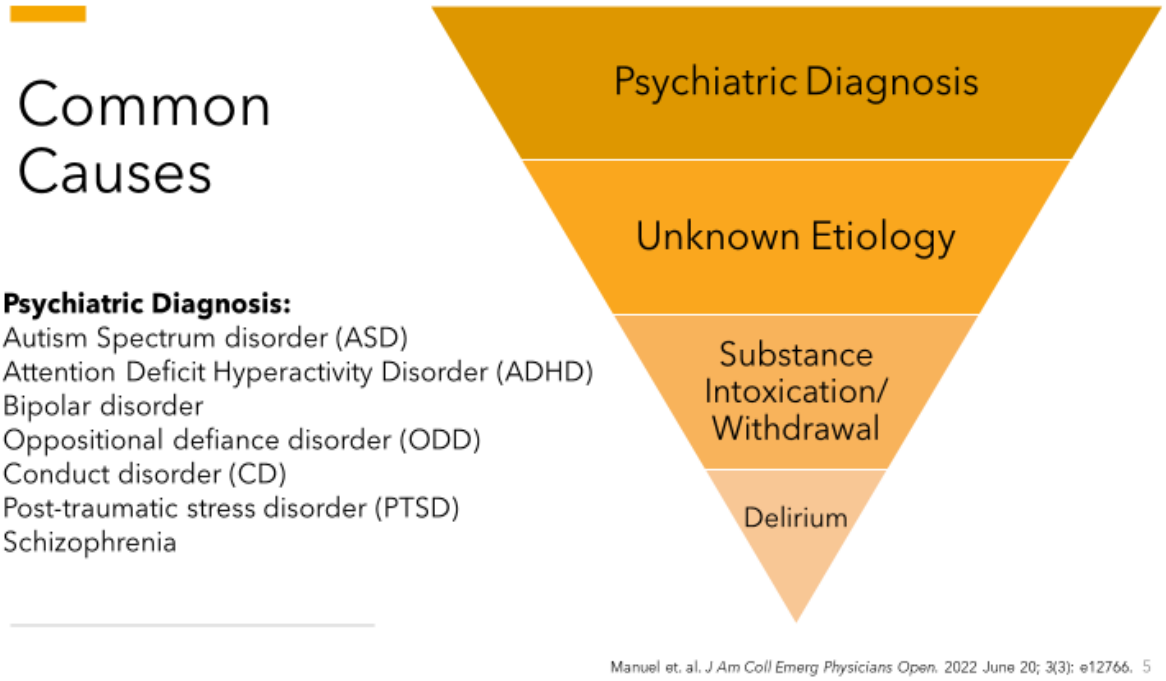
Management of Acute Agitation in Pediatric Patients

Katie Krausz, Pharm.D.
PGY1 Pharmacy Resident at St. Louis Children's Hospital



Neurotransmitter	Imbalance in Agitation	Causing…
Dopamine	Excess	Poor impulse control Increased aggression Mania
Norepinephrine	Excess	Hyperactivity Panic attacks Restlessness
Serotonin	Deficient	Increased anxiety Impulsive aggression
GABA	Deficient	Hallucinations Disorganized behavior

BETA Consensus Document

A. Goals of Therapy
   a. Collaborative practice
   b. Treat based off etiology
      i. Example: If a patient is hungry, find the patient something to eat.
   c. Non-pharm management first
      i. Verbal de-escalation is key in management of acute agitation

Exploring the Role of Potassium Binders to Manage Hyperkalemia:
The Advancement of Heart Failure and Chronic Kidney Disease Management

Tessa Johanning, PharmD
PGY-1 Pharmacy Resident
SSM Health St. Mary's Hospital – St. Louis
November 15, 2022

No financial disclosure or conflicts of interest to disclose

Learning Objectives:

1. Identify patients at risk for developing hyperkalemia.
2. Differentiate adverse effects associated with agents used for management of hyperkalemia.
3. Discuss available literature representing the efficacy and safety associated with the use of potassium binders in heart failure and/or chronic kidney disease.
4. Select patients who may benefit from potassium binder therapy.

Active Learning Questions:

1. Which of the following patients has the greatest risk of developing hyperkalemia?
   a. 70 year old male with chronic kidney disease on losartan
   b. 33 year old female with atrial fibrillation on potassium supplementation
   c. 60 year old male with heart failure on spironolactone
   d. 82 year old female with hypertension on amlodipine

2. Which of the following matches the correct medication to its corresponding adverse effects?
   a. Sodium polystyrene sulfonate - peripheral edema
   b. Patiromer - hypomagnesemia
   c. Sodium zirconium cyclosilicate - acute bowel necrosis

3. If you were recommending patiromer for a patient, which of the following statements would you use to support your decision?
   a. The DIAMOND study showed that 84% of patients with HFrEF and RAASI related hyperkalemia could achieve specified target doses of RAASI with the use of patiromer.
   b. The DIAMOND study showed that 84% of patients with HFrEF and Stage 4 CKD with hyperkalemia could achieve specified target doses of RAASI therapy with the use of patiromer.
   c. The HARMONIZE study showed patiromer reduced hyperkalemia in patients with HF, DM, or CKD, regardless of RAASI use or baseline potassium level.
   d. The HARMONIZE study showed sodium zirconium cyclosilicate reduced hyperkalemia in patients with HF, DM, or CKD, regardless of RAASI use or baseline potassium level.

4. Which of the following patient scenarios may warrant the use of outpatient potassium binder therapy based on current available literature?
   a. A patient with PMH of HFpEF and T2DM on losartan 50 mg daily and empagliflozin 10 mg daily with a potassium of 4.9 mEq/L
   b. A patient with PMH of T2DM and HTN on lisinopril 20 mg with a potassium of 5.2 mEq/L
   c. A patient with PMH of CKD and HFrEF on lisinopril 40 mg daily and spironolactone 25 mg daily with a potassium of 5.8 mEq/L
   d. A patient with PMH of HFrEF and CKD on candesartan 16 mg daily and eplerenone 50 mg daily with a potassium of 6.5 mEq/L

Abbreviations:

ACEI: angiotensin-converting enzyme inhibitors
ADRs: adverse drug reactions
ARB: angiotensin II receptor blockers
ARNI: angiotensin receptor/neprilysin inhibitor
BID: two times a day
CI: confidence interval
CKD: chronic kidney disease
CV: cardiovascular
eGFR: estimated glomerular filtration rate
GDMT: guideline directed medical therapy
GI: gastrointestinal
HF: heart failure
HFrEF: heart failure with reduced ejection fraction
HK: hyperkalemia
K^+: potassium
KDIGO: Kidney Disease Improving Global Outcomes
MACE: major adverse cardiac events
MI: myocardial infarction
MRA: mineralocorticoid receptor antagonists
NSAIDs: Nonsteroidal anti-inflammatory drugs
NYHA: New York Heart Association
QOL: quality of life
RAAS: renin-angiotensin-aldosterone system
RAASI: renin-angiotensin-aldosterone system inhibitors
SPS: sodium polystyrene sulfonate
SZC: sodium zirconium cyclosilicate
TID: three times a day
UACR: urine albumin creatinine ratio

Hyperkalemia[1,2,3,4,5]

Normal Potassium Homeostasis

- Potassium (K^+) is the most abundant cation in the intracellular fluid (98%)
- Maintaining proper distribution of K^+ across cell membrane is critical for normal cell function
- K^+ is excreted by the kidneys (90%) and the gastrointestinal (GI) tract (10%)
- Normal kidneys have a large capacity to excrete K^+ and maintain a normal concentration depending on how much K^+ is present based on diet and medications
- Aldosterone is the key regulator of potassium homeostasis and urinary potassium excretion
- Aldosterone acts in the distal convoluted tubule of the nephron, causing sodium retention and potassium excretion
- Patients with chronic kidney disease (CKD) and heart failure (HF) are more prone to developing hyperkalemia (HK)

Risk Factors

Diet	Disease	Medications	Others
K^+ supplements	eGFR < 60 mL/min/1.73 m^2	RAASI	History of hyperkalemia
Salt substitutes	Diabetes mellitus	Potassium-sparing diuretics	Caucasian
K^+ rich foods	Heart failure	NSAIDs	Advanced age
	Tubular acidosis		

Diagnosis of Hyperkalemia

Potassium Levels	Classifications (KDIGO)	Clinical Presentation
>5.0	Mild	Asymptomatic
≥5.5	Moderate	Muscle weakness, ECG changes, life threatening arrhythmias, paralysis, sudden death
≥6.0	Severe	

- Standard normal range for serum K^+
  - 3.5 – 5.0 mEq/L
- Hyperkalemia is an elevated serum K^+
  - > 5.0 mEq/L
- Electrocardiogram (ECG) changes may be suggestive of hyperkalemia
  - ECG changes with increasing K^+ levels
    - Peaked T wave
    - Prolonged PR interval, wide QRS duration, peaked T wave
    - Loss of P wave, sinusoidal wave
- Rule out pseudo-hyperkalemia
  - A falsely high potassium caused by poor phlebotomy technique, hemolysis, laboratory processing, thrombocytosis, and leukocytosis which can lead to inappropriate intervention

Risks of Hyperkalemia

- HK is associated with muscle weakness, paralysis, and cardiac arrhythmias which lead to increased risk of hospitalization, progression of kidney disease, and even sudden death
- As serum K^+ levels deviate from normal levels, rates of morbidity (including major adverse cardiac events (MACE)) and mortality increase
- There is a U-shaped association between serum potassium and mortality in all groups, with lowest all-cause mortality in controls with potassium values between 4.0 and <5.0 mEq/L

- Patients with the combination of HF, CKD, and DM are at the highest risk of mortality versus those with HF, CKD or DM alone
- All-cause mortality has been shown to be significantly elevated for every 0.1 mEq/L change in K^+ <4.0 and ≥5.0 mEq/L
- Hyperkalemia is associated with higher hospitalization rates and higher hospitalization costs

Incidence of Hyperkalemia[6,7,8]

- Prevalence of HK is 2-3% in the general population
- Patients with CKD, HF, and DM and those using RAASI are at 2-3 times higher risk for hyperkalemia
- The risk of RAASI-induced hyperkalemia is particularly high in patients with HF and concomitant CKD and/or DM
    - Approximately 50% of these patients experience two or more recurrences of hyperkalemia within 1 year

Role of RAASI in HFrEF/CKD

Heart Failure[8,9]

- RAASI therapy (ACEI/ARB/MRA/ARNI) is the cornerstone therapy for patients with heart failure with reduced ejection fraction (HFrEF)
- MACE and death rates are consistently lower in patients treated with RAASI (21-25%) than those not treated with a RAASI (~62-63%)
- 2022 American Heart Association (AHA) HF guidelines recommend up-titrating RAASI up to maximum tolerated dose to reflect doses used in clinical trials

Chronic Kidney Disease[10]

- 2017 AHA guidelines for hypertension recommend using ACEI/ARB as first-line therapy for patients with CKD stage 3 or higher or for patients with CKD stage 1 to 2 with albuminuria
- ACEI/ARB reduce the risk of death, cardiovascular events and slow the progression of kidney disease
- Clinical guidelines recommend using maximum tolerated dose of RAASI with CKD based on results from randomized controlled trials showing the best benefits with moderate to high doses

CKD Stages	eGFR (mL/min/1.73m^2)
Stage 1 Normal	>90
Stage 2 Mild	60-89
Stage 3A Moderate	45-59
Stage 3B Moderate	30-44
Stage 4 Severe	15-29
Stage 5 End Stage	<15

Common Practice Regarding RAASI and Hyperkalemia[11]

Suboptimal Use of RAASI

- RAASI discontinuation and down-titrating to sub-maximal doses are the most common strategies for treatment of RAASI-associated HK
- When RAASI are discontinued due to HK, they are seldom reinitiated in clinical practice
- Suboptimal use and dosing of RAASI is common despite the benefits for reducing mortality and morbidity in patients with HF and CKD
- A study by Epstein et al. in 2015, analyzed RAASI dosing in patients before and after at least 1 hyperkalemia event
    - Discontinuation and down-titration of RAASI dose was more common after moderate-severe hyperkalemia

    - Patients on a maximum dose of a RAASI were down-titrated to a sub-maximum dose or discontinued the RAAS inhibitor nearly half the time (47%) after moderate-to-severe hyperkalemia events and 38% of the time after mild events
- Patients on sub-maximum doses or discontinued RAASI therapy showed consistently worse outcomes including increased mortality rates compared with patients on maximum doses, irrespective of comorbidity status or patient age
    - Over 50% of patients with CKD stages 3 to 4 who discontinued RAASI experienced an adverse outcome or died compared with 47.4% of patients on sub-maximum doses and 42.6% of patients on maximum doses (all comparisons $p < 0.05$)
    - Nearly 60% of patients with HF who discontinued RAASI experienced an adverse outcome or mortality compared with 52.3% of patients on sub-maximum doses and 44.3% of patients on maximum doses (all comparisons $p < 0.05$)

RAASI Therapy and HK: A Therapeutic Dilemma

- Patients who benefit most from RAASI are often those at the greatest risk of severe hyperkalemic events
- While RAASI therapy improves long-term prognosis, increased serum K^+ worsens short-term prognosis
- Currently, no universally accepted consensus exists on best practices for monitoring or management of chronic HK
- Traditional options for treatment of emergent/acute hyperkalemia are not suitable for long-term use and are impractical in the outpatient setting
    - IV calcium, sodium bicarbonate, insulin and dextrose, nebulized beta-adrenergic agonists
- Two novel K^+ binding agents patiromer and sodium zirconium cyclosilicate (SZC), have been shown to normalize elevated serum K^+ levels, maintain normokalemia over time, and prevent recurrent HK

Guideline Recommendations Regarding RAASI Therapy and Hyperkalemia

Society	Serum K^+ (mEq/L)	Recommendations for RAASI therapy in setting of HK
2022 American College of Cardiology/American Heart Association/ Heart Failure Society of America[9]	> 5.0 > 5.5	Use ACEI/ARB with caution (MRAs are not recommended) For patients taking a RAASI, the effectiveness of K^+ binders (patiromer, SZC) to improve outcomes by facilitating continuation of RAASI therapy is uncertain
2021 European Society of Cardiology[12]	>5.0 to ≤6.5 >6.5	In patients with chronic or recurrent HK on RAASI therapy, a K^+ binder may be initiated when K^+ is >5.0 mEq/L. Closely monitor K^+ and continue K^+ lowering therapy unless another treatable etiology for HK is identified. If not taking maximum-tolerated guideline-recommended RAASI dose, start K^+ lowering therapy and titrate RAASI when K^+ is <5.0 mEq/L Discontinue or reduce RAASI therapy; K^+ lowering therapy may be started; closely monitor serum K^+
2022 Kidney Disease: Improving Global Outcomes[13]	> 5.0	Review concurrent drugs and moderate potassium intake Consider: diuretics, sodium bicarbonate, and/or GI cation exchangers Reduce dose or discontinue ACEI/ARB therapy in setting of uncontrolled hyperkalemia as last resort if mitigation strategies are ineffective at achieving normal serum potassium levels

Potassium binders[14,15,16]

Key Characteristics of Potassium Binders

	Sodium Polystyrene Sulfonate (SPS) (KAYEXALATE®)	Patiromer (VELTASSA®)	Sodium Zirconium Cyclosilicate (SZC) (LOKELMA®)
FDA approval (year)	1958	2015	2018
MOA	Nonspecific cation binding in exchange for sodium	Polymer exchange resin; exchanges potassium for calcium	Selective K^+ binding in exchange for sodium and hydrogen
Selectivity for K^+ ion	Nonselective; also binds calcium and magnesium	Selective; also binds magnesium	Highly selective; also binds ammonium
Location of K^+ binding	Colon	Predominantly distal colon	Binds throughout GI tract
Dosing	15 g 1-4 times daily	8.4 g once daily (can adjust dose by 8.4 g daily as needed at one week intervals to obtain desired K^+ level)	5 – 10 g TID for up to 48 hours; for continued treatment, the recommended dose is 10 g once daily
Time to normokalemia	Unconfirmed	Within 1 week	Within 24 hours for 84% of patients
Onset of action	Hours to days	4-7 hours	1 hour following first dose
Adverse drug reactions	Anorexia, constipation, diarrhea, fecal impaction, GI concretions, ischemic colitis, nausea, vomiting	Constipation, hypomagnesemia, diarrhea, nausea, abdominal discomfort and flatulence	Mild-moderate edema
Warnings	Intestinal necrosis; electrolyte disturbances; fluid overload	Worsening of GI motility; hypomagnesemia	GI motility disorders; edema
Contraindications	Hypersensitivity; Obstructive bowel disease; Neonates with reduced gut motility	Known hypersensitivity	None
Drug interactions	Antacids, laxatives, digitalis, sorbitol, lithium, thyroxine; take 3 hours apart; 6 hours apart in patients with gastroparesis	Take 3 hours apart from other oral drugs	Take 2 hours apart from oral medication with gastric pH-dependent bioavailability

Primary Literature

- Recent literature shows that administration of the K^+ lowering agents, patiromer or SZC, may allow RAASI initiation or up-titration in a larger proportion of patients

Patiromer Studies:

- PEARL-HF[17]
    - Phase II RCT; n=105
    - Patients with HF and an indication to initiate spironolactone therapy with either CKD (Stage 3 or higher) or a history of HK resulting in discontinuation of RAASI
    - Patiromer, compared with placebo, lowered serum K^+ levels and resulted in fewer patients developing hyperkalemia and more patients tolerating a dose increase of spironolactone to 50 mg/day over 4 weeks
- AMETHYST-DN[18]
    - Phase II RCT; n=306
    - Outpatients with K^+ >5.0 mEq/L
    - Confirmed the efficacy of patiromer as a K^+ lowering agent in patients with hyperkalemia with diabetes and CKD (Stage 3-4), on RAASI over 52 weeks
    - Excluded patients with NYHA Class III or IV HF
    - Common adverse effects were constipation (6.3%), diarrhea (5.6%), hypokalemia (5.6%) and hypomagnesemia (8.6%) of patients on patiromer
- OPAL-HK[19]
    - Phase III RCT; n=243
    - Patients with Stage 3-4 CKD and K^+ 5.1-6.4 mEq/L with or without HF stabilized on RAASI
    - Mean change in K^+ after 4 weeks with patiromer BID -1.01 mEq/L ($p < 0.001$)
    - After 4 weeks of therapy, patients were split into patiromer vs placebo for another 8 weeks which resulted in hyperkalemia recurrence in 43% of patients on patiromer vs 91% on placebo ($p < 0.001$)
    - 94% of patients on patiromer were able to continue RAASI therapy by the end of the randomized phase compared to 44% of placebo patients

DIAMOND (2022): Patiromer for the management of hyperkalemia in heart failure with reduced ejection fractions: the DIAMOND trial[20]

- Study design
    - Multicenter, double-blind, phase III randomized control trial
    - 1642 patients were screened for eligibility, and 1195 patients were enrolled in the run-in phase lasting up to 12 weeks
        - Patiromer and ACEI/ARB/ARNI and MRA were initiated/optimized with weekly visits
            - Titrated up to maximum of three 8.4 g packs/day of patiromer
            - MRA titrated to 50 mg/day and $\geq$50% recommended doses of other RAASI
    - 878 patients successfully completed the run-in-phase and were randomly assigned to continue patiromer (n =439) vs placebo (n=439)
    - RAASI agents and doses administered at the end of the run-in phase where continued after randomization and were maintained or adjusted at investigator discretion
    - K^+ was measured at baseline, day 3, week 1, 2, 6, 18 and every 3 months after until end of study
    - Designed to evaluate whether patiromer-enabled RAASI therapy can improve clinical outcomes in patients with HFrEF with either hyperkalemia or history of hyperkalemia-related compromise of RAASI therapy

        - Original primary endpoint: Time to cardiovascular (CV) death or first CV hospitalization
            - Changed due to impact of COVID-19
- Purpose (modified)
    - To investigate the impact of patiromer on K^+ levels and its ability to enable specified target doses of RAASI use in patients with HFrEF
- Objectives (modified)
    - Primary endpoint
        - Mean change in K^+ level from baseline
    - Secondary endpoints
        - Time to the first event of hyperkalemia (>5.5 mEq/L)
        - Lack of durable enablement of MRA at target dose (time to discontinuation or reduction of target MRA dose for at least 14 days or until end of the study)
        - All investigator-reported adverse events of hyperkalemia (first and recurrent)
- Inclusion
    - Adults ≥18 years with NYHA Class II-IV HFrEF (EF ≤ 40%) and one of the following:
        - Current HK (>5.0 mEq/L) while receiving RAASI (ACEI/ARB/ARNI and/or MRA)
        - Normokalemic at screening, but history of HK (>5.0 mEq/L) leading to dose reduction or discontinuation of RAASI therapy due to hyperkalemia in the previous 12 months
- Exclusion
    - eGFR <30 mL/min/1.73 m^2
    - Acute decompensated HF or any major CV event within the last 4 weeks
    - Systolic blood pressure <90 mmHg or symptomatic hypotension

- Baseline characteristics
    - At screening, 354 (40.3%) patients had HK and 524 (59.7%) had a normal serum potassium

Characteristics prior to randomization	**Patiromer** n=439 (%)	**Placebo** n=439 (%)
Women	112 (25.5)	126 (28.7)
Region: Central/Eastern Europe	350 (79.7)	349 (79.5)
Hyperkalemia at screening	182 (41.5)	172 (39.2)
NYHA Class II	221 (50.3)	251 (57.4)
NYHA Class III	208 (47.4)	178 (40.7)
CKD		
• Stage 2	159 (36.2)	172 (39.2)
• Stage 3	182 (41.5)	190 (43.3)
ACEI/ARB/ARNI at 100% target dose	275 (62.6)	285 (64.9)
MRA at 100% target dose	437 (99.5)	430 (97.9)

- Statistical analysis
    - T-test used to calculate required sample size to compare two means
        - 820 patients (410 per treatment group) were needed to detect a mean between-group difference of 0.116 with a power of 90% and two-sided alpha of 0.05
    - Primary endpoint assessed using a mixed model for repeated measures with adjustment for pre-specified baseline covariate of geographic region, sex, diabetes, serum potassium, and eGFR
    - Secondary endpoints were analyzed through point estimates by treatment group including:
        - Cox proportional hazards regression model for time to the first event of hyperkalemia of >5.5 mEq/L and time to event of discontinuation or reduction of MRA dose to below target
        - Negative binomial regression was used to analyzed investigator-reported adverse events of HK

- All endpoints were tested for statistical significance for a two-side alpha of <0.05

- Results
  - Run-in period
    - Of the 1038 patients who completed the run-in phase, 878 (84.6%) achieved ≥50% of target dose of the combination RAASI therapy
  - Randomized period

Endpoints	Patiromer n=439	Placebo n=439	Outcome (95% CI); p-value
Primary outcome			
Mean change in K^+ (mEq/L)	0.03	0.13	Difference -0.10 (-0.13 to -0.07); < 0.001
Secondary outcomes			
Number of patients with HK event (K^+ >5.5 mEq/L)	61 (13.9)	85 (19.4)	HR 0.63 (0.45 to 0.87); 0.006
Number of patients with MRA reduction	61 (13.9)	83 (18.9)	HR 0.62 (0.45 to 0.87); 0.006
Total number of HK events	225	316	HR 0.66 (0.53 to 0.81); <0.001

    - There was a significantly greater change from baseline K^+ to end of study in participants with eGFR <45 mL/min/1.73 m^2 [mean change (95% CI) −0.19 (−0.26, −0.12)] compared to participants with eGFR ≥45 ml/min/1.73m^2 [mean change (95% CI) −0.08 (−0.11, −0.04)], p= 0.003
    - 4.1% of patients in the patiromer group compared to 3.2% in the placebo group passed due to cardiovascular death
    - There were 17 HF hospitalizations in the patiromer group vs 20 in the placebo group
  - Safety outcomes
    - Median duration of follow up was 27 weeks (13-43 weeks)
    - Median number of serum potassium assessments for each participant was 5
    - 2.7% in patiromer group vs 2.5% in the placebo group discontinued study drug due to adverse events
    - Proportion of patients with any adverse events was similar in the patiromer (72.9%) and placebo (74.0%) groups
    - ADRs (patiromer vs placebo):
      - Diarrhea: 19 (4.3%) vs 15 (3.4%)
      - Constipation: 11 (2.5%) vs 5 (1.1%)
      - Nausea: 4 (0.9%) vs 4 (0.9%)
      - Hypokalemia: 66 (15.0%) vs 47 (10.7%)
    - The majority of hypokalemic events were mild: 57 (13.0%) in the patiromer group vs 42 (9.6%) in the placebo group
    - Severe hypokalemic events were reported in one patient (0.2%) in each group

- Strengths
  - Study design
  - Represents the largest randomized experience in HF patients with any K^+ binder
  - Included patients with combined CKD and HF

- Limitations
  - Changed primary endpoint
  - Lower enrollment than expected
  - Duration of study
  - Hyperkalemia defined as >5.5 mEq/L
  - Excluded patients with eGFR <30 mL/min/1.73 m^2
- Conclusions
  - After the run-in phase, 84% of patients with HFrEF and RAASI-related hyperkalemia could achieve specified target doses of the RAASI therapy, including an MRA, when treated with patiromer
  - The randomized phase showed that discontinuation of patiromer was associated with a rise in serum potassium, an increased incidence of hyperkalemia events and fewer patients being maintained on MRA at target doses
  - Treatment with patiromer was safe and well tolerated
  - The effects of patiromer on the primary endpoint were consistent across all pre-specified subgroups, including patients with and without chronic kidney disease, providing evidence for the potential of RAASI enablement across risk factors with the use of patiromer
  - The use of patiromer in patients with HFrEF and RAASI-related hyperkalemia was associated with significantly lower serum potassium, fewer hyperkalemia episodes, concurrent use of high doses of MRAs, and overall higher RAASI use
  - Further prospective trials will be needed to confirm if using patiromer to enhance RAASI use can help to improve clinical outcomes

SZC Studies:

- HARMONIZE[21]
  - Phase III, 2-staged RCT; n=258
  - Outpatients with HK (>5.1 mmol/L)
  - Baseline characteristics: Mean of K^+ 5.6 mEq/L, CKD (66%), HF (36%), and DM (66%), 70% of patients were on RAASI
  - Normokalemia was rapidly obtained in 98% patients following SZC 10 g TID for 48 hours (mean K^+ 4.5 mEq/L)
  - Normokalemia (K^+ <5.1 mEq/L) was maintained with SZC 5-15 g daily for 28 days in 90% of patients compared to 48% of patients on placebo ($p < 0.001$).

Primary Endpoint	Placebo	SZC 5 g	SZC 10 g	SZC 15 g
Mean K^+ level days 8-29 (mEq/L)	5.1	4.8	4.5	4.4

Adverse event	Placebo	SZC 5 g	SZC 10 g	SZC 15 g
Edema	2/85 (2.4%)	1/45 (2.2%)	3/51 (5.9%)	8/56 (14.3%)
Hypokalemia	0/85 (0%)	0/45 (0%)	5/51 (9.8%)	6/56 (10.7%)

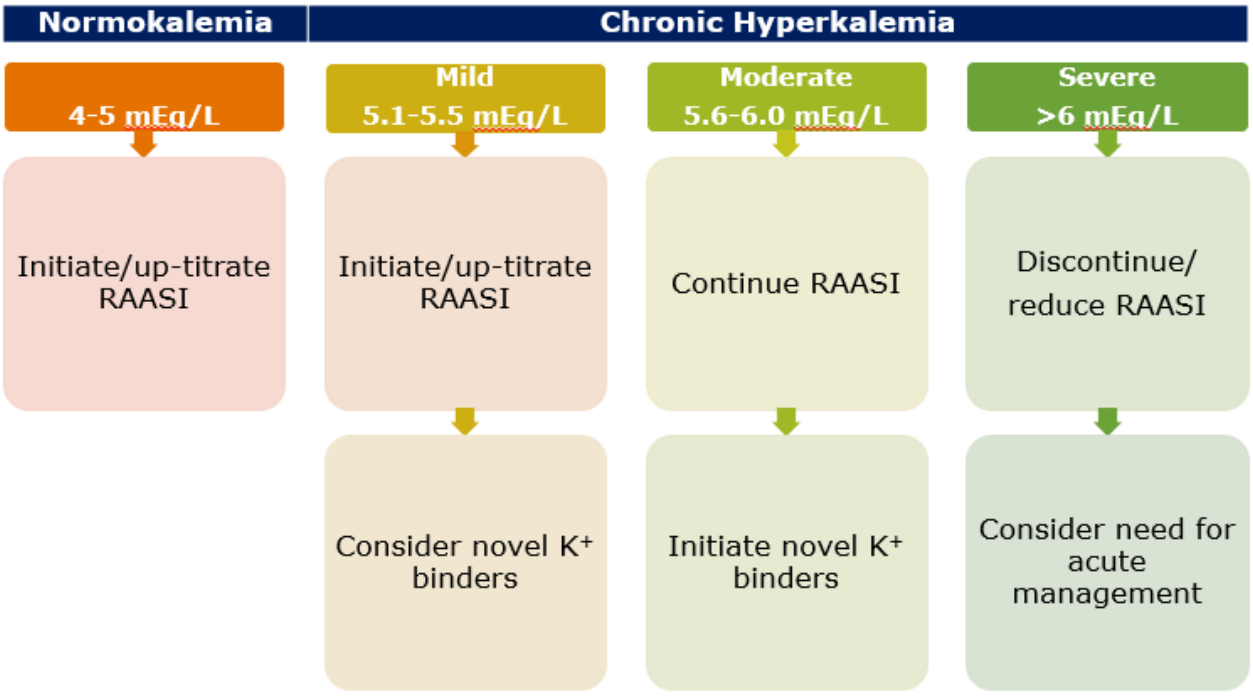
- Post-hoc analysis[22]
  - Multicenter, single-arm, open label phase III trial (n=751)
  - Outpatients with HK (≥5.1 mEq/L) given SZC 10 g TID for 24-72 hours until normokalemia followed by once daily SZC 5-15 g daily for 12 months
  - Stratified by baseline eGFR (mL/min/1.73 m^2): CKD (1-3 vs 4-5)
  - 100% with eGFR <30 vs 95% with eGFR >30 achieved normokalemia within 72 hours

- Normokalemia was maintained for up to 12 months regardless of CKD stage
- Patients with eGFR <30 required higher doses of SZC to maintain normokalemia than those with eGFR >30
- Most common ADRs in eGFR <30 vs eGFR >30 mL/min/1.73 m^2
  - Hypertension 15% vs 8%
  - Peripheral edema 13% vs 8%
  - Urinary tract infection 12% vs 6%

Limitations to Real-World Initiation

- Cost
  - Currently, both novel potassium binders are only available as brand-name medications; VELTASSA® (patiromer) and LOKELMA® (SZC)
    - VELTASSA® 8.4 g → 30 packets = $1,022.52
    - LOKELMA® 10 g → 30 packets = $716.85
- Increased medication burden, risk of side effects, and risk of drug interactions
  - Patients with HF and CKD often have other comorbidities requiring numerous medications for management
  - Adding novel potassium binders to regimens may be difficult to implement especially when considering timing of these medications around other interacting medications
- Additional monitoring for electrolyte imbalances (Mg and K^+)
  - There are currently no monitoring guideline recommendations for initiation of novel potassium binders when used in the outpatient setting
- Guideline recommendations for initiation vary
- Unknown long-term effects/feasibility >12 months

Potential Candidates for $K^{\pm}$ binders to enable RAASI therapy in HFrEF and CKD



*Duration of therapy and monitoring parameters to be determined on a patient by patient basis

- Alternative options for optimization of RAASI in HK
    - Initiate diuretic or increase its dose if necessary (especially if volume overloaded)
    - Initiate sodium bicarbonate if acidotic

- Clinical Considerations
    - For patients with HF and CKD, evaluate interactions with other concurrent medications, GI discomforts, magnesium derangements with patiromer, and edema caused by increased sodium load with SZC (5 g SZC contains 400 mg sodium)

Presenter's Conclusions

- Based on current literature, patiromer and SZC appear to have a potential role as maintenance treatment for HK and in initiating, maintaining, and titrating RAASI therapy in patients with CKD and HF
- The use of patiromer and SZC in patients with HFrEF and RAASI-related hyperkalemia is associated with significantly lower serum potassium, fewer hyperkalemia episodes, and overall higher RAASI use
- There is evidence for efficacy in reducing HK incidence up to 12 months with patiromer and SZC. Both are well tolerated after up to 12 months of exposure, however we are lacking large-scale post-marketing studies
- Must further assess real-world implementation of outpatient potassium binders to enable GDMT optimization
- Clinical outcomes data is still lacking

Future Directions

Upcoming Trial (2023): The LIFT trial: study protocol for a double-blind, randomized, placebo-controlled trial of K+ -binder Lokelma for maximization of RAAS inhibition in CKD patients with heart failure[23]

- Study Design/Methods:
    - Participants with CKD and HF in a 1:1 randomized, double-blind, placebo-controlled trial in which participants will receive either SZC or placebo
    - Will up-titrate RAASI therapy while monitoring their serum K^+ levels and adjusting their SZC dose if necessary
    - Total study period will be 18 months
        - 130 participants will be enrolled for approximately two months each following screening
- Primary outcome
    - Proportion of participants who achieve maximum RAASI dose while maintaining normokalemia
- Secondary outcomes
    - Participants reaching maximum RAASI dose without severe hyperkalemia; time from randomization to hyperkalemia; time from randomization to severe hyperkalemia; number of RAASI dose escalations per participant; final doses of RAASI therapy; changes in quality of life score, eGFR, albumin-creatinine ratio, serum sodium, troponin T; number and duration of hospital admissions; and within-participant change in serum potassium compared to baseline
- Discussion:
    - This trial will be the first to examine the use of SZC for the maximization of RAASI dosing in patients with advanced CKD and HF. It will assess the impact of achieving target RAASI dosing on hospital admission rates and duration of stay, with the hope that optimum RAASI treatment will translate into reduced morbidity and improved QOL

References

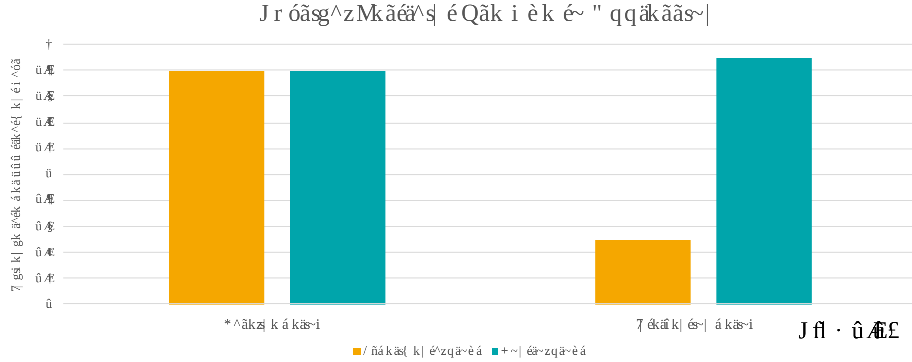
1. Clase CM, Carrero JJ, Ellison DH, et al. Potassium homeostasis and management of dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) Controversies Conference. *Kidney Int*. 2020;97(1):42-61.
2. Di Lullo L, Ronco C, Granata A, et al. Chronic hyperkalemia in cardiorenal patients: risk factors, diagnosis, and new treatment options. *Cardiorenal Med*. 2019;9(1):8-21.
3. Momoniat T, Ilyas D, Bhandari S. ACE inhibitors and ARBs: Managing potassium and renal function. *Cleve Clin J Med*. 2019;86(9):601-607.
4. Xu Y, Fu EL, Trevisan M, et al. Stopping renin-angiotensin system inhibitors after hyperkalemia and risk of adverse outcomes. *Am Heart J*. 2022;243:177-186.
5. Collins AJ, Pitt B, Reaven N, et al. Association of serum potassium with all-cause mortality in patients with and without heart failure, chronic kidney disease, and/or diabetes. *Am J Nephrol*. 2017;46(3):213-221.
6. Silva-Cardoso J, Brito D, Frazão JM, et al. Management of RAASi-associated hyperkalemia in patients with cardiovascular disease. *Heart Fail Rev*. 2021;26(4):891-896.
7. Fonseca C, Brito D, Branco P, Frazão J, Silva-Cardoso J, Bettencourt P. Hyperkalemia and management of reninangiotensin-aldosterone system inhibitors in chronic heart failure and systolic dysfunction: a systematic review. *Rev Port Cardiol*. 2020;39(9):517–541.
8. Muhlestein JB, Kammerer J, Bair TL, et al. Frequency and clinical impact of hyperkalaemia within a large, modern, real-world heart failure population. *ESC Heart Fail*. 2021;8(1):691-696.
9. Heidenreich PA, Bozkurt B, Aguilar D, et al. 2022 AHA/ACC/HFSA Guideline for the Management of Heart Failure: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2022;145(18):e895-e1032.
10. Whelton PK, Carey RM, Aronow WS, et al. 2017 ACC/AHA/AAPA/ABC/ACPM/AGS/APhA/ASH/ASPC/NMA/PCNA Guideline for the Prevention, Detection, Evaluation, and Management of High Blood Pressure in Adults: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Hypertension*. 2018;71(6):e13-e115.
11. Epstein M, Reaven NL, Funk SE, McGaughey KJ, Oestreicher N, Knispel J. Evaluation of the treatment gap between clinical guidelines and the utilization of renin-angiotensin-aldosterone system inhibitors. *Am J Manag Care*. 2015;21(11 Suppl):S212-20.
12. McDonagh TA, Metra M, Adamo M, et al. 2021 ESC Guidelines for the diagnosis and treatment of acute and chronic heart failure. *Eur Heart J*. 2021 Sep 21;42(36):3599-3726.
13. de Boer IH, Khunti K, Sadusky T, et al. Diabetes management in chronic kidney disease: a consensus report by the American Diabetes Association (ADA) and Kidney Disease: Improving Global Outcomes (KDIGO). *Diabetes Care*. 2022:dci220027.
14. US Food and Drug Administration. VELTASSA (patiromer) for Oral Suspension. Highlights of Prescribing Information. 2021.
15. US Food and Drug Administration. LOKELMA. Highlights of Prescribing Information; US Food and Drug Administration: Silver Spring, MD, USA, 2021.
16. Kayexalate [package insert]. Bridgewater, NJ: Sanofi-aventis U.S. LLC; 2017.
17. Pitt B, Anker SD, Bushinsky DA, et al. Evaluation of the efficacy and safety of RLY5016, a polymeric potassium binder, in a double-blind, placebo-controlled study in patients with chronic heart failure (the PEARL-HF) trial. *Eur Heart J*. 2011;32(7):820-8.
18. Pitt B, Bakris GL, Weir MR, et al. Long-term effects of patiromer for hyperkalaemia treatment in patients with mild heart failure and diabetic nephropathy on angiotensin-converting enzymes/angiotensin receptor blockers: results from AMETHYST-DN. *ESC Heart Fail*. 2018;5(4):592-602.
19. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med*. 2015;372(3):211-21.

20. Butler J, Anker SD, Lund LH, et al. Patiromer for the management of hyperkalemia in heart failure with reduced ejection fraction: the DIAMOND trial. *Eur Heart J*. 2022;43(41):4362-4373.
21. Kosiborod M, Rasmussen HS, Lavin P, et al. Effect of sodium zirconium cyclosilicate on potassium lowering for 28 days among outpatients with hyperkalemia: the HARMONIZE randomized clinical trial. *JAMA*. 2014;312(21):2223-33.
22. Roger SD, Lavin PT, Lerma EV, et al. Long-term safety and efficacy of sodium zirconium cyclosilicate for hyperkalaemia in patients with mild/moderate versus severe/end-stage chronic kidney disease: comparative results from an open-label, phase 3 study. *Nephrol Dial Transplant*. 2021;36(1):137-150.
23. Murphy D, Ster IC, Kaski JC, Anderson L, Banerjee D. The LIFT trial: study protocol for a double-blind, randomised, placebo-controlled trial of K+-binder Lokelma for maximisation of RAAS inhibition in CKD patients with heart failure. *BMC Nephrol*. 2021;22(1):254.

" qqäkããsî k s| gsi k| éã flNB " NMãg~äk ± ß

	/ ñákäs{ k| é^zqä~èá Ωflü†£üæ	+~| éä~z5 ä~èá Ωflüß°ßæ
*^ãkz| k	¢¢ü	¢¶ü
7| ékâîk| és~| π	ü°§	¢¶§

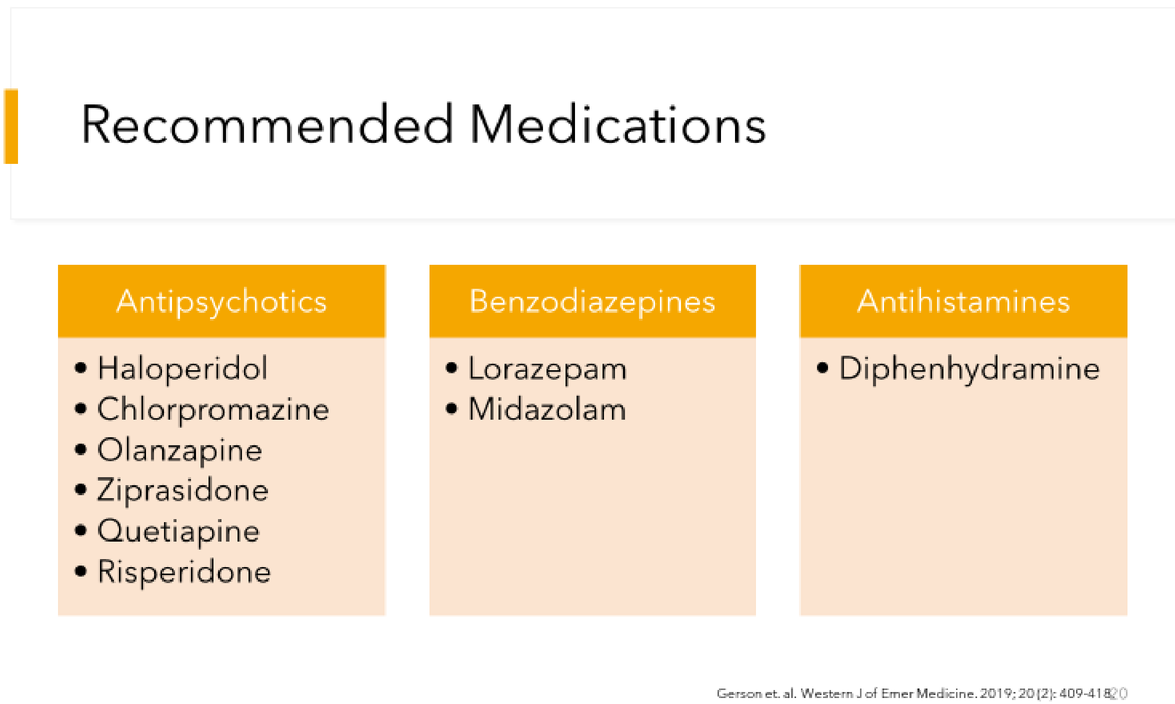
πá fl · ûÆûü



Jfl · ûÆ£

/ ñákäs{ k| é^zqä~èá fl î käf ^zi k√käg^z^és~| qä~èá

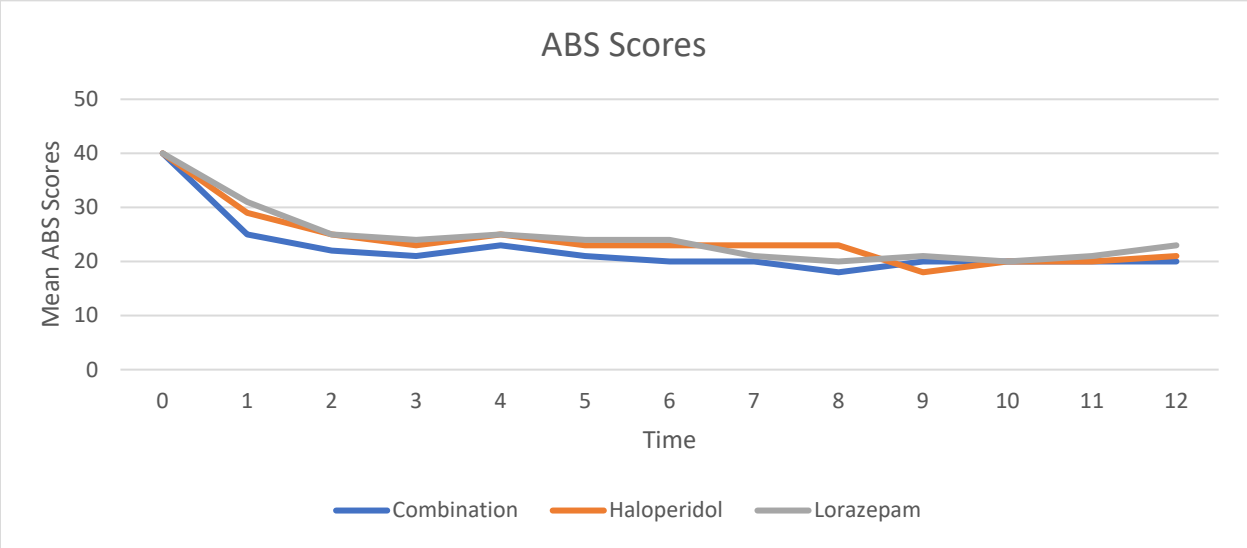
+kz- ≠q^ kéÆzÆä~| éJãógr Æû†† " á±ü°∝ü √ûÆ ü¶



Medication	Mechanism of Action
Haloperidol	Antagonizes dopamine-2
Ziprasidone	Antagonizes dopamine-2, serotonin, alpha-1 and histamine-1
Olanzapine	Antagonizes dopamine-1, serotonin, alpha-1, histamine-1, and muscarinic-1
Chlorpromazine	Antagonizes dopamine-2, histamine-1, and muscarinic-1
Risperidone	Antagonizes dopamine-2, serotonin, and alpha-1
Quetiapine	Antagonizes dopamine-2, serotonin, and histamine-1

Haloperidol (+lorazepam):

Methods	Primary Objective	Results	Conclusions
Double-blind, prospective, randomized study in adults in ED (n=98) IM haloperidol 5mg, IM lorazepam 2mg or combination of therapies	Change from baseline in ABS scores and BPRS scores	Combination vs. Lorazepam vs. Haloperidol: p = 0.04	Combination of lorazepam and haloperidol lower ABS scores more than monotherapy of haloperidol or lorazepam



Ziprasidone:

Methods	Primary objective	Results	Conclusion
Retrospective, nonrandom study in adolescents (n = 52)	Compare efficacy and safety of IM ziprasidone to IM haloperidol and lorazepam	**Restraint duration:** Z: 55 min, H+L: 65 min p=NS **Rescue medications:** Z: 2/28, H+L: 1/24 p=0.6	Ziprasidone is equally effective as the combination of haloperidol and lorazepam

Olanzapine:

Methods	Primary Objective	Results	Conclusions
Retrospective chart review of patients less than 18 years treated with IM ziprasidone or olanzapine	Provide information on dosing, response, safety and tolerability	**Number of doses of emergency medication**: O: 11 vs. Z: 21; p=0.009 **Number of aggressive episodes:** O: 9 vs. Z: 14; p=0.497	IM ziprasidone and IM olanzapine are equally effective

Chlorpromazine:

Methods	Primary Objective	Results	Conclusion
Retrospective chart review in patients <18 years (n=145)	Compare effectiveness and safety of IM chlorpromazine vs. IM olanzapine in treating aggression in pediatrics	Pre-IM BARS score: C: 6.26; O: 6.29 Post-IM BARS score: C: 3.21; O: 2.71 p=0.004	Olanzapine lowers BARS score more than chlorpromazine, but both are efficacious

Risperidone and Quetiapine

Methods	Primary Objective	Results	Conclusions
Prospective, rater-blinded study comparing risperidone, olanzapine, quetiapine and haloperidol	Change in baseline in MOAS total score and the MOAS categories of aggression	See below	No difference between risperidone, quetiapine and olanzapine

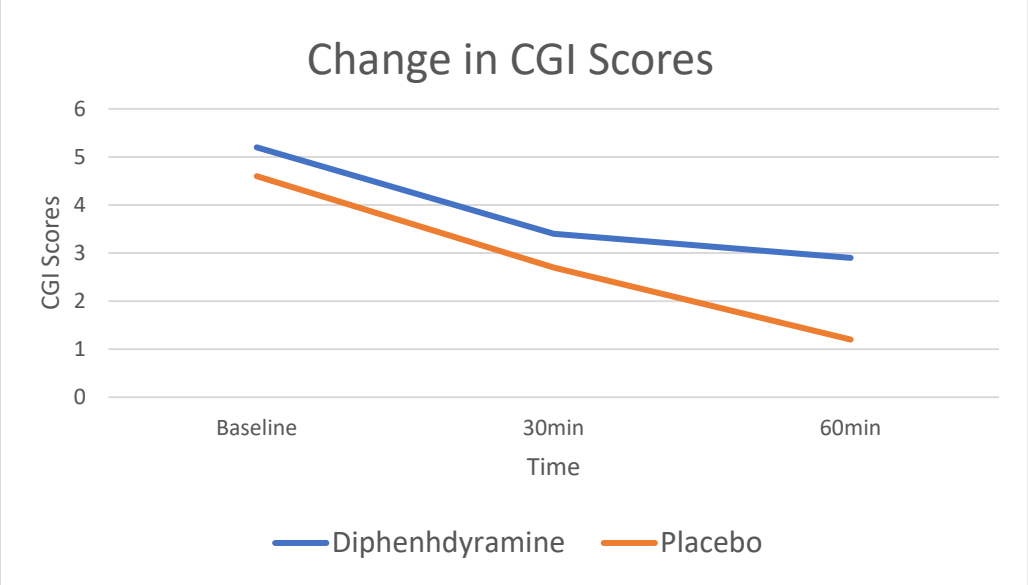
MOAS Total Score	Risperidone	Olanzapine	Quetiapine	Haloperidol	P value
Baseline	7.52	6.79	7.95	9.54	
Endpoint	0.26	0.50	0.05	0.18	0.551

Side effects of Antipsychotics:

Adverse Event	Risperidone	Olanzapine	Quetiapine	Haloperidol	P value
Abnormal gait	7.4%	8.3%	4.6%	7.1%	0.964
Dizziness	3.7%	12.5%	18%	3.6%	0.204
EPS	7.4%	0	0	21.4%	0.012
Headache	3.7%	8.3%	4.6%	7.1%	0.888
Hypotension	7.4%	17%	14%	14%	0.780
Somnolence	11.1%	21%	7%	18%	0.338

Diphenhydramine:

Patients	Method	Results	Conclusion
Male patients (n=21) aged 5-13 years	Double blind, placebo-controlled trial IM Diphenhydramine vs. placebo	See below	Diphenhydramine is no better than placebo for acute agitation



Benzodiazepines:

Methods	Methods	Results		Conclusions
Randomized, prospective, double-blind controlled trial in adults (n=111)	Compare efficacy in sedation between lorazepam, midazolam and haloperidol	Mean time to sedation: L: 32.2 min H: 28.3 min M: 18.3 min $p < 0.05$	Mean time to arousal: L: 217.2 min H: 126.5min M: 81.9 min $P < 0.05$	Midazolam sedates patients the quickest and wears off first. All medications are effective sedation medications.

Medication formulations:

Medication	IM	Tablet	Liquid	ODT
Diphenhydramine	Yes	Yes	Yes	
Haloperidol	Yes	Yes	Yes	
Chlorpromazine	Yes	Yes	Yes	
Olanzapine	Yes	Yes		Yes
Quetiapine		Yes		
Risperidone		Yes		Yes
Lorazepam	Yes	Yes	Yes	
Midazolam	Yes		Yes	

Recommendations:

I always recommend:

Medication	Patient population	With ____ agitation	Because…
PO Olanzapine, Risperidone, or Quetiapine	In patients with a known psychiatric illness and able/willing to take PO	Mild, moderate, or severe	• Targets the neurotransmitters involved with psychiatric illness and acute agitation • Proven efficacy • Improved side effect profile

IM Olanzapine	In patients with a known psychiatric illness and unable/unwilling to take PO	Moderate-severe	• Targets neurotransmitters involved with psychiatric illness and acute agitation • Proven efficacy • Improved side effect profile
PO Diphenhydramine	In patients with an unknown etiology for agitation able to take PO	Mild	• Does not target neurotransmitters involved with psychiatric illness or acute agitation • Benign side effect profile

I sometimes recommend…

Medication	Patient Population	In a situation where…	Because…
PO or IM Chlorpromazine	In patients with a known psychiatric illness	The patient is unresponsive to olanzapine, risperidone or quetiapine	• Targets neurotransmitters involved with psychiatric illness and acute agitation • Proven efficacy • Worse side effect profile compared to olanzapine, risperidone and quetiapine
PO or IM Haloperidol + Lorazepam	In patients with a psychiatric illness	The patient is Moderately-severely agitated and unresponsive to all other agents	• Only targets one neurotransmitter involved with psychiatric illness and acute agitation • Risk of dystonic reactions in pediatric patients

PO or IM Benzodiazepines	In patients with agitation due to an unknown etiology	The patient is moderately-severely agitated	• Does not target neurotransmitters involved with psychiatric illness or acute agitation • Too sedating

Triple Antithrombotic Therapy in Patients with Atrial Fibrillation Post-PCI

Jordan Welch, Pharm.D.
PGY-1 Pharmacy Practice Resident
SSM Health DePaul Hospital
Jordan.Welch@ssmhealth.com

Learning Objectives

1. Define triple antithrombotic therapy
2. Identify safety and efficacy parameters associated with triple antithrombotic therapy
3. Develop a treatment plan based on guideline and primary literature recommendations in patients with atrial fibrillation post-percutaneous coronary intervention

Abbreviations

AC: anticoagulation
ACS: acute coronary syndrome
AF: atrial fibrillation
CABG: coronary artery bypass graft
CAD: coronary artery disease
DAPT: dual antiplatelet therapy
DOAC: direct oral anticoagulant
GI: gastrointestinal
Hbg: hemoglobin
HF: heart failure
ICH: ischemic hemorrhage
MI: myocardial infarction
OAC: oral anticoagulation
PCI: percutaneous coronary intervention
RCT: randomized controlled trial
SAPT: single antiplatelet therapy
SIHD: stable ischemic heart disease
TIA: transient ischemic attack
VKA: vitamin K antagonist

Background

Atrial Fibrillation

- Irregularly irregular rhythm in which the atrial beat out of sync with the ventricles
- Complications: CAD, MI, HF, stroke, increased morbidity and mortality
- Treatment: rate and/or rhythm control + anticoagulation
    - Anticoagulation if CHA_2DS_2VASc score ≥ 2

Acute Coronary Syndrome

- Sudden decreased blood flow to heart musculature, usually caused by plaque rupture and formation of thrombosis
- Types: NSTEMI, STEMI, Unstable angina
- Percutaneous coronary intervention can be used in select patient populations to open the occluded vessel(s)
- Patients that undergo PCI now qualify for DAPT
    - SIHD:
        - BMS: ≥ 1 month DAPT
        - DES: ≥ 6 months DAPT
    - ACS:
        - BMS/DES: ≥ 12 months DAPT

Atrial Fibrillation and Acute Coronary Syndrome

- Triple antithrombotic therapy
    - Anticoagulation
        - DOAC preferred
    - Aspirin
    - $P2Y_{12}$ inhibitor
        - Clopidogrel preferred

Question 1: Which of the following is considered triple antithrombotic therapy?

a. Aspirin + fondaparinux + warfarin
b. Aspirin + prasugrel + clopidogrel
c. Apixaban + cangrelor + tissue plasminogen activator
d. Aspirin + edoxaban + clopidogrel

Primary Literature Review

1. WOEST 2013
    a. Randomized, open-label, multicenter controlled trial
    b. Primary outcome: any bleeding episode within 1 year of PCI
    c. Secondary outcomes: composite of death, MI, stroke, target-vessel revascularization, stent thrombosis
    d. Conclusion: Triple therapy was associated with a statistically significant increase in bleeding complications. Double therapy was not associated with a clinically significant increase in thrombotic events. Triple therapy was associated with an increase in all-cause death.
2. ISAR-Triple 2015
    a. Randomized, open-label, multicenter controlled trial
    b. Primary outcome: composite of death, MI, stent thrombosis, stroke, or TIMI major bleed
    c. Secondary: composite CV death, MI, stent thrombosis, ischemic stroke; TIMI major bleed
    d. Conclusion: Clopidogrel therapy for six weeks as compared to six months was not superior in regard to net clinical outcomes. Ischemic or bleeding events were did not differ in statistical significance between groups.
3. PIONEER- AF PCI 2016
    a. International, multicenter, randomized, open-label, 3-parallel group controlled trial
    b. Primary outcome: occurrence of clinically significant bleeding (composite of major and minor bleeding according to TIMI score, or bleeding requiring medical attention)
    c. Secondary outcomes: individual components of the primary endpoint, composite of death from CV causes, MI stroke; stent thrombosis
    d. Conclusion: Both treatment groups with rivaroxaban were associated with a lower risk of clinically significant bleeding compared to standard triple antiplatelet therapy with VKA. MACE and stent thrombosis was similar amongst groups.
4. RE-DUAL 2017
    a. International, multicenter, open-label, randomized controlled trial
    b. Primary outcomes: ISTH major or clinically relevant non-major bleeding
    c. Secondary outcomes: composite of thromboembolic events, death, or unplanned revascularization

d. Conclusion: In patients with non-valvular AF undergoing PCI, dabigatran at two different doses with a $P2Y_{12}$ inhibitor resulted in a lower risk of major or clinically relevant non-major bleeding compared to triple therapy with warfarin. Dual therapy with dabigatran was non-inferior to warfarin with respect to the composite thrombotic events, death, or unplanned revascularization.

ACC/AHA Guidelines for Management of AF and Complicating ACS

- Patients with a CHA_2DS_2-VASc score of at least 2 should receive anticoagulation (COR I: LOE B-R)
- Clopidogrel should be used over prasugrel in triple therapy (COR IIa: LOE B-NR)
- Double therapy with a $P2Y_{12}$ inhibitor and a VKA is reasonable to use over triple therapy (COR IIa: LOE B-R)
- Double therapy with a $P2Y_{12}$ inhibitor and low-dose rivaroxaban 15 mg daily is reasonable to use over triple therapy (COR IIa: LOE B-R)
- Double therapy with a $P2Y_{12}$ inhibitor and dabigatran 150 mg BID is reasonable to use over triple therapy (COR IIa: LOE B-R)
- Transition from triple therapy to double therapy at 4 to 6 weeks may be considered (COR IIb: LOE B-R)

Primary Literature Review

1. AUGUSTUS 2019
    a. Prospective, randomized, multicenter, multinational, two-by-two factorial clinical trial
        i. Open-label: apixaban and VKA
        ii. Double-blind: aspirin and placebo
    b. Primary outcome: ISTH major or clinically relevant non-major bleeding
    c. Secondary outcome: composite of death or ischemic events
    d. Conclusion: Apixaban and a $P2Y_{12}$ inhibitor resulted in an absolute risk reduction of 4.2% in major or clinically relevant non-major bleeding compared to the treatment groups with a VKA, aspirin, or both, without an increase rate of ischemic events. It was also associated with a 3.9% absolute risk reduction in death or hospitalization. Aspirin was associated with a 7.1% absolute risk increase in major or clinically relevant non-major bleeding.
2. ENTRUST-AF PCI 2019
    a. Randomized, multicenter, multinational, open-label, non-inferiority trial
    b. Primary outcome: ISTH major or clinically relevant non-major bleeding
    c. Secondary outcomes:
        i. Composite CV death, stroke, systemic embolic events, MI and stent thrombosis
        ii. Net clinical benefit, ISTH major bleeding, intracranial and fatal ISTH bleeding, CRNM, minor bleeding, any ISTH-defined bleeding, BARC bleed, TIMI bleed
    d. Conclusion: Amongst patients with AF post-PCI, anticoagulation with edoxaban 60 mg once daily with a P2Y12 inhibitor was non-inferior to triple therapy with a VKA regarding major and clinically relevant non-major bleeding. There were not significant differences in ischemic events.
3. Systematic review and meta-analysis
    a. Trials: AUGUSTUS, ENTRUST-AF, RE-DUAL, PIONEER-AF PCI

b. High-certainty evidence: Dual therapy was associated with a lower risk for **TIMI major bleed** (RD, -0.013 [95% CI, -0.025 to -0.002]), **TIMI major and minor bleeding** (RD, -0.031 [-0.049 to -0.012]) compared with triple therapy
c. Moderate-certainty evidence: In regard to ICH, no statistically significant difference was seen between dual and triple therapy (RD, -0.004 [CI, -0.009 to 0.000])
d. Low-certainty evidence: dual therapy had an inconclusive effect compared with triple therapy on risks for all-cause mortality (RD, 0.004 [CI -0.010 to 0.017]), cardiovascular mortality (RD, 0.001 [CI-0.011 to 0.013]), MI (RD, 0.003 [CI, -0.010 to 0.017]), stent thrombosis (RD, 0.003 [CI, -0.005 to 0.010]), and MACE (RD, 0.003 [CI, -0.016 to 0.023]), no statistically significant difference in effect on stroke risk (RD, -0.003 [CI -0.010 to 0.005])
    i. Upper bounds of the CI were compatible with a possible increase in risk for ischemic outcomes in dual vs. triple therapy
e. Conclusion: High-certainty evidence that the dual therapy with the DOAC reduces risk for bleeding compared to the triple therapy group with VKA. Low-certainty evidence shows inconclusive effects of dual versus triple therapy in risk for death and ischemic events (MI, stent thrombosis, stroke, and MACE). Sensitivity analyses were compatible with a possibility of increased risk for ischemic events in the dual therapy group.

ECS Guidelines for Management of AF: Focus on Post-PCI

- ACS
    - Early cessation of aspirin (≤1 week) and continuation of dual therapy for up to 12 months is recommended (CI:LA)
    - Triple therapy for longer than 1 week after ACS should be considered when the risk of stent thrombosis outweighs the bleeding risk (CIIa:LC)
- Chronic Coronary Syndrome
    - Early cessation of aspirin (≤1 week) and continuation of dual therapy for up to 6 months is recommended
    - Triple therapy for longer than 1 week after ACS should be considered when the risk of stent thrombosis outweighs the bleeding risk, with a total duration ≤1 month (CIIa:LC)

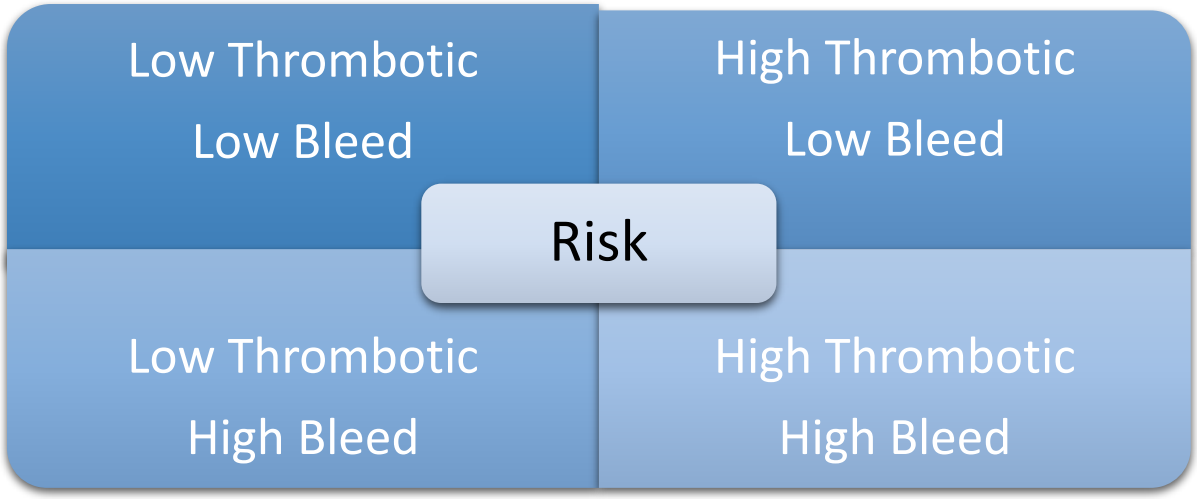
Question 2: Which of the following states are true based on the meta-analysis?

a. VKA triple therapy is associated with a statistically significant decrease in ischemic events compared to DOAC dual therapy
b. DOAC dual therapy reduces the risk for bleeding compared to triple therapy with VKA without a statistically significant increase in ischemic events
c. Sensitivity analyses showed that there was a decrease in ischemic events in the DOAC dual therapy group
d. Dual therapy has a conclusive effective compared to triple therapy that is decreases all-cause mortality, CV mortality, MI, stent thrombosis, and MACE

Triple Antithrombotic Therapy – Bleeding and Thrombosis Risk Evaluation

- Bleeding risk

    - HAS-BLED score: 0 = low, 1-2 = moderate, ≥3 = high
- Thrombosis risk
    - High risk: high CHA_2DS_2VASc score, recent PCI or stroke, and history of CKD



Application to Clinical Practice

Post-PCI	**Low thrombotic, low bleed risk**	**Low thrombotic, high bleed risk**	**High thrombotic, low bleed risk**	**High thrombotic, high bleed risk**
0-1 month	DOAC + $P2Y_{12}$ Inhibitor	DOAC + $P2Y_{12}$ Inhibitor	DOAC + $P2Y_{12}$ Inhibitor + ASA	DOAC + $P2Y_{12}$ Inhibitor
>1-6 months	DOAC + $P2Y_{12}$ Inhibitor	DOAC + $P2Y_{12}$ Inhibitor	DOAC + $P2Y_{12}$ Inhibitor	DOAC + $P2Y_{12}$ Inhibitor
>6-12 months	DOAC + $P2Y_{12}$ Inhibitor	DOAC + $P2Y_{12}$ Inhibitor	DOAC + $P2Y_{12}$ Inhibitor	DOAC only*
>12 months*	DOAC only	DOAC only	DOAC only	DOAC only

Time from PCI	Default	Patients at high thrombotic risk/low bleed risk	Patients at low thrombotic risk/high bleed risk
Peri-PCI	Triple therapy	Triple therapy	Triple therapy
1 month	OAC + SAPT	Triple therapy	OAC + SAPT
3 months		OAC + SAPT	
6 months			
12 months			OAC
>12 months	OAC	OAC	

JM is a 67-year-old male patient is admitted to your cardiac floor after undergoing a PCI for a STEMI. Patient's PMH is significant for AF (on apixaban 5 mg BID), DM, and PAD. The patient has a a CHA_2DS_2VASc score of 4 and a HAS-BLED score of 5. Which regimen and duration best suits JM?

a) DOAC + P2Y12 inhibitor for 0-6 month

b) DOAC only for 12 months

c) DOAC + P2Y12 inhibitor + ASA for >1-6 months

d) DOAC + P2Y12 inhibitor + ASA for 0-1 month

Treatment Summary

Triple therapy of OAC, a $P2Y_{12}$ inhibitor, and ASA carries a high bleeding risk compared to OAC and a $P2Y_{12}$ inhibitor double therapy, without a statistically significant increase in efficacy

The CHA_2DS_2-VASc and HAS-BLED scores can be used to evaluate the thrombotic and bleeding risks, respectively, and can help guide therapy selection and duration

Treatment regimens should be individualized to each patient

References

1. Lippi G, Sanchis-Gomar F, Cervellin G, et al. Global epidemiology of atrial fibrillation: An increasing epidemic and public health challenge [published correction appears in Int J Stroke. 2020 Jan 28;:1747493020905964]. *Int J Stroke*. 2021;16(2):217-221.
2. Secemsky EA, Butala NM, Kartoun U, et al. Use of Chronic Oral Anticoagulation and Associated Outcomes Among Patients Undergoing Percutaneous Coronary Intervention. *J Am Heart Assoc*. 2016;5(10):e004310. Published 2016 Oct 17.
3. Tsao C, Aday A, Almarzooq Z, et al. Heart disease and stroke statistics – 2022 update: a report from the American Heart Association. *Circulation*. 2022;145:e153–e639.
4. Gwyn JCV, Thomas MR, Kirchhof P. Triple antithrombotic therapy in patients with atrial fibrillation undergoing percutaneous coronary intervention: a viewpoint. *Eur Heart J Cardiovasc Pharmacother*. 2017;3(3):157-162.
5. Oldgren J, Wallentin L, Alexander JH, et al. New oral anticoagulants in addition to single or dual antiplatelet therapy after an acute coronary syndrome: a systematic review and meta-analysis. *Eur Heart J*. 2013;34(22):1670-1680.
6. Angiolillo DJ, Goodman SG, Bhatt DL, et al. Antithrombotic Therapy in Patients With Atrial Fibrillation Treated With Oral Anticoagulation Undergoing Percutaneous Coronary Intervention: A North American Perspective-2018 Update. *Circulation*. 2018;138(5):527-536.
7. Alexander JH, Lopes RD, James S, et al. Apixaban with antiplatelet therapy after acute coronary syndrome. *N Engl J Med*. 2011;365(8):699-708.
8. Picard F, Tadros V, Asgar A, et al. Triple antithrombotic therapy in atrial fibrillation patients with an indication for oral anticoagulation undergoing percutaneous coronary intervention. *Circulation*. 2015;8:e003217.
9. Leon MB, Baim DS, Popma JJ, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. *N Engl J Med*. 1998;339(23):1665-1671.
10. Dewilde WJ, Oirbans T, Verheugt FW, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. *Lancet*. 2013;381(9872):1107-1115.
11. Fiedler KA, Maeng M, Mehilli J, et al. Duration of Triple Therapy in Patients Requiring Oral Anticoagulation After Drug-Eluting Stent Implantation: The ISAR-TRIPLE Trial. *J Am Coll Cardiol*. 2015;65(16):1619-1629.
12. Gibson CM, Mehran R, Bode C, et al. Prevention of Bleeding in Patients with Atrial Fibrillation Undergoing PCI. *N Engl J Med*. 2016;375(25):2423-2434.
13. Cannon CP, Bhatt DL, Oldgren J, et al. Dual Antithrombotic Therapy with Dabigatran after PCI in Atrial Fibrillation. *N Engl J Med*. 2017;377(16):1513-1524.
14. January C, Wann S, Calkins H. et al. 2019 focused update of the 2014 guideline for the management of patients with atrial fibrillation. *Circulation*. 2019;140:e125–e151.
15. Lopes RD, Heizer G, Aronson R, et al. Antithrombotic Therapy after Acute Coronary Syndrome or PCI in Atrial Fibrillation. *N Engl J Med*. 2019;380(16):1509-1524.
16. Vranckx P, Valgimigli M, Eckardt L, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. *Lancet*. 2019;394(10206):1335-1343.
17. Khan SU, Singh M, Valavoor S, et al. Dual Antiplatelet Therapy After Percutaneous Coronary Intervention and Drug-Eluting Stents: A Systematic Review and Network Meta-Analysis. *Circulation*. 2020;142(15):1425-1436.
18. Hendricks G, Potpara T, Dagres N, et al. 2020 ESC guidelines for the diagnosis and management of atrial fibrillation. Eur Heart J. 2020;42(5):373-498.
19. Pisters R, Lane DA, Nieuwlaat R, et al. A novel user-friendly score (HAS-BLED) to assess 1-year risk of major bleeding in patients with atrial fibrillation: the Euro Heart Survey. *Chest*. 2010;138(5):1093-1100.

20. Hussain A, Minhas A, Sarwar U, Tahir H, et al. Triple Antithrombotic Therapy (Triple Therapy) After Percutaneous Coronary Intervention in Chronic Anticoagulation: A Literature Review. *Cureus*. 2022;14(2):e21810. Published 2022 Feb 1.
21. Hussain A, Minhas A, Sarwar U, et al. Triple Antithrombotic Therapy (Triple Therapy) After Percutaneous Coronary Intervention in Chronic Anticoagulation: A Literature Review. *Cureus*. 2022;14(2):e21810. Published 2022 Feb 1.
22. Angiolilo D, Goodman S, Bhatt D, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention. *Circulation*. 2018;138:527–536.