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CONTEMPORARY REVIEW

Cardiovascular Diseases That Have Emerged From the Darkness

Barry J. Maron, MD; Martin S. Maron, MD; Mathew S. Maurer, MD; Ethan J. Rowin, MD; Bradley A. Maron, MD; Nazzareno Galiè, MD

ABSTRACT: It is important for both the patient and physician communities to have timely access to information recognizing rapid progress in the diagnosis and treatment of familiar but relatively uncommon cardiovascular diseases. Patients with 3 cardiovascular diseases (ie, hypertrophic cardiomyopathy, pulmonary arterial hypertension, and transthyretin (TTR) cardiac amyloidosis (ATTR)]), once considered rare without effective management options and associated with malignant prognosis, have now benefited substantially from the development of a variety of innovative therapeutic strategies. In addition, in each case, enhanced diagnostic testing has expanded the patient population and allowed for more widespread administration of contemporary treatments. In hypertrophic cardiomyopathy, introduction of implantable defibrillators to prevent sudden death as well as high-benefit:low-risk septal reduction therapies to reverse heart failure have substantially reduced morbidity and disease-related mortality (to 0.5% per year). For pulmonary arterial hypertension, a disease once characterized by a particularly grim prognosis, prospective randomized drug trials with aggressive single (or combined) pharmacotherapy have measurably improved survival and quality of life for many patients. In cardiac amyloidosis, development of disease-specific drugs can for the first time reduce morbidity and mortality, prominently with breakthrough ATTR-protein–stabilizing tafamidis. In conclusion, in less common and visible cardiovascular diseases, it is crucial to recognize substantial progress and achievement, given that penetration of such information into clinical practice and the patient community can be inconsistent. Diseases such as hypertrophic cardiomyopathy, pulmonary arterial hypertension, and ATTR cardiac amyloidosis, once linked to a uniformly adverse prognosis, are now associated with the opportunity for patients to experience satisfactory quality of life and extended longevity.

Key Words: amyloid ■ drug therapy ■ heart failure ■ hypertrophic cardiomyopathy ■ implantable cardioverter-defibrillator ■ pulmonary hypertension ■ sudden death

Medical conditions once considered largely untreatable without effective management options, and with obstacles to reliable clinical identification can be associated with an impaired flow of information regarding innovations that reduce disease burden. Important progress in diagnosis and treatment of relatively uncommon cardiovascular diseases may be underrecognized in the practicing physician community and general public.

As clinical investigators long engaged with such diseases, we regard this review as an opportunity to present evidence substantiating clinical innovations and paradigms that have significantly reduced mortality and morbidity in 3 important but complex cardiovascular conditions: hypertrophic cardiomyopathy (HCM), pulmonary arterial hypertension (PAH), and ATTR (transthyretin) cardiac amyloidosis (Figures 1 and 2). Although each of these diseases is notable for once being considered ominous and uncompromising, we report here those relevant medical achievements that have transformed contemporary clinical practice for afflicted patients.

HYPERTROPHIC CARDIOMYOPATHY

Historical Perspectives

HCM is an inherited and globally distributed heart disease known for 60 years,[15,16] characterized by

Correspondence to: Barry J. Maron, MD, HCM Institute, Tufts Medical Center, Boston, MA 02111. E-mail: barrymaron1@gmail.com

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Nonstandard Abbreviations and Acronyms

AMBITION	Ambrisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension
APOLLO	The Study of an Investigational Drug, Patisiran (ALN-TTR02), for the treatment of Transthyretin (TTR)-Mediated Amyloidosis
ATTR	(transthyretin) cardiac amyloidosis
HCM	hypertrophic cardiomyopathy
mPAP	mean pulmonary artery pressure
PAH	pulmonary arterial hypertension

heterogeneous clinical profile and natural history including progressive heart failure, atrial fibrillation/embolic stroke, and highly visible sudden deaths in the young (including competitive athletes)[1] (Figure 1). After its initial comprehensive clinical description in 1964,[17] HCM was regarded for many years as rare and grim, and difficult to reliably diagnose or effectively manage. Early on, available treatments were limited to β-blockers and high-risk surgical myectomy, with overall disease-related mortality once considered to be 6% per year.[1,18] However, over the past 20 years, patients with HCM have benefited greatly from major advances in diagnosis and management, as well as an enhanced understanding of natural history, ultimately evolving into a contemporary treatable disease, achieving a >10-fold reduction in mortality (Figures 2 and 3).[1,2,107]

Diagnosis

Several epidemiologic studies have shown HCM to be a relatively common inherited heart disease with an estimated prevalence of 1:500 considering the disease phenotype or 1:200 more broadly accounting for familial transmission and genetic diagnosis, and presenting at virtually any age from childhood to the elderly.[1,19]

Contemporary imaging with echocardiography and cardiovascular magnetic resonance imaging has demonstrated the morphologic heterogeneity of the HCM phenotype comprising numerous patterns of left ventricular (LV) hypertrophy ranging from mild and segmental to massive.[20,21] Also, laboratory genetic testing has identified a subgroup of relatives with sarcomeric gene mutations considered pathogenic who do not express LV hypertrophy, but are capable of developing the disease phenotype and transmitting the mutant gene to offspring as an autosomal dominant trait.[23]

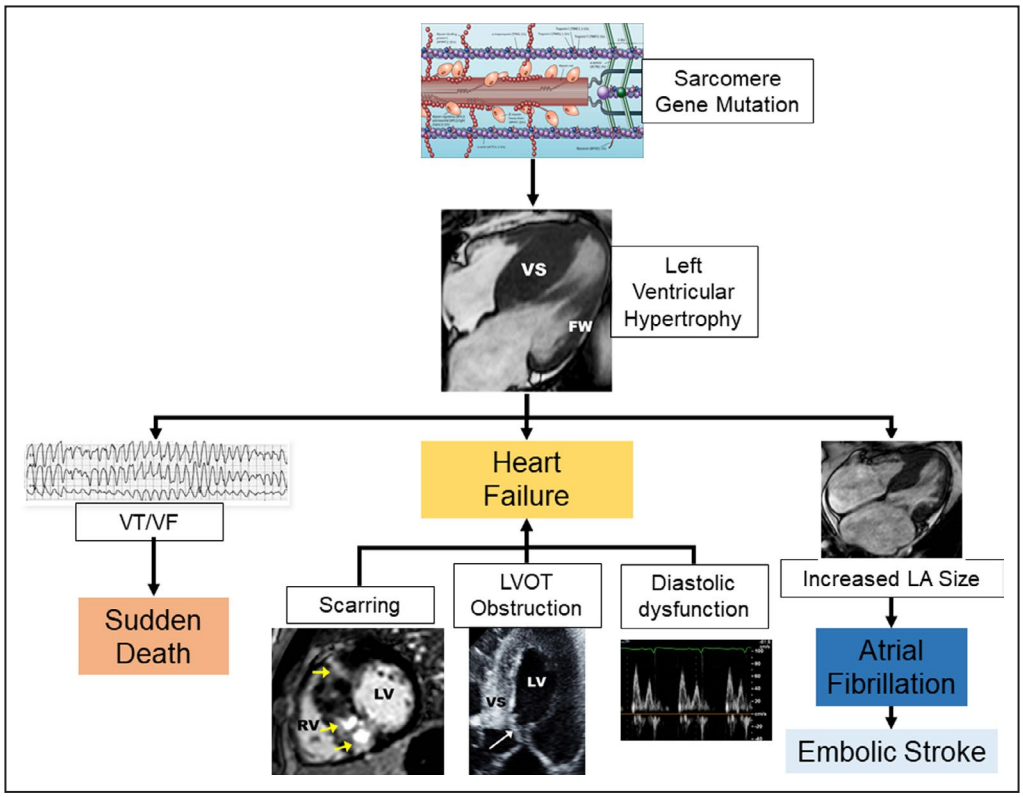

Figure 1. Hypertrophic cardiomyopathy: clinical spectrum and outcome.
FW, free wall; LA indicates left atrium; LV, left ventricle; LVOT, left ventricular outflow tract; RV, right ventricle; VS, ventricular septum; and VT/VF, ventricular tachycardia/ventricular fibrillation.

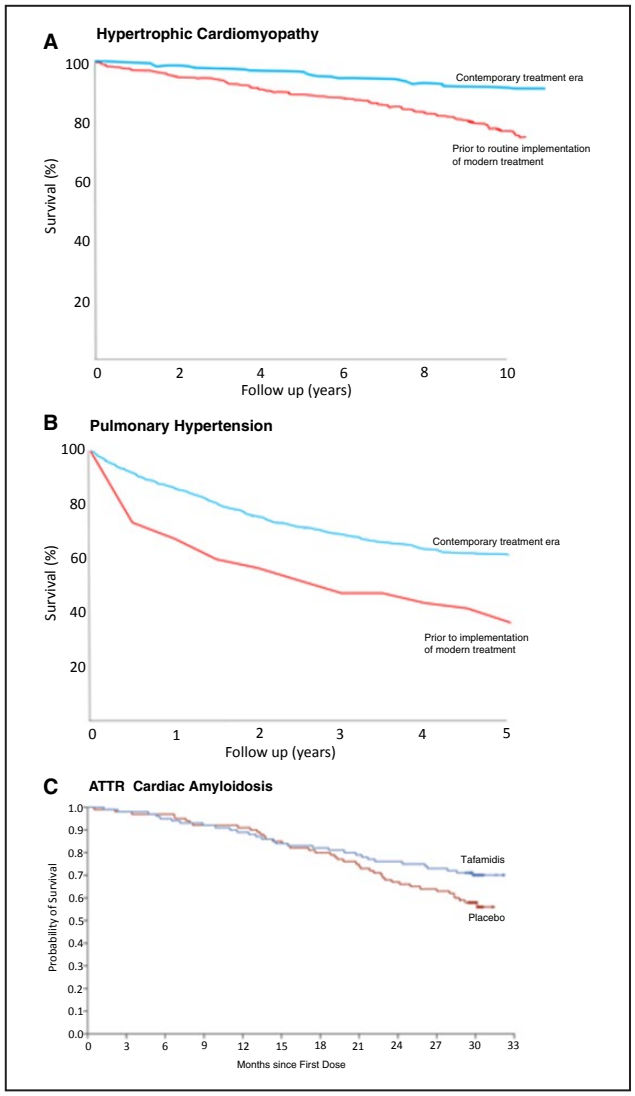

Figure 2. Constructed Kaplan-Meier curves showing reduction in all-cause mortality associated with contemporary treatment advances for 3 diseases.
A, Hypertrophic cardiomyopathy, current treatment vs prior eras.[1–6] **B**, Pulmonary arterial hypertension, current treatment vs pretreatment era.[7–12] **C**, ATTR (transthyretin) cardiac amyloidosis, treatment with tafamidis vs conventional treatment.[13,14]

Treatment Advances and Clinical Course

Notably, for patients who develop disease-related complications, innovative clinical interventions have favorably altered natural history, making the dismal early reputation acquired by HCM now obsolete.[1–6,24–39,107,108] Specifically, reversal (or modification) of clinical course is now possible with contemporary treatment modalities that target specific adverse pathways[1,2,24]: (1) sudden death risk, (2) progressive heart failure due to LV outflow obstruction, (3) refractory heart failure in nonobstructive patients, and (4) consequences of atrial fibrillation. However, HCM has not proven to be a uniformly progressive condition, given that even in a referral cohort about one-half of patients experience stable clinical course with little or no symptomatology, and most others (90%) incur only one of the potential adverse pathways.[24]

Primary prevention of arrhythmic sudden death became a reality in HCM with the introduction of implantable cardioverter-defibrillators to the patient population in 2000[3] for terminating potentially lethal ventricular tachyarrhythmias (3%–4% per year in high-risk cohorts),[1,2,4,5,24–27,32,33] using an enhanced risk stratification algorithm that identifies those patients susceptible to sudden death events and candidates for implantable defibrillators with high sensitivity (ie, 95%).[5] Reversal of advanced heart failure due to LV outflow obstruction can be achieved with low-risk:high-benefit surgical septal myectomy[28–31] (or its selective alternative, percutaneous alcohol septal ablation),[38] Symptom relief by one or more New York Heart Association functional class is attainable in >90% of patients, also associated with low operative mortality (0.6%) when performed in high-volume HCM surgical environments.[28–31] Advanced heart failure therapies[35,36] have been effective, with a 5-year survival of up to 90% after transplant in end-stage nonobstructive patients; aggressive anticoagulation prophylaxis mitigates atrial fibrillation-related embolic stroke.[34]

Traditional pharmacologic options with negative inotropic agents, such as β-blockers, verapamil, and disopyramide, can control symptoms for variable periods of time in many patients, but rarely alter the long-term clinical course of HCM. Relevant in this regard is the potential introduction of mavacamten into the HCM treatment armamentarium, a novel small-molecule selective allosteric inhibitor of cardiac myosin ATPase that mitigates actin-myosin cross-bridging, acting clinically as a strong negative inotropic agent to reduce LV contractility, outflow obstruction, and symptoms.[108] Although not approved for use by the Food and Drug Administration at the time of this writing, mavacamten and other drugs in this class would potentially have the palliative capability of controlling symptoms and delaying myectomy in some patients, but also with a risk of excessive systolic dysfunction and heart failure.

The current HCM-related mortality rate has been reduced to only 0.5% per year (10-year survival after diagnosis 95%), a consequence of contemporary management strategies using implantable defibrillators, septal reduction, and anticoagulant drugs, but also reflecting the diversity of the HCM clinical spectrum, which includes many patients with low lifetime risk; 95% of patients with HCM are in New York Heart Association classes I/II at long-term follow-up, including some who experience benign clinical course with extended longevity often without requiring major treatment interventions[1,2] (Figure 1-3). HCM has become an uncommon primary cause of premature death largely due to progressive refractory heart failure in the absence of outflow obstruction.[37] Consequently, the

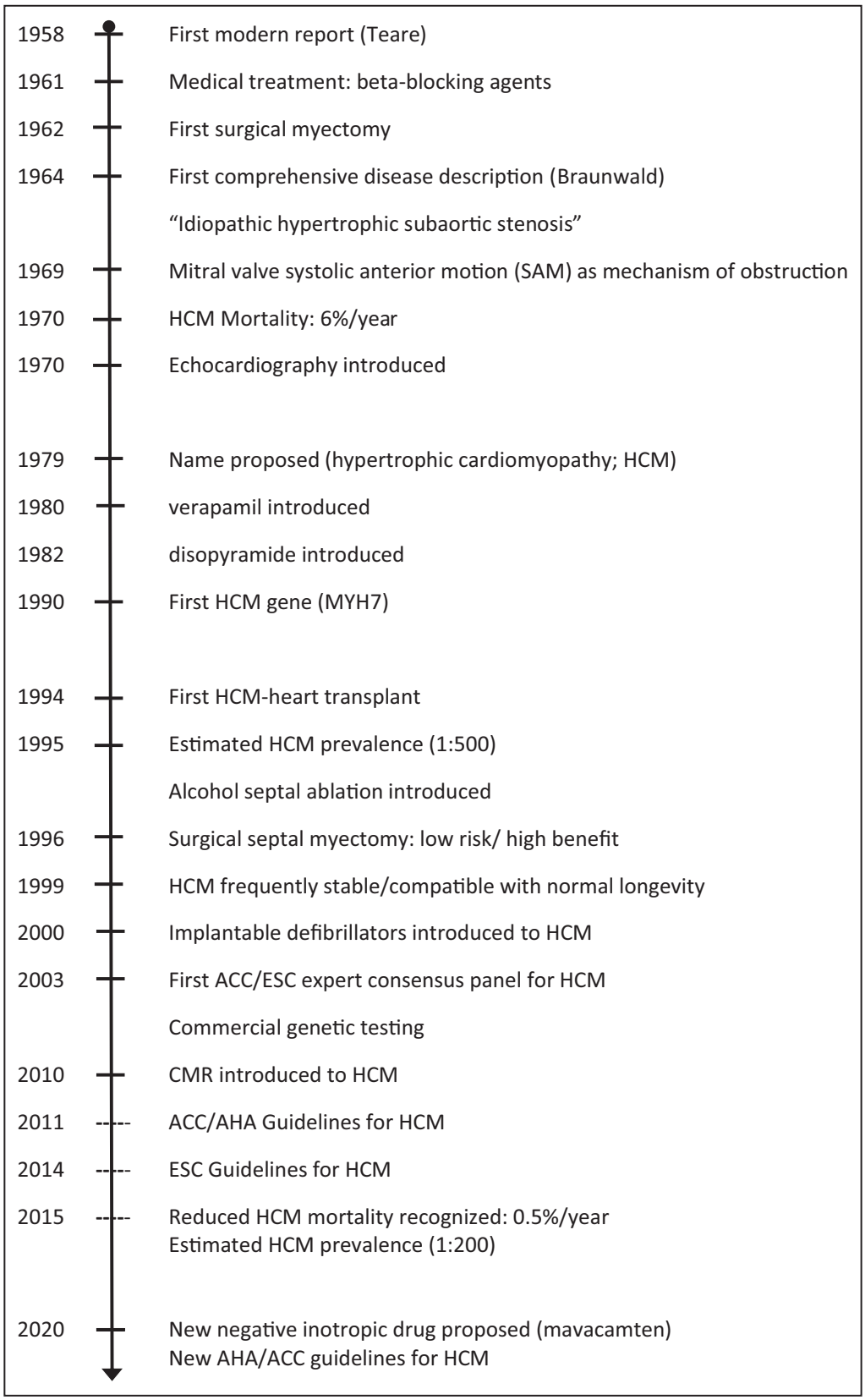

Figure 3. Timeline of clinical advances in hypertrophic cardiomyopathy (HCM).
ACC indicates American College of Cardiology; AHA, American Heart Association; CMR, cardiovascular magnetic resonance; ESC, European Society of Cardiology; and SAM, systolic anterior motion.

HCM-related mortality rate is lower than other cardiac (or noncardiac) disease-related causes that constitute the overall risks of living (eg, cancer or congestive heart failure).[6]

Conclusions

After more than a half century, advances in therapeutics, diagnostics, and understanding of the HCM disease spectrum and its relevant mechanisms, pursued relentlessly by clinical investigators and practitioners using evidence-based and guideline-directed personalized treatment strategies, have transformed HCM into a starkly different disease entity. Over the past several years, HCM has evolved from a condition once considered uniformly progressive with a poor prognosis and limited management options to a highly treatable disease with low morbidity and mortality, offering potential for normal or extended longevity. These management paradigms, which include substantial reduction in the long-standing, highly visible risk for arrhythmic sudden death, have resulted almost solely from a multitude of real-world clinical studies and registry observations, but with limited insights from molecular and basic science.

Therefore, because of heterogeneity of disease presentation, treatment options for HCM are more diverse than for PAH or cardiac amyloidosis, and have transformed HCM into a highly treatable disease in which the vast majority of patients can now harbor a reasonable expectation for normal or extended longevity with good quality of life. To this purpose, dedicated multidisciplinary HCM centers have emerged, implementing specialized disease management.[1,2] Future challenges for HCM include an increased number of cardiac surgeons experienced with the myectomy operation, and wider dissemination and implementation of contemporary treatment strategies, including in the most populous regions and countries (eg, China and India) where particularly large numbers of patients with HCM reside.

PULMONARY ARTERIAL HYPERTENSION

Historical Perspectives

Perhaps no other cardiovascular disease has been characterized by such a profoundly dismal prognosis as pulmonary arterial hypertension (PAH), which includes the idiopathic (formerly primary pulmonary hypertension), the heritable, and associated forms.[7] Through the first World Health Organization symposium on PAH in Geneva in 1975[40] and until the mid-1990s, PAH was universally regarded as an unrelenting essentially untreatable condition of young women with virtually 100% mortality within 2 to 3 years after diagnosis (median survival 2.8 years),[8] even acquiring the designation "kingdom of the near dead."[9]

Although classified as a rare condition (<1% of the general population, estimated at 30 000 patients in the United States), PAH is likely more common than initially believed.[7,9,109] Diagnosis of PAH requires increased pulmonary artery pressure and pulmonary vascular resistance (≥3.0 WU), with normal pulmonary arterial wedge pressure (≤15 mm Hg), unrelated to left heart or valvular disease or other causes of pulmonary hypertension,[109] and measured by cardiac catheterization under resting conditions. A proportion patients can be reliably identified by noninvasive estimates of pulmonary artery pressure with Doppler echocardiography.[41]

PAH is characterized by vascular injury with obliterative arteriopathy due to different processes including vasoconstriction, inflammation, proliferation, and thrombosis of the distal pulmonary arterial branches. These pathogenic events lead to right ventricular afterload, cavitary dilation, and systolic dysfunction, with the end-stage pathophysiology defined by decompensated right heart failure[7,9,109] (Figure 4).

The clinical profile of PAH has changed substantially since its modern description 70 or more years ago as vascular (arteriolar) sclerosis,[10] now with an increasing proportion of severely affected men and older age at diagnosis (ie, average 50 years old).[7,109] PAH has accumulated substantial evidence over 25 years from a series of 43 short-term randomized clinical trials leading to regulatory approval of 12 pharmacologic agents responsible for changing the course of the disease (Figures 2,4,5).[7,11,42–52,109] PAH may also affect pediatric patients, often associated with genetic disorders and/or congenital heart disease with uncertain prognosis.[53]

Treatment Advances and Clinical Course

Drug strategies in PAH have largely focused on exerting vasodilatory activity with reverse remodeling, selectively targeting pulmonary arterioles. All 12 PAH-approved pharmacotherapies modulate 1 of 3 major signaling pathways administrated with a variety of me thodologies[7,11,42–52,109]: (1) prostacyclin signaling (eg, epoprostenol, iloprost, treprostinil, selexipag),[11,45,50] (2) endothelin receptor antagonists (eg, ambrisentan, macitentan, bosentan),[46,48,51] and (3) nitric oxide bioactivity (eg, tadalafil, sildenafil, riociguat).[49,52,54] In a subset of patients with PAH, high-dose calcium channel blockers have sustained clinical resolution,[55–57] including in patients initially experiencing beneficial response to vasodilator therapy.[57]

Historically, about 30 years ago, continuous intravenous administration of epoprostenol was approved as a landmark treatment for PAH.[11,45] Oral therapy

followed, with clinical trials and meta-analyses showing that PAH-specific therapy with single drugs (and later with combinations) could improve exercise capacity, cardiopulmonary hemodynamics, and survival, as well as reduce the time to clinical worsening.[11,42–52,54–56]

PAH-related mortality has been reduced substantially. Three-year survival is now 70% compared with <50% in the era before approval of pulmonary vasodilator therapy (1980–1995),[10] albeit still progressive, with a significant annual mortality of about 10% per year, 20-fold that of HCM.[7,58,59,109] In a meta-analysis, short-term pharmacotherapy reduced mortality by 43%,[45] and a Spanish registry reported 1-, 3-, and 5-year survival of 87%, 75%, 65%, respectively.[59] Risk stratification tools have emerged to define the standards for successful treatment: 6-minute walk distance >440 m, peak oxygen consumption >15 mL/min per kg, right atrial area <18 cm^2 on echocardiography, cardiac index >2.5 L/min per m^2, and absent or low symptom burden with routine physical activity.[58,60]

Most recently, PAH has transitioned to an early-aggressive strategy in newly diagnosed patients,[7,58,60] including recommendations for initiating dual drug therapy to target multiple different pathways.[61–63] This shift to a combined treatment strategy, culminated in the multicenter randomized double-blind and placebo-controlled AMBITION (Ambrisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension) trial.[63] Combined administration of oral ambrisentan and tadalafil in comparison to monotherapy resulted in control of disease progression, with lower risk of clinical failure and PAH hospitalizations, and improved quality of life and exercise tolerance. These pharmacotherapy advances are notable, given that the only definitive intervention for PAH is bilateral lung transplantation associated with 5-year 30% mortality.[64]

Diagnosis

Clinical definition of pulmonary hypertension of any cause (including PAH) traditionally requires mean pulmonary artery pressure (mPAP) of ≥25 mm Hg measured by right heart catheterization at rest.[7,9,10,40,58,109] However, this hemodynamic criterion was based only on expert consensus opinion >40 years ago in the absence of normative data or evidence of associated clinical risk.[40,58] In 2016, a large consecutive national referral cohort (n=21 727) demonstrated a continuous relationship between mPAP and adjusted all-cause mortality beginning at mPAP 19 to 20 mm Hg.[12] Normal mPAP is 14±3 mm Hg (upper limit 20 mm Hg) in healthy volunteers.

As a result of this and other supportive epidemiologic studies[41,64–69] in well-characterized at-risk subpopulations, a revised definition of pulmonary hypertension has been proposed by lowering the mPAP level to ≥20 mm Hg, including patients with PAH.[65,70,71] This evolution in diagnostic criteria has implications for earlier pulmonary hypertension diagnosis and preventive treatment,[12,65–71,73] although there have not as yet been prospective clinical trials focused on patients specifically in the mPAP range of 20 to 24 mm Hg.

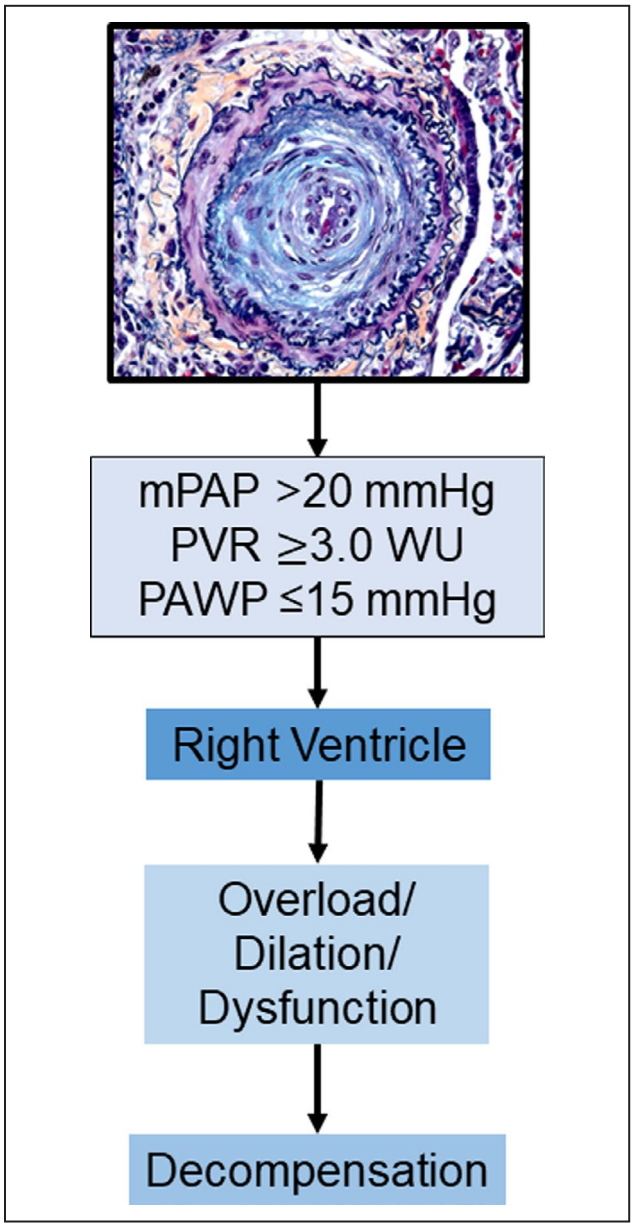

Figure 4. Pulmonary arterial hypertension (PAH): pathophysiology and outcome, showing an example of the severe primary abnormality of PAH from a patient with marked medial and intimal thickening and luminal narrowing of small pulmonary arteries.
mPAP indicates mean pulmonary arterial pressure; PAWP, pulmonary artery wedge pressure; PVR, pulmonary vascular resistance; and WU, Wood units.

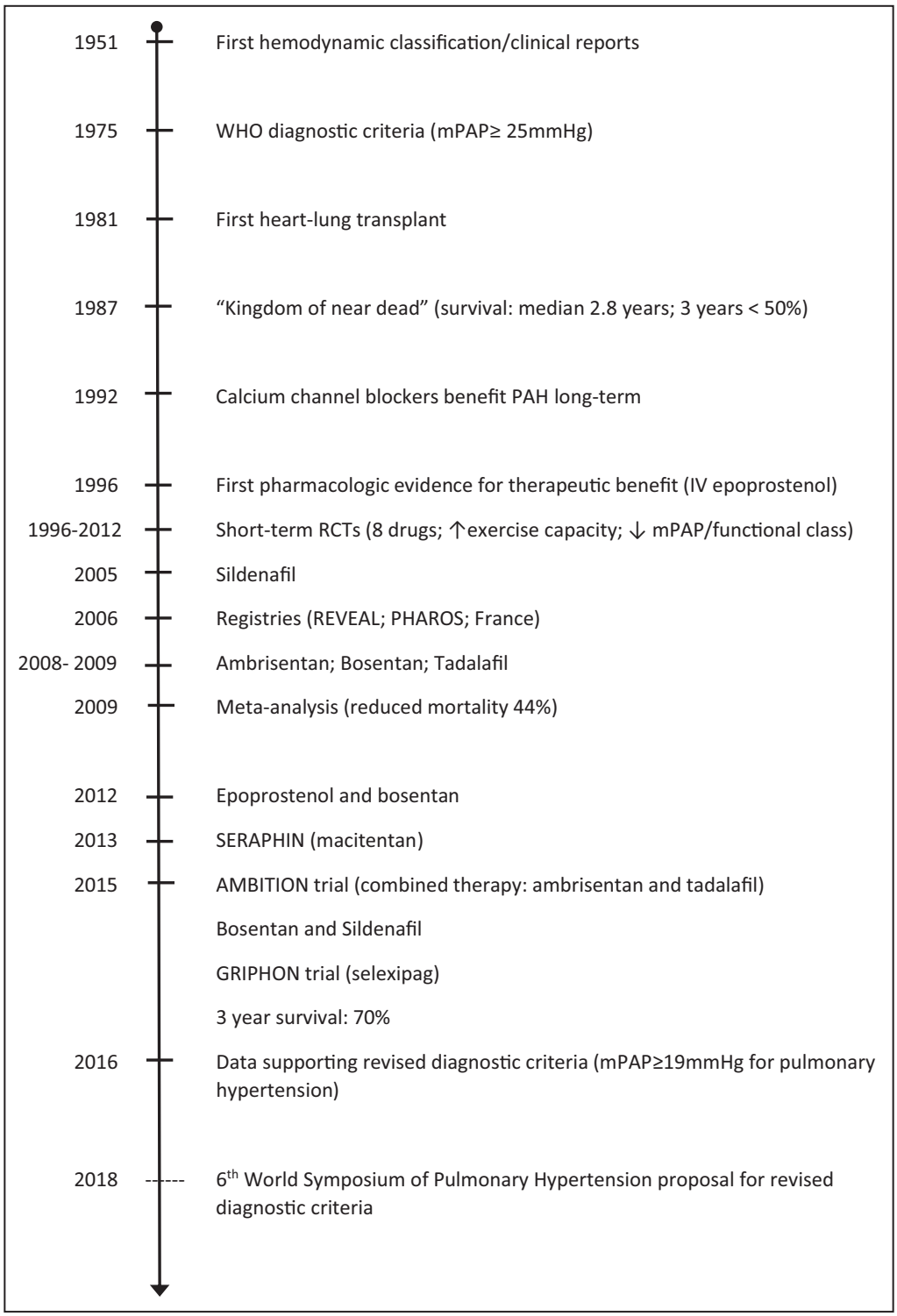

Figure 5. Timeline of clinical advances in pulmonary hypertension.
AMBITION indicates Ambrisentan and Tadalafil Combination Therapy in Subjects With Pulmonary Arterial Hypertension; IV, intravenous; mPAP, mean pulmonary artery pressure; PAH, pulmonary arterial hypertension; PHAROS, Pulmonary Hypertension Assessment and Recognition of Outcomes in Scleroderma; RCTs, randomized controlled trials; REVEAL, Registry to Evaluate Early and Long-Term PAH Disease Management; SERAPHIN, Study With an Endothelin Receptor Antagonist in Pulmonary Arterial Hypertension to Improve Clinical Outcome; and WHO, World Health Organization

Expanding the definition of PAH further by reducing the pulmonary vascular resistance threshold from 3.0 to 2.2 WU would also represent an opportunity to capture patients earlier in their clinical course and has been considered in the literature,[72,73,110] but not as yet incorporated into official guidelines on classifications. Consequently, contemporary PAH diagnosis in conjunction with data assembled from randomized clinical trials and large prospective registries have contemporized PAH demographics, epidemiology, and prognosis.

Conclusions

The modern therapeutic approach to PAH in the clinical trial era evolved from an earlier period when success was measured by delaying mortality in end-stage disease, including reliance on lung transplantation. A disease that was without effective treatment for decades, PAH is now characterized by evidence-based decision-making with aggressive pharmacotherapy guided clinical management (Figure 5). As a result, PAH has become a treatable cardiovascular disease with a realistic aspiration for impeding disease progression and improving survival, although perhaps not yet with the promise of long-term life expectancy (Figure 2).

Nevertheless, underrecognition and misdiagnosis of PAH persists in the community, underscoring the potential benefits of specialty referral centers of excellence.[74] Diagnosis often requires a high index of clinical suspicion, given that PAH is usually associated with nonspecific signs and symptoms, similar to those characteristic of other cardiac and pulmonary diseases.

CARDIAC AMYLOIDOSIS

Historical Perspectives

ATTR cardiac amyloidosis, the most common type of systemic amyloidosis, an underdiagnosed cause of restrictive cardiomyopathy and heart failure with preserved ejection fraction in the aging population (>60 years), has been historically regarded as untreatable, with a rapidly progressive clinical course. Although cardiac amyloidosis is not a new disease and has been recognized for at least 50 years, only in the past decade have noninvasive diagnosis and disease-specific therapy been accessible to increasing numbers of patients. Of the 3 diseases discussed here, ATTR cardiac amyloidosis is the most recent to emerge as a treatable condition (Figures 2).[13,75–82]

Cardiac amyloidosis is caused by aggregation and deposition of the misfolded transthyretin amyloid protein and fibrils (synthesized in the liver) deposited within the extracellular myocardium, resulting in increased left ventricular wall thickness.[83–86] The disease process derives either from inherited mutations (eg, ATTRv, variant) or an acquired aging form (eg, ATTRwt, wild type; previously termed senile cardiac amyloidosis), leading to debilitating heart failure symptoms with diffuse fibrosis, diastolic dysfunction, atrial fibrillation, conduction system disease, or peripheral polyneuropathy[13,75–82] (Figure 6).

ATTR cardiac amyloidosis has been universally associated with poor survival and prognosis (median survival 3.6 years after diagnosis), dependent on the extent of cardiac involvement.[13,75–82] Although ATTR cardiac amyloidosis has been generally considered uncommon, recognition is increasing and its precise

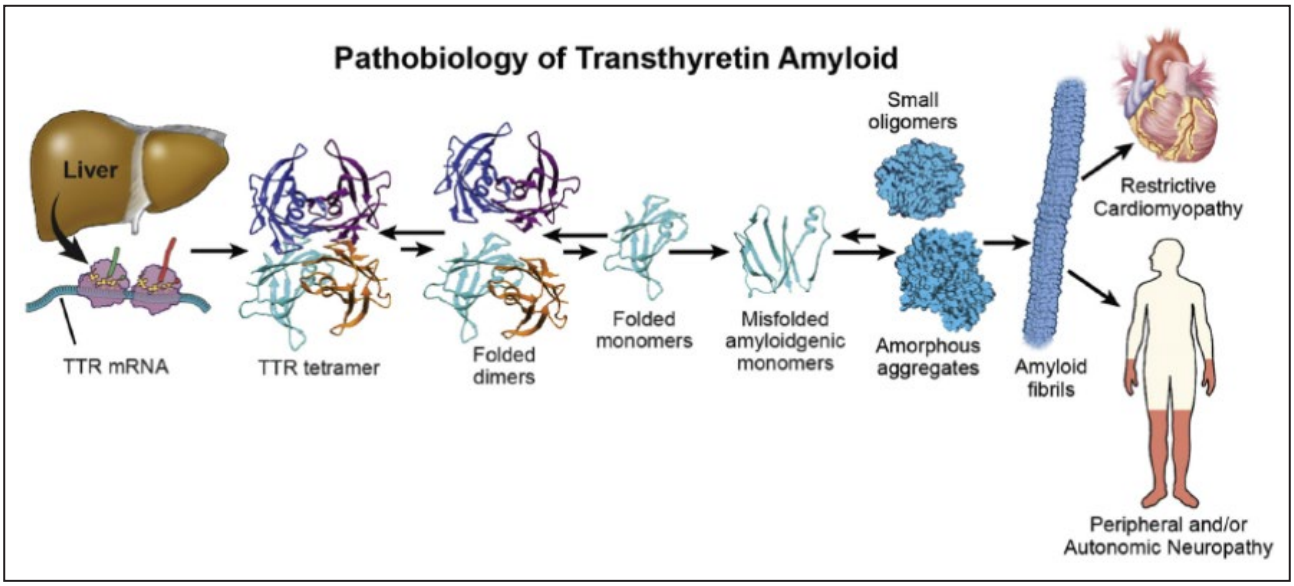

Figure 6. ATTR (transthyretin).
Pathophysiology of ATTR amyloid cardiomyopathy.

prevalence is unresolved. Deposits of ATTR-amyloid have been identified at autopsy in 25% of hearts from patients >80 years old, 13% of those hospitalized for heart failure with preserved ejection fraction, 16% with aortic stenosis undergoing transcatheter aortic valve replacement, and 5% of those diagnosed with HCM.

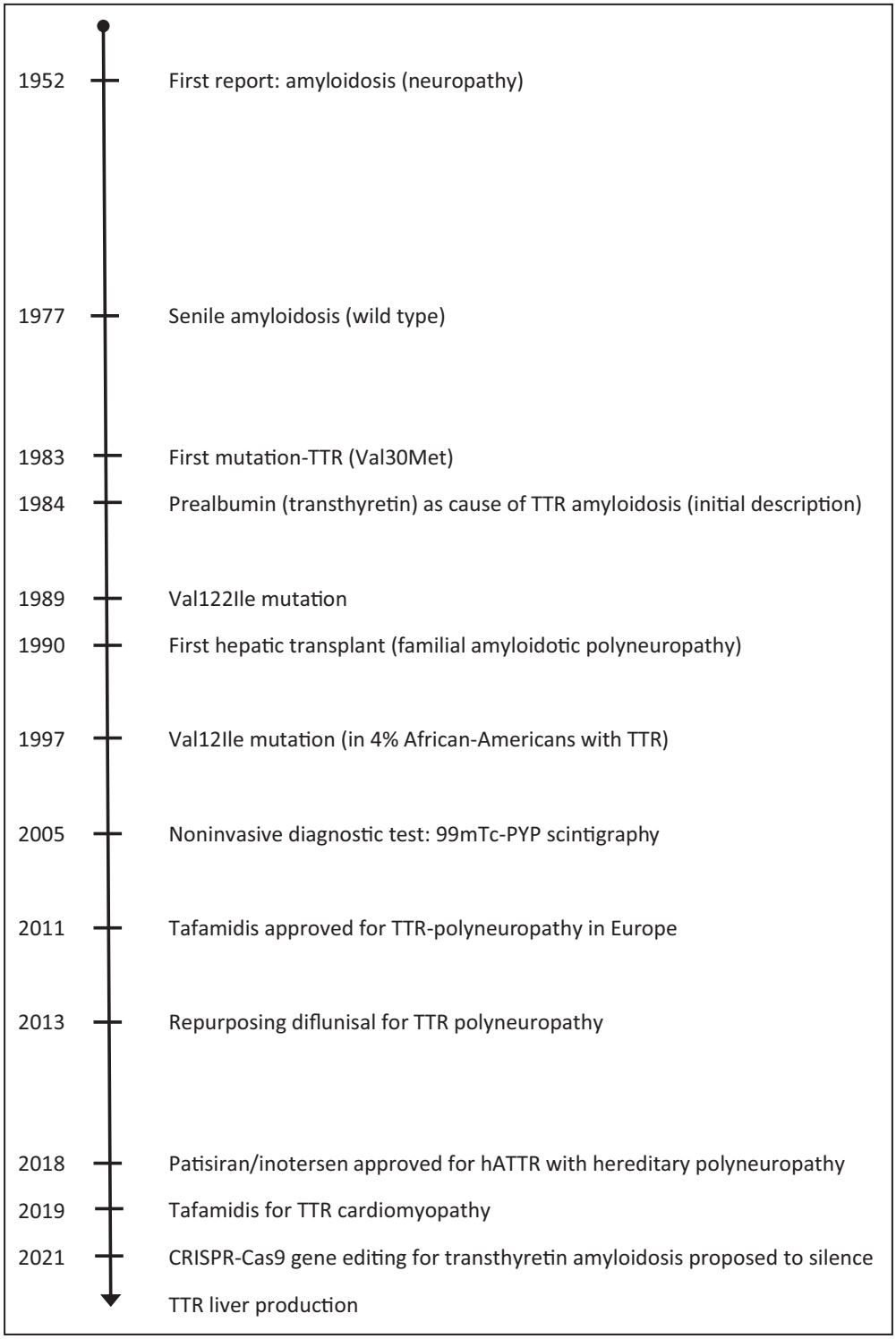

Figure 7. Timeline of clinical advances in TTR (transthyretin) cardiac amyloidosis.
99mTc-PYP indicates technetium TC 99M pyrophosphate; hATTR, hereditary ATTR (transthyretin) cardiac amyloidosis; Val30met, variant in which methionine replaces valine at the 30th position of TTR protein (Portuguese variant); and Val122Ile, variant in which isoleucine replaces valine at the 112nd position of TTR protein.

Diagnosis

Seminal advances in basic science,[83–86] diagnosis, and treatment[13,75–82] have emerged that substantially change the clinical landscape of ATTR cardiac amyloidosis (Figure 7), for the first time contributing to reversal of its dismal reputation. For much of its history, clinical identification has frequently been delayed or missed because of limited specificity and unreliability of diagnostic tests, including electrocardiography, echocardiography, and cardiovascular magnetic resonance imaging, as well as logistical and interpretive difficulties associated with endomyocardial and extracardiac biopsy and histopathology.

However, noninvasive diagnosis specific for ATTR cardiac amyloidosis now allows reliable, more frequent, and earlier clinical identification without the requirement for invasive cardiac biopsy.[87–89,90] Namely, over the last 10 to 15 years, there has been substantial interest in the technetium-labeled pyrophosphate nuclear scintigraphy scan (99mTc-PYP radiotracers that bind to deposited cardiac amyloid fibrils) in combination with blood and urine testing to assess monoclonal proteins and exclude light chain amyloid cardiomyopathy, which has proved highly sensitive and specific for ATTR cardiac amyloidosis permitting earlier diagnosis.[87–89,90]

Treatment Advances and Clinical Course

Oral tafamidis (Vyndaqel; Pfizer), initially approved in the European Union in 2011 to delay peripheral nerve impairment in transthyretin amyloid polyneuropathy, is the first Food and Drug Administration–approved treatment for ATTR cardiac amyloidosis (in May 2019),[14,91–95] representing a breakthrough shift in targeted management (Figure 2C), of a previously untreatable disease.[14] Now, patients with cardiac ATTR amyloidosis are being offered hope with evidence that tafamidis targets the basic disease mechanism by selectively stabilizing and inhibiting ATTR amyloid formation.[83–86,96]

Tafamidis slows disease progression, representing a distinctive alternative to older medical remedies that were not disease-specific for amyloidosis and largely confined to supportive heart failure measures (eg, diuretics, aldosterone antagonists, anticoagulants, antiarrhythmic drugs),[13,75,76,80–83] or in rare cases heart transplant.[97] In a multicenter international randomized, double-blind, placebo-controlled study (n=441) over 30 months, orally administered tafamidis was associated with an excellent safety profile and 33% reduction in all-cause mortality, 32% reduction in the rate of cardiovascular-related hospitalizations, while impeding decline in functional capacity and quality of life; 7 to 8 patients were needed to treat to prevent 1 death over 2.5 years[14] (Figure 2). Tafamidis is more effective when administered early in the course of the disease before significant cardiac dysfunction and advanced heart failure has developed. Two TTR silencing drugs inhibiting TTR hepatic synthesis and expression, patisiran (Onpattro)[98] and inotersen (Tegsedi)[99] have achieved Food and Drug Administration approval for TTR-related polyneuropathy. APOLLO showed that patisiran decreased left ventricular wall thickness, global longitudinal strain, NT-proBNP (N-terminal pro-B-type natriuretic peptide) and adverse cardiac outcome compared with placebo.[100] Whether silencers are more effective than stabilizers and the potential benefits of combination therapy will be determined by future trials.

Conclusions

TTR protein stabilizing tafamidis and other rapidly emerging novel therapies for cardiac amyloidosis, coupled with widely available noninvasive nuclear scintigraphy, represent a new standard of care, and promise upsurge in diagnoses of cardiac ATTR. Leveraging emerging therapies such as tafamidis, with efficient disease recognition, will permit more timely initiation of treatment to slow disease progression, potentially mitigating those pathologic and functional changes that dictate prognosis.

Nevertheless, remaining obstacles for ATTR cardiac amyloidosis are its perceived rarity and heterogeneous expression, an enduring reputation as an incurable condition, and the paucity of dedicated amyloidosis centers offering specialized care. Also, cardiac ATTR often presents with nonspecific symptoms to a diverse group of clinicians (ie, hematologists, neurologists, and cardiologists) that can result in delayed or incorrect diagnosis of HCM or other conditions associated with LV wall thickening and heart failure.

A currently evolving dilemma is recognition that tafamidis may not be cost-effective at a high price (list price $225 000 per year), the most expensive cardiovascular medication now available.[101–103] This is a particular concern because hereditary transthyretin amyloidosis ATTR[95] disproportionately affects a minority population in the United States, and therefore tafamidis has the potential to increase health disparities due to unequal access to treatment.[104]

FINAL PERSPECTIVES AND DETERMINANTS OF PROGRESS

The 3 major but relatively uncommon cardiovascular conditions discussed here were once considered ominous and essentially untreatable (or even hopeless), conveying highly uncertain futures to affected patients.

Although these diseases are driven by different morphologies, clinical presentations, pathophysiology, and diagnostic criteria, they are nevertheless similar with regard to heterogeneity in clinical presentation and the importance of early recognition.

Most importantly, there is now sufficient objective progress for all 3 of these diseases to warrant changing the clinical narrative to one of optimism. Often, medical science has been forced to overcome numerous obstacles, including the reluctance of industry and the wider physician community to support diseases considered rare and essentially untreatable, to nevertheless develop novel medical and interventional therapies that have substantially reduced morbidity and mortality (Figure 2).

With PAH, pharmacologic strategies have been formulated, consistent with principles of evidence-based personalized medicine, to improve functional capacity and survival, albeit not yet providing extended longevity. Over the years, a series of randomized clinical trials with single drugs (or combinations) have identified a variety of 12 beneficial medical strategies with naturally occurring or synthetic compounds.[11,42–52]

In ATTR cardiac amyloidosis, significant clinical advances have evolved more gradually. Diagnostic nonbiopsy nuclear imaging has made the ATTR cardiac amyloidosis diagnosis much more accessible to the practicing community, permitting earlier initiation of pharmacologic treatment. Introduction of tafamidis as the first disease-specific drug, designed specifically to stabilize and/or inhibit amyloid TTR protein formation, is capable of reducing mortality and improving quality of life.[14]

HCM is much more common than PAH and cardiac amyloidosis (1:200–1:500 of the general population, respectively),[19] with the advantage of being carefully scrutinized clinically in large patient populations for >50 years. As a result, management innovations and a variety of targeted treatments used in HCM cohorts (eg, implantable defibrillators to prevent sudden death and high-benefit:low-risk myectomy surgery to reverse heart failure), have surpassed the other 2 diseases making HCM a highly treatable condition consistent with normal or extended longevity.

We have searched for unifying themes that could explain the seminal advances in therapeutics and diagnostics that have evolved into clinical practice for HCM, PAH, and ATTR cardiac amyloidosis, and could potentially provide relevant insights for application to other cardiac or noncardiac diseases.

Although there is no evidence that treatment and diagnostic strategies were systematically coordinated or facilitated, one consistent factor that emerges from each of the 3 complex diseases is an association with dedicated clinical investigators focused on the specific patient population over their professional careers (up to 50 years in some cases). Without such allegiance to relatively uncommon diseases with dismal prognosis, these conditions would be easily forgotten or ignored.

For PAH, treatment strategies evolved by the selection of drugs for early randomized trials that were tailored to the basic disease pathophysiology (ie, to relax and dilate pulmonary arterioles) to reverse remodeling along the molecular pathways of prostacyclin signaling, endothelin receptor antagonists, or nitric oxide bioactivity. Such assembly of evidence in a rare disease such as PAH is unique and required a high degree of global cooperation by investigators and centers for patient recruitment.

For example, epoprostenol, one of the first drugs shown to be effective in PAH, is a synthetic analog of prostacyclin with acknowledged vasodilatory properties.[11,45] In contrast, sildenafil, which blocks the enzyme phosphodilsterase,[52] followed a much different pathway, beginning in 1989 as a drug developed by Pfizer for chest pain in patients with ischemic heart disease to dilate coronary arteries and then adopted as a treatment for erectile dysfunction (as Viagra) based on its vasodilatory properties that increase arterial blood flow, and only later to PAH based on this pathophysiology.

In the case of ATTR cardiac amyloidosis, seminal biophysical studies of transthyretin (prealbumin) and elucidation of the basic biology of the disease led to the development of tafamidis in the laboratory as a molecular disease-specific and structure-based drug, which in turn resulted in creating a pharmaceutical company and ultimately well-designed interventional trials. The classic model of a basic science discovery leading to specific drug development followed by clinical trials that has been demonstrated by tafamidis is unique among the 3 diseases analyzed here.[96]

The scenario in HCM has been much different, because most of the important current therapies are interventional, with the progress due to innovations in clinical science and practice, independent of the 30-year unfulfilled basic science aspiration for a molecular cure that eradicates the causative HCM gene and therefore the overall disease process. Specifically, the implantable defibrillator was adopted from coronary artery disease by clinical investigators searching for a strategy to prevent sudden death in HCM,[3–5,20,25] but initially without assurance that device therapy would be effective in high-risk patients given the unique underlying electrophysiologic substrate characteristic of HCM.

Septal myectomy operation was designed 60 years ago specifically for patients with HCM and subaortic obstruction by Dr. Andrew G. Morrow at the National Institutes of Health (who himself had the same disease),[106] even before the precise mechanism by which outflow gradients are generated was completely understood (ie, mitral valve systolic anterior motion).

Strategies for the management of atrial fibrillation in HCM have been modified from other cardiac diseases. In contrast, mavacamten, although not yet approved by Food and Drug Administration, has recently become a first-in-class HCM-specific negative inotropic drug designed with a molecular structure to suppress LV contractility and therefore reduce outflow gradients and symptoms.[108]

CONCLUSIONS

It is unfortunate that the recognition of significant progress in medicine, and particularly with complex cardiovascular diseases, may evolve slowly. Also, general acceptance of important innovations may require time to penetrate the consciousness of the public, patients, and practicing community. In this review it was our intention to underscore and provide visibility for recent paradigm shifts in diagnosis and management that have changed the clinical course and perceptions on 3 important and less common cardiovascular diseases discussed here: HCM, PAH, and cardiac amyloidosis.

ARTICLE INFORMATION

Affiliations

Division of Cardiology, HCM Institute, Tufts Medical Center, Boston, MA (B.J.M., M.S.M., E.J.R.); Cardiac Amyloidosis Center, Columbia University Irving Medical Center, New York–Presbyterian Hospital, New York, NY (M.S.M.); Division of Cardiovascular Medicine, Brigham & Women's Hospital and Harvard Medical School, Boston, MA (B.A.M.); Alma Mater Studiorum University of Bologna, Bologna, Italy (N.G.); and S. Orsola University Hospital, Bologna, Italy (N.G.).

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REFERENCES

1. Maron BJ. Clinical course and management of hypertrophic cardiomyopathy. *N Engl J Med*. 2018;379:655–668. DOI: 10.1056/NEJMra1710575.
2. Maron BJ, Rowin EJ, Casey SA, Maron MS. How hypertrophic cardiomyopathy became a contemporary treatable genetic disease with low mortality: shaped by 50 years of clinical research and practice. *JAMA Cardiol*. 2016;1:98–105. DOI: 10.1001/jamacardio.2015.0354.
3. Maron BJ, Shen W-K, Link MS, Epstein AE, Almquist AK, Daubert JP, Bardy GH, Favale S, Rea RF, Boriani G, et al. Efficacy of implantable cardioverter-defibrillators for the prevention of sudden death in patients with hypertrophic cardiomyopathy. *N Engl J Med*. 2000;342:365–373. DOI: 10.1056/NEJM200002103420601.
4. Maron BJ, Spirito P, Shen W-K, Haas TS, Formisano F, Link MS, Epstein AE, Almquist AK, Daubert JP, Lawrenz T, et al. Implantable cardioverter-defibrillators and prevention of sudden cardiac death in hypertrophic cardiomyopathy. *JAMA*. 2007;298:405–412. DOI: 10.1001/jama.298.4.405.
5. Maron MS, Rowin EJ, Wessler BS, Mooney PJ, Fatima A, Patel P, Koethe BC, Romashko M, Link MS, Maron BJ. Enhanced ACC/AHA strategy for prevention of sudden death in high risk patients from a hypertrophic cardiomyopathy center. *JAMA Cardiol*. 2019;4:644–657.
6. Maron BJ, Maron MS, Rowin EJ. Perspectives on the overall risk of living with hypertrophic cardiomyopathy. *Circulation*. 2017;135:2317–2319.
7. Galie' N, Humbert M, Vachiery J-L, Gibbs S, Lang L, Torbicki A, Simonneau G, Peacock A, Vonk-Beghatti M, Noordegraaf A, et al. 2015 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension. The Joint Task Force for the diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology (ESC) and the European Registry Society (ESR). *Eur Respir J*. 2015;46:1855–1856.
8. D'Alonzo GE, Barst RJ, Ayres SM, Bergofsky EH, Brundage BH, Detre KM, Fishman AP, Goldring RM, Groves BM, Kernis JT. Survival in patients with primary pulmonary hypertension. Results from a national prospective registry. *Ann Intern Med*. 1991;115:343–349. DOI: 10.7326/0003-4819-115-5-343.
9. Galie' N, Palazzini M, Manes A. Pulmonary arterial hypertension: from the kingdom of the near-dead to multiple clinical trial meta-analysis. *Eur Heart J*. 2010;31:2080–2086.
10. Dresdale DT, Michtom RJ, Schultz M. Recent studies in primary pulmonary hypertension, including pharmacodynamic observations on pulmonary vascular resistance. *Bull N Y Acad Med*. 1954;30:195–207.
11. Barst RJ, Rubin LJ, Long WA, McGoon MD, Rich S, Badesch DB, Groves BM, Tapson VF, Bourge RC, Brundage BH, et al. A comparison of continuous intravenous epoprostenol (prostacyclin) with conventional therapy for primary pulmonary hypertension. *N Eng J Med*. 1996;334:296–301. DOI: 10.1056/NEJM199602013340504.
12. Maron BA, Hess E, Maddox TM, Opotowsky AR, Tedford RJ, Lahm T, Joynt KE, Kass DJ, Stephens T, Stanislawski MA, et al. Association of borderline pulmonary hypertension with mortality and hospitalization in a large patient cohort: insights from the Veterans Affairs Clinical Assessment, Reporting and Tracking Program. *Circulation*. 2016;133:1240–1248. DOI: 10.1161/CIRCULATIONAHA.115.020207.
13. Ruberg FL, Grogan M, Hanna M, Kelly JW, Maurer MS. Transthyretin amyloid cardiomyopathy. JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;73:2872–2891. DOI: 10.1016/j.jacc.2019.04.003.
14. Maurer MS, Schwartz JH, Gundapaneni B, Elliott PM, Merlini G, Waddington-Cruz M, Kristen AV, Grogan M, Witteles R, Damy T, et al.; ATTR-ACT Study Investigators. Tafamidis treatment for patients with transthyretin amyloid cardiomyopathy. *N Engl J Med*. 2018;379:1007–1016. DOI: 10.1056/NEJMoa1805689.
15. Teare D. Asymmetrical hypertrophy of the heart in young adults. *Br Heart J*. 1958;20:1–8. DOI: 10.1136/hrt.20.1.1.
16. Maron BJ, Rowin EJ, Maron MS. Global burden of hypertrophic cardiomyopathy. *JACC Heart Fail*. 2018;6:376–378.
17. Braunwald E, Lambrew CT, Rockoff SD, Ross J, Morrow AG. Idiopathic hypertrophic subaortic stenosis. I. A description of the disease based on an analysis of 64 patients. *Circulation*. 1964;30(suppl 4):3–119.
18. Elliott PM, Anastasakis A, Borger MA, Borggrefe M, Cecchi F, Charron P, Hagege AA, Lafont A, Limongelli G, Mahrholdt H, et al. 2014 ESC guidelines on diagnosis and management of hypertrophic cardiomyopathy. *Eur Heart J*. 2014;35:2733–2779.
19. Semsarian C, Ingles J, Maron MS, Maron BJ. New perspective on the prevalence of hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2015;65:1249–1254.
20. Maron BJ, Maron MS. The remarkable 50 years of imaging in HCM and how it has changed diagnosis and management: from M-mode echocardiography to CMR. *JACC Cardiovasc Imaging*. 2016;9:858–872.
21. Rowin EJ, Maron BJ, Maron MS. The hypertrophic cardiomyopathy phenotype viewed through the prism of multimodality imaging: clinical and etiologic implications. *JACC Cardiovasc Imaging*. 2020;13:2002–2016.
22. Maurizi N, Michels M, Rowin EJ, Semsarian C, Girolami F, Tomberli B, Cecchi F, Maron MS, Olivotto I, Maron BJ. Clinical course and significance of hypertrophic cardiomyopathy without left ventricular hypertrophy. *Circulation*. 2019;139:830–833. DOI: 10.1161/CIRCULATIONAHA.118.037264.
23. Burke MA, Cook SA, Seidman JG, Seidman CE. Clinical and mechanistic insights into the genetics of cardiomyopathy. *J Am Coll Cardiol*. 2016;68:2871–2886.

24. Rowin EJ, Maron MS, Chan RH, Hausvater A, Wang W, Rastegar H, Maron BJ. Interaction of adverse disease related pathways in hypertrophic cardiomyopathy. *Am J Cardiol*. 2017;120:2256–2264. DOI: 10.1016/j.amjcard.2017.08.048.
25. Maron BJ, Rowin EJ, Maron MS. Paradigm of sudden death prevention in hypertrophic cardiomyopathy. *Circ Res*. 2019;125:370–378. DOI: 10.1161/CIRCRESAHA.119.315159.
26. Maron BJ, Rowin EJ, Casey SA, Lesser JR, Garberich RF, McGriff DM, Maron MS. Hypertrophic cardiomyopathy in children, adolescents, and young adults associated with low cardiovascular mortality with contemporary management strategies. *Circulation*. 2016;133:62–73. DOI: 10.1161/CIRCULATIONAHA.115.017633.
27. Maron BJ, Casey SA, Olivotto I, Sherrid MV, Semsarian C, Autore C, Ahmed A, Boriani G, Francia P, Winters SL, et al. Clinical course and quality of life in high risk patients with hypertrophic cardiomyopathy and implantable cardioverter-defibrillators. *Circ Arrhythm Electrophysiol*. 2018;11:e005820. DOI: 10.1161/CIRCEP.117.005820.
28. Kotkar KD, Said SM, Dearani J, Schaff HV. Hypertrophic obstructive cardiomyopathy: the Mayo Clinic experience. *Ann Cardiothorac Surg*. 2017;6:329–336. DOI: 10.21037/acs.2017.07.03.
29. Hodges K, Rivas CG, Aguilera J, Borden R, Alashi A, Blackstone EH, Desai MY, Smedira NG. Surgical management of left ventricular outflow tract obstruction in a specialized hypertrophic obstructive cardiomyopathy center. *J Thorac Cardiovasc Surg*. 2019;157:2289–2299. DOI: 10.1016/j.jtcvs.2018.11.148.
30. Ommen SR, Maron BJ, Olivotto I, Maron MS, Cecchi F, Betocchi S, Gersh BJ, Ackerman MJ, McCully RB, Dearani JA, et al. Long-term effects of surgical septal myectomy on survival in patients with obstructive hypertrophic cardiomyopathy. *J Am Coll Cardiol*. 2005;46:470–476. DOI: 10.1016/j.jacc.2005.02.090.
31. Ball W, Ivanov J, Rakowski H, Wigle ED, Linghorne M, Ralph-Edwards A, Williams WG, Schwartz L, Guttman A, Woo A. Long-term survival in patients with resting obstructive hypertrophic cardiomyopathy comparison of conservative versus invasive treatment. *J Am Coll Cardiol*. 2011;58:2313–2321. DOI: 10.1016/j.jacc.2011.08.040.
32. Schinkel AF, Vriesendorp PA, Sijbrands EJ, Jordaens LJ, ten Cate FJ, Michels M. Outcome and complications after implantable cardioverter-defibrillator therapy in hypertrophic cardiomyopathy: systematic review and meta-analysis. *Circ Heart Fail*. 2012;5:552–559. DOI: 10.1161/CIRCHEARTFAILURE.112.969626.
33. Vriesendrop PA, Schinkel AE, Van Cleemput J, Willems R, Jordaens JLM, Theuns DAMJ, van Slegtenhorst MA, de Ravel TJ, ten Cate FJ, Michels M. Implantable cardioverter-defibrillators in hypertrophic cardiomyopathy: patient outcomes, rate of appropriate and inappropriate interventions, and complications. *Am Heart J*. 2013;166:496–502. DOI: 10.1016/j.ahj.2013.06.009.
34. Rowin EJ, Hausvater A, Link MS, Abt P, Gionfriddo W, Wang W, Rastegar H, Estes NAM, Maron MS, Maron BJ. Clinical profile and consequences of atrial fibrillation in hypertrophic cardiomyopathy. *Circulation*. 2017;136:2420–2436. DOI: 10.1161/CIRCULATIONAHA.117.029267.
35. Rowin EJ, Maron BJ, Abt P, Kiernan MS, Vest A, Costantino F, Maron MS, DeNofrio D. Impact of advanced therapies for improving survival to heart transplant in patients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2018;121:986–996. DOI: 10.1016/j.amjcard.2017.12.044.
36. Kato TS, Takayama H, Yoshizawa S, Marboe C, Sohulze C, Farr M, Naka Y, Mancini D, Maurer MS. Cardiac transplantation in patients with hypertrophic cardiomyopathy. *Am J Cardiol*. 2012;110:568–574. DOI: 10.1016/j.amjcard.2012.04.030.
37. Rowin EJ, Maron BJ, Carrick RT, Patel PP, Koethe B, Wells S, Maron MS. Outcomes in patients with hypertrophic cardiomyopathy and left ventricular systolic dysfunction. *J Am Coll Cardiol*. 2020;75:3033–3043. DOI: 10.1016/j.jacc.2020.04.045.
38. Sorajja P. Alcohol septal ablation for obstructive hypertrophic cardiomyopathy: a word of balance. *J Am Coll Cardiol*. 2017;70:489–494. DOI: 10.1016/j.jacc.2017.06.011.
39. Elliott PM, Gimeno JR, Thaman R, Shah J, Ward D, Dickie S, Esteban WTT, McKenna WJ. Historical trends in reported survival rates in patients with hypertrophic cardiomyopathy. *Heart*. 2006;92:785–791. DOI: 10.1136/hrt.2005.068577.
40. World Health Organization. *Primary Pulmonary Hypertension Report on a WHO Meeting*. World Health Organization; 1975.
41. Huston JH, Maron BA, French J, Huang S, Thayer T, Farber-Eger EH, Wells QS, Choudhary G, Hemnes AR, Brittain EL. Association of mild echocardiographic pulmonary hypertension with mortality and right ventricular function. *JAMA Cardiol*. 2019;4:1112–1121. DOI: 10.1001/jamacardio.2019.3345.
42. Farber HW, Miller DP, Poms AD, Badesch DB, Frost AE, Rouzic E-L, Romero AJ, Benton WW, Elliott CG, McGoon MD, et al. Five-year outcomes of patients enrolled in the REVEAL registry. *Chest*. 2015;148:1043–1054. DOI: 10.1378/chest.15-0300.
43. Humbert M, Sitbon O, Chaouat A, Bertocchi M, Habib G, Gressin V, Yaici A, Weitzenblum E, Cordier J-F, Chabot F, et al. Pulmonary arterial hypertension in France: results from a national registry. *Am J Respir Crit Care Med*. 2006;173:1023–1030. DOI: 10.1164/rccm.200510-1668OC.
44. Humbert M, Sitborn O, Simmoneau G. Treatment of pulmonary arterial hypertension. *N Engl J Med*. 2004;351:1425–1436. DOI: 10.1056/NEJMra040291.
45. Rubin LJ, Mendoza J, Hood M, McGoon M, Barst R, Williams WB, Diehl JH, Crow J, Long W. Treatment of primary pulmonary hypertension with continuous intravenous prostacyclin (epoprostenol). Results of a randomized trial. *Ann Intern Med*. 1990;112:485–491. DOI: 10.7326/0003-4819-112-7-485.
46. Galie' N, Rubin LJ, Hoeper M, Jansa P, Al-Hiti H, Meyer G, Chiossi E, Kusic-Pajic C, Simonneau G. Treatment of patients with mildly symptomatic pulmonary arterial hypertension with bosentan (EARLY study): a double-blind, randomized controlled trial. *Lancet*. 2008;371:2093–2100.
47. Galie N, Manes A, Negro L, Palazzini M, Bacchi-Reggiani ML, Branzi A. A meta-analysis of randomized controlled trials in pulmonary arterial hypertension. *Eur Heart J*. 2009;30:394–403. DOI: 10.1093/eurheartj/ehp022.
48. Galiè N, Olschewski H, Oudiz RJ, Torres F, Frost A, Ghofrani HA, Badesch DB, McGoon MD, McLaughlin VV, Roecker EB, et al. Ambrisentan for the treatment of pulmonary arterial hypertension: results of the ambrisentan in pulmonary arterial hypertension, randomized, double-blind, placebo-controlled, multicenter, efficacy (ARIES) study 1 and 2. *Circulation*. 2008;117:3010–3019. DOI: 10.1161/CIRCULATIONAHA.107.742510.
49. Galiè N, Brundage BH, Ghofrani HA, Oudiz RJ, Simonneau G, Safdar Z, Shapiro S, White RJ, Chan M, Beardsworth A, et al. Tadalafil therapy for pulmonary arterial hypertension. *Circulation*. 2009;119:2894–2903. DOI: 10.1161/CIRCULATIONAHA.108.839274.
50. Sitbon O, Channick R, Chin KM, Frey A, Gaine S, Galiè N, Ghofrani H-A, Hoeper MM, Lang IM, Preiss R, et al. Selexipag for the treatment of pulmonary arterial hypertension. *N Engl J Med*. 2015;373:2522–2533. DOI: 10.1056/NEJMoa1503184.
51. Pulido T, Adzerikho I, Channick RN, Delcroix M, Galiè N, Ghofrani H-A, Jansa P, Jing Z-C, Le Brun F-O, Mehta S, et al. Macitentan and morbidity and mortality in pulmonary arterial hypertension. (SERAPHIN investigators). *N Eng J Med*. 2013;369:809–818. DOI: 10.1056/NEJMoa1213917.
52. Galiè N, Ghofrani HA, Torbicki A, Barst RJ, Rubin LJ, Badesch D, Fleming T, Parpia T, Burgess G, Branzi A, et al. Sildenafil citrate therapy for pulmonary arterial hypertension. *N Engl J Med*. 2005;353:2148–2157. DOI: 10.1056/NEJMoa050010.
53. Haarman J, Kerstjens-Frederikse WS, Vissia-Kazemier TR, Breeman KTN, Timens W, Vos YJ, Roofthooft MTR, Hillege HL, Berger RMF. The genetic epidemiology of pediatric pulmonary arterial hypertension. *J Pediatr*. 2020;225:65–73. DOI: 10.1016/j.jpeds.2020.05.051.
54. Ghofrani H-A, D'Armini AM, Grimminger F, Grunig E, Humbert M, Jing Z-C, Keogh AM, Langleben D, Kilama MO, Fritsch A, et al. Riociguat for the treatment of chronic thromboembolic pulmonary arterial hypertension. *N Engl J Med*. 2013;369:330–340.
55. Rich S, Kaufmann E, Levy PS. The effect of high doses of calcium channel blockers on survival in primary pulmonary hypertension. *N Engl J Med*. 1992;327:76–81. DOI: 10.1056/NEJM199207093270203.
56. Rich S, Brundage BH. High-dose calcium channel blocking therapy for primary pulmonary hypertension: evidence for long-term reduction in pulmonary arterial pressure and regression of right ventricular hypertrophy. *Circulation*. 1987;76:135–141. DOI: 10.1161/01.CIR.76.1.135.
57. Sitbon O, Humbert M, Jais X, Loos V, Hamid AM, Provencher S, Garcia G, Parent F, Herve P, Simonneau G. Long-term response to calcium channel blockers in idiopathic pulmonary arterial hypertension. *Circulation*. 2005;111:3105–3111. DOI: 10.1161/CIRCULATIONAHA.104.488486.

58. Maron BA, Nazzareno G. Pulmonary arterial hypertension diagnosis, treatment, and clinical management in the contemporary era. *JAMA Cardiol*. 2016;1:1056–1065.
59. Escribano-Subias P, Blanco I, Lopez-Mesequer M, Lopez-Guarch CJ, Roman A, Morales P, Castillo-Palma MJ, Segovia J, Gomez-Sanchez MA, Barbera JA, et al. Survival in pulmonary hypertension in Spain: insights from the Spanish registry. *Eur Respir J*. 2012;40:596–603. DOI: 10.1183/09031936.00101211.
60. Galiè N, Channick RN, Frantz RP, Grunig E, Jing ZC, Moiseeva O, Preston IR, Pulido T, Safder Z, Tamura Y, et al. Rick stratification and medical therapy of pulmonary arterial hypertension. *Eur Respir J*. 2019;53:1801889.
61. Kemp K, Savale L, O'Callaghan DS, Jais X, Montani D, Humbert M, Simonneau C, Sitbon O. Usefulness of first-line combination therapy with epoprostenol and bosentan in pulmonary arterial hypertension: an observational study. *J Heart Lung Transplant*. 2012;31:150–158. DOI: 10.1016/j.healun.2011.11.002.
62. McLaughlin V, Channick RN, Ghofrani H-A, Lemarié J-C, Naeije R, Packer M, Souza R, Tapson VF, Tolson J, Al Hiti H, et al. Bosentan added to sildenafil therapy in patients with pulmonary arterial hypertension. *Eur Respir J*. 2015;46:405–413. DOI: 10.1183/13993003.02044-2014.
63. Galiè N, Barberà JA, Frost AE, Ghofrani H-A, Hoeper MM, McLaughlin VV, Peacock AJ, Simonneau G, Vachiery J-L, Grünig E, et al.; for the AMBITION Investagors. Initial use of ambrisentan plus tadalafil in pulmonary arterial hypertension. *N Eng J Med*. 2015;373:834–844. DOI: 10.1056/NEJMoa1413687.
64. Crawford TC, Leary PJ, Fraser CD III, Suarez-Pierre A, Magruder JT, Baumgartner WA, Zehr KJ, Whitman GJ, Masri SC, Sheikh F, et al. Impact of the new pulmonary hypertension definition on heart transplant outcomes: expanding the hemodynamic risk profile. *Chest*. 2020;157:151–161. DOI: 10.1016/j.chest.2019.07.028.
65. Maron BA, Kovacs G, Vaidya A, Bhatt DL, Nishimura RA, Mak S, Guazzi M, Tedford RJ. Cardiopulmonary hemodynamics in pulmonary hypertension and heart failure. JACC Review Topic of the Week. *J Am Coll Cardiol*. 2020;76:2671–2681.
66. Maron BA, Choudhary G, Khan UA, Jankowich MD, McChesney H, Ferrazzani SJ, Gaddam S, Sharma S, Opotowsky AR, Bhatt DL, et al. Clinical profile and underdiagnosis of pulmonary hypertension in US veteran patients. *Circ Heart Fail*. 2013;6:906–912. DOI: 10.1161/CIRCHEARTFAILURE.112.000091.
67. Assad TR, Maron BA, Robbins IM, Xu M, Huang S, Harrell FE, Farber-Eger EH, Wells QS, Choudhary G, Hemnes AR, et al. Prognostic effect and longitudinal hemodynamic assessment of borderline pulmonary hypertension. *JAMA Cardiol*. 2017;2:1361–1368. DOI: 10.1001/jamacardio.2017.3882.
68. Kolte D, Lakshmanan S, Jankowich MD, Brittain EL, Maron BA, Choudhary G. Mild pulmonary hypertension is associated with increased mortality: a systemic review and meta-analysis. *J Am Heart Assoc*. 2018;7:e009729. DOI: 10.1161/JAHA.118.009729.
69. Maron BA, Brittain EL, Choudhary G, Gladwin MT. Redefining pulmonary hypertension. *Lancet Respir Med*. 2018;6:168–170. DOI: 10.1016/S2213-2600(17)30498-8.
70. Simonneau G, Montani D, Celermajer DS, Denton CP, Gatzoulis MA, Krowka M, Williams PG, Sousa R. Haemodynamic definitions and updated clinical classification of pulmonary hypertension. *Eur Respir J*. 2019;53:1801913. DOI: 10.1183/13993003.01913-2018.
71. Simonneau G, Hoeper MM. The revised definition of pulmonary hypertension: exploring the impact on patient management. *Eur Heart J Suppl*. 2019;21(suppl K):K4–K8. DOI: 10.1093/eurheartj/suz211.
72. Maron BA, Brittain EL, Hess E, Waldo SW, Barón AE, Huang S, Goldstein RH, Assad T, Wertheim BM, Alba GA, et al. Pulmonary vascular resistance and clinical outcomes in patients with pulmonary hypertension: a retrospective cohort study. *Lancet Respir Med*. 2020;8:873–884. DOI: 10.1016/S2213-2600(20)30317-9.
73. Maron BA, Humbert M. Adding an important piece to the pulmonary vascular resistance puzzle in pulmonary arterial hypertension. *Eur Respir J*. 2020;56:2000962. DOI: 10.1183/13993003.00962-2020.
74. Pi H, Kosanovich CM, Handen A, Tao M, Visina J, Vanspeybroeck G, Simon MA, Risbano MG, Desai A, Mathier MA, et al. Outcomes of pulmonary arterial hypertension are improved in a specialty care center. *Chest*. 2020;158:330–340.
75. Conners LH, Sam F, Skinner M, Salinaro F, Sun F, Ruberg FL, Berk JL, Seldin DC. Heart failure resulting from age-related cardiac amyloid disease associated with wild-type transthyretin: a prospective, observational cohort study. *Circulation*. 2016;133:282–290. DOI: 10.1161/CIRCULATIONAHA.115.018852.
76. Rapezzi C, Merlini G, Quarta CC, Riva L, Longhi S, Leone O, Salvi F, Ciliberti P, Pastorelli F, Biagini E, et al. Systemic cardiac amyloidoses: disease profiles and clinical course of the 3 main types. *Circulation*. 2009;120:1203–1212. DOI: 10.1161/CIRCULATIONAHA.108.843334.
77. Maurer MS, Hanna M, Grogan M, Dispenzieri A, Witteles R, Drachman B, Judge DP, Lenihan DJ, Gottlieb SS, Shah SJ, et al. Genotype and phenotype of transthyretin cardiac amyloidosis. THAOS (Transthyretin Amyloid Outcome Survey). *J Am Coll Cardiol*. 2016;68:161–172. DOI: 10.1016/j.jacc.2016.03.596.
78. Quarta CC, Solomon SD, Uraizee I, Kruger J, Longhi S, Ferlito M, Gagliardi C, Milandri A, Rapezzi C, Falk RH, et al. Left ventricular structure and function in transthyretin-related versus light-chain cardiac amyloidosis. *Circulation*. 2014;129:1840–1849. DOI: 10.1161/CIRCULATIONAHA.113.006242.
79. Chacko L, Martone R, Bandera F, Lane T, Martinez-Naharro A, Boldrini M, Rezk T, Whelan C, Quarta C, Rowczenio D, et al. Echocardiographic phenotype and prognosis in transthyretin cardiac amyloidosis. *Eur Heart J*. 2020;41:1439–1447. DOI: 10.1093/eurheartj/ehz905.
80. Maurer MS, Bokhari S, Damy T, Dorbala S, Drachman BM, Fontana M, Grogan M, Kristen AV, Lousada I, Nativi-Nicolau J, et al. Expert consensus recommendations for the suspicion and diagnosis of transthyretin cardiac amyloidosis. *Circ Heart Fail*. 2019;12:e006075. DOI: 10.1161/CIRCHEARTFAILURE.119.006075.
81. Kittleson MM, Maurer MS, Ambardekar AV, Bullock-Palmer RP, Chang PP, Eisen HJ, Nair AP, Nativi-Nicolau J, Ruberg FL. Cardiac amyloidosis. Evolving diagnosis and management. A scientific statement from the American Heart Association. *Circulation*. 2020;142:e7–e22. DOI: 10.1161/CIR.0000000000000792.
82. Lane T, Fontana M, Martinez-Naharro A, Quarta CC, Whelan CJ, Petrie A, Rowczenio DM, Gilbertson JA, Hutt DF, Rezk T, et al. Natural history, quality of life, and outcome in cardiac transthyretin amyloidosis. *Circulation*. 2019;140:16–26. DOI: 10.1161/CIRCULATIONAHA.118.038169.
83. Blake CC, Geisow MJ, Oatley SJ, Rerat B, Rerat C. Structure of prealbumin: secondary, tertiary and quaternary interactions determined by Fourier refinement at 1.8A. *J Mol Biol*. 1978;121:339–356.
84. Kanda Y, Goodman DS, Canfield RE, Morgan FJ. The amino acid sequence of human plasma prealbumin. *J Biol Chem*. 1974;249:6796–6805. DOI: 10.1016/S0021-9258(19)42128-5.
85. Saraiva MJ, Birken S, Costa PP, Goodman DS. Amyloid fibril protein in familial amyloidotic polyneuropathy, Portuguese type. Definition of molecular abnormality in transthyretin (prealbumin). *J Clin Invest*. 1984;74:104–119. DOI: 10.1172/JCI111390.
86. Holmgren G, Steen L, Ekstedt J, Groth C-G, Ericzon B-G, Eriksson S, Andersen O, Karlberg I, Nordén G, Nakazato M, et al. Biochemical effect of liver transplantation in two Swedish patients with familial amyloidotic polyneuropathy (FAP-met 30). *Clin Genet*. 1991;40:242–246. DOI: 10.1111/j.1399-0004.1991.tb03085.x.
87. Perugini E, Guidalotti PL, Salvi F, Cooke RMT, Pettinato C, Riva L, Leone O, Farsad M, Ciliberti P, Bacchi-Reggiani L, et al. Noninvasive etiologic diagnosis of cardiac amyloidosis using Tc-3, 3-diphoshponо-1, 2 propanodicaboxylic acid scinitigraphy. *J Am Coll Cardiol*. 2005;46:1076–1084.
88. Hanna M, Ruberg FL, Maurer MS, Dispenzieri A, Dorbala S, Falk RH, Hoffman J, Jaber W, Soman P, Witteles RM, et al. Cardiac scintigraphy with technetium-99-m labeled bone-seeking tracers for suspected amyloidosis. JACC review topic of the week. *J Am Coll Cardiol*. 2020;75:2851–2862. DOI: 10.1016/j.jacc.2020.04.022.
89. Gillmore JD, Maurer MS, Falk RH, Merlini G, Damy T, Dispenzieri A, Wechalekar AD, Berk JL, Quarta CC, Grogan M, et al. Nonbiopsy diagnosis of cardiac transthyretin amyloidosis. *Circulation*. 2018;133:2404–2412. DOI: 10.1161/CIRCULATIONAHA.116.021612.
90. Bokhari S, Castano A, Pozniakoff T, Deslisle S, Latif F, Maurer MS. (99m)Te-pyrophosphast scintigraphy for differentiating light-chain cardiac amyloidosis from the transthyretin-related familial and senile cardiac amyloidosis. *Circ Cardiovasc Imaging*. 2013;6:195–201.
91. Keohane D, Schwartz J, Gundapaneni B, Stewart M, Amass L. Tafamidis delays disease progression in patients with early stage transthyretin familial amyloid polyneuropathy: additional supportive analyses from the pivotal trial. *Amyloid*. 2017;24:30–36. DOI: 10.1080/13506129.2017.1301419.

92. Maurer MS, Grogan DR, Judge DP, Mundayat R, Packman J, Lombardo I, Quyyumi AA, Aarts J, Falk RH. Tafamidis in transthyretin amyloid cardiomyopathy: effects on transthyretin stablilization and clinical outcomes. *Circ Heart Fail*. 2015;8:519–526. DOI: 10.1161/CIRCHEARTFAILURE.113.000890.
93. Bulawa CE, Connelly S, DeVit M, Wang L, Weigel C, Fleming JA, Packman J, Powers ET, Wiseman RL, Foss TR, et al. Tafamidis, a potent and selective transthyretin kinetic stabilizer that inhibits the amyloid cascade. *Proc Natl Acad Acad USA*. 2012;109:9629–9634. DOI: 10.1073/pnas.1121005109.
94. Coelho T, Maia LF, Martins da Silva A, Waddington Cruz M, Plante-Bordeneuve V, Lozeron P, Suhr OB, Campistol JM, Conceicao IM, Schmidt HH-J, et al. Tafamidis for transthyretin familial amyloid polyneuropathy: a randomized, controlled trial. *Neurology*. 2012;79:785–792. DOI: 10.1212/WNL.0b013e3182661eb1.
95. Rapezzi C, Elliott P, Damy T, Nativi-Nicolau J, Berk JL, Velazquez EJ, Boman K, Gundapaneni B, Patterson TA, Schwartz JH, et al. Efficacy of tafamidis in patients with heredity and wild-type transthyretin amyloid cardiomyopathy. *JACC Heart Fail*. 2021;9:115–123.
96. Johnson SM, Connelly S, Fearns C, Powers ET, Kelly JW. The transthyretin amyloidoses: from delineating the molecular mechanism of aggregation linked to pathology to a regulatory agency approved drug. *J Mol Biol*. 2012;421:185–203. DOI: 10.1016/j.jmb.2011.12.060.
97. Barrett CD, Alexander KM, Zhao H, Haddad F, Cheng P, Liao R, Wheeler MT, Liedtke M, Schrier S, Arai S, et al. Outcomes in patients with cardiac amyloidosis undergoing heart transplantation. *JACC Heart Fail*. 2020;8:461–468. DOI: 10.1016/j.jchf.2019.12.013.
98. Solomon SD, Adams D, Kristen A, Grogan M, Gonzalez-Duarte A, Maurer MS, Merlini G, Damy T, Slama MS, Brannegan TH, et al. Effects of patisiran, and RNA interference therapeutic, on cardiac parameters in patients with hereditary transthyretin-mediated amyloidosis. *Circulation*. 2019;139:431–443.
99. Benson MD, Waddington-Cruz M, Berk JL, Polydefkis M, Dyck PJ, Wang AK, Planté-Bordeneuve V, Barroso FA, Merlini G, Obici L, et al. Inotersen treatment for patients with hereditary transthyretin amyloidosis. *N Engl J Med*. 2018;379:22–31. DOI: 10.1056/NEJMoa1716793.
100. Minamisawa M, Claggett B, Adams D, Kristen AV, Merlini G, Slama MS, Dispenzieri A, Shah AM, Falk RH, Karsten V, et al. Association of patisiran, an RNA interference therapeutic, with regional left ventricular myocardial strain in hereditary transthyretin amyloidosis: the APOLLO study. *JAMA Cardiol*. 2019;4:466–472. DOI: 10.1001/jamacardio.2019.0849.
101. Gurwitz JH, Maurer MS. Tafamidis—a pricey therapy for a not-so-rare condition. *JAMA Cardiol*. 2020;5:247–248. DOI: 10.1001/jamacardio.2019.5233.
102. Kazi DS, Bellows BK, Baron SJ, Shen C, Cohen DJ, Spertus JA, Yeh RW, Arnold SV, Sperry BW, Maurer MS, et al. Cost effectiveness of tafamidis therapy for transthyretin amyloid cardiomyopathy. *Circulation*. 2020;141:1214–1224. DOI: 10.1161/CIRCULATIONAHA.119.045093.
103. Hlatky MA. Willingness to pay for high cost medications. *Circulation*. 2020;141:1225–1226. DOI: 10.1161/CIRCULATIONAHA.120.045966.
104. Damrauer SM, Chaudhary K, Cho JH, Liang LW, Argulian E, Chan L, Dobbyn K, Guerraty MA, Judy R, Kay J, et al. Association of the V122I hereditary transthyretin amyloidosis genetic variant with heart failure among individuals of African and Hispanic/Latino ancestry. *JAMA*. 2019;322:2191–2202.
105. Maron BJ, Rowin EJ, Maron MS. Hypertrophic cardiomyopathy: is a "cure" coming… or it already here? *Am J Med*. 2020;133:886–888.
106. Maron BJ, Roberts WC. The father of septal myectomy for obstructive HCM, who also had HCM: the unbelievable story. *J Am Coll Cardiol*. 2016;67:2900–2903. DOI: 10.1016/j.jacc.2016.05.002.
107. Maron BJ, Rowin EJ, Casey SA, Link MS, Lesser JR, Chan RHM, Garberich RF, Udelson JE, Maron MS. Hypertrophic cardiomyopathy in adulthood associated with low cardiovascular mortality with contemporary management strategies. *J Am Coll Cardiol*. 2015;65:1915–1928.
108. Olivotto I, Oreziak A, Barriales R, Abraham TP, Masri A, Garcia-Pavia P, Saberi S, Lakdawala NK, Wheeler MT, Owens A, et al. Mavacamten for treatment of symptomatic obstructive hypertrophic cardiomyopathy (EXPLORER-HCM): a randomized, double-blind, placebo-controlled, phase 3 trial. *Lancet*. 2020;396:759–769.
109. Galie' N, Hoeper MM, Humbert M, Torbicki A, Vachiery J-L, Barbera JA, Beghatti M, Corris P, Gaine S, Gibbs JS, et al. Guidelines for the diagnosis and treatment of pulmonary hypertension. The Task Force on diagnosis and treatment of pulmonary hypertension of the European Society of Cardiology and European Respiratory Society. *Eur Heart J*. 2009;30:2493–2537.
110. Ratwatte S, Anderson J, Strange G, Corrigan C, Collins N, Celermajer DS, Dwyer N, Feenstra J, Keating D, Kotlyar E, et al.; PHSANZ Registry. Pulmonary arterial hypertension with below threshold pulmonary vascular resistance. *Eur Respir J*. 2020;56:1901654. DOI: 10.1183/13993003.01654-2019.