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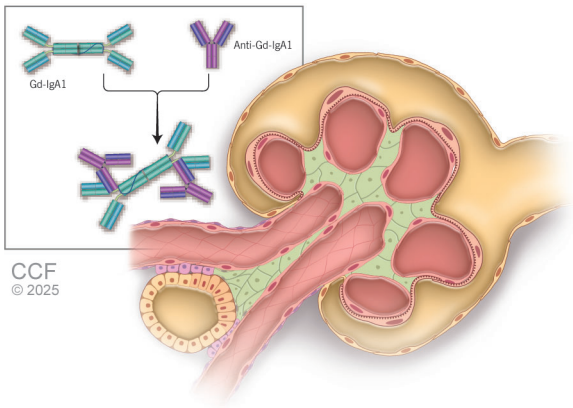

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Allopurinol hypersensitivity is rare, bad, and partially avoidable, but allopurinol can still be used effectively

In this issue of the *Journal*, Bocchi et al[1] remind us of the propensity of allopurinol to cause severe, life-threatening systemic hypersensitivity reactions and erythroderma. These reactions are fortunately quite rare (a few per thousand patient years), but allopurinol is one of the drugs most commonly associated with Stevens-Johnson syndrome and toxic epidermal necrolysis. Mortality associated with the latter likely remains greater than 20%.

Fear of this adverse effect led to the generation of dosing guidelines in 1984 with the hope of minimizing the occurrence of allopurinol hypersensitivity syndrome (AHS) and severe dermatitis.[2] Those guidelines were based on pharmacokinetic data and have never been clinically validated as necessary or effective. Furthermore, if adhered to, likely fewer than a third of patients will have their serum urate level reduced to the minimal target level (< 6 mg/dL) needed to successfully treat their gout. This is especially true when applying the guidelines in patients with chronic kidney disease (CKD), an extremely frequent comorbidity in patients with gout.[3] Valid concern over the possibility of this severe reaction, and a superficial understanding of the dosing guidelines based on creatinine clearance,[2] have contributed to widespread undertreatment, including allopurinol underdosing, of patients with gout. Additionally, there remains an unsupported fear of renal toxicity from "treat-to-target" allopurinol dosing in patients with CKD.

Hande at al[2] astutely recognized that a large fraction of patients experiencing AHS had "renal insufficiency." They meticulously described the pharmacokinetics of allopurinol and its active metabolite oxypurinol, which is renally cleared in parallel with creatinine. They calculated the dose of allopurinol needed at different rates of creatinine clearance to achieve an oxypurinol serum level equal to what would be obtained with a 300-mg dose of allopurinol in a patient with normal kidney function. The assumption was that allopurinol doses higher than 300 mg, especially in the setting of "renal insufficiency," would result in toxic levels of oxypurinol.

A corollary of this dosing based on estimated glomerular filtration rate (eGFR) was that 400 mg became the maximal dose, even in patients with a normal eGFR. This reasoning works well with predicting side effects from medications like the aminoglycosides, but does not necessarily fit with toxicity that is immunologically based, which is the case for allopurinol. Additionally, an allopurinol dose of 300 mg is too low for many patients with gout; the US Food and Drug Administration dosing is limited to 800 mg (doses > 800 mg have not been sufficiently studied). Forty years later, it still has not been demonstrated that adherence to Hande et al's guidelines[2] for maintenance dosing of allopurinol will reduce the frequency of AHS or provide adequate urate-lowering therapy for patients with gout and CKD.

CKD remains a recognized risk factor for the development of AHS, but the risk does not seem to be based on direct tissue damage from a toxic level of oxypurinol. Other risk factors include

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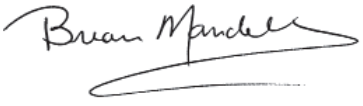
the presence of the *human leukocyte antigen (HLA)-B*58:01* gene variant and, curiously, the *initiating* but not the *maintenance* dose of allopurinol. Oxypurinol can activate CD8+ T cells via direct binding to HLA-B*58:01 molecules, in a concentration-dependent manner,[4] although the minority of patients with this allele will experience a toxic reaction. The explanation for why the combination of CKD and the presence of this HLA class I molecule increases the likelihood of AHS remains elusive. Nonetheless, the American College of Rheumatology recommends HLA testing in patients belonging to groups with a high prevalence of the *HLA-B*58:01* allele.[5] This includes persons of Han Chinese, Korean (those with CKD), and Thai descent, and African Americans (with an allele prevalence of about 4%). Implementation of a screening program in Taiwan with avoidance of allopurinol in patients positive for the allele markedly reduced the occurrence of AHS.[6]

The shadow of the Hande et al guidelines[2] still hangs over clinical decision-making. There remain discrepant guidelines on how to manage dosing of allopurinol in the setting of CKD. Two large database observational studies[7,8] and some smaller studies,[9] though their findings are biologically difficult to explain, have contributed significantly to our pragmatic approach to treating the patient with gout and CKD. Keller et al[8] used a US Medicaid database of more than 400,000 people and confirmed the increased risk of AHS in those populations with the *HLA-B*58:01* haplotype or CKD, but, importantly, also noted that patients who received an initial (not maintenance) allopurinol dose higher than 100 mg (based on prescription data) were at greater risk of developing allopurinol reactions.

Using a similar approach, Bathini et al[7] studied 47,315 patients 66 years or older with CKD and eGFR less than 60 mL/min/1.73 m^2. They evaluated the effect of the initial allopurinol prescription strength (> 100 mg vs ≤ 100 mg) on subsequent hospitalization for a severe skin reaction within 180 days after starting the medication (the time period in which almost all allopurinol hypersensitivity reactions occur). They found a significant difference in the hospitalization rate: 0.4% vs 0.18% in high- vs low-dosed patients. Importantly, they also noted that, after 180 days, there was no increase in the occurrence of AHS in patients with CKD whose allopurinol dose was titrated upward vs those who stayed at a low dose. This is important because 100 mg is not likely to provide a clinically relevant lowering of serum urate. That allopurinol, after starting at a low dose, can be titrated upward has been supported by Stamp et al[9,10] from New Zealand and endorsed by the American College of Rheumatology.[5]

My own practice, which is not directly supported by any rigorously derived evidence, is to start all patients on an allopurinol dose of 50 mg, regardless of their renal function. I do this because it may reduce the likelihood of severe allopurinol adverse reactions, especially in the setting of CKD. For patients in whom after discussion we have decided that there is no urgency in resolving tophaceous deposits, and thus do not plan on starting enzyme replacement therapy with a uricase, there is no urgency to rapidly reduce the serum urate to my desired target level (I usually aim for 5.5–6 mg/dL, lower in the presence of palpable tophi or demonstrated erosive bone disease). By starting patients at a low dose and slowly titrating upward to ultimately attain the target serum urate, I believe we can reduce the likelihood of "mobilization flares" of their gout.[11] I also try to use anti-inflammatory prophylaxis against flares in all patients, and I try to check the *HLA-B*58:01* status of those at higher risk of having this haplotype before starting allopurinol.

I believe that allopurinol appropriately currently remains the first-line urate-lowering therapy for most patients with gout. It is easily titratable to a therapeutic dose and is affordable. The presence of CKD should not present an insurmountable obstacle to using the drug long term, particularly if there are any concerns with the use of febuxostat or probenecid, which, at present, are the only real alternatives in the United States. Fortunately, several new potential urate-lowering drugs are in late stages of clinical development.



Brian F. Mandell, MD, PhD
Editor in Chief

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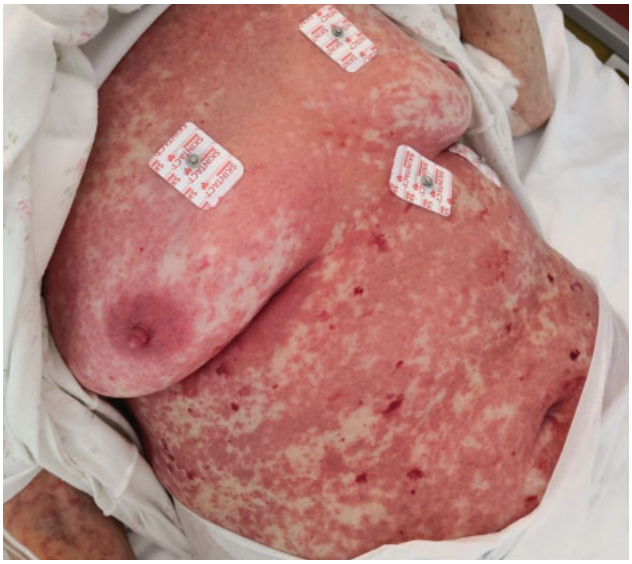
Severe cutaneous reaction induced by allopurinol



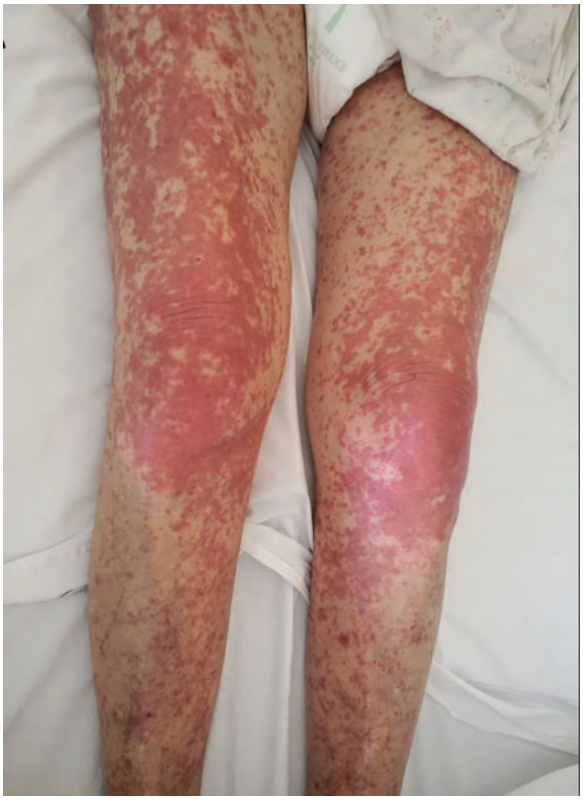


Figure 1. Widespread maculopapular rash on the trunk (left) and on the legs (right).

An 86-year-old woman presented to the emergency department with fatigue, malaise, a widespread maculopapular rash on the trunk and the extremities (**Figure 1**), and painful blistering and erosions of the oral mucosa (**Figure 2**). Medical history was remarkable for hypertension. Medications included amlodipine and allopurinol; the patient started the latter medication for gout 3 weeks before the current presentation.

Laboratory testing revealed leukopenia (white blood cell count 2.85 × 10^9/L [reference range 3.4–9.6]); elevated serum creatinine (1.7 mg/dL [0.73–1.22]) and blood urea nitrogen (90 mg/dL [8–24]), reflecting dehydration; elevated C-reactive protein (50 mg/L [< 5]); and a normal procalcitonin level (0.02 ng/mL [< 0.05]). Blood and urine cultures were negative. The patient did not have eosinophilia, and alanine transaminase and aspartate transaminase were within normal limits.

Because the rash developed soon after allopurinol was started, we suspected a severe drug cutaneous eruption like Stevens-Johnson syndrome (SJS)/toxic epidermal necrolysis (TEN), a type IV hypersensitivity reaction, and discontinued allopurinol. The patient declined skin biopsy to confirm the diagnosis.

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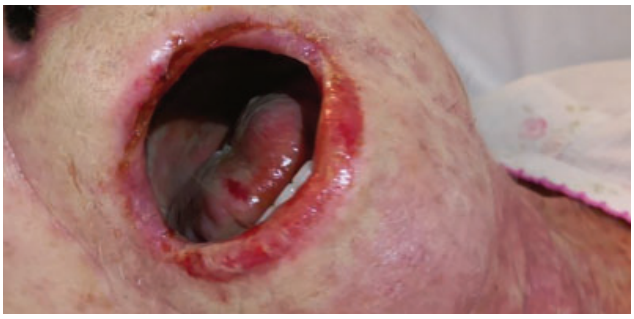

Figure 2. Painful blistering and erosions of the oral mucosa.

The patient was transferred to the local burn unit, where she was treated with hydration, wound care, artificial nutrition, and intravenous immunoglobulin and did well.

SJS AND TEN

TEN (formerly known as Lyell syndrome) is a rare severe mucocutaneous reaction that manifests as a maculopapular rash with blistering of skin and conjunctival, oral, and genital mucosae. It is defined as detachment of more than 30% of the skin, differentiating it from SJS, which is defined as detachment of less than 10% of the skin. Our patient had SJS/TEN overlap, which is defined as involvement of 10% to 30% of the skin.[1]

Drug exposure with a subsequent hypersensitivity reaction is the cause of most SJS/TEN cases.[1] Current theories about the etiopathology of SJS/TEN point to a portion of the drug molecule (hapten) that is introduced by antigen-presenting cells to T lymphocytes specific for that antigenic pattern. This process triggers a type IV, or delayed, hypersensitivity reaction to the culprit drug after about 2 to 3 weeks of exposure. T lymphocytes infiltrate the skin, producing cytokines and chemokines that are responsible for the clinical manifestations involving the skin and mucosal surfaces.[2]

Allopurinol as a cause

Allopurinol is one of the most common causes of SJS/TEN. The risk for developing these cutaneous drug reactions is increased when the dosage exceeds 200 mg/day, especially in elderly patients who are treated with 300 mg/day or more.[3] Other drugs that may trigger SJS/TEN include antiepileptics (eg, phenytoin, lamotrigine, carbamazepine), sulfonamide antibiotics, and nonsteroidal anti-inflammatory drugs.[4]

The 2020 American College of Rheumatology guidelines[5] conditionally recommend screening for the *human leukocyte antigen (HLA)-B*58:01* allele in certain populations before starting allopurinol, as carriers of this allele have a higher risk of TEN than noncarriers. Populations with high allele frequency include people of Han Chinese (10%–15%), Korean (12%), and Thai (6%–8%) ancestry, and African Americans (almost 4%).[3]

Diagnosis and management

Diagnosis relies mainly on clinical signs. When the diagnosis is not clear, a skin biopsy is indicated for confirmation. Analysis of skin specimens from affected areas typically reveals full-thickness epidermal necrosis.[2] Differential diagnoses include linear immunoglobulin A dermatosis, pemphigus, acute generalized exanthematous pustulosis, and staphylococcal scalded skin syndrome.[1]

The mortality rate in TEN ranges from 25% to 35% due to risk of bloodstream infections and renal failure from loss of fluids from the blisters.[2] Aside from suspending the offending drug, treatment of all patients with SJS/TEN includes adequate fluid resuscitation, artificial nutrition (if needed) enriched in protein to help repair skin tissue, pain control, antibiotic therapy in case of sepsis, antithrombotic and gastric ulcer prophylaxis, and the use of nonadherent dressings. Immunomodulatory drugs like cyclosporine have shown some benefit.[6] The combination of plasmapheresis and intravenous immunoglobulins may reduce mortality.[7] Resolution of the disease can take several weeks.[6,7]

Avoiding future exposure to drugs of the same pharmacologic class as the drug that triggered SJS/TEN is suggested because there can be cross-reactivity (eg, antiepileptics with aromatic structures such as phenytoin, carbamazepine, and phenobarbital or beta-lactam antibiotics).[8]

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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Amoxicillin rash in infectious mononucleosis

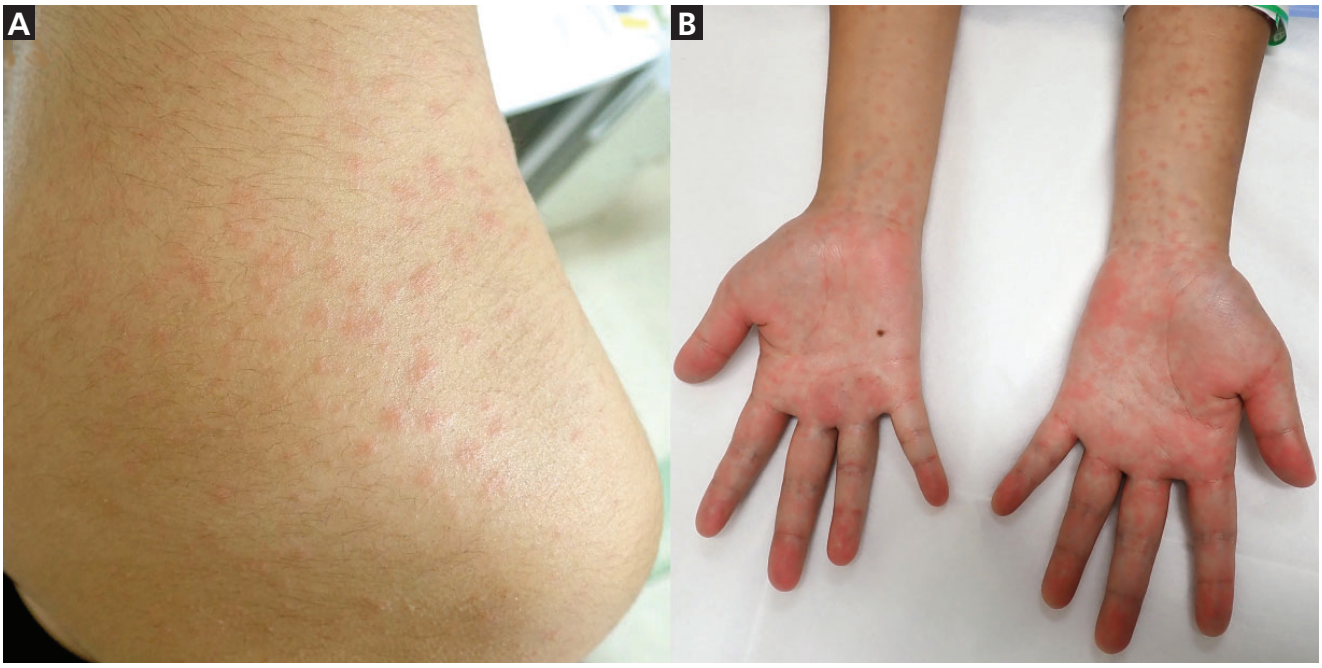

Figure 1. Faint generalized erythematous papules and macules with mild pruritus on the patient's (A) right shoulder and (B) hands, including the palms.

A previously healthy 23-year-old woman was referred to our medical center with a 2-day history of a generalized pruritic rash. Seventeen days before presentation, she noticed bilateral swelling in her neck, and 3 days later she developed a fever (39.0°C [102.2°F]) and sore throat. Subsequently, she visited a local clinic where she had a rapid antigen-detection test, which was positive for group A *Streptococcus*, and she was prescribed a 10-day course of amoxicillin. Her fever and sore throat improved, but the neck swelling persisted. The rash that prompted her current visit developed on the day she completed amoxicillin therapy.

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The patient had no history of allergic reactions, and it was unclear whether she had previously been exposed to beta-lactam antibiotics. Because of her work as a part-time piano teacher, she had regular contact with children.

Physical examination showed bilateral tonsillar enlargement; bilateral posterior cervical lymphadenopathy with tenderness; and maculopapular exanthem on the face, trunk, and limbs, including the palms and soles (**Figure 1**). Laboratory tests revealed an elevated white blood cell count of 10.7×10^9/L (reference range 3.3–8.6) and 11.5% atypical lymphocytes. Eosinophil count, alkaline phosphatase, aspartate aminotransferase,

and alanine aminotransferase were within normal limits. Additional tests showed elevated immunoglobulin (Ig) M and IgG antibodies to Epstein-Barr virus capsid antigen and were negative for IgG antibody to Epstein-Barr virus nuclear antigen, cytomegalovirus antibody, and human immunodeficiency virus antigen and antibody tests.

Amoxicillin rash against a background of infectious mononucleosis was diagnosed. All symptoms resolved by the outpatient follow-up visit 10 days after initial presentation, and the patient was lost to follow-up.

RASH AFTER AMOXICILLIN USE IN INFECTIOUS MONONUCLEOSIS

Amoxicillin rash often occurs after a patient with infectious mononucleosis is given an antimicrobial agent. The rash—a diffuse pruritic maculopapular exanthem that often involves the palms and soles—typically appears 7 to 10 days after antimicrobial administration and resolves within a week.[1,2] The differential diagnosis of skin lesions in patients with infectious mononucleosis includes Gianotti-Crosti syndrome (also known as infantile papular acrodermatitis, it is characterized by an erythematous papular rash on the face and limbs that clears in several weeks), Stevens-Johnson syndrome, and viral infections such as varicella-zoster virus and enterovirus[3]; not all these entities have this appearance.

Group A streptococcal infection can co-occur with infectious mononucleosis. Because antimicrobial therapy is warranted to treat the bacterial infection, patients with coinfection are at risk of amoxicillin rash.[4] For example, a study of 222 children with acute group A streptococcal pharyngitis found that up to 18% had an Epstein-Barr virus coinfection.[5] However, distinguishing between a true coinfection and group A streptococcal colonization is challenging.[4] Therefore, administering antibiotics to treat confirmed symptomatic group A streptococcal pharyngitis is still reasonable to prevent rheumatic fever and complications and reduce infection, even if there is a possible Epstein-Barr virus coinfection.

Amoxicillin rash incidence in patients with infectious mononucleosis traditionally has been thought to be as high as 95%,[1,4] but recent studies suggest that it may be much lower, ranging from 15% to 33%.[2,6,7] This discrepancy may be attributed to possible contamination of the antibiotics used in an earlier era or to differences in age, ethnicity, and genetics in study participants.[2] Although rash frequency is high among patients with infectious mononucleosis after administration of amoxicillin or ampicillin, a recent study found that the frequency of rash with these antibiotic agents is similar to that of other antibiotics.[8] Thus, prescribing alternative non–beta-lactam antibiotics for group A streptococcal pharyngitis may not necessarily lower the risk of rash.

Drug allergy, intolerance, or hypersensitivity

The most plausible cause of amoxicillin rash in infectious mononucleosis is a transient virus-mediated immune change that decreases antigenic tolerance and leads to a delayed-type hypersensitivity reaction to the antibiotic.[2] This transient immunostimulation is distinct from a beta-lactam allergy. An amoxicillin rash occurring in the setting of infectious mononucleosis may not indicate a true penicillin allergy, although reliable data are scarce regarding the frequency of rash recurrence after readministration of a beta-lactam antibiotic in patients with a diagnosis of infectious mononucleosis and history of amoxicillin rash.[2]

However, it is possible that a true and persistent drug hypersensitivity can arise during the course of infectious mononucleosis. In one study, 5 of 8 patients with infectious mononucleosis who developed a rash after aminopenicillin use had positive amoxicillin patch tests more than 3 months after infectious mononucleosis was completely resolved.[2,9] It is crucial to note that the study did not differentiate between preexisting or inherent drug allergies and true hypersensitivity reactions newly induced by Epstein-Barr virus infection. To date, no high-quality studies have rigorously distinguished between these 2 reaction types and accurately estimated the risk of persistent drug hypersensitivity after an Epstein-Barr virus infection.

While clinicians should avoid diagnosing penicillin allergy in patients with an amoxicillin rash during an infectious mononucleosis episode, patients should be involved in the decision to conduct allergy testing to differentiate between a transient immunostimulation-related amoxicillin rash and a true beta-lactam allergy. Clinicians should also be vigilant and carefully assess a rash that occurs in patients with acute pharyngitis, considering the possibility of Epstein-Barr virus infection.

DISCLOSURES

The author reports no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Should I start anticoagulation in my patient newly diagnosed with pulmonary hypertension?

A: The decision about starting anticoagulation along with targeted therapy in patients with pulmonary hypertension hinges on the subtype of pulmonary hypertension the patient has. A review of the latest guidelines from the European Society of Cardiology (ESC) and the European Respiratory Society (ERS)—and the evidence to date—can help guide decision-making.[1] But first, let's look at why we consider anticoagulation for pulmonary hypertension in the first place.

See related article, page 344

WHY CONSIDER THERAPEUTIC ANTICOAGULATION IN PULMONARY ARTERIAL HYPERTENSION?

Pulmonary hypertension is defined as a mean arterial pulmonary pressure of 20 mm Hg or higher measured during right heart catheterization, and patients diagnosed with the disease are grouped according to the underlying cause of the elevated pulmonary artery pressure (**Table 1**).[1] Before targeted medical therapy for pulmonary hypertension was developed, anticoagulation therapy (mainly vitamin K antagonists) was prescribed in about 90% of patients with World Health Organization (WHO) group I pulmonary hypertension, ie, pulmonary arterial hypertension.[2,3] This practice was driven by evidence showing hypercoagulability in patients with pulmonary arterial hypertension, including an increased prevalence of thrombotic lesions, activation of the coagulation system, and resistance to fibrinolysis.[3] With the development of targeted medical therapies, the frequency of therapeutic anticoagulation in these patients has dropped from 90% to 50%, according to data from the Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension (COMPERA),[2] Registry to Evaluate Early and Long-Term PAH Disease Management (REVEAL),[4] and other trials.[3]

Evidence shows that the procoagulant and fibrinolytic activity of the pulmonary arterial endothelium is altered in pulmonary arterial hypertension. This is reflected by increased plasma levels of von Willebrand factor and plasminogen activator inhibitor type 1 observed in patients with this form of pulmonary hypertension.[5] Notably, plasminogen factor inhibitor is found in higher concentrations in arterial samples compared with mixed venous samples, suggesting intrapulmonary production. Further, in response to the vascular abnormalities in pulmonary hypertension, platelets release mediators with procoagulant, mitogenic, and vasoconstrictor effects that contribute to the prothrombotic state, including thrombin, thromboxane A2, platelet-activating factor, serotonin, platelet-derived growth factor, transforming growth factor beta, and vascular endothelial growth factor.[5,6] It is unclear whether thrombosis and platelet dysfunction are causes—or consequences—of pulmonary arterial hypertension.

Pulmonary hypertension is a progressive condition that can lead to right-sided heart failure. The presence of right ventricular dysfunction has been identified as a potential risk factor for venous thromboembolism, although the evidence supporting this association is not strong.[7] Left-sided heart failure, however, is considered an independent risk factor for venous thromboembolism.[2] Furthermore, patients with pulmonary

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TABLE 1
World Health Organization (WHO) classification of pulmonary hypertension

WHO classification	Etiology
Group I: pulmonary arterial hypertension	Idiopathic; drug- or toxin-related; associated with connective tissue disease, human immunodeficiency virus infection, portal hypertension, congenital heart disease, schistosomiasis; persistent pulmonary hypertension of the newborn; pulmonary arterial hypertension with venous or capillary involvement
Group II: pulmonary hypertension associated with left heart disease	Heart failure, valvular heart disease, congenital or acquired heart conditions leading to postcapillary pulmonary hypertension
Group III: pulmonary hypertension associated with lung disease, hypoxia, or both	Obstructive lung disease or emphysema, restrictive lung disease, lung disease with mixed pattern, hypoventilation syndromes, hypoxia without lung disease, developmental lung disease
Group IV: pulmonary hypertension associated with pulmonary artery obstruction	Chronic thromboembolic pulmonary hypertension, other pulmonary artery obstructions (malignant tumors, sarcomas)
Group V: pulmonary hypertension with unclear or multifactorial mechanisms	Hematologic disorders, systemic disorders, metabolic disorders, chronic renal failure with or without dialysis, fibrosing mediastinitis, pulmonary tumor thrombotic microangiopathy

Based on information from reference 1.

hypertension can have significant dyspnea on exertion, resulting in immobility, which is a risk factor for venous thromboembolism.[5–7]

IN WHICH PULMONARY HYPERTENSION GROUPS SHOULD ANTICOAGULATION BE CONSIDERED?

According to the 2022 ESC/ERS guidelines for the diagnosis and treatment of pulmonary hypertension,[1] the decision about starting anticoagulation in patients with pulmonary arterial hypertension (WHO group I pulmonary hypertension) should be individualized, while lifelong anticoagulation is recommended in patients with chronic thromboembolic pulmonary hypertension (WHO group IV).

Pulmonary arterial hypertension (WHO group I)

Current evidence regarding anticoagulation therapy in patients with pulmonary arterial hypertension remains insufficient, with conflicting results from major registry studies such as COMPERA[2] and REVEAL[4] and the most recent meta-analyses done by Khan et al[6] and Wang et al[8] (**Table 2**).[2,4,6,8–12] COMPERA[2] compared patients with idiopathic pulmonary arterial hypertension who received anticoagulation therapy (predominantly vitamin K antagonists) with those who did not receive it, and found a significant survival benefit for those receiving anticoagulants. These findings are consistent with the results of the meta-analysis conducted by Khan et al.[6] REVEAL,[4] however, showed no significant survival benefit for patients with group 1 pulmonary hypertension who received anticoagulation therapy compared with those who did not receive it. This lack of benefit may be explained by REVEAL's inclusion of patients with more severe disease, characterized by lower functional status, multiple comorbidities, and need for multiple therapies at time of enrollment. These findings were consistent with the Wang et al[8] meta-analysis.

Anticoagulation therapy is generally not recommended in pulmonary arterial hypertension associated with human immunodeficiency virus (HIV) or systemic sclerosis due to the higher risk of bleeding (systemic sclerosis and HIV) and potential drug interactions (HIV).[1] Vitamin K antagonists are recommended for pulmonary arterial hypertension associated with connective tissue diseases *if* the patient is predisposed to thrombophilia (eg, antiphospholipid syndrome). In patients with pulmonary arterial hypertension due to congenital heart disease, anticoagulation may be considered in the presence of a large pulmonary artery aneurysm with thrombus, history of thromboembolic events, or both.[1]

Chronic thromboembolic pulmonary hypertension (WHO group IV)

Non–vitamin K antagonist oral anticoagulants are recommended in the first 3 months after acute pulmonary embolism is diagnosed.[13] Diagnostic reevaluation for chronic thromboembolic pulmonary disease

TABLE 2
Meta-analyses and original studies evaluating anticoagulation therapy in PAH

Study, design, population	Outcomes	Results	Comments and limitations
Rich et al (1992)[9] Prospective post hoc cohort analysis of 64 patients with PAH	5-year survival	Improved survival in the 35 patients who received VKA	VKA started if lung perfusion scan was abnormal
Ngian et al (2012)[10] Prospective multicenter cohort of 117 patients with incident CTD-PAH	3-year survival	Improved survival in patients with CTD-PAH who received VKA	Lack of information on length of therapy and presence of concomitant venous thromboembolism or atrial fibrillation
Johnson et al (2012)[11] Retrospective cohort study of 66 patients with idiopathic PAH and 98 patients with SSc-PAH	3-year survival Time from PAH diagnosis until death from all causes Probability that VKA improved median survival by ≥ 6 months	VKA showed low probability for improving survivability in idiopathic PAH and SSc-PAH	Small study size Included all patients exposed to VKA regardless of minimum duration or dosing Didn't include all prognostic factors for survival of patients with PAH
COMPERA (2014)[2] Prospective post hoc cohort analysis of 1,283 patients with PAH (800 idiopathic, 208 SSc-PAH)	3-year survival	Improved survival in patients with idiopathic PAH who mainly received VKA, but not in other forms of PAH	Lack of information on length of therapy and presence of concomitant venous thromboembolism or atrial fibrillation
REVEAL (2015)[4] Prospective post hoc cohort analysis of 144 patients with idiopathic PAH and 43 with SSc-PAH who received VKA anytime during study, matched with 187 who did not	3-year survival	Similar survival between 2 groups Lower survival in patients with SSc-PAH who had taken VKA	Lack of information on length of therapy and presence of concomitant venous thromboembolism or atrial fibrillation Mix of prevalent and incident cases
HEMA-HTP (ongoing)[12] Prospective multicenter cohort of 203 patients (88 PAH, 115 chronic thromboembolic pulmonary hypertension); 152 on VKA, 51 on direct oral anticoagulants, 4 on combined antiplatelet therapy	Major bleeding (International Society on Thrombosis and Haemostasis definition)	Preliminary results showed significant bleeding risk, with 22 patients experiencing major bleeding (12 with PAH, 10 with chronic thromboembolic pulmonary hypertension) Two patients died from major bleeding	
Khan et al (2018)[6] Systematic review and meta-analysis of 12 studies (8 retrospective, 4 prospective); 2,512 patients (1,342 on anticoagulation; 1,170 controls)	Impact of adjunctive oral anticoagulants in PAH and whether response differed by PAH subtype	Anticoagulation significantly reduced mortality in overall PAH group—reduction most significant in idiopathic PAH, with no difference in CTD-PAH Increased mortality seen in patients with SSc-PAH on anticoagulation therapy	Absence of randomized clinical trials Heterogeneity of results, possibly secondary to various concomitant therapies Possibility of publication bias
Wang et al (2020)[8] Systematic review and meta-analysis of 8 observational studies (1,812 patients with idiopathic PAH)	Efficacy of anticoagulation therapy in idiopathic PAH	No significant difference in survivability in treated vs untreated patients with idiopathic PAH	Absence of randomized clinical trials Definitions and patient inclusion criteria differed between the 8 studies, leading to bias Unbalanced patient characteristics

COMPERA = Comparative, Prospective Registry of Newly Initiated Therapies for Pulmonary Hypertension; CTD = connective tissue disease; HEMA-HTP = Bleeding Frequency Under Anticoagulant Treatment in Pulmonary Hypertension; PAH = pulmonary arterial hypertension; REVEAL = Registry to Evaluate Early and Long-Term PAH Disease Management; SSc = systemic sclerosis; VKA = vitamin K antagonist

or chronic thromboembolic pulmonary hypertension is recommended (class 1 recommendation) for patients who, after this time period, have new-onset dyspnea or exercise limitations. The guidelines say this evaluation should include a ventilation-perfusion scan or computed tomography pulmonary angiography to assess for persistent perfusion defects, along with evaluation for pulmonary hypertension using echocardiography.[13]

If, after 3 months, pulmonary hypertension is evident or persists, therapeutic anticoagulation with a vitamin K antagonist is needed indefinitely.[13] Although non–vitamin K antagonist oral anticoagulants have been used, this practice is not backed by robust evidence from randomized clinical trials, and these agents have been shown to have a higher incidence of recurrent thromboembolic events.[1]

Patients with chronic thromboembolic pulmonary disease should be screened for antiphospholipid syndrome, as the syndrome is present in 10% of them.[1] Once antiphospholipid syndrome is diagnosed, lifelong vitamin K antagonist use is indicated, regardless of pulmonary hypertension status.

ANTICOAGULANT CHOICE, INTERNATIONAL NORMALIZED RATIO GOALS, AND BLEEDING RISK

Currently, the choice of therapeutic anticoagulants is limited to vitamin K antagonists because these agents have fewer interactions with targeted therapy for pulmonary arterial hypertension. There are no randomized clinical trials comparing the efficacy of vitamin K antagonists vs non–vitamin K antagonist oral anticoagulants in patients with pulmonary arterial hypertension.[3,4]

The goal international normalized ratio in WHO group IV pulmonary hypertension has not been well defined, and the current goal of 2.0 to 3.0 has been extrapolated from venous thromboembolism studies.[3] The 2022 ESC/ERS guidelines[1] do not identify an international normalized ratio goal, while some studies recommended a goal of 1.5 to 2.0.[3]

Before starting anticoagulation therapy for pulmonary arterial hypertension or thromboembolic pulmonary hypertension, the risk of bleeding should be discussed with the patient. We do not have data from a completed prospective randomized controlled trial on the risk of major bleeding with anticoagulation therapy in either of these pulmonary hypertension subtypes. However, an ongoing trial (Bleeding Frequency Under Anticoagulant Treatment in Pulmonary Hypertension[12]) is looking at the risk of major bleeding in these patient populations.Preliminary results showed a high risk of major bleeding, including fatal bleeding, but we will have to wait for the full results to identify the specific risk factors for the bleeding.

THE BOTTOM LINE

With the dramatic evolution of modalities for the management of pulmonary hypertension over the past 2 decades, a main dilemma is the adjuvant use of anticoagulation to prolong survival. The 2022 ESC/ERS guidelines[1] suggest that the decision to start anticoagulation in patients with pulmonary arterial hypertension should be individualized, and we agree with this recommendation, while anticoagulation is recommended in all patients with chronic thromboembolic pulmonary hypertension. Vitamin K antagonists are the preferred agents. Anticoagulation is not recommended in patients with pulmonary arterial hypertension due to systemic sclerosis or HIV due to high risk of bleeding in both conditions and drug interactions in HIV.

Comparative studies are needed to explore the risks and benefits of vitamin K antagonists vs non–vitamin K antagonist oral anticoagulants, given that the latter are often preferred because of their ease of use. Moreover, robust prospective randomized clinical trials are needed to assess whether anticoagulant therapy provides a survival benefit in patients diagnosed with pulmonary arterial hypertension.

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Nitrogen: The unsung hero of vascular physiology

IN DAY-TO-DAY MEDICAL PRACTICE, the seventh element on the periodic table—nitrogen—may not come to mind often. But it is more exciting than you might think. In fact, there is an entire nitrogen cycle that you probably learned but forgot about to make room for the much more popular carbon and water cycles.

Associate Editor Adam Brown, MD, discusses an angle related to the article "Should I start anticoagulation in my patient newly diagnosed with pulmonary hypertension?" on page 339.

Nitrogen is all around us. It makes up 80% of our atmosphere, and we have learned to extract it from the air and inject it into our soil (known as *nitrogen fixation*) to grow crops. Nitrogen is a component of amino acids and of DNA and RNA, and it's crucial for protein synthesis. Inhaling certain forms of nitrogen leads to a stumbling gait and fits of laughter, yet nitrogen in another form is a common explosive.

What may *not* be appreciated is the importance of the nitrogen compound nitric oxide in vascular physiology. An article in this issue of the *Journal* presents a question about starting a patient newly diagnosed with pulmonary hypertension on anticoagulants, but therapeutic options can also include medications that manipulate a tissue's response to nitric oxide.[1] The journey to understand nitric oxide's role in vasodilation, and how it could be used therapeutically, had many stumbling blocks along the way, but a combination of discoveries eventually led to breakthroughs in treating angina, erectile dysfunction, and pulmonary arterial hypertension.

THE NERVES AND VESSELS

Our nitric oxide journey must start with understanding the link between nerves and blood vessels. In the 19th century, the French physiologist Dr. Claude Bernard[2] performed experiments by severing the cervical sympathetic ganglion in rabbits, which resulted in increased "calorification" (heat production) and vasodilation (widening of visible vessels in the thin skin of an albino rabbit's ear). This was the first clear demonstration of neural regulation of blood vessel physiology.[3] Decades would pass, during which there was much controversy and arguing among neurologists, before we understood *how* the nerves influence vasodilation or vasoconstriction—was it electricity or some kind of neurotransmitter?

The hormone adrenaline was discovered in 1894 and found to mimic the sympathetic nervous system, triggering vasoconstriction and elevating blood pressure.[4] Acetylcholine, a neurotransmitter, was later discovered to be a potent vasodilator, but the mystery of its full involvement in physiology took much longer to unravel because acetylcholine was difficult to detect in tissues. Acetylcholine is tightly regulated, so it is rapidly broken down by acetylcholinesterase on release from the nerve. The breakthrough came by using eserine, an extract from the Calabar bean and a known neurotoxin, which inhibited acetylcholinesterase and prevented acetylcholine from breaking down.[4] Once acetylcholine could be measured, its function as a key mediator of the parasympathetic nervous system, including lowering blood pressure by vasodilation, was quickly recognized.

NITRIC OXIDE'S LINK TO ACETYLCHOLINE

In 1976, Furchgott and Zawadzski[5] used a bioassay and tissue culture to understand the mechanism of *how* acetylcholine interacts with vascular smooth muscle to cause relaxation. Metal probes inserted into the lumen of a rabbit aorta measured the force exerted

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from the smooth muscle contracting or dilating against the probes when the aorta was exposed to various substances such as histamine, serotonin, angiotensin, and acetylcholine. The 2 doctors recognized a problem: when the isolated rabbit aorta was exposed to acetylcholine, no relaxation occurred. In the process of preparing the tissue, filter paper was used to rub the endothelial cells off the lumen of the aorta to allow acetylcholine direct access to the smooth muscle. They repeated the experiment multiple times until finally trying the experiment *without* rubbing away the endothelial lining, and voilà! The rabbit aorta dilated on contact with acetylcholine.[5]

The discovery that endothelial cells were important to vasodilation was critical. It would later be found that acetylcholine activates the formation of nitric oxide, as a gas, within endothelial cells, which is then diffused out of the cells and into the neighboring smooth muscle, triggering additional second messengers (eg, cyclic guanosine monophosphate and cyclic adenosine monophosphate) and smooth muscle relaxation.[6] This was a major achievement in understanding vascular physiology.

THERAPEUTIC USE OF NITROGEN AND TROUBLE WITH TACHYPHYLAXIS

As our understanding of nitric oxide's role in vasodilation evolved, treatment of hypertension was the obvious medical application, but there was a catch. Nitrogen-based compounds were used therapeutically long before we knew the role nitric oxide played in vasodilation. In the middle 19th century, nitroglycerin (which gets broken down to nitric oxide) began to be used in patients with anginal chest pain.[7] It's not clear why nitroglycerin was chosen to treat angina, but it's possibly because nitroglycerin ingestion caused tachycardia and thus had a clear physiologic effect on the heart.[6] However, a major limitation of therapeutic nitrogen was recognized very early: tachyphylaxis. In the early days of treating angina, a doctor noted his patient's chest pain responded to inhaling 5 to 10 drops of nitrite from a cloth, but efficacy waned with continued use, and the patient required increased doses to have the same response.[7] It became clear that, if nitrogen compounds were given continuously, patients rapidly developed a tolerance.

At the dawn of the 20th century, workers in trinitrotoluene factories were also aware that constant exposure to nitrate-containing compounds led to tachyphylaxis.[7] Workers often complained of headaches and a racing heart on Monday, and their symptoms would slowly resolve over the course of the week. Nitrate tolerance is short-lived, so after a day or 2 off on the weekends, symptoms would start again on Monday. This phenomenon was referred to as *Monday disease*.[7] It became practice for some workers to take home pieces of nitrate over the weekend to rub on their skin until returning to work on Monday, continuing the exposure and preventing the headaches they experienced when returning to work.[7–9]

CIRCUMVENTING TACHYPHYLAXIS AND THE BREAKTHROUGH

Like most things in medicine, overcoming nitrogen tolerance is complicated because nitric oxide doesn't act alone. Nitric oxide stimulates smooth muscle relaxation and vasodilation, but a series of second messengers are also triggered once nitric oxide diffuses into the smooth muscle cell, leading to decreased calcium levels and smooth muscle relaxation.[6] Given that tachyphylaxis develops in response to exogenous nitric oxide, could the second messengers, instead of nitric oxide, be manipulated to increase vasodilation and bypass tachyphylaxis?

In the middle 1980s, Pfizer's cardiovascular research division was looking for a novel target to treat hypertension and chose phosphodiesterase type 5 (PDE5).[6] PDE5 breaks down the second messengers responding to nitric oxide, decreasing the vasodilatory response. The goal was to *inhibit* PDE5, thus allowing the continuation of smooth muscle response to nitric oxide. Sildenafil was developed with hopes of treating hypertension and angina through PDE5 inhibition. The results of the initial trials are widely known in the medical world—men on the PDE5 inhibitor noted the development of erections.[6] The pursuit of sildenafil as a treatment for angina or hypertension was sidelined, and it became a blockbuster medication to treat erectile dysfunction.

THE PULMONARY ARTERIAL HYPERTENSION CONNECTION

Research on sildenafil provided evidence that not all vascular physiology is the same. The effect of PDE5 inhibitors on lowering *peripheral* blood pressure was modest, but certain tissues, such as the corpus cavernosum of the penis, have a profound response to the drug.[6] Further research explored the role of PDE5 in vascular territories throughout the body. Using a combination of animal models and human tissue, a particularly high expression of PDE5 was found in lung tissue.[6,10] Nitric oxide turns out to be an important regulator of oxygenation and blood flow (ventilation-perfusion matching)

in the pulmonary vessels. As alveoli are aerated and expand, vascular endothelial cells are stretched and release nitric oxide, leading to vasodilation and increased blood flow to the well-oxygenated alveoli.[9] With a clearer sense of the roles nitric oxide and PDE5 play in pulmonary physiology, attention turned once again to treating pulmonary arterial hypertension with sildenafil.

Experiments with a chronically hypoxic rodent model demonstrated that treatment with a PDE5 inhibitor protected the mice from developing pulmonary hypertension.[6] Soon, multiple case reports were published on the efficacy of PDE5 inhibition in patients with pulmonary arterial hypertension, resulting in the SUPER-1 (Sildenafil Use in Pulmonary Hypertension) trial in 2002[11] that showed improvements in the 6-minute walk as well as pulmonary hemodynamics. Based on these favorable outcomes, the US Food and Drug Administration approved sildenafil in 2005 for the treatment of pulmonary arterial hypertension. Multiple medications are now approved to treat pulmonary arterial hypertension, including 2 PDE5 inhibitors.

CONCLUSION

Any farmer will proclaim the benefits of nitrogen in soil, but not every clinician can explain why nitrogen is critical to understanding vascular physiology. Nitric oxide's role in vasodilation was revealed because of a series of experiments and leaps in knowledge over the 19th and 20th centuries. The first was the discovery of the Calabar bean's importance in measuring and understanding acetylcholine's role in vasodilation.[4] Then the physical manipulation of the vascular lumen led to the recognition that a gas (nitric oxide) communicates between endothelial cells and vascular smooth muscle.[5,6] Further trial and error demonstrating nitric oxide's limitations as a therapeutic agent inspired the idea to manipulate second messengers with PDE5 inhibitors to circumvent tachyphylaxis.[6] Clinical use of these PDE5 inhibitors provided evidence that they target vessels in specific tissues, finally leading to a breakthrough in pulmonary arterial hypertension management.[6,10,11] The journey of nitric oxide's role in physiology shows the many steps required to develop a new therapeutic, as well as what a therapeutic can then teach us about normal physiology.

Next time you're looking at the periodic table of the elements, focus on atomic number 7, take a deep breath and hold it, feel those alveoli stretch, and appreciate the work of the vascular endothelial cells and the burst of nitric oxide.

DISCLOSURES

Dr. Brown has disclosed consulting and teaching and speaking for Amgen and Chemocentryx.

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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: My adult patient's hypercholesterolemia is not responding to statins—what's next?

A 65-year-old man with a history of hypercholesterolemia and hypertension well controlled on losartan 25 mg daily presents for follow-up on his cholesterol. He has no history of smoking, alcohol use, or heart disease. In addition to losartan, he has been taking rosuvastatin 40 mg daily for the past 2 months. Despite these measures, he has been unable to achieve his goal low-density lipoprotein cholesterol (LDL-C) level of less than 100 mg/dL. His lipid panel is LDL-C 165 mg/dL, high-density lipoprotein 45 mg/dL, and total cholesterol 210 mg/dL. Before starting statin therapy, his lipid panel was LDL-C 185 mg/dL, high-density lipoprotein 45 mg/dL, and total cholesterol 230 mg/dL. His current 10-year risk of atherosclerotic cardiovascular disease (ASCVD) is 14.6%. What are the next steps in managing this patient's hypercholesterolemia?

A: In adults at risk of ASCVD, multiple factors can account for lack of response to statin therapy, ranging from poor compliance to other diagnoses. Further diagnostic studies may be indicated and other treatments can be considered if LDL-C goals are not met after a trial with statin therapy.

STATIN HYPORESPONSIVENESS DEFINED

Statin hyporesponsiveness is the inability to achieve target LDL-C levels despite maximally tolerated more potent statin therapy.[1] Target LDL-C varies based on ASCVD risk; according to the latest American College of Cardiology guidelines, the target includes a percent reduction and a goal level.[2]

For primary prevention, it is recommended that patients age 40 to 75 with intermediate ASCVD risk (7.5% to < 20%) achieve a 30% to 49% reduction in LDL-C with a goal LDL-C of less than 100 mg/dL.[2,3] The recommendation for patients with high ASCVD risk (≥ 20%) is a 50% or greater reduction in LDL-C with a goal LDL-C of less than 70 mg/dL.[2,3]

For secondary prevention in patients age 40 to 75 with ASCVD labeled not very high risk, the recommendation is also LDL-C reduction of 50% or greater and a goal LDL-C of less than 70 mg/dL.[2,3] For secondary prevention in very-high-risk patients, including those who have a history of either multiple major ASCVD events or 1 major ASCVD event with multiple high-risk factors, the goal is LDL-C reduction of 50% or greater and a lower goal LDL-C of 55 mg/dL.[2–4]

Inability to achieve these targets on statins alone is deemed an insufficient response to statins.

EVALUATING STATIN HYPORESPONSIVENESS

Factors contributing to statin hyporesponsiveness can be multifactorial and include medication nonadherence, underlying lipid disorders, pharmacogenomic factors, and environmental factors.[1] Evaluation of statin resistance requires a comprehensive review of all potential causes (**Figure 1**).[5]

Noncompliance and analytic error in laboratory testing

The first steps are to ensure that patients are taking their medication and that laboratory testing is accurate. Statin noncompliance is the most commonly cited reason for persistent hypercholesterolemia.[6] Factors contributing to noncompliance include pill burden and, in some cases, side effects such as myalgias. Patients should be asked routinely about their statin use, and particularly about when they take their

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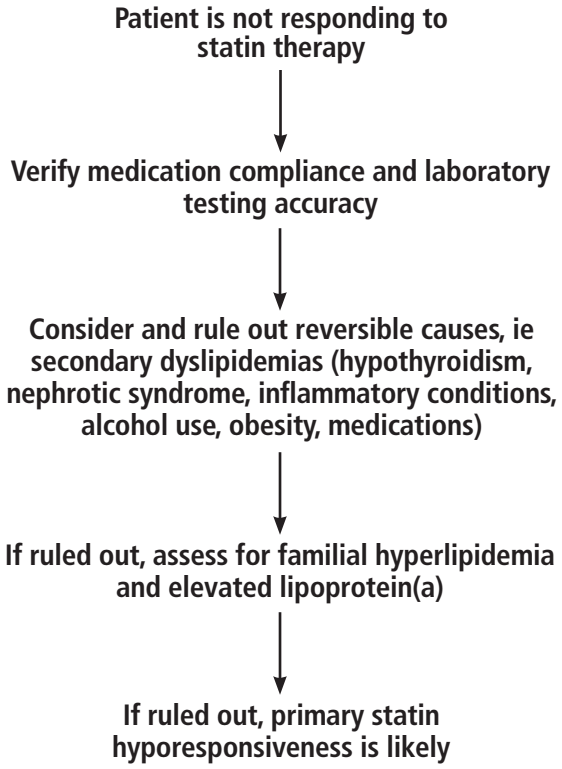

Figure 1. Clinical approach to evaluating statin hyporesponsiveness.

Based on information from reference 5.

statin, as some statins are most effective when taken at bedtime. Some clinicians monitor compliance with electronic health records, patient questionnaires, and routine pill counts.[5]

Patients whose noncompliance is related to statin intolerance due to side effects such as myalgias may respond to an alternative statin, a lower-dose statin, intermittent dosing, or an alternative lipid-lowering agent.[7] Typically, at least 2 different statins should be tried before transitioning to an alternative lipid-lowering agent.[5] Notably, a large meta-analysis that included more than 4 million patients showed an overall prevalence of statin intolerance of 9.1%, suggesting that the prevalence of statin intolerance may be overestimated.[8]

Laboratory test inaccuracy due to LDL-C variations in fasting vs nonfasting states can make a patient appear to be statin-hyporesponsive. It is essential to repeat testing on multiple occasions and note the fasting state so that LDL-C values can be compared over time. Other methods of calculating LDL-C that are less affected by triglyceride levels, such as the Sampson-NIH or Martin-Hopkins equations, can also be used to ensure accuracy.[5]

When compliance and laboratory test accuracy have been addressed, secondary dyslipidemia, common lipid disorders such as familial hypercholesterolemia, and elevated lipoprotein(a) should be considered.

Secondary dyslipidemias

The workup for statin-hyporesponsive hypercholesterolemia begins with ruling out reversible causes of hypercholesterolemia, or secondary dyslipidemias. These include hypothyroidism, nephrotic syndrome, inflammatory conditions, alcohol use, obesity, and medications. Common medications that can cause hyperlipidemia include antiretroviral therapy for human immunodeficiency virus infection, amiodarone, phenytoin, carbamazepine, corticosteroids, and cyclosporine. When a reversible cause of secondary dyslipidemia is identified, the first step is treatment of the underlying cause followed by repeat LDL-C testing. If the LDL-C is still elevated, a second lipid-lowering agent can be added.[5]

Familial hyperlipidemia

If secondary dyslipidemia is ruled out, the evaluation should assess for familial hypercholesterolemia caused by mutations in the gene encoding the LDL receptor (*LDLR*).[5] The Dutch Lipid Clinic Network criteria,[9] Simon Broome criteria,[10] or the American College of Cardiology/American Heart Association guidelines can be used for diagnosis.[11] The major forms of familial hypercholesterolemia are heterozygous and homozygous[5]:

- Heterozygous familial hypercholesterolemia consists of mutations in 1 allele or different mutations in both alleles, and LDL-C levels can be 2 to 3 times above normal
- Homozygous familial hypercholesterolemia consists of the same mutation in both alleles, and LDL-C can be up to 10 times above normal.

Response to statin therapy in familial hypercholesterolemia depends on the remaining function of the LDL receptor, which is determined by the type of mutation present. Patients with *LDLR* mutations that completely inactivate receptor activity are often resistant to statins altogether. Some patients with familial hypercholesterolemia may benefit from a second lipid-lowering agent in addition to statin therapy, but many patients, particularly those with the homozygous form, do not benefit from second agents and ultimately require referral to a lipid specialist.[5]

Elevated lipoprotein(a)

The workup should include measurement of lipoprotein(a), an LDL-like molecule with a prothrombotic

TABLE 1
Nonstatin lipid-lowering agents

Lipid-lowering agent	Mechanism of action	LDL-C reduction	When to consider using
Ezetimibe	Inhibits cholesterol absorption in the small intestine	15%–22% (23%–25% in combination with a statin)	First-line agent if insufficient response seen with statins alone
PCSK9 inhibitor	Prevents PCSK9, an enzyme involved in the degradation of LDL receptors on liver cells, from binding to LDL receptors, reducing receptor degradation and, in turn, increasing LDL-C clearance	55%–65%[13]	Second-line agent if LDL-C targets are not met with statin and ezetimibe combination therapy Can be first line if > 25% reduction in LDL-C is required or patient is deemed very high risk[a]
Inclisiran	Small interfering RNA that binds to messenger RNA of PCSK9, limiting production of the enzyme	49.9%–52.3%	For patients deemed very high risk who are not achieving LDL-C targets on statins alone
Bempedoic acid	Decreases cholesterol synthesis in the liver by inhibiting adenosine triphosphate citrate lyase	16.5% (36.2% in combination with ezetimibe)	For patients deemed very high risk who are not achieving LDL-C targets on statins alone
Evinacumab	Monoclonal antibody that inhibits angiopoietin-like 3, a protein that reduces the activity of lipases involved in lipid hydrolysis, thus increasing lipid metabolism	47.1%	For patients with homozygous familial hypercholesterolemia
Lomitapide	Inhibits microsomal triglyceride transfer protein, which is involved in the assembly of apolipoprotein B and the production of very-low-density lipoprotein	25%–51%	For patients with homozygous familial hypercholesterolemia

[a]Very high risk: history of either multiple major atherosclerotic cardiovascular disease (ASCVD) events or 1 major ASCVD event with multiple high-risk factors (age > 65, heterozygous familial hypercholesterolemia, history of prior coronary artery bypass grafting or percutaneous coronary intervention outside of a major ASCVD event, diabetes, hypertension, chronic kidney disease, smoking, persistent LDL-C elevation despite therapy with maximum statin and ezetimibe, congestive heart failure history).[2]

LDL = low-density lipoprotein; LDL-C = low-density lipoprotein cholesterol; PCSK9 = proprotein convertase subtilisin/kexin type 9

Based on information from reference 3.

apolipoprotein(a) protein attached to the atherogenic apolipoprotein B-100 component.[5,12] The combination of the atherogenic apolipoprotein B-100 component with a prothrombotic apolipoprotein(a) results in markedly increased ASCVD risk that is not reduced by lifestyle changes, statins, or other lipid-lowering agents.[12] Traditional LDL-C calculations reported on lipid panels include lipoprotein(a), and it is reasonable to check the lipoprotein(a) level when assessing for statin hyporesponsiveness. If it is elevated, an additional nonstatin agent could be added to maximize LDL-C lowering.[5]

No treatments targeting lipoprotein(a) specifically are approved, but trials are under way.[12] Examples include antisense oligonucleotides like pelacarsen that bind apolipoprotein(a) messenger RNA to prevent translation; small interfering RNA molecules like olpasiran and lepodisiran that degrade apolipoprotein(a) messenger RNA; and oral agents such as muvalaplin that disrupt the noncovalent interactions between apolipoprotein(a) and apolipoprotein B-100.[12]

PRIMARY HYPORESPONSIVENESS

If the initial workup is negative, then primary statin hyporesponsiveness can be considered. Pharmacogenetic factors likely drive primary statin hyporesponsiveness. Genetic mutations affecting statin responsiveness can be involved in either the lipid metabolic pathway or metabolism of the drug itself. Commonly affected genes

(and the proteins they encode) in the lipid metabolic pathway include *APOA1* (apolipoprotein A1), *LPA* (apolipoprotein[a]), and PCSK9 (proprotein convertase subtilisin/kexin type 9); genes involved in drug metabolism that are affected include *SLCO1B1* (organic anion transporting polypeptide 1B1), *CYP3A4* (cytochrome P450 3A4), and *CYP7A1* (cytochrome P450 7A1). Although pharmacogenetic testing can be pursued, it may have low clinical significance, and it would be reasonable to instead add a second nonstatin agent.[5]

NONSTATIN ALTERNATIVES

Statins remain the primary treatment for patients with hypercholesterolemia, but newer nonstatin cholesterol-lowering agents can be used for patients with statin-resistant hypercholesterolemia (**Table 1**).[2,3,13] Ezetimibe, a first-line nonstatin therapy, inhibits cholesterol absorption in the small intestine and reduces LDL-C levels up to 25% when taken in combination with a statin.[3,13,14]

PCSK9 inhibitors such as evolocumab and alirocumab are also effective. These are monoclonal antibodies that bind PCSK9 molecules and subsequently prevent LDL receptor degradation. This class of lipid-lowering agents has been shown to reduce LDL-C levels by 55% to 65% when added to statin therapy.[13] Inclisiran, a small interfering RNA molecule, is an effective LDL-C–lowering agent that also acts on PCSK9 and catalyzes the breakdown of PCSK9 messenger RNA.

Bempedoic acid is an adenosine triphosphate citrate lyase inhibitor that lowers LDL-C by inhibiting cholesterol synthesis upstream of statins. Evinacumab is an angiopoietin-like 3 inhibitor that drives increased lipid metabolism, and lomitapide inhibits apolipoprotein-B assembly, leading to reduced LDL-C levels.[3]

Selecting a nonstatin

Initial treatment for all patients at risk of ASCVD should include statin therapy to achieve LDL-C targets as outlined by the American College of Cardiology expert consensus decision pathway for nonstatin therapies.[2] Additional agents can be considered for patients unable to achieve their target LDL-C despite maximally tolerated statin therapy. The initial nonstatin agent of choice is ezetimibe because of its cost, safety profile, and tolerability.[2,3] If LDL-C targets are not met with ezetimibe, then PCSK9 inhibitors can be used in addition to or in place of ezetimibe.

If a patient requires a greater than 25% reduction in LDL-C despite treatment with maximally tolerated statin therapy or is deemed to be very high risk (eg, an LDL-C greater than 190 mg/dL), it is reasonable to initiate PCSK9 inhibitors before trying ezetimibe; ezetimibe typically can only lower LDL-C by 25%.[3,14] Inclisiran or bempedoic acid can also be used in these very-high-risk patients.

Patients with homozygous familial hypercholesterolemia benefit the most from agents such as evinacumab and lomitapide.[3]

THE BOTTOM LINE

Many patients do not meet their target LDL-C levels with statin therapy alone and require further investigation for causes such as secondary dyslipidemia, familial hypercholesterolemia, and elevated lipoprotein(a). The advent of novel, nonstatin lipid-lowering agents offers more options for lowering LDL-C levels. For patients who have an inadequate response to statin therapy, nonstatin lipid-lowering agents should be introduced alongside statin therapy to further reduce ASCVD risk, as recommended by the American College of Cardiology expert consensus decision pathway for nonstatin therapies.[2]

DISCLOSURES

The authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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REVIEW

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Direct oral anticoagulants: Challenging prescribing scenarios in everyday practice

ABSTRACT

Direct oral anticoagulants (DOACs) are preferred to vitamin K antagonists for treating venous thromboembolism and nonvalvular atrial fibrillation, primarily because of comparable efficacy, consistent dosing, and fewer drug-drug interactions. However, major trials that led to the approval of DOACs excluded subsets of patients who are challenging to treat in the primary care setting, including patients with extreme body weight, advanced kidney disease, and advanced cirrhosis, and those who have undergone bariatric surgery. The authors review the available evidence and outline current recommendations to help guide the appropriate use of DOACs in these patients.

KEY POINTS

- Apixaban and rivaroxaban are safe in patients with a body mass index less than 50 kg/m^2 or weight less than 150 kg. Data are limited for other extreme body weights.
- All DOACs can be used in patients with mild to moderate kidney impairment, but safety and efficacy varies in those with severe impairment or end-stage kidney disease.
- DOACs can be used in patients with Child-Pugh class A or B liver cirrhosis, except for rivaroxaban, which may be avoided in Child-Pugh B disease. All DOACs should be avoided in patients with Child-Pugh C disease.
- In those who have had bariatric surgery, the type of procedure determines which DOAC can be used, if at all.

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Direct oral anticoagulants (DOACs) have replaced vitamin K antagonists as the oral anticoagulants of choice for treatment of venous thromboembolism (VTE) and nonvalvular atrial fibrillation. Direct factor Xa inhibitors (apixaban, edoxaban, and rivaroxaban) and direct thrombin inhibitors (dabigatran) are preferred to vitamin K antagonists because these agents have comparable efficacy, fixed dosing with no need for monitoring, fewer drug-drug interactions, and better adverse effect profiles.[1] However, the phase 3 randomized controlled trials that led to the approval of DOACs excluded several patient populations whose comorbidities are commonly encountered in daily clinical practice, including those with extreme body weight, advanced kidney disease, and advanced liver disease, and those who have undergone bariatric surgery. Because available evidence is limited, selecting anticoagulants for these patients can be challenging, and cautious decision-making is warranted.

EXTREME BODY WEIGHT

Populations with extreme body weight, including severe obesity (> 120 kg or body mass index [BMI] ≥ 40 kg/m^2) and those who are underweight (< 60 kg or BMI < 18.5 kg/m^2), have been underrepresented in clinical trials evaluating DOACs in VTE and atrial fibrillation. This is problematic because the pharmacokinetics and pharmacodynamics of DOACs are variable in patients with extreme obesity.[2] Studies have shown that body weight has minimal impact on

the pharmacokinetic and pharmacodynamic profiles of rivaroxaban and apixaban, and has a modest effect on the profile of dabigatran.[2,3] For dabigatran, weight had an inverse correlation with peak and trough concentrations. Data on edoxaban are lacking.

Evidence in VTE

Without clinical trial data, numerous single-centered retrospective cohort studies have evaluated the use of DOACs (predominantly apixaban and rivaroxaban) in patients with severe obesity and VTE or atrial fibrillation and have shown comparable safety and efficacy with vitamin K antagonists.[4–6] In a real-world study with more than 8,600 patients in the rivaroxaban arm and more than 5,900 in the warfarin arm (approximately 41% of all participants had BMI ≥ 40 kg/m^2), those taking rivaroxaban had a significantly lower risk of VTE recurrence (7.0% vs 8.2%, hazard ratio [HR] 0.85, 95% confidence interval [CI] 0.75–0.97) and a similar risk of major bleeding (4.1% vs 3.6%, HR 1.11, 95% CI 0.89–1.37) compared with those taking a vitamin K antagonist.[7]

Recent observational prospective data from the START-Register (Survey on Anticoagulated Patients Register) study, which included patients with both VTE and atrial fibrillation, showed no difference in VTE recurrence, stroke, and systemic embolism between DOACs and vitamin K antagonists in those with severe obesity (mean BMI 42 kg/m^2).[8] A retrospective database analysis of patients on apixaban, dabigatran, or rivaroxaban for VTE found no difference in VTE recurrence in patients weighing 120 kg or more (mean BMI 41.2 kg/m^2) compared with patients weighing less than 120 kg (mean BMI 28.7 kg/m^2).[9]

Despite these encouraging data, retrospective data from the Mayo Clinic VTE Registry, which included more than 2,500 patients with weights ranging from 27 kg to 263 kg, showed that treatment with DOACs was associated with a higher incidence of major bleeding in patients weighing less than 60 kg vs those weighing 60 to 120 kg and more than 120 kg.[10] Moreover, patients with cancer weighing more than 120 kg who were treated with rivaroxaban had a higher VTE recurrence rate compared with the other weight groups.

Evidence in atrial fibrillation

In a post hoc analysis of the ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial, in 982 patients who weighed more than 120 kg, including 258 patients with weight greater than 140 kg, risk of stroke, systemic embolism, and major bleeding were comparable in those receiving apixaban and vitamin K antagonists.[11] Post hoc analysis of other prospective atrial fibrillation studies that included patients with a BMI greater than 40 kg/m^2 showed no evidence of inferior safety or efficacy with DOACs compared with vitamin K antagonists.[12]

Numerous retrospective observational studies have, in fact, demonstrated DOACs have better safety and efficacy (apixaban had the best safety and efficacy, followed by rivaroxaban and dabigatran) than warfarin in patients with atrial fibrillation at the extremes of body weight (BMI < 18.5 kg/m^2 and > 40 kg/m^2).[13] In a meta-analysis of 18 studies involving 387,205 patients with obesity and atrial fibrillation, compared with vitamin K antagonists, DOACs were associated with significant reductions in ischemic stroke (odds ratio [OR] 0.70, 95% CI 0.66–0.75), hemorrhagic stroke (OR 0.47, 95% CI 0.35–0.62), systemic embolism(OR 0.67, 95% CI 0.54–0.83), and major bleeding (OR 0.62, 95% CI 0.54–0.72).[14]

A subanalysis of the ELDERCARE-AF (Edoxaban Low-Dose for Elder Care Atrial Fibrillation Patients) trial showed that low-dose edoxaban (15 mg once daily) resulted in a lower stroke or systemic embolism rate compared with placebo in patients 80 years or older with atrial fibrillation who weighed 45 kg or less (HR 0.36, 95% CI 0.16–0.80); however, this benefit was accompanied by a numerically higher rate of major bleeding (HR 3.05, 95% CI 0.84–11.11).[15]

The Ascension Health registry, which included more than 2,500 adult patients with low body weight (weight ≤ 60 kg or BMI < 18.5 kg/m^2) receiving treatment for atrial fibrillation or VTE, compared vitamin K antagonists with DOACs (apixaban or rivaroxaban) and found no difference in thromboembolism (P = .38), composite major plus clinically relevant nonmajor bleeding (P = .18), and all-cause mortality (P = .12).[16]

Guideline recommendations

In 2021, the International Society on Thrombosis and Haemostasis (ISTH) updated its recommendations to suggest using rivaroxaban or apixaban for VTE treatment in patients with BMI greater than 40 kg/m^2 or weight greater than 120 kg, but recommended avoiding dabigatran and edoxaban due to lack of sufficient data.[3] However, the ISTH guidance statements do highlight the paucity of data for higher BMIs (ie, 50 kg/m^2 or greater and weight greater than 150 kg), and DOACs should ideally be avoided in this subset of patients. ISTH also suggests not monitoring drug-specific DOAC peak or trough levels to guide management decisions because of the lack of data.

TABLE 1
Direct oral anticoagulant use in extreme body weight

Condition	Body mass index or weight		
	≥ 50 kg/m² or > 150 kg	40–49 kg/m² or 120–150 kg	< 18.5 kg/m² or < 60 kg
Venous thromboembolism	Data limited	Apixaban and rivaroxaban may preferably be used	Data scarce, but DOACs may be used
Atrial fibrillation	Data limited	Apixaban, rivaroxaban, and dabigatran can be used	Apixaban is preferred; reduce dose to 2.5 mg twice daily if creatinine clearance > 1.5 mg/dL or age > 80, or both; other DOACs may also be considered

Based on information from references 3 and 17.

The 2023 American College of Cardiology and American Heart Association guideline[17] neither favors nor discourages the use of DOACs for atrial fibrillation in those with severe obesity. In patients weighing 60 kg or less, apixaban use is safe, and dose reduction is recommended when a patient is also older than 80 years or has serum creatinine greater than 1.5 mg/dL, or both.

Summary

Table 1 outlines which DOACs can be used for treatment of VTE or atrial fibrillation in patients with extreme body weight.[3,17] For patients with severe obesity and VTE or atrial fibrillation, the use of DOACs should be based on informed decision-making between clinicians and their patients. Apixaban and rivaroxaban can be used to treat both as long as BMI is less than 50 kg/m² or weight is less than 150 kg, beyond which data are limited and DOACs should be avoided. While DOACs may be used for both VTE and atrial fibrillation in patients weighing less than 60 kg, given the scarcity of data and lack of guidance recommendations, individualized decision-making based on patient preference is warranted.

KIDNEY DYSFUNCTION

All DOACs are eliminated by the kidneys to some degree, with dabigatran being the most dependent on kidney function (80%), followed by edoxaban (50%), rivaroxaban (35%), and apixaban (27%).[18] In patients with creatinine clearances of 50 to 80 mL/min, 30 to 50 mL/min, and 30 mL/min or less, DOAC area under the plasma drug concentration–time curves are higher than for those with normal kidney function, as follows[19]:

- Dabigatran: 1.5, 3.2, and 6.3 times higher
- Rivaroxaban: 1.4, 1.5, and 1.6 times higher
- Apixaban: 1.16, 1.29, and 1.38 times higher
- Edoxaban: 1.32, 1.74, and 1.72 times higher.

Evidence

Moderate kidney impairment. In patients with creatinine clearance of 30 to 50 mL/min and VTE or atrial fibrillation, DOACs are preferred to vitamin K antagonists due to similar efficacy and lower rates of major bleeding, particularly intracranial bleeding.[20]

Severe kidney impairment (creatinine clearance 15–29 mL/min) data are limited to retrospective or manufacturer-provided reports measuring plasma drug levels without prospective clinical outcomes.[20,21] The phase 3 randomized controlled trials that led to the approval of DOACs for VTE and atrial fibrillation excluded patients with creatinine clearance less than 30 mL/min (for dabigatran, edoxaban, and rivaroxaban) and creatinine clearance less than 25 mL/min (for apixaban).[22–29] Although the US Food and Drug Administration labels for apixaban and rivaroxaban have not entirely excluded their use in severe kidney disease based on pharmacokinetic and pharmacodynamic data, their safety and efficacy in this setting are currently unknown.[21]

Patients on dialysis. Clinical data from a meta-analysis of 3 randomized trials that included 383 patients with atrial fibrillation on hemodialysis found that the use of DOACs was associated with a significant reduction in stroke (relative risk 0.42; 95% CI 0.18–0.97; $P = .04$) and a numeric, but statistically nonsignificant, trend toward a lower incidence of major bleeding compared with vitamin K antagonists (relative risk 0.75, 95% CI 0.45–1.28, $P = .29$).[30]

Apixaban use in patients on dialysis is based on limited pharmacokinetic and pharmacodynamic

data.[31,32] In a study involving patients on hemodialysis, the standard dose of apixaban (5 mg twice daily) led to supratherapeutic trough levels (ie, above the 90th percentile of the predicted levels for this same dose in patients with preserved kidney function).[31] A reduced dose of apixaban (2.5 mg twice daily) also resulted in significant drug accumulation at steady state, but the drug exposure was comparable with that of the standard dose of apixaban in patients with preserved kidney function.[31] Data from a study of patients on peritoneal dialysis have also shown wide variation in apixaban concentration range.[32] The area under the plasma drug concentration–time curve was significantly higher in patients on peritoneal dialysis compared with those on hemodialysis, and supratherapeutic trough levels were observed even with the reduced dose of apixaban.

Recommendations based on kidney function

In patients with acute VTE and creatinine clearance of 15 to less than 30 mL/min, updated manufacturer information recommends rivaroxaban based on clinical pharmacologic data and post hoc analysis by kidney function from phase 3 clinical trials.[33] However, the safety of this approach has never been demonstrated by prospective randomized controlled trial data. There are also emerging data from small-scale retrospective studies on the safety and efficacy of apixaban compared with warfarin in patients with kidney failure and on dialysis, but consensus guidelines have not recommended apixaban in this subset of patients.[34]

In patients with atrial fibrillation and creatinine clearance of 15 to 30 mL/min, the American College of Cardiology and American Heart Association 2023 guideline[17] recommends using a standard or reduced dose of apixaban (a dose reduction is indicated if any 2 of the following are present: serum creatinine ≥ 1.5 mg/dL, age ≥ 80 years, or body weight ≤ 60 kg), reduced dose of rivaroxaban (15 mg once daily), standard dose of dabigatran (75 mg twice daily), and standard dose of edoxaban (30 mg once daily). For patients with creatinine clearance less than 15 mL/min or on hemodialysis, standard or a reduced dose of apixaban (same reduction criteria as above) or reduced dose of rivaroxaban can be considered, while dabigatran and edoxaban are contraindicated.

Summary

DOAC recommendations based on kidney impairment are listed in **Table 2**.[17,19,27,28,31,33,34] For acute VTE in kidney disease, avoiding all DOACs for patients with end-stage renal disease and patients who are on dialysis is warranted given the absence of robust prospective data. Reduced-dose edoxaban and standard-dose apixaban may be used for patients with severe kidney impairment, but avoid rivaroxaban and dabigatran. The creatinine clearance thresholds vary for each DOAC.

In patients with atrial fibrillation and end-stage renal disease or on dialysis, a standard or reduced dose of apixaban or reduced dose of rivaroxaban can be used, while dabigatran and edoxaban are not advised. For severe kidney impairment, a standard or reduced dose of apixaban and edoxaban could be used.

All DOACs can be used in patients with VTE or atrial fibrillation and mild to moderate kidney impairment (creatinine clearance ≥ 30 mL/min).

LIVER CIRRHOSIS

Liver cirrhosis increases the risk of both thrombosis and bleeding, making effective anticoagulation very challenging.[35] All DOACs are metabolized in part by the liver, and hepatic dysfunction can potentially amplify the risk of bleeding.

Evidence

DOAC trials excluded patients with advanced liver disease, and specific randomized controlled trials of any DOACs in chronic liver disease are lacking.[17] Therefore, evidence supporting the use of DOACs in liver cirrhosis is limited.

Guideline recommendations based on Child-Pugh class

Child-Pugh class helps assess the severity of liver disease and is essential to determine appropriate anticoagulation therapy for patients with cirrhosis. Class A indicates mild hepatic impairment, B indicates moderate impairment, and C indicates severe liver disease.[35]

The ISTH 2024 guidance[36] offers recommendations on anticoagulation for VTE and atrial fibrillation in patients with cirrhosis, based on the limited available evidence. For patients with Child-Pugh A or B cirrhosis and VTE, a DOAC, low-molecular-weight heparin, or vitamin K antagonist is suggested. For patients with Child-Pugh C cirrhosis, low-molecular-weight heparin alone or as a bridge to vitamin K antagonist in those with a normal baseline international normalized ratio should be used.

The ISTH statement also emphasizes that anticoagulants should not be withheld in patients with moderate thrombocytopenia secondary to advanced liver disease. Instead, when the platelet count falls below 50×10^9/L, ISTH[36] advises case-by-case decison-making, considering factors such as the thrombosis location, size, and extension risk; the presence of active bleeding or other bleeding risk factors; and patient preference.

TABLE 2
Direct oral anticoagulant recommendations and dosages based on kidney function

Condition and direct oral anticoagulant	Creatinine clearance, mL/min			
	< 15 or on hemodialysis	15 to < 30	30 to < 50	≥ 50
Nonvalvular atrial fibrillation				
Apixaban	Not studied[a]	5 mg twice daily or 2.5 mg twice daily[b]	5 mg twice daily or 2.5 mg twice daily[b]	5 mg twice daily or 2.5 mg twice daily[b]
Edoxaban	Recommendations cannot be provided	30 mg once daily[c]	30 mg once daily[c]	60 mg once daily[d]
Rivaroxaban	Not studied[e]	Treat as moderate impairment; 15 mg once daily (not studied)	15 mg once daily	20 mg once daily
Dabigatran	Recommendations cannot be provided	75 mg twice daily[f]	150 mg twice daily	150 mg twice daily
Venous thromboembolism				
Apixaban	No prospective clinical data on efficacy and safety	No prospective clinical data on efficacy and safety	10 mg twice daily; transition to 5 mg twice daily after 7 days	10 mg twice daily; transition to 5 mg twice daily after 7 days
Edoxaban	Recommendations cannot be provided	30 mg once daily[c]	30 mg once daily[c]	60 mg once daily[d]
Rivaroxaban	Avoid	No prospective clinical data on efficacy and safety	15 mg twice daily; transition to 20 mg once daily after 21 days	15 mg twice daily; transition to 20 mg once daily after 21 days
Dabigatran	Recommendations cannot be provided	Recommendations cannot be provided	150 mg twice daily	150 mg twice daily

Note: Additional adjustments needed for concomitant use of P-glycoprotein or cytochrome P450 3A4 inhibitors, or both, are not included.

[a]Expected pharmacokinetic and pharmacodynamic profile as in ARISTOTLE (Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation) trial.[27]

[b]Reduce dose in patients with at least 2 of the following: age ≥ 80, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL.[17]

[c]Patients with creatinine clearance < 30 mL/min were not included in randomized clinical trials.[31]

[d]Do not use in patients with creatinine clearance > 95 mL/min due to increased risk of ischemic strokes.[19]

[e]Expected pharmacokinetic and pharmacodynamic profile as in ROCKET AF (Rivaroxaban Once Daily Oral Direct Factor Xa Inhibition Compared With Vitamin K Antagonism for Prevention of Stroke and Embolism Trial in Atrial Fibrillation).[28]

[f]Not based on prospective clinical data.[17]

Based on information from references 17, 33, and 34.

For patients with Child-Pugh A or B cirrhosis and atrial fibrillation, anticoagulation with standard-dose DOACs is recommended, consistent with cardiology guidelines for patients without liver disease.[36] In patients with Child-Pugh C cirrhosis and atrial fibrillation, however, there is insufficient evidence to assess the benefit and risk of anticoagulation for stroke prevention, and all DOACs should be avoided. Furthermore, specific DOACs cannot be recommended for stroke prevention in patients with cirrhosis and atrial fibrillation because of inadequate in vivo pharmacokinetic or clinical evidence.

Note that, while ISTH does not discriminate among DOACs for use in patients with Child-Pugh A or B cirrhosis, the 2023 American College of Cardiology and American Heart Association guideline[17] specifically recommends avoiding rivaroxaban for patients with Child-Pugh B cirrhosis and atrial fibrillation. Rivaroxaban pharmacokinetic studies have shown a greater than 2-fold increase in area under the plasma drug concentration–time curve and a significant plasma concentration increase ($P < .0001$) in patients with Child-Pugh B cirrhosis vs healthy patients, potentiating bleeding risk.[37]

TABLE 3
Direct oral anticoagulant dosages and precautions in liver disease

Condition and direct oral anticoagulant	Child-Pugh class		
	A	B	C
Nonvalvular atrial fibrillation			
Apixaban	5 mg twice daily or 2.5 mg twice daily[a]	Limited clinical experience; recommendations cannot be provided	Avoid
Edoxaban	60 mg once daily	Avoid	Avoid
Rivaroxaban	20 mg once daily	Avoid[b]	No clinical data available; avoid[b]
Dabigatran	150 mg twice daily	Large intersubject variability, but no evidence of a consistent change in drug exposure; use with caution or avoid	No clinical data available; avoid
Venous thromboembolism			
Apixaban	10 mg twice daily; transition to 5 mg twice daily after 7 days	Limited clinical experience; recommendations cannot be provided	Avoid
Edoxaban	60 mg once daily	Avoid	Avoid
Rivaroxaban	15 mg twice daily; transition to 20 mg once daily after 21 days	Avoid[b]	No clinical data available; avoid[b]
Dabigatran	150 mg twice daily	Large intersubject variability, but no evidence of a consistent change in drug exposure; use with caution or avoid	No clinical data available; avoid

Note: Class A is mild hepatic impairment, B is moderate impairment, and C is severe liver disease. Additional adjustments needed for concomitant use of P-glycoprotein or cytochrome P450 3A4 inhibitors, or both, are not included.

[a]Reduce dose in patients with at least 2 of the following: age ≥ 80, body weight ≤ 60 kg, serum creatinine ≥ 1.5 mg/dL.[17]

[b]Drug exposure and bleeding risk may be increased.[17,37]

Based on information from reference 36.

Patients with cirrhosis should also be evaluated for the presence of esophageal varices before starting anticoagulation, and pharmacotherapy to minimize bleeding risk should be started.[35]

Summary

For both VTE and atrial fibrillation in liver disease, DOACs are reasonable agents to use in patients with Child-Pugh A and B disease. The only exception is rivaroxaban, which should be avoided in patients with Child-Pugh B disease due to unfavorable pharmacokinetic and pharmacodynamic profiles. DOACs should be avoided in patients with Child-Pugh C disease due to lack of data (**Table 3**[17,36,37]).

BARIATRIC SURGERY

The 4 common bariatric surgeries are as follows:

- Gastric banding: an adjustable silicone band is placed around the stomach to restrict food intake
- Gastric sleeve: the stomach is resected longitudinally to reduce its volume and thereby restrict food intake
- Roux-en-Y gastric bypass: the stomach is initially stapled to create a small pouch that is subsequently connected to the jejunum, bypassing the duodenum, resulting in both caloric restriction and malabsorption
- Biliopancreatic diversion with duodenal switch: the gastric pouch is reattached more distally to the terminal ileum, causing caloric restriction and malabsorption.

Anatomic changes from bariatric surgery may alter the bioavailability of DOACs by decreasing absorptive surfaces, reducing caloric intake, or both.[38] In addition, specific DOACs are absorbed in different areas of the gastrointestinal tract. Apixaban is absorbed primarily in the duodenum, with some absorption in the stomach,

TABLE 4
Direct oral anticoagulant use for treatment of venous thromboembolism and nonvalvular atrial fibrillation after bariatric surgery

Gastric banding	All direct oral anticoagulants can be used because the gastrointestinal anatomy is preserved
Gastric sleeve	Apixaban may be a preferred option because of the intact duodenum; avoid rivaroxaban and dabigatran because they are predominantly absorbed in the stomach; edoxaban requires an acidic environment for optimal absorption, which may be altered
Roux-en-Y gastric bypass Biliopancreatic diversion with duodenal switch	All direct oral anticoagulants should be avoided due to inadequate absorption after extensive loss of the stomach and proximal small intestines

distal small bowel, and colon, whereas rivaroxaban is absorbed primarily in the stomach and, to some extent, in the proximal and distal intestines. Dabigatran is absorbed predominantly in the lower stomach and duodenum, while edoxaban is absorbed primarily in the duodenum.

Evidence

Data specific to DOAC use after bariatric surgery are limited to pharmacokinetic and pharmacodynamic studies with a small number of patients or case reports. For patients with atrial fibrillation who have undergone bariatric surgery, emerging data show comparable safety and efficacy of DOACs with vitamin K antagonists.[39] However, no formal guidelines have been published.

Recommendations based on bariatric procedure

While the American Society of Hematology 2020 guidelines[40] recommend against using DOACs in patients who have undergone bariatric surgery, the ISTH 2021 guidance statement[3] offers a more flexible approach. It suggests that DOACs may be considered in patients with VTE but should be avoided in the acute setting after bariatric surgery for at least 4 weeks due to decreased absorption. Parenteral therapy may be used instead to ensure predictable anticoagulation. This recommendation was made, however, despite the lack of robust prospective clinical data or substantial pharmacokinetic and pharmacodynamic data. In addition, ISTH[3] suggests obtaining a DOAC trough level to check drug absorption and bioavailability, even though this strategy has not been validated and standardized assays are not widely available.

All DOACs can be used in patients with gastric banding because the gastrointestinal anatomy is preserved with this surgery, so absorption is unlikely affected.

In theory, apixaban could be used in patients who have undergone gastric sleeve surgery because of the intact duodenum; however, no data support the safety and efficacy of this approach. Rivaroxaban and dabigatran should be avoided because they are predominantly absorbed in the stomach. Edoxaban requires an acidic environment for optimal absorption, which may be altered by gastrectomy.

Given the lack of prospective data, all DOACs should be avoided after Roux-en-Y gastric bypass and biliopancreatic diversion with duodenal switch due to inadequate absorption after extensive loss of the stomach and proximal small intestines.

Summary

The type of bariatric surgery determines whether, and which, DOACs could potentially be used (**Table 4**). Moreover, the decision to use DOACs to treat atrial fibrillation after bariatric surgery should be individualized and based on patient preference.

CONCLUSION

DOACs have become the preferred treatment for VTE and atrial fibrillation because of their favorable efficacy, safety, and ease of use compared with vitamin K antagonists. However, real-world use of DOACs in specific patient populations, including those with extreme body weight, advanced kidney and liver disease, and after bariatric surgery, presents unique challenges. Clinicians should rely on currently available guidelines to identify patients who may benefit from DOACs as well as those who should avoid using DOACs.

A final word of caution: it is important to consider common drug-drug interactions with DOACs because the concomitant use of P-glycoprotein or cytochrome P450 3A4 inhibitors, or both, can impact their safety and efficacy.[40]

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High-output heart failure from arteriovenous dialysis access: A structured approach to diagnosis and management

ABSTRACT

High-output heart failure can be a complication of having an arteriovenous fistula (or graft) for hemodialysis access. This review details the pathophysiology, diagnosis, and management of this serious but underdiagnosed condition.

KEY POINTS

The diagnosis of arteriovenous high-output heart failure relies on strong clinical suspicion and should incorporate noninvasive methods such as transthoracic echocardiography and color duplex ultrasonography of the access site before proceeding with right heart catheterization to confirm the diagnosis.

In patients with this condition, right heart catheterization will demonstrate a decrease in intracardiac filling pressures and cardiac indices when the fistula is temporarily occluded.

Definitive treatment includes either ligating or banding the fistula. The decision requires a multidisciplinary approach involving specialists in cardiology, vascular surgery, and nephrology—and the patient.

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Arteriovenous high-output heart failure, a consequence of blood shunting through an arteriovenous fistula created for hemodialysis access, is serious and underrecognized.

Middle-aged adults with moderately or severely reduced kidney function are at high risk of developing heart failure.[1] In 2022, 131,194 Americans with chronic kidney disease progressed to end-stage kidney disease, of whom 82% started hemodialysis,[2] and the prevalence of heart failure in this population was 25%.[3] Some of these patients with heart failure will have heart failure secondary to a high-output fistula. Although this condition was reported as early as the 1960s,[4] its exact incidence and prevalence are hard to estimate, as it lacks a universal definition or criteria.

Arteriovenous high-output heart failure is likely underdiagnosed, as most clinicians are unaware of when to evaluate for it and are unfamiliar with how to evaluate for it. Untreated, arteriovenous high-output heart failure has a high mortality. In a series of 120 patients at Mayo Clinic who had high-output heart failure, the 3-year mortality rate was 38%.[5] Thus, it needs to be recognized and treated promptly.

This narrative review details the pathophysiology, epidemiology, diagnosis, and management of arteriovenous high-output heart failure. Although we mostly talk about patients who have an arteriovenous fistula, the same information applies to those who have a prosthetic arteriovenous graft.

TABLE 1
Common causes of high-output heart failure

Cause	Mechanism
Obesity	Vasoactive adipokines released from visceral adipose tissue lead to peripheral vasodilation, decreased systemic vascular resistance, and increased cardiac output Paracrine release of fatty acids from ectopic adipose tissue can result in direct lipotoxicity-mediated alterations in myocardial metabolism, leading to negative cardiac remodeling[5]
End-stage liver disease (cirrhosis)	Systemic circulation of vasodilators from increased portal pressures results in splanchnic vasodilation and overall decreased systemic vascular resistance and increased cardiac output[8]
Arteriovenous shunting	Connection to the lower-resistance venous system decreases both afterload and systemic vascular resistance while increasing venous return to the right and left ventricle, leading to increased cardiac output[7]
Hypercapnic lung disease (chronic obstructive pulmonary disease, connective tissue disease, bronchiectasis)	Long-standing hypercapnia-induced peripheral vasodilation results in decreased systemic vascular resistance, leading to increased cardiac output[7]
Sepsis (acute and long-standing)	Interleukin 1, interleukin 6, and tumor necrosis factor–induced endocapillary leak and peripheral vasodilation decrease systemic vascular resistance, leading to increased cardiac output[9]
Anemia (severe)	Increased renal nitric oxide production leads to peripheral vasodilation, lower systemic vascular resistance, and increased cardiac output[9]
Hyperthyroidism	Increased thyroid hormone production causes increased cardiac contractility, increased heart rate, and decreased systemic vascular resistance, leading to increased cardiac output[10]
Pregnancy	Peripartum increased stroke volume, chronotropy, and increased endothelial synthesis of vasodilating prostaglandins result in decreased systemic vascular resistance and increased cardiac output[11]
Vitamin B_1 deficiency, beriberi	Vitamin B_1 is a necessary cofactor for aerobic metabolism; severe deficiency results in a switch to anaerobic metabolism, leading to a buildup of pyruvate and lactic acid, causing systemic vasodilation, decreased systemic vascular resistance, and increased cardiac output[9]
Myeloproliferative disease	Poorly understood; proposed mechanisms include myeloproliferative neoplasm causing increased metabolism by malignant cells, extramedullary hematopoiesis, or anemia[12]

DUE TO BLOOD SHUNTING

Heart failure is a clinical syndrome that results from any structural or functional impairment in ventricular filling or ejection of blood at rest or with exertion.[6] It is called *high-output* heart failure if the cardiac index is higher than 3.9 L/min/m^2 or the cardiac output is higher than 8.0 L/min.[7] The classification of heart failure by output is different from the classification system by ejection fraction (reduced, mildly reduced, and preserved). Most patients with arteriovenous high-output heart failure have a preserved ejection fraction.

Common causes of high-output heart failure and their mechanisms are listed in **Table 1**.[5,7,8–12]

In arteriovenous high-output heart failure (**Figure 1**), the fistula that was created for dialysis access allows blood to shunt from the arterial system to the lower-pressure venous system, resulting in increased right ventricular preload with compensatory right ventricular hypertrophy and dilation.[7] This increased right ventricular preload also increases left ventricular preload and stroke volume, which, along with decreased total peripheral resistance, results in increased cardiac output.[7]

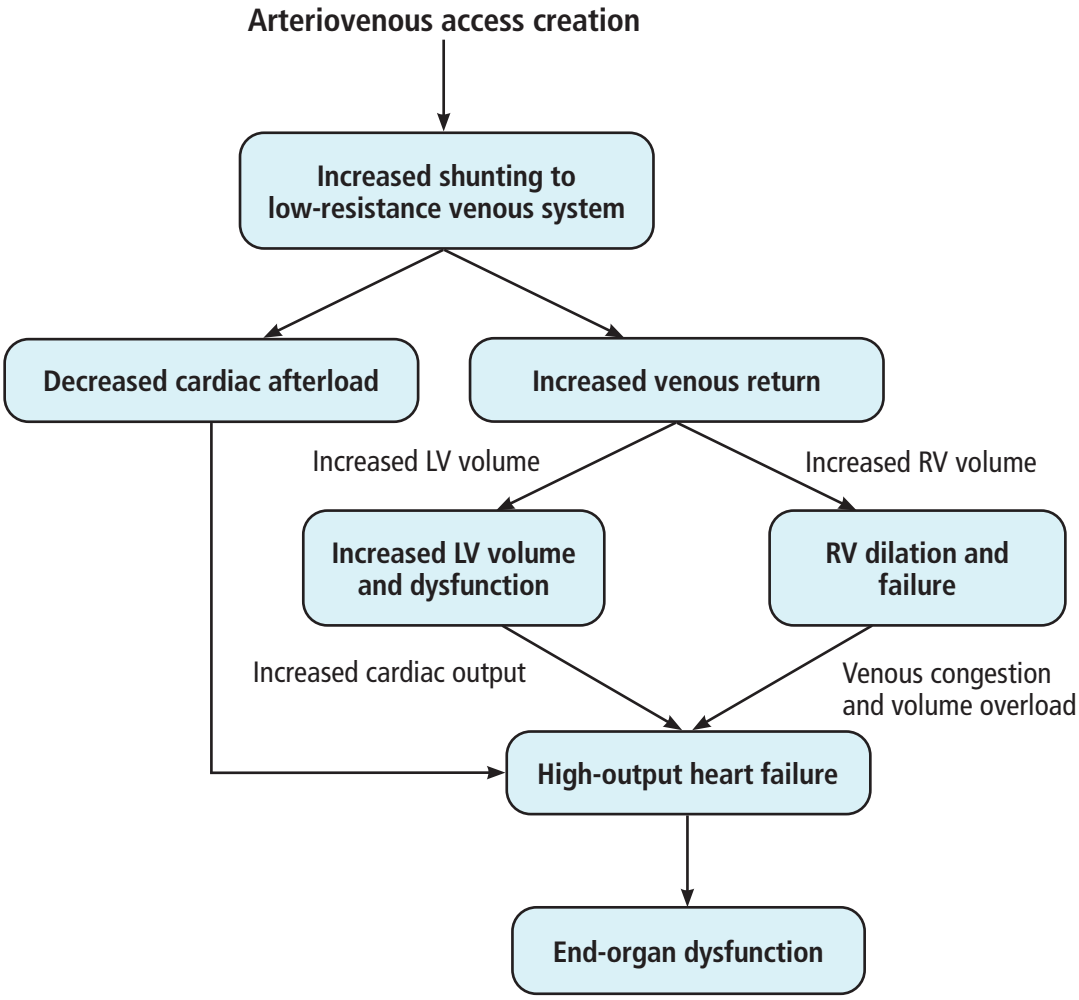

Figure 1. Pathophysiology of arteriovenous high-output heart failure. Creation of arteriovenous access, with mixing of arterial and venous blood, leads to increased shunting into the lower-resistance venous system, resulting in decreased cardiac afterload and increased venous return. These changes impact the right and left ventricles, contributing to the development of high-output heart failure.

LV = left ventricle; RV = right ventricle

Over time, increased preload can lead to left ventricular hypertrophy with impaired diastolic filling, and later progress to left ventricular dilation with impaired systolic function.[7,13] These changes can begin as soon as 3 to 14 days after the fistula is created.[13,14] Factors specific to chronic kidney disease such as hypertension, upregulation of profibrotic cytokines, and impaired iron utilization can also contribute to negative cardiac remodeling.[15]

Although systemic vascular resistance is decreased, renovascular resistance is paradoxically increased, resulting in reduced renal blood flow and subsequent activation of the renin-angiotensin-aldosterone system, thus promoting inappropriate volume retention.[7,13,14] Over time, this volume retention and cardiac remodeling create a state of volume overload with ineffective circulating volume leading to symptomatic heart failure. If left untreated, this ineffective circulating volume can result in end-organ damage.

THE HIGHER THE FLOW, THE HIGHER THE RISK

The higher the rate of blood flow through the fistula, the higher the risk of high-output heart failure.[7,16] Several factors affect the blood flow rate and the risk of heart failure.

Location. Fistulas placed more proximally, where the artery is bigger—4 to 6 mm in diameter or more—have higher flow and are associated with higher risk.[3,7] Begin et al[17] reported that in a series of 45 patients, 24 to 28 weeks after fistula creation the mean flow through brachiocephalic (proximal) fistulas was 1,285 mL/min, which was nearly twice as much as that through distal radiocephalic (distal) fistulas (647 mL/min).

Time. Arteriovenous fistulas may continue to dilate over time, resulting in significantly increased venous return.

Existing structural heart disease, which is common in patients with end-stage kidney disease before they get their fistula, is associated with higher risks of heart failure and death after starting hemodialysis. These changes include a mildly reduced to reduced left ventricular ejection fraction (< 45%) and right ventricular dysfunction, both of which increase the risk of heart failure exacerbations and are associated with a nearly 2-fold higher risk of death following arteriovenous fistula creation.[18,19] These structural changes are believed to further accelerate the pathophysiology of high-output heart failure.[5,19] Importantly though, most patients with arteriovenous high-output heart failure have a preserved left ventricular ejection fraction, ie, 50% or higher.

End-stage kidney disease itself also increases the risk of high-output heart failure through the mechanisms of hypertension, arteriosclerosis, and chronic anemia.[5]

Comorbidities. Additionally, patients who have any of the comorbidities listed in **Table 1** before getting their fistula are at higher risk of multifactorial high-output heart failure.

DIAGNOSIS: A STRUCTURED APPROACH

Although there are no validated risk-stratification tools or algorithms for diagnosing and managing arteriovenous high-output heart failure, we propose an algorithm (**Figure 2**) that starts with noninvasive assessments and progresses to invasive testing only when indicated.

Noninvasive assessments first

History. Patients present with typical symptoms of heart failure such as dyspnea, orthopnea, paroxysmal nocturnal dyspnea, decreased exercise tolerance, peripheral edema, and fatigue.[6]

The sequence of events—fistula creation first, then heart failure onset or worsening—is critical. Arteriovenous high-output heart failure should be strongly suspected if heart failure newly arises or if admissions for decompensated heart failure increase after the fistula is created and no other precipitating factor is evident, especially if the patient's fistula is high up in the arm.[20]

How long after fistula creation do symptoms arise? Information is mostly limited to case reports, but the onset may be dramatic and immediately follow the procedure, or occur more insidiously months to years later as the flow through the fistula increases, concurrent with cardiac remodeling.[3] There is no system for categorizing the time of onset of symptoms, but we propose calling it *early* if symptoms arise less than 6 weeks after the fistula was created, *intermediate* if they arise 6 weeks to 12 months later, and *late* if more than 12 months have passed.

An additional clue could be a paradoxical worsening in heart failure symptoms with the use of guideline-directed medical therapy—specifically, therapy aimed at decreasing cardiac afterload and lowering blood pressure, as these patients already have significantly low systemic vascular resistance.

Physical examination. A knowledgeable and experienced health practitioner should regularly examine the access site to monitor for flow dysfunction, either high or low.[20,21] On palpation, a thrill, pulsatility, and arteriovenous collapsibility are modestly sensitive signs (compared with ultrasonography as the gold standard) for detecting stenosis (ie, low flow) but not high flow through the fistula.[20,21]

Physical findings that should raise suspicion for high-output heart failure include widened pulse pressure, hyperdynamic precordium, a new systolic murmur (secondary to increased flow), and an abnormally large aneurysmal fistula.[20] However, no physical examination techniques have demonstrated reliable reproducibility for arteriovenous high-output heart failure surveillance.

Molecular biomarkers are of uncertain utility

Many biomarkers have been studied for stratifying the risk of high-output heart failure in patients with arteriovenous fistulas.

Brain natriuretic peptide (BNP) and **N-terminal pro–brain natriuretic peptide (NT-proBNP)** levels correlate with the risk of death in patients with end-stage kidney disease,[22] including those on hemodialysis.[23] Both increase after the fistula is created, and they correlate with increased left ventricular diastolic dysfunction.[13,24] NT-proBNP levels decrease after patients with end-stage kidney disease receive a kidney transplant and subsequently have their fistula ligated (see below).[25,26] However, neither BNP nor NT-proBNP have consistently been found to correlate with cardiac output in patients with end-stage kidney disease, and therefore they have not been shown to predict the

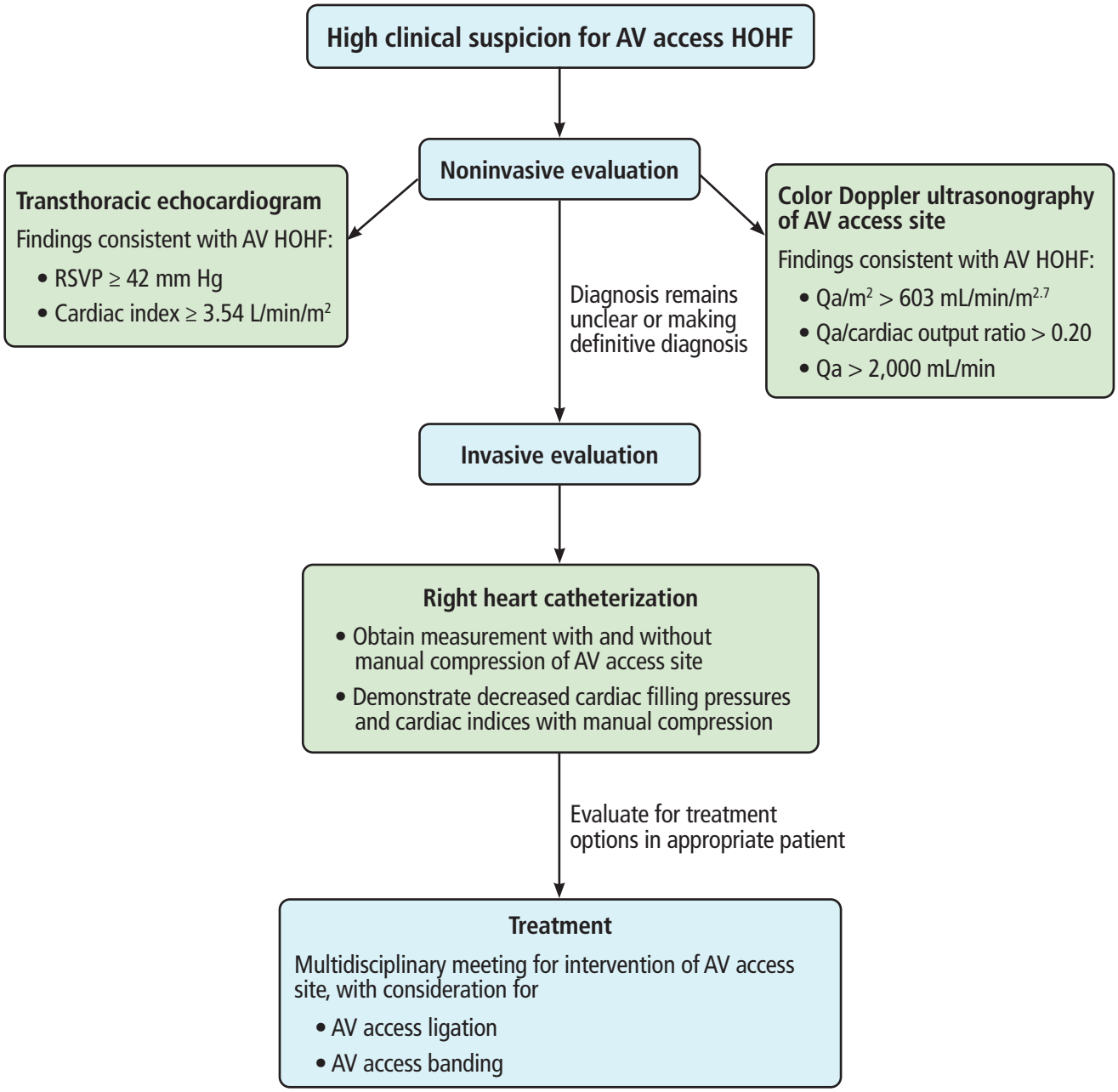

Figure 2. Algorithm for evaluating arteriovenous (AV) access–associated high-output heart failure (HOHF). The evaluation process begins with a high clinical suspicion. Initial assessment is with noninvasive modalities, followed by invasive diagnostic techniques if noninvasive methods are inconclusive or to confirm the diagnosis definitively.

Qa = vascular access blood flow; RSVP = right ventricular systolic pressure

onset of high-output heart failure.[7,13] Additionally, both NT-proBNP and BNP are renally cleared, and their concentrations are directly affected by hemodialysis.[23]

Atrial natriuretic peptide. Iwashima et al[13] found atrial natriuretic peptide levels to be weakly associated with increased cardiac output following arteriovenous fistula creation. However, no other studies have reproduced this finding. Further, the absolute values of both BNP and atrial natriuretic peptide and their percent increase after arteriovenous fistula creation have not

been consistently found to correlate with the blood flow rate through the fistula, further limiting their role in high-output heart failure risk stratification.[7,27]

Cardiac troponins have demonstrated prognostic value in diagnosing myocardial steal syndrome after a fistula is created, but not the onset of high-output heart failure.[3,28]

Newer biomarkers such as suppression of tumorigenicity 2, growth and differentiation factor 15, and galectin 3 have demonstrated associations with left ventricular structural changes, heart failure exacerbations, and cardiovascular mortality in patients on hemodialysis.[5,7] However, testing for these biomarkers is not widely available, and they have not been assessed for correlation with the onset of high-output heart failure.

Transthoracic echocardiography for those with new, suspected, or worsening heart failure

Transthoracic echocardiography is recommended for all patients with new or suspected heart failure as well as those with established heart failure with worsening symptoms.[6,29]

Patients with arteriovenous high-output heart failure can have nonspecific findings corresponding to systolic dysfunction, including increased left ventricular end-diastolic diameter and volume, as well as reduced global longitudinal strain pattern.[27,30] Transthoracic echocardiography can also show characteristics associated with diastolic dysfunction, including an elevated ratio of mitral inflow velocity between diastole and atrial contraction.[5]

Reddy et al,[5] in a retrospective study of 120 patients with known high-output heart failure, found that a cardiac index 3.54 L/min/m^2 or higher on transthoracic echocardiography had a sensitivity of 62% and specificity of 96% for detecting high-output heart failure (area under the receiver operating curve [AUC] 0.85, $P < .0001$). They also found a Doppler-estimated right ventricular systolic pressure of 42 mm Hg or higher had a 92% sensitivity and 100% specificity (AUC 0.97, $P < .0001$). However, these findings can be present in heart failure of multiple etiologies, not just high-output heart failure, and should therefore only be used to further support a suspicion of high-output heart failure in patients with a history and physical examination consistent with this diagnosis, but not by themselves to risk-stratify or diagnose this condition.

Estimated systemic vascular resistance calculated from transthoracic echocardiography could serve as an independent predictive tool for identifying arteriovenous high-output heart failure.[5] However, further studies are needed to validate its reproducibility.

Before performing transthoracic echocardiography, one should try to get the patient down to their dry weight (ie, their weight at the end of dialysis sessions) by removing fluid using intermittent hemodialysis or diuretics. This is to minimize the impact of volume overload on cardiac output measurements, as patients with end-stage kidney disease with significant volume overload may exhibit higher cardiac output attributable to the excess volume.[31]

Color duplex ultrasonography to measure the flow through the fistula

Measuring the rate of flow through the fistula provides critical information about the site's suitability for hemodialysis access as well as the risk of arteriovenous high-output heart failure. The blood flow rate should be greater than 500 or 600 mL/min for an arteriovenous access to be considered mature and adequate for hemodialysis.[20,21] However, high flow rates have been consistently shown to increase the risk of high-output heart failure.[3,16,30,32]

Color duplex ultrasonography is the most common and well-studied technique for measuring the flow.[21,33] It is widely available and relatively inexpensive.[20,21] Its sensitivity is up to 91%, and its specificity is up to 97% compared with fistulography for detecting stenosis.[34] On the negative side, scar tissue, calcification, hematoma, and severe extremity edema can hinder its accuracy. It can also be limited by operator-dependence.[20,21]

Arteriovenous flow can also be measured using magnetic resonance angiography, or indirectly during hemodialysis using ultrasonography dilution or thermodilution.[21] The cost, limited availability, time required, and risk of adverse effects of each limits their practicality.

Unfortunately, after a fistula has matured, there is no consensus on the role of routine surveillance of arteriovenous flow to prevent high-output heart failure.

How much flow is too much? Multiple studies have tried to find the threshold blood flow rate above which cardiac remodeling begins in patients without existing heart failure, or at which surveillance for high-output heart failure should begin.

Saleh et al,[30] in a study of 100 patients on dialysis without existing structural heart disease, found that a flow rate greater than 2,000 mL/min correlated with significantly greater left ventricular dilation as measured by left ventricular end-diastolic diameter, left ventricular end-diastolic volume, and left ventricular mass. Higher flow has also been associated with right ventricular dilation and is an independent risk factor for impaired right ventricular function.[14,35]

The European Society for Vascular Surgery guideline says that a blood flow rate exceeding 1,500 mL/min warrants regular flow measurements and echocardiography to monitor for signs of heart failure, but does not specify time intervals for each.[21] The National Kidney Foundation's guideline does not specify a flow rate warranting further surveillance.[20]

Similarly, there is no universally accepted blood flow rate threshold that results in high-output heart failure. Information about this possible threshold has previously been limited to case reports. Basile et al[16] found a rate greater than 2,000 mL/min had a sensitivity of 89% and specificity of 100% for predicting arteriovenous high-output heart failure (AUC 0.99). This finding was later supported by a study of patients without diabetes on hemodialysis that found significantly greater prevalence of heart failure symptoms in patients with a vascular access flow rate greater than 2,000 mL/min ($P < .05$).[36]

The ratio of arteriovenous access blood flow rate to cardiac output has also been used for risk stratification of high-output heart failure.[16,27,37] Historically, a ratio of 0.20 or 0.30 or greater has been used as a cutoff for high-output heart failure risk; however, this ratio was largely guided by case reports.[19,38–40] Basile et al[16] found a ratio of 0.20 or greater had a 100% sensitivity and 74.7% specificity for identifying high-output heart failure (AUC 0.92).

More recently, the flow rate indexed to the patient's height has been proposed as a better prognosticator for high-output heart failure than the flow rate alone. In a cohort of patients with end-stage kidney disease, all of whom had a vascular access blood flow rate greater than 2,000 mL/min, only 60% of patients had heart failure symptoms.[37] Within this subset, a flow rate indexed to height of 603 mL/min/m$^{2.7}$ or greater demonstrated a sensitivity of 100%, specificity 60%, positive predictive value 83%, and negative predictive value 100% for detecting high-output heart failure (AUC 0.75).

Our recommendations. In view of the high mortality rate associated with arteriovenous high-output heart failure, we believe invasive testing should be considered if the patient has any of the following:

- An arteriovenous access flow rate of 2,000 mL/min or greater,
- A flow rate/cardiac output ratio of 0.20 or greater, or
- A flow rate indexed to height of 603 mL/min/m$^{2.7}$ or greater.

Color duplex ultrasonography of the arteriovenous access should be done as soon as possible after transthoracic echocardiography to prevent confounding interventions, such as volume removal, from affecting the patient's hemodynamics in the interval.

INVASIVE ASSESSMENT: RIGHT HEART CATHETERIZATION

Definitive diagnosis of arteriovenous high-output heart failure requires right heart catheterization, which should be considered only after all the noninvasive studies have been done and the findings have suggested this diagnosis.

Initial measurements should be done without manipulating the arteriovenous fistula. In a patient with arteriovenous high-output heart failure, they will show increased intracardiac pressures including pulmonary capillary wedge pressure, mean pulmonary artery pressure, and mean right atrial pressure; a low to normal systemic vascular resistance; and a high cardiac output and index.[5,40] Then, the fistula should be temporarily occluded and the measurements repeated. Occlusion is commonly performed using an inflated blood pressure cuff.

The essential criterion for diagnosing high-output heart failure is reversibility of both the intracardiac pressures and cardiac indices with temporary occlusion of the arteriovenous fistula. This is particularly important when coexisting ischemia or valvopathy is present that can also be contributing to heart failure.[39] There are no established absolute values or percentage decreases from baseline of either the intracardiac filling pressures or cardiac output or index that establishes the diagnosis of high-output heart failure, however.

Compressing the fistula can also elicit a decrease in heart rate and increase in blood pressure, commonly called the Nicoladoni-Israel-Branham sign. However, this phenomenon is neither sensitive nor specific for high-output heart failure.[3]

A limitation of this procedure is that if the fistula is really big it may be hard to occlude completely, leading to false-negative findings. Another limitation is that some patients cannot tolerate lying flat without shortness of breath or hypoxia. To overcome this, dialysis to remove volume may be necessary; however, this may lead to lower intracardiac filling pressures and cardiac indices, increasing the chance for false-negative diagnosis.

TREATMENT OPTIONS

Ligation

Definitive treatment of arteriovenous high-output heart failure involves removing the shunt pathway through ligation of the fistula site. However, this leaves the patient without ready dialysis access and therefore

is only an acceptable option in those who have received a successful kidney transplant or are suitable candidates for peritoneal dialysis.

Retrospective studies and meta-analyses have shown improvements in cardiac remodeling, ejection fraction, and function after ligation.[26] In a randomized controlled trial in patients with end-stage kidney disease who had received successful kidney transplants, those who had their fistulas ligated had significantly lower NT-proBNP levels and cardiac indices at follow-up compared with patients who did not, whose NT-proBNP levels went up and whose cardiac indices did not change ($P < .001$).[32]

Improvements in heart-failure symptoms and quality of life following arteriovenous fistula ligation have also been observed in case series and retrospective studies.[25,40,41] In a retrospective cohort of 113 patients who successfully received kidney transplants, 29 (26%) had their fistulas closed, mostly because of heart failure symptoms, and their symptoms and exercise capacity improved afterward.[25]

Will prophylactic ligation *prevent* high-output heart failure? In a randomized controlled trial in 28 kidney transplant recipients with a flow rate greater than 1,500 mL/min through their fistulas, no patients in the ligation group developed high-output heart failure, while 5 of 13 (38.5%) of the nonligation group did.[42]

Whether arteriovenous fistula ligation in high-output heart failure decreases the mortality rate remains unclear.[26,42] Studies have found lower 3-year all-cause mortality rates in patients who underwent fistula ligation following kidney transplant than in their counterparts, but this difference was lost after adjustment for confounders.[43] Additionally, the studies showing the benefit of ligation included only patients who had undergone successful kidney transplantation or candidates for peritoneal dialysis. These restrictions limit the generalizability of ligation as a treatment for many patients with end-stage kidney disease who are not current candidates for either peritoneal dialysis or kidney transplantation.

Also, an important consideration is that many transplant recipients experience fistula failure and need to go back on dialysis: as many as 20% by 5 years after transplant, and 50% at 10 years—even as the number of patients on the renal transplant list also continues to grow.[44,45] Many of these patients already have limited vascular access, so the decision to ligate must be multidisciplinary and shared between the cardiologist, nephrologist, vascular surgeon, and patient.

Banding

This procedure offers an alternative to ligation for managing arteriovenous high-output heart failure. It involves surgical dissection down to the fistula and applying bands at various points along its length.[28,46] The bands reduce the radius of the fistula, thereby increasing resistance and decreasing the flow. A study in 50 patients demonstrated more than a 50% reduction in flow following banding, from 3,070 ± 95 mL/min before to 1,490 ± 105 mL/min immediately after ($P < .001$).[47]

Several banding techniques exist,[28,47,48] including precision banding with ultrasonography guidance and the minimally invasive limited ligation endoluminal-assisted revision (MILLER) procedure. In 12 patients with arteriovenous high-output heart failure and average arteriovenous fistula flow of 2,280 mL/min, precision banding resulted in an average reduction of flow of 70% or more, with an improvement in heart failure symptoms in all patients of the cohort.[28] Similarly, in 183 patients with symptomatic heart failure and high arteriovenous fistula flow, the MILLER procedure resulted in complete relief of heart failure symptoms and improved functional capacity in all patients at an average follow-up time of 11 months following band placement.[48]

Despite these improvements, the overall long-term success rates of banding remain low, with high-flow recurrence rates as high as 52% within months of the procedure.[46,47] Other complications reported with banding include stenosis resulting in inadequate flow for hemodialysis access, thrombosis, limb ischemia, distal aneurysms, and infections.[47,48] As with ligation, the decision to perform banding requires a multispecialty meeting with shared consensus between clinicians and patient.

External stenting

Stenting to reduce vascular access flow is a novel method for managing arteriovenous high-output heart failure. However, this technique has shown inconsistent long-term success.[49]

PROMPT DIAGNOSIS NEEDED

High-output heart failure remains an underrecognized but serious complication of arteriovenous access for hemodialysis. Its diagnosis requires a high clinical suspicion and should involve measuring the blood flow through the arteriovenous fistula followed by right heart catheterization to confirm the diagnosis. The high mortality rate and paradoxical worsening with conventional heart failure guideline-directed medical therapy mandate early and prompt diagnosis.

DISCLOSURES

Dr. Ghobrial has disclosed consulting for Edwards Lifesciences, Medtronic, and W.L. Gore & Associates. Dr. Hanna has disclosed serving as an advisor or review panel participant for Akcea Therapeutics, Alexion, Alnylam, Eidos Therapeutics, and Pfizer and consulting for Novo Nordisk. Dr. Finet has disclosed being an advisor or review panel participant for the American Board of Internal Medicine Advanced Heart Failure and Transplant Cardiology Board Examination and Wolters-Kluwer. The other authors report no relevant financial relationships which, in the context of their contributions, could be perceived as a potential conflict of interest.

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REVIEW

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IgA nephropathy: Update on pathogenesis and treatment

ABSTRACT

The pathogenesis of immunoglobulin (Ig) A nephropathy is described through a "4-hit" model involving production of galactose-deficient IgA, production of autoantibodies to galactose-deficient IgA, and subsequent deposition of immune complexes in the kidney glomerulus. Diagnosis remains dependent on a kidney biopsy, often after hematuria or proteinuria is detected on urinalysis. The cornerstone of therapy still involves renin-angiotensin-aldosterone system inhibitors or corticosteroids; however, new therapies targeting key aspects of the pathogenesis of IgA nephropathy are being introduced.

KEY POINTS

- IgA nephropathy is a relatively common autoimmune glomerular disease that can be diagnosed only by biopsy.
- Proteinuria reduction remains the most important treatment target.
- Treatment now includes sodium-glucose cotransporter 2 inhibitors and endothelin receptor antagonists in addition to renin-angiotensin-aldosterone system inhibitors and corticosteroids.
- New therapies target multiple pathogenic "hits" to reduce proteinuria and preserve kidney function.

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A MAJOR CAUSE OF KIDNEY FAILURE in children and adults, immunoglobulin (Ig) A nephropathy is the most common primary glomerulonephritis; its worldwide incidence is at least 2.5 per 100,000.[1]

There has been a tremendous lag in the treatment of the disease since its histologic features were first described in 1968 by Berger and Hinglais.[2] For decades, nephrologists have had little more than renin-angiotensin-aldosterone system (RAAS) inhibitors or corticosteroids in their treatment armamentarium. Thanks to a recent transformation in our understanding of and therapeutic approach to IgA nephropathy, in the near future, there may be more therapeutic options for IgA nephropathy than for any other glomerular disease. Opportunities for new therapies stem from the acknowledgment by the US Food and Drug Administration (FDA) that proteinuria reduction is an acceptable trial end point[3] in the path to drug approval. This recent innovation is also a direct consequence of years of basic science research that has refined our understanding of the pathogenesis of IgA nephropathy into a framework of "4 hits," with each hit representing a target of novel therapies.

This review addresses the current approach to management of IgA nephropathy and therapeutic options we can soon expect.

THE 4 HITS OF IgA NEPHROPATHY

IgA nephropathy is an autoimmune disease of mucosal type IgA[1] characterized by deposition of immune complexes in the glomerulus. Its pathogenesis is now firmly established and understood as the 4-hit hypothesis (**Figure 1**).[1] The

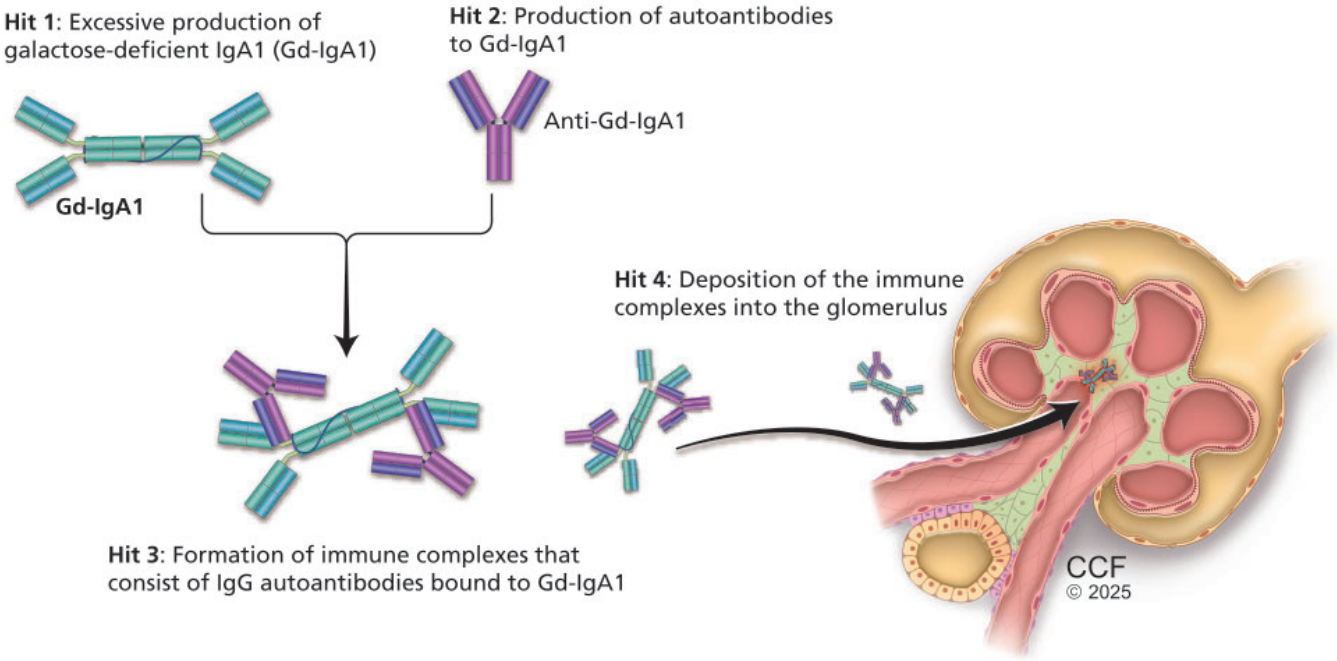


Figure 1. Pathogenesis of immunoglobulin (Ig) A nephropathy: the "4-hits" hypothesis.

4 hits comprise a complex interplay of genetic factors (involving polymorphisms in human leukocyte antigen, complement, and gut mucosal immunity) and environmental factors such as the gut microbiome, all of which contribute to the development of IgA nephropathy.

Hit 1: excessive production of galactose-deficient IgA1

Galactose-deficient IgA1 in IgA nephropathy lacks the terminal galactose moieties at the hinge region of the molecule.[1,4] The primary site for production of galactose-deficient IgA1 is now believed to be the gut and nasal mucosa.[2] Many factors have been implicated in the production of galactose-deficient IgA1.

Genetics may influence the O-galactosylation of the IgA hinge region.[5] Abnormal galactosylation of IgA can be an inherited trait, but this alone is insufficient for development of IgA nephropathy.

Cytokines, including serum B-cell activating factor (BAFF) and a proliferation-inducing ligand (APRIL), are important regulators of mucosal B-cell survival and proliferation. BAFF and APRIL promote the formation of galactose-deficient IgA1–producing plasma cells in the mucosa.[6]

Alterations in the composition of the gut microbiome (which communicates with mucosal-associated lymphoid tissue) have been implicated in IgA nephropathy.[7] Mucosal dysbiosis may be related to dysregulated mucosal IgA synthesis. Recently, it was shown that patients with IgA nephropathy have a relative overgrowth of mucin-degrading bacteria,[8] which are capable of deglycosylating IgA1.

Hit 2: production of autoantibodies to galactose-deficient-IgA1

Antibodies, either IgG or IgA, recognize the galactose-deficient hinge region of galactose-deficient IgA1, a neoepitope.[1] Routine immunofluorescence on kidney biopsy detects IgA bound to galactose-deficient IgA1 as the predominant immune complex deposited; however, evidence supports the presence of IgG autoantibodies, which also play a role in the pathogenesis of the disease.

Hit 3: formation of immune complexes consisting of IgG autoantibodies bound to galactose-deficient IgA1

Clinical and histologic activity correlate with the level of circulating immune complexes.[1,4] Additionally, alternative complement and terminal complement activity have been shown to correlate with the concentration of galactose-deficient IgA1.

Hit 4: deposition of immune complexes into the glomerulus

The effect of the immune complexes on mesangial cells within the glomerulus drives kidney injury.[9,10] Deposition of immune complexes activates mesangial cells, leading to production of inflammatory molecules such as interleukin-6 and platelet-derived growth factor and complement, which signal infiltration of monocytes and mediate glomerular injury.

TABLE 1
Immunoglobulin (Ig) A nephropathy and its mimics

	IgA nephropathy[1,12]	Systemic IgA vasculitis[1,12]	IgA-dominant postinfectious glomerulonephritis[13]	Proliferative glomerulonephritis with monoclonal IgA deposits[14]
Clinical presentation	Varied, can present with a range of clinical syndromes: microscopic hematuria (more common than macroscopic), acute kidney injury, rapidly progressive glomerulonephritis, macroscopic hematuria with concurrent respiratory or gastrointestinal infection (ie, synpharyngitic hematuria) Involvement limited to kidneys	More common in children Extrarenal involvement (leukocytoclastic vasculitis; rash; joint pain; gastrointestinal, pulmonary, neurologic involvement)	Older adults, hypocomplementemia, acute kidney injury with hematuria and proteinuria	Rare; involvement limited to kidneys
Kidney biopsy	Dominant mesangial IgA staining on immunofluorescence microscopy with variable IgG staining and frequent C3 staining; chunky, irregular mesangial IgA staining on immunofluorescence Polyclonal light chain deposition with lambda more intense than kappa		Endocapillary hypercellularity, often with neutrophils, on light microscopy Dominant IgA staining with dominant or codominant C3 staining and absent or weak IgG staining; chunky, irregular mesangial IgA staining; lambda not dominant light chains on immunofluorescence microscopy Subepithelial hump-shaped immune deposits on electron microscopy	Membranoproliferative pattern on light microscopy Monotypic light chain deposition of IgA kappa more intense than lambda
Pathogenesis	4-hit model		Unclear: likely a host-pathogen interaction with superantigens stimulating host T-cell response	Unclear: rarely associated with malignancies despite monoclonal deposition of IgA
Associations	Primary and secondary[a] distinguished by presence of associated systemic disease	Upper respiratory or gastrointestinal infection	*Staphylococcus aureus* infection, diabetes	Myeloma (rarely)

[a]Common secondary: liver disease, celiac disease, inflammatory bowel disease, viral (human immunodeficiency virus, hepatitis B and C), ankylosing spondylitis, rheumatoid arthritis, systemic lupus erythematosus, psoriasis, Sjögren syndrome, tumors (lung, renal, lymphoma).

Based on information from references 1,12–14.

The role of complement

Complement plays a prominent role in mesangial injury and is a major driver of glomerular inflammation.[11] C3 is deposited in the mesangium, activating both the alternative and lectin pathways. In vitro studies provide evidence of alternative pathway proteins such as complement components C5, C6, and C9 and other membrane attack complex antigens in the glomeruli

of patients with IgA nephropathy, whereas markers for classical pathway activation such as C1q and C4 are less prominent. Complement factor H–related protein competes with the binding of factor H, a regulator protein, leading to an increase in the activity of the alternate complement pathway.

DIAGNOSIS REQUIRES CLINICAL SUSPICION AND KIDNEY BIOPSY

Despite advances in understanding the pathogenesis of IgA nephropathy, diagnosis requires a kidney biopsy. Clinical suspicion arises from the presence of acute kidney injury, hematuria, or proteinuria. Uncommonly, patients present with gross hematuria or synpharyngitic hematuria (hematuria with pharyngitis), a presentation seen more often in younger patients (< 40 years).[1] In older populations, IgA nephropathy can be clinically occult with worsening kidney function and microscopic hematuria. While routine screening is common in countries with a high prevalence, such as Japan and China, there are no screening guidelines in the United States. Therefore, timely referral to nephrology upon discovery of hematuria or proteinuria is critical.

Histologic examination of the kidney biopsy specimen with immunofluorescence microscopy will show IgA deposits in the mesangium or capillary loops accompanied by mesangial changes (proliferation and expansion). Serologic markers, while extensively studied and now frequently used in clinical trials, require further validation before they can be applied in the clinic.

Alternative diagnoses must be considered when histopathology reveals IgA staining, as there are numerous mimics of primary IgA nephropathy (**Table 1**).[1,12–14] Systemic disease states associated with IgA nephropathy, labeled *secondary IgA nephropathy*, include IgA vasculitis, viral infections (human immunodeficiency virus, hepatitis), autoimmune disease (inflammatory bowel disease, psoriasis), cirrhosis, IgA-dominant postinfectious glomerulonephritis, and proliferative glomerulonephritis with monoclonal IgA deposits.

Once the diagnosis is established, the characteristic findings are used to determine prognosis and clinical outcomes. Secondary IgA nephropathy and IgA vasculitis have been largely excluded from clinical trials and carry a different prognosis than primary IgA nephropathy.

PROGNOSTIC TOOLS

Oxford Classification of IgA nephropathy

The Oxford Classification of IgA nephropathy was introduced in 2009.[15] The purpose was to create a standardized histopathologic scoring system using 4 variables that correlate most strongly with patient outcomes, in addition to showing adequate agreement among nephropathologists. The variables are mesangial hypercellularity (M), endocapillary hypercellularity (E), segmental glomerulosclerosis (S), and tubular atrophy/interstitial fibrosis (T), reported as the *MEST score*. The system was updated in 2016 to incorporate crescents (C) to further aid in predicting renal outcomes (**Table 2**).[15,16]

M, S, and T were found to be independent predictors of glomerular filtration rate (GFR) decline in the original Oxford cohort, but E lesions were not conclusively predictive of decline.[17] Similar associations in GFR decline were seen in patients with endocapillary hypercellularity (E) independent of immunosuppression.[18,19] The Oxford cohort did not control for immunosuppression, leading to a treatment bias. Further, patients with E lesions were more likely to receive immunosuppression. Collectively, this evidence supports the perception that endocapillary lesions are responsive to immunosuppressive treatment and contribute to the decline of kidney function if not treated with immunosuppression.

Although helpful for diagnostic standardization and prognosis, this scoring system does not consider the presence of hypertension, degree of proteinuria, or reduced GFR.

International IgA nephropathy risk prediction tool

The introduction of the international IgA nephropathy risk prediction tool further refines risk stratification by integrating histologic and clinical factors to predict renal outcomes at the time of biopsy and up to 7 years.[20] It was derived in a multiethnic international cohort with biopsy-proven idiopathic IgA nephropathy and is designed to predict the risk of a 50% decline in estimated GFR or end-stage kidney disease after biopsy.

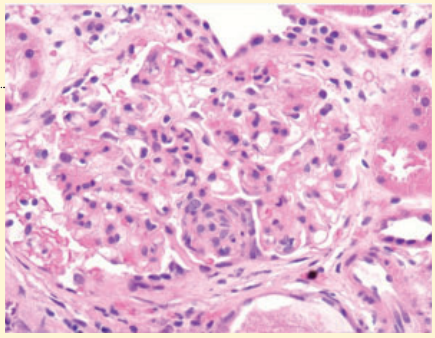
This web-based prediction tool includes the estimated GFR at the time of biopsy, systolic and diastolic blood pressure at the time of biopsy, proteinuria, age, race, use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, MEST score, immunosuppression use at or before kidney biopsy, and the number of months after a kidney biopsy that the clinician will determine the risk of progressive IgA nephropathy.

Criticisms of the IgA nephropathy prediction tool include its lack of dynamic longitudinal monitoring ability and the absence of modern therapies (endothelin receptor antagonists and sodium-glucose cotrans-

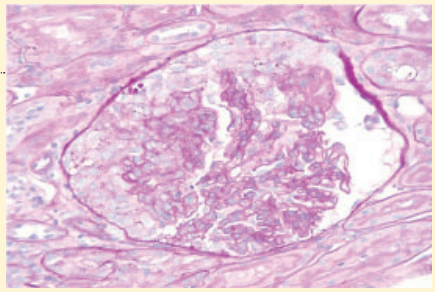
TABLE 2
Oxford Classification of immunoglobulin A nephropathy: MEST-C score

Histologic feature	Definition[15,16]	Prognosis
Mesangial hypercellularity	≥ 4 mesangial cells in any mesangial area of a glomerulus M0: < 50 glomeruli M1: ≥ 50 glomeruli	M1 is predictive of worse outcomes vs M0[15]
Endocapillary proliferation	Increased number of cells in glomerular capillary lumen E0: absent E1: present	E1 is independently associated with worse renal survival in patients who receive no immunosuppression, and does not predict outcomes in studies where patients receive immunosuppression Patients with endocapillary proliferation (E1) are more likely to receive immunosuppression, which is associated with improved outcomes in these patients[16]
Segmental glomerulosclerosis	Adhesion or sclerosis that does not involve the entire glomerulus S0: absent S1: present	S1 is predictive of worse outcomes compared with S0[15]
Tubulointerstitial fibrosis	Percentage of tubular atrophy and interstitial fibrosis of cortical area T0: absent or ≤ 25% of tubules T1: 26%–50% of tubules T2: > 50% tubules	Presence of tubulointerstitial fibrosis (T1 or T2) is strongest predictor of adverse renal outcomes[16]
Crescents, cellular or fibrocellular	Extracapillary cell proliferation > 2 cell layers and < 50% of matrix C0: absent C1: 1%–24% of glomeruli C2: > 25% of glomeruli	C1 is not predictive if immunosuppression is used C2 is predictive of worse outcomes regardless of immunosuppression[16]

Mesangial hypercellularity and endocapillary proliferation (hematoxylin and eosin stain, magnification ×400)



Crescent formation (periodic acid–Schiff stain, magnification ×400)



Images courtesy of Leal Herlitz, MD, Cleveland Clinic Anatomic Pathology.

porter [SGLT] 2 inhibitors). Also, it was not validated to guide the use of immunosuppression.[20]

Proteinuria as an indicator of kidney function

The goal of therapy in IgA nephropathy, as in all kidney disease, is to prevent progression to end-stage kidney disease by decreasing the rate of GFR loss. The main therapeutic targets in IgA nephropathy include reducing proteinuria and controlling blood pressure. The severity of proteinuria remains the strongest indicator of kidney outcome. The KDIGO (Kidney Disease: Improving Global Outcomes) guidelines[21] recommend reducing proteinuria to less than 1 g per day as a surrogate marker for improved kidney outcome, and consideration of

immunosuppressive therapy if unable to achieve proteinuria levels lower than 1 g per day with conservative management such as RAAS blockade. However, recent large registry data have revealed that 30% of patients with time-averaged proteinuria of 0.44 to less than 0.88 g/g (of creatine) developed kidney failure within 10 years.[22] It is therefore clear that patients with IgA nephropathy and lower degrees of proteinuria may benefit from more intensive disease management.

Currently, the goal of therapy is proteinuria of less than 0.5 g and absence of hematuria. These targets have not been well studied in a prospective therapeutic trial, however, and we do not yet know the risk or benefit of attempting to achieve such targets. Several new trials and therapeutics have emerged that require an update to our approach to diagnosis and treatment of IgA nephropathy.

CURRENT TREATMENT OPTIONS

Nonimmunosuppressive therapy

Treatments targeting RAAS reduce proteinuria and preserve nephrons across the spectrum of glomerular diseases, including IgA nephropathy. Use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers carries a strong recommendation in the most recent KDIGO guidelines,[21] along with a target blood pressure of 120/70 mm Hg or lower and lifestyle modifications that include smoking cessation, weight reduction, salt restriction (< 2 g/day), and exercise. KDIGO guidelines no longer recommend fish oil for IgA nephropathy.

New nonimmunosuppressive therapy options include the SGLT-2 inhibitors and dual endothelin receptor and angiotensin receptor antagonists.

SGLT-2 inhibitors. There have been no dedicated trials to evaluate IgA nephropathy outcomes with the use of these agents. However, IgA nephropathy was well represented in DAPA-CKD (Dapagliflozin in Patients With Chronic Kidney Disease),[23] a randomized controlled trial that evaluated the effect of dapagliflozin in patients with chronic kidney disease and albuminuria due to various causes. In a prespecified analysis of DAPA-CKD, 270 patients with IgA nephropathy treated with dapagliflozin had a 26% reduction in proteinuria compared with placebo. Additionally, the primary outcome (sustained decline in estimated GFR of 50% or more, end-stage kidney disease, or death from a kidney disease–related or cardiovascular cause) occurred in only 6 (4%) participants on dapagliflozin vs 20 (15%) on placebo (hazard ratio 0.29; 95% confidence interval [CI] 0.12–0.73), offering a 71% risk reduction. Criticisms of this trial include the lack of adequate blood pressure control with angiotensin-converting enzyme inhibitors or angiotensin receptor blockers in the run-in period compared with other trials in IgA nephropathy, in addition to recruitment of older patients and exclusion of patients with recent immunosuppression use.

The safety and efficacy of the **dual endothelin and angiotensin receptor antagonist sparsentan** in IgA nephropathy was recently evaluated in the PROTECT (Efficacy and Safety of Sparsentan Versus Irbesartan in Patients With IgA Nephropathy) trial.[24] In this large randomized, active-controlled study, adults with high-risk IgA nephropathy (> 1 g proteinuria per day) received sparsentan or irbesartan 300 mg daily. The primary efficacy end point was a change from baseline to week 36 in the urine protein-creatinine ratio based on a 24-hour urine sample. The sparsentan group saw a 49.8% proteinuria reduction compared with 15.1% in the irbesartan group, which was maintained until the 110-week trial ended. At 2 years, the estimated GFR chronic rate of change (from weeks 6 to 110) was −2.7 mL/min/1.73 m^2/year with sparsentan and −3.8 mL/min/1.73 m^2/year with irbesartan (difference 1.1 mL/min/1.73 m^2/year, 95% CI 0.1–2.1).

The rate of adverse events was similar in the 2 groups, with more hypotension and acute kidney injury occurring in the sparsentan group. Due to the potential hepatotoxicity and fetal toxicity of endothelin receptor antagonists, the FDA requires the Risk Evaluation and Mitigation Strategy for sparsentan, mandating liver function monitoring for patients on the drug and, for those capable of becoming pregnant, maintaining contraception while on treatment and 1 month after. RAAS blockers should be stopped when converting to sparsentan.

On the strength of the 36-week data showing proteinuria reduction, the FDA granted accelerated approval to sparsentan for patients with IgA nephropathy deemed high risk for progression; recently, the drug obtained full approval.

It is currently not known whether the addition of SGLT-2 inhibitors to dual endothelin receptor and angiotensin receptor antagonists or endothelin receptor antagonists will add further proteinuria reduction and estimated GFR benefit. The results of an open-label extension of the PROTECT trial are awaited.

The **endothelin receptor antagonist** atrasentan was recently granted accelerated approval based on findings from the phase 3 ALIGN (Atrasentan in Patients With IgA Nephropathy) trial.[25]

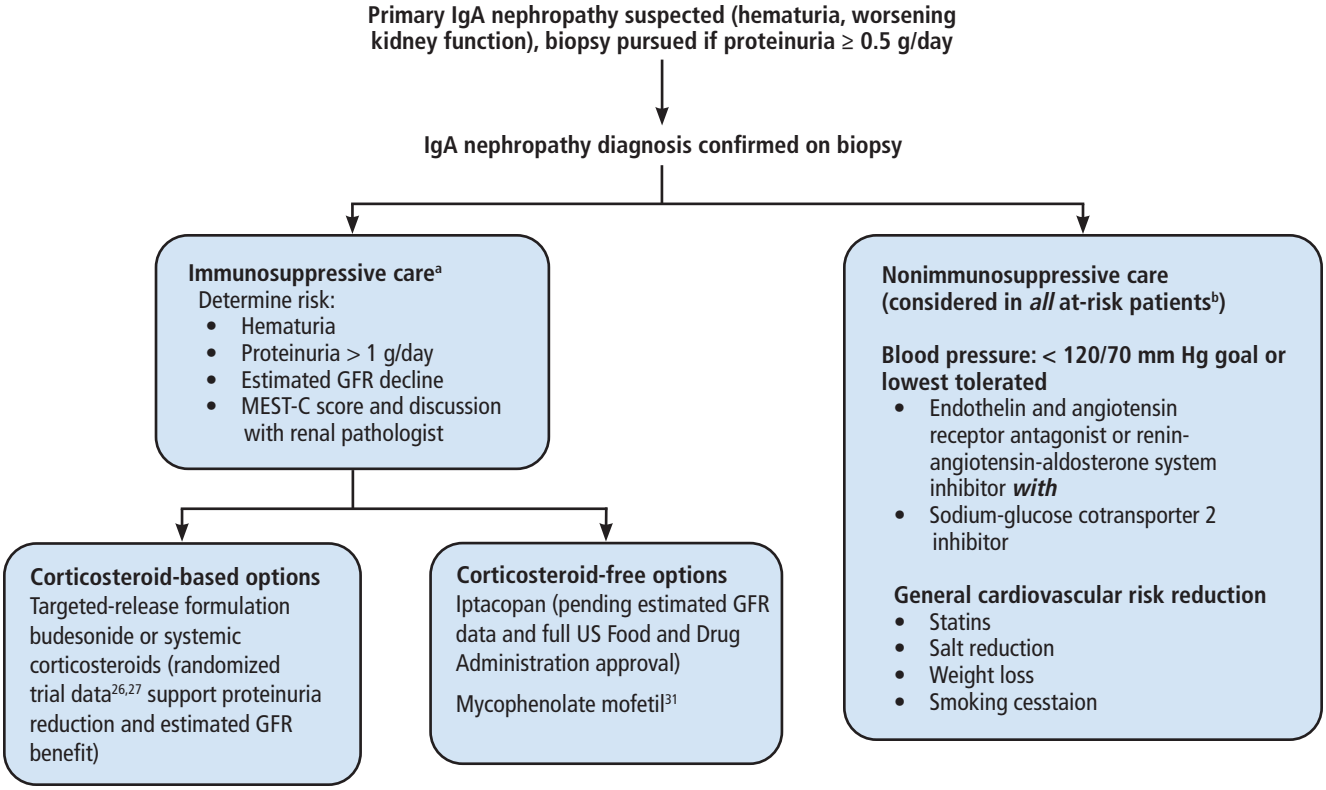


Figure 2. Our approach to immunoglobulin (Ig) A nephropathy.

[a]We monitor patients receiving immunosuppressive therapy with assessment of blood pressure and protein-creatinine ratio, renal function panel, and urinalysis every 3 months.

[b]Those with proteinuria > 0.5 g/day.

GFR = glomerular filtration rate; MEST-C = mesangial hypercellularity, endocapillary proliferation, segmental glomerulosclerosis, tubulointerstitial fibrosis, crescents

Immunosuppressive therapy

Systemic corticosteroids are frequently used in IgA nephropathy, yet their role in management of this disease is controversial. Several randomized controlled trials and meta-analyses that examined corticosteroid use in IgA nephropathy have had conflicting results. Modern randomized controlled trials such as STOP-IgAN (Supportive Versus Immunosuppressive Therapy for the Treatment of Progressive IgA Nephropathy)[26] and TESTING (Therapeutic Evaluation of Steroids in IgA Nephropathy Global)[27] have best represented the use of systemic corticosteroids and their risks, which were likely underreported in older studies.[28]

STOP-IgAN[26] was a relatively small randomized controlled trial testing the safety and efficacy of immunosuppressive therapy combined with supportive care compared with supportive care alone. Immunosuppressive therapy consisted of corticosteroids for those with estimated GFR of 60 mL/min/1.73 m^2 or greater, and cyclophosphamide followed by azathioprine and corticosteroids for those with estimated GFR between 30 and 59 mL/min/1.73 m^2. Of the 337 patients entering the run-in phase, 106 responded to supportive care after 6 months, which included RAAS blockade, smoking cessation, and cholesterol-lowering with statins; these were not randomized. Only 5% in the supportive-care arm reported complete remission (ie, urine protein-creatinine ratio < 0.2 g/24 hours and stable renal function with a fall in estimated GFR < 5 mL/min/1.73 m^2 from baseline) compared with 17% in the immunosuppressive arm. At the end of the 3-year trial, there was no difference in estimated GFR between the groups. Not surprisingly, immunosuppression with corticosteroids saw higher rates of weight gain, impaired glucose tolerance, and serious adverse events such as infection. STOP-IgAN therefore solidified the value of supportive or nonimmunosuppressive care in IgA nephropathy.

The **TESTING trial** was a randomized clinical trial comparing oral methylprednisolone (0.6–0.8 mg/kg/day for 2 months and then tapering, with a treatment period

of 6 to 8 months) with placebo, carried out in a predominantly East Asian population.[27] While methylprednisolone resulted in a lower likelihood of the primary end point (40% decline in estimated GFR, end-stage kidney disease, or death due to kidney failure), it came at the price of serious infections, including 2 infection-related deaths, and the investigators suspended the trial.

The trial resumed recruitment after the methylprednisolone dose was reduced (0.4 mg/kg/day for 2 months, tapered over 6 to 9 months) and prophylactic antibiotics were mandated.[29] The primary composite end point occurred in 28.8% (74 patients) of the methylprednisolone group vs 43.1% (106) of the placebo group (hazard ratio 0.53, 95% CI 0.39–0.72, $P < .001$) over a mean follow-up of 4.2 years. Despite the reduced steroid dose, serious adverse events were 4 times higher in the methylprednisolone group than in the placebo group: 37 vs 8 total events that occurred in 28 (10.9%) vs 7 (2.8%) participants.

Finally, **targeted-release formulation (TRF) budesonide** is the only immunosuppressive drug fully approved by the FDA to treat IgA nephropathy. The hypothesis is that TRF budesonide is delivered directly to the small bowel and Peyer patches, where the galactose-deficient IgA is produced, interrupting a key mediator of IgA nephropathy. In theory, because of extensive first-pass metabolism, less drug would reach the systemic circulation and limit glucocorticoid toxicity.

The NefIgArd (Efficacy and Safety of Nefecon in Patients With Primary IgA [Immunoglobulin A] Nephropathy) trial,[30] a phase 3 randomized trial, evaluated TRF budesonide vs placebo in patients with proteinuria of 1 g or more over a 9-month period. TRF budesonide resulted in significantly reduced proteinuria and sustained estimated GFR benefit over a 2-year follow-up. However, like other trials of systemic corticosteroids for IgA nephropathy, the proteinuria returned after TRF budesonide was stopped, and steroid-related side effects were more common in the TRF budesonide group, including weight gain, facial edema, acne, peripheral edema, and hypertension.

Treatment recommendations

The landscape for treatment of IgA nephropathy has changed rapidly and will continue to change in the coming months and years. **Figure 2**[26,27,31] presents the authors' recommended approach, with these considerations:

- A proteinuria threshold of 0.5 g/day is the new cutoff for warranting a biopsy, as opposed to the traditional value of 1 g/day or greater.
- While the MEST-C score cannot be used to guide immunosuppressive therapy, we advise considering it in addition to a direct discussion with the renal pathologist who interpreted the biopsy.
- Nonimmunosuppressive therapy should be considered in conjunction with immunosuppressive therapy.
- There is inadequate evidence to support superiority of TRF budesonide over systemic corticosteroids, and this decision is made on a case-by-case basis.

Note that this approach can include use of mycophenolate mofetil as a corticosteroid-free immunosuppressive option. A randomized trial of 170 Chinese patients with IgA nephropathy showed mycophenolate mofetil when added to supportive care (renin-angiotensin system blockade) reduced the risk of the primary composite outcome (doubling of serum creatinine, end-stage kidney disease, or death due to kidney or cardiovascular cause) compared with supportive care alone.[31]

FUTURE TREATMENT OPTIONS

A variety of treatment options are under investigation for the management of IgA nephropathy targeting the different "hits" in the pathogenesis model (**Table 3**).[24,25,30,32–47]

Complement inhibitors. Significant research is focused on the complement cascade, reflecting the key role of the complement system in the development of IgA nephropathy. Several complement inhibitors are being studied in phase 2 and 3 trials, with mixed results.[32–40] There has been much focus on inhibition of the alternative pathway of complement, which impacts the deposition of immune complexes in the glomerulus (the fourth hit in the pathogenesis model of IgA nephropathy).

Iptacopan (LNP023), an oral factor B inhibitor that prevents the activity of the alternative pathway C3 convertase, was evaluated in 66 patients with IgA nephropathy in a phase 2 trial.[32] At 6 months, participants who received iptacopan 200 mg twice daily had a 40% reduction in proteinuria compared with placebo. In a follow-up phase 3 trial, iptacopan showed a significant reduction in proteinuria at 9 months compared with placebo.[38] It was recently granted accelerated approval by the FDA.

The complement inhibitor class of drugs will likely be used in cases of IgA nephropathy that are resistant to traditional treatments, including corticosteroids, and have a significant inflammatory component on kidney biopsy, or those where a steroid-sparing regimen is ideal. There is interest in correlating the intensity

TABLE 3
Recently approved and future treatment options for immunoglobulin A nephropathy

	Drugs	Status
Recent approvals	Endothelin and angiotensin receptor antagonist: sparsentan[24]	Full approval
	Endothelin receptor antagonist: atrasentan[25]	Accelerated approval
	Corticosteroid: targeted-release formulation budesonide[30]	Full approval
	Complement inhibitor: iptacopan[32,38]	Accelerated
Future (not approved) treatment options	Complement inhibitors[33–35,37,39,40]	
	Avacopan, ravulizumab, cemdisiran, vemircopan, pegcetacoplan	Phase 2 and 3 trials in progress
	IONIS-Fb-LRx	Phase 3 trial in progress
	Narsoplimab	Phase 3 negative trial
	RO7434656	Phase 3 trial in progress
	ARO-C3	Phase 1 trial in progress
	B-cell–depleting therapies[41–45]	
	Atacicept	Phase 3 trial in progress
	Sibeprenlimab, zigakibart, telitacicept	Phase 2 and 3 trials in progress
	Plasma cell inhibitors[46,47]	
	Felzartamab, mezagitamab, bortezomib	Phase 2 trials in progress

of C3 staining on immunofluorescence microscopy of kidney biopsies and the potential response to complement inhibition.

Inhibition of antibody-producing B cells (targeting the second and third hits in IgA nephropathy pathogenesis) has also emerged as a therapeutic target for the management of IgA nephropathy. While rituximab has not been shown to be beneficial, other B-cell receptor targets have shown some initial success, including APRIL (a proliferation-inducing ligand), BAFF (B-cell activating factor), and plasma cell receptors.[48,49] APRIL and BAFF regulate B-cell survival.

APRIL may help to specifically produce IgA1 molecules by controlling the immunoglobulin class switch recombination.[48,49] Several monoclonal antibodies against APRIL are currently under investigation, including sibeprenlimab, zigakibart, and atacicept.[41–45] A phase 2b clinical trial of atacicept showed a significant reduction in proteinuria compared with placebo, and a phase 3 clinical trial is under way.[44]

Antiplasma cell therapies (second and third hits in IgA nephropathy pathogenesis) are also being investigated as potential treatment options.[46,47] Monoclonal antibodies to CD38 (felzartamab and mezagitamab) are being assessed in early-stage clinical trials.[46] Larger studies are needed to assess the efficacy of this approach in the management of IgA nephropathy.

NEW UNDERSTANDING AND NEW CHALLENGES

Advances in our understanding of the pathogenesis, prognosis, and, most important, therapeutic options for IgA nephropathy have been significant. For decades, treatment options have been limited, with many reaching end-stage kidney disease within their lifetime. Recognition of the disease still depends on urinalysis and quantification of proteinuria, but with new therapies on the horizon, there is hope that awareness will increase.

For the treating clinician, the management of IgA nephropathy is a complex clinical scenario. The 4-hit model provides a blueprint for the pathogenesis, allowing targeted management of the disease, but appropriate use of novel therapies and assessment of response remain significant challenges. Among the questions to consider are the following:

- How should these drugs be combined, if at all?
- How long should each therapy be given?
- Do newer therapies result in a true reduction in the rate of end-stage kidney disease?

Also important are conversations for patients and clinicians on cost and access to therapy. Ongoing study, debate, and conversation within the nephrology community are needed to prioritize these novel therapies and develop guidelines.

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