HOSPITAL MEDICINE™
SUMMIT

Proceedings from the 2021 Hospital Medicine Summit

INTEGRITY
CONTINUING EDUCATION

Proceedings from the 2021 Hospital Medicine Summit

Program Overview

Since 2014, Integrity Continuing Education, Inc. has produced the Hospital Medicine Summit (HMS), a multidisciplinary educational initiative designed specifically for hospital-based and internal medicine clinicians. Now in its seventh year, HMS remains committed to providing clinically relevant educational updates from leading experts on conditions that are commonly encountered by healthcare clinicians practicing in the hospital setting.

This monograph summarizes recent clinical trial data, practical strategies, and detailed discussions presented by nationally renowned experts during the 2021 virtual conference. The topics include the use of antiplatelet therapy for the prevention of secondary stroke, the management of acute and chronic hyperkalemia from hospital to home, and the role of echocardiography in early detection and evaluation of treatment response in patients with pulmonary arterial hypertension.

These proceedings from the 2021 Hospital Medicine Summit are designed for multidisciplinary teams leading the way healthcare should be delivered to optimize patient care experience and outcomes.

Program Chair

Alpesh Amin, MD, MBA, MACP, SFHM, FACC, FRCP, FHSA
Professor & Chair, Department of Medicine
Executive Director, Hospital Medicine
University of California, Irvine

Release date: December 17, 2021
Expiration date: December 17, 2022
Estimated time to complete activity: 0.5 hours

Target Audience
This educational activity has been designed to meet the needs of physicians, physician assistants, nurse practitioners, registered nurses, and pharmacists who practice in hospital, internal medicine, and chronic-care settings.

Learning Objectives

Restoring Balance From Hospital to Home: Updates on the Management of Acute and Chronic Hyperkalemia

- Discuss the importance of screening for, identifying, and assessing hyperkalemia
- Describe current prescribing information for novel therapies in the effective management of acute and chronic hyperkalemia
- Discuss recent safety and efficacy data supporting the use of novel therapies in patients with hyperkalemia
- Review multidisciplinary strategies for achieving optimal outcomes from hospitalization through discharge and outpatient follow-up

The Role of Echocardiography in Early Detection and Evaluation of Treatment Response: Predicting Prognosis in Patients With Pulmonary Arterial Hypertension

- Describe the role of echocardiography in the early diagnosis of PAH and prediction of prognosis in patients with high-level risk factors
- Summarize recent data regarding the impact of combination therapy on risk reduction and prognosis in patients with PAH
- Discuss the value of patient-focused management and interdisciplinary approaches to support the care of patients with PAH

Getting It Right the First Time: Antiplatelet Therapy for Secondary Stroke Prevention

- Describe the epidemiology and disease burden of primary and recurrent stroke
- Summarize modifiable risk factors and current guideline recommendations for the effective prevention of recurrent secondary stroke
- Define the evolving standard of care in secondary stroke prevention evidenced by recent clinical trial outcomes involving antiplatelet therapies and anticoagulants
- List practical strategies to enhance a multidisciplinary approach to improve secondary stroke prevention

Directions To Learner

There are no fees for participating and receiving CME/CE credit for this activity. During the period of December 17, 2021 through December 17, 2022, participants must:

- Read the learning objectives and faculty disclosures
- Complete the pretest
- Study the educational activity
- Complete the posttest and the evaluation form

A statement of credit will be issued only upon receipt of a completed activity evaluation form and a completed posttest with a score of 70% or better. Pharmacists must check the CPE monitor for their credits within 60 days of the activity.

Pretest **Posttest & Evaluation**

Read Monograph ▸

Contact Information

For information about ACCME accreditation of this activity, please contact Integrity Continuing Education, Inc. at (855) 835-4004 or hms@integrityce.com.

For information about ACPE or ANCC accreditation of this activity, please contact Global at (303) 395-1782 or cme@globaleducationgroup.com.

Media

Internet

Accreditation

Physician Continuing Education

ACCME ACCREDITED WITH COMMENDATION

Accreditation Statement

Integrity Continuing Education, Inc. is accredited by the Accreditation Council for Continuing Medical Education (ACCME) to provide continuing medical education for physicians.

Credit Designation

Integrity Continuing Education, Inc. designates this enduring activity for a maximum of **0.5 *AMA PRA Category 1 Credit*™**. Physicians should claim only the credit commensurate with the extent of their participation in the activity.

Pharmacist Accreditation Statement

ACPE

Global Education Group is accredited by the Accreditation Council for Pharmacy Education as a provider of continuing pharmacy education.

Credit Designation

Global Education Group designates this continuing education activity for 0.5 contact hour (0.05 CEUs) of the Accreditation Council for Pharmacy Education. (Universal Activity Number - 0530-9999-21-291-H01-P.)

This is a knowledge-based activity.

Nursing Continuing Education

Global Education Group is accredited with distinction as a provider of nursing continuing professional development by the American Nurses Credentialing Center's Commission on Accreditation.

This educational activity for 0.5 contact hour is provided by Global Education Group. Nurses should claim only the credit commensurate with the extent of their participation in the activity.

Disclosure Of Conflicts Of Interest

Integrity Continuing Education, Inc. and Global Education Group require instructors, planners, managers, and other individuals who are in a position to control the content of this activity to disclose any real or apparent conflict of interest they may have as related to the content of this activity. All identified conflicts of interest are thoroughly vetted by Integrity Continuing Education, Inc. and Global Education Group for fair balance, scientific objectivity of studies mentioned in the materials or used as the basis for content, and appropriateness of patient care recommendations. All relevant financial relationships have been mitigated.

The following faculty/planners reported the financial relationships or relationships to products or devices they have with ineligible companies related to the content of these CME activities:

Alpesh Amin, MD, MBA, MACP, SFHM, FACC, FRCP, FHSA
Consulting fees: Aseptiscope, Heart Rite, and Sprightly

The following project managers/planners: Lindsay Borvansky, Ashley Cann, Donna Fausak, Andrea Funk, Liddy Knight, Kim Rodriguez, Rhys Williams, RN, MSN, FNP, Maria Rovere, MTSC, and Patima Tanapat, PhD, reported that they or their spouses/life partners, have no financial relationships or relationships to products or devices with commercial interests related to the content of this CME/CE activity.

Disclosure Of Unlabeled Use

This educational activity may contain discussion of published and/or investigational uses of agents that are not indicated by the FDA. Integrity Continuing Education, Inc. does not recommend the use of any agent outside of the labeled indications.

The opinions expressed in the educational activity are those of the faculty and do not necessarily represent the views of any organization associated with this activity. Please refer to the official prescribing information for each product for discussion of approved indications, contraindications, and warnings.

Disclaimer

The information provided at this activity is for continuing education purposes only and is not meant to substitute for the independent medical judgment of a physician relative to diagnostic and treatment options of a specific patient's medical condition.

Provider Statement

This CME activity for ACCME credit is provided by Integrity Continuing Education, Inc.

This CE activity for ANCC and ACPE credit is jointly provided by Global Education Group and Integrity Continuing Education, Inc.

Supporter Acknowledgement

This activity is supported by educational grants from Actelion Pharmaceuticals US, Inc., a Janssen Pharmaceutical Company of Johnson & Johnson, and AstraZeneca Pharmaceuticals.

Table of Contents

The Role of Echocardiography in Early Detection and Evaluation of Treatment Response: Predicting Prognosis in Patients With PAH

Introduction 6
Diagnosis and Screening for PAH 6
Evaluating Prognosis in PAH 7
Treatment of PAH 8
Multidisciplinary Approaches and Patient-Centered Care 8
Summary of Key Points 8
References 9

Getting It Right the First Time: Antiplatelet Therapy for Secondary Stroke Prevention

Epidemiology and Burden of Stroke 10
Prevention of Recurrent Stroke 10
- Lifestyle Changes 10
- Vascular Risk Factor Management 10
- Antithrombotic Therapy 11

Evolving Standards of Care in Stroke Prevention: Combined Antithrombotic Therapy 12
The Central Role of the Multidisciplinary Care Team in Stroke Care: A Focus on Patient Discharge 12
Summary of Key Points 12
References 13

Restoring Balance from Hospital to Home: Updates on the Management of Acute and Chronic Hyperkalemia

Epidemiology and Burden of Hyperkalemia 14
Prevention and Management of Hyperkalemia 14
- Early Identification of Hyperkalemia 14
- Continue RAASi at Optimal Dose 14
- The Role of Potassium-binding Agents 14
- New and Emerging Data 15
- Emerging Agent with Potential Benefit to Hyperkalemia 15

Optimizing Multidisciplinary Care and Transitions from Hospital to Home 16
Summary of Key Points 16
References 17

The Role of Echocardiography in Early Detection and Evaluation of Treatment Response:

Predicting Prognosis in Patients With PAH

I. Introduction

Pulmonary arterial hypertension (PAH) is a rare chronic vascular disease characterized by progressive pulmonary vascular resistance (PVR), leading to right ventricular (RV) failure and ultimately death. Approximately 500–1000 new cases are reported in the US each year.[1] It occurs more frequently in women, affects all ages, and, in the absence of intervention, is the most severe form of pulmonary hypertension (PH).[2] In the absence of treatment, the reported 5-year mortality rate associated with PAH ~40%.[3,4] Consequently, the central goal in PAH care is early detection to enable prompt initiation of treatment to prevent RV failure.

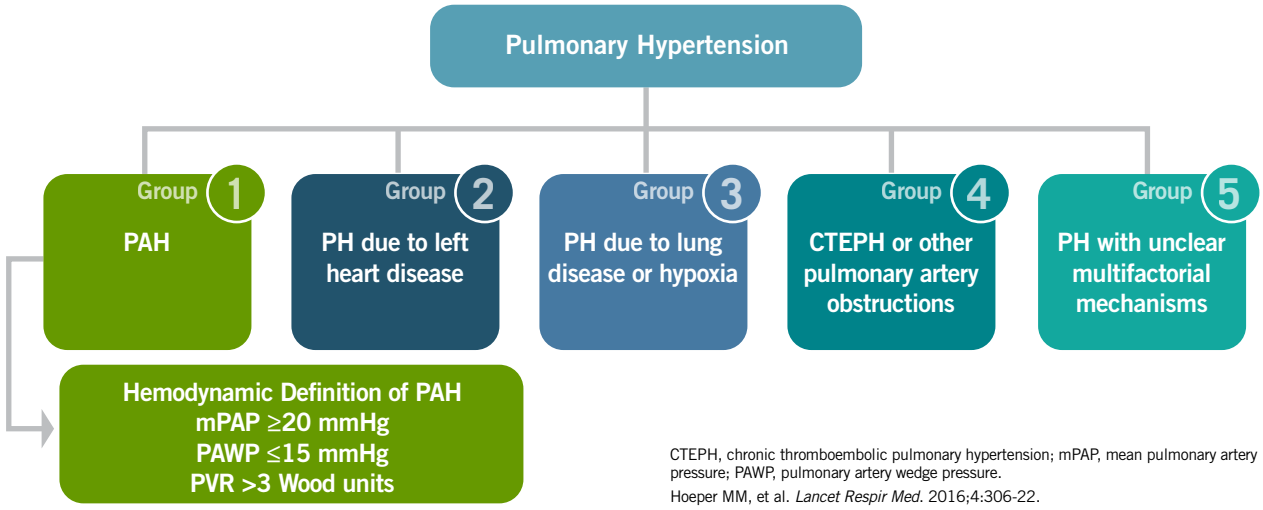
The World Health Organization (WHO) classifies PH into five distinct groups (**Figure 1**).[5] Group 1 PH, which comprises PAH, is defined pathophysiologically by the presence of plexiform lesions and hemodynamically by mean pulmonary arterial pressure (mPAP) >20 mmHg, pulmonary arterial wedge pressure (PAWP) ≤15 mmHg, and PVR ≥3 Wood units (WU). PAH subtypes include idiopathic, heritable, and drug/toxin-induced PAH, as well as those associated with certain systemic conditions, specifically, connective tissue disease and to a lesser extent systemic lupus erythema, HIV, portal hypertension, liver disease, and schistosomiasis. Also included in the Group 1 classification are two rare diseases that are difficult to distinguish from PAH: PVOD and pulmonary capillary hemangiomatosis, and persistent PH of the newborn.

II. Diagnosis and Screening for PAH

Early diagnosis of PAH can be challenging as initial symptoms, which occur primarily with exertion, are nonspecific. The most common are dyspnea, fatigue, weakness, other nonspecific symptoms, angina, and syncope; ~90% of patients with PAH present with dyspnea.[6] Less commonly, patients may present early on with dry cough and exercise-induced symptoms. In more advanced cases, abdominal distension and peripheral edema (signs of right heart failure) become apparent.[6] Symptoms specific to underlying causes of PAH may also be observed; for example, telangiectasia, digital ulceration, and sclerodactyly are typical in systemic scleroderma- and connective tissue disease (CTD)-associated PAH, whereas inspiratory crackles are associated with

Figure 1

WHO Classification of Pulmonary Hypertension



CTEPH, chronic thromboembolic pulmonary hypertension; mPAP, mean pulmonary artery pressure; PAWP, pulmonary artery wedge pressure.

Hoeper MM, et al. *Lancet Respir Med.* 2016;4:306-22.

interstitial lung disease (ILD), and spider nevi, testicular atrophy, palmar erythema, and asterixis may be seen with liver disease.[6] Likewise, clubbing is also a feature of liver disease, as well as coronary heart disease (CHD), ILD, and pulmonary veno-occlusive disease (PVOD).[6]

Physical exam findings indicative of pulmonary artery pressure elevation include parasternal lift, loud P2, RV S3, pansystolic murmur of tricuspid regurgitation, and diastolic murmur of pulmonary regurgitation. As PAH progresses, elevated jugular venous pressure (JVP), hepatomegaly, ascites, peripheral edema, and cool extremities also become evident.[6]

The differential diagnosis of PH is broad and includes heart failure, congestive cardiomyopathy, dilated systolic diastolic heart failure, coronary artery disease (CAD), other left-sided heart disease, aortic stenosis, mitral stenosis, aortic regurgitation, mitral regurgitation, pulmonary embolism, chronic thromboembolic pulmonary hypertension (CTEPH), and lung diseases (eg, COPD and ILD). Therefore, along with the physical exam, the diagnostic workup for suspected PAH should also include echocardiography, ventilation-perfusion (V/Q) scan, pulmonary function tests (PFTs), chest CT (HRCT), B-type natriuretic (BNP)/N-terminal (NT)-proBNP measurement, six-minute walk test (6MWT), and right heart catheterization (RHC).[1,6,7]

Because early diagnosis is critical for improving PAH outcomes, screening of at-risk populations is of paramount importance. Patients who should be screened include those with CTD, human immunodeficiency virus (HIV), sickle cell disease, liver disease, and CHD, as well as those using certain medications/drugs.[8] While RHC remains the gold standard for measuring RV hemodynamics and is required for PAH diagnosis, the procedure is invasive and often associated with complications, making it unsuitable for screening.[9] Echocardiography, on the other hand, is noninvasive and can provide meaningful hemodynamic estimates to guide next steps in management. Indeed, current European Society of Cardiology/European Respiratory Society (ESC/ERS) guidelines recommend echocardiography to assess the probability of PH and inform decisions about whether to initiate RHC.[6,10] (**Figure 2**)

III. Evaluating Prognosis in PAH

Several strategies may be used to evaluate PAH prognosis. Perhaps most important is the identification of WHO functional class (FC); the 5-year survival rate associated with WHO FC 1 vs WHO FC 4 is ~90% vs ~50%.[3] In addition to WHO FC, additional prognostic measures are highlighted in the ESC/ERS guidance on risk assessment.[6] These include dyspnea, signs of right heart failure and the rate of its progression, the presence or absence of syncope, six-minute walk distance (6MWD), cardiopulmonary exercise tolerance test, and NTproBNP/BNP, echo or magnetic resonance imaging (MRI) findings, right atrial size, and hemodynamics. Another approach that can be easily applied in the clinic is the use of the REVEAL Risk Score (RRS), which considers not only PH subgroup, but also age, comorbidities, and FC.[11] Because RRS provides numerical information, it can not only guide treatment selection, but also help gauge treatment response when followed over time.

Figure 2

Guidelines for Echocardiographic Evaluation of Patients With Suspected PH

Echocardiographic probability of PH in symptomatic patients with a suspicion of PH

Peak TRV (m/s)	Presence of Other Echo 'PH Signs'*	Echocardiographic Probability of PH
≤2.8 or not measurable	No	Low
≤2.8 or not measurable	Yes	Intermediate
2.9–3.4	No	
2.9–3.4	Yes	High
>3.4	Not required	

Echocardiography is recommended to assess the "level of probability of PH," and results should be interpreted to support the decision to initiate cardiac catheterization.

Echocardiographic signs suggesting PH used to assess the probability of PH in addition to TRV measurement

A — The Ventricles**	B — Pulmonary Artery**	C — Inferior Vena Cava and Right Atrium**
Right ventricle/left ventricle basal diameter ratio >1.0	RV outflow Doppler acceleration time <105 msec and/or midsystolic notching	Inferior cava diameter >21 mm with decreased inspiratory collapse (<50% with a sniff or <20% with quiet inspiration)
Flattening of the interventricular septum (LV eccentricity index >1.1 in systole and/or diastole)	Early diastolic pulmonary regurgitation velocity >2.2 m/sec	Right atrial area (end-systole) >18 cm^2
	PA diameter >25 mm	

*See bottom table; **Echocardiographic signs from ≥2 different categories (A/B/C) from the list should be present to alter the level of echocardiographic probability of PH.

LV, left ventricular; PA, pulmonary artery; TRV, tricuspid regurgitation velocity.

Galie N, et al. *Eur Heart J.* 2016;37(1):67-119.

IV. Treatment of PAH

The goals of PAH management are to reduce and lessen the severity of symptoms, prevent clinical worsening (ideally, achieve improvement), and improve hemodynamic measures, survival, exercise capacity, and overall quality of life (QoL). Patients should be regularly evaluated in a consistent, systematic manner with care coordinated between local physicians and PH centers.[12] Contributing causes should be treated aggressively and patients encouraged to participate in supervised exercise activity and maintain current immunizations (influenza, pneumococcal pneumonia, and COVID-19).[12] Pregnancy, hypoxia, nonessential surgery, and intubation should be avoided if possible.[12] Lastly, providers should consider when it is appropriate to incorporate palliative care services.[12]

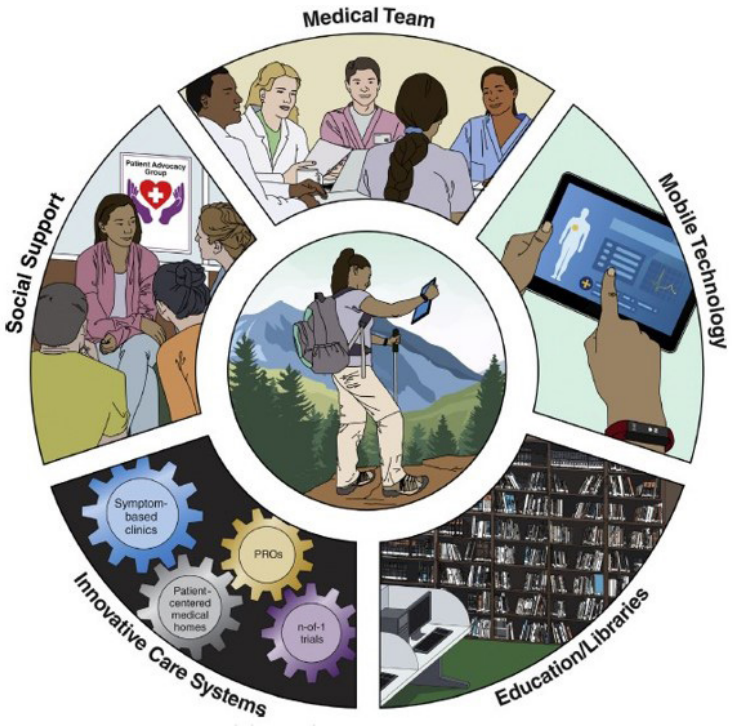
With regard to pharmacologic PAH treatment, a wide range of therapies targeting the NO, endothelial, and prostacyclin pathways have shown good efficacy and safety, and are FDA approved.[2,13] Although approval for these agents was given in the context of monotherapy, the standard of care has recently undergone a significant shift based on evidence that combination therapy is universally superior to monotherapy.[6] In the pivotal AMBITION trial, initial combination therapy with ambrisentan plus tadalafil reduced the risk for clinical failure vs either agent alone (HR=0.50; 95% CI, 0.35–0.72; $P < 0.001$).[14] Combined therapy was also associated with improvements in NT-proBNP, levels, clinical response rate, & 6MWT. Adverse events (AEs) were more common with combined therapy vs monotherapy, but did not lead to increased discontinuation. Subsequently, significant efforts have been made to determine the added therapeutic value of the inclusion of a third agent. Findings from the TRITON trial showed that upfront triple vs double therapy (macitentan + tadalafil + selexipag/placebo) did not improve outcomes but resulted in more frequent AEs.[15] However, later post hoc analyses along with recent work have made it clear that additional studies are needed.[16,17] In a small retrospective study by D'Alto et al, triple upfront combination therapy was associated with clinical and hemodynamic improvement and right-sided heart reverse remodeling.[18] More recently, a study by Boucly et al found that upfront triple therapy was independently associated with a lower mortality risk (HR=0.29; 95% CI, 0.11–0.80; $P = 0.017$), and that among patients initiated on a parenteral prostacyclin, those on triple therapy had a higher survival rate than those on monotherapy or dual therapy.[19]

V. Multidisciplinary Approaches and Patient-Centered Care

Patients with PAH have a range of concerns, many of which are often not immediately apparent to providers, spanning a broad range extending beyond traditional PAH parameters. Recent surveys have identified patient concerns arising at the time of diagnosis, as well as others that manifest over the course of disease management.[20] Among these are fears related to delayed diagnosis, being managed by multiple physicians and institutions, and invasive procedures, as well as disease impact on health-related QoL, employment, education, social life, intimacy, and finances. Furthermore, patients report persistent anxieties about isolation, loneliness, exclusion, lack of understanding by others, need for information, and inability to perform routine activities.

To provide patients with optimal disease treatment and address the full spectrum of their concerns, a multidisciplinary, collaborative approach is key. Although improving care begins with the medical team, complementary strategies are also important (**Figure 3**).[21] Patient education; support from social services, and family and patient support groups; the use of mobile technology; and opportunities to participate in innovative care systems (eg, clinical trials) all contribute to empowering patients, enabling them to better understand their disease and engage in self-management.

Figure 3



VI. Summary of Key Points

PAH is a chronic vascular disease characterized progressive PVR, RV failure, and eventual heart failure, if left untreated. Early recognition, accurate diagnosis, and treatment based on patient risk are central to avoiding morbidity and mortality. Although RHC is required for diagnosis, echocardiography plays a key role in detecting PAH in the preclinical stages, as well as evaluating prognosis, treatment options, and therapeutic response. Multiple approved treatments for PAH targeting the NO, endothelial, and prostacyclin pathways have shown good safety and efficacy, particularly when used in combination. Along with the use of these treatments, a multidisciplinary, patient-centered approach to care that involves collaboration between PH centers, patients, and caregivers can significantly improve health outcomes for patients with PAH.

References

1. Pulmonary Arterial Hypertension. National Organization for Rare Disorders. Accessed October 21, 2021. https://rarediseases.org/rare-diseases/pulmonary-arterial-hypertension/

2. Humbert M, Sitbon O, Simonneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med.* 2004;351(14):1425-1436.

3. Farber HW, Miller DP, Poms AD, et al. Five-year outcomes of patients enrolled in the REVEAL Registry. *Chest.* 2015;148(4):1043-1054.

4. McLaughlin VV, Shillington A, Rich S. Survival in Primary Pulmonary Hypertension. *Circulation.* 2002;106(12):1477-1482.

5. Hoeper MM, Humbert M, Souza R, et al. A global view of pulmonary hypertension. *Lancet Respir Med.* 2016;4(4):306-322.

6. Galiè N, Humbert M, Vachiery JL, et al. 2015 ESC/ERS Guidelines for the diagnosis and treatment of pulmonary hypertension: The Joint Task Force for the Diagnosis and Treatment of Pulmonary Hypertension of the European Society of Cardiology (ESC) and the European Respiratory Society (ERS): Endorsed by: Association for European Paediatric and Congenital Cardiology (AEPC), International Society for Heart and Lung Transplantation (ISHLT). *Eur Heart J.* 2016;37(1):67-119.

7. Stringham R, Shah NR. Pulmonary arterial hypertension: an update on diagnosis and treatment. *Am Fam Physician.* 2010;82(4):370-377.

8. Kiely DG, Lawrie A, Humbert M. Screening strategies for pulmonary arterial hypertension. *Eur Heart J Suppl.* 2019;21(Suppl K):K9-k20.

9. Todaro MC, Carerj S, Zito C, Trifirò MP, Consolo G, Khandheria B. Echocardiographic evaluation of right ventricular-arterial coupling in pulmonary hypertension. *Am J Cardiovasc Dis.* 2020;10(4):272-283.

10. Jang AY, Shin MS. Echocardiographic screening methods for pulmonary hypertension: A practical review. *J Cardiovasc Imaging.* 2020;28(1):1-9.

11. Benza RL, Gomberg-Maitland M, Miller DP, et al. The REVEAL Registry risk score calculator in patients newly diagnosed with pulmonary arterial hypertension. *Chest.* 2012;141(2):354-362.

12. Klinger JR, Elliott CG, Levine DJ, et al. Therapy for pulmonary arterial hypertension in adults: Update of the CHEST guideline and expert panel report. *Chest.* 2019;155(3):565-586.

13. Yerly P, Prella M, Aubert JD. Current management of pulmonary arterial hypertension. *Swiss Med Wkly.* 2016;146:w14305.

14. Galiè N, Barberà JA, Frost AE, et al. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Engl J Med.* 2015;373(9):834-844.

15. Chin KM, Sitbon O, Doelberg M, et al. Three- versus two-drug therapy for patients with newly diagnosed pulmonary arterial hypertension. *J Am Coll Cardiol.* 2021;78(14):1393-1403.

16. McLaughlin V, Chin K, Doelberg M, et al. Initial triple oral therapy in pulmonary arterial hypertension (PAH): Extended long-term outcome data from TRITON. *J Heart Lung Transplant.* 2021;40(4, Supplement):S108.

17. Galie N, Sitbon O, Doelberg M, et al. Long-term outcomes in newly diagnosed pulmonary arterial hypertension (PAH) patients receiving initial triple oral combination therapy: insights from the randomised controlled TRITON study. *Eur Heart J.* 2020;41(Supplement_2).

18. D'Alto M, Badagliacca R, Argiento P, et al. Risk reduction and right heart reverse remodeling by upfront triple combination therapy in pulmonary arterial hypertension. *Chest.* 2020;157(2):376-383.

19. Boucly A, Savale L, Jaïs X, et al. Association between initial treatment strategy and long-term survival in pulmonary arterial hypertension. *Am J Respir Crit Care Med.* 2021;204(7):842-854.

20. McGoon MD, Ferrari P, Armstrong I, et al. The importance of patient perspectives in pulmonary hypertension. *Eur Respir J.* 2019;53(1).

21. Wohlfahrt P, Stehlik J, Pan IZ, Ryan JJ. Empowering people living with heart failure. *Heart Fail Clin.* 2020;16(4):409-420.

Getting It Right the First Time: Antiplatelet Therapy for Secondary Stroke Prevention

I. Epidemiology and Burden of Stroke

Stroke is the fifth leading cause of mortality, as well as accounting for approximately 15–18% of all cardiovascular disease-related death, in the US.[1] Furthermore, it is also a leading cause of serious long-term disability, with greater than half of patients over 65 years of age reporting persistent reductions in mobility following a stroke.[1] In general, stroke is associated with a range of short- and long-term consequences spanning across different domains.[2] Among these are various pain syndromes, depression, cognitive impairment, gait instability, falls, and fractures, which collectively have a substantial detrimental impact on patient independence and overall health-related quality of life.[3-6] The estimated economic impact of these stroke-related outcomes has been reported to be nearly $46 billion.[1] This includes both direct and indirect costs related to health care services, therapies, and diminished work productivity.

Of the greater than 795,000 strokes that occur each year, 25% are recurrent.[7] After a stroke or transient ischemic attack (TIA), the probability of a secondary event is approximately 10%, 15%, and 18% at 1 week, 1 month, and 3 months, respectively; by 10 years, 40% of patients who have had a stroke or TIA will have experienced a recurrence.[8,9] Although the risk of recurrent stroke or TIA is high, it can be significantly mitigated with appropriate secondary stroke prevention measures.[10]

II. Prevention of Recurrent Stroke

Lifestyle Changes

The vast majority of risk for ischemic and hemorrhagic stroke can be attributed to modifiable risk factors such as high blood pressure (BP), poor diet, physical inactivity, smoking, and abdominal obesity.[11] Nevertheless, despite the well-documented benefits associated with control of these modifiable risk factors, they remain poorly controlled among stroke survivors.[12-14] In an effort to help address this issue, the American Heart Association/American Stroke Association (AHA/ASA) has made specific recommendations related to nutrition, exercise, smoking, alcohol consumption, and substance use.[10] Briefly, patients are encouraged to adhere to a Mediterranean-type diet, reduce sodium intake (for those with hypertension [HTN]), and engage in an exercise routine that includes aerobic activity and, ideally, is accompanied by behavioral counseling. Additionally, the AHA/ASA recommends a program supervised by a health care provider in addition to rehabilitation for patients with deficits in ability to exercise, and ≥3 min of standing/light exercise every 30 minutes for patients who sit for long uninterrupted periods. Counseling with or without drug therapy to achieve smoking cessation (or reduction) is strongly recommended, along with avoidance of environmental tobacco smoke. Lastly, recommendations related to alcohol consumption and substance use generally advocate restriction or elimination altogether, accompanied by education on associated health risks, and counseling and specialized services as appropriate.

Vascular Risk Factor Management

The AHA/ASA has also provided detailed guidance regarding other prevention strategies in relation to the management of hypertension, hyperlipidemia, blood glucose, and obesity:

Brief Overview of Recommendations	
Hypertension	Following a stroke or TIA, strategies for reducing risk for stroke recurrence in patients with HTN include individualized antihypertensive therapy, with a target BP of <130/80 mm Hg for the majority of patients. For those without a history of HTN a target BP ≥130/80 mmHg is recommended, with the suggestion that antihypertensive medication can be beneficial to achieving this goal.

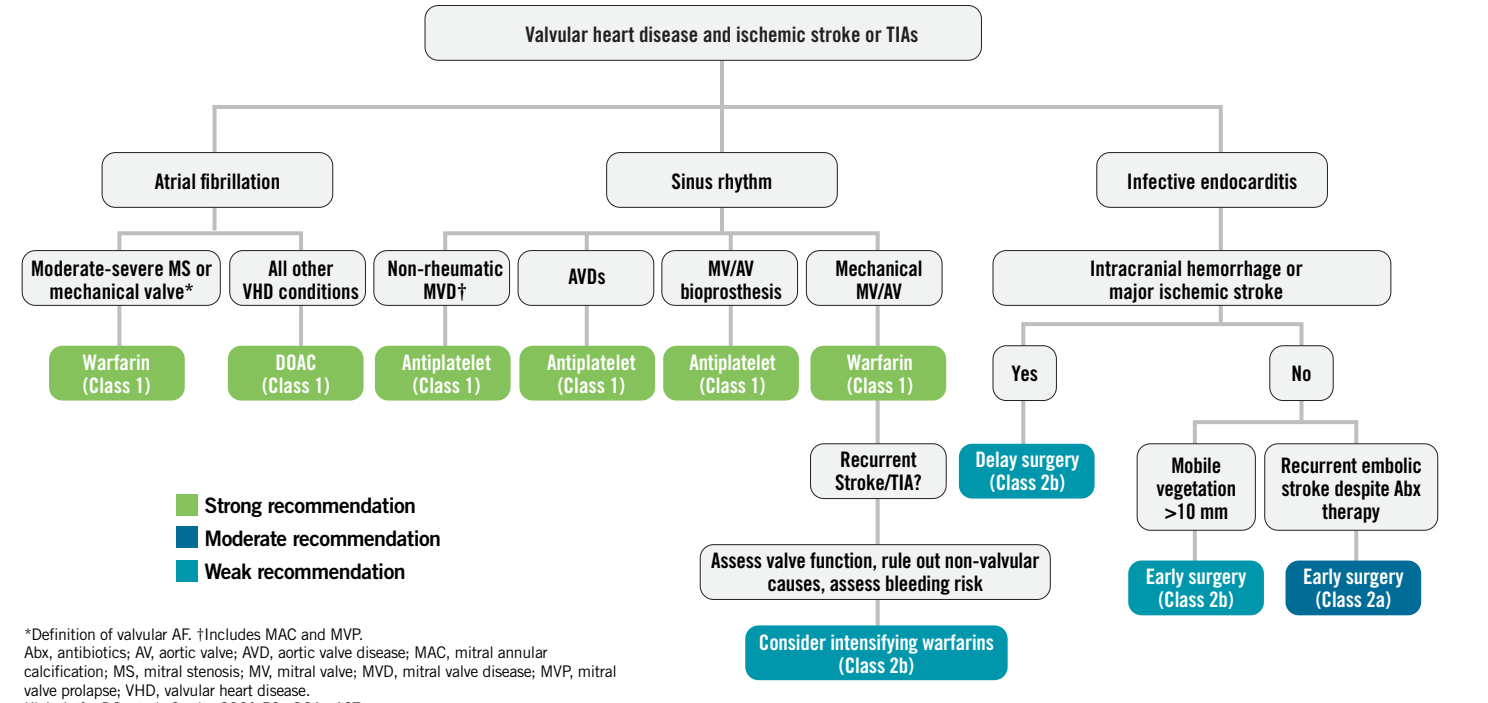
Brief Overview of Recommendations	
Hyperlipidemia	For patients with ischemic stroke, no known coronary heart disease, no major cardiac sources of embolism, & low-density lipoprotein cholesterol (LDL-C) >100 mg/dL, atorvastatin is recommended to prevent stroke recurrence. To reduce risk for major cardiovascular (CV) events, patients with ischemic stroke or TIA and atherosclerotic disease should be treated with a lipid-lowering therapy and a statin, as well as ezetimibe (if needed), with an LDL-C target of <70 mg/dL. For those already on a maximally tolerated statin dose plus ezetimibe who have an LDL-C >70 mg/dL, a PCSK9i is also recommended. In general, patients with stroke or TIA and hyperlipidemia should be regularly evaluated to ensure adherence to therapy and lifestyle changes, and to assess the effects of LDL-C–lowering medication.
Glucose management	Following a TIA or ischemic stroke, patients should be screened for prediabetes/diabetes. For those with diabetes, an individualized multidimensional care plan to achieve glycemic control that includes glucose-lowering agents with proven CV benefit to target an A1C ≤7% is recommended. For those with prediabetes, lifestyle intervention is recommended.
Obesity	In general, patients who have had an ischemic stroke or TIA should have their body mass index (BMI) calculated at the time of event and annually thereafter, to screen for and to classify obesity. Patients who are either overweight or obese should be encouraged to lose weight to improve atherosclerotic cardiovascular disease (ASCVD) risk factor profile. Referral to an intensive, multicomponent, behavioral lifestyle-modification program to achieve sustained weight loss can help patients achieve weight goals.

Antithrombotic Therapy

Currently, antithrombotic therapies for secondary stroke prevention include antiplatelets (aspirin, clopidogrel, aspirin–extended–release dipyridamole, and ticagrelor) and anticoagulants (warfarin and the direct oral anticoagulants [rivaroxaban, apixaban, dabigatran, and edoxaban]). Based on evidence to date, AHA/ASA guidelines recommend treatment that includes early dual antiplatelet therapy (DAPT; 90 days) followed by single antiplatelet therapy (SAPT) for patients with minor stroke occurring <24 hours prior or TIA with a high risk for recurrence. Patients with minor stroke >24 hours priors or with TIA who are not high risk may be initiated on SAPT. In contrast, anticoagulant therapy (warfarin or warfarin plus aspirin depending on various factors) is generally recommended for patients with cardiomyopathy and ischemic stroke or TIA in sinus rhythm. For patients with a history of ischemic stroke or TIA and different heart conditions, the treatment algorithm is somewhat more complex; an anticoagulant *or* antiplatelet may be considered depending on individual patient/disease characteristics (**Figure 1**).

Figure 1

Recommended Antithrombotic Regimen: Patient's History of Ischemic Stroke or TIA and Different Heart Conditions



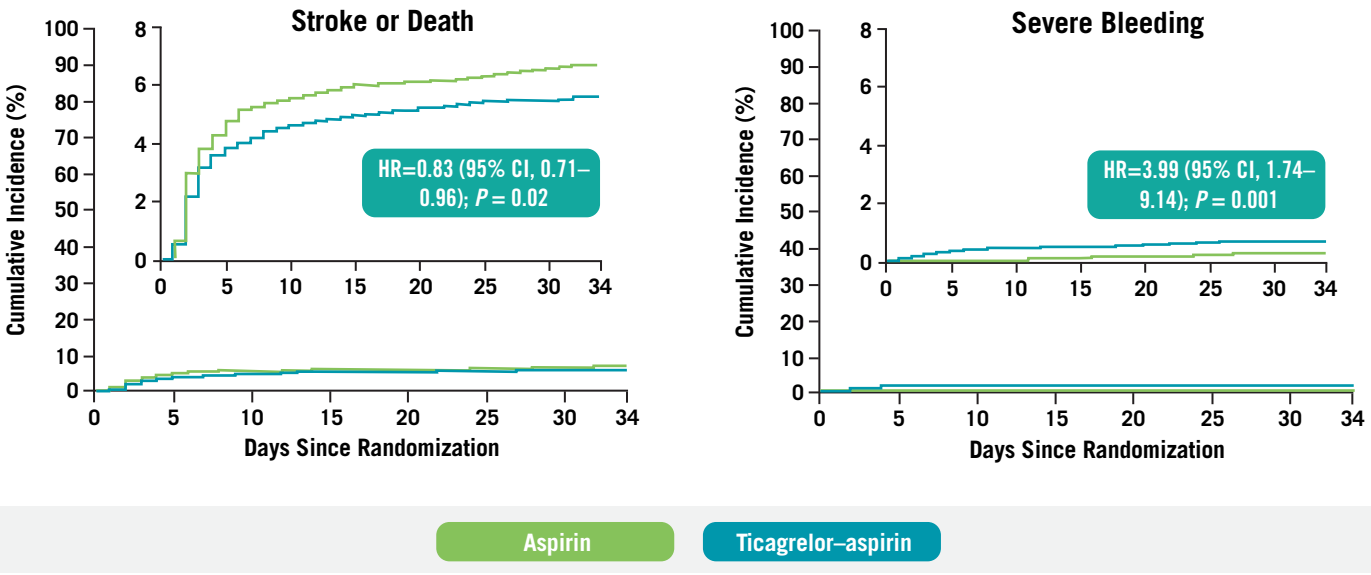
*Definition of valvular AF. †Includes MAC and MVP.
Abx, antibiotics; AV, aortic valve; AVD, aortic valve disease; MAC, mitral annular calcification; MS, mitral stenosis; MV, mitral valve; MVD, mitral valve disease; MVP, mitral valve prolapse; VHD, valvular heart disease.
Kleindorfer DO, et al. *Stroke.* 2021;52:e364-e467.

III. Evolving Standards of Care in Stroke Prevention: Combined Antithrombotic Therapy

Although historical studies of DAPT for secondary prevention of ischemic stroke suggested that the long-term risks for bleeding would outweigh the potential benefits, perspectives on this issue have undergone an important shift based on subsequent clinical trial evidence.[15-17] In the CHANCE and POINT trials, combined clopidogrel and aspirin treatment was associated with reduced early risk of new stroke in patients with acute minor stroke or TIA. Initially, there were concerns about bleeding risks due to an increase in DAPT-associated major hemorrhage observed in POINT.[17] However, pooled analysis of the two trials later showed that the benefits of DAPT occurred primarily during first 21 days after stroke/TIA, suggesting a role for DAPT in the short-term that could offset the risks over the long-term.[18] Likewise, data from the recent THALES trial revealed a significant benefit of short-term DAPT with aspirin and ticagrelor after stroke (albeit with an increased risk for severe bleeding) (**Figure 2**).[15] In the exploratory analysis of the THALES data, investigators found that DAPT may confer even greater prophylactic benefits specifically among patients with symptomatic atherosclerotic vascular disease (ipsilateral atherosclerosis stenosis).[19] Based on the findings of these three key clinical trials, short-term DAPT has now become the standard of care following a qualifying TIA or minor ischemic stroke.[10]

Figure 2

THALES: Ticagrelor–Aspirin vs Aspirin Alone in Acute Ischemic Stroke or TIA



HR, hazard ratio.
Johnston SC, et al. *N Engl J Med.* 2020;383:207-217.

IV. The Central Role of the Multidisciplinary Care Team in Stroke Care: A Focus on Patient Discharge

Effective prevention of stroke recurrence requires a multidisciplinary approach.[20] Prior to discharge, multidisciplinary care teams should provide patients with education and help them develop personalized care plans that incorporate their goals and preferences. As part of the discussion, providers should address the following topics: health literacy, adequate understanding of diagnosis, effective management of personal risk factors, medication adherence, long-term cost considerations, and follow-up care. More specifically, the healthcare team should ensure that patients understand exactly what a stroke is and that they are fully aware of their risk factors, particularly those that can be modified. Because the risk for recurrence is particularly high in the first 30 days, patients should also be made aware that prompt follow up with a neurologist is crucial. Ideally, an appointment should be made by the discharge team prior to the patient leaving the hospital.

V. Summary of Key Points

Primary and recurrent stroke remains a leading cause of disability and mortality among US adults. The vast majority of risk for stroke is attributable to modifiable factors, including high BP, poor diet, physical inactivity, smoking, and abdominal obesity. Current guidelines recommend a multidisciplinary approach to secondary stroke prevention that focuses on a healthy lifestyle and vascular risk factor control, as well as appropriate pharmacologic intervention. The use of combined antithrombotic therapy for secondary stroke prevention requires careful assessment of the trade-off between ischemic and bleeding complications. Whereas long-term DAPT after stroke is not recommended, recent randomized controlled trials support a role for short-term DAPT.

References

1. Stroke facts. Centers for Disease Control. May 25, 2021. Accessed October 21, 2021. https://www.cdc.gov/stroke/facts.htm

2. Balami JS, Chen RL, Grunwald IQ, Buchan AM. Neurological complications of acute ischaemic stroke. *Lancet Neurol.* 2011;10(4):357-371.

3. Carod-Artal FJ. Determining quality of life in stroke survivors. *Expert Rev Pharmacoecon Outcomes Res.* 2012;12(2):199-211.

4. O'Donnell MJ, Diener H-C, Sacco RL, Panju AA, Vinisko R, Yusuf S. Chronic pain syndromes after ischemic stroke. *Stroke.* 2013;44(5):1238-1243.

5. Zhang X, Bi X. Post-stroke cognitive impairment: a review focusing on molecular biomarkers. *J Mol Neurosci.* 2020;70(8):1244-1254.

6. Kapral MK, Fang J, Alibhai SMH, et al. Risk of fractures after stroke. *Neurology.* 2017;88(1):57.

7. Virani SS, Alonso A, Benjamin EJ, et al. Heart disease and stroke statistics-2020 update: a report from the American Heart Association. *Circulation.* 2020;141(9):e139-e596.

8. Coull AJ, Lovett JK, Rothwell PM. Population based study of early risk of stroke after transient ischaemic attack or minor stroke: implications for public education and organisation of services. *BMJ.* 2004;328(7435):326.

9. Mohan KM, Wolfe CD, Rudd AG, Heuschmann PU, Kolominsky-Rabas PL, Grieve AP. Risk and cumulative risk of stroke recurrence: a systematic review and meta-analysis. *Stroke.* 2011;42(5):1489-1494.

10. Kleindorfer DO, Towfighi A, Chaturvedi S, et al. 2021 guideline for the prevention of stroke in patients with stroke and transient ischemic attack: a guideline from the American Heart Association/ American Stroke Association. *Stroke.* 2021;52(7):e364-e467.

11. O'Donnell MJ, Xavier D, Liu L, et al. Risk factors for ischaemic and intracerebral haemorrhagic stroke in 22 countries (the INTERSTROKE study): a case-control study. *Lancet.* 2010;376(9735):112-123.

12. Razmara A, Ovbiagele B, Markovic D, Towfighi A. Patterns and predictors of blood pressure treatment, control, and outcomes among stroke survivors in the United States. *J Stroke Cerebrovasc Dis.* 2016;25(4):857-865.

13. Lin MP, Ovbiagele B, Markovic D, Towfighi A. "Life's Simple 7" and long-term mortality after stroke. *J Am Heart Assoc.* 2015;4(11).

14. Lin AM, Lin MP, Markovic D, Ovbiagele B, Sanossian N, Towfighi A. Less than ideal. *Stroke.* 2018:Strokeaha118022644.

15. Johnston SC, Amarenco P, Denison H, et al. Ticagrelor and aspirin or aspirin alone in acute ischemic stroke or TIA. *N Engl J Med.* 2020;383(3):207-217.

16. Wang Y, Wang Y, Zhao X, et al. Clopidogrel with aspirin in acute minor stroke or transient ischemic attack. *N Engl J Med.* 2013;369(1):11-19.

17. Johnston SC, Easton JD, Farrant M, et al. Platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trial: rationale and design. *Int J Stroke.* 2013;8(6):479-483.

18. Pan Y, Elm JJ, Li H, et al. Outcomes associated with clopidogrel-aspirin use in minor stroke or transient ischemic attack: a pooled analysis of clopidogrel in high-risk patients with acute non-disabling cerebrovascular events (CHANCE) and platelet-oriented inhibition in new TIA and minor ischemic stroke (POINT) trials. *JAMA Neurol.* 2019;76(12):1466-1473.

19. Amarenco P, Denison H, Evans SR, et al. Ticagrelor added to aspirin in acute nonsevere ischemic stroke or transient ischemic attack of atherosclerotic origin. *Stroke.* 2020;51(12):3504-3513.

20. Doehner W, Mazighi M, Hofmann BM, et al. Cardiovascular care of patients with stroke and high risk of stroke: the need for interdisciplinary action: A consensus report from the European Society of Cardiology Cardiovascular Round Table. *Eur J Prev Cardiol.* 2020;27(7):682-692.

Restoring Balance From Hospital to Home: Updates on the Management of Acute and Chronic Hyperkalemia

I. Epidemiology and Burden of Hyperkalemia

Early identification of hyperkalemia is critical as this disease occurs in up to 73% of patients with chronic kidney disease (CKD) and up to 40% of patients with chronic heart failure (HF). Hyperkalemia is associated with increased hospitalizations and mortality, especially when potassium testing and monitoring are not frequently performed.[1] Furthermore, severe hyperkalemia is an independent predictor of all-cause and in-hospital mortality; the morality rate for patients with hyperkalemia is 30% due in large part to arrhythmias that lead to cardiac arrest. A serum potassium level of > 6 mEq/L is considered to be severe hyperkalemia (some sources place this cutoff point at ≥ 7 mEq/L), while moderate hyperkalemia is measured at 5.5-6 mEq/l and ≤ 5.4 mEq/L is considered mild.[1]

Several factors impact the risk of hyperkalemia, including chronic kidney disease (CKD), an initial serum potassium level of > 4.8 mEq/L without renin-angiotensin-aldosterone system (RAAS) inhibitor (RAASi) use, some medications, and HF and diabetes mellitus (DM) with reduced kidney function. The medications most commonly implicated in hyperkalemic events are RAASi's and beta-blockers,[2,3] which both interfere with the RAAS and impair the ability of the kidneys to remove potassium for excretion.[4] In addition to these common risk factors, hyperkalemia is often caused by pseudohyperkalemia, potassium cellular shift and redistribution, excessive potassium intake, and decreased renal excretion.[5,6] Individuals at high risk for hyperkalemia (HK) are > 65 years old, male gender, with DM, a decline in kidney function defined as > Stage 3 CKD, hypertension (HTN), and/or chronic HF, and those treated with drugs that inhibit renal potassium excretion.[7-11]

Hyperkalemia is a common electrolyte imbalance marked by an elevated serum potassium of > 5.5 mEq/L in patients with kidney disease. Acute in-hospital presentations can include conduction abnormalities and cardiac arrhythmias, muscle weakness with possible paralysis, and fatigue and vomiting. However, potassium levels are dynamic, patients are often asymptomatic, and hyperkalemia can be chronic, making diagnosis difficult and underscoring the importance of monitoring.[1, 6, 12, 13]

II. Prevention and Management of Hyperkalemia

Early Identification of Hyperkalemia

Despite the risk of HK with RAASi use, a retrospective analysis showed that, within the first three months, neither serum potassium nor serum creatinine levels were measured in 34% of patients with HF and newly prescribed spironolactone (N = 840). In those who did have follow-up laboratory measurements (n = 551), 15% had developed HK and 6% had developed severe HK. Once HK is identified, the cause must be determined to minimize or prevent future episodes.[14]

Continue RAASi at Optimal Dose

A retrospective analysis of >200,000 patients in an electronic health records database who had been prescribed RAASi for CKD, HF, and/or DM showed a clear connection between lower, suboptimal, or discontinued RAASi doses and increased rates of death or adverse cardiorenal events. Guidelines for CKD, HF, and DM all recommend that RAASi's be prescribed at the **full optimal** labeled dose to yield improved outcomes of lower mortality and reduced numbers of cardiorenal events.[15]

The Role of Potassium-binding Agents

RAASi's, including angiotensin converting enzyme inhibitors (ACEi) and angiotensin receptor blockers (ARBs), are a cornerstone in the treatment of patients with DM, HF, and/or CKD due to the proven ability of these medications to reduce target organ damage and mortality. New potassium-binding agents can be taken to prevent or reduce hyperkalemia, while allowing patients to continue RAASi at optimal dose.[6] These nonabsorbable agents increase potassium excretion through the gastrointestinal (GI) tract: patiromer exchanges potassium for Ca^{2+} in the colon, while sodium zirconium cyclosilicate (SZC) selectively binds potassium ions and exchanges them for Na^{+} and H^{+} throughout the entire intestine. Patiromer received FDA approval in 2015 and SCZ was approved in 2018.[16-18] Sodium polystyrene sulfonate (SPS) is a potassium binder originally approved in 1958, but this agent is often not well tolerated. SPS has been observed to have drug-drug interactions with antacids and laxatives, lithium, thyroxine, and sorbitol. In addition, the SPS package insert notes that concomitant use of sorbitol may contribute to the risk of intestinal necrosis.[17-19]

A Top-level Comparison of Potassium Binders			
	SPS[1]	Patiromer[2]	SCZ[3]
Molecule[4]	Nonspecific, Na^+-containing organic resin	Selective, NA^+-free organic polymer	Selective, NA^+-containing inorganic crystalline silicate
Onset of effect[4]	Unknown*	7 hr	1 hr
Time to normokalemia[5]	Undetermined	79% after 4 wk	98% w/in 48 hr
Dosing[1-3]	Orally: 15–60 g, 1–4x/d; Rectally: 30–50 g/6 hr	8.4–25.2 g 1x/d	Starting: 10 g 3x/d up to 3 days; Maintenance: 5 g, 10 g, 15 g 1x/d
Safety[4]	GI symptoms, hypokalemia, hypernatremia, volume overload	GI symptoms, hypokalemia, hypomagnesemia	Hypokalemia, edema

*Presume 7–10 hrs because SPS is dependent on a high concentration of K^+ in colon. PI: 3x/day up to 48 hrs; dosing based on ZS-005 trial: 82% of pts achieved normokalemia w/in 24 hrs.

1. Sodium polystyrene sulfonate (branded name) PI, 2017. **2**. Patiromer (branded name) PI, 2020. **3**. Sodium zirconium cyclosilicate (branded name) PI, 2020. **4**. Di Nicola L, et al. *J Nephrol.* 2018;31:653-664. **5**. Pitt B, Bakris GL. *Hypertension.* 2015;66:731-738

New and Emerging Data

Both patiromer and SZC are FDA approved based upon results of several phase II and phase III studies. The safety and efficacy of patiromer in patients with CKD, HF, Type 2 DM, and/or HTN with hyperkalemia have been demonstrated in several studies, including PEARL-HF, AMETHYST-DN, and OPAL-HK, which achieved their primary endpoints and reduced serum potassium in short- and long-term treatment. A recent substudy of OPAL-HK, conducted in older CKD patients taking RAASi, showed that patiromer reduced recurrent hyperkalemia and was well tolerated in this subgroup. The AMBER study showed patiromer was effective in decreasing serum potassium levels and maintaining the use of spironolactone in persons with resistant HTN. Patiromer has also been shown to be effective in decreasing serum potassium levels for patients on hemodialysis.[20-22] Common adverse events (AEs) included constipation, diarrhea, nausea and vomiting, hypokalemia, and hypomagnesemia.[23]

The FDA approval of SZC is supported by data from three double-blind, placebo-controlled trials and two open-label trials (ZS-003, HARMONIZE, HARMONIZE Extension, ZS-005, and DIALIZE), which showed the onset of action was 1.0 hour and the median time to achieving normal potassium levels in the blood was 2.2 hours (92% of patients achieved normal potassium levels within 48 hours from baseline). The treatment effect of SZC was maintained for up to 12 months, and its potassium-lowering efficacy was maintained irrespective of the use of RAASi.[24-28]

The Phase IIIb DIALIZE trial investigated the efficacy and safety of SZC for the treatment of hyperkalemia in patients with end-stage renal disease (ESRD) on hemodialysis and showed that 41.2% of patients with hyperkalemia on stable hemodialysis receiving SZC maintained predialysis normal potassium levels (4-5 mmol/L) on at least three out of four dialysis treatments after the long interdialytic interval and did not require urgent rescue therapy, as compared to 1.0% of patients receiving placebo (OR 68.8, $P < 0.001$).[24-28] Overall, the common AEs associated with SZC included GI events and a dose-dependent risk of edema; the drug was well tolerated with a low potential for drug interactions.[23]

Emerging Agent with Potential Benefit to Hyperkalemia

Recent DAPA-HF trial results indicate a potential role for dapagliflozin, a sodium-glucose transport protein 2 (SGLT2) inhibitor, in the management of hyperkalemia. Dapagliflozin reduces the risk of hyperkalemia in patients with HF and reduced ejection fraction. Mild hyperkalemia (serum potassium > 5.5 mmol/L) and moderate-to-severe hyperkalemia (> 6.0 mmol/L) occurred in 182 (11.1%) and 23 (1.4%) patients treated with dapagliflozin compared to 204 (12.6%) and 40 (2.4%) of placebo patients. Dapagliflozin reduced risk for mild hyperkalemia by 14% and moderate-to-severe hyperkalemia by 50% ($P = .01$) compared to placebo, and incidence of moderate-to-severe hyperkalemia was reduced from 1.7 to 1.0 per 100 person-years with dapagliflozin.[29]

III. Optimizing Multidisciplinary Care and Transitions from Hospital to Home

A multidisciplinary approach is critical to the successful management of hyperkalemia and optimal patient outcomes. At discharge, multidisciplinary care teams should provide patients with education geared toward individualized treatment plans. This education must ensure the patient understands that hyperkalemia is too much (not too little) potassium in the blood and that potassium is a *necessary* nutrient for proper heart and muscle function and should not be completely avoided. The care team should also explain why kidney disease and HF place the patient at risk of hyperkalemia. In addition to the provision of key patient education at discharge, there is a need for improved inpatient and post-discharge management of patients with hyperkalemia **(Figure 1).**[30] After discharge, early outpatient follow-up after hospitalization may reduce readmission for persons with chronic disease who may be at risk for HK.[31-32]

Figure 1

Unmet Inpatient and Postdischarge Needs in Management of Patients With Hyperkalemia

Study Design and Patient Population

Retrospective cohort study using a large US claims database

Hyperkalemia cohort
Patients with hyperkalemia-related hospitalization

VS

Nonhyperkalemia cohort
Patients without evidence of hyperkalemia

Cohorts were matched 1:1 on age, CKD stage, heart failure, dialysis treatment, RAASi use, and major diagnostic categories of the hospitalization (N=4426 pairs)

Results

Hyperkalemia cohort	Postdischarge outcomes (1-year)	Nonhyperkalemia cohort
$68,861	Total costs	$38,482
1.0	IP admissions	0.4
2.0	ED visits	1.2
49.6	OP visits	39.1
0.15	30-day readmissions	0.09
10.5	Total length of stay (days)	5.8

Note: all *P* values <.001
Results remained robust in multivariable regressions adjusting for additional comorbidities, characteristics of the hospitalization, and medication use

Conclusion: HK-related hospitalizations were associated with significant postdischarge burden. This suggests an unmet need for the inpatient and postdischarge management of hyperkalemia patients.

IP, inpatient; ED, emergency department; OP, outpatient.
Betts KA, et al. *Kidney Int Rep.* 2020;5(8):1280-1290. doi:10.1016/j.ekir.2020.06.004

IV. Summary of Key Points

Hyperkalemia is a common and potentially life-threatening electrolyte imbalance most frequently seen in patients with advanced CKD and HF. Yet, this diagnosis can be missed as patients are often asymptomatic. RAASi use is one of many potential causes of hyperkalemia; however, discontinuing RAASi treatment may not be the right answer as multiple studies show worse patient outcomes when RAASi is discontinued or reduced, especially in patients with HF and CKD. Recent studies support the use of potassium-binding agents to mitigate against hyperkalemia and optimize RAASi use. In addition to discharging patients at optimal/full RAASi dose, it is critical to quickly diagnose hyperkalemia, frequently monitor potassium levels, and apply a multidisciplinary approach to patient education and treatment.

References

1. Rosano GMC, Tamargo J, Kjeldsen KP, et al. Expert consensus document on the management of hyperkalemia in patients with cardiovascular disease treated with renin angiotensin aldosterone system inhibitors: coordinated by the Working Group on Cardiovascular Pharmacotherapy of the European Society of Cardiology. *Eur Heart J.* 2018;4:180-188.

2. Lazich I, Bakris GL. Prediction and management of hyperkalemia across the spectrum of chronic kidney disease. *Semin Nephrol.* 2014;34(3):333-339. doi:10.1016/j.semnephrol.2014.04.008

3. Tromp J, van der Meer P. Hyperkalaemia: aetiology, epidemiology, and clinical significance. *Eur Heart J.* 2019;21(Suppl A):A6-A11.

4. Clase CM, Carrero J-J, Ellison DH. Potassium homeostasis and management dyskalemia in kidney diseases: conclusions from a Kidney Disease: Improving Global Outcomes (KDIGO) controversies conference. *Kidney Int.* 2020:97:42-46.

5. Palmer BF, Clegg DJ. Physiology and pathophysiology of potassium homeostasis. *Adv Physiol Educ.* 2016;40:480-490.

6. Palmer BF, Clegg DJ. Diagnosis and treatment of hyperkalemia. *Cleve Clin J Med.* 2017;84:934-942.

7. KDIGO. KDIGO clinical practice guideline on the management of blood pressure in chronic kidney disease. January 2020. https://kdigo.org/wp-content/uploads/2016/10/KDIGO-BP-Management-GL-public-review-draft-8Feb2020.pdf

8. Hayes J, Kalantar-Zadeh K, Lu JL, Turban S, Anderson JE, Kovesdy CP. Association of hypo- and hyperkalemia with disease progression and mortality in males with chronic kidney disease: the role of race. *Nephron Clin Pract.* 2012;120(1):c8-c16. doi:10.1159/000329511

9. Einhorn LM, Zhan M, Hsu VD, et al. The frequency of hyperkalemia and its significance in chronic kidney disease. *Arch Intern Med.* 2009;169(12):1156-1162. doi:10.1001/archinternmed.2009.132

10. Jain N, Kotla S, Little BB, et al. Predictors of hyperkalemia and death in patients with cardiac and renal disease. *Am J Cardiol.* 2012;109(10):1510-1513. doi:10.1016/j.amjcard.2012.01.367

11. 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. doi:10.1159/000479802

12. De Nicola L, Lullo LD, Paoletti E, Cupisti A, Blanchi S. Chronic hyperkalemia in non-dialysis CKD: controversial issues in nephrology practice. *J Nephrol.* 2018;31:653-664.

13. Littmann L, Gibbs MA. Electrocardiographic manifestations of severe hyperkalemia. *J Electrocardiol.* 2018;51:814-817.

14. Shah KB, Rao K, Sawyer R, Gottlieb SS. The adequacy of laboratory monitoring in patients treated with spironolactone for congestive heart failure. *J Am Coll Cardiol.* 2005;46(5):845-849. doi:10.1016/j.jacc.2005.06.010

15. 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-S220.

16. Pitt B, Bakris GL. New potassium binders for the treatment of hyperkalemia: current data and opportunities for the future. *Hypertension.* 2015;66:731-738.

17. Patiromer (Veltassa®) package insert. May 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2018/205739s016lbl.pdf. Accessed May 27, 2020.

18. Sodium zirconium cyclosilicate (Lokelma®) package insert. April 2020. Accessed May 27, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2020/207078s003lbl.pdf

19. Sodium polystyrene sulfonate (Kayexalate™) package insert. Accessed April 28, 2020. https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/011287s026lbl.pdf

20. Pitt B, Anker SD, Bushinsky DA, et al; PEARL-HF Investigators. 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;32:820–828.

21. Bakris GL, Pitt B, Weir MR, et al; AMETHYST-DN Investigators. Effect of patiromer on serum potassium level in patients with hyperkalemia and diabetic kidney disease: the AMETHYST-DN randomized clinical trial. *JAMA.* 2015;314:151-161.

22. Weir MR, Bakris GL, Bushinsky DA, et al. Patiromer in patients with kidney disease and hyperkalemia receiving RAAS inhibitors. *N Engl J Med.* 2015;372:211-221.

23. Wai H-T, Meah N, Katira R. *Br J Cardio.* 2021; doi:10.5837/bjc.2021.014

24. Packham DK, Rasmussen HS, Lavin PT, et al. Sodium zirconium cyclosilicate in hyperkalemia. *N Engl J Med.* 2015;372:222-231.

25. 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;312:2223-2233.

26. Roger SD, Spinowitz BS, Lerma EV, et al. Efficacy and safety of sodium zirconium cyclosilicate for treatment of hyperkalemia: an 11-month open-label extension of HARMONIZE. *Am J Nephrol.* 2019;50:473-480.

27. Spinowitz BS, Fishbane S, Pergola PE, et al. Sodium zirconium cyclosilicate among individuals with hyperkalemia. *Clin J Am Soc.* 2019;14:798-809.

28. Fishbane S, Ford M, Fukagawa M, et al. A phase 3b, randomized, double-blind, placebo-controlled study of sodium zirconium cyclosilicate for reducing the incidence of predialysis hyperkalemia. *J Am Soc Nephrol.* 2019;30:1723-1733.

29. Kristensen SL, Docherty KF, Jhund PS, et al. Dapagliflozin reduces the risk of hyperkalaemia in patients with heart failure and reduced ejection fraction: a secondary analysis DAPA-HF. Presented at ESC Virtual Congress 2020, August 29, 2020.

30. Betts KA, Woolley JM, Mu F, et al. Postdischarge health care costs and readmission in patients with hyperkalemia-related hospitalizations. *Kidney Int Rep.* 2020;5(8):1280-1290. Published 2020 Jun 11. doi:10.1016/j.ekir.2020.06.004

31. Hernandez AF, Greiner MA, Fonarow GC, et al. Relationship between early physician follow-up and 30-day readmission among Medicare beneficiaries hospitalized for heart failure. *JAMA.* 2010;303(17):1716-1722. doi:10.1001/jama.2010.533

32. Rayan N, Baird R, Masica A. Rapid response team interventions for severe hyperkalemia: evaluation of a patient safety initiative. *Hosp Pract (1995).* 2011;39(1):161-169. doi:10.3810/hp.2011.02.387