ISSN 1933-088X

Advances in Pulmonary Hypertension

Vol 23, No 2; 2025

Official Journal of the Pulmonary Hypertension Association

Shaping the Future of Pulmonary Hypertension: New Treatment Pathways, Technological Advances, and Equitable Drug Development

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Program Description

The mission of *Advances in Pulmonary Hypertension* is to serve as the premiere forum for state-of-the-art information regarding diagnosis, pathophysiology, and treatment of pulmonary hypertension (PH). The 2018 Nice revision of the World Symposium on Pulmonary Hypertension (Simmonneu G, Montani D, Celermajer DS, et al. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. Eur Respir J. 2019;53(1). DOI:10.1183/13993003.01913-2018) serves as a guide to categories of PH addressed in *Advances in Pulmonary Hypertension*. While focusing on Group 1 PH (PAH: pulmonary arterial hypertension), the other categories (Group 2, PH due to left heart disease; Group 3, PH due to lung diseases and/or hypoxia; Group 4, PH due to pulmonary artery obstructions; Group 5, PH with unclear and/or multifactorial mechanisms) are also addressed. This mission is achieved by a combination of invited review articles, roundtable discussions with panels consisting of international experts in PH, and original contributions.

Objectives

- Provide up-to-date information regarding diagnosis, pathophysiology, and treatment of PH.
- Serve as a forum for presentation and discussion of important issues in the field, including new paradigms of disease understanding and investigational trial design.

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Pulmonary Hypertension
Official Journal of the Pulmonary Hypertension Association

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Advances in Pulmonary Hypertension is directed to cardiologists, pulmonologists, rheumatologists, pediatricians, internists, and other health care professionals involved in the treatment of patients with PH.

Advances in Pulmonary Hypertension: Official Journal of the Pulmonary Hypertension Association is a quarterly publication directed by an editorial board of renowned pulmonary hypertension (PH) experts with oversight by PHA's Scientific Leadership Council. The mission of *Advances in PH* is to assist physicians in their clinical decision-making by informing them of important trends affecting their practice and providing an analysis of the impact of new findings and current information in peer-reviewed publications. Each article is reviewed and approved by members of the Editorial Board.

While most articles are invited by the Editorial Board, the following submissions will be considered for publication:

- Reviews that summarize and synthesize peer-reviewed literature to date on relevant topics
- Letters to the Editor
- Clinical case studies

Submitted manuscripts are reviewed by the Editorial Board and other experts in the field. Acceptance of manuscripts is determined by factors such as quality, relevance, and perceived value to clinical decision-making.

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Research has played a critical role in the advancement of care in patients with pulmonary hypertension. Studies suggest that enrollment into clinical trials is beneficial to participating patients[1] and that institutions participating in clinical trials have better disease-related outcomes.[2] I frequently tell my mentees that involvement in clinical research makes you a more thoughtful clinician and that working as a clinician makes you a savvier clinical researcher. This issue of *Advances in Pulmonary Hypertension*, guest edited by Drs. Cascino, Gomberg-Maitland and Pullamsetti, tackles several critical topics in pulmonary hypertension research.

Much has been learned about the pathophysiology of pulmonary arterial hypertension. Understanding the interface of the various pathways involved, however, can be overwhelming. The promise of multiomics, so elegantly described by Reem and colleagues in this issue, allows the integration of current knowledge for better disease targeting with therapy. This will make it easier to identify new paradigms of therapeutic approach, such as blocking tyrosine kinase, and with appropriate risk stratification, can encourage judicious use of combinations of different treatments based on clinical necessity. The hope is to one day be able to rapidly characterize patients and better identify the therapeutic approach that achieves the best clinical response, so-called *precision medicine*.[3]

For future studies to have applicability to our patient population, we must ensure enrollment of diverse patient populations. Gaps in minority patient enrollment are troubling, and Milinic and colleagues discuss potential solutions. The past decade has witnessed increasing challenges of patient recruitment, and many US studies have turned to the addition of international sites. It's important to realize that such decisions can compromise the generalizability and applicability of results.[4]

Outcomes continue to steadily improve for patients diagnosed with pulmonary hypertension but remain far from optimal.[5] Only through continued focus on research can further progress be achieved.

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Meeting every 5 years, the World Symposium on Pulmonary Hypertension provides a regular opportunity to invigorate the field of pulmonary hypertension (PH) by bringing diverse stakeholders together to summarize the state of the art. The most recent Symposia held in June in Barcelona served as a reminder of how far the field has come and how much opportunity there is to continue advancing care. This issue of *Advances in Pulmonary Hypertension* is focused on that future—highlighting innovations in treatment pathways, cutting-edge technology for understanding the disease process and management strategies, and strategies for improving equity in the development of novel therapies. This edition brings together thought leaders who elaborate on opportunities from drug development to implementation of clinical care.

Reem El Kabbout, MSc, and team highlight how cutting-edge multiomics data integrating genomic, epigenomic, transcriptomic, proteomic, and metabolomic information have informed our understanding of and can be harnessed to unravel the complexities of pulmonary arterial hypertension (PAH). This will enable not only the identification of functionally important molecular pathways and the improvement of patient outcomes through targeted therapies and precision medicine but also the development of better diagnostics. In the comprehensive review, both the challenges of multiomics and the promise of the technology in a thorough and accessible manner for the Pulmonary Hypertension Association community are discussed.

Next, Dr. Madgula and colleagues examine the evidence behind and the potential for using implantable hemodynamic monitors in the management of PH. Remote wireless monitoring is currently a 2b recommendation for heart failure patients who are on optimal guideline-directed medical and device therapy with either continued elevation in natriuretic peptide levels or a heart failure hospitalization in the past year. With a small study supporting the safety and ongoing larger trials evaluating the efficacy, in the review, the potential of implantable hemodynamic monitors is expertly laid out as a patient-centric therapy that could facilitate rapid medication titration and timely identification of clinical deterioration to improve outcomes.

Dr. Frantz then explores the potential for tyrosine kinase inhibition in the treatment of PAH. Dr. Frantz succinctly explains the benefits and adverse events that have thus far been identified in using tyrosine kinase inhibitors to treat PAH. In doing so, he highlights both the promise and what needs to happen to have a fifth therapeutic target in the treatment of PAH.

Dr. Miller and colleagues then highlight the state-of-the-art PH risk stratification. The authors discuss opportunities to improve risk stratification through additional phenotyping and how to consider risk stratification in clinical trial design before concluding with opportunities for further refinement of risk models.

Lastly, Lia Barros, DNP, and colleagues lay forth a pathway to equitable representation in PAH clinical trials. Through the identification of multilevel barriers to equitable participation, the authors provide a framework to systematically improve access to clinical trials for all people with PH.

Together, this issue is focused on the future of PAH management and care. We thank the authors for their insights and participation. As you explore this issue, we hope you are impressed with the progress and challenged to achieve continued success.

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 DOI:10.21693/1933-088X-23.2.32

REGULAR ARTICLE

Multiomics Integration for Identifying Treatment Targets, Drug Development, and Diagnostic Designs in PAH

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Unraveling the complexities of pulmonary arterial hypertension (PAH) is challenging due to its multifaceted nature, encompassing molecular, cellular, tissue, and organ-level alterations. The advent of omics technologies, including genomics, epigenomics, transcriptomics, metabolomics, and proteomics, has generated a vast array of public and nonpublic datasets from both humans and model organisms, opening new avenues for understanding PAH. However, the insights provided by individual omics datasets into the molecular mechanisms of PAH are inherently limited. In response, efforts are increasing to develop integrative omics approaches designed to synthesize multidimensional omics data into a cohesive understanding of the molecular dynamics of PAH. In this review, we discuss various strategies for integrating multiomic data and illustrate their application in PAH research. We explore the challenges encountered and the profound potential of leveraging omics data for comprehensive molecular insight as well as for the identification of novel therapeutic targets and biomarkers specific to PAH. Furthermore, in this review, we seek to elucidate the process and rationale behind conducting integrative omics studies in PAH, raising critical questions about the feasibility and future prospects of multiomic integration in unraveling the complexities of this disease.

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a fatal vasculopathy characterized by pulmonary vasoconstriction and adverse remodeling of the distal pulmonary arteries. Progression of the disease is manifested by a significant increase in pulmonary artery pressure, which strains the right ventricle (RV), leading to hypertrophy and ultimately heart failure, the leading cause of death in PAH patients.[1] The pathogenesis of PAH is complex and involves sophisticated interactions between multiple organs—including the lungs, RV, bone marrow, and spleen—and different cell types—including smooth muscle cells, endothelial cells, fibroblasts, and inflammatory cells.[2]

The advent of omics technologies has advanced our understanding of the molecular intricacies of PAH, revealing extensive molecular dysfunction through genomic, epigenomic, transcriptomic, proteomic, and metabolomic studies.[3] While authors of studies of individual omic layers have uncovered potential new therapeutic targets and biomarkers, it is increasingly recognized that a narrow focus on single-omic facets provides an incomplete picture of the intricate mechanisms linking molecular variations to clinical disease manifestations. Biological systems are manifested

Key Words—multiomic, transcriptomic, proteomic, pulmonary hypertension
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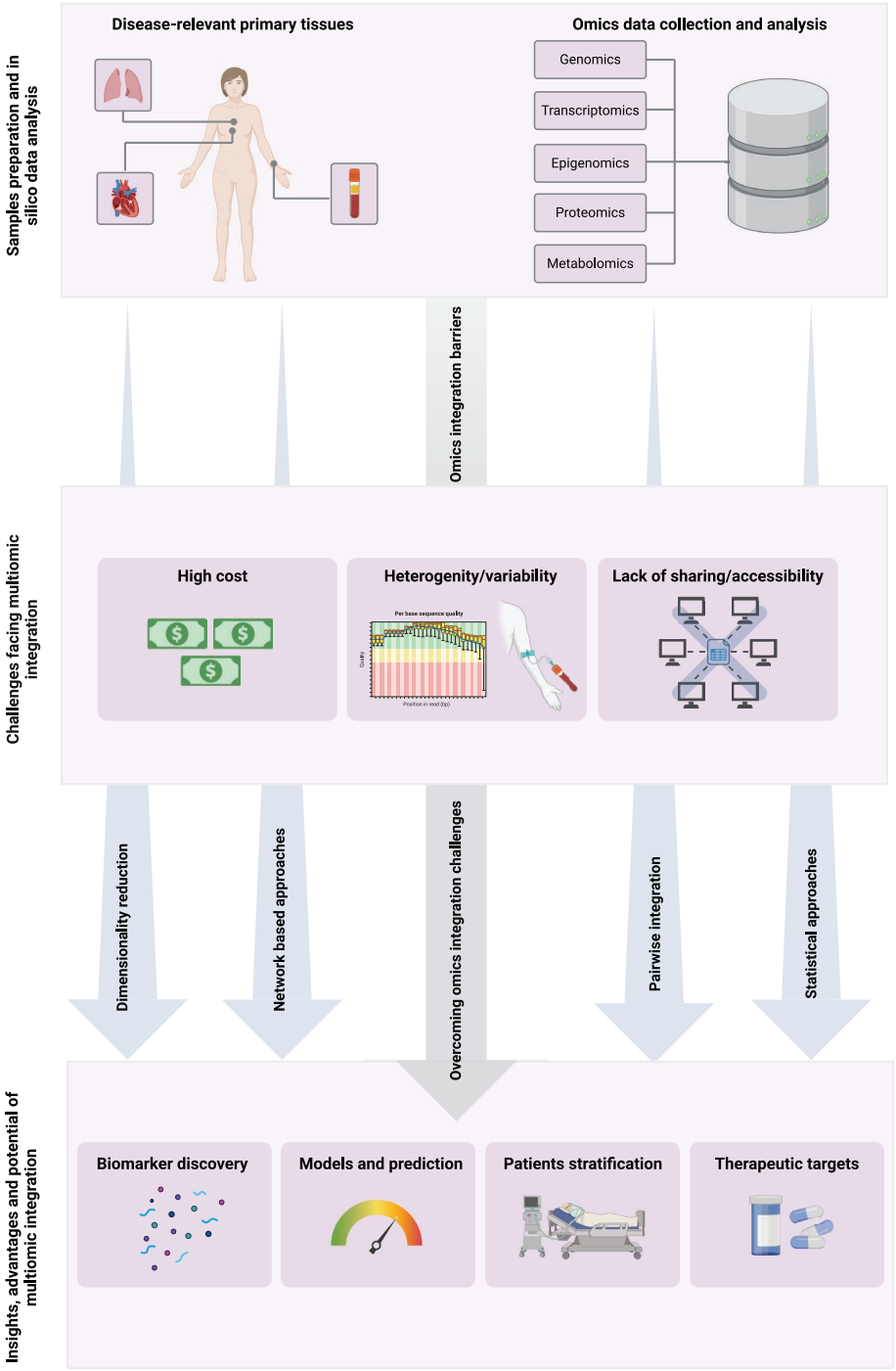

Figure 1: Navigating omic data integration: methods and challenges. Multiomics combines data from multiple platforms, offering comprehensive insight into biological systems. It begins with meticulous sample collection and preparation, encompassing various biological specimens like blood and tissue, pivotal for capturing a wide array of omic information, such as genomics, transcriptomics, epigenomics, proteomics, and metabolomics. The integration of multiomic data faces notable challenges in analysis and synthesis, including the high costs of omics technologies, computational complexities, dataset variability, and limited data sharing among researchers. Nevertheless, by harnessing machine learning and statistical approaches—including pairwise integration, dimensionality reduction, and network-based methodologies—the integration process unlocks invaluable insights. These include the identification of novel biomarkers, therapeutic targets, and the development of enhanced risk prediction models, thereby illustrating the transformative power of integrated omic data in pushing the boundaries of our understanding of complex biological systems.

by complex networks and interactions that span multiple omic domains and underlie the pathology of PAH.[4]

The integration of multiomic data is essential to unravel the complex mechanisms of PAH and provide the basis for novel therapies and interventions. However, this integrative approach poses significant computational challenges, ranging from the development of sophisticated statistical methods to the creation of comprehensive databases that link omic levels to biological functions and disease states.[5] Addressing these challenges requires computational and programming expertise not traditionally found in biological laboratories. The move toward multiomic integration requires a collaborative effort that brings together the knowledge of biologists, bioinformaticians, and computer scientists. This interdisciplinary collaboration is critical to overcoming the computational hurdles of multiomic data analysis, thereby moving PAH research into a new era of discovery and therapeutic development.

In this review, we will explore the field of integrative multiomic studies and their central role in advancing our understanding of PAH. First, we will provide an insightful overview of the core omics data types central to PAH research. Building on this foundation, we will explore the principles of multidimensional data integration and provide a thorough examination of the cutting-edge methods and tools that are shaping this vibrant area of study (Figure 1). Through a series of illustrative examples, we will highlight the real-world applications and significant achievements of multiomic studies in PAH, demonstrating their ability to unravel the intricacies of the disease. Finally, we will discuss the current challenges and limitations of integrative multiomic approaches and assess the gap between expectations and actual achievements, challenging common myths and highlighting the tangible benefits these studies offer.

MULTIOMIC: WHAT ARE WE TALKING ABOUT?

Multiomics, also known as integrated omics or panomics, combines multiple

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datasets to analyze, visualize, and interpret the mechanisms of biological processes.[6] It aims to identify molecular markers by uncovering genomic, transcriptomic, proteomic, and metabolic changes and capturing spatiotemporal dynamics.[7] Multiomics provides insights into molecular functions, interactions, and cellular outcomes, helping to identify predictive biomarkers and drug targets and refine disease prognosis.[8] An understanding of single-omics strategies is essential before embarking on multiomics analysis, especially in PAH where each approach provides unique insights into the molecular mechanisms of the disease.

Genomics

Genomic techniques are designed to explore interindividual variation at both the germline and somatic levels by sequencing the genome of interest.[9] The evolution from first-generation Sanger sequencing to the eventual third-generation long-read sequencing has facilitated whole genome/exosome sequencing with sufficient depth to characterize the mutational landscape within a given sample.[10] For example, advances in genomics have revealed heterozygous germline mutations in the BMPR2 gene as the primary genetic cause of most cases of familial PAH, with over 600 mutations identified. These mutations, including nonsense, frameshift, splice-site, missense, and copy number variants, are prevalent in over 75% of affected families. Authors of genomic studies have also identified more than mutations in 18 other genes such as ACVRL1, ENG, SMAD9, and TET2, advancing our understanding and paving the way for targeted diagnostics and therapies.[11–14]

Epigenomics

Epigenetics, the study of heritable traits or stable changes in cell function without changes in DNA sequence, encompasses histone modification, DNA methylation, and noncoding RNA (ncRNA) regulation.[15] Epigenomics studies these modifications across the genome and provides insights into their role in cellular processes and disease development.[16] Techniques such as chromatin immunoprecipitation sequencing (ChIP-Seq) map histone modifications, while assay for transposase-accessible chromatin sequencing reveals the dynamics of chromatin accessibility.[17] Whole-genome bisulfite sequencing and DNA methylation microarrays profile DNA methylation patterns, and RNA sequencing (RNA-Seq) unveils ncRNA modifications.[18,19] Epigenetic modifications play a critical role in PAH, with DNA hypermethylation associated with abnormal cell proliferation and resistance to apoptosis in small pulmonary arteries. Authors of studies have identified hypermethylation of specific genes such as BMPR2 and SOD2 in PAH, influencing disease pathogenesis.[20,21] Epigenetic age acceleration observed in PAH patients suggests accelerated aging in key tissues and blood components.[22] In addition, omic technologies have highlighted the regulatory role of ncRNAs, such as miR-17-5p and miR-23a-3p in PAH pathology, affecting potent signaling pathways like BMP/SMAD.[23,24]

Transcriptomics

Transcriptomics techniques such as next-generation sequencing and RNA microarrays enable the profiling of differentially expressed genes. These methods provide insight into distinguishing normal from disease states by quantifying mRNA abundance across thousands of genes.[25,26] Bulk RNA-Seq provides a broad overview but lacks resolution of individual cell behavior, in contrast with single-cell RNA-Seq, which dissects transcriptomes at high resolution and identifies distinct cell types and states. The newly developed spatial RNA-Seq technology (spatial transcriptomics) preserves the spatial context of RNA expression and maps gene expression within tissue architecture for comprehensive studies of biological systems.[25]

Transcriptomic studies in PAH have provided tremendous insight into disease mechanisms and therapeutic targets. Rodor et al.[27] uncovered the involvement of endothelial cells in PAH inflammation by demonstrating upregulated major histocompatibility complex class II pathways in a mouse model. Similarly, Potus et al.[14] identified decreased TET2 expression in peripheral blood mononuclear cells from PAH patients, suggesting a role in disease pathophysiology. Single-cell RNA-Seq allows detailed cellular examination, highlighting gene expression variations within specific cell groups.[28] Notably, activation of the NF-κB pathway in monocytes and dendritic cells has been observed in experimental PAH models.[29] Moreover, comparative transcriptomic analyses revealed dysregulated genes across pulmonary artery cell clusters in PAH.[30] On the other hand, spatial transcriptomics revealed immune cell patterns near damaged vessels in rat lungs with induced PAH, shedding light on the nuances of the disease.[31] These advances provide insights into the pathogenesis of PAH and potential therapeutic strategies, underscoring the importance of omics technologies in unraveling complex diseases.

Proteomics

Proteomics investigates the functional implications of all proteins expressed in cells, tissues, or organisms, using mass spectrometry-based techniques to analyze the flow of protein signals.[32] High-resolution mass spectrometers, including LTQ™Orbitrap™ and MALDI-TOF-TOF, accurately measure protein masses. Given the central role of proteins in biological processes, accurate measurement of proteome changes during disease development is critical for biomarker discovery.[33] In PAH, Hołda et al.[34] used iTRAQ-based LC-MS to analyze the RV proteome in MCT-induced PAH rats, revealing early upregulation of fatty acid β-oxidation and myosin-7 proteins and late overexpression of fibrosis-related proteins. Le Ribeuz et al.[35] identified differentially expressed proteins in PAH-related cells, suggesting that KCNK3 deficiency induces cancer-related functions. In lung lobectomy homogenates, increased CLIC4 and decreased haptoglobin levels were associated with PAH.[36] Plasma proteomic analysis in idiopathic/heritable PAH identified survival-associated proteins.[37] With advances in proteomic technologies, O-link and SomaScan have emerged as critical tools, providing advanced capabilities to explore

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the intricate protein landscape within biological systems. O-link technology uses proximity extension assays for precise, high-throughput quantification of protein levels across multiple targets simultaneously, even in small sample volumes.[38] In contrast, SomaScan employs a large library of aptamers to measure over 7000 proteins in a single run, providing unparalleled data breadth.[39] Both technologies have played a pivotal role in PAH research, revealing novel biomarkers and therapeutic targets and advancing our understanding of the molecular mechanisms of the disease. For instance, Boucherat et al.[40] used O-link to identify proteins associated with cardiac fibrosis in PAH patients, including latent transforming growth factor beta binding protein 2 (LTBP-2), which correlates with RV function, whereas Rhodes et al.[41] used SomaScan to identify 6 prognostic proteins in a UK PAH cohort, complementing NT-proBNP and clinical risk factors for patient risk stratification. The authors of these studies have underscored the importance of proteomic analysis in elucidating pathological pathways and disease progression in PAH.

Metabolomics

Metabolomics, a branch of omics, is instrumental in elucidating the metabolic pathways underlying physiological or pathological processes. Using proton nuclear magnetic resonance spectroscopy or mass spectrometry, metabolomics analyzes biological samples to reveal intricate metabolic signatures.[42] Over the past decade, the importance of metabolomics in identifying novel circulating markers of PAH has increased dramatically.[43] In a PAH animal model (Sugen5416 plus the ovalbumin immunization), metabolomics revealed elevated levels of oxidized glutathione, xanthine, and uric acid, leading to increased xanthine oxidase-mediated reactive oxygen species release, which is known to impair pulmonary artery function.[44] In addition, analysis of lung tissue from patients with advanced PAH revealed metabolic pathways that contribute to pulmonary artery remodeling, including imbalanced arginine pathways and altered heme metabolites.[45] Moreover, metabolite profiling in idiopathic/heritable PAH patients identified altered nucleosides, energy metabolism intermediates, and decreased sphingomyelins, steroids, and phosphatidylcholines, which correlated with disease severity and patient survival.[37] The authors of these studies have underscored the role of metabolomics in elucidating PAH mechanisms and its potential for in-depth phenotypic characterization and prognostic assessment.

NAVIGATING INTO MULTIDIMENSIONAL DATA

Integrating single-omic data into multidimensional/omic data is a challenging task that is crucial for understanding pathogenic mechanisms and identifying diagnostic or prognostic biomarkers. This transformative process merges information from different omics domains into comprehensive models.[7] Data preprocessing, including rigorous quality control and normalization, ensures biological comparability across data types.[46] Various integration tools, such as clustering, predictive modeling, and network-based methods, cater to specific data combinations and require careful selection to balance statistical robustness with biological relevance. The chosen methodology depends on the research objective, whether it is biomarker discovery, therapeutic target identification, or mechanistic insight.[47] For biomarker discovery, clustering and predictive modeling prioritize data-driven insights, while authors of mechanistic studies tend to integrate biological context with data patterns using pairwise integration and network-based methods.[48,49] The choice between supervised and unsupervised strategies also plays a crucial role in integration methodologies, with supervised approaches enhancing predictive modeling and biomarker discovery, while unsupervised strategies uncover novel patterns and enrich mechanistic explorations.[50] A thoughtful selection process, considering biological nuances and data characteristics, is essential to unlock the full potential of multiomic research, especially in complex diseases like PAH.

CLUSTERING/ DIMENSIONALITY REDUCTION-BASED APPROACHES

Clustering and dimensionality reduction are fundamental techniques in data science that simplify complex datasets and facilitate their interpretation. These methods unify disparate data types into a coherent analytical space, easing downstream integration and analysis.[51] Clustering categorizes data points based on similarity to identify disease subtypes or patterns relevant to diagnosis and prognosis. Techniques such as hierarchical clustering and k-means clustering reveal hidden structures in the data, shedding light on disease subpopulations and potential markers.[52] Dimensionality reduction simplifies data by reducing the number of variables considered, improving manageability and analysis. Methods such as principal component analysis (PCA) and multidimensional scaling distill complex datasets into informative components, preserving essential information while eliminating redundancy.[53] The integration of multiomic data through clustering and dimensionality reduction is revolutionizing our understanding of biological systems and disease mechanisms. These methods enable researchers to gain unprecedented insights into and drive innovation in biomedical research.[54] Techniques such as CIA/MCIA and FALDA demonstrate how dimensionality reduction fuses molecular data, facilitating the discovery of new disease subtypes and biomarkers while improving our understanding of complex biological interactions.[55] This approach promises more precise and effective therapeutic strategies in the future.

In PAH, clustering and dimensional data reduction are commonly used in the unsupervised analysis of single-omic data to investigate whether datasets naturally segregate into groups based on experimental conditions (eg, PAH versus control, treated versus untreated).[56–58] However, their use in a multiomic context is less common. Multiomic data integration via clustering has emerged as a cornerstone in PAH research to aid in sample classification and biomarker identification. This approach leverages

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different omic layers to unravel complex biological networks in PAH, providing a holistic view of disease pathology and facilitating precise sample clustering. As a result, unique cluster-specific biomarkers are discovered, offering promising avenues for targeted therapies and personalized medicine in PAH.[59] For example, Wang et al.[60] used a comprehensive approach, integrating mRNA, lncRNA, circRNA, and miRNA expression profiles of pulmonary artery samples, to differentiate hypoxia-induced pulmonary hypertension rats from controls. This unsupervised hierarchical clustering categorized samples into distinct groups based on molecular signatures, revealing the molecular landscape underlying PAH pathogenesis. Similarly, researchers integrated transcriptome and proteome analyses to differentiate between control and decompensated RV in PAH patients. They used RNA-Seq and proteomic approaches to study RV tissue from patients clinically categorized as control, compensated RV, and decompensated RV. PCA and unsupervised clustering revealed a distinct separation of decompensated RV samples, demonstrating the robustness of integrated omics in delineating pathological states in PAH. Such approaches not only enhance our understanding of the heterogeneity of PAH but also provide valuable insights into potential biomarkers and therapeutic targets for this complex disease.

PREDICTIVE MODELING APPROACHES

Predictive modeling has emerged as a powerful approach in the field of multiomics and big data exploration. It involves a series of steps, including collecting and merging data from multiple sources, selecting relevant features, training models, validating results, and translating findings into clinical practice.[40,61,62] First, disparate data, such as patient records and genetic databases, are combined into comprehensive datasets. Then relevant biomarkers are identified using feature selection techniques to train machine learning models that predict disease outcomes. These models are evaluated using validation datasets, with biomarkers that show strong predictive ability being prioritized for further validation. Notably, this method does not require prior knowledge of omics integration, relying instead on algorithm training.[63] Common machine learning methods include logistic regression, support vector machines, random forests, neural networks, Bayesian models, and boosting techniques.[61] In summary, predictive modeling provides a robust and data-driven means to unravel complex biological processes and discover clinically relevant biomarkers in multiomic datasets.

In PAH, Pi et al.[43] conducted a comprehensive analysis of metabolomic data from 117 PAH patients to uncover metabolites and metabolic pathways associated with indicators of disease severity and RV vulnerability. Their investigation focused on 5 key outcomes: RV dilation, NT-proBNP levels, REVEAL 2.0 score, 6-minute walk distance, and mortality. They first examined overall metabolic differences and their associations with these outcomes, followed by a detailed analysis of individual metabolites and pathways. The team used multivariate analysis techniques such as PCA and partial least squares discriminant analysis to understand global metabolic variation in relation to disease severity. Associations between outcomes and metabolites were assessed using linear and Cox regression analyses, adjusting for relevant factors. Of note, 65 metabolites were identified as associated with mortality, leading to the development of a predictive model using 11 consistent metabolites. This model, validated in an external cohort, shows promise for improving the care of PAH patients.[43] In a similar study, researchers integrated transcriptomic and proteomic analyses to characterize RV changes in PAH patients with RV dysfunction. They identified 5 proteins—LTBP-2, COL6A3, COL18A1, TNC, and CA1—that were elevated in the blood of PAH patients. Predictive modeling was used to associate these proteins with patient survival were established, with LTBP-2 showing additional predictive value compared with conventional risk assessment methods.[40] These findings underscore the potential of omic studies and predictive modeling to advance our understanding of PAH pathogenesis and improve biomarker discovery. Nevertheless, the application of predictive modeling approaches in a multiomic context in PAH remains relatively unexplored.

Pairwise Omics Data Integration

Pairwise omics data integration has emerged as a promising approach in biomarker discovery and understanding of disease mechanisms, enabling the identification of molecular signatures associated with disease etiology, progression, and treatment response.[64] Pairwise omic data integration involves combining two omic datasets, such as genomics and transcriptomics or transcriptomics and proteomics, to uncover molecular relationships and interactions.[65] A widely used approach is the analysis of expression quantitative trait loci (eQTLs), which stands out as a prominent method for pairwise integration, linking genetic variation with changes in transcriptomic profiles.[66] The analysis of eQTLs serves as a method to elucidate the relationships between genetic variants (genomic data) and gene expression (transcriptomic data). Several computational methods for performing eQTL analyses exist, each offering unique advantages and tailored approaches to uncover the intricate relationships between genetic variation and gene expression patterns. These methods include robust computational algorithms such as GEMMA and Matrix eQTL.[67,68] Other approaches, such as Bayesian methods and machine learning algorithms, provide flexible and versatile tools for eQTL analysis.[69] Moreover, recent advances in single-cell sequencing technologies have paved the way for cell-specific eQTL mapping, enabling the dissection of transcriptional regulatory networks at unprecedented resolution.[70] In PAH, eQTL analyses decode the complex interplay between genetic variation and gene expression dysregulation. Authors of studies have explored the relationship between genomic alterations and gene expression patterns in PAH, identifying potentially novel eQTL associated with immune-related pathways, shedding light on PAH pathophysiology, and offering insights into patient characterization

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and identification. For example, Prohaska et al.[71] identified genome-wide single nucleotide polymorphisms associated with RASA3 expression in PAH patients and associated with disease severity and mortality. Similarly, Ulrich et al.[72] performed transcriptome-wide eQTL analysis and uncovered novel genetic influences on gene expression variability, particularly in immune-related pathways, emphasizing the utility of eQTL in characterizing PAH patients.

Correlation analysis, another widely used approach, quantifies pairwise associations between omic features (eg, genes, proteins, metabolites) across samples, revealing coregulated or coexpressed molecular signatures.[73] Additionally, pathway analysis tools map molecular features to known biological pathways, helping to identify dysregulated pathways associated with disease phenotypes.[74] For example, Hou et al.[75] used high-throughput sequencing to study mRNA and lncRNA interactions in PAH pathogenesis. They integrated cis and trans assays, constructed a lncRNA-mRNA coexpression network based on Pearson correlation coefficients, and established a lncRNA-miRNA regulatory network. Functional analysis revealed regulatory networks involving 285 mRNAs and 147 lncRNAs, highlighting the importance of transcriptome and epigenome integration in understanding lncRNA-mRNA interactions in PAH.[75] Moreover, Chelladurai et al.[76] performed a pairwise integrative analysis, combining RNA-Seq and ChIP-Seq, to compare the transcriptional profile of fibroblasts derived from individuals with PAH against healthy controls. This comprehensive approach uncovered a robust correlation between the altered histone modification signatures with the aberrant gene expression pattern observed in PAH fibroblasts.[76] Similarly, researchers have focused on pairwise integration of transcriptomic and proteomic data to uncover mechanisms of RV dysfunction and identify novel biomarkers to assess RV function in PAH. This combination of knowledge is critical to elucidate molecular mechanisms and improve our understanding of PAH.[40,56]

Network-Based Methodologies

Network-based methods play a critical role in multiomics integration by modeling complex interactions between biological molecules, facilitating the identification of key regulatory elements, pathways, and potential therapeutic targets.[77] These methods fall into 2 main categories based on network construction: those that use established, experimentally validated interactions sourced from scientific literature databases and those that use correlational or statistical approaches.[78] Networks based on established interactions include protein-protein interaction (PPI) networks from sources such as STRING and BioGRID, gene regulatory networks detailing the relationships between transcription factors and target genes, and pathway-based networks from databases such as KEGG and Reactome.[79] In contrast, statistical methods such as weighted gene coexpression network analysis (WGCNA) and correlation networks compute pairwise correlations or use advanced machine learning techniques to infer functional associations or coregulation between omics features, potentially revealing novel interactions.[80] While established interaction-based networks are valued for their accuracy, correlational or statistical methods are essential for their ability to explore and hypothesize novel biological connections, albeit with the risk of false positives. In the field of PAH, network-based approaches provide a systemic understanding of the molecular mechanisms driving pathogenesis and facilitate the identification of regulatory elements, signaling pathways, and therapeutic targets.

For example, Li et al.[82] characterized differentially expressed genes in PAH lungs and constructed a PPI network to evaluate functional relationships between hub genes using the STRING database. This tool integrates multiple data sources, including experimental evidence and computational predictions, to predict and visualize protein interactions. It assigns confidence scores to these interactions based on supporting evidence, facilitating the creation of a visual network where proteins are nodes and their interactions are edges.[81] Through this analysis, the study authors identified 9 hub genes that were significantly upregulated in PAH lung tissue compared with control, revealing connections to pathways involved in DNA-templated transcription, sister chromatin cohesion, mitotic nuclear division, and regulation of actin cytoskeleton. These findings provide potential mechanistic insights into the development of PAH by elucidating the interplay of biological processes at the molecular level within PPI networks, which will facilitate the identification of novel therapeutic targets.[82]

While several statistical network approaches are available for PAH research, WGCNA is the most widely used method. For example, Kasavi[83] conducted a comprehensive study integrating omics data by analyzing genome-wide gene and miRNA expression patterns in idiopathic PAH patients and controls. Using WGCNA in R, the author constructed a gene coexpression network to identify clusters of highly correlated genes, which were then integrated with the human PPI network to uncover novel molecular insights. Using miRNA-target gene interactions from the miRTarbase database, the author aimed to unveil molecular signatures and potential therapeutic drug candidates.[83] Similarly, Duo et al.[84] applied a WGCNA approach to identify key modules associated with PAH and to develop a diagnostic signature and immune landscape for the disease. Their research contributed to a better understanding of the molecular mechanisms underlying PAH and provided valuable insights for diagnostic and therapeutic advances in PAH.[84]

CHALLENGES ASSOCIATED WITH MULTIOMIC RESEARCH

Over the past decade, the advent of omics technologies has revolutionized our understanding of disease etiology and led to groundbreaking discoveries in the identification of novel biomarkers and therapeutic targets in PAH. This transformative shift has broadened the scope of research methodologies, allowing us to examine molecular changes comprehensively, including global transcriptomic and proteomic changes, rather than focusing solely on individual genetic

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or protein components. By adopting this holistic approach, researchers have gained deeper insights into the intricate molecular landscape of disease, unraveling its complexity and elucidating key biological pathways and mechanisms involved. However, the next frontier is to integrate multiple layers of omic data to obtain a unified view and identify multiomic hubs affected in PAH, ultimately improving our understanding of its pathophysiology, accelerating biomarker discovery, and prioritizing potential therapeutic targets. However, the integration multiomic data poses several challenges (Figure 1), including the need for diverse expertise (biological, computational, and programming skills), data heterogeneity, and the significant costs associated with such approaches. Consequently, authors of previous studies on PAH have predominantly focused on single-omic analyses, while integrated multiomic approaches remain largely unexplored in the field. Overcoming these challenges is crucial for unlocking the full potential of multiomic integration and advancing our understanding and treatment of complex diseases such as PAH.

The heterogeneity and variability inherent in omics research can be broadly categorized into 2 main types. The first type encompasses the biological variability inherent in the samples themselves and the criteria used to include or exclude them. This category includes factors such as the age, sex, and origin of the biological subjects as well as the methods used to obtain the tissues. For instance, differences in blood samples obtained via venipuncture versus right heart catheterization may introduce variability. Similarly, when working with tissue biopsies, the specific part of the tissue collected (eg, superior versus inferior or left versus right lung sections) and the method of collection (autopsy versus biopsy) warrant careful consideration to accurately interpret omics data. In addition, the selection of a control cohort, which could range from healthy individuals without any comorbidities to patients without a diagnosis of PAH or individuals undergoing lung cancer resection, can significantly influence the data. The second type of heterogeneity arises from data processing decisions, such as the choice of reference genome, alignment methods (eg, STAR versus HISAT2), various cutoffs and quality control measures, and the analytical pipelines employed, which are often subject to individual investigator preferences. This lack of consensus on omics data analysis methods, combined with the lack of standardized methodologies for data collection, processing, and analysis across different omics studies, poses challenges for reproducibility and comparability of results across studies. For example, a recent systematic review highlighting the epigenetic changes associated with RV dysfunction underscores the reproducibility issues among authors of studies using microarrays to investigate microRNAs involved in RV failure in PAH.[85] This variability underscores the critical need for standardized approaches in omics research to improve the comparability and reliability of findings.

The financial burden associated with multiomics research has become increasingly apparent with the advent of advanced technologies like single-cell analyses, spatial transcriptomics, and Olink proteomics. While these methods are transformative, they significantly increase the cost of conducting large cohort studies. As a result, data mining of previously published datasets is emerging as a compelling research methodology to mitigate both the financial constraints and the sample availability challenges. This is particularly relevant for rare diseases such as PAH, where obtaining tissue samples from organs such as the RV and lungs can be difficult for many laboratories. However, relying on previously published data to supplement new research brings its own set of complexities, particularly regarding the reproducibility of results. One major issue is that metadata, which are crucial for understanding the context and conditions under which the data were collected, are not always completely or readily available to the research community. Furthermore, some datasets may not be shared or accessible at all, limiting their utility for further investigation and slowing the pace of new discoveries in the field. This lack of accessibility does not serve the interests of patients, scientific advancement, or research progress. This scenario complicates efforts to replicate studies or build on existing research and underscores the need for better standards and practices for data sharing and documentation in the multiomics field.

PROMISES OF MULTIOMICS INTEGRATION FOR IDENTIFYING NOVEL BIOMARKERS AND TREATMENT TARGETS

The incorporation of multiomic approaches into PAH research is still in its infancy, primarily nestled within the domain of basic science to improve our foundational comprehension of the disease. Multiomic analyses in PAH aim to unravel complex biological mechanisms, including the impact of histone modifications on the transcriptome, the regulatory functions of ncRNA on gene expression, and the delineation eQTLs.[72,86–90] Such exploratory endeavors are pivotal because they contribute to building a robust framework of fundamental biological knowledge, albeit with a delayed trajectory toward direct clinical applicability. Notwithstanding the invaluable insights afforded by basic science research, the foray of multiomic methodologies into the clinical and translational research landscape of PAH has been relatively limited. To date, the application of multiomic approaches has focused primarily on the identification and prioritization of potential biomarkers, notably through the detection of gene alterations at both the transcriptomic and proteomic levels in the RV and blood of patients suffering from RV failure due to PAH[40] as well as the establishment of gene expression profiles and identification of novel protein alterations in the lungs of patients afflicted with PAH to gain further insight into novel biomarkers that characterize this disease.[91] Similar analysis has been used to discover novel therapeutic targets in PAH.[87] However, the superior efficacy of a comprehensive multiomic biomarker panel that includes specific markers from epigenomics, proteomics, and metabolomics over traditional single-omic strategies remains an underexplored

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frontier. Similarly, the exploration of the benefits of panomic therapeutic strategies that may emerge from multiomic research is still in its preliminary stages.

CONCLUSION

In conclusion, the integration of multiomic data holds significant potential and promises for unraveling the complexities underlying the pathophysiology of PAH. However, evolving from theoretical research to tangible clinical applications remains a major challenge. The journey to effectively bridge the gap between groundbreaking multiomic discoveries and their clinical application is a daunting task, highlighting an urgent need for continued research and innovation in this field. Moreover, this journey requires not only advancements in technology and analytics but also a multidisciplinary approach that encompasses clinicians, researchers, and patients. By fostering collaboration across these diverse areas, we can accelerate the translation of multiomic insights into treatments that significantly improve patient outcomes, pushing the boundaries of what is currently possible in PAH care.

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REGULAR ARTICLE

New Treatment Pathways, Drug Development and Clinical Trial Designs: Incorporation of Risk Stratification

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INTRODUCTION

Pulmonary arterial hypertension (PAH) is a rare disease characterized by remodeling of the pulmonary vasculature leading to increases in pulmonary vascular resistance and pulmonary pressures and ultimately right ventricular (RV) failure and death.[1–3] While significant advances have been made in the evaluation and management of patients with PAH, the mortality for these patients remains high.[3] To better tailor therapy and predict clinical course, several risk-stratification tools have been developed. Incorporating these tools into routine clinical practice has enabled practitioners to determine the severity of disease at the time of diagnosis, select an appropriate initial therapeutic regimen, and modify treatment based upon subsequent serial risk reassessments. Unfortunately, despite the availability of these risk tools, use remains suboptimal with a reliance on physician gestalt which often underestimates patients' objective risk.[4,5] In this review, we discuss the incorporation of risk stratification in the treatment of PAH and its use in clinical trials.

RISK STRATIFICATION IN PAH

The risk-stratification tools in current clinical use have been developed through data generated by large PAH registries. The currently available risk-stratification tools include the US-based Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL) 2.0 and REVEAL Lite 2, the Swedish/Comparative Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA) score, the French Pulmonary Hypertension Network Registry (FPHN) score, the Swedish PAH registry (SPAHR) risk score, and the ESC/ERS risk assessment tool.[6–12] These multiparametric risk scores have been validated and include variables for patient demographics, functional capacity, biomarkers, imaging parameters, and hemodynamics.

Current guidelines recommend performing risk stratification at the time of initial diagnosis and at follow-up evaluations.[12] Of the available risk scores, each differs in terms of the variables incorporated, variables required for score calculation, and their applicability (Table 1). The ESC/ERS guidelines score and the REVEAL 2.0 score include the most variables for assessing initial risk. In comparison with the European-based risk scores, the REVEAL 2.0 score has been validated in different PAH patient populations and can act as a continuous score that includes nonmodifiable variables such as sex, age, and World Health Organization (WHO) group subtype.[6,7] The REVEAL Lite 2.0 is an abridged version of the REVEAL 2.0 score that includes 6 modifiable variables to risk-stratify patients.[8] The FPHN and COMPERA 2.0 risk scores are the most abbreviated by including only the most prognostic variables in assessing PAH risk, which are WHO-FC, 6-minute walk distance (6MWD), and Brain natriuretic eptide (BNP)/N-terminal prohormone brain natriuretic peptide (NT-proBNP) and classifying patients into 3 or 4 risk strata based on various cutoffs for these variables.[9–11]

A notable issue with current risk stratification in PAH is the overcategorization of patients into the intermediate risk group. Authors of previous studies have showed that, when using the 2015 ESC-based guidelines for risk stratification, up to 60%–70% of patients are classified as intermediate risk.[12] To help address this, the updated 2022 ESC guidelines used BNP and 6MWD to further subclassify patients into intermediate low- and intermediate high-risk strata with the recommendation that a 4-strata risk tool be used for follow-up evaluation of PAH patients.[12,13] A recent analysis of PAH patients from the GoDeep meta-registry evaluated the predictive value of several PAH risk scores. While the various risk scores have their strengths and weaknesses, the authors of this study found the REVEAL risk scores to have superior and more granular risk prediction than the ESC/ERS and COMPERA risk scores.[14]

TREATMENT ALGORITHM AND RISK STRATIFICATION

Use of risk stratification in PAH has led to development of evidence-based treatment pathways for patients based

Key Words—pulmonary hypertension, risk stratification, prognosis, clinical trials, end points
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Disclosure: Alexandria Miller declares no conflict of interest. Sandeep Sahay declares the following conflicts of interest; consultant and advisor for Janssen, Merck, Morphic, ATXA, United Therapeutics, Keros, Liquidia, and Gossamer Bio; member of End Point Adjudication Committee for GSK; Chair and member of DSMB for NIH funded trials; and research support to institute from Bayer, United Therapeutics, Merck, Goassamer, Bio, Respira, and Keros Therapeutics. Scott Visovatti declares the following conflict of interest as a consultant for United Therapeutics.

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Table 1. Summarization of PAH Risk Scores

Risk Assessment Tools	ESC/ERS Guidelines 2022[12,a]	REVEAL 2.0[6,7]	REVEAL 2.0 Lite[8]	SPAHR[10]	FPHN (Noninvasive)[11]	COMPERA 2.0[9]
Variables	Signs of right heart failure	WHO Group 1 Subgroup	BNP/NT-pro BNP[b]	NYHA/WHO-FC	NYHA/WHO-FC	NYHA/ WHO-FC
	Progression of symptoms	Demographics: male > 60 y	6MWD (m)[b]	6MWD	6MWD	6MWD
	Syncope	Renal function (eGFR < 60)	NYHA/ WHO-FC[b]	NT-pro BNP	BNP/NT-proBNP	BNP/ NT-proBNP
	NYHA/WHO-FC	NYHA/WHO-FC	Systolic blood pressure (mmHg) < 110	Echocardiogram (RA area, pericardial effusion)		
	6MWD	Systolic BP (mmHg) < 110	Heart rate (beats·min^{-1}) > 96	Hemodynamics (RAP, CI, SvO2)		
	CPET (pVO2, VE/VCO2)	Heart rate (beats·min^{-1}) > 96	Renal runction (eGFR < 60)			
	BNP/NT-pro BNP	All cause hospitalizations < 6 months				
	Echo (RA area, TAPSE/sPAP, pericardial effusion)	6MWD (m)				
	Cardiac MRI (RVEF, SVI, RVESVI)	BNP/NT-proBNP				
	Hemodynamics (RAP, CI, SVI, SvO2)	Pericardial effusion on echocardiogram				
		% predicted DLCO < 40				
		mRAP > 20 mmHg within 1 y				
		PVR < 5 WU on RHC				
Model characteristics						
Variables required	3	7	3[b]	No minimum	3	3
Calculation of score	Sum score of variables and divide by No. variables, round to nearest decimal	Sum of score of variables and add 6	Sum of score of variables and add 6	Sum score of variables and divide by No. variables, round to nearest integer	No. low-risk goals met	Sum score of variables and divide by No. variables, round to nearest integer
No. risk strata	3	3	Continuous score	3	3	4

Abbreviation: 6MWD, 6-minute walk distance; BNP, brain natriuretic pepetide; BP, blood pressure; CI, Cardiac Index; CPET, cardiopulmonary exercise test; DLCO, diffusing capacity of lungs; eGFR, estimated glomerular filtration rate; NT-pro BNP, N-terminal BNP; mRAP, mean right atrial pressure; MRI, magnetic resonance imaging; NYHA/WHO-FC, New York Heart Association/World Health Organization Functional Class; pVO2, peak volume of oxygen uptake; PVR, pulmonary vascular resistance; RA, right atrial; RAP, right atrial pressure; RHC, right heart catheterization; RVEF, right ventricular ejection fraction; RVESVI, right ventricular end systolic volume index; SVI, stroke volume index; SvO2, venous oxygen saturation; TAPSE/sPAP, tricuspid annular plane systolic excursion/systolic pulmonary artery pressure ratio; VE/VCO2, minute ventilation/carbon dioxide production ratio; WU, Woods units.

[a]Initial Risk Stratification Tool.
[b]Must include at least 2 of these variables.

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on initial and follow-up risk assessment. The 2022 ESC guidelines recommend those at low/intermediate risk at initial evaluation be started on dual combination therapy with endothelin receptor antagonists and phosphodiesterase inhibitor (class I) and those at high risk be started on triple therapy with addition of prostacyclin-based therapy (class IIa).[12] Subsequent titration of therapy is based on risk reassessment at follow up. Since our treatment of PAH is guided by risk assessment, being able to risk-stratify patients at the time of diagnosis and over time is critical for titration of medical therapy and early referral for lung transplantation consideration.

Despite improvements in our treatment algorithm of PAH patients, our therapies still fail to substantially change patient risk scores over time,[12] suggesting room for improvement in our current risk-stratification systems. To improve our risk-stratification tools, several variables are under investigation. Notably, risk scores are currently lacking an assessment of RV function as a part of their risk assessment. Authors have shown that the addition of RV assessment to current risk scores has increased the prognostic impact of these risk scores.[15–17] In a recent retrospective analysis of the single-center registry, it was found that the addition of echocardiographic parameters such as left ventricular end diastolic eccentricity index improved the prognostic power of the REVEAL Lite 2.0 score to predict outcomes of disease progression.[15] This was taken a step further by El-Kersh et al. with the creation of a REVEAL-ECHO score, which retrospectively evaluated the ability of 4 variables (RV size, RV function, severity of tricuspid regurgitation, and the presence of a pericardial effusion) to further risk-stratify PAH patients.[18] This score was found to appropriately reclassify patients' risk, particularly for those presenting for follow up in the low and intermediate REVEAL risk score classification.[16] Another promising risk-stratification parameter is the tricuspid annular plane systolic excursion/systolic pulmonary artery pressure (TAPSE/SPAP) ratio, a measure of RV-arterial uncoupling[17] that has been found to be prognostic in PAH.[19,20] Other novel blood biomarker, genetic, functional, and hemodynamic parameters are being evaluated for the ability to contribute to risk-stratification assessments.[21]

Another challenge relates to the fact that PAH patient demographics have changed since risk-stratification tools were first introduced. For example, the mean age of diagnosis continues to increase, and patients diagnosed with PAH now have more cardiopulmonary comorbidities, both of which worsen their prognosis.[22] Further confounding the situation is the finding that older patients with PAH are less likely than the younger cohort to improve their risk profile or be on more aggressive treatment.[22,23] Based upon ESC guidelines, PAH patients with cardiopulmonary comorbidities are treated with initial oral monotherapy regardless of risk, given their decreased tolerance of PAH-based therapies.[12] Developing risk scores that better account for this new demographic of PAH patients is critical to tailor therapy for these patients.

Current initiatives in the field of PAH risk stratification include efforts to better understand interrelatedness between multiple variables as well as how best to give weight to risk variables. Newer analytical models based upon Bayesian networks have shown promise as tools capable of providing a more personalized risk assessment.[21,24] A Bayesian-network-derived prediction model called PHORA was recently validated in PAH patients from the REVEAL and COMPERA registries and showed better discriminatory power than either score alone. Studies to validate this model of risk stratification across a broader range of PAH patient data are ongoing.[24]

CLINICAL TRIAL DESIGN AND RISK STRATIFICATION

Clinical trials in PAH have historically incorporated 6MWD as the primary endpoint. While 6MWD is a marker used for risk stratification and prognostication in PAH, it can be affected by other patient factors and comorbidities, and its change over time is not clearly associated with mortality outcomes.[25,26] Clinical trial design in PAH subsequently shifted to looking at composite endpoints reflecting time to clinical worsening (CW). Though more clinically useful, this type of trial design requires long follow-up periods and larger patient populations to find meaningful differences in outcomes; these limitations add complexity and cost to trials. The composite metrics were also challenging to interpret, as many patients enrolled in these trials were already on a background of PAH therapy. Composite endpoints looking at clinical improvement offer a more meaningful outcome for patients that is easier to evaluate over time but are not currently endorsed by the FDA.[27,28] Recently, risk scores have been explored as surrogates for clinical trial endpoints in multiple post hoc analyses of previous clinical trial data (Table 2).

A novel approach to evaluating the ability of a risk score to predict survival and CW-free survival in a clinical trial involved a post hoc analysis of the PATENT 1 and PATENT 2 trials involving riociguat. This examination of the effect of riociguat versus placebo in PAH patients demonstrated that baseline and 12-week REVEAL risk score as well as change in risk score were significantly associated with both survival and CW-free survival.[29]

A post hoc analysis of the FREEDOM-EV trial, which evaluated the effect of oral treprostinil therapy versus placebo on 690 patients with PAH, evaluated the therapy responsiveness of 4 risk scores (noninvasive French risk assessment, 4-strata COMPERA, REVEAL 2.0, and REVEAL Lite 2.0) at baseline and 12-week follow up. It was demonstrated that follow-up risk scores at 12 weeks were able to predict CW better than baseline risk assessment. In addition, the risk scores improved with treatment.[30] The authors concluded that risk scores may be surrogate markers for CW.

Sitbon et al. explored the prognostic and predictive value of the REVEAL 2.0 risk calculator for morbidity and mortality in the GRIPHON study. This clinical trial randomized 1156 patients with PAH to selexipag versus placebo. In the post hoc analysis, patients were evaluated for their number of low-risk criteria (WHO-FC, 6MWD, and N-terminal proBNP) as well as their

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Table 2. Summary of Post Hoc Analysis of Clinical Trial Outcomes with Risk Scores

Clinical Trial	PATENT 1-2[27]	FREEDOM-EV[28]	GRIPHON[29]	Meta-Analysis[30,a]
No. patients	396	690	1156	2508
Treatment	Riociguat	Oral treprostinil	Selexipag	—
Primary endpoint	6MWD	CW event[b]	Composite—death, any cause, or complication related to PAH	CW event[c]
Risk scores assessed	REVEAL 2.0 (RRS)	FPHN, COMPERA 2.0, REVEAL 2.0, REVEAL 2.0 Lite	FPHN (noninvasive), REVEAL 2.0 (RRS)	COMPERA, COMPERA 2.0, REVEAL 2.0, REVEAL Lite 2.0, FPHN (noninvasive)
Results	RRS: –0.6 ± 1.4 versus –0.1 ± 1.6 ($P = 0.31$); 20%–30% RR of death for 1 pt reduction in baseline and 12-wk RRS in long-term follow up	All risk scores at week 12 regardless of treatment predicted relative risk; REVEAL 2.0/REVEAL 2.0 Lite: 1 pt decrease at 12 wk associated with 62% decrease relative risk of CW event (HR 0.38, $P < 0.001$)	Increase in low-risk criteria 18.6% versus 27.5% for placebo versus selexipag; risk score improvement in RRS 8.2% versus 14.6% for placebo versus selexipag	Attaining low risk status for all risk scores associated with longer time to CW event or death. Mediation analysis showed poor correlation with treatment effect and risk scores to CW event (0.07–0.13)

Abbreviations: CW, clinical worsening; HR, heart rate; PAH, pulmonary arterial hypertension; pt, point; RR, relative risk; RRS, REVEAL risk score.

[a]GRIPHON, AMBITION, SERAPHIN.
[b]Death, hospitalization for PAH, disease progression, initiation of prostacyclin, unsatisfactory long term clinical response.
[c]All-cause death, hospitalization for worsening PAH, lung transplantation, atrial septostomy, discontinuation of study treatment for worsening PAH, initiation of parenteral prostacyclin therapy, or decrease of at least 15% in 6-min walk distance from baseline, combined with either worsening of WHO Functional Class from baseline or the addition of an approved PAH treatment.

REVEAL 2.0 risk category at baseline and serially through the study. It was shown that patients treated with selexipag were more likely to increase their number of low-risk criteria and improve their REVEAL 2.0 risk score over the course of the study. These findings suggest that clinical improvement in risk scores could be a surrogate marker for trial endpoints.[31]

A recent meta-analysis of PAH trials by Blette et al. provides a different perspective.[30] The authors included 3 large, randomized PAH clinical trials in their post hoc analysis (AMBITION, GRIPHON, and SERAPHIN), using time to CW as the primary outcome and time to all-cause mortality as the secondary outcome. Importantly, they assessed the surrogacy of 5 risk scores (COMPERA, COMPERA 2.0, REVEAL 2.0, REVEAL Lite 2, and the noninvasive FPHR) for improvement in long-term CW and survival. While this analysis showed an improvement in risk scores and delay in time to CW in the treatment arms, weak correlation was found between the treatment effect and the attainment of low-risk status. The ordinal improvement in risk scores correlated somewhat better with treatment effect but not enough to infer surrogacy. While limitations to this analysis exist, including generalizability to a larger PAH patient cohort and missing data in the compilation of some risk scores, the author suggested further interrogation is needed before risk scores can be consider as surrogates for endpoints in clinical trials.[30]

While the post hoc design of these 4 innovative studies must be acknowledged, they suggest that risk scores offer an appealing option as clinical trial endpoints in future PAH clinical trials.

CONCLUSION AND FUTURE DIRECTIONS

PAH is a complex disease, and our understanding of the various phenotypes and factors that affect prognosis in this patient populations continues to evolve. Current risk tools have advanced our ability to predict clinical outcomes, and post hoc analyses suggest risk scores hold promise as clinical trial endpoints. However, current risk tools have limitations, in part because they are based on assumptions including a linear relationship between variables and outcomes.[31] Further refinement of risk models perhaps based upon novel Bayesian and/or machine-learning-based approaches may provide more accurate, individualized prognosis by considering nonlinear relationships between variables and outcomes as well as a wider variety of parameters. This next generation of risk tools will no doubt improve the effectiveness of treatment pathways and clinical trial design. In the meantime, essential next steps include validation of current risk models as valuable clinical trial outcomes using a prospective trial design.

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REGULAR ARTICLE

CardioMEMS® and Remote Hemodynamic Monitoring in Pulmonary Hypertension

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INTRODUCTION

Pulmonary hypertension (PH) is a result of precapillary remodeling (isolated precapillary PH) or postcapillary pulmonary venous congestion (isolated postcapillary PH [IpcPH]). Some patients demonstrate combined precapillary and postcapillary PH (CpcPH). Determining the etiology of PH is essential to guide management, and diagnosis is confirmed with invasive hemodynamic assessment with a right heart catheterization (RHC).

Pulmonary arterial hypertension (PAH) is a chronic progressive disease characterized by precapillary PH resulting from adverse remodeling of the pulmonary vasculature, ultimately leading to right ventricular failure. The most recent guidelines from the European Society of Cardiology/European Respiratory Society define PAH based on mean pulmonary artery (PA) pressure >20 mmHg and pulmonary vascular resistance of >2 Woods units, assuming normal left atrial or wedge pressure.[1] Several risk-stratification tools used in the management of PH, such as the REVEAL 2.0 risk score or the European Society of Cardiology/European Respiratory Society risk stratification table, use hemodynamic variables such as right atrial pressure, pulmonary vascular resistance, cardiac index, and pulmonary arterial oxygen saturation, typically obtained by invasive assessment.[1,2] Recognition and management of worsening hemodynamics may allow for earlier intervention and alter prognosis using these risk stratification tools, but repeated invasive assessment carries minor but nonnegligible risks.[3]

In patients with PH, a sophisticated hemodynamic assessment is often required to monitor response to treatment and to prevent the progression of the disease to worsening heart failure (HF). Decongestion strategies in these patients aim at preventing HF hospitalizations, which can ultimately affect mortality.[4] Traditional nurse-led teams have been very successful in the management of HF.[5] Wearable and implantable hemodynamic monitors (IHMs) have been developed to determine left atrial pressure, thoracic impedance, and pulmonary pressures.[6–12] Several monitors attached to heart rhythm devices have also been developed and are used commercially but have only had limited success.[13–15] In this article, we discuss the role of the CardioMEMS IHM in patients with left-sided HF including those with PH and in patients with PAH. We discuss the advantages, disadvantages, and future directions in the utility of remote hemodynamic monitoring in PH patients.

Key Words—CardioMEMS, remote hemodynamic monitor
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Disclosure: None of the authors have any relevant conflicts of interest to disclose.

CardioMEMS IMPLANTABLE REMOTE HEMODYNAMIC MONITORING SYSTEM

CardioMEMS is the only commercially available IHM. It has been studied in several large, randomized trials in left-sided HF, irrespective of ejection fraction (EF), and small pilot studies in patients with PAH. The CardioMEMS system uses microelectromechanical technology with a piezoelectrical membrane to measure PA pressures.[16] Distortion of the piezoelectrical membrane in the sensor changes the resonance frequency signal, corresponding to a pressure shift. This change in pressure shift can be measured with the help of an external measurement system that helps capture data from the implanted device.[16] The frequency at which these measurements will be recorded is at the discretion of the managing provider. The implanted device measures about 45 mm in length and 10 mm in width (Figure 1).

CardioMEMS in Left-Sided HF and CpcPH

The CardioMEMS IHM was studied first in the CHAMPION trial (2011).[18] The study assessed the rate of HF-related hospitalizations in patients with New York Heart Association (NYHA) class III symptoms from left heart disease. Both the study and the control cohorts underwent device implantation, but the IHM data were only used for clinical decision making in the study arm.[18] About 78% of the patients had a

 DOI:10.21693/1933-088X-23.2.48

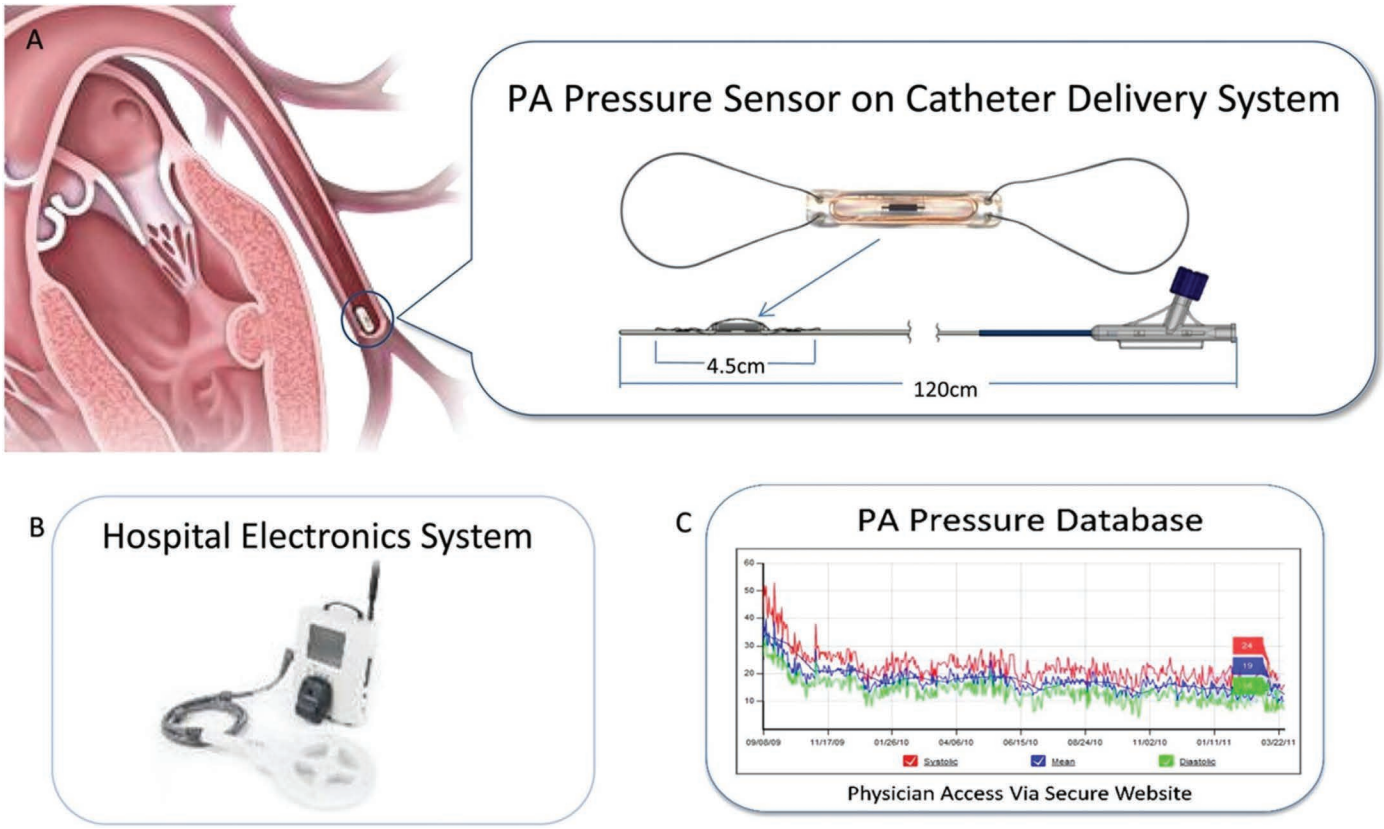

Figure 1: The CardioMEMS heart failure sensor. (**A**) The sensor is implanted into the distal pulmonary artery using a transcatheter delivery system. (**B**) The measurement system consists of an antenna and a measurement unit. (**C**) Hemodynamic data are transmitted to a Website accessible to the patient's heart failure (HF) clinician.[17]

left ventricular EF (LVEF) of less than 40%, with a mean age of 61 years. At 6 months, a 28% reduction in HF-related hospitalization in the study group was found (hazard ratio [HR] = 0.70, 95% confidence interval [CI] = 0.60–0.84; $P < 0.0001$).[18] By the end of the study, at 15 months, the study group had a 39% reduction in HF-related hospitalizations. Freedom from device-related complications was 98.6%, and freedom from sensor failure was 100%, further demonstrating the safety of the device.[18] An open-label long-term follow-up of this population showed a persistent reduction in HF-related hospitalizations at an additional 13 months.[19] Compared with the prior randomized duration, this control group had a significant reduction in HF-related hospitalizations when their hemodynamic data were available to their providers (HR = 0.52, 95% CI = 0.40–0.69).[19] This study led to U.S. Food and Drug Administration (FDA) approval of the CardioMEMS system in 2014 for patients with NYHA class III symptoms with one HF-related admission in the year preceding implantation.[20]

A retrospective analysis of the CHAMPION trial population was performed to assess the outcomes concerning World Health Organization (WHO) group II PH.[21] Patients without PH were at lower risk for mortality (HR = 0.31, 95% CI = 0.19–0.52, $P < 0.0001$) and lower risk of hospitalization (0.37/year versus 0.77/year, HR = 0.49, 95% CI = 0.39–0.61, $P < 0.001$).[21] A significant reduction in HF hospitalizations in patients with and without PH was found; however, in patients with PH, a reduction in the composite endpoint of death and HF hospitalizations was found with access to IHM data (HR = 0.74, 95% CI = 0.55–0.99, $P = 0.04$) but no difference in survival (HR = 0.78, 95% CI = 0.50–1.22, $P = 0.28$).[21] Further, in the CHAMPION trial population, a 30% increase in mortality for every 5 mmHg increase was found in PA pressure in patients with an EF of about 68%.[19]

The GUIDE-HF trial was a second randomized trial assessing the benefit of CardioMEMS.[22] Inclusion criteria in this trial included patients with NYHA class II–IV symptoms with a recent HF hospitalization and/or elevated natriuretic peptides.[22] Like the CHAMPION trial, the device was implanted in the study and control groups. The PA pressure measurements of the control group were unavailable for review in clinical decision making. The primary endpoint consisted of all-cause mortality and total HF events, including HF hospitalizations and urgent HF visits.[22] The study failed to meet superiority for its primary endpoint (HR = 0.88, 95% CI = 0.74–1.05). Also, no significant reduction in prespecified HF-related events was found (HR = 0.85, 95% CI = 0.70–1.03). The study enrollment and follow-up were affected by the COVID-19 pandemic.[22] A pre-COVID-19 sensitivity analysis, however,

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showed a reduction in HF event rate (HR = 0.76, 95% CI = 0.61–0.95).[22]

The MEMS-HF study was a prospective, nonrandomized study that enrolled patients with NYHA class III symptoms who had an HF-related hospitalization the preceding year.[23] During the first 6 months after implantation, HF hospitalizations decreased by 62% (HR = 0.38, 95% CI = 0.31–0.48), and over the 12 months of follow-up, HF hospitalizations decreased by 66% (HR = 0.34, 95% CI = 0.26–0.44).[23] Patient-reported quality of life scores, including the Kansas City Cardiomyopathy Questionnaire (KCCQ), EQ-5D-5 L questionnaire, and the Patient Health Questionnaire depression module, were assessed and showed improvement at 6 months that persisted at 12 months.[23]

A subanalysis of the MEMS-HF study was performed, assessing for any difference in outcomes based on the presence of PH.[24] A total of 106 patients' RHC tracings were analyzed, and they were divided into 3 groups: no PH (31 patients), IpcPH (38 patients), and CpcPH (36 patients).[24] During the 12-month follow-up, the systolic, diastolic, and mean PA pressures decreased in the latter 2 groups, whereas the mean and diastolic PA pressures decreased in patients without PH.[24] HF hospitalization reductions were comparable in the CpcPH group (0.639 events/patient-year; HR = 0.37) and the IpcPH group (0.72 events/patient-year; HR = 0.45).[24] The group without PH had the most significant benefit (0.26 events/patient-year; HR = 0.17, $P = 0.04$ versus IpcPH/CpcPH groups).[24] A substantial improvement in quality of life and NYHA class was found in all the subgroups.[24]

Remote hemodynamic monitoring of PA pressures has also been performed in patients with left-sided HF to assess the effect of empagliflozin in the EMBRACE-HF trial. This study showed that empagliflozin significantly reduced PA diastolic pressures as assessed with the CardioMEMS system, and this effect was seen as early as 1 week after drug initiation.[25]

The MONITOR-HF study assessed for quality-of-life improvement and reduced HF-related hospitalizations in patients with remote hemodynamic monitoring with CardioMEMS versus standard of care in Europe.[26] This study enrolled participants with NYHA class III symptoms irrespective of baseline EF.[26] It was a randomized, open-label multicenter trial. The trial enrolled 348 patients with a median age of 69 years.[26] Fifty percent of the patients had ischemic cardiomyopathy, and 27.9% had LVEF greater than 40%.[26] The primary outcome was a mean change in KCCQ score at 12 months. At 12 months, mean changes of +7.05 (95% CI = 2.77–11.33) for the study group and −0.08 (95% CI = −3.76 to 3.60) with $P = 0.013$ for the control group were found in KCCQ. No significant difference in cardiovascular death or all-cause mortality was found. However, the NT-proBNP and 6-minute walk distances at 12 months significantly differed, favoring the study group.[26]

Table 1 summarizes trials that assessed the safety and clinical efficacy of IHMs.

CardioMEMS and Durable Left Ventricular Assist Devices

The INTELLECT 2-HF study is a multicenter, prospective, nonrandomized, observational study that assessed the feasibility and clinical utility of CardioMEMS in patients with durable left ventricular assist devices (LVADs).[27] Fifty-two patients with HeartMate II and 29 patients with HeartMate 3 LVADs with existing or newly implanted CardioMEMS sensors were followed for a total of 6 months.[27] The population was stratified into responders (average reduction of PA diastolic pressures by at least 1 mmHg over 6 months) and nonresponders (average decrease of PA diastolic pressures by less than 1 mmHg over 6 months). A significant improvement in 6-minute walk distance among responders (266 m versus 322 m; $P = 0.025$) was found compared with no change in nonresponders. Further, patients whose PA diastolic pressure was less than 20 mmHg for over half of the study duration had a significantly lower rate of HF-related hospitalization (12% versus 38.9%; $P = 0.005$).[27]

CardioMEMS in HF with Preserved EF

Trials studying the use of CardioMEMS IHMs looked at outcomes irrespective of EF. However, a GUIDE-HF subanalysis assessed the outcomes by EF in guideline-defined subgroups of EF ≤ 40%, 41%–49%, and ≥50%.[28] A bimodal distribution of LVEF was found, with the majority in the HF with reduced EF (53%) and HF with preserved EF (HFpEF; 40%) subgroups. Patients in the HFpEF subgroup tended to be White, older, female, and with higher body mass index, higher blood pressure, lower rates of coronary artery disease, and lower estimated glomerular filtration rates. The NT-proBNP, KCCQ12 scores, and 6-minute walk distances were similar across the spectrum.[28] Across all subgroups, a significant reduction was found in the primary endpoint of composite HF hospitalizations, urgent care visits related to HF, and all-cause mortality. These results seen in the HFpEF population, unlike drug therapy studies in which the efficacy of drugs alone declines in reaching these same primary endpoints, indicate the importance of targeting filling pressures to reduce morbidity and mortality.[28]

CardioMEMS and PAH

While the above-noted studies assessed the safety and utility of CardioMEMS in left-sided HF patients, many of whom had secondary PH, a small proof-of-concept pilot study evaluated the safety and feasibility of implantation in the PAH population.[29] In this study, the CardioMEMS device was implanted in 27 patients with PAH and NYHA class III or IV symptoms.[29] The device was implanted in the cardiac catheterization lab and calibrated with RHC PA pressures and thermal and/or indirect Fick cardiac output (CO) assessment.[29]

CardioMEMS-derived CO was calculated using a proprietary algorithm based on PA pressure waveform, Pulmonary artery pressures, heart rate, and reference CO. The total pulmonary resistance could also be calculated based on device parameters. The mean age in their study was 51 years; 92% were women, and 81% had NYHA class III symptoms.[29] The median weekly transmission compliance was 98.2%.[29] Of the 28 attempted implant procedures, 1 procedural complication occurred with microperforation of the PA during the

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Table 1. Studies of Implantable Remote Device Monitors[a]

Study, y	Author	Trial design	Inclusion criteria	N	Results
PREDICT, 2006	Packer et al.[10]	Prospective, blinded frequent ICG testing	Currently stable HF patients with recent clinical decompensation	212 patients	59 with 109 WHF events[b]; frequent ICG is predictor of WHF events within 14 d ($P = 0.0002$)
COMPASS Trial, 2008	Bourge et al.[12]	Prospective, multicenter, randomized, single-blind, parallel controlled trial	NYHA FC III–IV, all implanted with Chronicle IHM	Total 274; 134 in the OMT arm; 140 in the OMT + management based on IHM	21% reduction in rate of HF-related events compared with control ($P = 0.33$); retrospective analysis, 36% reduction ($P < 0.03$) in time to first HFH
CHAMPION, 2010	Abraham et al.[18]	Multicenter, single-blind trial; patients blinded to assignment group; investigators had access to all data	NYHA FC III + previous HFH	Total 390; 270 in PAP + standard of care versus 120 in control receiving standard of care only	83 versus 120 HFH; 39% reduction of HFH in treatment arm ($P < 0.0001$)
MEMS-HF, 2020	Angermann et al.[23]	Assessing success of CardioMEMS in Europe	NYHA FC III + HFH in preceding 12 mo	234 patients	62% reduction in HFH, 5.1 ± 7.4 mmHg reduction in PAP, KCCQ and 9-item Health Questionnaire improvement; 86.2% survival, 98.3% free of device-related complications, 99.6% free of sensor failure
GUIDE, 2021	Lindenfeld et al.[22]	Multicenter, single blind; patients blinded to assignment; investigators blinded to control data	NYHA FC II–IV + recent HFH or abnormal proBNP	Total 1000; 497 to PAP + standard of care versus 503 standard of care only	No result in lower composite endpoint felt to have been affected by COVID-19 pandemic. Pre-COVID-19 impact analysis with possible benefit in lowering HFH rates
PROACTIVE HF III, 2023	Guichard et al.[11]	Prospective, randomized, controlled, single-blind multicenter trial	NYHA FC III	Enrolling after SIRONA 1 and SIRONA 2 confirmed the effectiveness of the Cordella PA sensor	Will also include patient engagement, self-reported symptoms, and remote GDMT titration
MONITOR-HF, 2023	Brugts et al.[26]	Open label, randomized trial	NYHA FC III	CardioMEMS versus no CardioMEMS	

Abbreviation: GDMT, guideline directed medical therapy; HF, heart failure; HFH, heart failure hospitalization; ICG, impedance cardiography; IHM, implantable hemodynamic monitor; KCCQ, Kansas City Cardiomyopathy Questionnaire; NYHA FC, New York Heart Association functional classification; OMT, optimal medical therapy; PA, pulmonary artery; PAP, pulmonary artery pressures; WHF, worsening heart failure.

[a]IHM assessing thoracic impedance and pulmonary hypertension. This does not include a list of combination hemodynamic and rhythm monitors. This does not include a list of left atrial pressure monitors.

[b]16 deaths, 78 HF hospitalizations, 10 emergency visits.

predeployment angiogram before any attempt at CardioMEMS deployment, and he or she died from this complication. Of the successful implants, no device-related serious adverse events occurred.[29] Long-term follow-up data showed a reduction in the average number of RHC per year (4.37 prior to device implant versus 1.99 postdevice implants).[30] All the devices remained functional. However, 8 patients required repeat RHC for device recalibration.[30]

The ARTISAN study is a prospective, multicenter, open-labeled trial currently enrolling patients to evaluate the effect

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of early and rapid treprostinil therapy to reduce mean PA pressures. In this trial, the CardioMEMS system is being used to follow the mean PA pressures of the participants. This study is expected to be completed in September 2024.[31] Another ongoing phase 2 study assessing a novel drug CS1 uses the CardioMEMS system to follow the participants' PA pressures.[32]

REMOTE MONITORING IN THE CONTEXT OF CONSENSUS GUIDELINES

The most recent guidelines for the management of HF were released in 2022 by the American College of Cardiology and the American Heart Association. These guidelines suggest that, in selected adult patients with NYHA class III HF and a history of HF hospitalization in the preceding year or elevated natriuretic peptide levels, while on maximally tolerated guideline-directed medical therapy, the usefulness of IHMs remains uncertain to reduce the risk of subsequent HF hospitalizations (2b, level of evidence B-R).[33] At the time of this review, no recommendations regarding the use of IHMs in patients with PAH exist.

OTHER HEMODYNAMIC MONITORING SYSTEMS

Chronicle IHM

The Chronicle IHM (Medtronic) was studied in the COMPASS-HF trial (2008).[12] This prospective, multicenter, randomized, single-blind, parallel-controlled trial was conducted among 274 patients with NYHA class III or IV symptoms.[12] Primary endpoints were freedom from system-related complications, freedom from pressure-sensor failure, and reduction in HF-related events.[12] The primary efficacy endpoint did not reach statistical significance despite the study group having a 21% lower rate of all-HF-related events.[12] After the study, the device failed to receive FDA approval for commercial use.

Cordella IHM

The Cordella PA pressure sensor (Figure 2) has been developed more recently. It was first studied for patients with HF, irrespective of their EF, with NYHA class III symptoms in the SIRONA first-in-human study.[34] The study's primary safety endpoint was

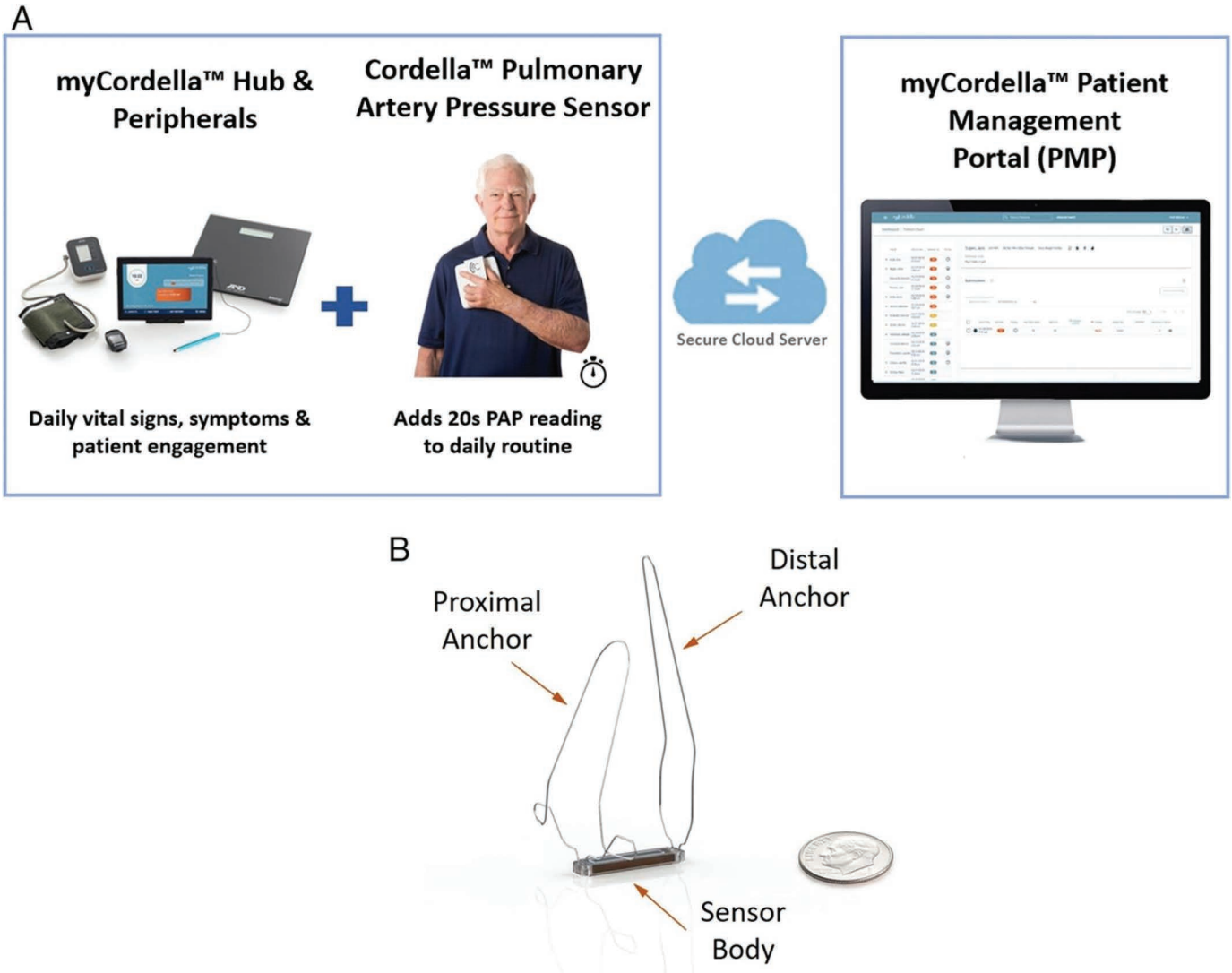

Figure 2: Cordella heart failure system consists of (**A**) the Cordella system and (**B**) The Cordella pulmonary artery (PA) pressure sensor.[34]

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freedom from device-related adverse events through 30 days postprocedure, and the primary efficacy endpoint was accuracy of the device PA pressure measurements, compared with a RHC.[34] A total of 15 patients underwent device implantation with a mean age of 71.4 years; 67% were male, and 53% had an EF greater than 40%.[34] At 90 days, no device-related adverse events occurred. At 90 days postimplantation, the primary efficacy endpoint was met in all patients.[34]

Subsequently, in the SIRONA 2 trial, the accuracy of the PA sensor was assessed compared with RHC.[35] In a total of 70 participants, the equivalence between the PA sensor and RHC for mean PA pressures was excellent, with measurements within equivalent bounds of −4 to 4 mmHg ($P = 0.003$).[35] The device safety profile was excellent, with 98.6% freedom from device-related complications and no reported pressure sensor failures.[35] Long-term follow-up of the SIRONA 2 cohort showed that, at 12 months, good agreement between the Cordella PA sensor and RHC continued, with the average difference for mean PA pressure being 2.9 ± 7.3 mmHg.[36] No pressure sensor failures were found, and 98.4% freedom from device/system-related complications occurred.[36] The device is now being studied for clinical effectiveness in a single-arm, PROACTIVE-HF trial.[11]

An advantage of the Cordella sensor is that it has no leads and does not require batteries. It is implanted in the right PA and interrogated via an external antenna in the handheld reader.[34] The specialized anchor design allows the sensor to be placed into an anterior branch, which along with its microelectronic mechanical system, makes reading from the anterior chest wall possible.[34] Pressure applied to the sensor causes deflections of the pressure-sensitive surface, resulting in a shift in the resonant frequency, which can be measured.[34]

Advantages of Remote Hemodynamic Monitoring: Expert guidelines recommend periodic hemodynamic monitoring for risk stratification and management of decisions, especially with persistent symptomatology and failure to respond to medical management.[1,33] Patients may require repeated hemodynamic assessment within a relatively short period, which can be cumbersome to tolerate and carries a small but identifiable risk of complications. In addition, remote monitoring can provide additional data regarding patients' hemodynamics in their home environment, which may be more reflective of their day-to-day hemodynamic burden of PH than an isolated RHC. Patients can also transmit their PA pressure readings from wherever they are, with the thought that a change in pulmonary pressures can be identified before the onset of symptoms and may provide any warning sign of decompensation, especially in patients who may live a distance away from their PH clinicians.

Further, while remote hemodynamic monitors provide only partial hemodynamic data, they offer a reduction in the number of invasive RHCs a patient may need to undergo in their lifetime. These may also increase access to health care among patients in rural communities where access to health care may be limited due to several reasons, as evidenced by an increase in HF hospitalizations among rural communities.[37] The rapid growth of telehealth services secondary to the COVID-19 pandemic provides an opportunity for us to address health care equity among these underserved populations,[38] and IHMs can play a vital role in achieving this.

Disadvantages of Remote Hemodynamic Monitoring: In addition to the risks associated with the implantation procedure itself, additional considerations exist. Despite having an IHM, these patients continue to require periodic RHC for complete hemodynamic assessment. Clinical worsening can be missed based on remote monitoring alone. It may be challenging to detect decompensated right HF without a parallel rise in pulmonary pressures in those falling off the Frank-Starling curve. Remote monitors measure pulmonary pressures at 1 time point when the patient is recumbent, so trends may not accurately reflect change with exercise.

The CardioMEMS system has proven to be cost effective, assuming that the trial outcomes are sustained and that the durability of the device stands. Real-world postmarketing surveillance data on durability and long-term outcomes would clarify its value.[39] Also, establishing a remote hemodynamic monitoring program requires immense institutional support. The device is implanted either by an interventional cardiologist or an advanced HF cardiologist. Programs then require dedicated coordinators or program managers to follow these patients closely and adjust therapy based on IHM readings with their providers. Given the variability in reimbursement patterns across payors and regions, assessing the number of patients required for programs to breakeven or even turn profitable is challenging.

FUTURE DIRECTIONS

In addition to IHMs, several novel devices are being studied for use in patients with PH. For instance, the use of accelerometers is being evaluated as an alternative to the traditional 6-minute walk distance as an objective measure of physical activity in patients with PH.[40] When remotely monitored by these devices, a reduction in physical activity has been hypothesized to precede clinical worsening and can help identify patients at risk of future hospitalizations.[40] Behavioral change techniques such as text message–based reminders have been shown to improve physical activity levels, ultimately leading to improved quality of life.[41] Using IHMs to complement other devices as a part of a larger digital ecosystem could be additive in improving patient care and quality of life.

CONCLUSIONS

Hemodynamic assessment is vital in the diagnostic classification and management of patients with PH. IHMs play a key role in managing patients with left-sided congestive HF and concomitant PH. Early intervention is possible based on timely recognition of decompensation prior to clinical deterioration, as seen in several studies. IHM use in PAH patients is still in its relative infancy. However, device implantation appears to be relatively safe and feasible in most PAH patients and, in theory, can play a pivotal role in rapid medication titration.

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Ideally, an implantable device that provides comprehensive hemodynamic data will allow for better management of our patients with PH, helping us manage both left- and right-sided HF.

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INVITED MANUSCRIPT

Tyrosine Kinase Inhibitors for Treatment of Pulmonary Arterial Hypertension

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Tyrosine kinase inhibitors are potentially exciting therapies for pulmonary arterial hypertension. However, pleiotropic and variable effects of multitargeted tyrosine kinase inhibitors have limited the ability to identify safe, well-tolerated, and effective agents. In this paper, a succinct description of the range of tyrosine kinase inhibitors that are relevant to pulmonary arterial hypertension (either treating or causing it) is provided. This includes a discussion of how the varied targeting of the agents impacts their therapeutic and adverse effects and how better understanding of the animal models is improving prediction of clinical effects. Proof of concept was obtained in the studies of oral imatinib, although excessive side effects and some cases of subdural hematoma in patients receiving imatinib who were on anticoagulation occurred. Alternative approaches include alteration of the dose, formulation or route of delivery of imatinib, and use of newer agents such as seralutinib that has potentially advantageous receptor targeting combined with inhaled delivery in an effort to reduce systemic effects. These approaches hold promise that ultimately effective new therapies for pulmonary arterial hypertension using tyrosine kinase inhibition will be forthcoming.

Tyrosine kinases are a family of enzymes that regulate critical processes involved in cellular proliferation. A large number of tyrosine kinase inhibitors (TKIs) have been developed and designed to target specific kinases felt to be important in disease states, particularly cancer. Targeting various tyrosine kinases involved in cancer has revolutionized the treatment and outcome of these conditions.

Pulmonary arterial hypertension (PAH) shares many features of a cancer-like state, including abnormal proliferation of pulmonary artery smooth muscle cells. Accordingly the potential for TKIs to treat PAH is logical. TKIs often target multiple tyrosine kinases to a variable extent, resulting in differing and pleiotropic effects. The effects of various TKIs can be tested in animal models of disease, providing additional proof of principle for use in humans. However, these models are imperfect in predicting both beneficial and harmful effects. As multiple TKIs have been studied and approved for use in humans, the understanding of how differences in target specificities translate to potential for both beneficial and adverse clinical effects is improving. TKIs relevant to PAH are shown in Table 1.

Sorafenib is a tyrosine and serine/threonine kinase inhibitor used to treat liver, renal, and thyroid cancers. In animal models, it had greater effect on right ventricular pressure and mass than imatinib. Limited open label studies in humans have shown variable effects with some signals of reduction in pulmonary artery pressure but also concern for fall in cardiac index. Nintedanib (Ofev) is a TKI with effects on platelet-derived growth factor, vascular endothelial growth factor, and fibroblast growth factor and is approved to treat several forms of pulmonary fibrosis. Animal studies have shown conflicting effects, varying from beneficial hemodynamic effects and improvement in pulmonary vascular lesions[1] and also some acute pulmonary arterial relaxation[2–4] to adverse pulmonary vascular effects.

Dasatinib, which is approved by the Food and Drug Administration for treating certain hematologic malignancies, has unfortunately been found sometimes to cause pleural effusions and pulmonary hypertension,[13,22,23] whereas the TKI imatinib, also approved by the Food and Drug Administration for the treatment of hematologic malignancies, has been shown to improve pulmonary hypertension. The adverse effects of dasatinib are believed to be potentially related to its targeting of the Src family of kinases, although more recent evidence suggests important effects on reactive oxygen species and vascular endothelial permeability.[12] Once such effects are recognized, animal studies may help predict the safety of other TKIs in this regard. For example, seralutinib does not have these effects on vascular permeability.[18]

Imatinib is a TKI that targets BCR-ABL and accordingly is highly effective for chronic myelogenous leukemia. It also targets platelet-derived growth factor receptor, which is upregulated in the pulmonary arteries in PAH.[24] Oral imatinib was shown initially in case series to result in improvement in hemodynamics, echocardiographic parameters of right ventricular function, and improvement in N-terminal prohormone of brain natriuretic peptide

Key Words—tyrosine kinase inhibitors, imatinib, seralutinib, pulmonary arterial hypertension, treatment
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Disclosure: RPF reports consulting agreements/advisory board participation with Gossamer Bio, Insmed, Janssen, and Merck, stock ownership with Merck, and royalties from UpToDate.

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Table 1. Tyrosine kinase inhibitors relevant to pulmonary arterial hypertension

Drug	Characteristic	Animal studies	Human studies
Sorafenib	Tyrosine and serine/threonine KI	Reduced RV pressure, mass > imatiinib[5]	Small case series,[6,7] concern of fall in cardiac index
Nintedanib	PDGF, VEGF, and FGF	Conflicting data; no effect versus pulmonary artery vasodilation, reduced RV fibrosis, variable effects on hemodynamics[1,8,9]	Small case series suggests worsening in PAH[9]
Dasatinib	Src, BCR-ABL	Worsening PH, increased ROS, vascular endothelial permeability, reduced KCNK3 signaling[10–12]	Cases of PAH with pleural effusions[13,14]
Oral imatinib	PDGF, BCR-ABL	Improved hemodynamics, vascular pathology but potential for cardiotoxicity[15]	Improved PVR but fluid retention, GI intolerance, SDH in patients on A/C[16]
Inhaled imatinib	PDGF, BCR-ABL	Inhibited development of PH[17]	Phase 2/3 study terminated due to lack of reduction in PVR
Inhaled seralutinib	PDGRα/β, CSF1R, c-Kit[18]	Improved hemodynamics, lung pathology more than oral imatinib; absence of adverse effects on pulmonary endothelial permeability[18,19]	Phase 2 positive for reduction in PVR, NT-proBNP, preservation of RV function[20,21]; phase 3 enrolling

Abbreviations: A/C, anticoagulation; CSF1R, colony-stimulating factor 1R; FGF, fibroblast growth factor; GI, gastrointestinal; KI, kinase inhibitor; NT-proBNP, N-terminal prohormone of brain natriuretic peptide; PAH, pulmonary arterial hypertension; PDGF, platelet-derived growth factor; PH, pulmonary hypertension; PVR, pulmonary vascular resistance; ROS, reactive oxygen species; RV, right ventricular; SDH, subdural hematoma; VEGF, vascular endothelial growth factor.

and functional class.[25] However, in that series, 2 patients who were on warfarin sustained subdural hematomas. A subsequent placebo-controlled study in 59 patients demonstrated improvement in pulmonary vascular resistance.[26] In the randomized placebo-controlled study Imatinib in Pulmonary Arterial Hypertension, a Randomized, Efficacy Study (IMPRES), imatinib improved the placebo-corrected 6-minute walk by 32 m (95% confidence interval, 12–52; $P = .002$) and reduced placebo-corrected pulmonary vascular resistance by 379 dyne·s·cm^{-5} (95% confidence interval, −502 to − 255; $P < .001$).[16] However, serious adverse events were more common with imatinib than with placebo (44% versus 30%), and discontinuations were also more common (33% versus 18%). In addition, 8 patients developed subdural hematomas on imatinib therapy, all of whom were on warfarin. There were also frequent gastrointestinal side effects and peripheral swelling.

Accordingly, although oral imatinib was effective in lowering pulmonary artery pressure and resistance and improving 6-minute walk distance in patients with PAH, including patients on maximal therapy with phosphodiesterase-5 inhibitors, endothelin receptor antagonists, and parenteral prostanoids, it was never approved by regulatory agencies for the treatment of PAH. The exact mechanism of the subdural hematoma risk is unclear but may reflect some effect of the drug on the cerebral vasculature that was permissive for bleeding. However, the signals of beneficial effects on the pulmonary vasculature set the stage for exploration of alternative strategies of using TKIs in PAH. There are also concerns about potential cardiotoxicity of oral imatinib mediated via ABL-related gene (c-Abl).[15] Efforts to establish a safe and effective lower dose of imatinib have also been proposed.[27]

ALTERNATIVE FORMULATION OF ORAL IMATINIB

An alternative formulation of imatinib has been developed (TNX-201, oral enteric-coated imatinib, Tenax Therapeutics, Chapel Hill, SC). It is hoped that this formulation may mitigate some of the gastrointestinal intolerance issues of imatinib. Thus far, no tolerability and efficacy studies in PAH have been conducted.

INHALED ROUTE OF ADMINISTRATION OF TKIS

Delivery of drugs impacting the pulmonary vasculature by inhalation is intrinsically attractive as a method to more selectively target the organ of interest. Absorption of the drug across the alveolar septal membrane into the blood can result in activity on the resistance vessels of the lungs. Systemic absorption does occur, but the blood levels tend to be much lower than those achieved with systemic administration, so off-target effects may be reduced although not necessarily fully avoided.

Inhaled Imatinib

Inhaled imatinib was shown to be reasonably tolerated in healthy adults.[28] The Inhaled Imatinib in PAH Clinical Trial (IMPAHCT, NCT05036135) was an innovative phase 2/3 study of inhaled imatinib, seeking to take advantage of the known effects of imatinib on pulmonary artery pressure and resistance but hoping to lessen systemic risks and side effects by virtue of the inhaled route of administration. Unfortunately the study failed to meet its primary endpoint of reduction in pulmonary vascular resistance, so the study was terminated. Full publication of the findings are awaited.

Inhaled Seralutinib

Seralutinib is a small-molecule inhibitor specifically designed with the goal of targeting multiple pathways believed to be important in the pathophysiology of pulmonary vascular disease. In animal models of PAH, including the monocrotaline rat and the Sugen hypoxia model, seralutinib reverses the pathological findings in the pulmonary vasculature and improves hemodynamics and right ventricular function. It targets platelet-derived growth factor receptors A and B, c-Kit, and colony-stimulating

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factor 1R (CSF1R).[18,19] CSF1R is a receptor on activated macrophages that may play a role in perivascular inflammation in PAH. It is more potent than imatinib against c-Kit and CSF1R kinases. It does not target BCR-ABL, so it is not anticipated to have cardiotoxicity, and does not impact pulmonary endothelial permeability in animal studies, so it is not anticipated to have the potential for pleural effusions/development of pulmonary hypertension in contradistinction to dasatinib.[18] In phase 1 and phase 2 studies (TORREY, NCT04456998), it appears to be well tolerated, with the most common side effect being cough, which is common with inhaled therapies.[20] Serious adverse effects were uncommon. The phase 2 (TORREY) study of inhaled seralutinib met its primary endpoint of a reduction in pulmonary vascular resistance. It also reduced N-terminal prohormone of brain natriuretic peptide and was associated with preservation of right ventricular function compared with placebo.[21] A pivotal phase 3 study (PROSERA) is currently recruiting (NCT05934526), with a primary endpoint of a 6-minute walk.

CONCLUSIONS

The promise of tyrosine kinase inhibition in the therapy of PAH has been more difficult to achieve than anticipated, reflecting the complexity of the effect of multitargeted TKIs and issues of tolerability. The key is to deliver an adequate dose of an effective drug to the pulmonary vasculature with an acceptable tolerability and safety profile. Enhanced understanding of receptor targeting of the various TKIs and the association of that targeting with either beneficial or adverse effects has expanded the ability of animal models to predict efficacy and safety. In this light, ongoing research holds great promise for identifying tyrosine kinase inhibitors that are safe and effective in the treatment of pulmonary arterial hypertension.

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REGULAR ARTICLE

Racial and Ethnic Equity in Pulmonary Arterial Hypertension Clinical Trials

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Over the last several decades, many new therapies have been developed for patients with pulmonary arterial hypertension (PAH). These therapies have led to meaningful improvements in patient outcomes. Despite these advances, little is known about disparities in PAH care and even less is known about equity in clinical trial inclusion. Lack of equitable representation in PAH clinical trials may impact our understanding of risks and benefits in specific populations and may limit uptake of new therapies in minoritized populations. In this review, we begin to explore the racial and ethnic breakdown of patients receiving care for PAH and among participants who take part in clinic trials. We suggest that we have not yet achieved our goal of equitable representation in clinical trials and finish with a discussion of potential barriers and pathways forward. It is likely that progress will depend on addressing a complex interplay of patient-facing and system-derived barriers to participation.

The focus of this review is to examine the Venn diagram of racial and ethnic equity, clinical trials, and pulmonary arterial hypertension (PAH). By way of brief background, PAH is a rare and severe clinical condition caused by progressive remodeling of the pulmonary vasculature, which leads to elevated pulmonary vascular resistance, worse right heart failure, decreasing functional status, and poor prognosis. Over the last several decades, a proliferation of therapies for patients with PAH and meaningful improvements in outcomes have developed; however, little is known about inequity in the care of patients with PAH, and even less is known about racial and ethnic equitable inclusion of participants with PAH in clinical trials.

The relevance of this issue is underscored by the fact that clinical trials are central to evaluating the efficacy of new therapies, identifying adverse effects, and expanding understanding of disease processes. Racial and ethnic minoritized individuals continue to experience worse health outcomes and have more limited access to advancing treatments. Unfortunately, clinical trials that are not representative of the population being treated may widen these existing disparities. Beyond ethical concerns of excluding minoritized populations, poorly representative sampling in clinical trial populations may compromise the external validity of studies and potentially diminish the ability to identify heterogeneity of treatment effects.[1]

Health equity is the assurance that "everyone has a fair and just opportunity to be as healthy as possible" which involves "recognizing and rectifying historical injustices, and providing resources according to need."[2,3] Based on this definition, several important foci need to be considered when ensuring fair access to health. The current review is focused on minoritized populations as defined by racial and ethnic identity, with a particular focus on the United States. Participation in US clinical trials is influenced by a legacy of profound injustices against Black and African Americans as well as Hispanic or Latinx communities.[4] Given this understanding of health equity and the focus on acknowledging and addressing past injustices, it is important to specifically concentrate on the experiences of ethnically and racially minoritized groups when pursuing health equity in clinical trials.

Thirty years after the National Institutes of Health Revitalization Act was passed, which intended to improve enrollment of minoritized populations into clinical trials, imbalanced representation in clinical trials and equitable recruitment remain significant public health issues.[5] Emblematically, among 20,692 US-based clinical trials, only 43% reported race and ethnicity data.[6] Equitable inclusion into clinical trials has become a major goal of National Institutes of Health initiatives, and this focus was included in the 2022

Key Words—PAH, equity, clinical trials, registries, inclusion
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Disclosure: No competing financial interests exist.

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Consolidated Appropriations Act. The Consolidated Appropriations Act requires studies of drugs or medical devices to include broad populations of participations based on age, gender, race, and ethnicity.

One key barrier to understanding equitable inclusion of participants in US-based PAH clinical trials is a lack of understanding of the racial and ethnic breakdown of patients living with PAH more broadly. Due to the rare nature of this disease, much of what we know about the demographics of patients living with PAH has come from observational studies conducted in economically developed countries organized into national and/or international disease registries. Even these data sources often have sparse descriptions of race and ethnicity and, in the US, have uniformly relied on voluntary enrollment. The reliance on voluntary observational registries to inform the appropriateness of clinical trial populations contributes substantial uncertainty as to whether we are achieving our stated goal of equity. Systematic features that limit minoritized patient participation in trials may similarly limit their participation in voluntary registries. This may give the impression of parity without achieving the goal of equity relative to the true patient population.

Efforts to understand the broader PAH disease population in the US began in the 1980s with the National Institute of Health Patient Registry for the Characterization of Primary Pulmonary Hypertension.[7] This was the first large PAH registry in the US and was comprised predominately of young White women. This racial and ethnic impression was also reflected in the Registry to Evaluate Early and Long-term PAH Disease Management (REVEAL Registry),[8] which categorized 3,515 patients from 55 centers within the United States. REVEAL suggested that 80% of participants were White, 14% were Black, 9% were Hispanic, and 6% of participants reported another race. This general trend has been reinforced by other US-based registries including the Pulmonary Hypertension Association Registry (PHAR, https://phassociation.org/phar/recent-research-and-the-pha-registry/), the Sphere registry, and the PAH Biobank. These US-based registries have reported a range of White participants from 72.3% to 79%, Black participants from 11% to 15.4%, Hispanic participants from 5.9% to 10%, and participants of another race between 10% and 12%. Only the PHAR specifically identifies participants who report Asian race (3.4% of the registry). One possible exception to a reliance on voluntary participation to characterize demographics is the Centers for Disease Control and Prevention (CDC) WONDER cohort.[9] CDC WONDER includes an attributable death database, and while this carries concern for conflating racial disparities in outcomes and prevalence, it does offer a nonvoluntary picture of the breakdown of death among patients identified as having PAH in the US. CDC WONDER would seem to reinforce the overall impression seen in voluntary registries with deaths among White patients with PAH comprising 83.7%, Black patients responsible for 13.1%, American Indian and Alaska Native patients at 0.8%, and Asian and Pacific Islanders at 2.4%.[10]

Taken together, the available data would seem to suggest that the population of patients with PAH in the US appears to include 20%–30% of patients identified as a minority and 70%–80% identified as White. The validity of these estimates may be cautiously supported by their similarity to the US census in 2020, which found that 71% of people in the US identified as White (61.6% identified as White alone). As such, while likely imperfect, this breakdown may be a reasonable benchmark to begin understanding equity in clinical trials at the national level. Relevantly, PHAR analyses suggest the racial distribution among people living with PAH varies widely by US census region.[11] It is important to recognize that, for any individual trial, the local region may have a different source population of individuals living with PAH, and it may not be appropriate to apply a national standard to assess equity.

Beginning with early therapies for PAH, the initial landmark trial of epoprostenol in 1996 did not include information on race, but subsequent large trials of bosentan (79.8% White participants) and sildenafil (86% White participants) suggested that White participants were likely overrepresented.[12–14] The proportion of non-White participants in international PAH clinical trials has increased over time, but this was primarily through expanding recruitment in Asia and Latin America, not through an increased recruitment in racially diverse populations within North America and Europe.[12] This is an important distinction because race and ethnicity may be associated with a range of social determinants of health that may be quite distinct between countries. In fact, we devote significant time in this review to focusing on issues from the vantage of the US. This is not because other countries and regions lack important barriers to health equity but because these barriers are likely specific and tied to the unique history, policies, and social context of each country. Thoughtfully unpacking each of these country-specific social constructs is beyond the scope of this review. As such, the focus on the US is grounded in practicality and a region with a wealth of PAH-focused research.

Importantly, non-Hispanic Black participants appear to be consistently underrepresented in clinical trial populations. In the recent analysis by Min et al, these participants only constituted about 4% of the overall clinical trial population when accounting for all geographic sites (although this increased to 9.8% when only considering US participants, which does begin to approach the percentage of Black individuals in the most recent US census). Nevertheless, this suggests Black participants were likely underrepresented in clinical trials relative to the US population and certainly underrepresented relative to the global population.[15] In a direct review of some of the largest randomized clinical trials for PAH therapies from the last decade, the pattern of underrepresentation by Black participants is similar. For example, in 2013, the PATENT-1[16] trial evaluated riociguat in 443 participants from 123 centers in 30 different countries. In PATENT-1, only 1% of participants were classified as Black (61% of participants were White, 31% as Asian, less than 1% as mixed race, and 5% categorized as other

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Table 1. Potential Barriers and Solutions to Inclusive Clinic Trials[a]

Patient-facing barriers	Possible individual-level solutions
Perceived risk	Clear and culturally informed study materials
Trust in the medical community	Patient- or community-engaged research
Relationship with provider	Providers introducing studies initially or community providers trained in research
Health literacy and awareness of trials	
Time commitment	Monetary support for time of work
Study distance to center	Reimbursement for travel
	Remote study visits
Study-team and institution derived	**Possible study- or institution-level solutions**
Diversity of the study team	Inclusive hiring practices
Awareness of unconscious bias	Bias and cultural competency training
Cultural competency of the study team	
Availability of study resources in multiple languages	Early translation of study materials
	Inclusion of budget for translation services
Inclusion criteria that favor imbalanced race or ethnicity	Unbiased registries to monitor inclusive enrollment
Lack of community outreach	Partner with community advocacy groups
A one-size-fits-all approach to increasing diversity	Qualitative approaches to engage minoritized communities

[a]Included themes from existing literature.[20,27–33]

or not reported). Subsequently, the SERAPHIN trial[17] evaluated macitentan in 250 participants from 151 centers across 39 countries. SERAPHIN's participants only included 2.6% Black participants (54.5% of the study population was White, 27.7% was Asian, 14.7% was Hispanic, and 0.4% were determined to be other). Even in the most contemporary trials, Black participants continue to be underrepresented. The PULSAR trial[18] of sotatercept included 4% participants who self-identified as Black (92% identified as White and 4% as other), and the subsequent STELLAR trial[19] of sotatercept only included 2.2% of participants who self-identified as Black (89.2% as White, 2.2% as Asian, 13% as other, and 8% as missing).

The mechanisms for lack of equitable inclusion in trials are not well understood, likely vary by region, and have not been studied in PAH. Evidence from cardiology and oncology studies suggests logistical barriers to participation include time commitment involved with participation, transportation, long distance to study centers, and financial burden.[20] Poor quality of communication from the research team regarding placebo versus interventional therapy arms may be an additional barrier in experimental studies. Certain language and cultural differences, especially within the context of informed consent, contribute to the decision to enroll in clinical studies.[21] Importantly, clinical trial enrollment also occurs within the broader context of race relations in the United States. The mechanisms for racial inequities in health care in general are numerous, operating on multiple levels and dimensions.[22,23] For Black individuals in the US, medical system distrust, especially in the context of clinical trial research, is rooted in a history of exploitation and mistreatment of Black individuals by the medical and research community.[4,24] The decision to participate in medical trials may be influenced by medical mistrust that is a result of current and historical systemic racism.[25,26]

In addition to these mechanisms in medicine and society more broadly, specific barriers may exist for rare diseases such as PAH. Fewer centers specializing in PAH means less access to centers for care, potentially less involvement in clinical studies, and delays in diagnosis and initiation of therapy. This may be exacerbated by insurance status and other social determinants of health that disproportionately affect minoritized populations. For example, patients with PAH in the lowest tercile of socioeconomic status had a higher risk of mortality in one study (hazard ratio of mortality was 2.98 after adjusting for age, sex, hemodynamics, World Health Organization group, and therapy).[27] Based on data from the REVEAL Registry and PHAR, Black and Hispanic patients were overrepresented among PAH participants in the lower income categories (15.98% and 10.20% of Black and Hispanic patients, respectively, in the lower 2 income groups compared with 6.49% and 4.57% in upper two income groups).[28] For minoritized individuals with PAH, systemic inequities that result in differential access to education, employment, and insurance may result in poorer health outcomes and affect access to clinical care including clinical trial participation.

In summary, these inequities in PAH clinical trials are important. Clinical trial recruitment that is not representative of the PAH population more broadly may impair understanding of drug effects, heterogeneity of treatment, and adverse effects of therapies. Unequal participation in trials also has the potential to limit trust in new drugs for which minoritized participants were not fully represented. While we have

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used percentages by race and ethnicity of patients living with PAH to try and understand the scope of the problem, we do not believe that a system of quotas for clinical trial participation is an appropriate solution. A target-based system in isolation has the potential to create a series of unintended effects including pressure on study teams to enroll minoritized population and an incentive that may inadvertently lead to coercion of participation which may exacerbate rather than ameliorate racially and ethnically motivated distrust in medical research.

The Food and Drug Administration published initial guidance in 2020 emphasizing the need to incorporate the following solutions: (1) broaden inclusion and exclusion criteria when able with careful attention to eligibility criteria in rare diseases; (2) trial design that is more accessible and less burdensome, for example, optimizing remote study visits; (3) culture competency training and a focus on patient-engaged research; (4) trial sites in locations with higher concentrations of ethnically and racially minoritized communities; and (5) use of electronic study materials whenever possible, including electronic consent forms (see Table 1).[29] Updated guidance in 2024 went on to highlight the importance of keeping unbiased, accurate disease registries to create an effective diversity action plan. Several key knowledge gaps need to be filled to improve the conduct of equitable PAH trials in the US. These gaps include but are not limited to a better understanding of the racial and ethnic representation among PAH patients more broadly, improved characterization of the overlap of race and ethnicity with other social determinants of health, and a much more nuanced understanding of the barriers that minoritized patients face to participation in registries and trials. Successful strategies for enhancing the representation of ethnically and racially minoritized individuals in clinical trials will need to account for the specific context of the disease—particularly for rare conditions like PAH—as well as the geographical and social contexts of the affected communities (solutions are summarized in Table 1). Community-engaged research which partners with minoritized populations to understand the research needs and priorities of these communities has shown significant promise in improving diversity of clinical studies.[30,31] Other patient-centered strategies may include providing monetary support for time and travel associated with participation, flexible study hours to accommodate those in the workforce, and recruiting diverse study teams and cultural congruency of teams.[32]

Traditional, deficit-based approaches to health disparities focus on characteristics within individuals or communities and often fail to account for a complex, multilevel system of inequity. In contrast, critical approaches incorporate race consciousness, intersectionality, and move away from deficit-based approaches that place the burden of fixing inequities on personal attributes of patients and their families. It is a combination of these approaches paired with the careful reform of clinical trial protocol, design, and organization that will move PAH clinical research toward representativeness and equity.[33,34] The careful study of patient-facing and system-derived barriers is vital to developing a fair and equitable system where minoritized populations want to be included in PAH clinical trials and such opportunities are afforded to them.

ACKNOWLEDGMENTS:

TM receives funding from the Cystic Fibrosis Foundation (005129D122—Milinic) and the National Institutes of Health (T32HL007287). PJL receives research funding and/or salary support from the National Institutes of Health (R61HL167848, R01HL152724, R33HL142539, and R01HL159886), PHAB (Mentored Award), and the Cystic Fibrosis Foundation Therapeutic Development Network (Medical Monitor). TM, PJL, and LMB participated in content conceptualization and manuscript writing.

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CASE STUDY

Pulmonary Artery Intimal Sarcoma and the Role for Vasodilator Therapy—A Case Report and Scoping Review

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Pulmonary artery sarcoma is a rare disease that is often misdiagnosed as acute or chronic pulmonary thromboembolism due to its clinical presentation and radiological findings. Often, right ventricular failure is observed due to pulmonary hypertension caused by the obstructive effect of the tumor and concomitant chronic thromboembolism. In this article, we report a rare case of a 60-year-old male patient presenting with dyspnea and imaging findings suggestive of a pulmonary embolism. He was treated with standard anticoagulation and thrombolytic therapy yet continued to have symptoms, with repeat imaging showing progression of disease. The patient subsequently underwent surgical resection of the obstructive lesion, with pathology revealing sarcoma. On follow-up clinic visits, our patient continued to endorse shortness of breath with evidence of pulmonary hypertension. Pulmonary artery sarcoma has been mainly documented through case reports, and treatment often centers around surgical resection and oncological intervention. Many of these patients often have right-sided heart failure. The goal of this review is to systematically search through the literature, identify vasodilatory therapies that have been used in patients with pulmonary artery intimal sarcoma, and characterize the role of pulmonary hypertensive medications.

INTRODUCTION

Pulmonary artery sarcoma (PAS) is an uncommon, but increasingly recognized, thoracic malignancy with only a few hundred cases reported in the literature.[1] The sarcoma arises from mesenchymal cells of the intimal layers of the pulmonary trunk and artery. It has a slight female predominance with no other associated risk factors currently known.[2] PAS results in significant morbidity and high mortality, with a median survival of just 1.5 months.[3] Typically, the disease presents in adulthood, with symptoms including dyspnea, cough, hemoptysis, chest pain, and weight loss. The clinical and radiological findings are often similar to those of thromboembolic disease, leading to delays in confirming the diagnosis. Due to the overall clinical picture of thromboembolic disease, the majority of these patients are diagnosed with chronic thromboembolic pulmonary hypertension (CTEPH).[4]

Given the rarity of PAS, only case reports and small case series have been published, the majority focusing on histopathological appearances and surgical aspects of its management. Surgery remains the mainstay of management for patients with PAS.[5] The role of additional chemotherapy and radiotherapy after surgical resection remains largely unproven. We present a case of a 60-year-old male presenting with dyspnea, with imaging demonstrating occlusion of the right pulmonary artery found to have PAS.

Additionally, we systematically searched through the literature to identify vasodilatory therapies that have been used in patients with pulmonary intimal sarcoma to characterize the role that pulmonary hypertensive medications may play.

ETHICS STATEMENT

The patient identified in this case study has provided written consent for the publication of their medical case, with the understanding that anonymized information will be shared for educational and research purposes. Given the nature of the case study, which does not involve any experimental procedures or interventions beyond standard medical care, institutional review board approval was not deemed necessary.

CASE

A 60-year-old male patient with a past medical history of transient ischemic attacks on lifelong anticoagulation with rivaroxaban, hypertension, and type 2 diabetes mellitus presented to his primary care doctor with complaints of 5 days of dyspnea. Vital signs demonstrated a heart rate of 106 beats per minute, blood pressure of 138/80 mm Hg, respiratory rate of 18 breaths per minute, and oxygen saturation of 95% on ambient air that remained above 90% with ambulation. Physical exam revealed nonlabored breathing with lungs that were clear to auscultation bilaterally. Electrocardiogram showed sinus tachycardia. A posteroanterior and lateral chest

Key Words—Pulmonary hypertension, pulmonary artery sarcoma, vasodilator therapy, palliative care
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Disclosure: The authors have no conflicts of interest.

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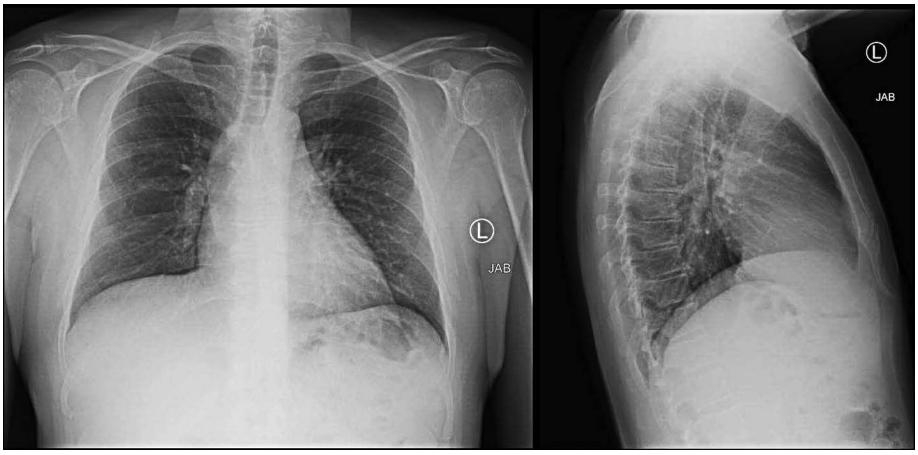

Figure 1: A posteroanterior and lateral chest x-ray obtained on patient initial presentation.

radiograph was unremarkable without any pulmonary infiltrates or consolidations (Figure 1). As he was already on rivaroxaban, the likelihood of pulmonary embolism was thought to be low. He was prescribed azithromycin and prednisone for presumed community-acquired pneumonia with close follow-up.

One week later, the patient continued to have persistent dyspnea despite treatment. Coronavirus disease 2019 and influenza testing were negative. The physical exam was otherwise unchanged from his previous visit. Due to his persistent symptoms with unclear etiology, he was sent to the emergency department for further evaluation. Serological testing, including complete blood count, basic metabolic panel, and liver function tests, were unremarkable. High-sensitivity troponin-T was elevated at 30 ng/L. Electrocardiogram again demonstrated sinus tachycardia.

A computed tomography (CT) pulmonary angiogram revealed an extensive right-sided pulmonary embolism extending from the bifurcation of the central pulmonary artery without extension of thrombosis in segmental and subsegmental vessels as well as the left pulmonary artery and lobe (Figure 2). Emergent echocardiogram showed an ejection fraction of 55% with severe enlargement of the right ventricular chamber and reduced systolic function. The estimated right ventricular systolic pressure was 69 mm Hg, with a peak tricuspid regurgitation velocity of 3.1 m/s. He was initiated on unfractionated heparin infusion for intermediate- to high-risk pulmonary embolism and underwent evaluation for thrombectomy with interventional radiology. Initial diagnostic pulmonary angiogram demonstrated patency of the main left pulmonary artery with preserved perfusion of the left lung. However, there was complete absence of flow of contrast within the main right pulmonary artery correlating to the complete thrombosis of the vessel. Due to the suspected extensive thrombus burden within the vessel, there was difficulty achieving the most adequate position of the guide sheath and catheter within the main right pulmonary artery for thrombectomy. Instead, catheter-directed thrombolysis was performed, with the infusion catheter being placed along the course of the main right pulmonary artery for maximal thrombolytic therapy.

During his hospitalization, he became hypoxic and required supplemental oxygen. An ultrasound of his bilateral lower extremities did not show any deep vein thrombosis, so interior vena cava filter was deferred. On hospitalization day 5, the patient had sudden acute chest pain with a heart rate of 83 beats per minute, blood pressure of 125/67 mm Hg, and oxygen saturation of 91% on 2 L nasal cannula. Repeated serologies again were unremarkable outside of a recurrent elevated high-sensitivity troponin at 39 ng/L. A repeat CT pulmonary angiogram was conducted that demonstrated progressive thrombosis with extension throughout the right main pulmonary artery, right lobar, segmental, and subsegmental arteries. New findings of left-sided segmental and subsegmental emboli along with a tiny embolus within the left main pulmonary artery were also revealed. Repeat thrombolysis was considered, but given the progression and extensive clot burden, this was deferred for evaluation of mechanical thrombectomy by cardiothoracic surgery. His clinical condition improved, with resolution of his chest pain and hypoxic respiratory failure as he returned to ambient air.

The patient was transferred to the university medical center 9 days after initial hospitalization for cardiothoracic surgery evaluation. Repeat CT pulmonary angiogram again demonstrated unresolved

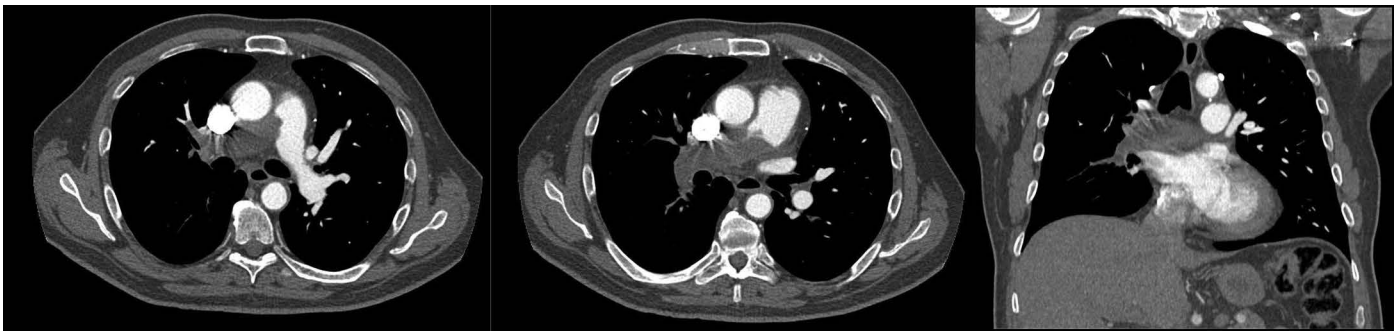

Figure 2: Computed tomography pulmonary angiogram revealing right-sided occlusion lesion extending from the bifurcation of the central pulmonary artery into the left pulmonary artery and lobe.

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thrombi that were unchanged from his prior scan. He underwent right and left heart catheterization that revealed a completely occluded right main pulmonary artery ostium, patent left main pulmonary artery main vessel, and triple-vessel disease, including mid-left anterior descending, mid-right coronary artery, and first obtuse marginal. Pulmonary artery pressure was elevated at 86 mm Hg, and pulmonary capillary wedge pressure was normal at 7 mm Hg. He underwent bilateral pulmonary endarterectomy and 3-vessel coronary artery bypass grafting 12 days into admission. Gross surgical specimens from the endarterectomy were sent for pathology evaluation. Postoperatively, he was transferred to the cardiac intensive care unit for monitoring, where he was initiated on intravenous milrinone and inhaled nitric oxide. His stay was complicated by acute renal failure from acute tubular necrosis that required short-term hemodialysis with eventual renal recovery. He was discharged 16 days after initial hospitalization presentation with warfarin for anticoagulation, furosemide for diuresis, sildenafil for pulmonary hypertension, and 2 L of supplemental oxygen.

One day after hospitalization, the pathology review of the specimens from the endarterectomy revealed the diagnosis of intimal sarcoma. The patient was established with oncology follow-up 1 week after hospitalization, and he underwent positron emission tomography-CT, with multiple bone lesions consistent with osseous metastasis. He was readmitted to the hospital with initiation of doxorubicin, ifosfamide, and mesna chemotherapy. He completed 6 cycles of chemotherapy with repeat positron emission tomography-CT, demonstrating resolution of his disease. He was considered to be in remission of his malignancy.

He followed up with the pulmonology clinic for his pulmonary hypertension that was still being treated with sildenafil around 6 months after initial discharge. He was World Health Organization functional class III with progressive dyspnea but no longer required supplemental oxygen. Pulmonary function testing demonstrated severe diffusion limitation, with diffusion capacity of carbon monoxide of 38% of predicted. Repeat echocardiogram demonstrated an improved ejection fraction of 65%, with improvement of right ventricular systolic function to normal and minimal tricuspid regurgitation jet with inability to calculate right ventricular systolic pressure. The patient was scheduled for repeat right heart cauterization with vasoreactivity testing to determine potential palliative trial of oral vasodilator therapy for his severe dyspnea.

Less than 1 week later, the patient had new-onset left-sided leg and foot weakness and underwent magnetic resonance imaging of his brain and lumbar spine that revealed osseous metastatic disease with multiple lesions within the brain. A biopsy of a lesion on his lumbar spine was performed but was unable to be identified due to complete necrosis of the tissue. Due to overall concern of recurrent metastatic intimal sarcoma, he was started on palliative radiotherapy for his brain metastasis.

Before initiation of radiotherapy, he presented to an outside emergency department after having seizure-like activity and was found to have worsening vasogenic edema on a CT head scan. He was hospitalized and had multiple complications, including atrial fibrillation with rapid ventricular response, acute renal failure, and *Clostridioides difficile* colitis. He progressively went into septic shock, requiring an upgrade to the intensive care unit and norepinephrine and intubation. Unfortunately, the poor prognosis of the patient's condition was discussed with the family, who decided to transition to comfort-only care. He expired after cessation of aggressive life support measures.

METHODS AND MATERIALS

The goal of this scoping review was to conduct a systematic search of the existing literature and to characterize the evidence supporting vasodilatory treatment regimens for PAS-associated pulmonary hypertension. The methodology for this scoping review was based on the protocol outlined by Arksey and O'Malley.[6]

The literature search, scope, and reporting of findings were guided by the following questions:

1. What treatments have been used to address pulmonary hypertension in patients with PAS?
2. What is the role of vasodilator therapy in patients with PAS with right heart failure?
3. Are there potential avenues for future research?

Search Strategy

The initial literature search was completed by our team librarians using the search terms "pulmonary artery sarcoma," "pulmonary hypertension," "vasodilator," "therapy," "right ventricular failure," "afterload reduction," "riociguat," "pulmonary artery balloon angioplasty," and "diuresis" on the databases PubMed, Ovid MEDLINE, Embase, Cochrane Library, Database of Abstracts of Reviews of Effects, Health Technology Assessment Database, NHS Economic Evaluation Database, and ClinicalTrials.gov.

The date January 1, 1995, was designated the start date for the literature review after a preliminary search on PubMed revealed an increase in "pulmonary artery sarcoma" publications under their "Results by Year" filter. The systematic search was conducted on the publications in electronic databases from January 1, 1995, to September 1, 2022. This neither includes unpublished ongoing studies as of September 1, 2022, nor conferences, newsletters, or book chapters.

All citations (880) were imported into EndNote X8.0.1 (Thomson Reuters). The citations were then deduplicated and uploaded into Covidence (Covidence, Melbourne, Australia), an online tool to help organize and facilitate the literature selection process.

Study Selection

Two team members independently reviewed each title and abstract for the initial screening process. A third member assisted with providing consensus for cases of disagreement. The screening process was iterative. Only articles that included vasodilatory treatment for PAS were included. Studies that partially fulfilled the inclusion criteria, such as those discussing only surgical or oncologic interventions, were not included in this study. Full articles were

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obtained, and their references were screened for additional relevant articles.

Charting the Data

The data from primary research articles (studies that generate new data) were compiled in a single spreadsheet. Secondary research articles, such as reviews, were not directly included in the data collection process, but they were consulted to determine additional studies that may not have been included through our screening process. Finally, individual case studies were grouped together and evaluated for common themes.

RESULTS

The total number of papers obtained from the initial database search was 880. After eliminating duplicates, this review began with 502 articles. After reviewing titles, 426 articles were excluded. Excluded articles encompassed a broad range of topics that did not discuss primary PAS. For example, articles that discussed embolic metastases of another malignancy, cardiac sarcomas, vasculitis, or congenital pulmonary artery abnormalities were not included.

In total, 76 articles were screened based on their abstracts. Articles that did not discuss both primary PAS and pulmonary hypertension were excluded, which brought the final count to 23 articles for full-text screening. Only 2 studies addressed the use of pulmonary hypertensive medications in the management of primary pulmonary sarcomas. The 21 excluded articles discussed pulmonary hypertension as a complication of the PAS but did not discuss its medical management outside of surgical resection or oncologic therapies. The preferred reporting items for systematic reviews and meta-analyses flow chart details the review process (Figure 3).

DISCUSSION

PAS is a rare tumor that arises in the central pulmonary arteries. Often, patients present with shortness of breath, with imaging suggestive of a pulmonary embolism. Despite anticoagulation or thrombolysis, lesion excision is usually performed to reveal the malignancy due to persistent symptoms by patients. Prognosis ranges from several months to a few years depending on the extent of disease, the presence of recurrence or metastasis after surgical resection, and the use of adjuvant therapy like radiation and chemotherapy. The evidence supporting the management of PAS is limited to case studies and series, all of which discuss the immediate surgical and oncologic management.

This case experience is unique because it adds to the medical management of PAS by using vasodilator therapy for pulmonary hypertension. The physiology of pulmonary hypertension from a primary malignancy in the pulmonary vasculature is different from that of an embolic process as the increase in pulmonary artery pressure occurs chronically, which allows for right ventricular compensation. The scoping review process has identified multiple case reports documenting the coexistence of pulmonary hypertension in patients with PAS, but only 2 studies discussed the use of vasodilatory therapy in postoperative management. None of these patients were continued on pulmonary hypertension treatment at discharge. Most patients died from within the same hospitalization of diagnosis, so the evidence for vasodilator therapy is minimal.

Interestingly, the scoping review process identified an area of research that involves using vasodilators for symptom palliation in patients with end-stage interstitial lung disease. By targeting the pulmonary blood vessels, sildenafil can help reduce pulmonary hypertension, a common complication of interstitial lung diseases. Bajwah et al[7] conducted a systematic review assessing the level of evidence of interventions aimed at improving dyspnea and other quality-of-life metrics in patients with fibrotic interstitial lung disease and concluded that there is moderate evidence for the use of sildenafil in improving patient's dyspnea and quality of life. Given pulmonary sarcoma's high morbidity and mortality, it is worthwhile to explore

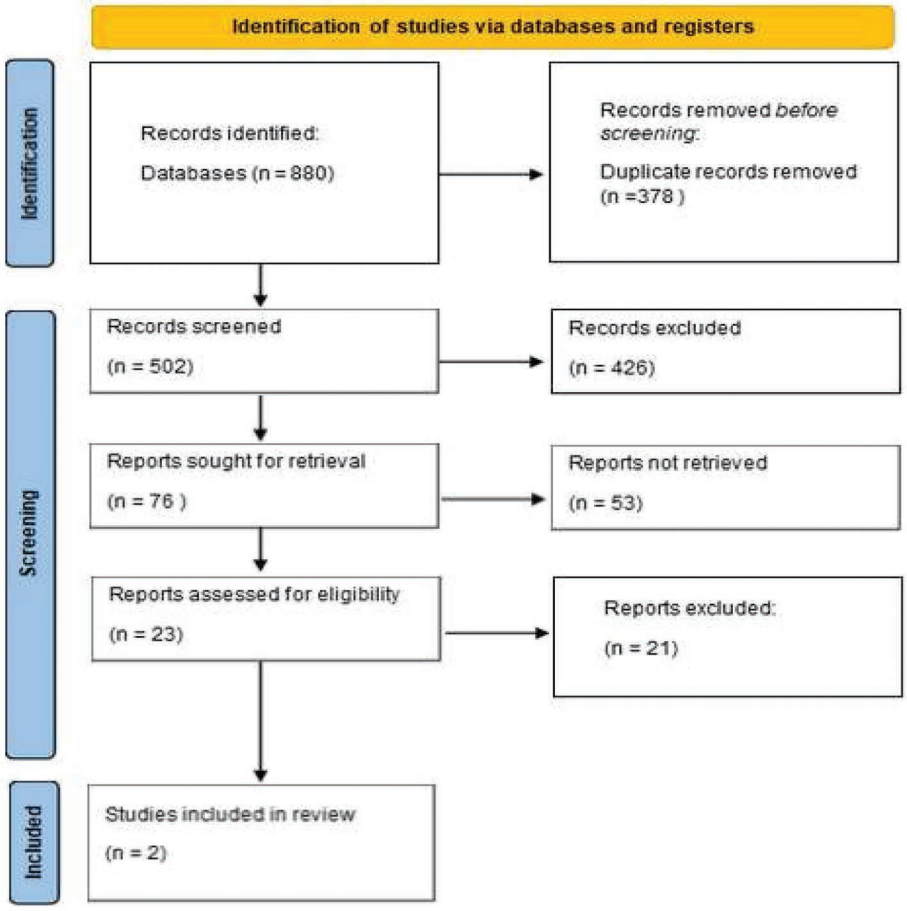

Figure 3: Preferred reporting items for systematic reviews and meta-analyses flow detailing the systematic review process.

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future uses of vasodilators for palliative purposes for patients with PAS.

Right ventricular heart failure pathogenesis from PAS is similar to that from CTEPH because both are caused by obstruction preventing perfusion of normal lung parenchyma. Right ventricular failure is the main cause of morbidity and mortality in pulmonary hypertension and CTEPH, so successful treatments should lead to improvements in right ventricular parameters. Thus, there may be a theoretical role for a medication like riociguat, a soluble guanylate cyclase stimulator approved to treat both pulmonary arterial hypertension and nonoperable CTEPH, in symptom palliation in patients with PAS.

Riociguat increases the production of cyclic guanosine monophosphate, leading to relaxation and dilation of blood vessels. In both preclinical and clinical studies, riociguat has demonstrated a beneficial impact on right ventricular structure and function. A range of hemodynamic parameters, including pulmonary vascular resistance, cardiac index, mean pulmonary artery pressure, and systemic vascular resistance, were improved in both pretreated and treatment-naive patients in PATENT-1 and in patients with inoperable CTEPH and persistent/recurrent CTEPH post-pulmonary endarterectomy (PEA) in CHEST-1.[8,9]

Given that riociguat has the ability to reduce pulmonary vascular resistance, there is a basis for considering its use in patients with PAS. By improving blood flow and reducing pressure in the pulmonary arteries, riociguat might help alleviate some of the symptoms associated with the condition, such as shortness of breath and chest pain. This may improve patient quality of life while more definitive therapy such as chemotherapy or surgical resection is being considered.

Currently, riociguat has the most evidence supporting its use in nonoperative CTEPH. However, there are other medications being studied for use in nonoperative CTEPH but have not been approved for use worldwide. Subcutaneous treprostinil showed improvement in right heart hemodynamic measurements (CTREPH trial), and it has been approved for use in Europe.[10] Macitentan is currently undergoing a phase 3 trial (MACiTEPH)[11] after positive results from the MERIT-1 study investigating the efficacy, safety, and tolerability of macitentan.[12] These agents may have potential palliative use in PAS, but their current use is pending additional studies.

This study is limited because it is a discussion of a single patient case. Additionally, the patient was started on pulmonary hypertensive medications for 3 months, but he died 6 months after diagnosis. Follow-up studies evaluating the progression of the patient's pulmonary hypertension were unable to be conducted due to the patient's passing. The prognosis of PAS is poor despite conventional surgical and oncologic therapy. However, this patient case does raise a new clinical question of whether incorporating a vasodilator medication for PAS-associated pulmonary hypertension could improve or prolong a patient's functional capacity and quality of life.

CONCLUSIONS

PASs are a rare thoracic malignancy that can lead to pulmonary hypertension through vascular obstruction. Vasodilatory medications are used to dilate the constricted blood vessels, reduce pulmonary hypertension, and improve blood circulation in the lungs. These therapies can result in alleviation of dyspneic symptoms and potentially improve patient quality of life.

We present a case of PAS in which the patient was started on vasodilatory treatment with the goal of symptom palliation. However, the effectiveness of vasodilatory therapy in PASs have not been studied as noted through a systematic search of the literature. There is moderate evidence supporting the use of vasodilators in end-stage interstitial lung disease for palliative purposes, and this could be applied to patients with PAS.

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