# Continuing foundational therapy in symptomatic heart failure: the key role of RAASi-based therapy

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**Breaking barriers in guideline-based RAASi therapy: Solving issues with hyperkalemia**


PHYSICIANS' ACADEMY FOR CARDIOVASCULAR EDUCATION
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# Continuing foundational therapy in symptomatic heart failure: the key role of RAASi-based therapy

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# Landmark trials have demonstrated that RAASi improves outcomes in patients with HFrEF

| | Study | Key Inclusion Criteria | Follow-up (years) | Treatment Arms | Key Findings |
|---|---|---|---|---|---|
| ACEi | **CONSENSUS**[1] (N=253) | NYHA class IV | 0.5 (mean) | Enalapril vs. placebo | **Enalapril reduced mortality by 40% at 6 months and 31% at 12 months** |
| ACEi | **SOLVD**[2] (N=2569) | NYHA class I-IV[a], LVEF ≤35% | 3.45 (mean) | Enalapril vs. placebo | **Enalapril reduced mortality by 16%** and the combination of mortality or hospitalization for worsening HF by 26% |
| ACEi | **ATLAS**[3] (N=3164) | NYHA class II-IV; LVEF≤30% | 3.8 (median) | Lisinopril low-dose (2.5-5 mg QD) vs. high-dose (32.5-35 mg QD) | **High-dose lisinopril group had** a non-significant reduction in mortality and CV mortality (8% and 10% reductions, respectively) and **a significant reduction in the combination of mortality or hospitalization for any reason by 12% compared to low-dose group** |
| MRA | **RALES**[4] (N=1663) | NYHA class III or IV; LVEF ≤35% | 2.0 (mean) | Spironolactone vs. placebo | **Spironolactone reduced risk of all-cause mortality by 30%** and hospitalization for worsening HF by 35% |
| MRA | **EMPHASIS-HF**[5] (N=2737) | NYHA class II; LVEF ≤35% | 1.75 (median) | Eplerenone vs. placebo | **Eplerenone reduced the composite of CV-related mortality or hospitalization for HF by 37%** and all-cause mortality and CV mortality by 24% each |
| ARNI | **PARADIGM-HF**[6] (N=8442) | NYHA class II-IV; LVEF≤40% | 2.25 (median) | LCZ696[b] vs. enalapril | **LCZ696[b] reduced risk of the combination of CV death or first hospitalization for worsening HF by 20%,** all-cause mortality by 16%, and first hospitalization for worsening HF by 21% |

[a]Approximately 90% were NYHA class II-III; [b]LCZ69 is the combination of the neprilysin inhibitor sacubitril and the ARB valsartan.
Abbreviations and References in slide notes.

# RAASi therapy is recommended by clinical guidelines for the management of chronic HFrEF and should be titrated to maximum tolerated doses

## 2021 ESC GUIDELINES FOR THE DIAGNOSIS AND TREATMENT OF ACUTE AND CHRONIC HEART FAILURE

ESC guidelines key message for pharmacological treatments indicated in patients with (NYHA class II–IV) HFrEF (LVEF ≤40%): ACEi or ARNI, beta-blockers, MRA, and SGLT2 inhibitors are recommended as cornerstone therapies for patients with HFrEF

| Recommendations | Class[a] | Level[b] |
|---|---|---|
| An ACEi is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. | I | A |
| A beta-blocker is recommended for patients with stable HFrEF to reduce the risk of HF hospitalization and death. | I | A |
| An MRA is recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. | I | A |
| Dapagliflozin or empagliflozin are recommended for patients with HFrEF to reduce the risk of HF hospitalization and death. | I | A |
| Sacubitril/valsartan is recommended as a replacement for an ACEi in patients with HFrEF to reduce the risk of HF hospitalization and death. | I | B |

**5.2.2 General principles of pharmacotherapy for heart failure with reduced ejection fraction**

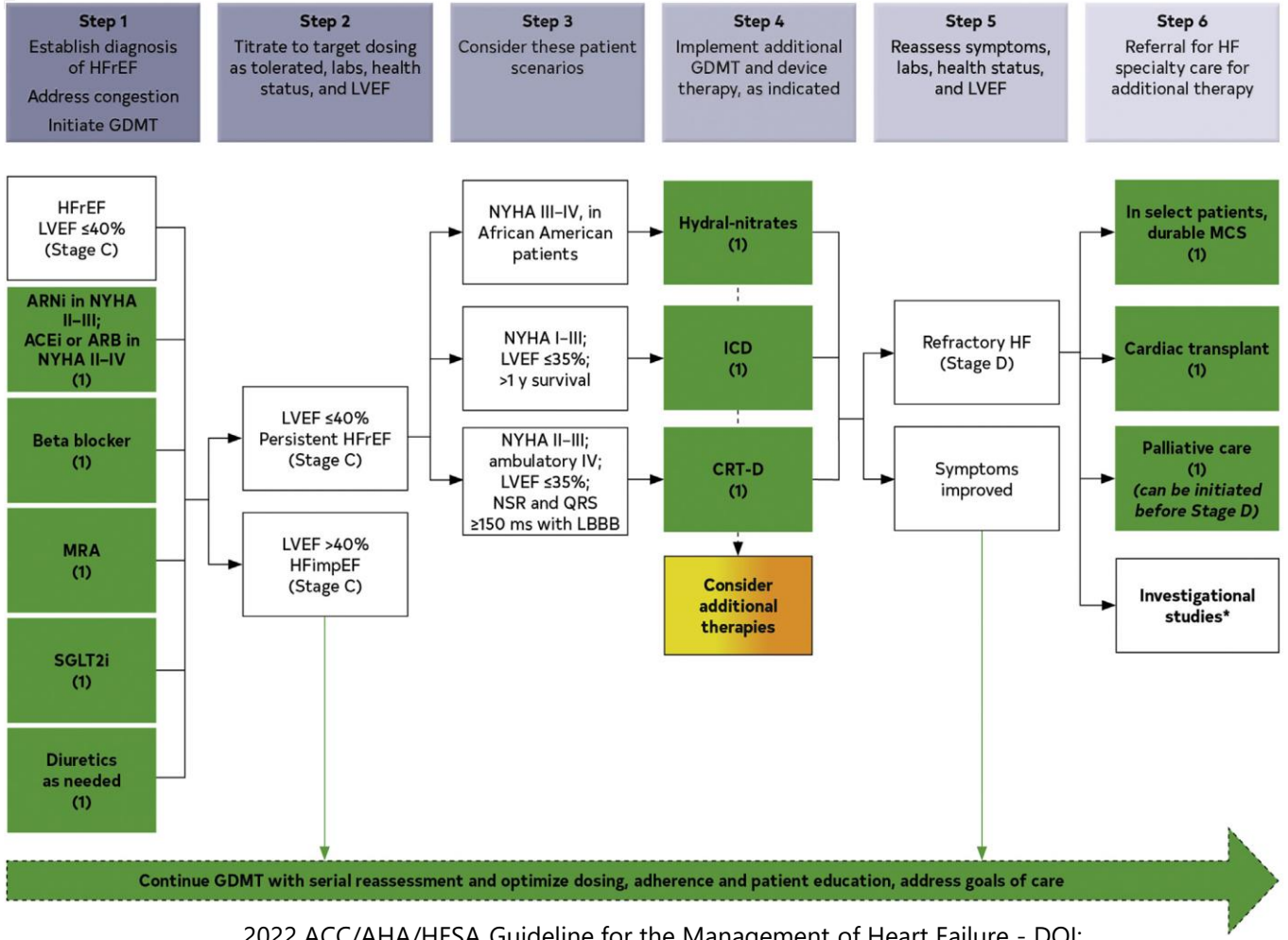
Modulation of the renin-angiotensin-aldosterone (RAAS) and sympathetic nervous systems with angiotensin-converting enzyme inhibitors (ACE-I) or an angiotensin receptor-neprilysin inhibitor (ARNI), beta-blockers, and mineralocorticoid receptor antagonists (MRA) has been shown to improve survival, reduce the risk of HF hospitalizations, and reduce symptoms in patients with HFrEF. These drugs serve as the foundations of pharmacotherapy for patients with HFrEF. The triad of an ACE-I/ARNI, a beta-blocker, and an MRA is recommended as cornerstone therapies for these patients, unless the drugs are contraindicated or not tolerated.[103–105] They should be uptitrated to the doses used in the clinical trials (or to maximally tolerated doses if that is not possible). This guideline still recommends the use of ARNI as a replacement for ACE-I in suitable patients who remain symptomatic on ACE-I, beta-blocker, and MRA therapies; however, an ARNI may be considered as a first-line therapy instead of an ACE-I.[106,107] The recommended doses of these drugs are given in *Table 8*. Angiotensin-receptor blockers (AR[illegible])

[a]Class of recommendation; [b]Level of evidence.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; ESC = European Society of Cardiology; HF = heart failure; HFrEF = heart failure with reduced ejection fraction; LVEF = left ventricular ejection fraction; MRA = mineralocorticoid receptor antagonist; NYHA = New York Heart Association; RAASi = renin-angiotensin-aldosterone system inhibitor; SGLT2 = sodium-glucose cotransporter 2.

McDonagh TA et al. *Eur Heart J*. 2021;42:3599-3726.

# GDMT for HFrEF




2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure - DOI: 10.1016/j.cardfail.2022.02.010

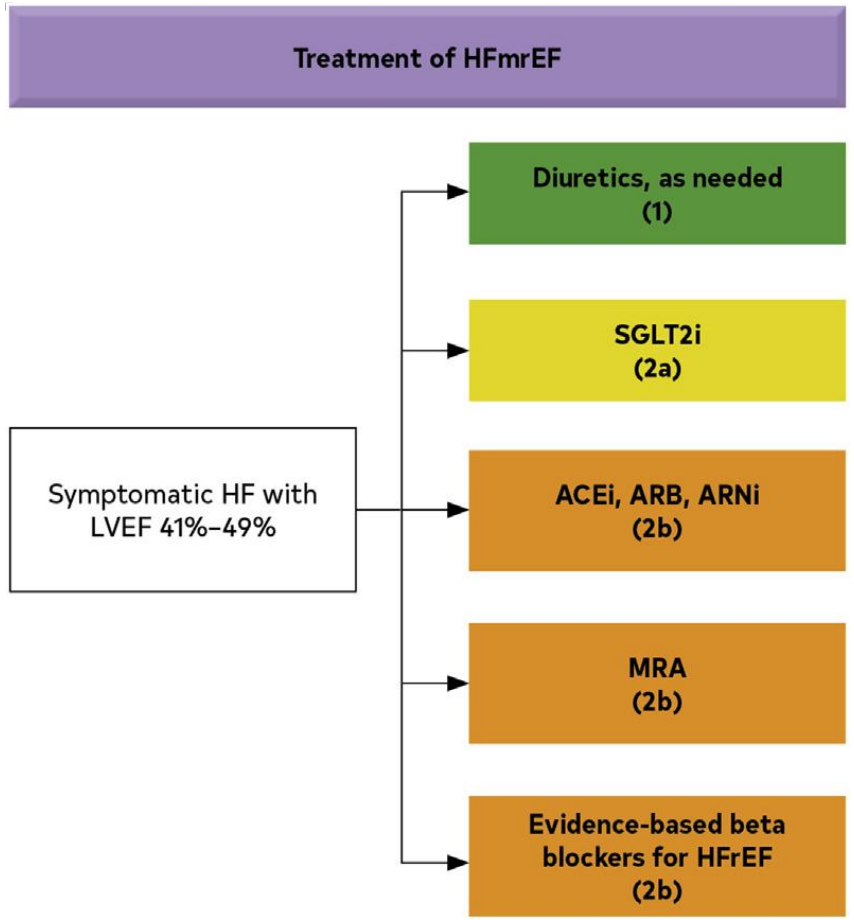
HFSA HEART FAILURE SOCIETY OF AMERICA

JCF Journal of Cardiac Failure

Heidenreich PA, *et al. J Card Fail* 2022

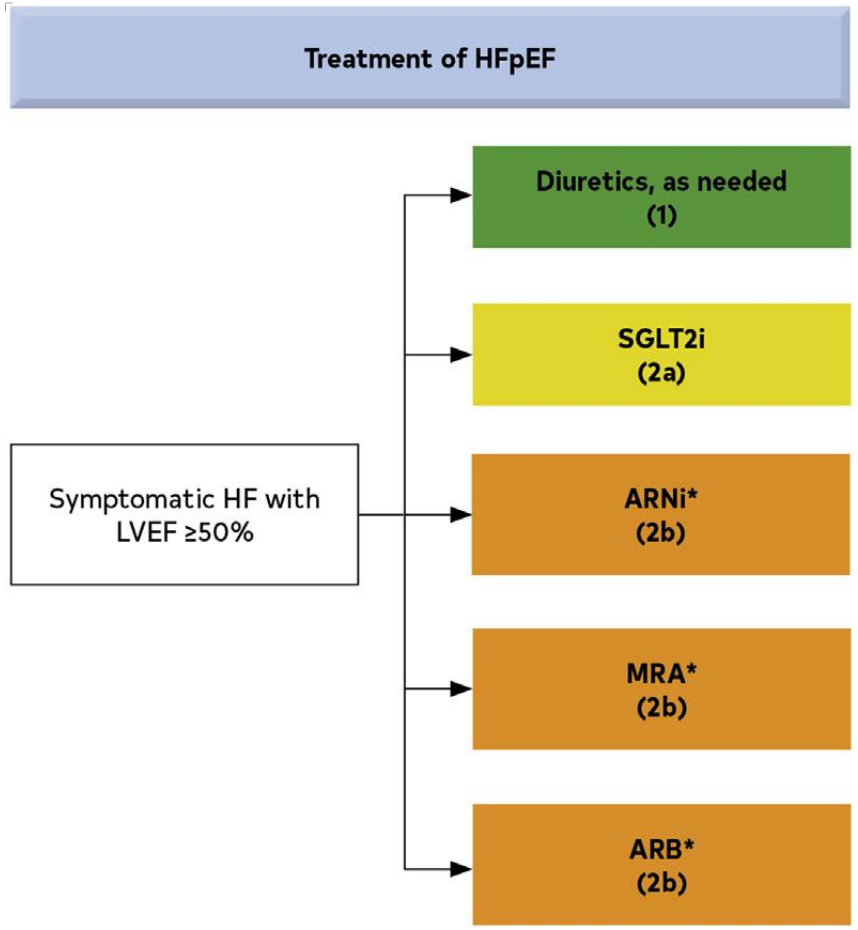
JHFS

# GDMT for HFmrEF




2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure - DOI: 10.1016/j.cardfail.2022.02.010

# GDMT for HFpEF



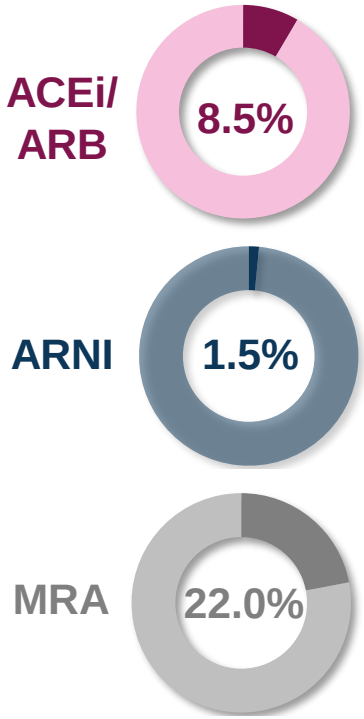

2022 ACC/AHA/HFSA Guideline for the Management of Heart Failure - DOI: 10.1016/j.cardfail.2022.02.010

# Despite proven benefits of RAASi, many patients with HFrEF are not at target doses

## CHAMP-HF Registry

Prospective, observational study in US outpatients with chronic HFrEF (N=2588) to evaluate the degree of titration of HFrEF GDMT (2015-2017)[1]

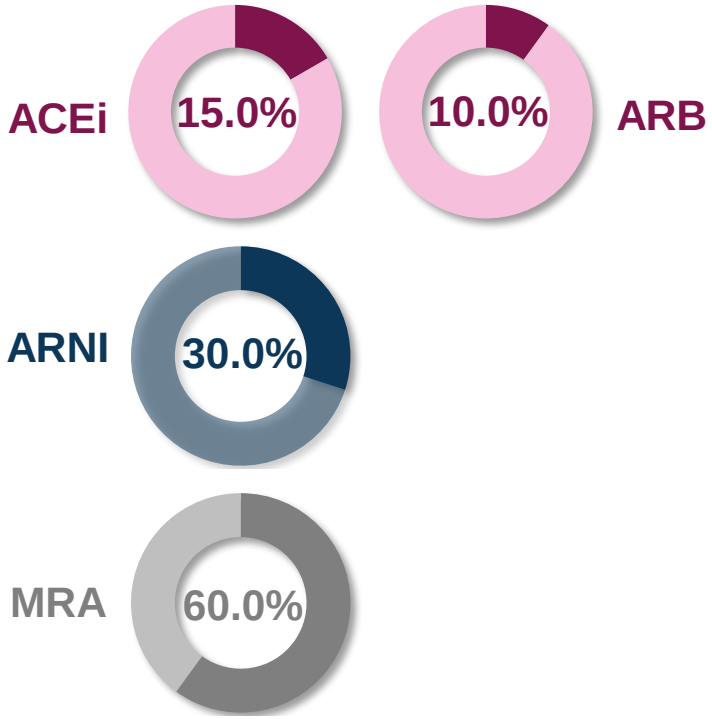
**Patients Achieving Target Doses at 1 Year**




## Savarese et al

Observational cohort study using data from healthcare databases in Sweden, UK, and US to identify patients (N=68,172) with new initiation of GDMT following recent hHF[a] (2016-2019)[2]

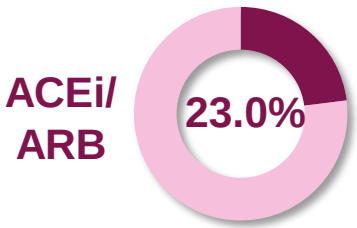
**Patients Achieving Target Doses at 1 Year**




## BIOSTAT-CHF

Multicenter, prospective, observational study in patients with HFrEF (N=2100) who were not previously on ACEi/ARB or receiving ≤50% of the target dose from 11 European countries (2010-2014)[3,4]

**Patients Achieving Target Doses at 9 Months**




[a]hHF defined as 7 days prior to initiation of GDMT in Sweden and US, and 30 days prior to initiation of GDMT in UK.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; BIOSTAT-CHF = BIOlogy Study to TAilored Treatment in Chronic Heart Failure; CHAMP-HF = Change the Management of Patients with Heart Failure; GDMT = guideline-directed medical therapy; HFrEF = heart failure with reduced ejection fraction; hHF = hospitalization for heart failure; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; UK = United Kingdom; US = United States.

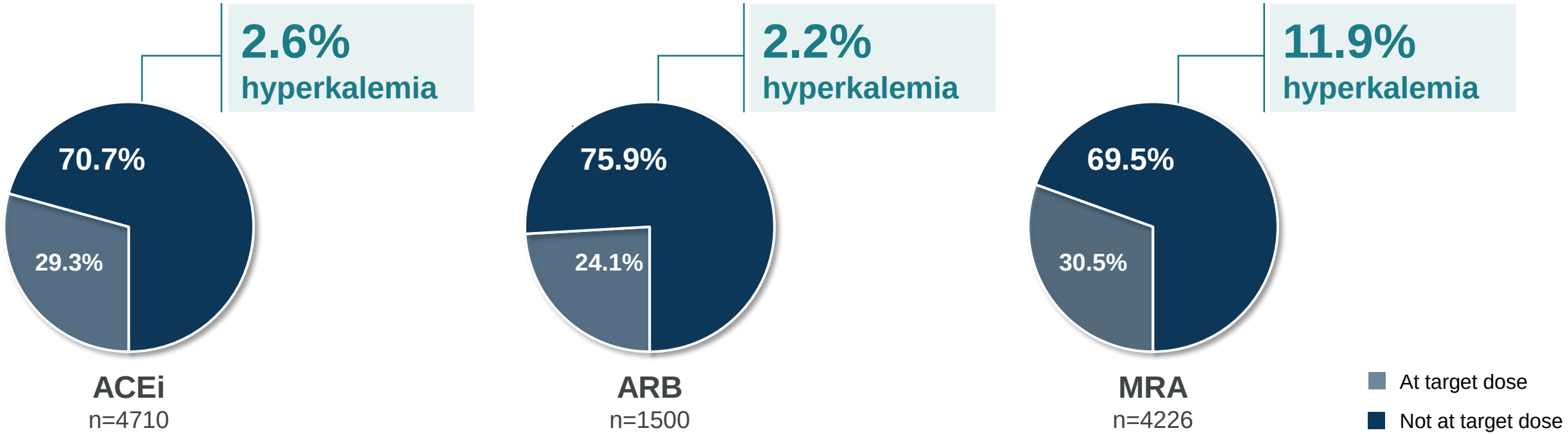
1. Greene SJ et al. *J Am Coll Cardiol*. 2019;73;2365-2383; 2. Savarese G et al. Online ahead of print. *Eur J Heart Fail*. 2021; 3. Voors AA et al. *Eur J Heart Fail*. 2016;18:716-726; 4. Kobayashi M et al. *Clin Cardiol*. 2021;44:780-788.


Rosano GMC, Coats AJS et al. Eur J Heart Fail. 2021 Jun;23(6):872-881.

# Hyperkalemia can be a barrier to target dose RAASi therapy in patients with heart failure

**Multinational, prospective, observational study of 7401 ambulatory patients with chronic heart failure from 21 European and Mediterranean countries (ESC-HF Long-term Registry) from May 2011 to April 2013**

## Patients that had hyperkalemia as a reason for not being at target dose RAASi[a]




Note: Hyperkalemia definition or diagnosis method was not provided in the study.

[a]Additional reasons for patients not being at target dose were: still in up-titration (33.7% for ACEis, 32.4% for ARBs, and 29.4% for MRAs), symptomatic hypotension (26.0% for ACEis and 25.9% for ARBs), worsening renal function (7.9% for ACEis, 10.1% for ARBs, and 9.7% for MRAs), cough (0.9% for ACEis), angioedema (0.2% for ACEis and 0.1% for ARBs), gynecomastia (2.0% for MRAs), and other/unknown (28.8% for ACEis, 29.3% for ARBs, and 46.9% for MRAs).

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ESC-HF = European Society of Cardiology-Heart Failure; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor.

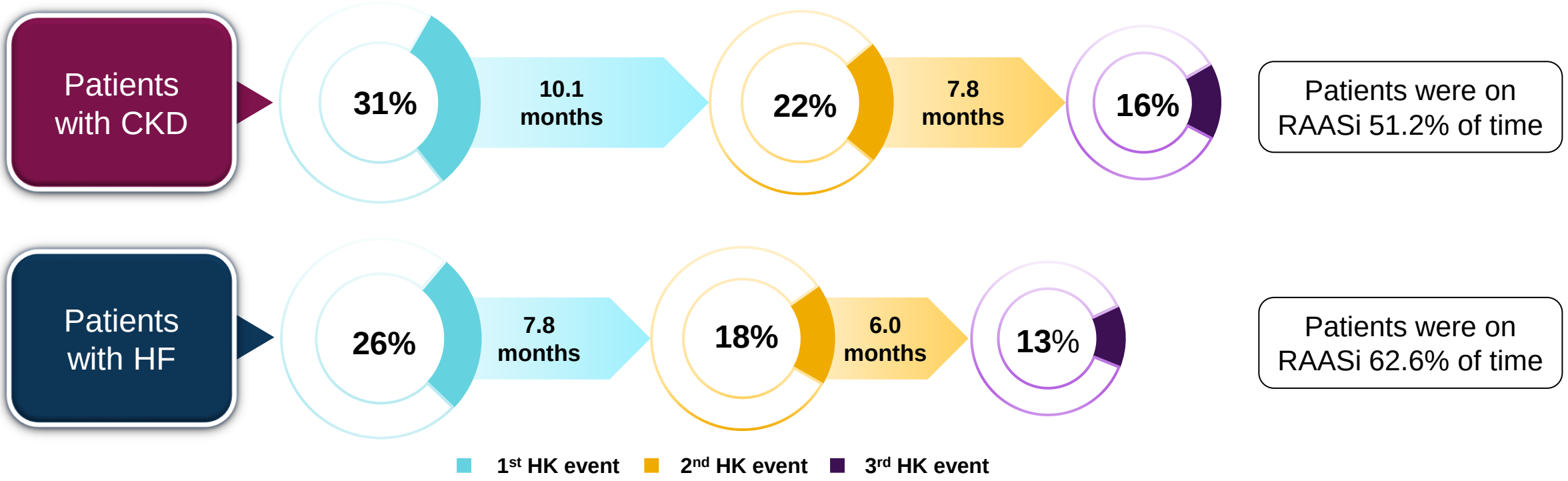


Maggioni AP et al. *Eur J Heart Fail*. 2013;15:1173–1184.

# Patients with CKD and HF have recurrent hyperkalemia episodes, with successively shorter time between the episodes

**Retrospective analysis using patient data from the CPRD database (medical records across the United Kingdom) linked to Hospital Episode Statistics between January 2008 and June 2018 in patients with a first diagnosis of CKD (n=297,702) or HF (n=84,210) and/or RAASi prescription (n=754,523)**

## Proportion of patients with recurrent hyperkalemia events



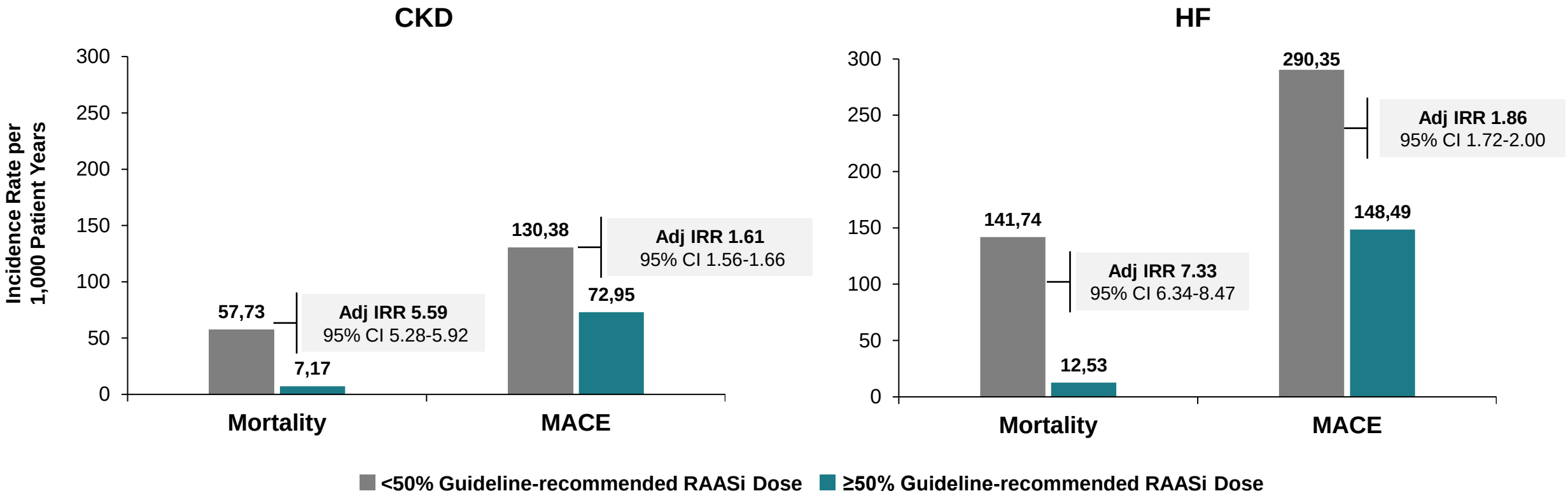

Note: Hyperkalemia defined as $K^+$ ≥5.0 mmol/L. RAASi includes ACEi, ARB, MRA, and RI. Patients could fall into one or more overlapping cohorts based on their cardiorenal comorbidities and/or prescription record for RAASi and their assignment to a cohort was updated over time.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin receptor blocker; CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; HF = heart failure; HK = hyperkalemia; MRA = mineralocorticoid receptor antagonist; RAASi = renin–angiotensin–aldosterone system inhibitor; RI = renin inhibitor.

Tafesse E et al. *Int J Clin Pract*. 2021;75:e13941.

# Optimizing RAASi therapy in patients with CKD and HF was associated with decreased mortality and MACE

**An observational, longitudinal cohort study of RAASi-prescribed patients with new-onset CKD (n=100,572) or HF (n=13,113) using data from the CPRD and linked Hospital Episode Statistics between January 2006 and December 2015[1]**




Note: Non-fatal MACE defined as a composite of non-fatal arrhythmia, HF, myocardial infarction, and stroke. Poison models were used to estimate adjusted IRRs and included covariates to control for patient characteristics and clinical histories. RAASi included specific ACEi, ARB, and MRA and the recommended dose was based on ESC 2016 guidelines[2] for the treatment of HF.[1]

ACEi = angiotensin-converting enzyme inhibitor; Adj = adjusted; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; CPRD = Clinical Practice Research Datalink; ESC = European Society of Cardiology; HF = heart failure; IRR = incidence rate ratio; MACE = major adverse cardiac events; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor.

1. Linde C et al. *J Am Heart Assoc*. 2019;8:e012655; 2. Ponikowski P et al. *Eur Heart J.* 2016;37:2129-2200.

# Discontinuation or downtitration of RASi after an episode of hyperkalemia

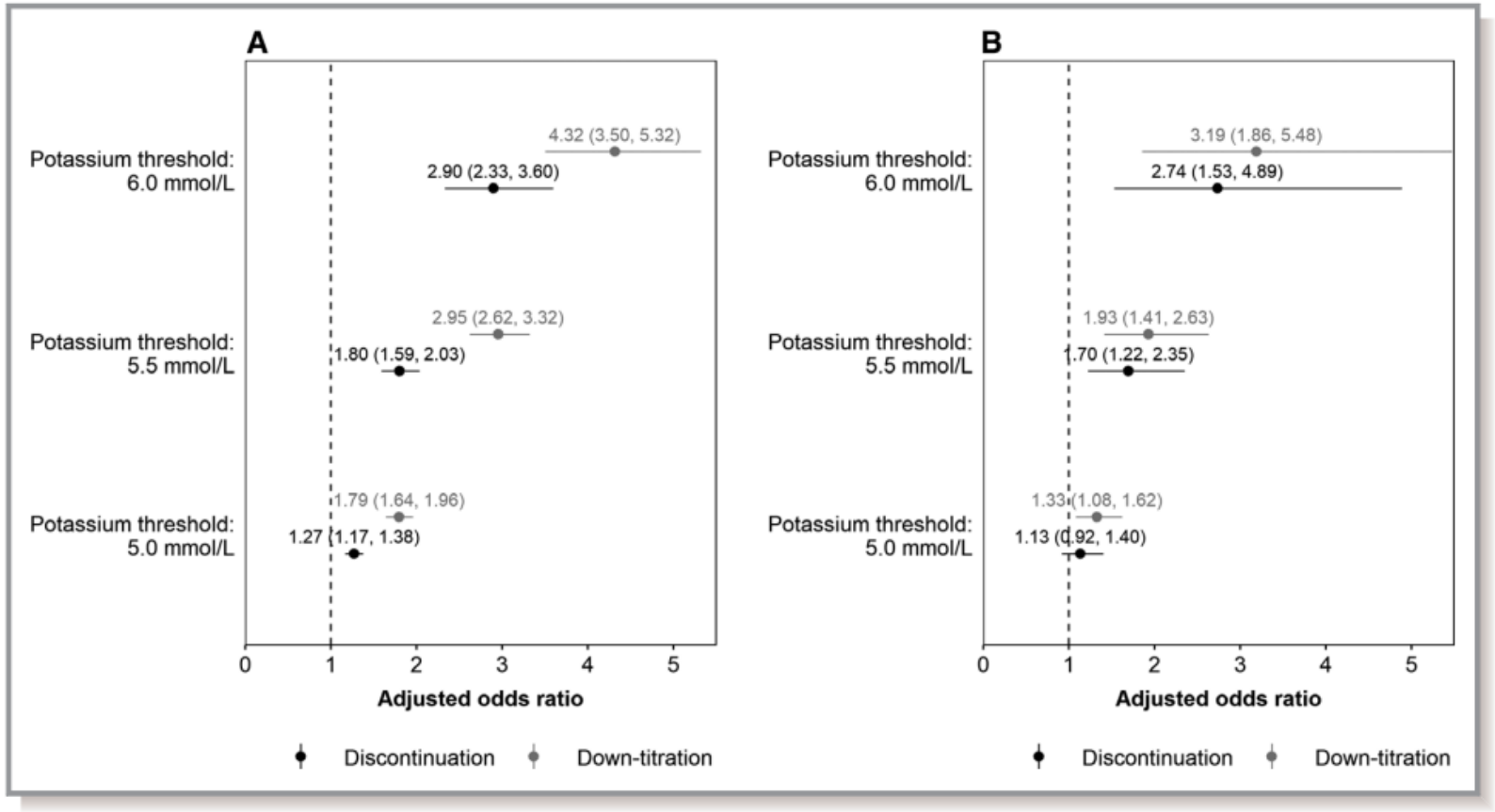
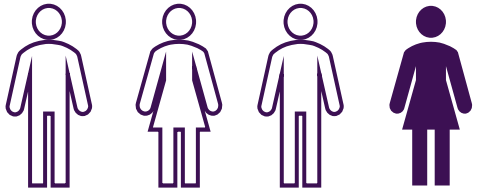



**Figure 3.** Adjusted odds ratios (and 95% CIs) for dose modification of renin–angiotensin–aldosterone system inhibitors, stratified by serum potassium ($K^+$) threshold for CKD patients (**A**) and HF patients (**B**). An odds ratio of 1 (dotted line) indicates the odds of discontinuation or down-titration under the defined threshold.


Linde et al. J Am Heart Assoc. 2019;8:e012655. DOI: 10.1161/JAHA.119.012655.

# In real world practice, discontinuation of RAASi therapy persists following a hyperkalemia event



**76%**

of patients were **not reintroduced to MRA therapy** during the subsequent year[1]

Mean duration of RAASi discontinuation was:[2]

**2.4 years**
in patients with CKD

**1.9 years**
in patients with HF

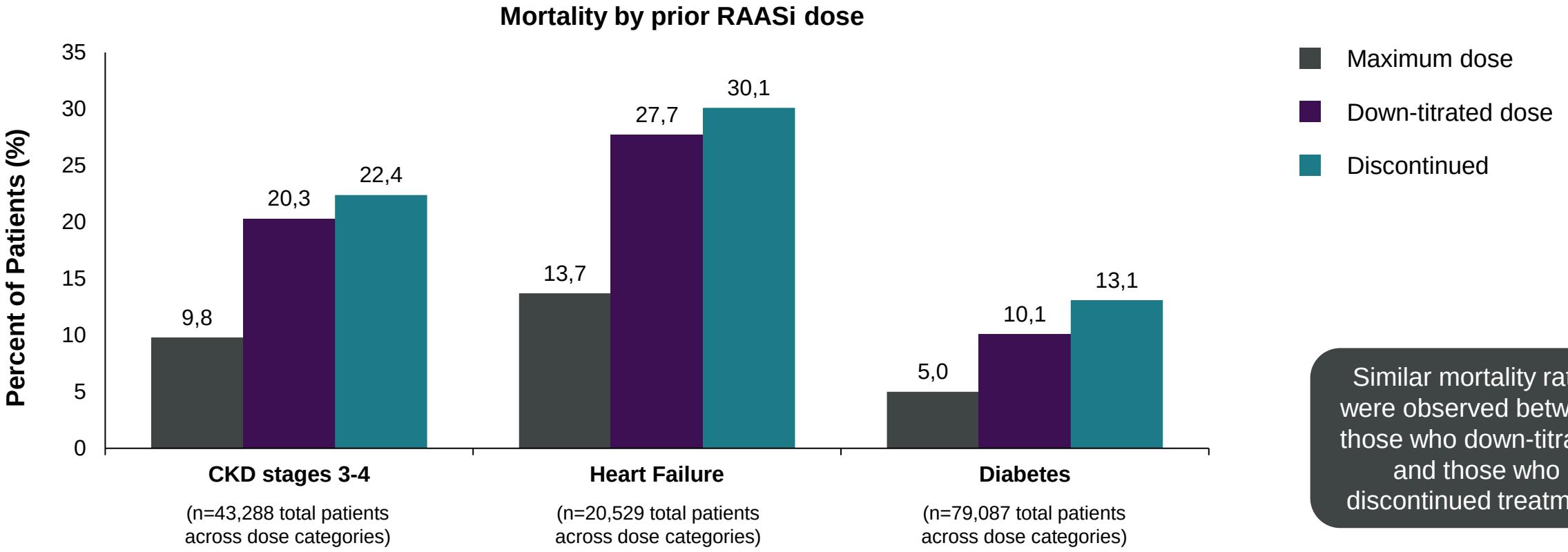
CKD = chronic kidney disease; HF = heart failure; MRA = mineralocorticoid receptor antagonist; RAASi = renin–angiotensin–aldosterone system inhibitor.



1. Trevisan M et al. *Eur J Heart Fail*. 2018;20:1217–1226; 2. Linde C et al. *J Am Heart Assoc*. 2019;8:e012655.

# Down-titration or discontinuation of RAASi therapy is associated with doubling of mortality across patient subtypes

**Retrospective analysis of a US database of electronic health records (Humedica; N>200,000) of patients ≥5 years of age with various comorbidities, with at least 2 serum $K^+$ readings, and with at least 1 outpatient RAASi prescription from 2007-2012**




Similar mortality rates were observed between those who down-titrated and those who discontinued treatment

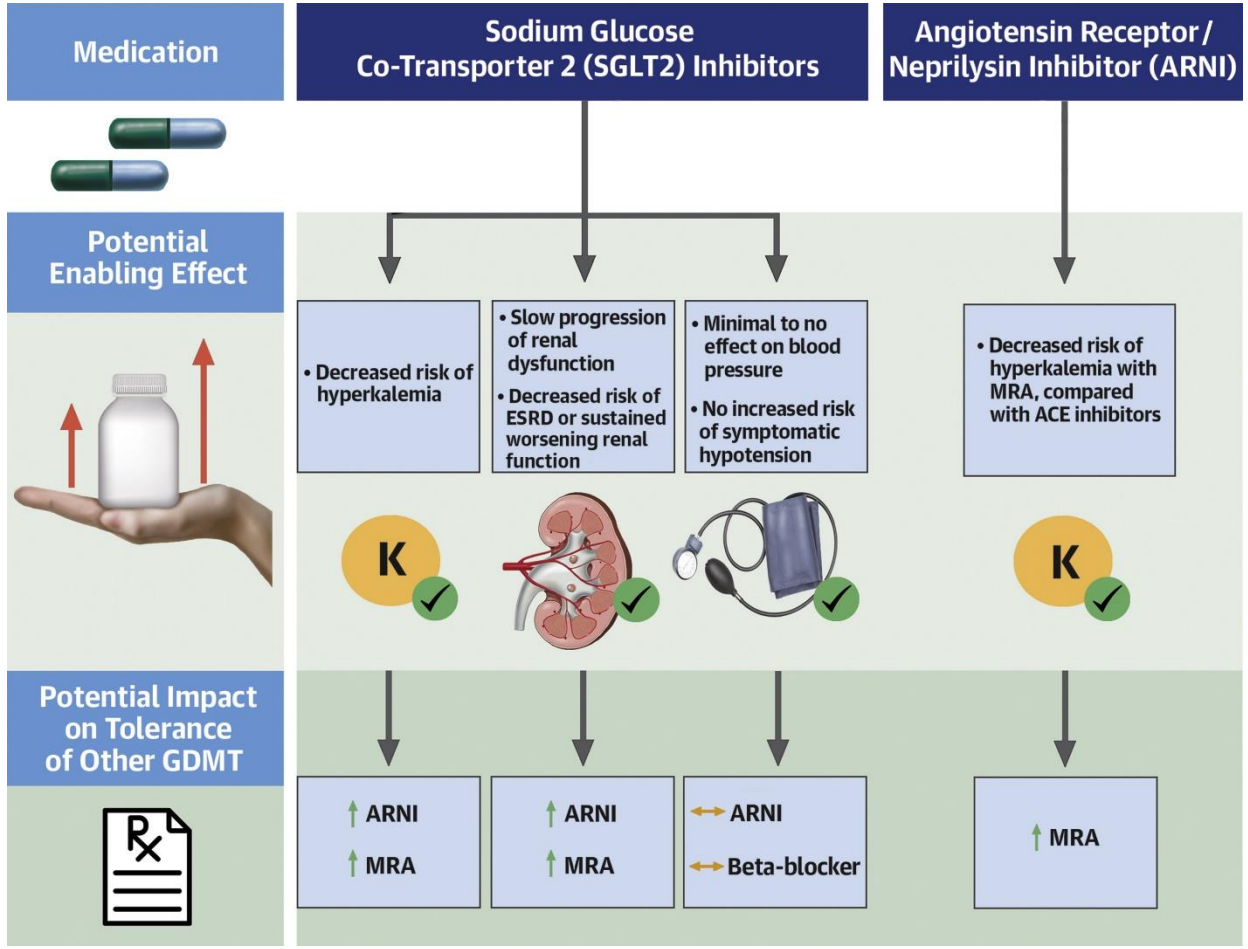
Note: RAASi includes ACEi, ARB, direct renin inhibitor, and select MRA.

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; CKD = chronic kidney disease; HK = hyperkalemia; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; US = United States.



Epstein M et al. *Am J Manag Care.* 2015;21:S212–S220.

# HFrEF GDMT: medications enabling tolerance of each other

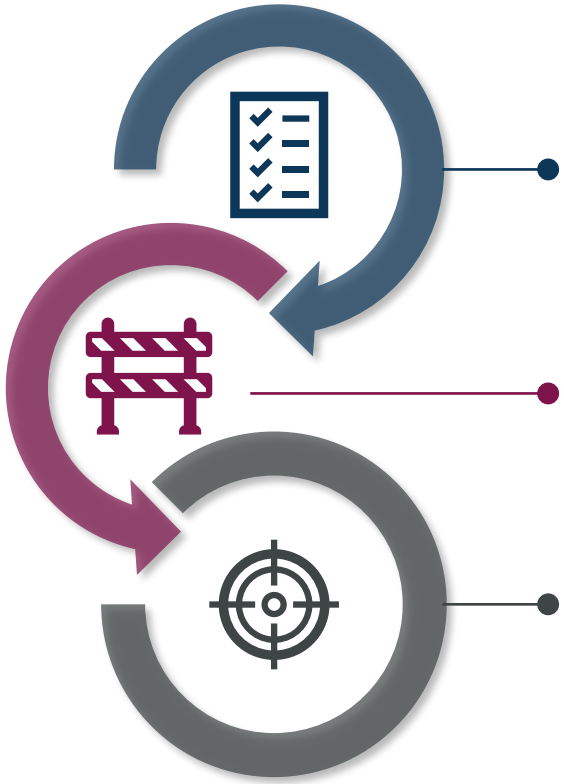



SGLT2i and ARNI may have roles for enabling use of other life-prolonging HFrEF medications

These effects may be largely mediated via potassium handling

Greene SJ, Butler J, Metra M. *Eur J Heart Fail.* 2021;23:1525-8

# Optimal RAASi in the patient with HF:



HF treatment guidelines state RAASi[a] therapy should be initiated and titrated to the highest approved dose that is tolerated to improve patient outcomes[1-3]

Despite these proven benefits of RAASi therapy, hyperkalemia can be a barrier to achieving and maintaining optimal RAASi therapy[4-7]

Management of hyperkalemia with potassium binders may allow for RAASi optimization[8-10]

ESC HF guidelines for the diagnosis and treatment of acute and chronic heart failure define RAASi therapy as ACEi, ARNI, and MRA.[3]

ACEi = angiotensin-converting enzyme inhibitor; ARB = angiotensin-receptor blocker; ARNI = angiotensin receptor-neprilysin inhibitor; CKD = chronic kidney disease; ESC = European Society of Cardiology; HF = heart failure; KDIGO = Kidney Disease: Improving Global Outcomes; MRA = mineralocorticoid receptor antagonist; RAASi = renin-angiotensin-aldosterone system inhibitor; RASi = renin-angiotensin system inhibitor.