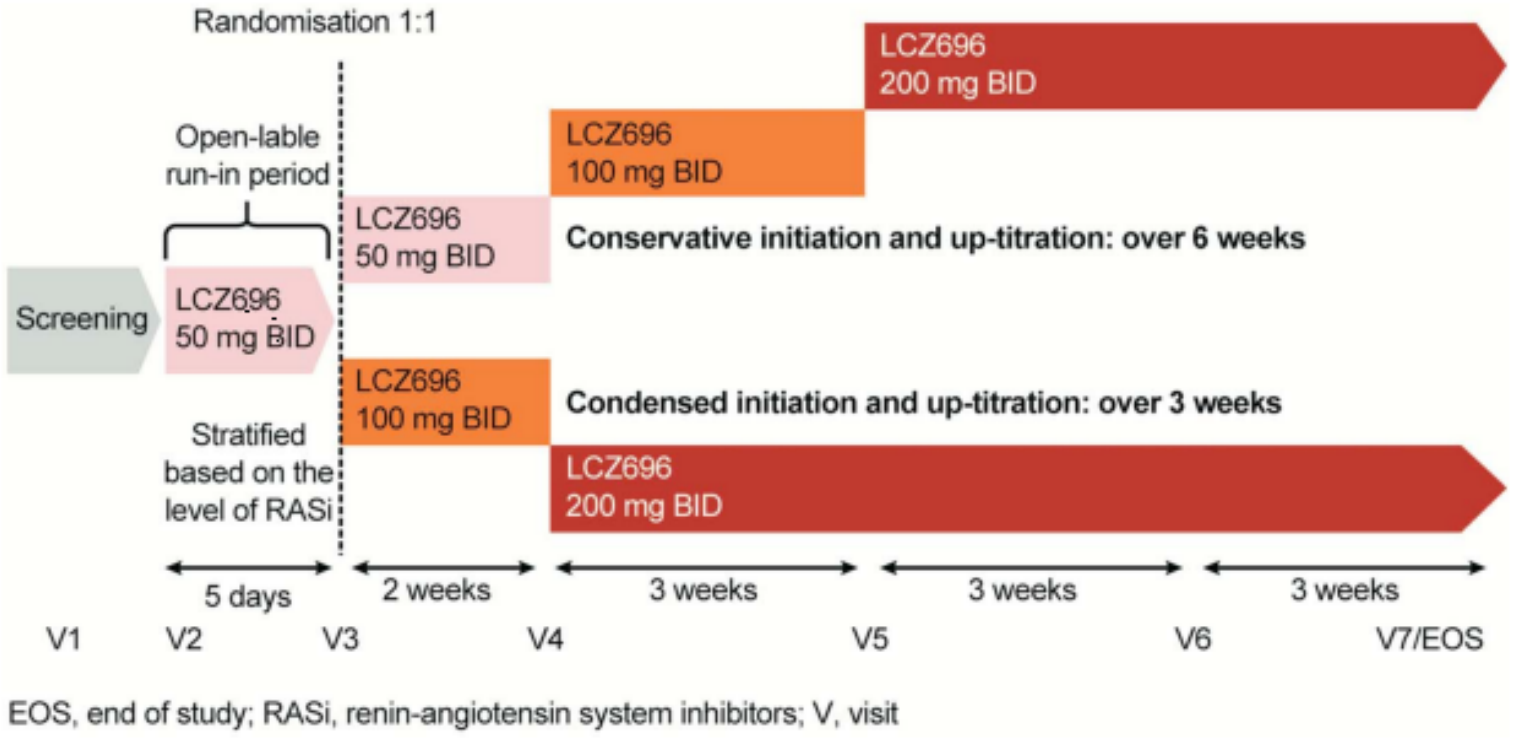
DOES BASELINE SBP PREDICT BP TOLERABILITY OF ARNI?

Summary

- Many patients with SBP < 110mmHg will have slight increase in SBP on ARNI
- SBP < 110mmHg at increased risk of hypotensive events
- Consider changing other therapy or temporary dose reductions first for hypotensive events

How to Safely Titrate to Maximize Tolerability?

TITRATION TRIAL



EOS, end of study; RASi, renin-angiotensin system inhibitors; V, visit

Senni S et al. Euro J Heart Fail. 2016.

TIRTATION TRIAL: 3 VS 6 WEEK

- Total population:
  - No difference in hypotension, WRF, or hyperkalemia (P > 0.05)

- Lower Baseline ACEI or ARB dose:
  - No difference in hypotension, WRF, or hyperkalemia (P > 0.05)

- **Successful Achievement and Maintenance of Goal Dose**:
  - No difference in 6 week (84.3%) vs 3 week (77.8%) titration (p=0.078)
  - Lower Baseline ACEI or ARB dose:
    - Greater success in 6 week (84.9%) vs 3 week (73.6%) titration (p=0.03)

Senni S et al. Euro J Heart Fail. 2016.

DOWN-TITRATION IN PARADIGM-HF

	ARNI	ACEI	P Value
Any Dose Down-titration	42%	43%	0.53
Up-Titration back to target dose	39.8%	35.3%	0.005
Reasons for Down-Titration			
Hypotension	21.7%	16.3%	<0.001
Percentage Re-Up-Titrated	36%	27%	0.026
Renal Dysfunction	8.7%	9.8%	0.29
Percentage Re-Up-Titrated	41%	28%	0.018
Hyperkalemia	6.7%	8.1%	0.13
Percentage Re-Up-Titrated	60%	56%	0.61

Vardeny O et al. Euro J Heart Fail. 2016.

Outcomes After Down-Titration

- Dose reduction was associated with a higher risk of primary outcome regardless of treatment arm compared to sustained goal doses
  - HR 2.5 (95% CI 2.2 – 2.7)

- **Among those unable to re-titrate back to goal doses**
  - ARNI continued to be superior to ACEI for primary outcome
    - Adjusted HR 0.81 (95% CI 0.67 – 0.89)

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Vardeny O et al. Euro J Heart Fail. 2016.

SUMMARY

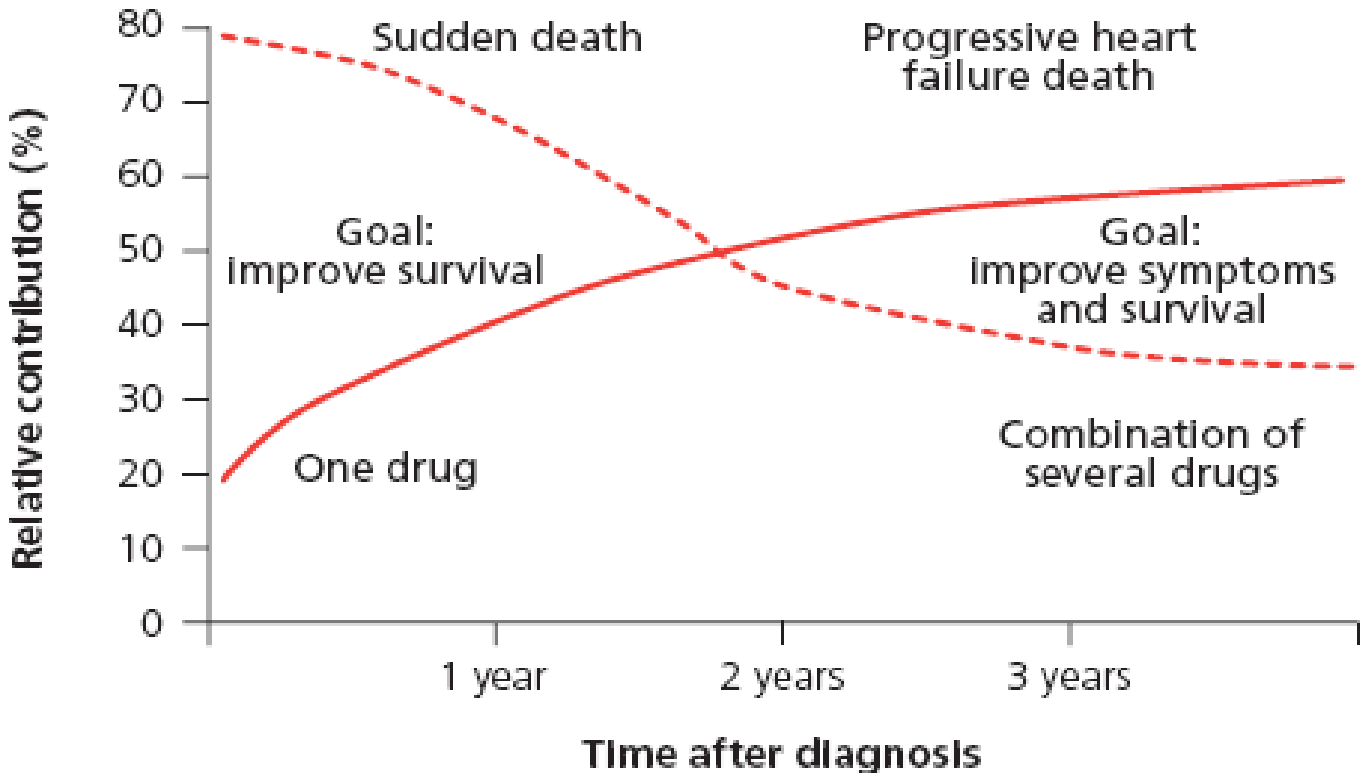
- Appropriate patient selection & time of initiation
- Systolic Blood Pressure at initiation and titration
- Evaluation of non-essential medications that impact blood pressure
- Slow titration in high risk patients

CASE 2

RS 65 YO WM presents to the HF clinic with a new diagnosis of HFrEF (EF 30% NYHA class II) with occasional dizziness, euvolemic on exam and feels better.

Medications	PMH
Lisinopril 5mg daily Furosemide 60mg daily	Diabetes Osteoporosis
Vitals	**Labs**
BP 98/77 mmHg HR 70bpm	Scr 1.0mg/dL K 4.3 mEq/L

Early Versus Late Stages of Chronic Heart Failure (CHF)



Willenheimer R, Slike B. Br J Cardiol.2005.

CLINICAL SCENARIOS

Scenario I:

Which beta blocker to initiate?

Consider metoprolol succinate for patients who are hypotensive on carvedilol, cannot tolerate much lower blood pressures, or patients with atrial fibrillation, COPD/asthma

Scenario 2:

Able to tolerate target doses of one and less than target doses of the other therapeutic agent?

Optimal SNS modulation with target doses of beta blocker appears to have the best effect on HFrEF outcomes (cardiovascular mortality, pump failure mortality, and sudden cardiac death)

HYPOTENSION

- Asymptomatic Hypotension
  - No action is required for asymptomatic hypotension provided there is no evidence of renal hypoperfusion

- Symptomatic Hypotension
  - Flexible diuretic dosing or dose reduction
  - Consider advising patient to take once-daily doses of ACEI in divided doses
  - Consider discontinuing or reducing the dose of other concomitant medications that may affect blood pressure (e.g., calcium antagonists, nitrates)
  - Check for orthostasis

BACK TO THE PATIENT

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Vitals	**Labs**
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Which one of the following is the best to recommend for this patient?

A. Add low dose metoprolol succinate

B. Increase lisinopril dose

C. Discontinue furosemide

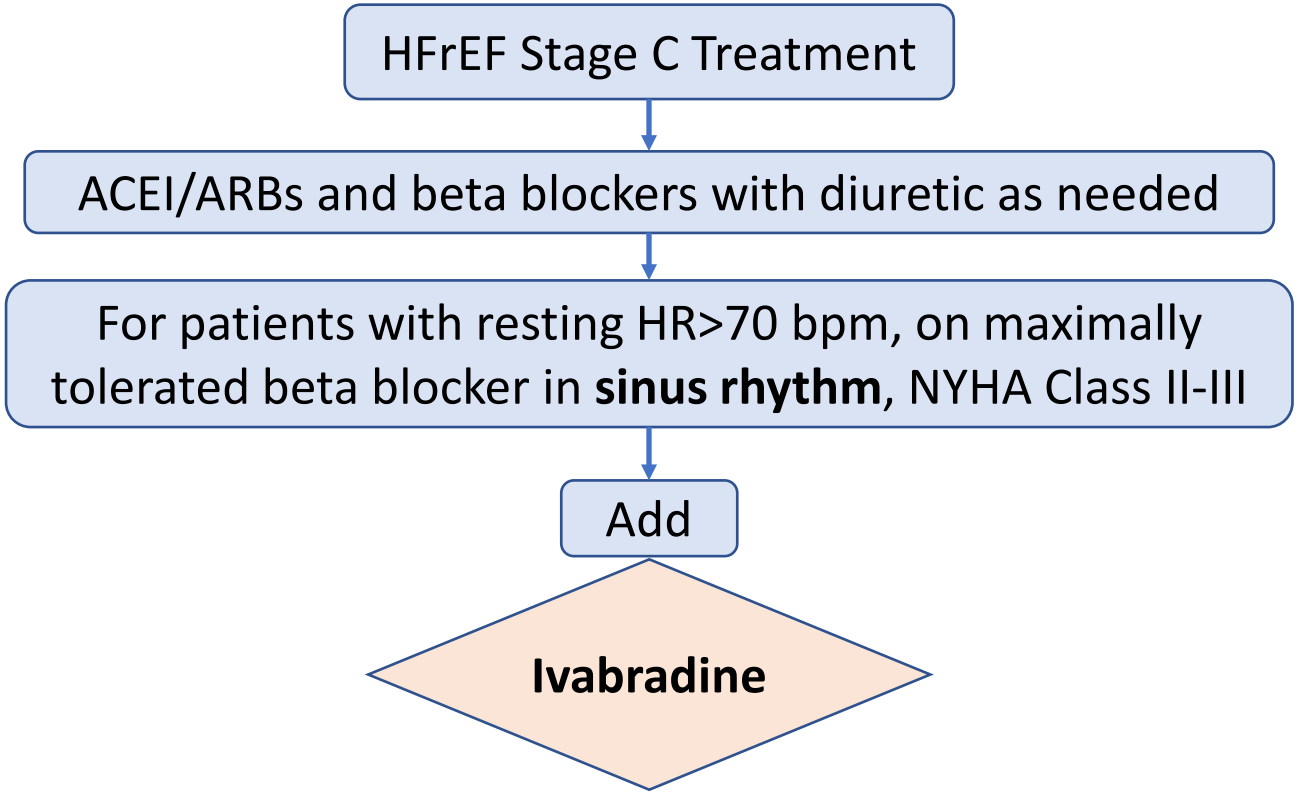
D. Add Spironolactone

CASE 3

A 60 -year-old male today presents at the clinic after discharge from hospital for worsening HF. His present symptoms include SoB when standing to cook for too long, bilateral lower extremity +1 pitting edema and some basal crackles on lung examination, EF 30-35%; NYHA Class III.

Medications		PMH
Metoprolol succinate 100mg daily Valsartan 160mg twice daily Furosemide 40mg twice daily Spironolactone 12.5 mg daily	Aspirin 81mg daily Atorvastatin 40mg daily KCL 40mg daily	Hospitalized for HF 3 times within the previous year
Labs		**Vitals**
K 4.5mEq/L Na 138 mEq/L	Scr 1.2mg/dL BNP 893pg/ml Home weights have been stable	BP 136/78 mmHg HR 77bpm

IVABRADINE: PLACE IN THERAPY



Yancy et al. JACC.2018.

Which One of the Following is Best to Recommend for this Patient?

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Labs		**Vitals**
K 4.5mEq/L Na 138 mEq/L	Scr 1.2mg/dL BNP 893pg/ml Home weights have been stable	BP 136/78 mmHg HR 77bpm

Which one of the following is the best to recommend for this patient?

A. Stop valsartan and initiate sacubitril/valsartan

B. Increase metoprolol succinate

C. Initiate ivabradine

D. Increase spironolactone

TRICKS AND TIPS FOR SUCCESSFUL TITRATION

1. Start low and go slow
2. Compensate before you initiate
3. Stabilize before switching
4. Mild- moderate renal worsening is acceptable
5. Watch potassium with AA
6. Try to stop Non GDMT* to make room for GDMT
7. Personalize care
8. Lifestyle counts
9. When to call – refer to advance therapies

*GDMT Guideline directed medical therapy

CASE 1

What is the best option for this patient?

A. Add Spironolactone

B. Decrease lisinopril

C. Increase carvedilol

D. Add Sacubitril/Valsartan

CASE 2

Which one of the following is the best to recommend for this patient?

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