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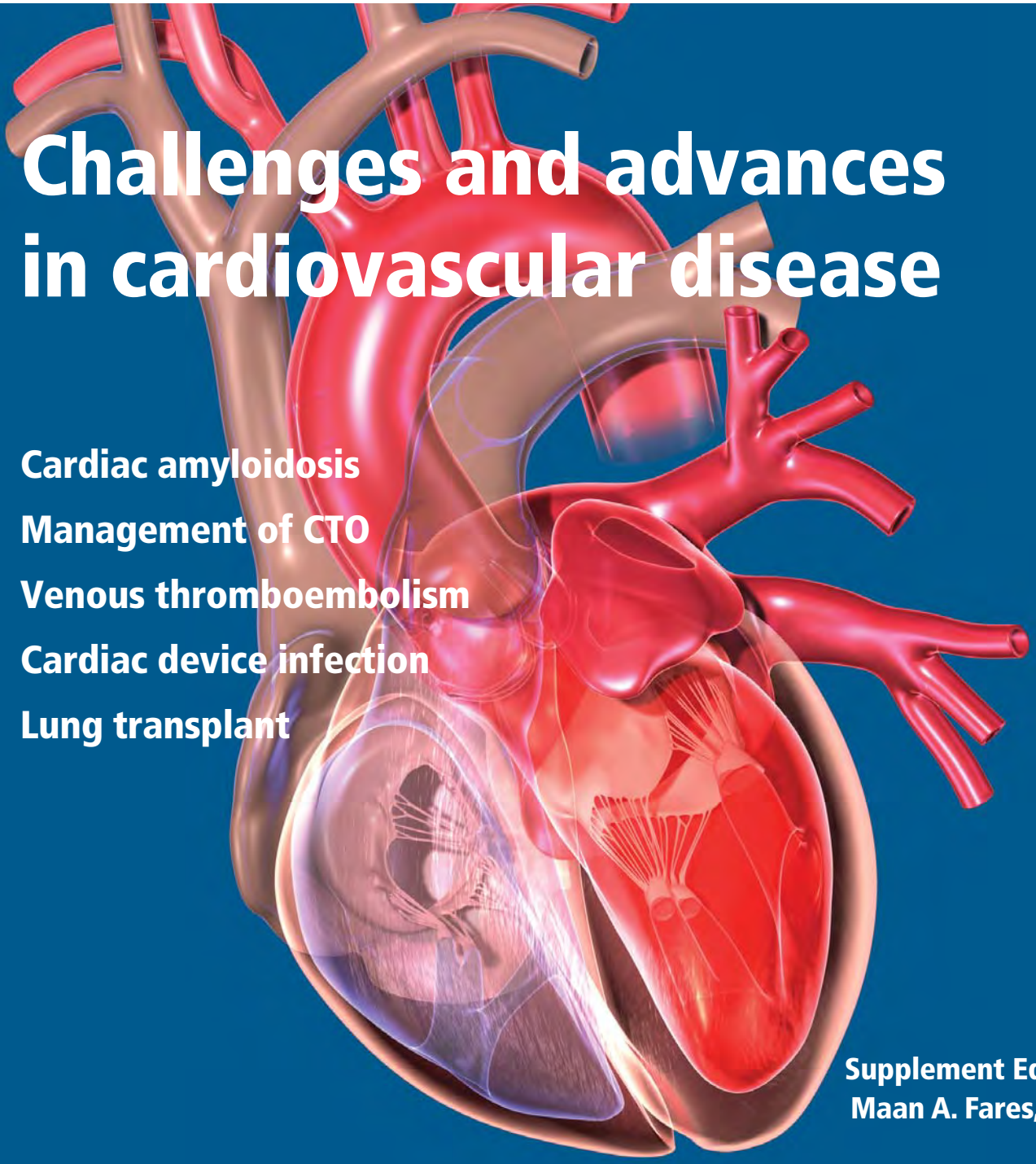

Challenges and advances in cardiovascular disease

Cardiac amyloidosis

Management of CTO

Venous thromboembolism

Cardiac device infection

Lung transplant

Supplement Editor
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Heart and Vascular Institute
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Table of Contents

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Introduction: Challenges and advances in cardiovascular disease

In cardiovascular medicine, advances in our understanding of disease processes, medical management, and interventional and surgical techniques have gone a long way toward improving the health of patients. But we face challenges and opportunities in how best to apply these discoveries to improve the quality of care we provide and do so without driving up costs or wasting resources.

This *Cleveland Clinic Journal of Medicine* supplement on cardiovascular disease aims to illuminate some of the challenges and advances in the management of cardiac amyloidosis, coronary artery chronic total occlusion, venous thromboembolism, implantable device infection, and lung transplant. In so doing, my colleagues present insights into *which* advances will benefit *which* patients to improve quality and contain cost.

Cardiac amyloidosis, sometimes called stiff heart syndrome, is the most common restrictive cardiomyopathy. Amyloid deposits in the heart muscle can affect conduction of electrical signals leading to arrhythmias and heart block. Joseph P. Donnelly, MD, and Mazen Hanna, MD, present a comprehensive review of cardiac amyloidosis and share exciting advances in the detection and treatment of this condition and clues to identify patients who may be affected by this often overlooked condition.

Also in this supplement, Jaikirshan Khatri, MD, and colleagues review the use of percutaneous coronary intervention (PCI) for patients with coronary artery chronic total occlusion (CTO). Though CTO is often considered benign, the affected myocardium is ischemic and patients with significant ischemic burden may benefit clinically from CTO PCI. A technically demanding procedure, CTO PCI success rates are highly operator-dependent.

John R. Bartholomew, MD, presents information about the management of venous thromboembolism (VTE) including recent changes to treatment guidelines. Patients with VTE require immediate treatment with anticoagulation therapy. Recent changes to treatment guidelines now recommend direct oral anticoagulants for patients with VTE and no cancer. Direct oral anticoagulants are an important new option for patients and further study would be beneficial to strengthen the level of evidence regarding which anticoagulation therapy is best for which patients.

Cardiac implantable electronic devices (CIEDs) improve quality of life and longevity for increasing numbers of patients with cardiac disease. Cameron T. Lambert, MD, and Khaldoun G. Tarakji, MD, MPH, discuss the types of CIED infections that occur in about 1% of patients receiving a first CIED. Prompt diagnosis improves the success of antibiotic therapy, device removal, and resolution of the infection.

Finally, Kenneth R. McCurry, MD, and Marie M. Budev, DO, MPH, discuss lung transplant for patients with end-stage lung disease. Lung transplant may be an option to extend survival and improve the quality of life for some patients. In this article, the authors review the selection criteria for lung transplant candidates, including when physicians should refer patients to lung transplant centers for evaluation and placement on the lung transplant waiting list.

We hope this supplement is a useful review of some of the challenges and advances in cardiovascular medicine and is beneficial to you and your clinical practice.

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Cardiac amyloidosis: An update on diagnosis and treatment

ABSTRACT

Cardiac amyloidosis (CA), once thought to be a rare disease, is increasingly recognized due to enhanced clinical awareness and better diagnostic imaging. CA is becoming of heightened interest to the cardiology community given more effective treatment strategies for light chain amyloidosis (AL), as well as emerging therapies for transthyretin amyloidosis (ATTR). Furthermore, reversing amyloid deposition in affected organs using monoclonal antibodies is actively being tested in clinical trials. A high index of suspicion and a systematic approach to the diagnosis of CA can lead to referral to a center of expertise for timely treatment.

KEY POINTS

AL and ATTR are the 2 main types of amyloidosis that affect the heart.

Serum and urine protein electrophoresis are inadequate laboratory tests to screen for AL given low sensitivity, and should be replaced by the serum free light chain assay as well as immunofixation of the serum and urine.

AL cardiac amyloidosis (AL-CA) requires timely diagnosis and referral to hematology due to high mortality without prompt treatment.

^{99m}Technetium pyrophosphate bone scintigraphy is an affordable, noninvasive tool that has revolutionized the diagnosis of ATTR cardiac amyloidosis (ATTR-CA).

The US Food and Drug Administration will likely approve new therapies for ATTR in late 2018.

Dr. Donnelly reported no financial interests or relationships that pose a potential conflict of interest with this article. Dr. Hanna reported that he served on a one-time advisory panel for Ionis Pharmaceuticals.

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WHAT IS AMYLOIDOSIS?

Amyloidosis is a protein deposition disease in which a specific precursor protein pathologically misfolds from its physiologic tertiary structure into a more linear shape dominated by β-pleated sheets. The misfolded protein aggregates into oligomers, eventually forming insoluble amyloid fibrils that deposit extracellularly in tissues. Both the circulating oligomers, which are cytotoxic, and the fibrils, which cause distortion of the tissue architecture, lead to organ dysfunction. Amyloid fibrils are rigid, nonbranching structures, 7 to 10 nanometers in diameter, with a characteristic appearance on electron microscopy. Affinity for Congo red staining, which binds to the β-pleated sheets, produces the pathognomonic "apple-green" birefringence when visualized under polarized light microscopy. Universal to all amyloid fibrils are chaperone proteins such as serum amyloid P (SAP) and glycosaminoglycans, as well as calcium. There are more than 30 different precursor proteins implicated in various amyloid diseases, arising as hereditary or nonhereditary, localized or systemic, with different organ involvement and prognosis.[1–3]

TWO MAIN TYPES OF CARDIAC AMYLOIDOSIS

Although there are many different amyloid diseases, 2 types account for over 95% of all cardiac amyloidosis (CA): immunoglobulin light chain amyloidosis (AL) and transthyretin amyloidosis (ATTR) (**Figure 1**).[4] Other amyloid types that can involve the heart include amyloid A, apolipoprotein AI, heavy chain, and atrial natriuretic peptide (ANP).

Light chain amyloidosis (AL)

AL, formerly called primary amyloidosis, is a clonal plasma cell disorder due to the overproduction and misfolding of antibody light chain fragments. It is a rare disease with about 3,000 new cases per year in the United States.[5] The median age at diagnosis is 63, although it can present in patients in their 30s and 40s.[5,6] It is a systemic disease that often affects the heart, but it can affect several other organs, most

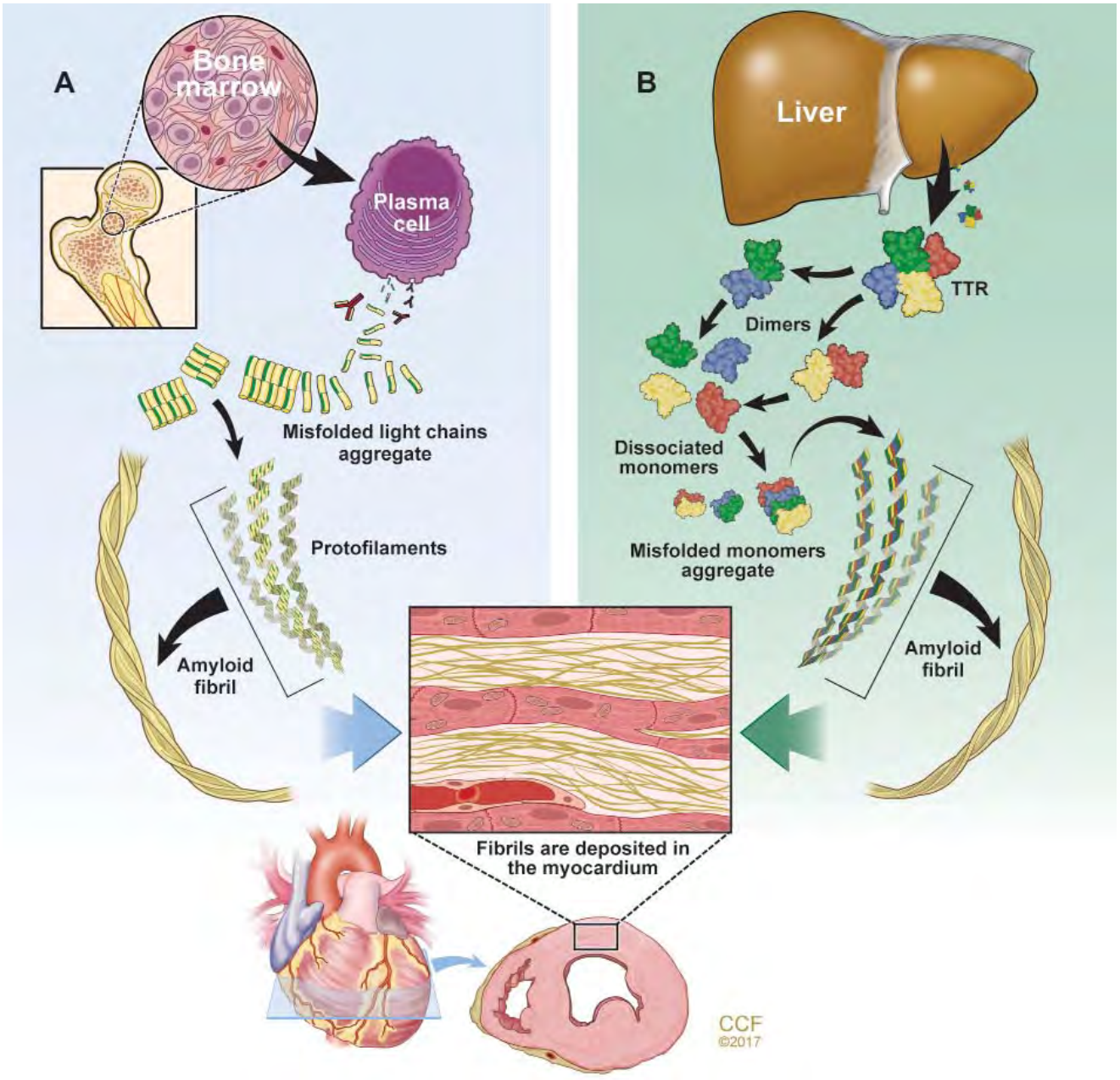


Figure 1. The 2 main types of amyloidosis that affect the heart. (A) Immunoglobulin light chain amyloidosis (AL) results from aberrant plasma cell production of monoclonal light chains that misfold. (B) Transthyretin amyloidosis (ATTR) results from transthyretin (TTR) produced by the liver that dissociates into monomers and misfolds. The misfolded proteins aggregate to form oligomers, protofilaments, and mature amyloid fibrils that deposit extracellulary in the interstitial space of the myocardium.

commonly the kidneys, gastrointestinal (GI) tract, and nervous system.[7]

AL is a more aggressive disease than ATTR, with a median untreated survival of less than 6 months in patients who present with heart failure.[8] Early diagnosis is crucial as mortality is high without prompt treatment.

Transthyretin amyloidosis (ATTR)

ATTR is due to misfolding of the liver-derived precursor protein transthyretin (TTR) (previously called prealbumin), either as an acquired wild-type variant (ATTRwt) or as a hereditary mutant variant (ATTRm). ATTRwt, known previously as senile CA, typically affects older males and presents as a late onset

hypertrophic restrictive cardiomyopathy, often preceded by carpal tunnel syndrome or spinal stenosis or both. The ATTRm variant, caused by one of many different point mutations in the *TTR* gene, can manifest as a polyneuropathy, cardiomyopathy, or a mixed phenotype that varies according to the specific mutation.

While ATTR portends a better prognosis than AL, it is still a progressive disorder with significantly reduced survival and quality of life. The median survival of patients with the ATTRwt variant is about 4 years and for patients with the ATTRm variant, survival depends on the mutation.[9] TTR is a protein tetramer composed of 4 identical 127-amino acid monomers noncovalently bound at a dimer-dimer interface (**Figure 1**). It is a transport protein for thyroxine and retinol binding protein. The dissociation of the tetramer is the rate-limiting step for amyloid fibrillogenesis. Differentiating the ATTRwt variant and the ATTRm variant is done by testing the *TTR* gene for a mutation.[1,3]

How common is the ATTRwt variant? The ATTRwt variant is often an unrecognized cause of diastolic heart failure in the elderly, with up to 25% of patients 85 and older showing ATTRwt amyloid deposits on autopsy studies.[10] A recent study showed that 13% of patients 60 and older hospitalized with heart failure with preserved ejection fraction had grade 2 to 3 uptake on ^{99m}technetium-pyrophosphate (^{99m}TcPYP) scintigraphy, which is consistent with ATTR-CA.[11] In 43 consecutive patients undergoing transcatheter aortic valve replacement, 11.6% were found to have significant uptake on ^{99m}TcPYP scan.[12] It is clear given the aging population that the ATTRwt variant will become the most common form of amyloidosis. It is much more common in white males, with a median age at diagnosis of 75.[13] Carpal tunnel syndrome (almost always bilateral) and spinal stenosis are present in about 50% of patients diagnosed with ATTRwt-CA and often precede clinical presentation of heart failure by 5 to 15 years.[14–17]

How common is the ATTRm variant? There are more than 100 point mutations in the *TTR* gene that lead to various familial TTR-related amyloid syndromes, either neuropathic (familial amyloid polyneuropathy [FAP]) or cardiomyopathic (familial amyloid cardiomyopathy).[18] The most common mutation in the United States is V122I in which there is an isoleucine substitution for valine at the 122nd amino acid position. This mutation is seen in African Americans, 3% to 4% of whom are heterozygote carriers.[19] Although the true penetrance is unknown, this mutation can lead to a late-onset restrictive cardiomyopathy with minimal neuropathy and is frequently misdiagnosed as hypertensive heart disease or diastolic heart failure. The median survival for V122I ATTRm-CA is about 2 years but likely depends on the stage at the time of diagnosis.[20] The second most common mutation in the United States, T60A, is seen in patients of Irish descent and causes a mixed neuropathy and cardiomyopathy.[17]

PATHOLOGY AND PATHOPHYSIOLOGY OF CA

Both AL-CA and ATTR-CA lead to diffuse amyloid fibril deposition in the heart causing thickening of both ventricles (**Figure 2A**).[4,21] In AL, the pattern of amyloid deposition is usually subendocardial and diffuse, whereas in ATTR (particularly ATTRwt), there can be patchy areas of transmural involvement. Phenotype may vary, particularly in ATTR, with a subset having asymmetric septal hypertrophy, mimicking hypertrophic cardiomyopathy (HCM).[22–24] In CA, the amyloid deposits are located extracellularly in the interstitium, surrounding the myocytes, however there can also be desposition in the small intramural coronary arteries. Unlike sarcoidosis, amyloid deposition can be found throughout the myocardial tissue, thus endomyocardial biopsy is nearly 100% sensitive for CA diagnosis.[4,25–28]

The atria are universally involved with interatrial septal thickening, which can lead to poor atrial function and increased rates of atrial fibrillation (ATTR more so than AL).[21,29] The conduction system can be affected causing varying degrees of heart block, as well as bundle branch block (ATTR more so than AL).[30] The valves are usually thickened, often associated with mild to moderate regurgitation. Pericardial involvement can lead to small pericardial effusions (large effusions are rare), and coronary involvement (classically, small intramural vessels) can lead to ischemia and angina with normal epicardial coronaries (AL more so than ATTR).[31–33]

Thickened left and right ventricular walls result in a nondilated ventricle that is stiff and poorly compliant, resulting in progressive diastolic filling abnormalities. Systolic dysfunction can be seen in severe and advanced disease. Importantly, ejection fraction measured by echocardiography is misleading in CA, as reduced end-diastolic volume produces a low stroke volume. For example, an ejection fraction of 50%, when starting at a significantly reduced end-diastolic volume (for example, 70 mL), leads to a significantly reduced stroke volume (35 mL) and, thus, cardiac output. This explains why patients with CA cannot usually tolerate reduced heart rates, as their cardiac output is dependent on heart rate.[34–36]

CLINICAL PRESENTATION

Patients with CA typically exhibit heart failure with preserved ejection fraction (otherwise known as diastolic heart failure). Dyspnea on exertion is common; however, some patients can present with more right-sided heart failure symptoms such as lower-extremity edema and ascites. Fatigue and weakness are related to low cardiac output and often attributed to nonspecific symptoms of aging. Because of the thickened ventricles, patients can often be misdiagnosed as having HCM with or without obstruction.[7,34] The first manifestation of CA may be atrial fibrillation, most commonly in ATTRwt-CA, or cardioembolic stroke. Atrial fibrillation can be present for years before CA is considered. Bundle branch block and complete heart block (more common in ATTR-CA than AL-CA) may lead to pacemaker implantation.[30] Angina with normal coronaries can occur, and a rare presentation may be cardiogenic shock due to diffuse ischemia.[31–33] Elderly patients with CA can present with low-flow, low-gradient aortic stenosis.[37]

Figure 2. Cardiac amyloidosis pathology. (A) The heart on autopsy reveals characteristic biventricular thickening as well as biatrial dilation and thickening of both atrioventricular valves. (B) Hemotoxylin and eosin staining shows diffuse amyloid deposition. (C) The characteristic "apple-green" birefringence of Congo red stain under polarized light. (D) Example of immunohistochemistry performed for amyloid typing, in this case positive for lambda light chain and negative for kappa light chain and transthyretin.

In the appropriate clinical context, several other symptoms should raise suspicion of CA (**Table 1**). Bilateral carpal tunnel syndrome is seen in patients with both AL and ATTR (more common in ATTRwt) and can precede clinical heart failure by several years.[7,14,17] Spinal stenosis is specific to patients with the ATTRwt variant and is due to amyloid infiltration of the ligamentum flavum.[15] Low to normal blood pressure in a previously hypertensive patient that leads to discontinuation or reduction of antihypertensive therapy is a clue to possible CA. Peripheral and autonomic neuropathy can occur in both AL and ATTRm and are uncommon in ATTRwt.[16] Other signs and symptoms of AL may include macroglossia and periorbital purpura or both (pathognomonic but infrequent), proteinuria (particularly nephrotic range), jaw claudication, and GI symptoms of diarrhea and weight loss.[7]

DIAGNOSIS

Diagnosis of CA starts with visualization of the 2-dimensional (2D) echocardiogram in conjunction with the electrocardiogram (ECG). The classic hallmark of CA is the combination of low voltage on ECG and increased left ventricular (LV) wall thickness on echocardiogram (**Figure 3**).[30] Subsequent laboratory tests, cardiac imaging, or tissue biopsy is used to confirm the diagnosis.

ECG

As opposed to that seen in true left ventricular hypertrophy (LVH), which leads to increased voltage on ECG, amyloid infiltration of the myocardium leads to lower voltage. Thus, what is indicative of LVH on echocardiogram combined with low voltage on the ECG is a classic finding for CA. However, only about 50% of patients with AL-CA and about 30% of patients with ATTR-CA meet true low-voltage criteria (QRS amplitude less than 5 mm in limb leads or less than 10 mm in precordial leads).[30,38] Hence, the absence of low-voltage criteria does not exclude the diagnosis of CA. Approximately 10% of patients with CA confirmed by biopsy met ECG criteria for LVH.[38] The key point is to consider the overall degree of voltage on the ECG relative to the degree of LV thickening on the echocardiogram, recognizing that

TABLE 1
Symptoms that raise suspicion of cardiac amyloidosis

Red Flags for Cardiac Amyloidosis	
Echocardiography: ▪ Low voltage on ECG and thickening of the septum/posterior wall > 1.2 cm ▪ Thickening of right ventricle free wall, valves	
Intolerance to beta-blockers or ACE inhibitors	
Low normal blood pressure in patients with a previous history of hypertension	
History of bilateral carpal tunnel syndrome, often requiring surgery	
AL	**ATTR**
HFpEF + nephrotic syndrome	White male age ≥ 60 with HFpEF + history of carpal tunnel syndrome and/or spinal stenosis
Macroglossia and/or periorbital purpura	African American age ≥ 60 with HFpEF without a history of hypertension
Orthostatic hypotension	New diagnosis of hypertrophic cardiomyopathy in an elderly patient
Peripheral neuropathy	New diagnosis of low flow, low gradient aortic stenosis in an elderly patient
MGUS	Family history of ATTRm amyloidosis

ACE = angiotensin-converting enzyme; AL = immunoglobulin light chain amyloidosis; ATTR = transthyretin amyloidosis; ECG = electrocardiogram; ATTRm = hereditary mutant variant ATTR; HFpEF = heart failure with preserved ejection fraction ("diastolic heart failure"); MGUS = monclonal gammopathy of undetermined significance

lower voltage than what would be expected may indicate possible infiltrative disease such as CA. The other main finding on the ECG in patients with CA is a pseudoinfarct pattern with Q waves in the early precordial leads mimicking a prior anteroseptal myocardial infarction.[38,39] This finding is seen in about 50% of patients (**Figure 3**).[39] Wide QRS complexes are more frequent in ATTR-CA and lower limb voltages are more frequent in AL-CA.[30]

Echocardiogram

The echocardiographic finding of LVH in patients with CA is misleading in that the LV thickening is due to infiltrating amyloid fibrils and not to myocyte hypertrophy. That said, the terms LVH and LV thickening are used interchangeably when describing the echocardiographic phenotype. LV wall thickness greater than 12 mm (6 mm to 10 mm is normal) in the absence of hypertension should prompt suspicion for CA.[34] LV thickening most often appears symmetric; however, occasionally it may exhibit asymmetric septal hypertrophy, particularly in ATTRwt-CA. In some cases, there may be a smaller subset that can actually have dynamic LV outflow obstruction similar to that seen in hypertrophic obstructive cardiomyopathy.[22–24] An important echocardiographic clue that can differentiate CA from other diseases is thickening of both the LV and right ventricle (**Figure 3**). Septal wall thickness and LV mass index are greater in ATTR-CA compared with AL-CA.[30] On average, the LV septum is around 15 mm in AL-CA and around 18 mm in ATTRwt-CA.[40] Historically, the characteristic myocardial "granular sparking" or "speckling" pattern has low sensitivity and specificity.[16] The left ventricle is not dilated; rather, the ventricular dimensions are usually smaller than normal. Although ejection fraction is usually preserved, cardiac output is low due to decreased ventricular volume.[37] Systolic dysfunction occurs late in the disease.[16] Diastolic dysfunction is universal, with a mitral inflow pattern that can range from stage I (abnormal relaxation) in early disease to stage III (restrictive filling pattern) in more advanced disease. Septal and lateral tissue Doppler velocities are very low in amyloid heart disease.[41] Another echocardiographic clue to diagnosis is thickening of the heart valves, which is not seen in hypertensive heart

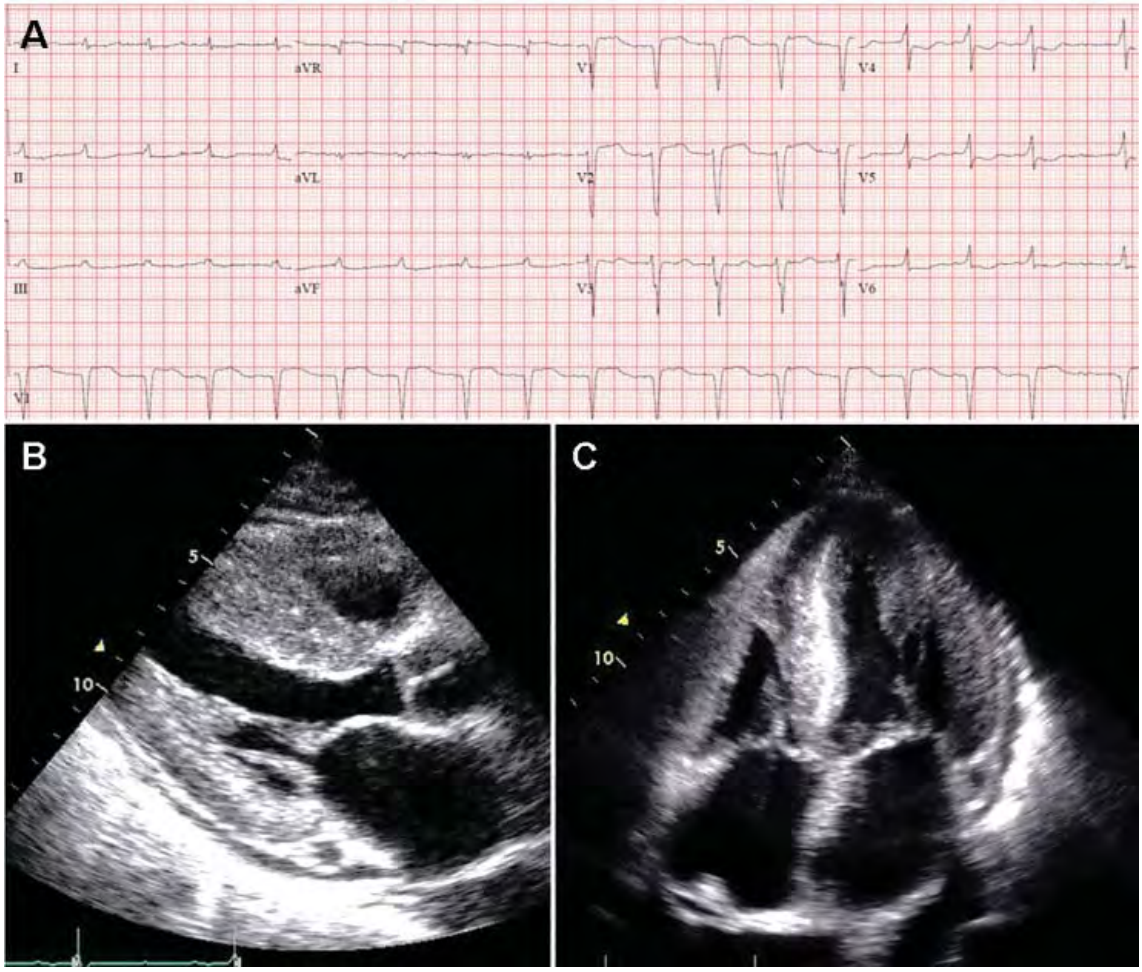


Figure 3. The classic hallmark of cardiac amyloidosis. (A) A 12-lead electrocardiogram showing atrial fibrillation, low voltage in the limb leads, and a pseudoinfarct pattern with Q waves in leads V1-V2. (B) Echocardiogram, parasternal long-axis view, showing increased septal and posterior left ventricular wall thickness, dilated left atrium, and thickening of the mitral valve. (C) Echocardiogram, apical 4-chamber view, showing diffuse thickening of both ventricles, biatrial dilation, and thickened mitral and tricuspid valve leaflets.

disease or hypertrophic cardiomyopathy. Biatrial dilation is common, and there can be thickening of the interatrial septum.

Laboratory testing

N-terminal pro-b-type natriuretic peptide (NT-proBNP) is universally elevated in CA and is typically higher in AL-CA than in ATTR-CA. Troponin T or troponin I or both may be chronically elevated in CA and likely signify small-vessel ischemia. In the appropriate clinical context of a thickened ventricle and heart failure, an elevated troponin value (outside of an acute coronary syndrome) should trigger suspicion for CA. Workup for a monoclonal protein process should always be done when considering CA to rule out AL. Serum and urine protein electrophoresis are insensitive tests to detect AL and should not be relied upon as a screening test. The serum free light chain (sFLC) assay, which measures free kappa and lambda light chain levels and reports the ratio, is a sensitive test that should be measured routinely along with immunofixation of the serum and urine. In AL, sFLC will reveal an abnormal kappa-lambda ratio. An abnormally low ratio (less than 0.26) suggests a monoclonal lambda light chain process, while an abnormally high ratio (greater than 1.65) suggests a monoclonal kappa light chain process. Immunofixation will reveal an M-protein. Because light chains are excreted by the kidney, the serum levels of both kappa and lambda will be elevated in renal dysfunction, but the ratio should remain normal.[16,31,34,40,42–47]

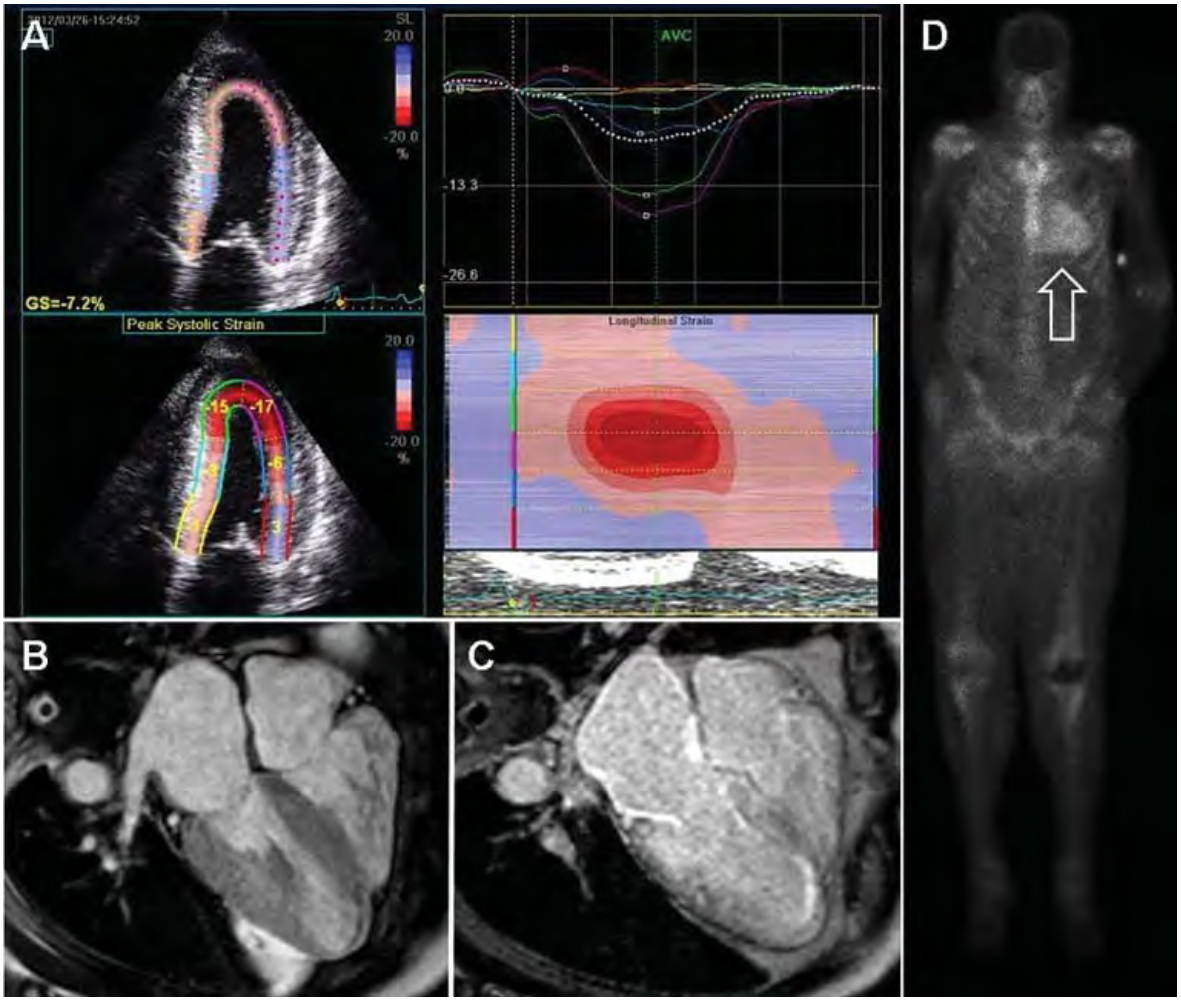


Figure 4. Noninvasive imaging for cardiac amyloidosis. (A) Longitudinal strain imaging using 2-dimensional speckle tracking echocardiography reveals the characteristic bull's-eye pattern of apical sparing. (B) Cardiac magnetic resonance imaging displays left ventricular and right ventricular thickening and (C) with contrast, a diffuse late gadolinium enhancement pattern that is diffuse and subendocardial, which also involves the right ventricle and left atrium. (D) ^{99m}Technetium pyrophosphate scan shows grade 3 myocardial radiotracer uptake characteristic of transthyrethin cardiac amyloidosis.

Advanced noninvasive diagnostic tools for CA

Over the past decade, the ability to diagnose CA noninvasively has dramatically improved with strain imaging using 2D speckle tracking echocardiography, cardiac magnetic resonance imaging (MRI), and nuclear bone scintigraphy. These diagnostic tools have given clinicians options to pursue the diagnosis of CA without directly proceeding to endomyocardial biopsy.

Longitudinal strain imaging using 2D speckle tracking echocardiography. Longitudinal strain imaging measures the actual deformation of myocardium in specific LV segments, and quantification is displayed as a polar map, with a more negative value coded in red and associated with better function. Our group, among others, has described a specific pattern in CA called "apical sparing," in which the apical LV segments have normal or near-normal strain compared with the mid and basal segments. The easily recognizable bull's-eye pattern on polar map can help differentiate CA from other forms of LV hypertrophy such has hypertension or HCM with good sensitivity and specificity (**Figure 4A**).[48]

Cardiac MRI. Cardiac MRI is useful for the diagnosis of CA (**Figure 4B, 4C**). Imaging after administration of gadolinium contrast shows a characteristic late gadolinium enhancement (LGE) pattern that is diffuse and subendocardial, and does not follow any particular coronary distribution.[49] LGE can also be seen in the right ventricle and the atrial walls, and can be transmural and patchy in ATTRwt-CA. This pattern is

highly sensitive (93%) and specific (70%) for CA with an overall negative predictive accuracy of 84%.[50]

One of the main limitations of cardiac MRI for the diagnosis of CA is the inability to give contrast in patients with reduced glomerular filtration rate. However, native T1-myocardial mapping techniques that do not require contrast show significantly increased native T1 times in CA and offer a promising alternative. Cardiac MRI parameters such as LGE, the difference in inversion time between the LV cavity and myocardium, native T1 mapping, and extracellular volume offer prognostic information. A greater than fivefold mortality increase is seen in CA patients with transmural LGE compared with those without LGE.[49,50]

^{99m}TcPYP scintigraphy. ^{99m}TcPYP, a radiotracer used in bone scans, was initially used in cardiology to quantify myocardial infarction due to its ability to localize calcium.[51] Its potential utility in CA came in 1982 when diffuse myocardial ^{99m}TcPYP uptake on cardiac radionucleotide imaging was noted in 10 patients with tissue-proven amyloidosis.[52] Several subsequent studies reproduced and expanded upon this observation and revealed its diagnostic value, specifically showing that there is significant uptake in ATTR-CA and no to mild uptake in AL-CA. This offers a significant advantage over other noninvasive modalities in that it not only confirms the diagnosis of CA but differentiates ATTR-CA.[16]

^{99m}TcPYP myocardial radiotracer uptake is graded by the semiquantitative visual score of cardiac retention, where grade 0 = no cardiac uptake, grade 1 = mild uptake less than bone, grade 2 = moderate uptake equal to bone, and grade 3 = high uptake greater than bone (**Figure 4D**).[42] Additionally, quantitative analysis of heart retention can be calculated drawing circular regions of interest over the heart and mirrored on the contralateral chest wall. A heart-to-contralateral ratio greater than 1.5 is consistent with the diagnosis of ATTR-CA.[53,54] In 2016, a multicenter study showed that grade 2 or 3 myocardial radiotracer uptake on bone scintigraphy in the absence of evidence of a monoclonal gammopathy was diagnostic for ATTR-CA, providing a cost-effective and noninvasive technique with a specificity and positive predictive value of 100% (confidence interval, 99.0–100%).[42]

Endomyocardial biopsy, right heart catheterization, and fat biopsy

Endomyocardial biopsy is essentially 100% sensitive for the diagnosis of CA.[25] The main risk of pursuing endomyocardial biopsy is about a 1% risk of right ventricular perforation leading to cardiac tamponade.[55] The other limitation to this approach is that not all centers are equipped to perform this procedure. Birefringence under polarized light microscopy is histopathologically diagnostic of CA; however, further subtyping by the pathologist to determine if it is AL or ATTR is absolutely crucial. Subtyping can be performed by immunohistochemistry with caution taken for misinterpretation. If there is any question of accuracy, the specimen should be sent for laser microdissection and mass spectroscopy for accurate identification of the precursor protein type (some centers routinely perform mass spectroscopy on all myocardial specimens).[16,31]

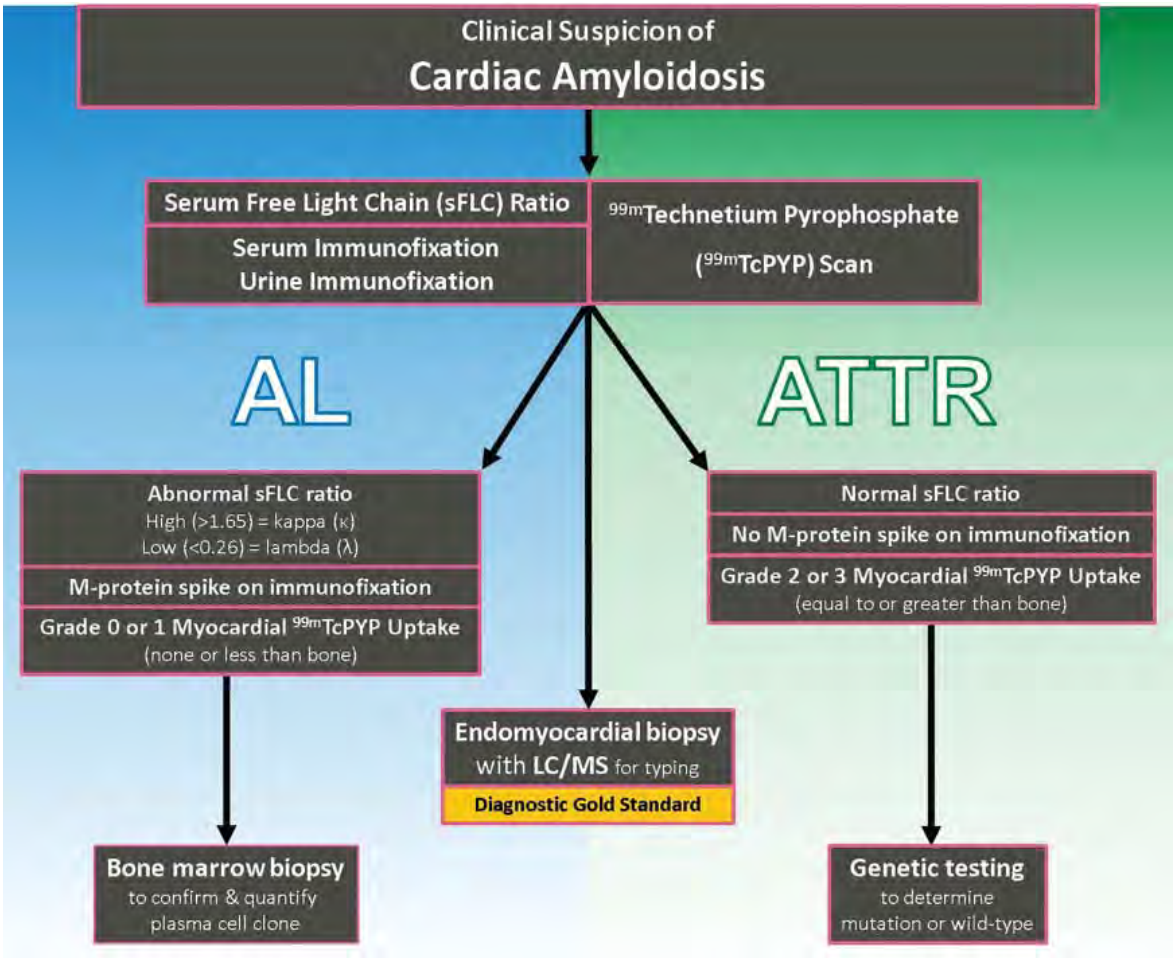
Right heart catheterization is nonspecific and shows restrictive hemodynamics. The right atrial waveform shows rapid x and y descents and the right ventricular tracing may show a dip-and-plateau pattern typical of restrictive cardiomyopathy. Cardiac output can be preserved but more commonly is low.[16,31]

Fat pad biopsy is 60% to 80% sensitive in AL, 65% to 85% sensitive in ATTRm, and only 14% sensitive in ATTRwt, with the accuracy dependent on the operator, pathologist, and how much tissue is removed (fat pad aspirate vs biopsy specimen).[56–58] Fat pad biopsy has diagnostic limitations, and a negative fat pad biopsy does not rule out amyloidosis.

DIAGNOSTIC ALGORITHM FOR CARDIAC AMYLOIDOSIS

The diagnostic algorithm for CA is predicated on the fact that most all CA in the U.S. is either AL or ATTR (**Figure 5**). For AL-CA, laboratory tests for the sFLC ratio and immunofixation of the serum and urine are performed. If these are normal, there is a high negative predictive value ruling out the diagnosis of AL-CA.[59]

In conjunction with laboratory tests, ^{99m}TcPYP scan of the heart can be ordered to investigate the possibility of ATTR-CA. Grade 2 to 3 myocardial uptake in the absence of a monoclonal plasma cell process is consistent with the diagnosis of ATTR-CA. Grade 0 or 1 myocardial uptake on ^{99m}TcPYP scan with an abnormal sFLC ratio or positive M protein on immunofixation suggests AL-CA and a bone marrow biopsy should be performed. If the patient has an abnormal sFLC ratio and grade 2 to 3 uptake on ^{99m}TcPYP scan, the diagnosis of ATTR-CA with unrelated monoclonal gammopathy of undetermined significance should be considered. However, this would need to be reconciled by pursuing endomyocardial biopsy and accurate tissue typing. If the ^{99m}TcPYP scan is negative, and the sFLC ratio is nor-



LC/MS = liquid chromatography/mass spectrometry

Figure 5. Diagnostic algorithm for cardiac amyloidosis (CA). Serum free light chain (sFLC) assay and serum/urine immunofixation are ordered to workup immunoglobulin light chain amyloidosis (AL). ^{99m}Technetium pyrophosphate (^{99m}TcPYP) scan is ordered to workup transthyretin amyloidosis (ATTR). Normal serum free light chains and normal immunofixation with a strongly positive ^{99m}TcPYP scan is diagnostic of ATTR-CA. Abnormal sFLC assay or immunofixation is suggestive but not diagnostic of AL-CA, and should prompt a bone marrow biopsy.

mal, and immunofixation is negative, a diagnosis of CA is very unlikely.[16,31,40,42–47]

If the diagnosis of ATTR-CA is made, genetic testing can determine the presence or absence of a mutation to differentiate ATTRm or ATTRwt, respectively. If the diagnosis of AL-CA is suggested, a bone marrow biopsy is necessary to identify and quantify the plasma cell clone.[16,31,40,42–47]

TREATMENT

Treatment of CA includes management of cardiac symptoms associated with CA and treating the underling amyloid disease. Several current and future pharmacotherapies for AL and ATTR are shown in **Table 2**.

Management of heart failure in cardiac amyloidosis

The main treatment of heart failure revolves around sodium restriction and diuretics to relieve congestion. This can prove challenging in many patients due to the narrow window between too high or too low filling pressures. A combination of loop diuretics and an aldosterone antagonist is most effective.[31,34,44,45] Torsemide is preferred over furosemide due to its superior bioavailability and longer duration of action, particularly since these patients have issues with gut edema and GI absorption. Due to dependence of the cardiac output on heart rate and the tendency for orthostatic hypotension, traditional neurohormonal antagonists including beta blockers and angiotensin-converting enzyme inhibitors are neither effective nor well tolerated.[60] However, in patients with atrial fibrillation,

TABLE 2
Amyloid-specific pharmacotherapies

<table>
<tr><th colspan="3">AL</th><th colspan="3">ATTR</th></tr>
<tr><td rowspan="6">Anti-plasma cell therapies</td><td rowspan="2">Alkylating agents</td><td>Melphalan</td><td rowspan="2">TTR silencers</td><td>siRNA</td><td>Patisiran</td></tr>
<tr><td>Cyclophosphamide</td><td>ASO</td><td>Inotersen (IONIS-TTR$_{Rx}$)</td></tr>
<tr><td rowspan="2">Proteasome inhibitors</td><td>Bortezomib</td><td rowspan="4">TTR stabilizers</td><td colspan="2">Diflunisal</td></tr>
<tr><td>Ixazomib</td><td colspan="2">Tafamidis</td></tr>
<tr><td>Immunomodulators</td><td>Pomalidomide</td><td colspan="2">Tolcapone</td></tr>
<tr><td>Anti-CD38 monoclonal antibody</td><td>Daratumumab</td><td colspan="2">AG10</td></tr>
<tr><td rowspan="2">Anti-amyloid antibody</td><td colspan="2" rowspan="2">NEOD001</td><td rowspan="4">Fibril disruptors</td><td colspan="2">Doxycycline + TUDCA</td></tr>
<tr><td colspan="2">Green tea extract</td></tr>
<tr><td colspan="2">Curcumin</td></tr>
<tr><td colspan="2">Anti-amyloid antibody</td><td>PRX004</td></tr>
<tr><td colspan="6">Ubiquitous Anti-Amyloid Fibril Antibody</td></tr>
<tr><td colspan="6">Monoclonal IgG1 anti-SAP antibody</td></tr>
</table>

AL = immunoglobulin (Ig) light chain amyloidosis; ASO = antisense oligonucleotide; ATTR = transthyretin amyloidosis; SAP = serum amyloid P component; siRNA = small interfering RNA; TTR = transthyretin protein; TUDCA = tauroursodeoxycholic acid

beta blockers may need to be used for rate control. Nondihydropyridine calcium channel blockers bind avidly to amyloid fibrils and are contraindicated due to risk of profound hypotension and syncope.[30,31,34,44,45] Digoxin is usually avoided in CA due to concerns of increased risk of toxicity; however, it may be used with caution for rate control in atrial fibrillation given its lack of negative inotropy.[61] Maintenance of normal sinus rhythm is preferable due to the importance of atrial contribution to cardiac output.

Anticoagulation in patients with atrial fibrillation and even in patients with normal sinus rhythm and poor atrial function is important due to the high risk of thromboembolic complications.[62] Pacemakers are indicated for heart block or symptomatic bradycardia.[63] The role of intracardiac defibrillators is controversial, but may be warranted in selected patients with AL-CA.[64,65]

AL treatment

Risk stratification and prognostication for AL. The most important determinant of clinical outcome in AL is the extent of cardiac involvement, as congestive heart failure and sudden cardiac death are the most common causes of death. The level of NT-proBNP and the level of either troponin T or troponin I have strong prognostic value and form the basis for the staging system in AL. Various iterations have evolved over the years, but the most widely adopted is the 4-stage system developed and validated by Mayo Clinic. This system uses a cutoff value at diagnosis for NT-proBNP greater than 1,800 ng/mL, troponin T greater than 0.025 µg/L, and the difference between kappa and lambda free light chain levels greater than 180 mg/L. Stage level increases by the number of cutoff values exceeded, with stage IV carrying a median survival of 6 months.[47] Additionally, the troponin T level can help risk-stratify patients being considered for autologous stem cell transplant. In a retrospective study, troponin T greater than 0.06 µg/L was associated with increased mortality following stem cell transplant.[66] Ultimately, prognosis in AL-CA is related to the hematologic response to chemotherapy.

Current treatment strategies for AL. The survival of patients with AL has improved over the years with the advent of more effective chemotherapeutic regimens that kill the underlying plasma cell clone producing the unstable light chains. The goal of treatment is to achieve a complete hematologic response with normalization of the affected light chain and

sFLC ratio as well as elimination of the M protein on immunofixation.

The development of the proteasome inhibitor bortezomib has improved efficacy and survival in AL causing a faster and more complete hematologic response than prior regimens.[43,67,68]

The most commonly used first-line treatment consists of a 3-drug combination with the alkylating agent cyclophosphamide, the proteasome inhibitor bortezomib, and the steroid dexamethasone, which is given weekly.[43] A retrospective study by Sperry et al[8] showed that patients receiving an alkylating agent, bortezomib, and a steroid had the best outcomes compared with other regimens.

For patients with refractory or relapsed disease, the CD38 monoclonal antibody daratumumab can be used if patients meet myeloma criteria and has been found to be effective thus far.[68,69] Newer proteasome inhibitors such as ixazomib, which is taken orally, are being studied in alternative combination regimens.[70] High-dose chemotherapy with autologous stem cell transplant can be considered in patients with an acceptable cardiac risk profile and may offer more complete and durable remission than chemotherapy, although this is controversial.[43,71]

The cardiologist's role in AL-CA. The hematologist directs the chemotherapy for AL but works closely with the cardiologist when there is cardiac involvement. The main role of the cardiologist is to manage volume status with diuretics, monitor for arrhythmia, and evaluate the cardiac response to treatment.[43,71] Cardiac response was traditionally measured by echocardiographic changes of wall thickness, diastolic function, and ejection fraction, as well as changes in New York Heart Association (NYHA) functional class.[67] However, it is uncommon to see reduction in LV wall thickness or significant improvement in ejection fraction and if it does occur, it is a slow process that usually takes more than 1 year. With the advent of longitudinal myocardial strain imaging, improvements in strain can be seen despite the lack of structural changes on echocardiogram.[72] In 2012, consensus criteria defined a cardiac response as a greater than 30% reduction in NT-proBNP.[73] Misfolded light chains are toxic to cardiomyocytes by causing increased oxidative stress and impairing contractility. Thus, reduction in light chain levels can lead to clinical improvement and significant reductions in NT-proBNP without changing amyloid fibril burden in the heart.

Heart transplant for patients with AL-CA. For patients who have a good hematologic response to initial chemotherapy but have limited predicted survival due to severe heart failure, heart transplant followed by autologous stem cell transplant, is a treatment strategy that can be considered. The patient must have clinically isolated severe cardiac disease, minimal amyloid burden in other organs, and a plasma cell clone that is responsive to therapy. Initial reports of heart transplant showed poor survival rates due to recurrent amyloid in the transplanted heart and progressive amyloid deposition in other organs. However, due to improved anti-plasma-cell-directed therapy and refinement in patient selection, outcomes have improved. Contemporary series of patients undergoing heart transplant followed by stem cell transplant showed that outcomes are almost comparable to heart transplant for other indications, with a 5-year survival rate of approximately 65%.[74]

Future therapies for AL. There is an AL amyloid-directed monoclonal antibody designed to remove amyloid fibrils from affected organs and is currently undergoing clinical trials. NEOD001, a humanized murine monoclonal antibody that targets an epitope exposed during light chain misfolding, binds to the light chain amyloid fibril and signals an immune response to clear the deposits. This agent has completed phase 1 and 2 clinical trials of 27 patients previously treated with at least 1 plasma cell-directed therapy. It showed good tolerability and achieved both renal and cardiac responses in most patients.[75]

A phase 2b clinical trial (NCT02632786) of patients with AL with a previous hematologic response to treatment and persistent heart dysfunction is underway and expected to be completed in January 2018. A phase 3 clinical trial (NCT02312206) of NEOD001 as an adjunct to chemotherapy is also ongoing and results are expected in February 2019.

ATTR treatment

Liver transplant for ATTRm amyloidosis for the V30M mutation that causes FAP was first described in 1990, but it has not been well validated in other mutations and is not a solution for ATTRwt.[76] Significant progress has been made over the past 2 decades in the understanding of the pathophysiologyy of ATTR, paving the way for promising advancements in pharmacotherapy. Presently, there are 3 classes of pharmacologic agents, grouped by the point of disease process each strategy targets:

- Block TTR synthesis at the translational level in hepatocytes
- Stabilize the TTR tetramer to inhibit the rate-determining step of amyloidogenesis
- Disrupt and clear the ATTR amyloid fibril.[77]

Block TTR synthesis. TTR messenger RNA (mRNA) can be targeted by "silencers" preventing translation, thereby reducing the production TTR protein by hepatocytes. The resultant sustained reduction of plasma TTR should decrease or halt amyloid deposition by making less TTR available to dissociate and deposit in the heart and nerves. There are 2 approaches to silencing TTR mRNA translation: small interfering RNA (siRNA) and antisense oligonucleotide (ASO).[77]

An siRNA, packaged in a lipid nanoparticle to ensure delivery to the liver, has been designed to bind to a conserved region of TTR mRNA, degrading the mRNA and reducing TTR protein expression. One siRNA, patisiran, completed the phase 3 APOLLO clinical trial (NCT01960348) in August 2017. It is an intravenous medication that requires premedication. The APOLLO trial studied patients with neuropathic variants of ATTRm, with a primary end point of neuropathy progression over 18 months. Patisrian met the primary end point and will likely be approved by the US Food and Drug Administration (FDA) by the third quarter of 2018. Given its target of a conserved 3' untranslated region of TTR mRNA, patisiran should theoretically yield benefits not just in FAP but to both ATTRm-CA and ATTRwt-CA.[68,77]

ASOs are single-stranded oligonucleotides, typically 20 nucleotides in length, that bind to mRNA and elicit enzymatic mRNA degradation and reduced protein expression. Inotersen (IONIS-TTR_{Rx}) is an ASO drug that targets a conserved region of TTR mRNA. Inotersen is administered by weekly subcutaneous injection. A phase 2/3 clinical trial (NCT01737398) completed in October 2017 studied the drug's efficacy in treating FAP, with a primary end point of neuropathy progression over 65 weeks. It met the primary end point and a subset of patients actually improved. Like patisiran, inotersen is likely to be approved by the FDA for a neuropathy indication by the third quarter of 2018 and may benefit patients with ATTRm-CA and ATTRwt-CA. More studies are needed in the ATTR cardiac population.[68,77]

Stabilize the TTR tetramer. The TTR tetramer has 2 thyroxine binding pockets that stabilize the structure when bound preventing dissociation. Dissociation of the tetramer, the rate limiting step for ATTR fibrillogenesis, can be reduced using pharmacologic agents that bind to the thyroxine binding pockets. Both new and repurposed agents have been found to stabilize the TTR tetramer, including diflunisal, tafamidis, tolcapone, and AG10.[68,77]

Diflunisal (Dolobid) is a nonacetylated salicylate nonsteroidal anti-inflammatory drug used for over 3 decades to treat arthritis and musculoskeletal pain. Unrelated to its anti-inflammatory properties, it interacts with TTR's thyroxine binding pocket to increase the stability of the tetramer. A 2013 randomized, placebo-controlled, international multicenter trial of 130 patients with FAP demonstrated a statistically significant slowing of polyneuropathy progression; however, 67 patients (diflunisal n = 27, placebo n = 40) did not complete the study.[78] A small study revealed diflunisal to be reasonably well-tolerated in ATTR-CA, and to date it is the only readily available pharmacotherapy for ATTR supported by a randomized, placebo-controlled trial.[79,80] Diflunisal may be considered for off-label use in patients with ATTR-CA with relatively preserved kidney function and no increased bleeding risk, taken under the supervision of a cardiologist who will monitor for fluid retention and changes in renal function.[77]

Tafamidis (Vyndaqel), like diflunisal, interacts with TTR's thyroxine binding pocket and increases tetrameric stability. A phase 2 open-label clinical trial studied the efficacy and tolerance of tafamidis in 31 patients with ATTRwt and NYHA functional class 1 and 2 followed for 1 year. Twenty-eight patients completed the study and 2 patients died. TTR stabilization at 6 weeks was achieved in 30 of 31 patients (96.8%), and success at 1 year in 25 of 28 patients (89.3%). No clinical progression occurred in 16 of 31 patients (51.5%), and tafamidis was generally well-tolerated, with diarrhea the most common side effect in 7 of 31 patients (22.6%).[81,82]

A phase 3 clinical trial (NCT01994889) is studying tafamidis vs placebo in patients with ATTRm-CA or ATTRwt-CA (excluding NYHA functional class 4) with the primary outcome measure of all-cause mortality and heart failure-related hospitalizations over 30 months. This is a large trial that enrolled 446 patients and data collection is expected to be completed in February 2018.

Tolcapone, approved by the FDA for Parkinson disease, has been found to be a potent TTR stabilizer by binding both thyroxine binding pockets of the TTR tetramer simultaneously. However, tolcapone has an FDA "black box" warning due to the risk of potentially fatal acute fulminant liver failure and is not currently used in ATTR therapy.[68] Nonetheless, it will likely undergo further study for ATTR.

Recruiting is underway for a phase 1 clinical trial of AG10, a potent selective TTR stabilizer (NCT03294707).[68]

Disruption and clearance of the ATTR amyloid

fibril. Even though treatment directed at blocking TTR synthesis or stabilizing the tetramer may be effective at preventing further deposition, the residual amyloid deposits persist and continue to affect organ function. With that need in mind, several agents that disrupt the amyloid formation process further downstream have been evaluated at a basic science level and in a few small nonrandomized open-label studies.[77]

Doxycycline is a tetracycline antibiotic with demonstrated effectiveness in disrupting mature amyloid fibrils in mouse models.[83] Tauroursodeoxycholic acid is a bile acid with the ability to disrupt prefibrillar amyloid components. This combination has been studied in patients with ATTR-CA in 2 small open-label trials, with only 1 having results published. There was no progression in NT-proBNP or wall thickness in a cohort of 7 patients who completed 12 months of treatment.[84] These data are nonrandomized and hypothesis-generating, as adequate studies would need to be performed to evaluate this hypothesis further. Because there are currently no FDA-approved therapies for ATTR, patients may be offered this combination fully informed that the data are limited. (Note: ursodiol is substituted for tauroursodeoxycholic acid, which is not available in the United States.)[68]

Green tea extract contains the polyphenol epigallocatechin-3-gallate, which has shown the ability for fibril disruption as well as TTR stabilization, importantly using a binding site separate from the thyroxine binding pocket (utilized in diflunisal and tafamidis). A small open-label study of 19 patients with ATTR-CA of whom 14 took green tea extract for 1 year reported a reduction in intraventricular septal wall thickness at 1 year, and in 9 patients a reduction of 12.5% in LV mass measured by cardiac MRI.[85]

Curcumin, the active ingredient in the household spice turmeric, has displayed in vitro promise as a TTR stabilizer by binding to the thyroxine binding pocket, and as an amyloid fibril disruptor by increasing macrophage degradation activity. Although there have only been preliminary animal studies, this supplement may be promising for further study in humans with ATTR-CA.[68]

PRX004 is a synthetic antibody designed to bind to non-native misfolded forms of TTR with the goal of potentially preventing deposition and promoting clearance of TTR aggregates.[86] A phase 1 open-label escalation trial (NCT03336580) in 36 patients with ATTRm is planned and, hopefully, will pave the way for further study.

Heart transplant for patients with ATTR-CA. Patients with ATTRwt-CA who are young enough to undergo heart transplant have displayed favorable outcomes given that it causes clinically isolated heart disease and is an indolent process that should not affect the transplanted heart over the average life span of the allograft. Patients with the ATTRm mutation V122I have been treated with heart transplant alone, with the thought process that again, due to the indolent nature of amyloid deposition, concomitant liver transplant may not be needed.[74] Thus far, 6 patients with this mutation have undergone successful transplant at our institution with heart alone, 1 of whom is 9 years posttransplant without any recurrent amyloid in the allograft. Patients with the T60A mutation that causes both polyneuropathy and cardiomyopathy require combined heart and liver transplant.[74]

Are there other therapies being studied to clear amyloid deposits and reverse organ dysfunction?

Extracellular deposits of amyloid fibrils, regardless of precursor protein, contain common elements such as calcium, glycosaminoglycans, and an SAP component. SAP stabilizes amyloid fibrils and makes them resistant to degradation. A monoclonal immunoglobulin G1 anti-SAP antibody has been designed to target the ubiquitous SAP component, signaling an immune response that leads to macrophage mediated clearance of amyloid fibrils, regardless of the type. Treatment with this approach was studied in a pilot trial of 16 patients mostly with AL, and within a 6-week period some of the patients had dramatic reversal of liver amyloid deposition.[2] This has paved the way for a phase 2 open-label trial to be performed in patients with AL-CA and ATTR-CA (NCT03044353) and plans for a randomized phase 3 trial in CA are in discussion. There is optimism that this therapy may achieve the holy grail of removing amyloid rather than just preventing further deposition.

CONCLUSION

The diagnosis of CA requires a high index of suspicion. The diagnostic tools have improved due to the availability of modern imaging techniques, and the advent of measuring the sFLC assay along with immunofixation of the serum and urine. The prognosis for patients with AL-CA used to be dismal, with very poor survival rates. The current treatment strategies that include proteasome inhibitors have significantly improved survival, emphasizing the importance of early diagnosis and prompt initiation of therapy. Monoclonal antibodies against plasma cells (daratumumab) and light chain amyloid deposits (NEOD001) have the potential to further improve

outcomes. The diagnosis of ATTR-CA used to be a futile academic pursuit given the lack of available therapies. However, there are several new FDA-approved agents on the horizon, including *TTR* gene silencers and stabilizers. CA is no longer considered to be rare and hopeless. Rather, it is more common than previously recognized and even more treatable.

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Management of coronary chronic total occlusion

ABSTRACT

Percutaneous coronary intervention (PCI) for coronary artery chronic total occlusion (CTO) is an important treatment to be used in conjunction with non-CTO PCI, coronary artery bypass grafting, and optimal medical therapy to achieve complete revascularization in patients with coronary artery disease.

KEY POINTS

Coronary CTO is not benign and is associated with ischemic burden.

There is a threshold of ischemic burden at which revascularization is superior to optimal medical therapy.

Revascularization based on physiology rather than angiography can produce superior clinical results.

CTO PCI procedures are technically demanding and heavily operator-dependent in order to achieve high success rates at an acceptably low complication rate.

In patients with stable coronary artery disease (CAD), the cornerstone of treatment is medical management to control symptoms such as angina and dyspnea on exertion. But in a select group of patients, percutaneous coronary intervention (PCI) is indicated in addition to medical management. Invasive and noninvasive hemodynamic assessments of coronary artery stenosis in conjunction with anatomic considerations play a role in decision-making and in advising patients on revascularization vs medical management. However, in the case of coronary artery chronic total occlusion (CTO), the decision-making process remains challenging due to limited evidence supporting clinical efficacy of CTO PCI, as well as practical considerations including lower success rates and higher complication rates in comparison with patent-vessel PCI.

CLINICAL VIGNETTE

A 42-year-old man, an avid runner with hyperlipidemia and a strong family history of premature CAD, presents with several months of declining exercise tolerance. His physical examination and electrocardiogram are unremarkable. Myocardial perfusion imaging shows stress-induced ischemia affecting about 20% of the inferolateral myocardium. He is then referred for coronary angiography.

Confidence in the appropriate treatment strategy is highly dependent on potential angiographic findings. All 3 of the following coronary angiograms could explain our patient's clinical presentation (**Figure 1**):

- Panel A: Discrete, high-grade stenosis of the mid-right coronary artery
- Panel B: Diffuse, multivessel disease involving the distal right coronary artery (B1) and the proximal left circumflex coronary artery (B2)
- Panel C: Total occlusion of the proximal right coronary artery with extensive left-to-right collaterals.

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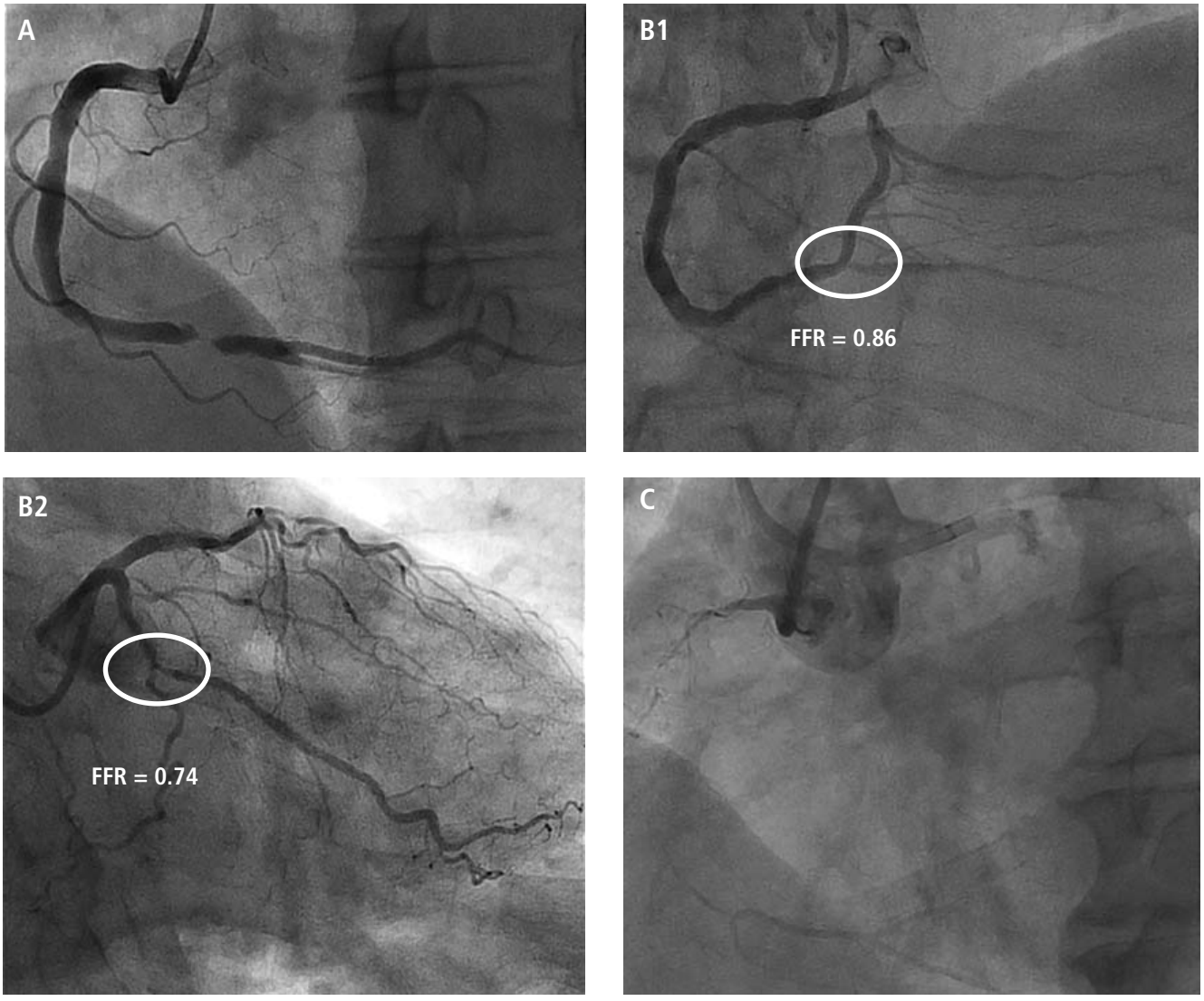

Figure 1. Results of angiography. (A) Discrete, high-grade mid-right coronary artery stenosis corresponds to abnormal stress test results and is appropriate for coronary intervention to treat the patient's symptoms. (B) Diffuse multivessel disease involves the distal right coronary artery (B1) as well as the proximal left circumflex coronary artery (B2). Based on fractional flow reserve (FFR), the left circumflex coronary artery lesion is hemodynamically significant and is thus an appropriate target for coronary intervention. Conversely, the right coronary artery lesion is not hemodynamically significant and can be managed medically. (C) Angiography shows total occlusion of the proximal right coronary artery with extensive left-to-right collaterals provided by the left coronary artery.

Treatment based on angiographic findings

In panel A, there is little to debate. The patient is likely to benefit from percutaneous revascularization of the right coronary artery to treat symptoms.

In panels B1 and B2, there is abundant evidence that the hemodynamic assessment of stenosis is superior to a visual estimate in directing PCI.[1,2] Hemodynamic assessments including fractional flow reserve (FFR) inform the risk-benefit analysis of percutaneous vs medical treatment of coronary stenosis. In the case of FFR, 0.8 represents an inflection point. The lower FFR values are below 0.8, the greater the benefit of PCI as opposed to medical therapy. Conversely, the greater FFR values are above 0.8, the greater the benefit of medical therapy as opposed to PCI.

However, in panel C, there is significant variability in the data supporting the best treatment strategy for symptomatic patients with CTO.

CORONARY CTO

Coronary CTO is defined as TIMI 0 flow for more than 3 months in an epicardial coronary artery. CTO

is not uncommon, seen on 30% of routine coronary angiograms. In the United States, attempt rates of PCI for CTO remain low and have been static at around 12.4%, representing less than 5% of total PCI volume.[3] In addition, success rates of CTO PCI are disappointingly low at 59% compared with success rates of patent-vessel PCI at 96%.[3] The most frequently cited barriers to CTO PCI are incomplete evidence for efficacy and concerns about safety. Because of the ongoing controversy about the risks and benefits of CTO PCI, it remains a class IIa indication in current American and European practice guidelines.[4,5] In addition, these procedures remain technically challenging, and thus variability in local expertise can influence the decision to manage patients medically or refer for CTO PCI.

Patients are often advised that CTO is benign. However, the myocardium affected by a CTO is ischemic. Collateral vessels do not provide adequate flow reserve. FFR data collected from CTOs that were successfully crossed and subsequently interrogated with a pressure wire prior to stenting show that the myocardium supplied by the reconstituted distal bed remains ischemic. This ischemic burden appears to be independent of the size and quality of collaterals.[6,7] In addition, a moderate stenosis in a donor coronary artery supplying collateral vessels to a CTO may result in an ischemic FFR as a consequence of coronary "steal" from the donor artery to the collateral vessels. The ischemic FFR in the donor artery can be corrected by treating the recipient CTO vessel.[8]

Similar to FFR, noninvasive assessment using myocardial perfusion imaging can define ischemic burden and a threshold for benefit of percutaneous vs medical management of CAD. Ischemia greater than 10% on myocardial perfusion imaging is associated with a high risk of major adverse cardiac events (MACE).[9] Similar findings were noted in the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial nuclear substudy, which showed superior reduction in angina and MACE in patients with greater than 10% ischemia on myocardial perfusion imaging treated with PCI vs medical therapy.[10] In the case of coronary CTO, ischemia greater than 12.5% is predictive of significant improvement in symptoms after intervention.[11]

PROGNOSIS AND DISEASE BURDEN

CTO is associated with adverse prognosis, implying the importance of incomplete revascularization. The Synergy Between Percutaneous Coronary Intervention With Taxus and Cardiac Surgery (SYNTAX) trial used a scoring system to direct surgical vs percutaneous revascularization strategies in patients with complex or multivessel CAD. A post hoc analysis of the SYNTAX trial showed that incomplete revascularization was associated with significantly higher rates of 4-year mortality and MACE.[12] This was likely from the ischemic burden remaining from incomplete revascularization. The presence of CTO was the strongest independent predictor of incomplete revascularization in the SYNTAX PCI arm. Similarly, the negative prognostic impact of having a CTO has been observed in a large population of patients followed prospectively after undergoing coronary angiography.[13] Furthermore, the presence of CTO in a non-infarct-related artery at the time of ST-elevation myocardial infarction appears to be an independent predictor of death at 30 days, with a persistent negative prognostic impact lasting for up to 36 months of follow-up.[14]

CLINICAL BENEFITS OF CTO PCI

In patients with significant ischemic burden, CTO PCI has multiple clinical benefits. Symptomatic relief based on the Seattle Angina Questionnaire appears to be similar to that obtained with coronary artery bypass grafting (CABG) at 1-month follow up.[15] Successful CTO PCI can have a positive impact on the risk of mortality in prospective[13] and retrospective observational studies.[16]

CTO intervention may also have beneficial effects on left ventricular systolic function in patients with viable myocardium in the corresponding coronary territory.[17] This improvement in systolic function appears to be sustained at 3 years of follow-up.[18] Meta-analysis of observational data in symptomatic and ischemic patients who underwent successful CTO PCI shows reduced rates of all-cause mortality and MACE and a reduced need for subsequent CABG.[19] This is in contrast to the frequently cited Occluded Artery Trial (OAT) trial, which showed no clinical benefit of PCI for a subacutely occluded infarct-related artery.[20]

An algorithimic approach to assessing the need for and the method of coronary revascularization is provided in **Figure 2**.

EVIDENCE-BASED BENEFITS

Evidence of the merits of CTO PCI from randomized clinical trials is mixed. The only published study to date, the Evaluating Xience and Left Ventricular Function in Percutaneous Coronary Intervention on Occlusions After ST-Segment Elevation (EXPLORE) trial, showed no difference in left ventricular systolic function 4 months after ST-elevation myocardial infarction in patients undergoing staged CTO PCI of a non-infarct-related artery vs optimal medical ther-

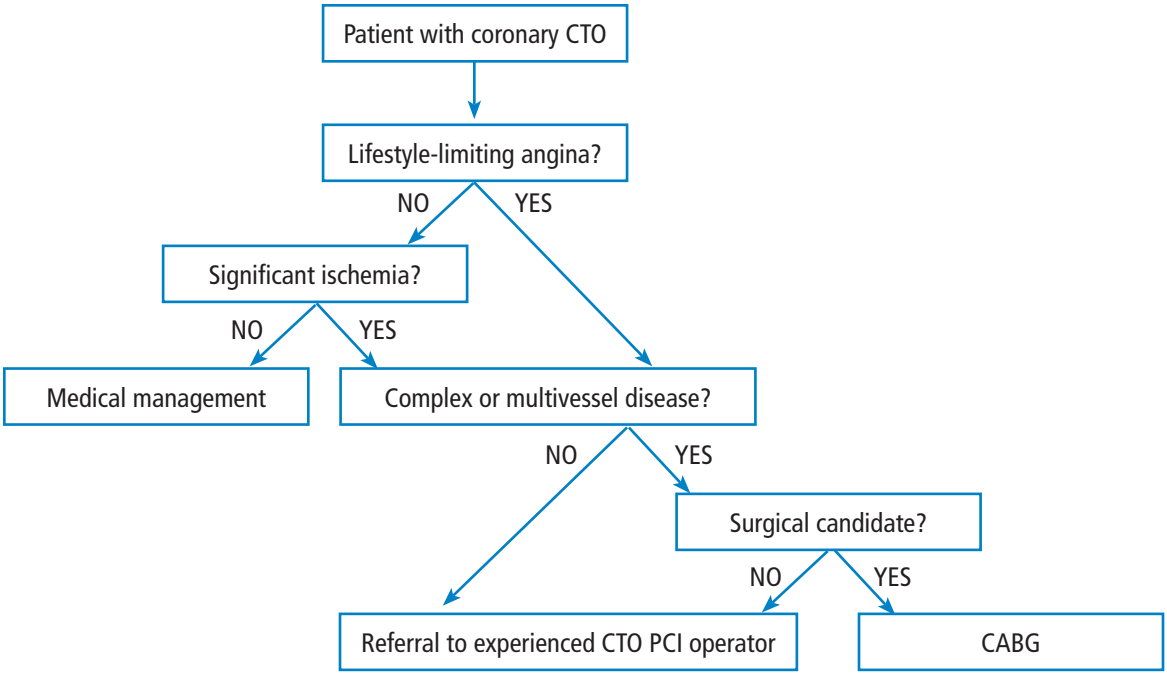

Figure 2. An algorithmic approach to determining the need for and the method of coronary revascularization in patients with coronary chronic total occlusion (CTO). Coronary artery bypass grafting (CABG) is preferable to percutaneous coronary intervention (PCI) in patients with complex or multivessel disease, whereas PCI is a reasonable option in patients with anatomically simple or single-vessel disease. Deciding on the appropriate treatment requires consultation with a surgeon and an interventionalist experienced in CTO PCI. Dual-injection angiography may be required to determine the technical feasibility of CTO PCI.

apy.[21] Two larger trials presented at scientific meetings in 2017 remain unpublished. One trial showed noninferiority of optimal medical therapy vs successful CTO PCI in reducing the composite end point of all-cause mortality, myocardial infarction, stroke, and repeat revascularization; the other trial showed significant improvement in quality of life measures using the Seattle Angina Questionnaire score and Canadian Cardiovascular Society angina classification in patients who underwent successful CTO PCI compared with medical management.

High-volume CTO PCI centers now report procedural success rates as high as 92.9%[22] and a correlation between the CTO PCI volume and CTO PCI success rates.[3] The dramatic improvement in success rates achieved by high-volume operators globally can be attributed to a combination of operator experience, improved technology, and widespread adoption of the hybrid algorithm, which has helped to improve efficiency and standardize treatment in CTO PCI based on angiographic criteria.[23] CTO PCI remains a highly specialized procedure, unique from patent-vessel PCI and with little correlation between total PCI volume and CTO PCI success rate. Despite recent advances, CTO PCI success remains heavily dependent on operator expertises, with a steep and long learning curve. In addition, the unique technical aspects of CTO PCI such as a retrograde and subintimal guidewire tracking that have accelerated procedural success are associated with higher rates of MACE compared with traditional antegrade and intraluminal guidewire tracking.[24,25] Therefore, CTO PCI requires unique considerations beyond standard PCI in terms of potential complications. Uncommon but potentially life-threatening complications such as donor artery thrombosis, collateral vessel trauma, gear entrapment, and radiation skin injury demand a specialized informed consent process for the patient.[26]

In light of incomplete evidence based on extensive observational data and limited randomized clinical trials, the decision to refer patients for CTO PCI requires a comprehensive clinical evaluation. We know from data derived from patients with patent but stenotic coronary arteries that physiologically rather than angiographically driven decisions to revascularize can produce superior clinical results. There is an ischemic burden threshold beyond which revascular-

Continued on page 38

Continued from page 30

ization is superior to optimal medical therapy. In this context, we know that CTO is not benign and is associated with ischemic burden. Consequently, patients with symptoms related to CTO represent a subset of patients with incomplete revascularization.

CONCLUSION

Despite recent advances, CTO PCI procedures remain technically demanding, and success with a low complication rate is heavily dependent on operator expertise. Therefore, CTO PCI should be used judiciously in patients with angina refractory to optimal medical therapy. It is an important tool to be used in conjunction with non-CTO PCI, CABG, and optimal medical therapy to produce favorable outcomes in patients with CAD.

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Update on the management of venous thromboembolism

ABSTRACT

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism, is a common cardiovascular disease associated with significant morbidity ranging from painful leg swelling, chest pain, shortness of breath, and even death. Long-term complications include recurrent VTE, postpulmonary embolism syndrome, chronic thromboembolic pulmonary hypertension, and postthrombotic syndrome (PTS). Management of VTE requires immediate anticoagulation therapy based on a risk assessment for bleeding. Direct oral anticoagulants (DOACs) have become an important option for patients as reflected in the most recent American College of Chest Physician treatment guidelines.

KEY POINTS

VTE treatment should begin immediately with heparin, low-molecular-weight heparin (LMWH), fondaparinux, or the DOACs (rivaroxaban or apixaban) in patients deemed appropriate based on a risk assessment for bleeding.

For patients with VTE and no cancer, long-term treatment with dabigatran, rivaroxaban, apixaban, or edoxaban is recommended over the vitamin K antagonists (VKA).

LMWH is recommended for the long-term treatment of VTE in patients with cancer.

For extended-duration anticoagulation, the DOACs (dabigatran, rivaroxaban and apixaban) and the VKA antagonists are options.

Compression stockings are no longer recommended for prevention of PTS in patients with acute DVT but may be beneficial symptomatically.

Dr. Bartholomew reported consulting/advisory fees from Janssen Pharmaceuticals.
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Venous thromboembolism (VTE) includes both deep vein thrombosis (DVT) and pulmonary embolism (PE). Although the exact incidence of VTE is unknown, an estimated 1 million people in the United States are affected each year, with about a third experiencing a recurrence within 10 years.[1] VTE affects hospitalized and nonhospitalized patients, is often overlooked, and results in long-term complications including postthrombotic syndrome (PTS) for DVT, postpulmonary embolism syndrome and chronic thromboembolic pulmonary hypertension for PE, and death.[2]

TREATMENT

Treatment for VTE should be initiated in the following cases:

- Proximal DVT of the lower extremity
- Symptomatic distal (calf vein) DVT
- Symptomatic upper extremity DVT (axillary-subclavian veins)
- PE
- Subsegmental PE in a patient at risk for recurrence
- Surveillance for subsegmental PE in a patient with no proximal DVT and a low risk of recurrence.

Once VTE is suspected, anticoagulation should be started immediately unless there is a contraindication such as a risk of bleeding. A risk assessment should be performed in all patients before and during anticoagulation therapy (**Table 1**).

In addition to anticoagulants, other more aggressive therapies for VTE may be appropriate, such as systemic thrombolysis in the case of PE or catheter-directed thrombolytic or pharmacomechnical therapies for DVT or PE, surgical intervention (acute pulmonary embolectomy), or placement of an inferior vena cava (IVC) filter.

This article reviews the management of VTE, highlighting the recent changes in treatment and prevention guidelines from the American College of Chest Physicians (ACCP).[3]

TABLE 1
Risk factors for bleeding with anticoagulation therapy

Age older than 65
Anemia
Antiplatelet therapy
History of bleeding
Poor anticoagulant control
Alcohol abuse
Cancer
Diabetes
Liver failure
Frequent falls
Nonsteroidal anti-inflammatory drug use
Renal failure
Recent surgery
Previous stroke
Thrombocytopenia

Data from reference 3.

Risk of bleeding

In assessing a patient's risk of bleeding for anticoagulation therapy (**Table 1**), the absence of risk factors is considered low risk for bleeding, the presence of 1 risk factor is considered intermediate risk, and 2 or more risk factors is considered high risk. Compared with low-risk patients, moderate-risk patients have a twofold increased risk of major bleeding and high-risk patients have an eightfold increased risk of major bleeding. This equates to an annualized risk of major bleeding of 0.8% for low-risk patients, 1.6% for moderate-risk patients, and greater than 6.5% for high-risk patients.[3]

Anticoagulants

Anticoagulants are used in the acute (first 0 to 7 days), long-term (7 days to 3 months), and extended (3 months to indefinite) treatment phases of VTE.[4] Anticoagulation therapy options include unfractionated heparin (UFH), low-molecular-weight heparin (LMWH), fondaparinux, vitamin K antagonists (VKAs) (ie, warfarin), and direct oral anticoagulants (DOACs) (**Table 2**).

Deciding on which anticoagulant to use depends on the indication, the patient's underlying condition, the patient's preference, and the patient's risk of bleeding. Heparin, the LMWHs, fondaparinux and the DOACs (rivaroxaban and apixaban) are the only agents approved by the US Food and Drug Administration (FDA) recommended for the acute treatment phase, while the DOACs and warfarin are anticoagulation options for the long-term and extended treatment phases. The LMWHs should be used for the patient with cancer and during pregnancy.

Unfractionated heparin. UFH is administered parenterally and can be used for the prevention and treatment of VTE. Heparin remains an option for initial treatment of patients with acute VTE and is generally preferred over LMWH for patients who may require advanced therapies, such as for hemodynamically unstable PE or iliofemoral DVT. It is also recommended for patients with renal failure.[3] Weight-based dosing (80 U/kg bolus followed by 18 U/kg/hour intravenous infusion) is recommended, targeting an antifactor activated clotting factor (anti-Xa) assay level of 0.3 IU/mL to 0.7 IU/mL. Heparin may also be given subcutaneously in an outpatient setting using an initial bolus of 333 U/kg followed by a subcutaneous dose of 17,500 U twice daily.[5]

Low-molecular-weight heparin. LMWHs are administered as weight-based subcutaneous injections and have indications for patients with acute VTE and for VTE prophylaxis. LMWHs are used for transitioning to warfarin, dabigatran, or edoxaban for long-term anticoagulation and are recommended over warfarin and DOACs for treatment of VTE in patients with cancer and in pregnant women.[3]

Enoxaparin (Lovenox), the most commonly used agent in the United States, is given either as a once-daily injection (1.5 mg/kg/day) or a twice-daily injection (1 mg/kg every 12 hours). It is also approved for VTE prophylaxis in patients undergoing hip or knee replacement surgery or abdominal surgery, or in patients with severely restricted mobility during acute illness. LMWH can also be given in patients with renal insufficiency (creatinine clearance [CrCL] < 30 mL/minute) after dose adjustment. No monitoring is required, although it is advised in pediatric patients, pregnant women, obese patients, and patients with renal insufficiency. If monitoring is required, an anti-Xa assay using LMWH as a reference standard should be done 4 hours after subcutaneous injection. The therapeutic range for enoxaparin is 0.5 IU/mL to 1.0 IU/mL for the 12-hour regimen and greater than 1.0 IU/mL for the once-daily dose. Other LMWHs available in the United States include dalteparin (Fragmin) and tinzaparin (Innohep). Each has its own specific indications.

Fondaparinux. Fondaparinux is an indirect factor Xa inhibitor, chemically related to LMWH. It is approved

TABLE 2
Anticoagulation agents for patients with venous thromboembolism by treatment phase

Patient	Acute (0 to ~7 days)	Long-term (~7 days to ~3 months)	Extended (~3 months to indefinite)
Most patients	UFH, LMWH, fondaparinux or DOACs (rivaroxaban or apixaban)	DOACs (rivaroxaban, apixaban, dabigatran, or edoxaban) or VKA (warfarin)	• Use same anticoagulant used in long-term phase • If first or second VTE is unprovoked proximal DVT of the leg or PE with low or moderate bleeding risk
Renal failure (CrCL < 30 mL/min) or liver failure with coagulopathy	UFH	VKA (warfarin)	Warfarin
Hemodynamically unstable PE patient	UFH or LMWH	N/A	N/A
Pregnancy or cancer patient	UFH or LMWH	LMWH	LMWH
Once-daily dosing	Fondaparinux or LMWH at 1.5 mg/kg/day	VKA (warfarin), rivaroxaban (after 21 days) or edoxaban	VKA (warfarin), edoxaban, rivaroxaban
Recurrent VTE	N/A	If on a non-LMWH anticoagulant, convert to LMWH If on LMWH, increase the dose	If on a non-LMWH anticoagulant, convert to LMWH If on LMWH, increase the dose
Need for reversal agent	UFH LMWH (partially reversible)	VKA (warfarin) Dabigatran	Warfarin Dabigatran

CrCL = creatinine clearance; DOAC = direct oral anticoagulant; DVT = deep vein thrombosis; LMWH = low-molecular-weight heparin; N/A = not applicable; PE = pulmonary embolism; UFH = unfractionated heparin; VKA = vitamin K antagonist; VTE = venous thromboembolism

Data from references 3 and 4.

for treatment of patients with acute VTE when used in combination with a VKA (warfarin) or dabigatran or edoxaban. It also has approval for VTE prophylaxis in patients undergoing hip fracture, hip or knee replacement, and abdominal surgery. Fondaparinux is administered as a once-daily subcutaneous injection of 2.5 mg for DVT prophylaxis and a body weight-based dose for the treatment of VTE (5 mg < 50 kg; 7.5 mg 50 to 100 kg; 10 mg > 100 kg).[6] Fondaparinux is contraindicated in patients with severe renal impairment (CrCL les 30 mL/min) and bacterial endocarditis.[6]

Warfarin. Warfarin, a VKA, was the mainstay of therapy for long-term and extended treatment of VTE until the advent of the DOACs. Warfarin must be coadministered with heparin, LMWH, or fondaparinux initially and continued as overlap therapy for a minimum of 5 days until the international normalized ratio [INR] is at least 2.0 for 24 hours.[4] Early initiation of a VKA on the first day of parenteral therapy is advised.

Warfarin remains the best option for patients on long-term or extended anticoagulation with liver dysfunction (elevated serum transaminases exceeding twice the upper limits of normal or active liver disease) or renal disease (CrCL < 30 mL/min), as well as patients unable to afford DOACs. Additionally, select patient populations may still be best served by warfarin as these groups were underrepresented or not included in DOAC trials, including pediatric patients, individuals with body weight less than 50 kg or greater than 150 kg, and patients with select types of thrombophilia (eg, antiphospholipid syndrome). Warfarin is also advised for patients with poor compliance, as international normalized ratio of prothrombin time (PT/INR) monitoring is required using a point-of-care testing device or during a visit to an anticoagulation clinic. DOACs do not require monitoring, and noncompliance will not be readily apparent.

Direct oral anticoagulants. The DOACs, which include the factor Xa inhibitors rivaroxaban (Xarelto), apixaban (Eliquis), and edoxaban (Savaysa) and the direct thrombin inhibitor dabigatran (Pradaxa), been studied extensively and shown to be noninferior to VKAs for treatment of VTE.[7] DOACs are currently recommended by the ACCP for long-term treatment

of VTE, and several have extended treatment recommendations for VTE over the VKAs.[3]

The advantages of DOACs include no need for PT/INR monitoring, a fixed dosage, shorter half-life, rapid onset of action (for monotherapy), and in most cases, no need for bridging for interventional or surgical procedures. Additional advantages may include a decreased burden of care for the physician and improved quality of life for the patient. DOACs are also the agents of choice for patients who prefer oral therapy (avoiding parenteral therapy), have limited access to an anticoagulation clinic (home bound or geographic inaccessibility for PT/INR monitoring), or have food or drug-drug interactions. Patients at risk of gastrointestinal bleeding or dyspepsia should avoid dabigatran, while apixaban may be preferred if there is a history of gastrointestinal bleeding.[8]

Rivaroxaban or apixaban can be used as monotherapy for the initial treatment of VTE, while a 5-day course of heparin, LMWH, or fondaparinux is necessary with dabigatran or edoxaban. Rivaroxaban has been approved by the FDA for use in the prevention and treatment of VTE.[9,10] For VTE prophylaxis, rivaroxaban is given orally at 10 mg once daily for 35 days for patients undergoing total hip replacement surgery and for 12 days for patients undergoing knee replacement surgery. For the treatment of VTE, rivaroxaban is given orally at 15 mg twice a day for the initial 21 days of treatment, followed by once daily at 20 mg per day for long-term treatment. It is also approved for extended-duration therapy in both 10-mg and 20-mg doses. In a recently published randomized double-blind trial of rivaroxaban compared with aspirin, the risk of a recurrent event was lower with either dose of rivaroxaban compared with aspirin without an increase in bleeding.[11] Rivaroxaban is contraindicated in patients with renal insufficiency (CrCL < 30 mL/min). Both the 15-mg and 20-mg tablets must be taken with food.

Apixaban is also approved for monotherapy of VTE and was found to be noninferior to standard therapy of LMWH and warfarin with less bleeding.[12] Apixaban is used for VTE prophylaxis in patients undergoing hip or knee replacement surgery, given at 2.5 mg twice daily beginning 12 to 24 hours postoperatively for 35 days (hip) or 12 days (knee). The acute-phase dosage is 10 mg twice daily for 7 days followed by 5 mg twice daily for long-term treatment of VTE. The recommended dose should be reduced to 2.5 mg twice daily in patients that meet 2 of the following criteria: age 80 or older; body weight of 60 kg or less; or with a serum creatinine 1.5 mg/dL or greater. Apixaban is also approved for extended treatment of VTE. In a randomized, double-blind study of 2 doses (2.5 mg and 5 mg, twice daily) of apixaban compared with placebo, apixaban reduced the risk of recurrent VTE without increasing the risk of bleeding.[13]

Both dabigatran and edoxaban require an initial 5-day overlap with a parenteral anticoagulant.[14,15] Dabigatran is given at 150 mg orally twice daily if the CrCL is greater than 30 mL/min for the long-term treatment of VTE. Edoxaban is given orally at 60 mg once daily but reduced to 30 mg once daily if the CrCL is 30 mL/min to 50 mL/min, if body weight is 60 kg or less, or with use of certain P-glycoprotein inhibitors. Dabigatran has been evaluated in 2 double-blind, randomized controlled trials comparing the extended use of dabigatran with warfarin or placebo in patients with VTE.[16] Dabigatran carried a lower risk of major or clinically relevant bleeding than warfarin but a higher risk than placebo. Dabigatran was noninferior to warfarin but significantly reduced the rate of recurrence in the placebo group.[16]

The major side effect observed with all DOACs is bleeding, but they have been proven safer particularly in the terms of major bleeding compared with the standard heparin-LMWH-VKA regimen for treatment of VTE.[17–19] The risk of major bleeding, and in particular intracranial bleeding, has been shown to be less with DOACs compared with VKAs in 2 meta-analysis trials.[17,18] Of the 4 new DOACs, only dabigatran currently has an anticoagulant-reversing agent (idarucizumab), although an antidote for the other 3 agents is awaiting FDA approval.[20]

Subsegmental pulmonary embolism

There is debate as to the need for treatment of patients with subsegmental PE. The most recent guidelines advise clinical surveillance over anticoagulation for patients with a low risk for recurrent VTE and no evidence for a proximal DVT.[3] However, individuals who are hospitalized, have reduced mobility, have active cancer or are being treated with chemotherapy, or have a low cardiopulmonary reserve should be considered for anticoagulation unless they have a high bleeding risk.

Thrombolytic therapy

Thrombolytic therapy may be beneficial in select patients with VTE and can be delivered systemically or locally per catheter-directed therapy (CDT). Both routes carry an increased risk of hemorrhage compared with standard anticoagulation. The Catheter-Directed-Venous Thrombolysis (CaVenT) trial and Thrombus Obliteration by Rapid Percutaneous

Endovenous Intervention in Deep Venous Occlusion (TORPEDO) trial compared CDT with standard therapy.[21,22] In CaVEnT, CDT resulted in increased clinical benefit during the 5-year follow-up but did not result in improved quality of life.[21] In the TORPEDO trial, patients with proximal DVT receiving percutaneous endovenous intervention and anticoagulation compared with anticoagulation alone demonstrated superiority in the reduction of PTS at greater than 2 years.[22] Early results of the Acute Venous Thrombosis: Thrombus Removal With Adjunctive Catheter-directed Thrombolysis (ATTRACT) trial show that most patients with DVT did not have a long-term benefit from CDT, buy they did have reduced leg pain and swelling and some had reduced risk of moderate-to-severe PTS.[23]

The 2012 and 2016 ACCP guidelines advise anticoagulant therapy over CDT for patients with acute DVT of the leg but suggest patients who may benefit are those with iliofemoral DVT with symptoms for less than 14 days, good functional status, a life expectancy greater than 1 year, and a low risk of bleeding.[3,4] This is in contrast to the 2008 CHEST guidelines that recommended patients who have extensive proximal DVT, who have a high risk of limb gangrene, who are at low risk of bleeding, and who otherwise have good functional status be given CDT if the expertise and resources are available.[24] It has been suggested that CDT promotes early recanalization and minimizes the incidence of PTS.

Thrombolytic therapy for acute PE remains controversial because there is no clearly established short-term mortality benefit. In the Pulmonary Embolism Thrombolysis (PEITHO) trial, thrombolysis prevented hemodynamic decompensation but increased the risk of major hemorrhage and stroke.[25] A lower dose (50 mg) of thrombolytic therapy was studied in the Moderate Pulmonary Embolism Treated With Thrombolysis (MOPPET) trial and was found to be safe and effective in the treatment of moderate PE.[26]

CDT has also been shown to be effective in the treatment of PE. The Ultrasound Acceleration Thrombolysis of Pulmonary Embolism (ULTIMA) trial demonstrated that catheter-directed thrombolysis with ultrasonographic guidance in patients with acute intermediate-risk PE was superior in reversing right ventricular dilatation without an increase in bleeding complications compared with UFH.[27] The Ultrasound-Facilitated, Catheter-Directed, Low-Dose Fibrinolysis for Acute Massive and Submassive Pulmonary Embolism (SEATTLE II) study found that this approach decreased right ventricular dilation, decreased pulmonary hypertension, decreased anatomic burden, and minimized the risk of intracranial hemorrhage in patients with massive and submassive PE.[28]

Alteplase (Activase) is a recombinant tissue-type plasminogen activator approved by the FDA for treatment of acute PE. Alteplase is administered as a 100-mg infusion over 2 hours. Because of favorable outcomes with prompt recognition and anticoagulation for PE, the ACCP guidelines recommend systemic thrombolysis for hemodynamically unstable patients (systolic blood pressure < 90 mm Hg) with acute PE and a low risk of bleeding using a peripheral vein.[3] These guidelines also recommend thrombolysis for the patient whose condition deteriorates after starting anticoagulant therapy but who have yet to develop hypotension.

If the appropriate expertise is available, CDT is suggested for patients with acute PE if they have hypotension and a high bleeding risk, have failed systemic thrombolysis, or are in shock that is likely to cause death before systemic thrombolysis can take effect.[3] An area of ongoing debate is whether there is a benefit for thrombolytic therapy in patients with submassive PE who are hemodynamically stable but have evidence of right ventricular dysfunction on echocardiography or computed tomographic angiography. Bleeding remains the most serious complication of thrombolytic therapy.[4]

Surgical interventions: Pulmonary embolectomy and IVC filters

Pulmonary embolectomy. According to ACCP guidelines, surgical pulmonary embolectomy for the initial treatment of PE is reserved for patients with massive PE (documented angiographically, if possible), shock despite heparin and resuscitation efforts, and failure of thrombolytic therapy or a contraindication to its use.[4] To date, there have been no randomized trials evaluating this procedure. Pooled data published by Stein et al[29] reported a 20% operative mortality rate in patients undergoing pulmonary embolectomy between 1985 and 2005 compared with 32% in patients undergoing the procedure before 1985. A more recent retrospective review of 214 patients undergoing surgical embolectomy for massive and submassive PE reported an in-hospital mortality rate of 11.7%, with the highest death rate (32.1%) in patients who had a preoperative cardiac arrest.[30] The use of surgical embolectomy has also been reported in patients with intermediate-risk to high-risk conditions (defined as elevated biomarkers and evidence of right heart strain on computed tomographic angiography or echocardiography).[19]

TABLE 3
Clinical features associated with a high risk of recurrent venous thrombosis

	Evidence	Clinical relevance
Absence of a temporary risk condition	Strong	High
Pulmonary embolism or proximal deep vein thrombosis	Strong	High
More than 2 thrombotic events	Strong	Restricted, consider bleeding risk during prolonged anticoagulation
Male sex	Strong	High
Residual vein thrombosis	Strong	Low
Vena cava filter	Strong	High
Continued estrogen use	Strong	High
Cancer	Strong	High
Postthrombotic syndrome	Moderate	Moderate
Overweight	Weak	Low

IVC filters. Current guidelines recommend against routine use of IVC filters for patients with DVT or PE who are able to be treated with anticoagulants.[3] Absolute indications for the placement of IVC filters include a contraindication to anticoagulation, complications of anticoagulation, and recurrent thromboembolism despite adequate anticoagulant therapy.[4] Relative indications for IVC filters are massive PE, iliocaval DVT, free-floating proximal DVT, cardiac or pulmonary insufficiency, high risk of complications from anticoagulation (frequent falls, ataxia), and poor compliance.

Retrievable filters may be considered for situations in which anticoagulation is temporarily contraindicated or there is a short duration of PE risk.[31] The current consensus guidelines advise that indications for placing a retrievable IVC filter are the same as for placing a permanent device.[31] An IVC filter alone is not effective therapy for VTE, and resumption of anticoagulation is recommended as soon as possible after placement.

DURATION OF TREATMENT

The duration of treatment following the diagnosis of VTE depends on the individual patient's risk of recurrence. Patients with unprovoked VTE have a risk of recurrence reported to be between 25% and 30% at 5 to 10 years after their event.[32,33] Risk factors for recurrence include unprovoked or proximal DVT or PE, certain underlying hypercoagulable conditions such as the antiphospholipid syndrome, and underlying active malignancy. Additional risk factors that may predispose the patient to recurrent VTE include placement of an IVC filter, elevated D-dimer levels following discontinuation of anticoagulation, advanced age, male sex, increased body mass index, the presence of the PTS, and residual vein thrombosis (**Table 3**).[32] Although the risk of recurrence decreases with longer durations of anticoagulation, clinicians must weigh the risk of bleeding against the risk of new thrombosis.

Current guidelines recommend 3 months of anticoagulation (long-term) for patients with an episode of acute proximal or isolated distal DVT of the leg or PE resulting from surgery or a nonsurgical transient cause.[3] Patients who have the antiphospholipid syndrome, who are homozygous for factor V Leiden, or who are doubly heterozygous for factor V Leiden and prothrombin gene mutation should be considered for longer (extended) anticoagulation. Extended anticoagulation is also recommended in patients with active cancer and in patients who have unexplained recurrent VTE (**Table 2**).[3]

The duration of treatment for unprovoked VTE remains controversial. In the most recent ACCP guidelines, indefinite or extended anticoagulation is indicated for patients with a low or moderate risk of bleeding for a first (and second) unprovoked VTE.[4] Patients with a high risk of bleeding with a first (or second) unprovoked VTE that is a proximal DVT of the leg or PE be treated for 3 months.[3,4] Three DOACs (rivaroxaban, apixaban, and dabigatran) have extended-duration indications. The 2016 ACCP guidelines suggest aspirin over no treatment for the patient who has decided to stop anticoagulation therapy, although the guidelines do not consider aspirin a reasonable alternative to anticoagulation.[34,35] Use of markers such as residual venous obstruction and D-dimer level in conjunction with the DASH score have been studied in an effort to predict the risk of recurrence and thus the duration

of anticoagulation.[36,37] Residual venous obstruction appears to be less useful than the D-dimer level as an indicator for recurrence. The D-dimer used in conjunction with the DASH prediction score may help to calculate recurrence risk based on the following predictors: abnormal D-dimer 3 weeks after stopping anticoagulation, age under 50, male sex, and hormone use at the time of the VTE.[38] DASH score assessment may help physicians decide whether to continue anticoagulation therapy but it has not been shown to be helpful in men.[4] A more recent study confirmed the validity of the DASH score with better prediction in patients under age 65. The recurrence rate was higher in the older population, suggesting that this population should be considered for prolonged treatment if the bleeding risk is acceptable.[39] Other prediction tools include the Vienna prediction model and the clinical decision rule "Men continue and HER DOO2"—ie, HER = hyperpigmentation, edema, redness; DOO = D-dimer ≥ 250 µg/L, obesity body mass index ≥ 30 kg/m^2, old age (≥ 65); 2 = high risk if more than 2 of these factors.[40,41]

SCREENING AND PREVENTION

Nearly 60% of all VTE events occur in hospitals and nursing homes.[42] Yet anticoagulant prophylaxis is used in only 16% to 33% of at-risk hospitalized medical patients compared with 90% of at-risk hospitalized surgical patients.[43] Adequate prophylaxis can reduce the incidence of VTE as demonstrated in a meta-analysis involving 19,958 patients, which revealed a 64% reduction in relative risk (RR) of a fatal PE, 58% reduction in RR of a symptomic PE, and a 53% reduction in RR of a symptomatic DVT.[43]

The consequences of VTE include symptomatic DVT and PE, fatal PE, the cost of investigating symptomatic patients, the risk and cost of treatment (bleeding), PTS, and chronic thromboembolic pulmonary hypertension. Heparin, enoxaparin, and fondaparinux are approved agents for prophylactic but each agent has specific indications. Factor Xa inhibitors, rivaroxaban, and apixaban are approved for use in patients undergoing total knee or hip replacement. More recently, the factor Xa inhibitor, betrixaban, has been approved for VTE prophylaxis for up to 42 days in adult patients hospitalized for acute medical illness.[44] For patients with increased bleeding risk who are unable to receive pharmacologic prophylaxis, intermittent pneumatic compression devices or graduated compression stockings should be used.

Compression stockings

Current ACCP guidelines advise against routine use of compression stockings to prevent PTS in patients who have had a DVT.[3] While current evidence suggests compression stockings do not prevent PTS, they reduce symptoms of acute or chronic DVT for some patients.

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Cardiac implantable electronic device infection

ABSTRACT

Increasing numbers of patients with cardiac disease have improved quality of life and longevity as a result of cardiac implantable electronic devices (CIEDs). CIED infections can involve the generator pocket, bloodstream, or cardiac structures and occur in about 0.5% of de novo CIED implants and approximately 2% of CIED replacements. Prompt diagnosis of CIED infection is beneficial to the success of antibiotic therapy and subsequent device removal to resolve the infection. Measures to prevent CIED infections include assessment of the indication and patient status, strict sterile surgical techniques, preoperative antibiotics, and adequate homeostasis. New surgical methods and CIED devices may also lead to reduction in CIED infections. Further research is needed to better quantify the incidence of CIED, risk factors, and efficacy of surgical techniques to prevent infections.

KEY POINTS

CIED use is increasing, as are the number of CIED infections, which are associated with significant morbidity and mortality.

Prompt diagnosis of CIED infection allows for early management with antibiotics and device removal, which is typically needed for resolution of the infection.

Prevention of CIED infection is an important strategy, and more research is needed to inform the incidence of CIED infection, risk factors, and devices and techniques to minimize the risk of infection.

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Cardiac implantable electronic devices (CIEDs) have become common tools to improve the quality of life and longevity of patients with cardiac disease over the last few decades.[1–4] CIEDs include implantable cardioverter defibrillators (ICDs), permanent pacemakers, biventricular pacemakers providing cardiac resynchronization therapy with or without a defibrillator, subcutaneous ICDs, and implantable loop recorders. With increasing approved indications, the number of CIEDs implanted each year continues to grow. This, paired with the aging population of patients receiving devices and their medical complexity, has led to a corresponding increase in device-related complications.[2,3] One of the most serious complications is CIED infection, which leads to significant morbidity and death. These infections also represent a significant cost burden to the healthcare system, with treatment costs for a CIED infection estimated at over $146,000 in 2008.[5]

SCOPE OF THE PROBLEM

More than half a million permanent pacemakers and ICDs are implanted each year in the United States, with more than 4 million implanted between 1993 and 2008.[5] The risk of infection is 0.5% to 1%, for a first-time implantation and 1% to 5% for a device replacement or upgrade.[1,2,5–9] These infections can involve the generator pocket, bloodstream, or cardiac structures, leading to infective endocarditis.[10] The timing of CIED infection appears to be bimodal in distribution: early infections usually occur as a result of the implantation procedure itself, whereas late infections occur in patients who are generally unwell or because of an insidious process that eventually crosses a threshold of clinical significance.[3,11,12]

Incidence and risk factors

Klug et al[13] investigated the incidence rate and risk factors of CIED infection prospectively in a large cohort of patients from 44 centers who underwent CIED implantation. Of 6,319 procedures, 4,465 were first implants and the other 1,854 were a replacement or revision; 42 patients (0.68%) developed CIED

TABLE 1
Pathogens identified in 816 patients with lead extraction or device removal for CIED infection

Pathogen	%	Pathogen	%
MRCoNS	18.8	Streptococci	2.5
MSCoNS	18.8	VSE	2.8
MSSA	15.8	VRE	1.4
MRSA	15	Anaerobes	1.6
Negative culture	13.2	Fungal	0.9
Gram negative	8.9	Mycobacteria	0.2

CIED = cardiac implantable electronic device; MRSA = methicillin-resistant *Staphylococcus aureus*; MSSA = methicillin-sensitive *Staphylococcus aureus*; MRCoNS = methicillin-resistant coagulase-negative staphylococcus; MSCoNS = methicillin-sensitive coagulase-negative staphylococcus; VRE = vancomycin-resistant Enterococcus species; VSE = vancomycin-sensitive Enterococcus species.

Data from reference 12.

infection by 12 months after the procedure, and the incidence of infection in replacement or revision cases was nearly twice the rate found in first implants.[13] Risk factors for CIED infection included renal failure, heart failure, diabetes, and fever within last 24 hours before CIED implantation.[14] The Implantable Cardiac Pulse Generator Replacement (REPLACE) registry found the 6-month incidence rate of CIED infection to be 1.4% after CIED replacement.[6]

Recently, there has been concern that the rate of newly infected CIEDs has outpaced the rate of newly implanted ones.[5,15] Voigt et al[15] reported a 12% increase in the rate of CIED implantation from 2004 to 2006 and an out-of-proportion 57% increase in the rate of CIED infection. A review from 2011 confirmed these findings, showing the annual CIED implantation incidence increased an average of 4.7% per year between 1993 and 2008.[5] This was probably driven by clinical trials that broadened the indications for ICD implantation for primary prevention.[16–19] Between 1993 and 2008, the rate of newly implanted devices increased by 96%, while the rate for newly infected CIEDs increased by 210%; the majority of this increase occurred after 2004.[5] The study showed that comorbidities in patients receiving CIEDs increased sharply starting in 2004—alluding to the contribution of comorbid medical conditions such as renal failure, respiratory failure, heart failure, and diabetes to infection risk.[5]

However, a major obstacle to defining the true incidence rate of CIED infection is the lack of a clear denominator. CIED infection is not limited to the first few months after implantation. In fact, over half of these patients present more than 1 year after the last CIED intervention.[12] Therefore, the number of patients at risk continues to grow each year and includes patients who underwent implantation that year or before, making it very difficult to compare infection rates. Additionally, the lack of a clear definition of CIED infection and the variations in duration of follow-up in different studies make it difficult to accurately assess the incidence of CIED infection.

PATHOGENESIS

A CIED can become infected at the time of implantation or pocket revision. The infection can then track along the endovascular portion of the leads resulting in endovascular infection and possibly endocarditis. A CIED can also become infected as a result of the hematogenous seeding of the leads or pocket during an episode of bacteremia. Most of these infections (70%) are caused by staphylococcal species, and many are becoming resistant to methicillin.[12] Other species include gram-negative organisms (9%), enterococci (4.2%), streptococci (2.5%), and fungi (1%) (**Table 1**). Despite clear evidence of clinical CIED infection, the cultures remain negative in about 13% of cases, perhaps because of the unfortunately common practice of starting antibiotic therapy before obtaining cultures or because of the need to incubate culture samples for a longer duration.[12] A longer incubation time is particularly important for infections involving *Proprionibacterium acnes*, an aerobic gram-positive rod commonly associated with acne vulgaris.[20]

DIAGNOSIS

Prompt and accurate diagnosis of CIED infection is critical as it allows for early management with antibiotic therapy and device removal. As the number of CIED implantations increases, providers on the front lines—emergency, family practice, and internal medicine physicians—will play an increasing role in recognizing and diagnosing CIED infection. Patients with CIED infection present with a range of signs and symptoms including fever, chills, erythema, swelling, drainage, tenderness, malaise, erosion, and warmth of the skin overlying the generator pocket.[2] In 55% of cases, patients present with localized pocket infection, while the remaining patients have signs of an endovascular infection without obvious pocket involvement.[12] Localized pocket infection is more common during the first year after device implantation. CIED-associated endovascular infections occur more commonly in patients with multiple

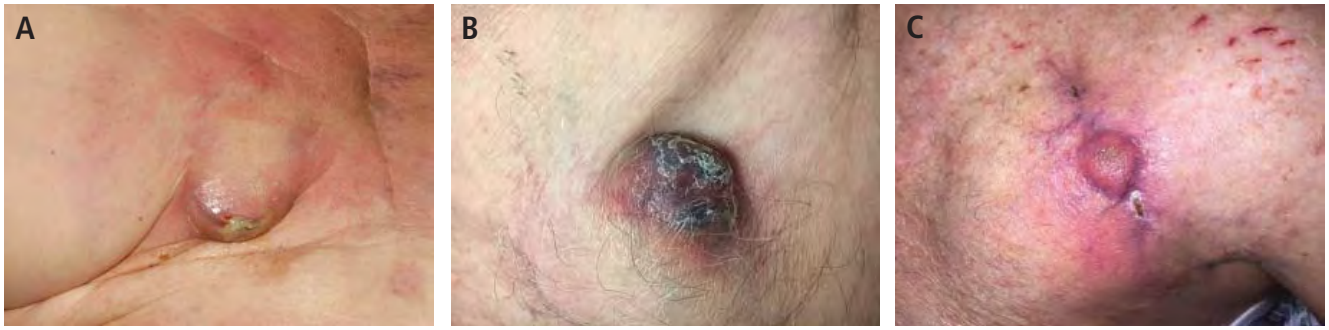

Figure 1. Pocket infection after placement of a cardiac implantable electronic device can present as erythema and drainage (A); swelling, skin necrosis, and eschar formation (B); and erythema, swelling, and bullae formation (C).

comorbidities including diabetes, renal failure, prior heart valve operation, rheumatic heart disease, and prior bloodstream infection.[2] Despite the theoretical divide in CIED infections (endovascular vs pocket), overlap is common: many patients with pocket infection show evidence of bacteremia and vegetations on the leads.

Physical examination of the pocket is critical as it may reveal visible signs of infection and support the diagnosis of localized pocket infection (**Figure 1**). Blood cultures are essential and should be collected before starting antibiotic therapy. Culture results assist in the diagnosis of CIED infection and also help identify the microorganism involved, and this information helps tailor the choice and duration of antibiotic therapy. Echocardiography (transthoracic and transesophageal) can assist the clinician in the diagnosis of CIED infection but requires careful interpretation because some patients with no signs or symptoms of infection can have small fibrinous strands or thrombi attached to the CIED leads.[14] These findings should only be interpreted in correlation to the clinical presentation.

Diagnosing pocket infection from the physical examination can be difficult due to the often subtle manifestations of the underlying pathophysiology and because visible changes to the pocket can occur over weeks and months. Furthermore, differentiating superficial infection, hematoma, seroma, and allergic reactions from deep pocket infection can be challenging. In cases when the diagnosis is not clear and there are no systemic findings of infection, conservative management with close follow-up is reasonable. Similarly, the diagnosis of endovascular infection is sometimes delayed because the symptoms are not very specific or because of a lack of awareness of the presence of a CIED and its role in endovascular infection.

MANAGEMENT

A multidisciplinary approach involving cardiology, infectious disease, electrophysiology, and cardiothoracic surgery teams is required to optimize outcomes in patients with CIED infection. CIED infection is particularly difficult to treat with antibiotic therapy alone because it involves infection of an implanted device and an associated biofilm that is resistant to the effects of antibiotics. Once infection is confirmed, antibiotic therapy serves as an adjunct to the complete removal of the hardware. Most patients receive 2 weeks of intravenous antibiotics after removal of an infected CIED, with longer courses for patients with *Staphylococcus aureus* infection or documented endocarditis.[21]

Infectious disease consultation is paramount in order to choose the appropriate type and duration of antibiotic therapy. Conservative approaches that involve using antibiotics alone or incomplete system removal have high failure rates with high rates of morbidity and mortality.[13,21–28] However, chronic antibiotic suppressive therapy may be considered as a palliative measure for patients who are not candidates for lead extraction.

DEVICE REMOVAL

Confirmation of CIED infection is a class I indication for device removal and the patient should be referred to an electrophysiologist. Transvenous lead extraction (TLE) is a percutaneous procedure performed by the electrophysiologist in the electrophysiology laboratory or hybrid operating room with cardiothoracic surgery support, and it is generally performed under general anesthesia with invasive hemodynamic monitoring. After opening and debriding the infected pocket, the generator is disconnected from the leads. After the lead tips are unscrewed from the myocardium, gentle traction is applied to determine if the

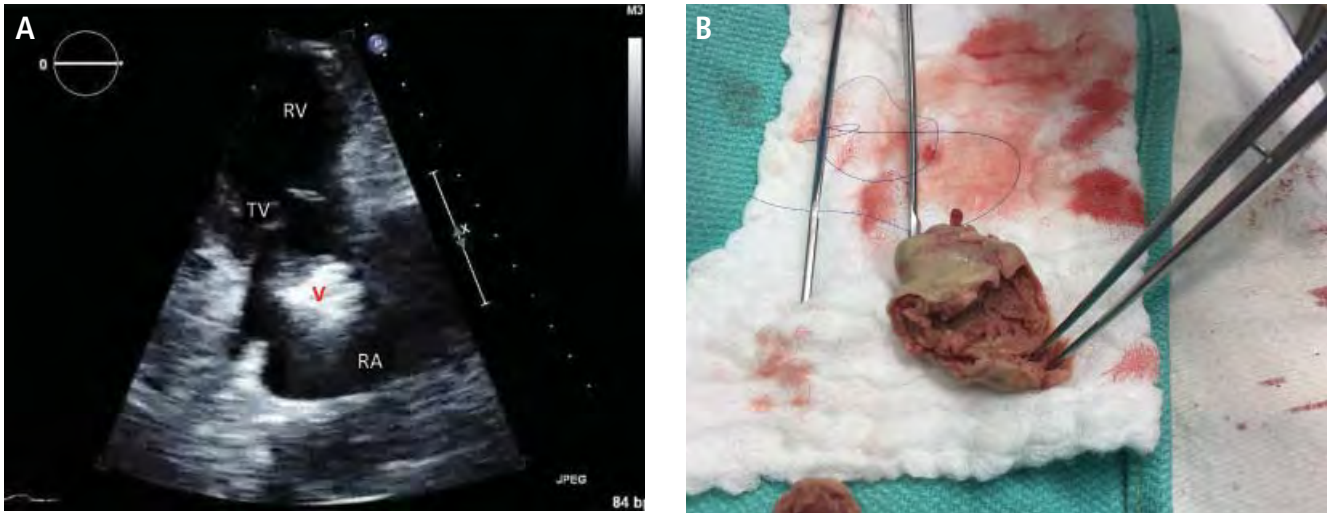

Figure 2. In a patient with endocarditis after cardiac implantable electronic device placement, transthoracic echocardiography shows a large vegetation (V) near the right atrium (RA), right ventricle (RV), and across the tricuspid valve (TV). This required surgical extraction of the organized vegetation along with the device and leads.

leads can easily be removed. If traction is unsuccessful, additional tools (both powered or mechanical sheaths) are used to complete the lead extraction[29]; the goal is to lyse and free the fibrotic attachments between parallel leads and between the leads and vessel wall or the myocardium. Once the lead is freed from the adhesions it can be removed safely.

The incidence of major complications with lead extraction is low (1.8%), but the procedure can be life-threatening.[30] Major complications include cardiac avulsion, vascular laceration, pericardial effusion, tamponade, hemothorax, valve injury, and death during the procedure.[30] Risk factors for major complications with TLE include renal failure, low body mass index, and the presence of a defibrillator coil on the lead.[30,31] In a large cohort of more than 3,000 patients requiring 6,000 TLE procedures at our tertiary care center, the incidence of catastrophic complications that required emergency cardiac surgery or vascular intervention was 0.8%.[32] Many of these patients were rescued through emergency surgical repair of a venous laceration or cardiac perforation but still had an in-hospital mortality rate of 36%. Surgical lead extraction is usually performed if percutaneous lead extraction has failed, if epicardial leads are present, if large vegetations are attached to the leads, or if surgery is warranted for valvular involvement with endocarditis (**Figure 2**).[14]

REIMPLANTATION

The need for reimplantation after removal of an infected CIED should be thought about before the extraction. In general, extracting an infected CIED should be viewed as an opportunity to reassess the need for the device. Almost one-third of patients who undergo extraction of infected CIED do not require immediate reimplantation.[2] This could be due to reversal of the initial indication, emergence of new clinical conditions, patient preference, or the lack of an absolute indication. If reimplantation is necessary, the new device is typically placed on the opposite side of the chest from the previously infected pocket site after blood cultures are negative for at least 72 hours.[21]

CIED INFECTION MORTALITY

Despite proper management with CIED removal supported by antibiotic therapy, CIED infection carries a high risk of death. The 30-day mortality is estimated to be between 5% and 6%.[33] In a large case series of 412 CIED extractions, there were 19 in-hospital deaths. Of these 19 deaths, 2 were related to the extraction itself with the other 17 related to sepsis, multiorgan failure, stroke, renal failure, or heart failure.[2] The 1-year mortality rate is also increased for this population; recent data show 1-year mortality rates of 8% to 17% despite device removal and antibiotic therapy.[2,34,35] This increased mortality rate was also demonstrated in a large cohort of Medicare patients undergoing CIED procedures.[36] Medicare patients with CIED infection had double the risk of death at 1 year compared with patients without infection.[36]

Risk factors for death at 1 year include worse baseline functional status, renal failure, and type of infection; eg, endovascular infection carries a risk of death 2 times higher than pocket infection.[37]

PREVENTION

Because CIED infection carries significant short-term and long-term mortality rates despite optimal management, the best strategy is prevention. Preventing CIED infection begins with the decision to implant a device with careful assessment of the indication, the timing of the procedure, and the patient's clinical status. CIED procedures are performed under strict sterile surgical techniques with great attention to the incision and proper closure. Surgical data favor the use of chlorhexidine-alcohol solutions for skin preparation compared with povidone-iodine solutions to prevent both superficial and deep surgical wound infections.[38] However, recent studies showed no significant difference between the 2 preparation methods in reducing rates of CIED infection.[39,40] In individuals colonized with *S aureus*, the risk of CIED infection can be reduced using a body wash containing chlorhexidine and a nasal spray containing mupirocin.[41,42]

Preoperative antibiotics

The use of preoperative antibiotics has been shown to reduce the risk of infection.[43] In a large prospective cohort of patients undergoing a de novo or secondary CIED procedure, the use of perioperative antibiotics was negatively associated with the risk of CIED infection.[13] This was later confirmed by a double-blind randomized trial of 1,000 patients undergoing permanent pacemaker or ICD initial implantation or generator replacement. This study was stopped prematurely as the use of antibiotics was clearly associated with a lower risk of CIED infection.[44] Therefore, prophylaxis with an antibiotic active against staphylococci before the incision is made is a class I indication to prevent infection.[1]

Currently, no data support giving prophylactic antibiotics after the procedure; however, the Prevention of Arrhythmia Device Infection Trial (PADIT) is currently comparing the risk of infection with conventional preoperative antibiotics vs a regimen of pre- and post-procedure antibiotics (clinicaltrial.gov: NCT01628666).

Hemostasis

Adequate hemostasis is critical, since the risk of CIED infection is 7 times greater with formation of a hematoma.[45] Heparin products, especially low-molecular-weight heparin, should be avoided at the time of CIED implantation. In patients at high risk for thromboembolism who are on warfarin therapy, the continuation of warfarin is associated with a lower incidence of hematoma compared with bridging with heparin in patients undergoing CIED procedures.[46] Therefore, if anticoagulation can be withheld, it is better to stop the anticoagulant before the procedure. When this is not possible or when it carries significant risk (eg, a patient with a mechanical mitral valve who needs a CIED implantation), it is better to maintain the patient on warfarin therapy with a therapeutic international normalized ratio rather than bridging with heparin products.

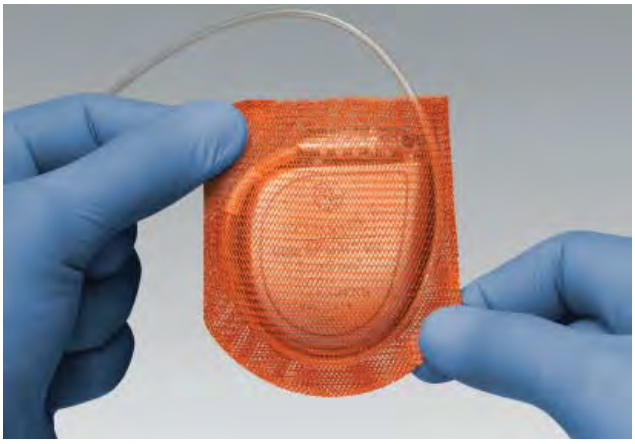

Figure 3. The TYRX absorbable antibacterial envelope is a mesh coated with the antibiotics rifampin and minocycline, which elute off the mesh within approximately 7 days. The mesh is completely absorbed into the body in about 9 weeks.

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Antibacterial envelop and new devices

A new development in the prevention of CIED infection is the TYRX absorbable antibacterial envelope (Medtronic Inc.) (**Figure 3**), a multifilament knitted mesh coated with the antibiotics rifampin and minocycline, which are released in the device pocket over 7 days. The first-generation envelope was nonabsorbable; the new product uses a fully bioabsorbable polymer that dissolves within 9 weeks. Data from nonrandomized studies using mainly the nonabsorbable version showed favorable outcomes in reducing the rate of CIED infections.[47,48] The World-wide Randomized Antibiotic Envelope Infection Prevention Trial (WRAP-IT) is a large randomized clinical trial assessing the efficacy of the absorbable envelope in reducing CIED infection rates in patients undergoing CIED replacement or upgrade.[49]

The development of new cardiac devices carries the potential of reducing certain types of infection. The subcutaneous ICD is an entirely subcutaneous system with no endovascular component, and therefore it can prevent endovascular infection, especially in patients at high risk of infection (eg, patients on

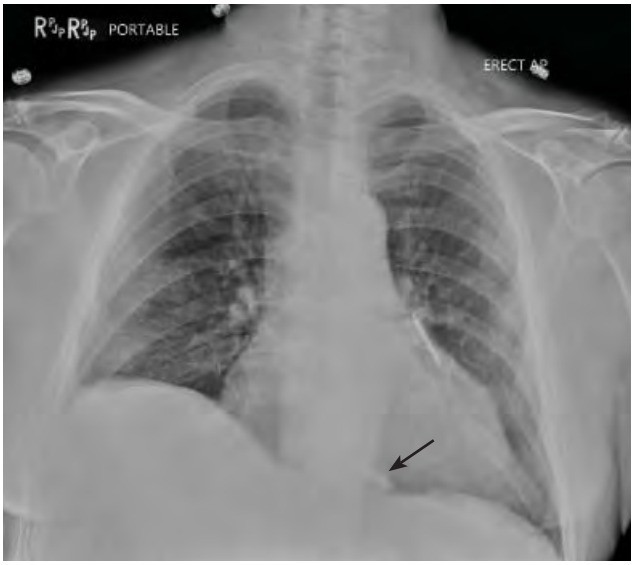

Figure 4. A leadless pacemaker in the right ventricle. The left atrial appendage exclusion clip is present.

hemodialysis).[50] On the other hand, the leadless pacemaker is a single-chamber pacemaker deployed percutaneously in the right ventricle without the need for a pocket, thereby eliminating the risk of pocket infection (**Figure 4**).[51,52] Whether the risk of endovascular infection will be reduced is not yet known.

CONCLUSION

CIED infection is a major complication that carries significant risk of morbidity and death. Early diagnosis and referral to a multidisciplinary treatment team is crucial to increasing the possibility of a cure. While device extraction has risks, it is nevertheless typically required for complete resolution of the infection. Large clinical trials are under way to address current knowledge gaps about CIED infection, including our understanding of the true incidence rate, risk factors, and efficacy of various implantation techniques. Future trends to minimize the risk of CIED infection include better screening, better diagnostic tools, new devices with fewer or no leads, longer battery life to minimize the need for additional procedures, and the use of supportive tools and products to minimize the risk of infection.

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Lung transplant: Candidates for referral and the waiting list

ABSTRACT

For patients with end-stage lung diseases, lung transplant may significantly extend survival and improve quality of life. Identifying patients that are likely to benefit from a lung transplant is essential to positive outcomes and to maximizing life expectancy for each patient. Prompt referral to and communication with an experienced lung transplant center allows for timely completion of the formal evaluation of candidacy and placement on the organ transplant waiting list. This article summarizes the selection criteria for lung transplant candidates, including when physicians should refer patients to transplant centers for evaluation and placement on the lung transplant waiting list.

KEY POINTS

Lung transplant is the therapy of choice for a growing number of patients with end-stage lung disease.

There are very few absolute contraindications to lung transplant. Potential contraindications and comorbidities can be discussed with the transplant center and vetted prior to listing for lung transplant.

The workup for a lung transplant varies among transplant centers across the country, thus good communication between referring providers and transplant centers is crucial to quality care.

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Lung transplant is the therapy of choice for a growing number of patients with end-stage lung diseases. Patients receiving a lung transplant are faced with many challenges including drug toxicities, infections, and the risk of rejection.[1] Despite these challenges, lung transplant may significantly prolong survival and improve quality of life for many patients.

CANDIDATES FOR LUNG TRANSPLANT

Identifying patients who are appropriate candidates for lung transplant is important to achieving favorable transplant outcomes and to maximizing life expectancy for each patient. The most recent edition of International Society for Heart and Lung Transplant (ISHLT) Guidelines for the Selection of Lung Transplant Candidates is an excellent guide to help physicians identify when to refer potential patients and to how to identify patients who are the most likely to benefit from lung transplant.[2]

Adults with end-stage lung disease are generally candidates for lung transplant if they meet the following criteria:

- A greater than 50% risk of death from lung disease within 2 years if a lung transplant is not performed
- A greater than 80% likelihood of surviving at least 90 days after the lung transplant procedure
- A greater than 80% likelihood of a 5-year survival posttransplant if graft function is preserved.[2]

These can only be estimated by transplant programs and not by the referring team in most cases.

Once a patient is identified as a candidate for lung transplant, early referral of patients to a lung transplant program has several advantages and is essential for positive outcomes. Early patient referral allows for timely completion of the formal evaluation of candidacy, patient and family education, as well as the opportunity for the patient and family to raise funds or use other resources to overcome financial hurdles.

Listing a patient on the transplant waitlist implies that the patient has a limited life expectancy without a lung transplant and that the risk-benefit ratio favors lung transplant since all other medical options have been exhausted.[1]

Each year, the number of new candidates added to the lung transplant waitlist grows (**Figure 1**). Since 2005, the allocation of organs for transplant has shifted from a time-based system to a risk of mortality-based system. The Lung Allocation System prioritizes candidates with the highest risk of mortality. Thus, the number of sicker and older patients on the wait list has increased since the implementation of the Lung Allocation System.[3] Because lung transplant is associated with significant perioperative morbidity and mortality, and older and sicker patients are being considered for listing, the contraindications and comorbidities should be vetted thoroughly prior to listing.

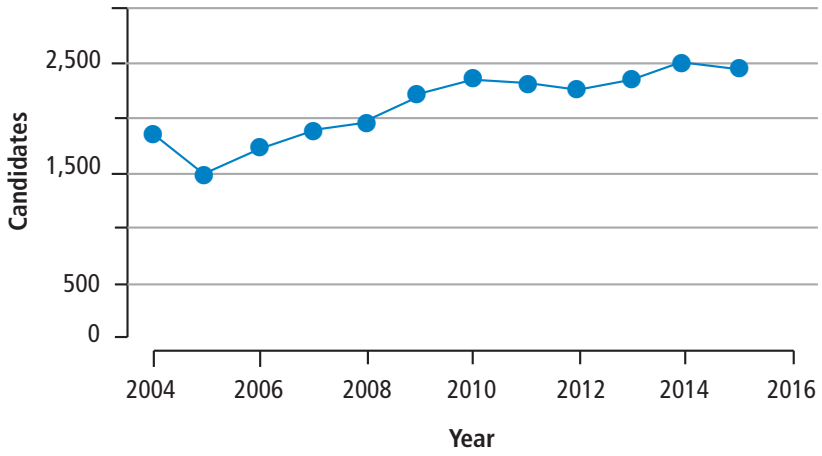

Figure 1. New candidates age 12 years and older on the lung transplant waiting list by year added.

Adapted from reference 4.

NONCANDIDATES FOR LUNG TRANSPLANT

There are very few absolute contraindications to lung transplant. Generally, most transplant centers in the United States agree that contraindications to lung transplant include conditions associated with increased risk of mortality, including:

- A recent history of a major malignancy. Patients with a 2-year, disease-free interval combined with a low predicted risk of recurrence may be considered in certain cases of localized, non-melanoma skin cancer. A 5-year, disease-free survival is strongly suggested in patients with a history of breast, bladder, or kidney cancer as well as in cases of sarcoma, melanoma, lymphoma and certain hematologic disorders.
- The presence of significant dysfunction of another major organ systems including the heart, liver, kidney, or brain unless a combined organ transplant can be considered and performed.
- Significant coronary heart disease not amenable to revascularization or intervention prior to or at the time of lung transplant.
- The presence of an acute medical condition including but not limited to sepsis and acute liver failure.
- Active *Mycobacterium tuberculosis* and other highly virulent or highly resistant microbes that are poorly controlled pretransplant.
- Severe obesity with a body mass index greater than 35.
- A history of nonadherence to medical therapy, psychiatric or psychological conditions that might lead to nonadherence, poor or limited social support system, and limited functional status not amenable to rehabilitation.
- Current substance abuse or dependence, including illicit substances, alcohol, and tobacco (nicotine-containing substances). Most centers require at least 6 months' abstinence from illicit substances prior to being added to the lung transplant waitlist.[2]

CANDIDATE COMORBIDITIES

Age

Many transplant centers in the US define the age cutoff for lung transplant at 65; however, some centers may consider candidates older than 65. Advanced age by itself should not be considered a contraindication to lung transplant. However, increased age is usually associated with other comorbid conditions that may increase perioperative and long-term morbidity and mortality. As mentioned previously, the number of older candidates for lung transplant has increased. In the US, 29% of the patients on the national waiting list in 2015 were over age 65.[4]

Past chest surgery

It is not uncommon for lung transplant candidates to have a history of chest surgery such as lung resection,

pleurodesis, or coronary artery bypass grafting. The limited literature regarding the outcomes for these patients suggests they may experience higher rates of bleeding, re-exploration, and renal dysfunction.[2] However, these patients should not be excluded from lung transplant and successful transplant outcomes have been achieved in this population by experienced centers.[5] In candidates with a history of chronic obstructive pulmonary disease (COPD) and lung-volume reduction surgery (LVRS), early case series indicate that these patients did well after lung transplant.[6] However, more recent data demonstrate that patients with prior LVRS who undergo lung transplant experience higher rates of bleeding, worse early graft dysfunction, and worse outcomes overall.[7] As with lung transplant candidates with previous chest surgery, lung transplant candidates with previous LVRS are best served by experienced transplant centers.

Hepatitis and HIV

Patients with a history of infection with hepatitis B, hepatitis C, or human immunodeficiency virus (HIV) are candidates for lung transplant at centers experienced with lung transplant in patients with these infections. Most centers advocate that patients with a history of hepatitis B or C have viral infection levels that are controlled or reduced as low as possible and that there is no evidence of portal hypertension or severe cirrhosis.[8,9] In the case of HIV, patients should have controlled disease with a negative or undetectable viral load and have no current acquired immunodeficiency defining illness.[10] Patients colonized with particular species of *Burkholderia cepacia* or *Mycobacterium abscessus* subspecies can be considered for lung transplant only at centers with established preoperative and postoperative protocols for these infections due to the increased risk of perioperative mortality associated with these organisms.[11,12]

DISEASE-SPECIFIC INDICATIONS

Chronic obstructive pulmonary disease

COPD (both non- and alpha-1 antitrypsin deficiency) is the most common indication for lung transplant and accounts for almost 32% of lung transplants worldwide.[13] Patients should be referred for lung transplant when medical therapies, surgical interventions (ie, LVRS) and pulmonary rehabilitation have been maximized. In COPD, the loss of lung function occurs over a long period of time but patients are often more limited by diminished quality of life as lung function slowly declines.

Patients with COPD should be referred for lung transplant if the body mass index, airflow obstruction, dyspnea, and exercise capacity (BODE) index is 5 to 6.[2] The original BODE index developed by Celli et al,[14] is a scoring system from 0 to 10 with a higher score indicating more severe disease and worse survival. A score of 5 to 6 indicates an estimated mortality of 60% at 4 yrs.[2,14,15] Other considerations for referral for lung transplant include the presence of hypercapnia with partial pressure of carbon dioxide greater than 50 mm Hg or higher or hypoxemia with partial pressure of oxygen less than 60 mm Hg or a forced expiratory volume at 1 sec (FEV_1) less than 25% predicted.

Patients with COPD should considered for listing for lung transplant if any one of the following criteria is met: BODE index of 7 or greater; FEV_1 less than 15% to 20%; 3 of more severe exacerbations during the preceding year; 1 severe exacerbation with acute hypercapnic respiratory failure; or presence of moderate to severe pulmonary hypertension.[2,16]

Cystic fibrosis

In patients with cystic fibrosis, lung transplant should be considered in patients with an estimated 2-year survival of less than 50% and with a New York Heart Association (NYHA) Functional Classification III or IV. Referral for lung transplant is recommended for patients with a rapid decrease in FEV_1 despite optimal therapy, female patients with declining weight and lung function, colonization or infection with nontuberculous mycobacterial disease, or cystic fibrosis-related diabetes. The development of pulmonary hypertension, reduction in walk distance, increasing antibiotic resistance, acute respiratory failure requiring noninvasive ventilation, worsening nutritional status, pneumothorax, and life-threatening hemoptysis despite embolization are all indications for referral for lung transplant.

Patients with cystic fibrosis with hypoxia or hypercapnia with declining lung function, needing long-term noninvasive ventilation, having more frequent exacerbations or exhibiting a decline in functional status should be listed for lung transplant.[2,17–19]

Restrictive lung disease

Patients with restrictive lung diseases, including interstitial pulmonary fibrosis (usual interstitial pneumonitis, nonspecific interstitial pneumonia), or interstitial lung disease, and hypersensitivity pneumonitis, should be referred for transplant evaluation at the time of diagnosis irrespective of lung function due to the unpredictable nature of these diseases.[20] Some clinicians may advocate for a trial of medical therapy

with antifibrotics, but this should be done in conjunction with transplant referral.

Patients should be listed for transplant if a 10% or greater decrease in FEV_1 occurred in the past 6 months (of note, even a 5% decrease in FEV_1 is associated with an overall poorer prognosis and warrants consideration of listing for transplant), if the diffusing capacity of the lung for carbon monoxide decreases 15% or greater during the 6-month follow-up, or if a decline of more than 50 meters is noted on the 6-minute walking test. A documented desaturation of less than 88% or a distance of less than 250 meters on the 6-minute walking test is another indication for listing. Any evidence of secondary pulmonary hypertension on right heart catheterization or on echocardiography or hospitalization for respiratory decline are also indications for listing.[21] In cases of scleroderma-associated interstitial lung disease or mixed connective tissue interstitial lung disease, similar guidelines for referral and listing should be followed.[2]

Pulmonary arterial hypertension

Patients with pulmonary arterial hypertension should be referred for lung transplant if any 1 of the following conditions is present: rapidly progressive disease; NYHA Functional Classification III or IV symptoms during escalating therapy; use of parenteral pulmonary arterial hypertension therapy; or known or suspected pulmonary veno-occlusive disease or pulmonary capillary hemangiomatosis.[2,22]

Patients with pulmonary arterial hypertension should be listed for lung transplant if any of the following are present: NYHA Functional Classification III or IV symptoms despite combination therapy; right heart catheterization demonstrating a cardiac index less than 2 L/min/m^2; mean right atrial pressure greater than 15 mm Hg; 6-minute walking test less than 350 meters; or development of pericardial effusion, hemoptysis, or signs of worsening right heart failure, including renal insufficiency, rising bilirubin or evidence of ascites.[2,22]

BRIDGE TO TRANSPLANT

Acute respiratory decompensation may occur in some candidates for lung transplant prior to listing for transplant or while on the transplant waitlist. In patients with failure of a single lung, a bridge to transplant may be necessary until a suitable organ is available. Mechanical ventilation and extracorporeal life support (ECLS) are 2 bridge strategies for lung transplant candidates. Mechanical ventilation is the most common lung transplant bridge strategy but it is less than ideal because it can lead to deconditioning and ventilator-associated infections that can negatively impact a patient's suitability for transplant.

ECLS techniques that allow spontaneous breathing and potentially ambulation, known as awake or ambulatory ECLS, is a popular bridge therapy. Ambulatory ECLS is used as an alternative to mechanical ventilation to avoid the complications of mechanical ventilation and allow patients to avoid sedation and participate in rehabilitation.[23] Irrespective of the therapy used as a bridge to transplant, patients considered for a bridge are optimally evaluated from a medical and psychosocial perspective prior to bridge therapy.

Both bridge therapies increase the risk of infection, bleeding, and neurologic events; thus, patients need to be assessed repeatedly for these risks to determine ongoing suitability for lung transplant. It is important to note that delayed referral of patients with advanced disease or patients in an acute exacerbation negatively impacts the evaluation for lung transplant, placement on the lung transplant waitlist, outcomes, and suitability for bridge transplant strategies.

CONCLUSION

To ensure good patient outcomes, the evaluation and selection of candidates for lung transplant requires communication between referring physicians and lung transplant centers. Physicians need basic knowledge of patient conditions appropriate for lung transplant and direct communication with lung transplant centers. The workup, required testing, and timing of listing for lung transplant varies among transplant centers across the country, making communication between the referring providers and transplant centers crucial to good patient care. An open, 2-way dialogue between referring providers and transplant centers facilitates listing patients for transplant in a timely manner, reduces delays, and improves outcomes.

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