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CME MOC

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Dealing with the "T" (testosterone)

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Does my patient have testosterone deficiency?

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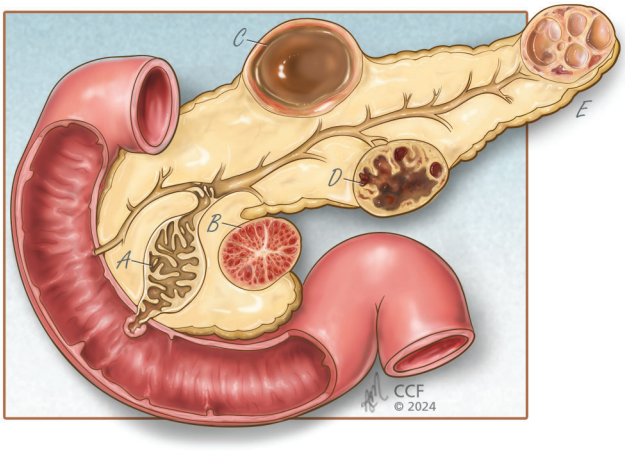

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Dealing with the "T" (testosterone)

Over the past few years, TV viewers have been inundated with commercials and infomercials extolling the value of testosterone supplementation for men with "low T" and various symptoms. So there is no surprise that during clinic visits questions arise regarding the need for testosterone level testing or concerns with empiric supplementation.

Testosterone levels (free and total) decrease in many men, seemingly as part of the normal aging process, but more markedly in men taking certain medications and in men with obesity, sleep disturbances, and several chronic diseases. Low testosterone levels have been variably associated with erectile dysfunction, fatigue, sarcopenia, depression, low libido, anemia, decreased bone density, and a host of other symptoms. Association of course is not equivalent to causation. The implication of that statement is that testosterone supplementation will not necessarily ameliorate all these conditions.

Shumaker et al[1] in this issue of the *Journal* concisely review the urologic perspective on the appropriate diagnosis of testosterone deficiency and potential therapeutic value of testosterone supplementation. They emphasize from the outset that the diagnosis of testosterone deficiency demands the presence of both clinical signs and appropriate laboratory evidence of low testosterone. Intrinsic to that statement is a challenge that presents itself in the primary care physician's and subspecialist's office: when to attribute nonspecific symptoms to low testosterone vs normal aging or comorbid medical conditions. This can be difficult even in the setting of low total testosterone (< 300 ng/dL per the American Urological Association).

An interesting question to me is whether there is a physiologic need for testosterone levels to decrease with male aging. If there is, supplementation with exogenous testosterone to attain the "normal" levels of a young male would not necessarily exert a major beneficial effect and might even be counter to other physiologic functions. To date, however, major adverse effects of testosterone supplementation in aging men with low or, in some short-term studies, normal levels have not been observed, the caveat being that large long-term studies do not exist. The recent TRAVERSE (Testosterone Replacement Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men) study[2] designed to address part of this question found no significant increase in major cardiovascular adverse events resulting from testosterone supplementation in middle-aged and older men with increased cardiovascular risk, low testosterone (< 300 ng/dL), and at least 1 symptom of hypogonadism. They did observe an increased occurrence of arrhythmias, including atrial fibrillation and thromboembolic events. The modestly low rate of volunteer adherence to the full protocol and a lower than anticipated rise in serum testosterone in the treated group are of note. Nonetheless, this and other randomized studies (reviewed by Diem et al[3]) provide some comfort that there is not likely a major risk of serious adverse effects in reasonably dosed, selected patients with hypogonadism at baseline.

The pragmatic clinical questions remain as to how much benefit is provided by testosterone supplementation, and for which symptoms. As noted by Shumaker et al,[1] there are some

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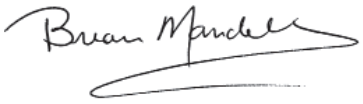
evidence-based benefits of testosterone supplementation, and it is reasonable to offer this treatment to select symptomatic men with documented hypogonadism and sexual dysfunction. Importantly, they discuss how hypogonadism must be appropriately confirmed. Despite admonitions in the literature to document hypogonadism prior to offering testosterone supplementation, this is not always adhered to in the real world. An ongoing challenge is to mesh patients' expectations of success, which have been ginned up by multiple TV advertisements and online tributes to various "T supplements," with randomized trial data. In 2020 the American College of Physicians[4] published a grounded clinical guideline, informed by randomized trial data,[3] addressing testosterone treatment of men with age-related hypogonadism.

The recommendations and conclusions from the evidence expressed in that guideline are few and succinct. The authors concluded that there is evidence for a modest effect size improvement in components of sexual dysfunction with testosterone supplementation (with "low-certainty evidence"), and that the perceived benefit should be reevaluated in patient discussions within a year of treatment initiation. Perhaps what should have greater impact on real-world practice (and patient expectations) is their recommendation[4] that clinicians "*not* initiate testosterone treatment in men with age-related low testosterone to improve energy, vitality, physical function, or cognition (… low-certainty evidence) [emphasis added]."

But randomized trials can sometimes offer surprises; even well-designed trials may not always reflect the complete "truth." Testosterone has previously been shown to increase bone density in men with hypogonadism,[5] and in practice, low testosterone is a sought cause of decreased bone density in men with unexplained osteoporosis. So it was an unexpected observation in a subtrial analysis[6] looking at fractures in participants of the TRAVERSE study[2] that the men with hypogonadism receiving testosterone supplementation actually had a numerically higher incidence of fractures than those receiving placebo. The fracture rate was low, the study may not have been long enough, the post-treatment testosterone level may not have reached the desired level, and bone densities in the participants before and after entry were not reported. The results were surprising nonetheless. This is consistent with other observations suggesting that testosterone may have many effects, but they may be modest enough to require large-scale, protracted clinical trials that include only participants with truly low testosterone levels to unequivocally demonstrate clinical effects.

Randomized testosterone clinical trials have demonstrated some benefits and other mixed results. In the real world, if a patient feels better taking testosterone supplementation, is it the "T" or is it a placebo effect? *If* supplementation is truly safe, does it matter? So the question of whether it has been demonstrated with certainty that long-term testosterone supplementation for the patient with age-associated hypogonadism (without complicating comorbidities) is benign remains relevant.



Brian F. Mandell, MD, PhD
Editor in Chief

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Should I start an SGLT-2 inhibitor in my patient with heart failure and chronic kidney disease?

To the Editor: The article by Sekerak and colleagues[1] is an excellent highlight of the sodium-glucose cotransporter 2 (SGLT-2) inhibitor family's pluripotent cardiorenal impacts. I offer several suggestions to optimize the utilization of this therapeutic class.

First, regarding dosing, while dapagliflozin 5 mg is approved by the US Food and Drug Administration for glycemic control, the heart failure and chronic kidney disease trials were done exclusively with 10 mg, which is the only approved dose for these indications. Similarly, empagliflozin 25 mg is intended for intensification of glycemic control. Use of 10 mg of either agent up front, irrespective of indication, fosters a "set it and forget it" approach that has been beneficial in uptake of this class, particularly in heart failure and chronic kidney disease.

Second, the authors write that clinicians should monitor for hyperkalemia. However, contemporary studies have allayed concerns about hyperkalemia. In patients with diabetes, SGLT-2 inhibitors have been shown to reduce the risk of hyperkalemia without increasing the risk of hypokalemia.[2] In EMPEROR-Reduced (Empagliflozin Outcome Trial in Patients With Chronic Heart Failure With Reduced Ejection Fraction), there was no difference in rates of hyperkalemia,[3] and in FIDELIO-DKD (Finerenone in Reducing Kidney Failure and Disease Progression in Diabetic Kidney Disease), use of SGLT-2 inhibitors decreased the rate of hyperkalemia associated with finerenone use.[4]

Third, the authors' recommendation to check a basic metabolic panel 2 to 4 weeks after initiating SGLT-2 inhibitor therapy may not be universally necessary, although it could be reasonable in elderly patients or if there are significant clinical concerns regarding volume status or other factors. As articulated by some experts,[5] contemporary studies have alleviated concerns regarding acute kidney injury, highlighting that the physiological dip in the estimated glomerular filtration rate (eGFR) induced by SGLT-2 inhibitors does not correlate with kidney injury and that, despite this dip, therapy should be continued. Therefore, for most patients, it seems reasonable to check laboratory values at the next routine round of laboratory testing rather than 2 to 4 weeks after initiation. This approach could reduce patient burden and prevent the misinterpretation of an expected eGFR dip leading to interruption of this critical therapy.

Taher Modarressi, MD
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In Reply: We thank Dr. Modarressi for his important and timely response. We agree with his recommendations for optimizing the utilization of this therapeutic class. Regarding dosing, we agree that the "set it and forget it" approach of starting an SGLT-2 inhibitor has been particularly beneficial for this class of medications. As opposed to other medications that require frequent titration and follow-up laboratory work, SGLT-2 inhibitors may be started earlier in patients with heart failure while other medications are added and titrated up.

We also agree that the role of routine laboratory testing for hyperkalemia has limited value, especially in light of new guidelines and data. Several studies have shown that hyperkalemia is not a common side effect of SGLT-2 inhibitors, and we agree that laboratory testing can be done on a case-by-case basis rather than routinely. Patients who can maintain adequate hydration generally will have limited side effects from SGLT-2 inhibitors. Additionally, while changes in serum creatinine levels and eGFR may be alarming at first, they do not correlate with kidney injury, and therapy should be continued regardless. For most patients, we agree that routine laboratory checks may be burdensome and unnecessary, and may lead to premature interruption of SGLT-2 inhibitor therapy.

Thus, overall we agree with Dr. Modarressi's statements and observations, and believe that SGLT-2 inhibitors may be started earlier in a patient's course because of the "set it

and forget it" approach. Most important, in light of new data and guidelines, patients with chronic kidney disease should have access to SGLT-2 inhibitor therapy to help mitigate cardiovascular risk. Additionally, follow-up laboratory tests may not be necessary in all patients given the remarkable safety profile of SGLT-2 inhibitors.

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Surgical and procedural management of benign prostatic hyperplasia

To the Editor: We read with interest the recent article by Drs. Sotimehin, Haile, and Gill regarding the management of benign prostatic hyperplasia (BPH).[1] We thank the authors for their evidence-based commentary.

Office-based procedures and the gold-standard surgical technique of transurethral resection of the prostate (TURP) for BPH are limited by prostate gland size.[1] For larger prostate glands, surgical techniques such as laser enucleation of the prostate or prostatectomy may be required.[2] However, many patients with BPH have contraindications to surgery, including the need for anticoagulant or antiplatelet treatment.

Prostate artery embolization (PAE) is an outpatient procedure performed under moderate sedation by experienced interventional radiologists. Multiple studies have demonstrated that PAE is most effective in large prostate glands, specifically glands with median lobe enlargement. Additionally, because PAE does not require general anesthesia, most medical comorbidities are not a contraindication. The low bleeding risk of PAE also makes it a good option for patients taking anticoagulant or antiplatelet medications.[3]

Multiple randomized controlled trials have compared the efficacy of PAE and TURP over follow-up periods of up to 24 months. Overall, these trials demonstrated that TURP is superior to PAE in improving clinical outcome parameters such as International Prostate Symptom Score and quality-of-life ratings. However, the differences between PAE and TURP were quantitatively small and were often not statistically significant. These trials also demonstrated a trend toward fewer adverse events with PAE than with TURP, particularly in terms of sexual dysfunction.[4,5]

The most recent American Urological Association guidelines for the management of lower urinary tract symptoms secondary to BPH include PAE, performed by an experienced physician, as a potential treatment option.[2] We agree that PAE can serve as a useful complement to office-based and surgical procedures, and with its addition we are able to offer effective and safe treatment for all patients, irrespective of prostate size, medical comorbidities, or need for anticoagulant or antiplatelet medications.

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doi:10.3949/ccjm.91c.02003

In Reply: We appreciate the timely and helpful commentary by Dr. Gadani and colleagues highlighting the recent inclusion of PAE in the American Urological

Association (AUA) guidelines for the management of lower urinary tract symptoms secondary to BPH.[1] As noted, PAE is a welcome addition to the urological armamentarium available for BPH treatment. We agree with their evidence-based perspectives and their assertion that PAE is a useful approach for certain patients with BPH. PAE also serves as a helpful approach to refractory hematuria of prostatic origin. Anecdotally, some have utilized PAE prior to robotic simple prostatectomy to reduce bleeding risk in patients who do not accept blood products, but outcomes and data to support this practice are lacking.

While PAE may serve as an option for BPH treatment in patients who are not surgical candidates, are at a high risk of bleeding, or who wish to preserve sexual function or minimize incontinence risk, similar to water vapor ablation, PAE is a treatment that relies upon tissue necrosis (instead by ischemia) and thus provides a delayed benefit for patients. The exact delay between treatment and improvement of lower urinary tract symptoms is incompletely understood, but likely relates to prostate size. Additionally, as with other newer BPH treatments, PAE lacks long-term follow-up data to elucidate its durability and subsequent BPH retreatment rates. This may stem from patients following up with urologists after PAE and not necessarily returning to the interventional radiology teams who completed the procedure.[2,3]

As the aim of our article was to provide a balanced overview of the risks and benefits of BPH procedures, it is worth highlighting some of the risks of PAE to complement the strengths and benefits of the procedures noted by Dr. Gadani and colleagues. A study comparing PAE to TURP found that PAE had a higher retreatment rate and greater risk of postprocedural urinary retention, and was less effective at alleviating bladder outlet obstruction, as evidenced by urodynamic (bladder pressure at maximum flow) measurments.[2–4] Radiation exposure must also be acknowledged, as this is exclusive to PAE relative to other BPH therapies. Additionally, there are unique risks of PAE that relate to its vascular basis, which include post-PAE (post-embolization) syndrome. This consists of nausea, vomiting, fever, pelvic pain, dysuria, and urinary frequency for several days after the procedure and occurs due to the presence of an infarcted tissue mass. Lastly, the risks of inadvertent embolization of vessels perfusing the bladder, rectum, and other neighboring structures must also be recognized.

As with BPH surgery, greater procedural experience likely drives a lower risk of PAE complications. As Dr. Gadani and colleagues note, PAE should be performed in centers with highly trained and highly experienced interventional radiologists. It has a particularly challenging learning curve and is technically demanding, with potentially lengthy procedures having an average fluoroscopy time of up to 50 minutes and procedure duration of up to 2 hours.[5] Taking all into account, the addition of PAE to the AUA guidelines is warranted, as it fills a necessary niche in the spectrum of BPH treatments. It is also evidence of the increasingly interdisciplinary approach to patient care that is occurring throughout healthcare. For the right patient, in the right scenario, and where there is necessary expertise, PAE can be facilitated optimally when interventional radiologists and urologists collaboratively manage patient care.[1]

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We thank those who reviewed manuscripts submitted to the *Cleveland Clinic Journal of Medicine* in 2023. Reviewing papers for the *Journal*—both for specialty content and for relevance to our readership—is an arduous task that involves considerable time and effort. Our publication decisions depend in no small part on the timely efforts of reviewers, and we are indebted to them for contributing their expertise this past year.

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BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: What are the management considerations for venous thromboembolic events in patients with cirrhosis?

A 61-year-old man with Child-Pugh class A cirrhosis, admitted to the hospital with community-acquired pneumonia, is diagnosed with left lower-extremity proximal deep vein thrombosis (DVT) with no evidence of impaired venous drainage. Admission laboratory values include:

- *Hemoglobin 10 g/dL (reference range 13.8–17.2 g/dL)*
- *Platelet count 60 × 10^9/L (150–400 × 10^9/L)*
- *Creatinine 1.0 mg/dL (0.7–1.3 mg/dL)*
- *International normalized ratio (INR) 1.8 (0.8–1.1).*

What is the appropriate management of his DVT?

A: This patient's treatment should start with a direct oral anticoagulant (DOAC) or low-molecular-weight heparin (LMWH).[1] His history suggests that the DVT was provoked by immobility secondary to pneumonia. Patient preference and drug cost should further guide management, as excellent adherence is needed to prevent future complications and recurrence.

INTERPRETING LABORATORY RESULTS: A TENUOUS BALANCE

Hemostatic laboratory abnormalities are common in patients with liver disease and can include thrombocytopenia, prolonged prothrombin time, prolonged activated partial thromboplastin time, elevated INR, and decreased fibrinogen. Patients with cirrhosis were previously thought to have an increased risk only of bleeding as opposed to an increased risk of thrombosis.[1] But current evidence argues for a "rebalanced" hemostatic state from reciprocal changes in both pro- and antihemostatic pathways.[2] Prothrombin time, activated partial thromboplastin time, and INR are often elevated in patients with cirrhosis because of low levels of coagulation factors as well as decreased levels of protein C, protein S, and antithrombin—all synthesized by the liver.[2] Additional hypercoagulable changes include the imbalance of von Willebrand factor with ADAMTS13 (a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13), hyperactive platelets, enhanced thrombin-generating capacity, and, occasionally, hypofibrinolytic states.[1]

Patients with cirrhosis are therefore susceptible to bleeding and thrombotic events secondary to this tenuous balance. A systematic review and meta-analysis that included 11 studies determined there was a significantly increased risk of pulmonary embolism and DVT (odds ratio [OR] 1.7) in patients with cirrhosis compared with controls.[3]

Predicting risk of venous thromboembolic events

Among several clinical scoring systems created to predict risk of a venous thromboembolic event (VTE), only 2 have included patients with liver disease.[1,4,5]

The **Padua Prediction Score** is calculated using 11 variables with associated point values.[4] Patients with cirrhosis whose Padua score was 4 or greater, considered high-risk, were significantly more likely to develop VTE (OR 12.7).[4]

The **International Medical Prevention Registry on Venous Thromboembolism** (IMPROVE) risk score was developed using data from 15,156 patients and

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included those with a history of hepatic failure.[5] The IMPROVE score is calculated using 7 variables with associated point values. Patients with an IMPROVE score greater than 2 may benefit from thromboprophylaxis. In patients whose score was greater than 4, approximately 5.7% developed VTE within 3 months.[5]

Each scoring system has limitations. Neither was prospectively validated specifically for patients with cirrhosis, although the IMPROVE model included 235 patients with prior hepatic failure.[5]

VTE PROPHYLAXIS: EVIDENCE IS LIMITED

Risk of VTE in patients with cirrhosis increases with prolonged hospitalization, immobilization, surgery, and male sex. Because of perceived increased bleeding risk in patients with cirrhosis, VTE prophylaxis has not been used routinely in this population, and evidence supporting it is limited. No randomized controlled trial has compared outcomes of VTE prophylaxis in patients with cirrhosis.[1,6] A large meta-analysis found that patients with cirrhosis have a 1.9% higher absolute risk of VTE than patients without cirrhosis.[3] The American Gastroenterological Association therefore recommends standard anticoagulation prophylaxis in hospitalized patients with cirrhosis as a conditional recommendation with very low certainty of evidence.[6] The European Association for the Study of the Liver (EASL) recommends that patients with cirrhosis who are at risk of VTE receive LMWH, noting that the strategy has unclear efficacy but a reasonable safety profile.[1]

DOACs are not currently approved by the US Food and Drug Administration (FDA) for VTE prophylaxis in hospitalized patients, and data are lacking to support their use in hospitalized patients with cirrhosis. Current American Society of Hematology guidelines recommend LMWH rather than unfractionated heparin (UFH) because LMWH requires less frequent administration.[7] Clinical judgment and VTE risk assessments may further aid clinicians. A meta-analysis that included more than 5,000 patients lacked sufficient evidence to advise for or against VTE prophylaxis in patients with cirrhosis, although its use was not associated with significant bleeding risk.[8]

TREATMENT: THE RISK-BENEFIT RATIO AND PATIENT ADHERENCE

Despite limited evidence for anticoagulation in patients with cirrhosis, VTE should be treated in the absence of absolute contraindications. Each patient must be considered carefully to ensure that benefits outweigh risks, as most studies excluded patients with active or recent bleeding. Duration of anticoagulant therapy is guided by whether the event is provoked or unprovoked, among other considerations. Patient adherence is critical for successful treatment and prevention of future complications.

Traditional anticoagulants

The EASL issued a weak recommendation for the use of vitamin K antagonists or LMWH in patients with Child-Pugh class A cirrhosis: LMWH is favored in patients with Child-Pugh class B and C cirrhosis, and UFH is recommended in the presence of renal impairment.[1]

Vitamin K antagonists are not ideal. They require frequent monitoring, have a narrow therapeutic range, and have many drug-drug interactions.[1] They are particularly challenging in patients with cirrhosis, whose altered INR baselines make it difficult to establish a therapeutic range. The relatively higher incidence of INR variability between laboratories in this patient population is also problematic. Vitamin K antagonists should be avoided in patients with cirrhosis who have a prolonged baseline prothrombin time and INR.[1,9]

The anticoagulant effect of LMWH has yet to be fully characterized in patients with cirrhosis, and traditional monitoring with anti-Xa assays may be unreliable.[1] Large randomized controlled studies comparing traditional anticoagulants are lacking in treating DVT and pulmonary embolism in patients with cirrhosis, but multiple studies have evaluated these agents in the treatment of portal vein thrombosis in this population and have suggested reasonable safety and efficacy of UFH and LMWH.[1]

The EASL guidelines strongly recommend use of DOACs in patients with Child-Pugh class A cirrhosis and cautious use in patients with Child-Pugh class B disease. The FDA recommends avoidance of oral Xa inhibitors in patients with Child-Pugh class B or C cirrhosis, but supports dabigatran for patients with Child-Pugh class A and B disease.[1]

Overall, more prospective investigation of DOAC safety and efficacy in this patient population is needed. Most evidence to date is based on case series, retrospective studies, and small observational studies. Retrospective data with DOACs in patients with cirrhosis and a variety of indications have shown safety and bleeding events comparable to those with traditional anticoagulants such as vitamin K antagonists, LMWH, and UFH.[1] In the context of portal vein thrombosis, edoxaban when compared with warfarin had a higher

proportion of patients with complete resolution of portal vein thrombosis, with less thrombosis progression and a similar rate of bleeding events.[10]

THE CLINICAL BOTTOM LINE

Patients with cirrhosis exhibit a rebalanced hemostatic state that makes them prone to VTE. The choice of anticoagulation for prophylaxis and treatment should be individualized, and prospective studies are needed to refine the decision-making progress.

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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ONE MINUTE CONSULT
BRIEF ANSWERS TO SPECIFIC CLINICAL QUESTIONS

Q: Does my patient have testosterone deficiency?

A: Diagnosis of testosterone deficiency (TD) requires the presence of relevant signs or symptoms along with biochemical evidence. Testosterone deficiency can prove challenging to diagnose and treat. The American Urological Association (AUA) endorses a total serum testosterone cutoff of less than 300 ng/dL in support of a diagnosis.[1] The prevalence of TD varies from 12% to 39% across men in their 50s to 80s.[2] Testosterone levels decline by approximately 1% yearly after the fourth decade of life.[3]

SIGNS, SYMPTOMS, AND COMORBIDITIES

The symptoms of TD are often nonspecific, particularly in older men, and include fatigue and poor memory and concentration. However, decreased libido, depression, erectile dysfunction, delayed ejaculation, and diminished facial and body hair growth are more specific indicators.[4] Physical examination findings that can support a diagnosis of TD include testicular atrophy, testicular masses, varicoceles, gynecomastia, and large waist circumference.[1]

Several comorbidities are commonly associated with TD. Evidence for a relationship between TD and obesity (body mass index > 30 kg/m^2) exists, with approximately half of men with obesity exhibiting reduced testosterone levels.[5] The low total testosterone observed in these patients may result from the lower sex hormone–binding globulin levels associated with obesity; however, free (biologically active) testosterone levels may be normal. Diabetes also has been identified as a comorbidity, with evidence suggesting that higher testosterone levels decrease the risk of having the disease.[6] Conditions that affect sleep are also related to TD. Diurnal variation in testosterone levels, with highest values in the morning hours, is associated with sleep. Sleep disturbances, therefore, can interfere with nocturnal testosterone production. Obstructive sleep apnea, in particular, has been described as a comorbidity with TD.[7] Other potential associated conditions include hypertension, hyperlipidemia, chronic obstructive pulmonary disease, chronic kidney disease, and rheumatoid arthritis.[2,8]

WHAT ARE THE CAUSES OF TESTOSTERONE DEFICIENCY?

The etiology of TD can be divided into acquired and congenital causes. The acquired causes include aging, obesity, testicular trauma or removal, pituitary disease (prolactinoma), infection, environmental factors, autoimmune processes, and medications such as narcotics, antidepressants, and glucocorticoids.[2,9,10] More recently, it has been suggested that cannabis use may result in reduced testosterone levels; however, higher-quality studies are needed to establish a definitive association.[11] Congenital causes of TD include Klinefelter syndrome, Kallmann syndrome (hypogonadotropic hypogonadism with anosmia), and disorders of sexual development.

HOW IS IT DIAGNOSED?

Historically, a lack of consistency in serum testosterone cutoffs has made TD challenging to diagnose. As noted, a total testosterone value of 300 ng/dL is considered the lower threshold for diagnosis. While age-specific cutoffs may be more appropriate, such cutoffs have not yet been adopted by guidelines. This AUA-endorsed cutoff was determined based on statistical evidence suggesting that below this value, men tend to experience more symptoms and respond better to treatment.[12] Importantly, in addition to biochemical evidence of the condition, related symptoms must be present.

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Serum testosterone collection is a crucial component of diagnosis. Total testosterone should be measured between 7:00 and 11:00 AM except for shift workers. At least 2 measurements showing a low testosterone value sampled at least 2 to 3 weeks apart are needed to meet diagnostic criteria.[1] If low testosterone is confirmed, serum luteinizing hormone should be measured in an effort to elucidate the cause. Higher luteinizing hormone values suggest primary TD (testicular failure of production) and lower values, secondary TD (hypothalamus or pituitary malfunction). If luteinizing hormone levels are low or normal (suggesting secondary TD), serum prolactin should be measured to help evaluate for the presence of a prolactinoma, a recognized potential cause of TD. In a patient who presents with gynecomastia, serum estradiol should be measured, as this sign can be caused by a decrease in the testosterone:estrogen ratio.[1] In patients with obesity who have low total testosterone, measuring free testosterone to confirm the diagnosis may be useful.

WHICH PATIENTS SHOULD BE TREATED?

Treatment is indicated if diagnostic criteria are met, symptoms are present, and the patient understands the risks and benefits of treatment. The primary goal of treatment is to alleviate associated symptoms. There are, however, additional benefits that testosterone therapy may provide for patients with certain comorbidities. Specifically, it may improve bone mineral density, blood glucose control, lean body mass, and anemia. Screening for related conditions (eg, osteoporosis, diabetes) also may be reasonable for patients presenting with TD. If TD can be explained by another condition, then that condition should be treated before testosterone therapy is started.[12]

The 2018 AUA guideline endorses a strong recommendation that men actively trying to conceive should not receive exogenous testosterone, as it will suppress the hypothalamic-pituitary-gonadal axis, inhibiting spermatogenesis.[1] In addition, the guideline suggests that testosterone therapy not be commenced for a period of 3 to 6 months after a cardiovascular event because of the potential for worse outcomes; however, further study of this association is warranted.[1,13]

TREATMENT OPTIONS

Multiple treatment options and protocols exist depending on the patient's preference and desire to maintain fertility. Routes of administration for exogenous testosterone include intramuscular and subcutaneous injections, subcutaneous pellet implantation, topical therapies, oral agents, and intranasal spray. For patients with fertility concerns, endogenous testosterone production can be promoted with selective estrogen receptor modulators such as clomiphene citrate, human chorionic gonadotropin, aromatase inhibitors such as anastrozole, or a combination of these. Of these agents for patients who wish to maintain fertility, only human chorionic gonadotropin is approved by the US Food and Drug Administration for use in males. The biochemical goal of treatment is to achieve a total testosterone level in the middle tertile of the normal reference range, approximately 450 to 600 ng/dL.[1]

RISKS AND CONSIDERATIONS OF TREATMENT

Testosterone replacement therapy has multiple benefits, but a few potential risks should be highlighted. Infertility is one of the more critical risks that must be discussed with the patient.[14] Other potential adverse effects include acne, fluid retention, exacerbation of obstructive sleep apnea, exacerbation of existing lower urinary tract symptoms related to benign prostate enlargement, and, while less commonly reported, gynecomastia.[12]

Elevated prostate-specific antigen is a notable phenomenon that is expected to occur after testosterone replacement therapy is started. Because the prostate is an androgen-sensitive organ, increased androgens will result in increased production of prostate-specific antigen. It must be remembered that in this case, the increase does not necessarily indicate a neoplastic process.[15] Based on clinical principle, the AUA recommends measuring prostate-specific antigen in men older than 40 before starting testosterone therapy in order to exclude a diagnosis of prostate cancer.[1] Beyond this, our practice is to use the prostate-specific antigen level measured after initiation of testosterone therapy as a baseline for future comparisons. The relationship between testosterone replacement therapy and prostate cancer risk is an area ripe for further research. When counseling patients, however, it should be made clear that currently there is no high-quality evidence linking testosterone therapy to prostate cancer development.

Another adverse effect that has been associated with testosterone therapy is an increased risk of venous thromboembolic events. This association has not been proven conclusively, however, and the AUA guideline recommends informing patients of this.[1] Furthermore, there is not yet robust, definitive evidence for testosterone therapy's effect on the risk for cardiovascular events (moderate recommendation; evidence level B).[1] While not yet incorporated into guidelines, results from the recent TRAVERSE (Testosterone Replacement

Therapy for Assessment of Long-term Vascular Events and Efficacy Response in Hypogonadal Men) study[16] suggest that testosterone therapy in men with hypogonadism does not increase the risk of major adverse cardiac events.

FOLLOW-UP

Following up with patients on testosterone therapy at a specific time interval is necessary to optimize outcomes. Measuring testosterone levels 1 to 2 months after treatment initiation is recommended. If testosterone levels increase adequately and symptoms are improved, therapy can continue indefinitely, with testosterone measurements taken every 6 to 12 months while the patient is being treated. Prostate-specific antigen also should be monitored at the same time interval, as should the hematocrit, with a goal of maintaining a hematocrit below 54%. If symptoms fail to improve after 3 to 6 months of treatment, cessation should be discussed, as TD may not be the cause of symptoms. In the case of an inadequate increase in testosterone levels, dose adjustment or medication change can be considered.[1]

WHEN TO REFER TO UROLOGY

Urology referral should be pursued when a patient with TD wishes to maintain fertility or is currently infertile. Other situations warranting referral include prostate-specific antigen values increasing beyond the new post-treatment baseline or lack of improvement in erectile function after treatment. In addition, any patient who currently has prostate cancer or has been treated for prostate cancer should be referred to a urologist.

DISCLOSURES

Dr. Bajic has disclosed being an advisor or review panel participant for Endo Pharmaceuticals. 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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Diagnosis and management of pancreatic cystic lesions for the non-gastroenterologist

ABSTRACT

Although most pancreatic cystic lesions do not progress to cancer, they create concern for patients and their primary care physicians. The lack of consensus guidelines on diagnosis and surveillance of these lesions can lead to a management conundrum. We review current guidelines on diagnosis and management.

KEY POINTS

Magnetic resonance cholangiopancreatography with dynamic magnetic resonance imaging is the test of choice for diagnosis and assessment of high-risk or worrisome characteristics in cysts. Pancreatic-protocol computed tomography and endoscopic ultrasonography are suitable options if magnetic resonance imaging is contraindicated.

High-risk clinical and laboratory features include obstructive jaundice, recurrent pancreatitis, elevated serum carbohydrate antigen 19-9, presence of cells demonstrating high-grade dysplasia or neoplasia, and new-onset or worsening diabetes.

Pancreatic cystic lesions with high-risk features and those with a known high risk of malignancy, such as main duct intraductal papillary mucinous neoplasms and solid pseudopapillary tumors, should be referred for surgical excision.

Depending on clinical symptoms, suspected pancreatic cystic lesion type, and the presence of certain high-risk features, the monitoring period might range from 3 months to 2 years.

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With the enhanced quality and increased frequency of abdominal cross-sectional imaging, pancreatic cystic lesions (PCLs) are incidentally detected in apparently asymptomatic individuals,[1] with a pooled prevalence of up to 8%.[2] Although most of these lesions do not progress to cancer, their high prevalence and unclear potential for malignancy raise concern for patients and primary care physicians.[3–5] Thus, before making management decisions, it is necessary to describe PCLs by combining clinical and imaging data to determine the risk of malignancy. Several organizations have released guidelines[6–10] on the diagnosis and surveillance of PCLs, each with subtle distinctions, and none are aimed specifically at primary care physicians. In this review, we present a summary of current guidelines for diagnosis and management.

EPIDEMIOLOGY

The prevalence of PCLs in the general population has not been thoroughly investigated due to the inherent difficulty of examining a typically asymptomatic condition. Due to the increased use of abdominal imaging and developments in high-resolution cross-sectional imaging,[11] the prevalence of PCLs has gradually increased over the past 10 years.[12] Depending on the imaging modality used, the proportion of incidentally discovered PCLs ranges from 0.2% to 45.9%, with a pooled prevalence of 8%.[2,5,13] The estimated prevalence also varies according to geographical region, with an estimated frequency of 12.6% in the United States and

TABLE 1
Characteristics of neoplastic pancreatic cystic lesions

Characteristic	Serous cystic neoplasms	Solid pseudo-papillary tumors	Mucinous cystic neoplasms	Intraductal papillary mucinous neoplasms	Cystic pancreatic endocrine neoplasm	Pancreatic ductal adeno-carcinoma
Malignant potential	Benign	Can progress to malignancy			Malignant	
Age group	50–60	20–30	40–50	60–70	50–60	60–70
Sex predilection	Female more often than male			None		
Characteristic findings on cross-sectional imaging (computed tomography or magnetic resonance imaging)	Multicystic with central stellate scar	Solid growth with cystic degeneration	Solitary, unilocular, found in body or tail	Multifocal, communicates with main pancreatic duct, dilated main pancreatic duct	Complex cystic mass, enhancement of the cyst wall, hypervascular rim, found in body or tail	Irregular hypoechoic mass associated with an abrupt cutoff of the main pancreatic duct with upstream dilation
Endoscopic ultrasonography-guided fine needle aspiration cyst fluid analysis	Lower carcino-embryonic antigen (< 5 ng/mL), higher glucose, lower amylase	Not applicable	Higher carcinoembryonic antigen (> 192 ng/mL), lower glucose (< 50 mg/dL), positive mucin stain		Not applicable	
Treatment	No intervention is recommended if asymptomatic	Surveillance with or without resection			Resection	

Data from references 6–10, 19.

South America, 8.6% in Europe, and 3.1% in Asia.[2] In general, the incidence of PCLs normally increases with age. However, certain PCLs demonstrate a higher propensity to develop in either females or males, as well as at specific ages or in particular locations within the pancreas.[2,14]

PCL CLASSIFICATION

PCLs are categorized as benign or neoplastic. Benign PCLs include simple cysts, lymphoepithelial cysts, and retention cysts. Neoplastic PCLs include serous cystic neoplasms, solid pseudopapillary tumors, mucinous cystic neoplasms, intraductal papillary mucinous neoplasms, cystic pancreatic endocrine neoplasms, and pancreatic adenocarcinomas with a cystic component.[2,14–18]

Benign PCLs

Simple cysts (also known as true epithelial cysts) are unilocular, lined by a single epithelial layer, have no communication with the pancreatic ductal system, and have no malignant potential.[16]

Lymphoepithelial cysts are more common in males in their 50s and are observed throughout the pancreas. They are sometimes mistaken for pseudocysts and have a mean size of 5 cm, and around half of them are multilocular.[17,18]

Retention cysts are dilated side branches of the pancreatic duct produced by blockage (eg, calculi, mucin), and they may have mucinous mucosal lining and can be difficult to differentiate from intraductal papillary mucinous neoplasms, PCLs with malignant potential.[19]

In some classification schemes, acute pancreatic fluid collection, pseudocyst, acute necrotic collection, and walled-off necrosis are considered benign inflammatory fluid collections, but these are not true PCLs because the contents are not lined by epithelial cells and the lesions are not always found in the pancreas.

Neoplastic PCLs

Table 1[6–10,19] lists the key epidemiologic, clinical, and imaging characteristics of neoplastic PCLs.

TABLE 2
High-risk and worrisome features in intraductal papillary mucinous neoplasms

High-risk features	Worrisome features
Main pancreatic duct size ≥ 10 mm	Main pancreatic duct size 5–9 mm
Obstructive jaundice and cyst in head of pancreas	Cyst ≥ 3 cm
Solid mass	Lymphadenopathy
Cancer or high-grade dysplasia on cytology	Elevated carbohydrate antigen 19-9 level
Mural nodule ≥ 5 mm	Mural nodule < 5 mm
	Cyst growth ≥ 5 mm/2 years
	Change in caliber of main pancreatic duct with distal pancreatic atrophy
	Thickened or enhancing cyst walls
	New-onset diabetes mellitus

Data from references 6 and 7.

Mucinous cysts are lined with a mucin-producing epithelium and include intraductal papillary mucinous neoplasms and mucinous cystic neoplasms.[6] The difference between mucinous cystic neoplasms and intraductal papillary mucinous neoplasms is the presence of a connection to the pancreatic ductal system. Mucinous cystic neoplasms do not communicate with the ductal system, whereas intraductal papillary mucinous neoplasms originate from the ductal system.[9,20]

Mucinous cystic neoplasms are found in the body and tail of the pancreas and are almost exclusively found in women ages 40 to 60 (with a peak incidence at age 40 to 50). These neoplasms have a characteristic ovarian-type stroma and have been found to be malignant in 0% to 34% of cases.[20,21]

Intraductal papillary mucinous neoplasms are divided into 3 types: main duct type, branch duct type, and mixed type. The mixed type involves the main duct and the branch duct, based on imaging studies with or without histology. Main duct intraductal papillary mucinous neoplasm causes dilation of the main pancreatic duct of more than 5 mm without other identified causes. Branch duct intraductal papillary mucinous neoplasms have a lower risk of malignancy, ranging between 12% and 47%, while main duct intraductal papillary mucinous neoplasms and mixed type have a higher risk of being malignant, ranging from 38% to 68%.[22]

Serous cystic neoplasms are most frequent in women between the ages of 50 and 60, exhibit a honeycomb appearance on imaging (many tiny cysts surrounding a central stellate scar with calcification), and have a negligible chance of becoming malignant.[22,23] There are 4 distinct morphological patterns: microcystic, macrocystic, mixed microcystic and macrocystic, and solid.[23,24]

Solid pseudopapillary tumors are large solid, cystic, or mixed solid-cystic tumors that primarily affect young women. Although their malignant potential has not been well investigated, these are certainly malignant tumors with both local and metastatic potential, and surgical excision is recommended.[25]

Other lesions with a cystic appearance include pancreatic adenocarcinomas with a cystic component and cystic pancreatic endocrine neoplasm.[7,26]

PCL CANCER RISK

Determining the cancer risk of PCLs should be approached in 2 steps. First, determine whether the cyst is neoplastic. Next, look for clinical and imaging signs that have been linked to an elevated risk of cancer and are described as "high-risk" or "worrisome" characteristics.[6]

High-risk clinical features include obstructive jaundice without other explanation, recurrent pancreatitis due to a PCL, a significantly elevated serum carbohydrate antigen 19-9 level, or, if cytology is obtained, the presence of cells demonstrating high-grade dysplasia or neoplasia, and new-onset or worsening diabetes. Worrisome characteristics include main pancreatic duct dilation greater than or equal to 5 mm, cyst size greater than or equal to 3 cm, and the presence of a solid component or mural nodule in the PCL.[6,7,9,10] Of the PCLs with malignant potential, mucinous cystic neoplasms and intraductal papillary mucinous neoplasms are the most commonly observed in clinical practice.

Table 2[6,7] lists the high-risk and worrisome traits for presumed intraductal papillary mucinous neoplasms. When 1 or more of these characteristics are present, the patient should be referred to a center of excellence for additional examination and treatment by a multidisciplinary expert group.

DIAGNOSIS

PCLs are frequently seen on cross-sectional imaging of the abdomen in asymptomatic patients. If a PCL is an incidental finding, dedicated magnetic resonance cholangiopancreatography with dynamic magnetic resonance imaging is the test of choice and should be

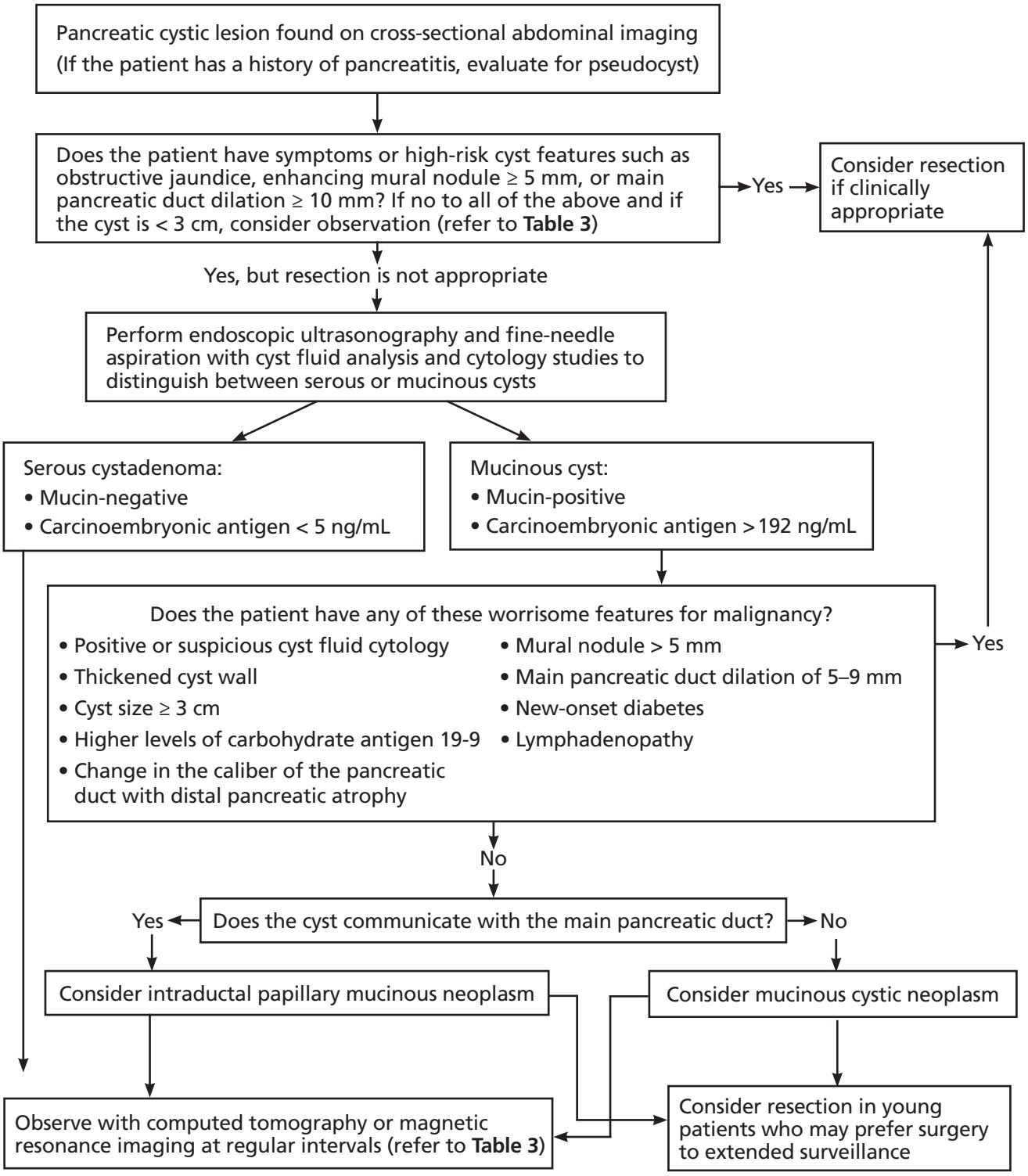

Figure 1. Strategy to evaluate and manage pancreatic cystic lesions.

TABLE 3
Approach to surveillance of pancreatic cystic neoplasms based on the different society guidelines

Cyst size	IAP[6] (Kyoto), 2023	ACG,[7] 2018	AGA,[9] 2015	ACR,[8] 2017	European consensus,[10] 2018[a]
< 1 cm	CT/MRI or EUS in 6 months and then every 18 months if stable	MRI every 2 years for 4 years	MRI in 1 year, then every 2 years for 5 years Stop if no significant change in the characteristics of the cyst after 5 years of surveillance	MRI/CT every 1 year for cysts 1.5 cm to < 2 cm and every 6 months for cysts 2.0–2.5 cm for 4 times, then lengthen the interval Stop after stability over 10 years	Surveillance every 6 months for 2 times with MRI with or without EUS or CA19-9 If stable, lifelong surveillance is recommended with annual MRI/EUS or CA19-9
1–2 cm		MRI every 1 year for 3 years then every 2 years for 4 years			
2–3 cm	CT/MRI or EUS every 6 months for 2 times and then every 12 months if stable	MRI/EUS every 6 months–1 year for 3 years then every year for 4 years		For cysts ≥ 2.5 cm, MRI/CT every 6 months for 4 times, and if stable over initial 2 years, MRI/CT yearly for 2 times, then every 2 years for 3 times, then stop if stable over 10 years	
> 3 cm	CT/MRI or EUS every 6 months	MRI/EUS every 6 months for 3 years then every year for 4 years	Pursue EUS-FNA	For patients age ≥ 80, imaging every 2 years for 2 times, and stop if cyst is stable	

[a]European consensus = European Study Group on Cystic Tumours of the Pancreas, United European Gastroenterology, European Pancreatic Club, European-African Hepato-Pancreato-Biliary Association, European Digestive Surgery, and the European Society of Gastrointestinal Endoscopy.

ACG = American College of Gastroenterology; ACR = American College of Radiology; AGA = American Gastroenterological Association; CA = carbohydrate antigen; CT = computed tomography; EUS = endoscopic ultrasonography; FNA = fine-needle aspiration; IAP = International Association of Pancreatology; MRI = magnetic resonance imaging

performed to identify the cyst characteristics and any high-risk or worrisome characteristics.[6–8]

In patients who are unable to undergo magnetic resonance imaging, pancreatic-protocol computed tomography and endoscopic ultrasonography are suitable options.[7] If the diagnosis is ambiguous, or if the PCL has clinical or radiologic worrisome features, endoscopic ultrasonography can give further diagnostic information.[3] Fine-needle aspiration for cystic fluid cytology and biomarker analysis can provide information on amylase concentration, intracystic glucose level, carcinoembryonic antigen levels, or molecular markers.[7,27,28] Notably, while certain PCLs can be accurately diagnosed using cross-sectional imaging with or without endoscopic ultrasonography with fine-needle aspiration for cytology, surgical pathology is required for definitive histologic classification.[29]

Lately, remarkable progress has been made in the identification and validation of molecular cyst fluid biomarkers such as KRAS, GNAS, SPINK1, interleukin-1-beta, cancer antigen 72-4, vascular endothelial growth factor-A, vascular endothelial growth factor receptor 2, prostaglandin E2, and methylated DNA biomarkers.[30–35] These biomarkers play a pivotal role in aiding the diagnostic process, contributing to improved accuracy in assessing PCLs.

MANAGEMENT AND PROGNOSIS

PCLs that have the potential to become malignant are managed by active monitoring or surgical excision. PCLs with high-risk characteristics, and those with a known high risk of malignancy, such as main duct intraductal papillary mucinous neoplasms and solid pseudopapillary tumors, should be referred for surgical excision. Patients with PCLs who have symptoms such as pancreatitis, nausea and vomiting caused by intestinal obstruction, or abdominal discomfort should undergo surgical evaluation regardless of cancer risk.

Patients with asymptomatic cysts and those without high-risk characteristics can undergo active surveillance, as the likelihood of advanced neoplasia is low. Surveillance is not advised for people older than 85 or people with too many medical comorbidities to undergo surgery.[6,7,9,10] Simple cysts and asymptomatic pseudocysts don't require monitoring.[7,9] Depending on clinical symptoms, suspected PCL type, and the existence of high-risk traits, the monitoring period might range from 3 months to 2 years.[6,7,9,10]

Due to its exceptional resolution and ability to discern the main pancreatic duct effectively, magnetic resonance imaging and magnetic resonance cholangiopancreatography are used for surveillance. On the other hand, endoscopic ultrasonography is reserved for patients displaying concerning characteristics, in addition to fine-needle aspiration of cyst fluid for a precise diagnosis through biomarker analysis. However, for lesions with no worrisome features, a combination of history, examination, and radiologic characteristics may commonly define the type of PCL and assess the risk of malignant degeneration.[26] **Figure 1** outlines a strategy to evaluate and manage PCLs.

The duration of PCL surveillance is debatable, with most current guidelines recommending the surveillance interval based on radiologic PCL appearance and changes over time compared with previous imaging,[6,7,10] while some advocate stopping after 5 years if the PCL is stable and has not progressed.[9] If the patient is unwilling to undergo pancreatic surgery or is unfit for surgery, then asymptomatic PCL surveillance may be stopped as it is unlikely to impact clinical management or survival.[6,7,10]

Experts advocate maintaining surveillance till age 75 and individualizing follow-up between ages 76 and 85 (**Table 3**).[6–10] It is also advised to inform patients that they may require continued surveillance even after undergoing partial pancreatic resection, as recurrence may occur in the remnant pancreas.[6,7,35,36] Although it is difficult to find strong prospective evidence that surveillance reduces mortality, studies have shown that PCLs with the potential to become malignant can take years to develop, and that pancreatic cancers detected through surveillance were more frequently at an earlier stage in patients with intraductal papillary mucinous neoplasms.[7,36]

CONCLUSION

Pancreatic cysts are frequently found incidentally on cross-sectional imaging. The possibility of malignancy varies depending on the type of PCL. Magnetic resonance cholangiopancreatography with dynamic magnetic resonance imaging is the preferred test to identify cyst characteristics and high-risk or worrisome features. PCLs with malignant potential are treated by close surveillance or surgical excision. A multidisciplinary team should assess PCLs with high-risk characteristics and those with a known high risk of malignancy, such as main duct intraductal papillary mucinous neoplasms, mucinous cystic neoplasms, and solid pseudopapillary tumors.

Because advanced neoplasia is unlikely, active surveillance is appropriate for asymptomatic cysts and those that do not have any high-risk characteristics. Surgery should be performed to remove high-risk PCLs or those that progress while under surveillance. The overall prognosis is favorable, with early detection and active surveillance serving as the cornerstones of management.

DISCLOSURES

Dr. Stevens has disclosed teaching and speaking for Abbvie Pharmaceuticals. 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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Hypertension and severe hyperreninemia in a young man

A 29-year-old man presented to the internal medicine clinic for evaluation of hypertension. His blood pressure at 2 separate clinic visits was 152/118 mm Hg and 156/116 mm Hg. He reported home measurements with systolic pressures in the 140s to 150s mm Hg and diastolic pressures in the 90s to 100s mm Hg. His elevated blood pressure was first noted in his late teens and managed with diet and lifestyle changes. He had never been prescribed antihypertensive medication.

His medical history was otherwise normal. He was not taking prescription or over-the-counter medications and said he did not use supplements, tobacco products, alcohol, or drugs. He was unaware of any family history of hypertension. He reported heavy snoring but had not experienced excessive daytime fatigue and was unaware of any apnea.

INITIAL EVALUATION AND MANAGEMENT

On examination, the patient's blood pressure was 156/116 mm Hg, heart rate 90 beats per minute, and body mass index 28.6 kg/m^2. His heart rhythm was regular with no extra heart sounds or murmurs. There was no carotid or abdominal bruit and no elevation in jugular venous pulsation. His lungs were clear to auscultation, with no wheezing or crackles. His extremities were without edema, and no focal neurologic deficits or funduscopic abnormalities were noted.

Laboratory test results

Notable results of initial laboratory testing were as follows:

- Serum potassium 3.5 mmol/L (reference range 3.5–5.0)
- Serum bicarbonate 30 mmol/L (21–31)
- Basic metabolic panel otherwise within normal limits
- Urinalysis with microscopic examination 0–2 red blood cells (0–2), 0–5 white blood cells (0–5), and negative urine protein
- Random urine microalbumin less than 7 mg/L (< 7)
- Hemoglobin, white blood cell count, and platelet count within normal limits
- Total cholesterol 227 mg/dL (< 200)
- High-density lipoprotein cholesterol 48 mg/dL (> 40)
- Low-density lipoprotein cholesterol 143 mg/dL (< 100)
- Triglycerides 182 mg/dL (< 150)
- Hemoglobin A1c 5.5% (4.7–5.6)
- Thyroid-stimulating hormone 1.62 mIU/L (0.55–4.78).

The patient was prescribed lisinopril 20 mg daily. Four weeks later, his blood pressure readings remained above goal, and chlorthalidone 25 mg daily was added. Unattended overnight sleep apnea testing at home revealed a respiratory-event index of 18.3 per hour, consistent with moderate obstructive sleep apnea. Nocturnal continuous positive airway pressure therapy was initiated, and he was encouraged to increase his physical activity and follow a low-sodium diet.

At follow-up 3 months later, his blood pressure was 120/80 mm Hg. Laboratory evaluation revealed a serum potassium of 3.2 mmol/L. Consequently, his chlorthalidone dosage was decreased to 12.5 mg daily and the lisinopril was increased to 40 mg daily. At his next office visit, his blood pressure was 121/70 mm Hg and his potassium had improved to 3.7 mmol/L.

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POSSIBLE SECONDARY HYPERTENSION

1 Which of the following is the most appropriate diagnostic test for this patient?

- ☐ Plasma renin and aldosterone
- ☐ Renal artery angiography
- ☐ Seated plasma fractionated metanephrines
- ☐ Early morning plasma cortisol

Evaluation for identifiable secondary causes of hypertension should be considered in patients diagnosed with hypertension under age 30, those with abrupt onset or sudden worsening of hypertension, and those with severe hypertension (ie, defined as blood pressure > 180/120 mm Hg).[1,2] Screening for secondary hypertension is also recommended in patients with resistant hypertension—defined as uncontrolled hypertension despite 3 antihypertensive drugs including 1 diuretic—or controlled hypertension requiring 4 medications.[1] Testing for specific forms of secondary hypertension can be guided by the history, physical examination, and basic laboratory results.[1,2]

Primary aldosteronism is a common cause of secondary hypertension, with a prevalence of about 10% to 20% in patients with hypertension.[3–5] Screening is recommended in those who present with severe or resistant hypertension, hypertension and spontaneous or diuretic-induced hypokalemia, hypertension with an adrenal lesion, hypertension with atrial fibrillation, or hypertension with obstructive sleep apnea.[1,3,6,7]

The first step in screening for primary aldosteronism is to assess plasma renin and aldosterone levels and calculate the aldosterone-to-renin ratio (ARR).[6,7] Primary aldosteronism is more prevalent than was previously realized and often goes undiagnosed.[3,5] Our patient has multiple indications to screen for primary aldosteronism, including hypertension with hypokalemia and hypertension with obstructive sleep apnea.

Renal vascular disease is another relatively common cause of secondary hypertension, with a prevalence of about 1% to 8% in patients with hypertension.[4] Atherosclerotic vascular disease is responsible for approximately 90% of cases of renal artery stenosis and typically affects patients over age 50 who have other vascular comorbidities or risk factors.[1] Fibromuscular dysplasia is a less common cause of renal artery stenosis in younger patients, usually women.[8] In a young man like our patient, renal artery stenosis is statistically less likely than primary aldosteronism. Screening for renal vascular disease could still be considered, but the initial screening test should be noninvasive imaging such as renal vascular duplex ultrasonography, magnetic resonance angiography of the abdomen, or computed tomographic angiography of the abdomen. Renal artery angiography is a confirmatory test that could be considered depending on initial imaging findings.[1]

Pheochromocytoma is a rare cause of secondary hypertension, with a prevalence of 0.1% to 0.6%.[1] Screening should be considered in patients with resistant hypertension, blood pressure lability, headache, sweating, palpitations, pallor, or a positive family history for pheochromocytoma, and in those with an adrenal lesion.[1] The pretest probability of pheochromocytoma in our patient is much lower than for primary aldosteronism or renal vascular disease.

Checking for plasma fractionated metanephrines is appropriate if there is high suspicion of pheochromocytoma. However, plasma metanephrines should be assessed only under standard conditions, with the patient in the supine position with an indwelling intravenous cannula. Measurements taken while the patient is seated are associated with a high rate of false-positive results. Alternatively, metanephrines and fractionated catecholamines can be assessed on a 24-hour urine collection.[9]

Hypercortisolism is a rare cause of secondary hypertension, with a prevalence of less than 0.1%.[1] Signs and symptoms may include weight gain, central obesity, facial plethora, proximal muscle weakness, striae, bruising without trauma, hirsutism, dorsal and supraclavicular fat pads, mental health problems, menstrual irregularities, hyperglycemia, and early-onset osteoporosis.[1,10] Screening for hypercortisolism can be done with an overnight 1-mg dexamethasone suppression test, 24-hour urine-free cortisol test, or late-night salivary cortisol testing.[11] An unsuppressed early morning cortisol test is sometimes used in case-detection of adrenal insufficiency but would not be useful in screening for cortisol excess.

CASE CONTINUED: PLASMA RENIN

Our patient was initially started on lisinopril monotherapy. A second agent, chlorthalidone, was added when blood pressure remained above goal after 4 weeks. Consensus guidelines recommend that for patients who present with blood pressure more than 20/10 mm Hg above goal, initial antihypertensive therapy should consist of 2 agents of different classes rather than monotherapy.[1] In our patient, it would have been appropriate to start treatment with combination drug therapy rather than waiting 4 weeks to start the second drug.

TABLE 1
Effects of antihypertensive drug classes on plasma renin and aldosterone

Medication class	Effect on plasma renin	Effect on plasma aldosterone
Beta-blockers	Decrease	Moderate decrease
Central agonists (eg, clonidine, alpha-methyldopa)	Decrease	Moderate decrease
Potassium-wasting diuretics	Increase	No change or moderate increase
Potassium-sparing diuretics	Increase	Moderate increase
Angiotensin-converting enzyme inhibitors	Increase	Moderate decrease
Angiotensin receptor blockers	Increase	Moderate decrease
Dihydropyridine calcium channel blockers	Moderate increase	No change or moderate increase
Renin inhibitors	Moderate decrease or increase[a]	Moderate decrease

[a]Renin inhibitors lower plasma renin activity but raise plasma renin concentration.

Based on information in reference 6.

Our patient's plasma renin concentration (PRC) was found to be 1,971 pg/mL (4.2–52.2), and the plasma aldosterone concentration was 11.3 ng/dL (< 35.3).

2 Which of the following causes of secondary hypertension is not associated with hyperreninemia?

- ☐ Juxtaglomerular cell tumor
- ☐ Renal artery stenosis
- ☐ Primary aldosteronism
- ☐ Scleroderma renal crisis

The enzyme renin is secreted by the juxtaglomerular apparatus, a specialized group of cells in the afferent arterioles of glomeruli. The renin-angiotensin-aldosterone system plays a central role in blood pressure regulation. Briefly, increased renin-angiotensin-aldosterone system activity raises blood pressure via arterial vasoconstriction and retention of sodium by the renal tubules. Normal physiologic stimuli for renin release include decreased renal arteriolar pressure sensed by baroreceptors, sodium and chloride depletion sensed by the macula densa in the distal renal tubules, and sympathetic (beta-1-adrenergic) activity. Renin secretion is regulated via negative feedback by angiotensin II.[12]

Primary aldosteronism is classically associated with low plasma renin. In fact, suppressed plasma renin is a criterion for the diagnosis of primary aldosteronism: autonomous aldosterone production leads to pathogenic sodium retention and volume expansion, resulting in negative feedback on renin secretion.[3,6]

Juxtaglomerular cell tumor, or reninoma, is a rare cause of secondary hypertension and hypokalemia. It leads to "primary" hyperreninemia via direct renin secretion from tumor cells.[13] "Secondary" hyperreninemia can be seen with any process that decreases renal arteriolar perfusion pressure, including renal artery stenosis, malignant hypertension, scleroderma renal crisis, and renal thrombotic microangiopathy. Hyperreninemia can occur secondary to excessive sympathetic activation, as in pheochromocytoma.[14] Secondary hyperreninemia can also be seen in the setting of sodium depletion, as occurs in salt-wasting disease states like Bartter or Gitelman syndrome or adrenal insufficiency. However, these are generally not associated with hypertension.

Measurement of plasma renin

Clinical measurement of plasma renin is mainly indicated in screening for primary aldosteronism. A high renin level is not specific to any one form of secondary hypertension. Two common assays are used to measure plasma renin:

- The plasma renin activity (PRA) assay quantifies renin in terms of its enzymatic activity expressed as the amount of angiotensin I generated per unit of time
- The PRC assay, sometimes referred to as the direct renin concentration, measures the mass of active renin directly.

PRA accounts for endogenous angiotensinogen levels and has less variation due to exogenous estrogen,

TABLE 2
Trend of plasma renin and aldosterone laboratory values in our patient

	Initial results while taking lisinopril and chlorthalidone	Rechecked 6 weeks later, with no medication changes	Rechecked after 4 weeks of verapamil monotherapy
Plasma renin concentration (reference range 4.2–52.2 pg/mL)	1,971 pg/mL	1,253 pg/mL	14.8 pg/mL
Plasma aldosterone concentration (< 35.3 ng/dL)	11.3 ng/dL	17.1 ng/dL	10.1 ng/dL

menstruation, pregnancy, and liver dysfunction. PRC correlates well with PRA, and many laboratories have adopted it because it is easier and less expensive to perform than PRA.[15] Our institution measures PRC via chemiluminescent immunoassay.

CASE CONTINUED: NEPHROLOGY REFERRAL

Further workup was pursued to evaluate possible causes of hypertension and hyperreninemia. Renal vascular duplex ultrasonography did not demonstrate evidence of renal artery stenosis. Contrast-enhanced computed tomography of the abdomen showed normal kidneys and adrenal glands without focal lesions. Plasma fractionated metanephrines were normal. The patient was referred to our nephrology hypertension clinic for further evaluation of elevated plasma renin. Repeat laboratory evaluation about 6 weeks after the initial check showed a PRC of 1,253 pg/mL and a plasma aldosterone concentration of 17.1 ng/dL. A "washout" of medications that affect plasma renin levels was pursued.

3 Which class of antihypertensive medication is not associated with an increase in plasma renin levels?

- ☐ Angiotensin-converting enzyme (ACE) inhibitors
- ☐ Angiotensin receptor blockers (ARBs)
- ☐ Thiazide and thiazide-like diuretics
- ☐ Direct renin inhibitors
- ☐ Beta-blockers

Many antihypertensive agents alter renin and aldosterone levels (**Table 1**).[6] When possible, screening for primary aldosteronism should be done in the absence of interfering medications.[6] For patients already on antihypertensive therapy, however, withdrawal of these medications may not be feasible, and delaying testing for medication washout can lead to missed screening opportunities. To improve case-detection rates, some authors have recommended a simplified approach in which patients who meet criteria for screening have their plasma renin and aldosterone levels checked without adjustment of existing medications.[3,16,17] At the time of initial screening, our patient was taking lisinopril and chlorthalidone, both of which can increase plasma renin levels.

ACE inhibitors and ARBs increase plasma renin by blocking the negative feedback of angiotensin II on renin secretion. Downstream, angiotensin II-mediated aldosterone secretion is diminished.[18] This rise in renin and drop in aldosterone can significantly decrease the ARR and lead to a false-negative screening result in patients with primary aldosteronism.[7,19]

Diuretics lead to increased renin secretion in compensation for natriuresis and reduced blood volume. Aldosterone is increased to a lesser degree, which can also result in a false-negative ARR.[7]

Direct renin inhibitors block the enzymatic activity of renin and prevent formation of angiotensin I and subsequently angiotensin II. This means that the observed effect of direct renin inhibitors on plasma renin varies depending on which assay is used. The PRA (measuring the amount of angiotensin I generated per unit time) decreases, while conversely the PRC (measuring the mass of renin present in plasma) increases due to reduced negative feedback by angiotensin II.[20]

Dihydropyridine calcium channel blockers have been associated with increased plasma renin in some studies,[19,21] while others reported a less significant effect.[18] Expert consensus guidelines still list this class among those that can confound renin and aldosterone measurements.[6,7] The mechanism by which dihydropyridine calcium channel blockers could increase renin is not fully understood, but may involve effects

on renal arteriolar baroreceptors, sympathetic activity, and the secondary natriuresis induced by this class.[12,19]

Beta-blockers and central alpha-2 agonists lead to a reduction in plasma renin by the inhibition of beta-adrenergic activity.[6,18] Aldosterone levels are reduced to a lesser extent, which can lead to a false-positive ARR.[7]

When medication adjustment is feasible, expert consensus guidelines recommend the substitution of antihypertensive drugs that have a minimal effect on plasma renin and aldosterone. These include hydralazine, nondihydropyridine calcium channel blockers, and alpha-2 adrenergic blockers. Medications that can interfere with renin and aldosterone measurements should be discontinued for at least 4 weeks.[6,7]

CASE CONCLUDED

In our patient, lisinopril and chlorthalidone were stopped, and acceptable blood pressure control was maintained using verapamil. Four weeks after these changes, the patient's PRC was rechecked and found to be within the normal range at 14.8 pg/mL (**Table 2**), indicating that the initial high PRC was secondary to combination ACE inhibitor and diuretic therapy.

The confounding effects of ACE inhibitors and diuretics on plasma renin and aldosterone levels are well recognized, but the magnitude of renin elevation in our patient was significantly higher than what has previously been reported. In prospective studies of normotensive volunteers and patients with essential hypertension, initiation of an ACE inhibitor or ARB has been associated with an average 4-fold to 6-fold increase in plasma renin.[21,22] In a recent meta-analysis of randomized controlled trials in patients with hypertension, the standardized mean increase in plasma renin after starting a thiazide or thiazide-like diuretic was about 1.5 times baseline, and the highest reported mean increase was about 7 times baseline.[23]

Our patient's initial PRC was more than 37 times the upper limit of normal, comparable to levels reported in association with reninoma.[13] It is understandable that this finding prompted imaging and nephrology referral.

TAKE-HOME POINTS

Primary aldosteronism is an underrecognized and treatable cause of secondary hypertension. Checking plasma renin and aldosterone levels without first adjusting medication may improve case-detection rates.[3,16,17] Results can still be reliably interpreted if renin is in the suppressed range.[19] In fact, a suppressed renin while on ACE inhibitor, ARB, or diuretic therapy should increase suspicion for primary aldosteronism.[3,24] However, when renin levels are not suppressed, a medication effect should be considered.

With broader application of screening for primary aldosteronism, it is critical to understand the effects of medications on plasma renin and aldosterone levels. As shown in our patient, ACE inhibitors and thiazide diuretics can lead to extremely high plasma renin levels, comparable to those seen with rare causes of secondary hypertension such as reninoma. Awareness of this possibility is critical when screening for primary aldosteronism in patients taking these medications, especially when taken in combination.

When evaluating a patient with elevated plasma renin—even extremely high levels—the effect of medications should be considered before pursuing additional diagnostic testing. Significant cost, radiation exposure, and psychological stress for the patient may be avoided if plasma renin levels are reassessed after confounding drugs are withdrawn.

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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Management of venous thromboembolism in patients with active cancer

ABSTRACT

Venous thromboembolism (VTE) is a major health burden in patients with cancer, causing morbidity, emergency room visits, hospitalizations, and death. Treatment is challenging, as it is necessary to balance the risk of recurrent thrombosis and bleeding associated with anticoagulants. Treatment paradigms are shifting from low-molecular-weight heparin monotherapy. Multiple recent randomized controlled trials have demonstrated the safety and efficacy of direct oral anticoagulants in this setting. Current studies are evaluating factor XI inhibitors as potential treatments for cancer-associated VTE.

KEY POINTS

- Patients with cancer are at a much higher risk of developing VTE than the general population.
- Low-molecular-weight heparin or direct oral anticoagulants are preferred over vitamin K antagonists. Direct oral anticoagulants are generally preferred, but caution is needed in patients at risk of bleeding.
- In the absence of bleeding concerns, anticoagulants should be continued for at least 6 months if the patient still has active cancer or metastatic disease or continues to receive systemic therapy.

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Venous thromboembolism (VTE) events, including deep vein thrombosis, pulmonary embolism, and visceral vein thrombosis, are common in patients with cancer and can have significant consequences. In a study of 4,466 patients with cancer, thromboembolism (including VTE and arterial events) was reported to be the second major cause of death (tied with infection), after cancer itself.[1] A recent large registry study showed higher rates of mortality, recurrent VTE, and bleeding in patients with active cancer when compared with patients with a history of cancer or no cancer.[2] Sharman Moser et al[3] compared patients with cancer with and without VTE and found those with VTE were more likely to be hospitalized (81.4% vs 35.2%), had longer hospital stays (20.1 days vs 13.1 days), and were more likely to visit the emergency room (41.5% vs 19.3%). Studies have shown a 39.5% increase in total healthcare costs in ambulatory patients with lung cancer and VTE,[4] as well as increased healthcare utilization, a 3-fold increase in the rate of hospitalization, and an annual increase in per-patient cost of approximately $29,000 for recurrent VTE.[5]

The pathogenesis of the thrombophilic state in patients with cancer is distinct from that in populations without cancer and is multifactorial.[6,7] Tumor cells can interact with host cells including endothelial cells, neutrophils, platelets, and monocytes. They promote the release of procoagulant factors and inflammatory cytokines that mediate endothelial dysfunction, including tumor necrosis factor alpha and interleukin-8.[6] Certain factors also

activate the coagulation cascade and remodel fibrin clot formation.[7–9] Certain types of cancer can lead to leukocytosis and increased generation of neutrophil extracellular traps that capture and activate platelets, increase tissue factor activity, and secrete proteinases that promote metastasis. Another mechanism is cancer-associated thrombocytosis.[6,7,10]

PRESENTATION OF VTE IN CANCER

VTE develops in 5% to 20% of patients with cancer, and approximately 20% of all VTE cases occur in patients with cancer.[11] Clinical and biologic factors that increase the risk of thromboembolism in patients with cancer include site of cancer, advanced stage (metastatic), use of central venous catheters, and treatment such as antiangiogenesis, chemotherapy, immunotherapy, surgery, hospitalization, and transfusion.[7,8,11]

VTE rates in patients with cancer are 4 to 7 times higher than in healthy individuals and are rising, possibly due to improved survival outcomes, use of thrombogenic cancer treatments (antiangiogenic agents, tyrosine kinase inhibitors, lenalidomide-based regimens, thalidomide), extensive use of central catheters, and increasing awareness.[12–14] Studies have shown the highest risk of VTE is in patients with pancreatic and brain cancers, although risk is considered high in patients with gastric, esophageal, ovarian, and hematologic malignancies, particularly multiple myeloma and non-Hodgkin lymphoma.[15,16] Because the prevalence of breast, prostate, and colorectal cancer is much higher, these cancers contribute to a significant proportion of VTE, despite having a lower relative risk.[14]

The risk of VTE recurrence is high even with administration of anticoagulation therapy, and various risk-assessment models are used to predict the risk in patients with cancer. Louzada et al[17] studied 543 patients with cancer and VTE and formulated the Ottawa model to predict risk of VTE recurrence, which was later validated. Findings from the Computerized Registry of Patients with Venous Thromboembolism (RIETE)[18] demonstrated the following risk factors for VTE recurrence: age less than 65, pulmonary embolism as initial VTE, and less than 3-month interval between cancer diagnosis and initial VTE.[18]

Deep vein thrombosis in patients with cancer mostly affects the veins in the lower limbs and usually presents as painful swelling and redness of the affected limb.[7,19] Physical examination findings may include unilateral erythema, warmth, tenderness, difference in calf or thigh circumference, dilated superficial veins, and localized pain along the course of the involved vein. Rarely, patients can develop deep vein thrombosis in the internal jugular vein that can present as neck pain, swelling, erythema, headache, blurred vision, dizziness, and even altered sensorium. Other unusual sites of VTE include splanchnic, mesenteric, and portal veins that can present as abdominal pain, ascites, or gastrointestinal tract bleeding, but these are most commonly found incidentally on staging or restaging scans for malignancy. VTE in cerebral veins may present as focal neurologic deficits or seizures.[20] The use of central venous catheters predisposes patients to upper-extremity deep vein thrombosis that presents with features similar to those of lower-limb deep vein thrombosis.[21]

Pulmonary embolism in cancer

Pulmonary embolism is another form of VTE presentation and can be a cause of sudden death.[7,22–26] Common symptoms include shortness of breath, chest pain that is worse on inspiration (pleuritic type), cough, orthopnea, calf pain or swelling, and hemoptysis. On examination, pulmonary embolism can present with tachycardia, tachypnea, rales, decreased breath sounds, loud S_2 heart sound, and jugular venous distention, as well as the S1Q3T3 pattern on electrocardiography (large S wave in lead 1, Q wave and inverted T wave in lead 3). This pattern indicates right ventricular strain and is rarely found in patients.

A recent study reported that patients with hematologic malignancies were less likely to develop pulmonary embolism (46% vs 55%) but had a higher risk of upper-extremity deep vein thrombosis (25% vs 18%) than patients with solid malignancies.[22]

Pulmonary embolism identified on contemporary imaging ordered for staging or restaging of primary cancer is termed *incidental* pulmonary embolism.[7,23–26] VTE can also be the first manifesting feature of underlying malignancy.[25] The rate of occult cancer may reach 10% at 12 months after the first unprovoked VTE event.[25]

In patients with cancer, VTE can be difficult to diagnose owing to overlapping symptoms, especially in patients receiving anticancer therapy,[7,26] with a large number of symptoms misattributed to the underlying malignancy rather than to VTE.[12,13]

DIAGNOSIS

An elevated D-dimer is nonspecific, especially in patients with cancer, as it can be elevated without thrombosis.[7,26] The high prevalence of VTE in patients with cancer decreases the negative predictive value and undermines clinical prediction rules in these patients.[26] Pretest probability based on the Wells or Geneva score is used to guide evaluation for pulmonary embolism.[7,27]

Patients at low or intermediate risk can be evaluated with the highly sensitive D-dimer assay, age-adjusted cutoffs, and no further testing if negative. However, some experts consider imaging for patients with intermediate risk even if the D-dimer is negative. If the D-dimer is positive, computed tomography pulmonary angiography is warranted, although ventilation-perfusion scan is preferred to limit radiation exposure and for patients with contrast allergy or renal failure. If the patient is at high risk based on pretest probability (Wells or Geneva scores), computed tomography is warranted and D-dimer is not necessary prior to imaging.[7,27]

Although the Wells score classifies patients as likely or unlikely to develop deep vein thrombosis and recommends D-dimer testing or ultrasonography based on the score, compression ultrasonography is the mainstay for diagnosing deep vein thrombosis. Because the prevalence of VTE is high in patients with cancer and has worse outcomes, there is a low threshold for diagnostic workup or compression ultrasonography for deep vein thrombosis of the extremities.

Despite low or intermediate risk based on pretest probability, proceeding with imaging is appropriate if clinical suspicion for VTE is high, as is common in patients with malignancy.[26,27]

The rate of incidental deep vein thrombosis in the extremities varies from less than 1% to as high as 7% and may significantly underestimate the actual prevalence, as systematic assessment of distal veins may not always be performed.[28] A recent meta-analysis showed the overall frequency of incidental pulmonary embolism to be 3.36% (95% CI 3.15%–3.57%), with variation depending on the site of the primary malignancy.[29]

TREATMENT

Appropriate treatment of VTE in patients with cancer is a challenge owing to the need to balance bleeding risks with the increased risk of recurrent VTE.[30–37] The mainstay of therapy is anticoagulation.[7] The type of cancer, thrombocytopenia due to cancer therapy, drug-drug interactions with systemic cancer therapeutics, bleeding risk, and nausea and vomiting associated with ongoing chemotherapy can further complicate management regarding the choice of anticoagulant drug, emphasizing the need for individualization.[7]

ANTICOAGULANT THERAPY OPTIONS

Vitamin K antagonists

Vitamin K antagonists inhibit the synthesis of vitamin K-dependent clotting factors (II, VII, IX, X). Traditionally, vitamin K antagonists (eg, warfarin) have been the mainstay of treatment in VTE.[14] Because of the need for regular laboratory monitoring, the narrow therapeutic range, dietary restrictions, and drug-drug interactions with commonly used chemotherapy agents such as 5-fluorouracil and less predictable pharmacology, the current practice has shifted toward the use of low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs).

LMWH

LMWH treatments have more predictable pharmacokinetic properties and better biologic availability, especially in patients with concerns for chemotherapy-induced emesis.[37] LMWH monotherapy has been the standard treatment for cancer VTE for the past 15 years.[26,30,31,34] Owing to efficacy shown in randomized studies, guidelines have recommended LMWH over vitamin K antagonists in patients with cancer.[30,31,38]

The first large study to address the benefit of LMWH in patients with cancer was CLOT (Randomised Comparison of Low-Molecular-Weight Heparin Versus Oral Anticoagulant Therapy for the Prevention of Recurrent Venous Thromboembolism in Patients With Cancer),[30] which randomized 672 patients with active cancer and acute symptomatic VTE to receive dalteparin 200 IU/kg subcutaneously for 5 to 7 days, followed by a coumarin derivative with a target international normalized ratio of 2.5 or dalteparin (200 IU/kg once daily for the first month, then 150 IU/kg) alone for 6 months. Analysis showed lower rates of recurrent VTE over a 6-month follow-up period in the LMWH group, with 8% of patients developing recurrent VTE compared with 15.8% in the vitamin K antagonist group (hazard ratio [HR] 0.48, 95% CI 0.30–0.77, $P = .002$).[30] No significant difference in major bleeding ($P = .27$) or any bleeding ($P = .09$) was reported between groups.[30]

A decade later, a larger, global randomized controlled trial, The Comparison of Acute Treatments in Cancer Hemostasis (CATCH),[31] compared outcomes with tinzaparin and warfarin and showed no statistical difference in rates of recurrent VTE or major bleeding, but it did identify a significant reduction in clinically relevant nonmajor bleeding in patients randomized to tinzaparin ($P = .004$).[31] However, current concerns with LMWH include the inconvenient subcutaneous route of administration and higher cost (at least in the United States) that may contribute to reduced patient adherence.[12]

DOACs

DOACs include oral direct thrombin inhibitors (dabigatran) and inhibitors of factor Xa (apixaban, edoxaban, and rivaroxaban). Apixaban, edoxaban, and rivaroxaban have been studied in the treatment of VTE in patients with cancer, but there have been no cancer-specific data published with dabigatran for this indication. Oral route, fixed dosage, and no requirement for routine monitoring or dietary restrictions as with vitamin K antagonists have increased the use of DOACs for long-term management.[32–36] However, DOACs have significant drug-drug interactions, particularly with inducers and inhibitors of cytochrome P450 3A4 and P-glycoprotein.[7,32] Immune-modulating agents (tacrolimus, dexamethasone, cyclosporine), tyrosine kinase inhibitors (nilotinib), topoisomerase inhibitors (etoposide), hormonal agents (bicalutamide), anthracyclines (idarubicin), and antimitotic agents (vinblastine, paclitaxel) have been known to cause interactions with DOACs.[32] Caution is needed when DOACs are used for treatment in conditions such as hepatic or renal impairment, thrombocytopenia, active mucosal lesions, and unresected mucosal tumors, or when administered together with antiplatelet therapy. DOACs have also been noted to increase the risk of bleeding in gastrointestinal and genitourinary cancers.[11]

Several randomized controlled trials have shown noninferiority of DOACs vs LMWH.[32–34] The Hokusai VTE Cancer trial proved noninferiority of the oral factor Xa inhibitor edoxaban (DOAC) over dalteparin (LMWH) in 1,050 patients with active cancer.[32] The primary end point (composite end point of first recurrent VTE or major bleeding within 12 months) occurred in 12.8% of patients in the edoxaban group vs 13.5% in the dalteparin group (HR with edoxaban 0.97, $P = .006$ for noninferiority).[33] The rates of recurrent VTE were not significantly different between groups (7.9% vs 11.3%, HR 0.71, 95% CI 0.48–1.06, $P = .09$). The edoxaban group had a higher rate of bleeding (6.9% vs 4.0%, HR 1.77, 95% CI 1.03–3.04, $P = .04$), particularly in patients with gastrointestinal cancers, both resected and unresected (12.5% vs 3.6%, HR 4.0, 95% CI 1.5–10.6, $P = .005$).[14,33]

Anticoagulation Therapy in Select Cancer Patients at Risk of Recurrence of Venous Thromboembolism (SELECT-D) was a randomized, open-label, multicenter trial involving 406 patients with cancer and symptomatic or incidental pulmonary embolism or symptomatic deep vein thrombosis of a proximal lower extremity that compared outcomes with rivaroxaban and dalteparin over a period of 6 months.[34] The rate of recurrent VTE was reduced in the rivaroxaban group, with no significant difference between groups for rate of major bleeding. However, the rate of clinically relevant nonmajor bleeding events was higher in patients randomized to the rivaroxaban group (13% vs 4%, HR 3.76, 95% CI 1.63–8.69).[34]

The Caravaggio trial[35] analyzed outcomes in 1,155 patients with cancer and symptomatic or incidental acute proximal deep vein thrombosis or pulmonary embolism randomized to receive either oral apixaban or subcutaneous dalteparin for 6 months. The primary outcome of recurrent VTE was higher in the dalteparin group, and contrary to the SELECT-D study,[34] the bleeding rate was not higher in the apixaban group.[35]

A meta-analysis including 4 randomized controlled studies comparing DOACs and LMWH showed a reduced rate of recurrent VTE (relative risk ratio [RR] 0.62, 95% CI 0.43–0.91, I^2 30%) without a higher likelihood of major bleeding (RR 1.31, 95% CI 0.83–2.08, I^2 23%).[36]

Consensus treatment approaches

In general, guidelines from various societies regarding treatment of acute VTE in patients with active cancer show a substantial consensus.[11,39–43] Both DOACs and LMWH are considered preferred treatment options. In the absence of risk factors such as renal failure, hepatic impairment, thrombocytopenia, drug-drug interactions, or upper-gastrointestinal malignancy with an intact primary tumor, DOACs are the preferred agents, whereas LMWH pharmaceuticals are preferred for those with these risk factors (**Figure 1**).[11,16,32,36,39–43]

There is a major knowledge gap regarding duration of treatment, as most clinical trials have focused only on the first 6 months of treatment. Current guidelines recommend that anticoagulants must be used for a minimum of 6 months and continued beyond at the same dose if the patient has active cancer or metastasis or is undergoing continued chemotherapy, provided there is no increased risk of bleeding. It is appropriate to use vitamin K antagonists in patients for whom access to DOACs or LMWH may be limited, such as in low-resource settings or for prohibitive copay costs. Treatment recommendations from various guidelines are summarized in **Table 1**.[11,27,39–43]

SPECIAL CONSIDERATIONS IN TREATMENT

Incidental pulmonary embolism

Treatment is recommended for all incidental VTE (pulmonary embolism, deep vein thrombosis, multiple subsegmental pulmonary embolism).[11] The American

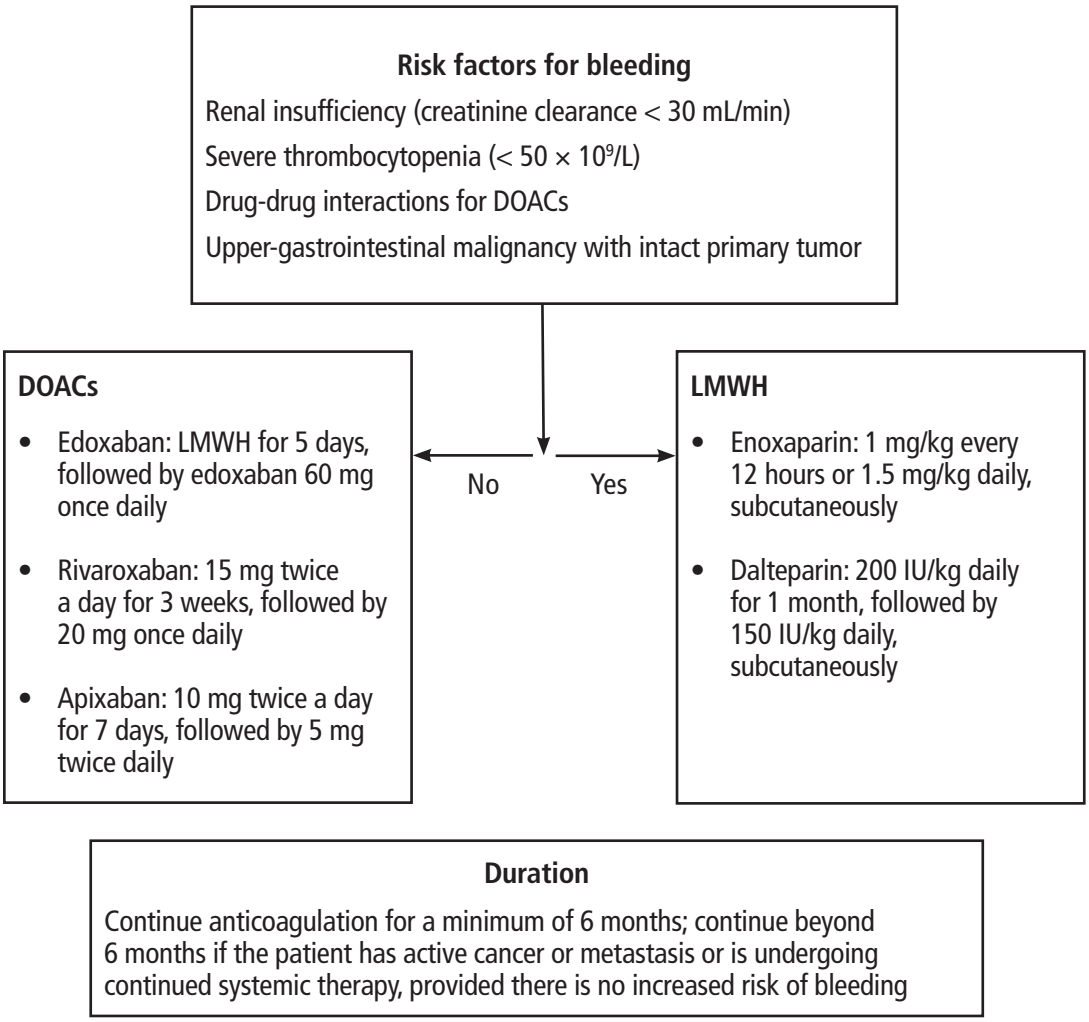

Figure 1. Approach to the treatment of acute venous thromboembolism in patients with cancer.

DOACs = direct oral anticoagulants; LMWH = low-molecular-weight heparin

Data from references 11,16,32,36,39–43.

Society of Hematology recommends short-term anticoagulation for 3 to 6 months for incidental pulmonary embolism in patients with cancer compared with observation alone.[11] However, isolated subsegmental pulmonary embolism can be observed on a case-by-case basis without anticoagulant therapy in the absence of ultrasonography-detected lower-limb deep vein thrombosis.[16]

It is our practice to screen for lower-extremity deep vein thrombosis in the presence of isolated subsegmental pulmonary embolism before deciding about anticoagulation. The decision to start anticoagulation for incidental visceral vein thrombosis must be based on diagnostic certainty, chronicity, extent of thrombus, bleeding risk, and patient preference, but the certainty of evidence is very low.[16]

Recurrence during anticoagulation

Patient adherence, medication dosage, and the probability of heparin-induced thrombocytopenia must be correctly assessed if a patient develops recurrent VTE while on anticoagulation. These patients should be transitioned to a therapeutic dose of LMWH if on other anticoagulants, and their dose should be increased by 25% if LMWH was being used at a therapeutic dosage at the time of VTE.[14,42] If the patient continues to experience recurrent thromboses, a further dose increase can be considered.[42] In the rare case of anticoagulation

TABLE 1
Guidelines for treatment of venous thromboembolism (VTE) in patients with cancer

Guidelines	Drugs	Treatment
American Society of Clinical Oncology	LMWH, fondaparinux, rivaroxaban, edoxaban, vitamin K antagonists	Initial (5–10 days): If parenteral anticoagulation used, LMWH preferred over unfractionated heparin
		Long-term (at least 6 months): LMWH, rivaroxaban, edoxaban
		DOACs: Caution with mucosal abnormalities, gastrointestinal and genitourinary cancers
		Vitamin K antagonists: If DOACs or LMWH unavailable
		Continue anticoagulation (beyond 6 months) in patients with active cancer such as metastatic disease, ongoing chemotherapy
International Society on Thrombosis and Haemostasis	Edoxaban, rivaroxaban, LMWH	DOACs: Acute VTE, low risk of bleeding and no drug interaction with ongoing systemic therapy
		LMWH/unfractionated heparin: Acute VTE, severe thrombocytopenia
		Shared decision-making regarding reduction in recurrence of VTE compared with higher bleeding risk with specific DOACs and patient preference
International Initiative on Thrombosis and Cancer	LMWH, edoxaban, rivaroxaban, apixaban	Initial treatment: LMWH recommended over unfractionated heparin or fondaparinux, DOACs as alternative
		Early maintenance (6 months): LMWH preferred over vitamin K antagonists
		Caution with DOACs in patients with gastrointestinal malignancy
		Long-term maintenance (beyond 6 months): Evaluate based on benefit-risk ratio, tolerability, and patient preference
American Society of Hematology	LMWH, apixaban, rivaroxaban, edoxaban	Initial treatment (first week): LMWH or rivaroxaban or apixaban
		Caution with DOACs in gastrointestinal malignancy, unfractionated heparin preferred over LMWH in renal insufficiency, creatinine clearance ≤ 30 mL/min
		Short-term treatment (3–6 months): DOACs (apixaban, rivaroxaban, edoxaban) preferred over LMWH
		DOACs: Caution in patients with gastrointestinal cancers, bleeding risks, drug interactions, cost
		Vitamin K antagonists preferred in renal insufficiency
		Long-term treatment (> 6 months): Recommended in patients with active cancer and absence of contraindications, DOACs or LMWH

DOACs = direct oral anticoagulants; LMWH = low-molecular-weight heparin

Data from references 11,27,39–43.

failure or absolute contraindication to the use of anticoagulants (such as active bleeding), inferior vena cava filters can be considered.[14,39,43] Retrievable filters are preferred and should be removed once contraindications to anticoagulation are safely addressed.[11]

Recurrence after stopping anticoagulation

As noted previously, anticoagulation must be resumed and continued indefinitely in the presence of risk factors such as active malignancy (ie, ongoing systemic therapy or metastatic disease), if there are no concerns for major bleeding risks.[11,27,39–43] Recurrent VTE after cancer treatment should prompt evaluation for cancer recurrence or a new primary malignancy. DOACs or LMWH can be used and dose-adjusted based on bleeding risk for primary VTE.

Thrombocytopenia

Thrombocytopenia, defined as platelet count less than 100×10^9/L,[16] can be the result of underlying malignancy or treatment with various chemotherapeutic agents. It is challenging to balance the risk of thrombosis and the risk of hemorrhage when managing patients with cancer and thrombocytopenia.[16] LMWH

is preferred in patients with thrombocytopenia, and studies are lacking regarding the safety of DOACs in such conditions. Samuelson Bannow et al[44] reviewed studies involving 121 patients and found that prolonged thrombocytopenia increased recurrent VTE in patients with cancer. Further, they suggested that DOACs may not be appropriate for these patients, that unfractionated heparin is considered a reasonable alternative in certain settings, and that therapeutic or reduced-dose LMWH anticoagulation is an option.[44] There was no significant difference in outcomes of recurrent VTE between the 2 treatment strategies, ie, therapeutic anticoagulation with platelet transfusion support or dose-modified anticoagulation if platelet counts were less than 50×10^9/L.[44]

With the risk of recurrent VTE highest within the first 30 days, full-dose anticoagulation for patients with platelet counts greater than 50×10^9/L is recommended.[43] Patients with symptomatic segmental or proximal pulmonary embolism, proximal deep vein thrombosis, or history of recurrence should receive therapeutic-dose anticoagulation with platelet transfusion to maintain platelet counts above 40 to 50×10^9/L. Patients with incidental subsegmental pulmonary embolism or distal deep vein thrombosis can receive dose-modified anticoagulation (50% of the prophylactic dose of LMWH) for platelet counts between 25 and 50×10^9/L.[43]

After the initial 30-day period, a dose-modified strategy is suggested for platelet counts between 25 and 50×10^9/L.[16,43,44] If the platelet count drops below 25×10^9/L, anticoagulation should be temporarily discontinued and then restarted once the count rises. Further, an inferior vena cava filter can be considered only for patients with contraindications to anticoagulants.

Renal insufficiency

Patients with creatinine clearance less than 30 mL/min have been excluded from many randomized controlled trials, leaving a lack of data on efficacy and safety of DOACs and therefore raising concern. A post hoc analysis of the CLOT trial showed a decreased rate of recurrent VTE with LMWH compared with vitamin K antagonists (HR 0.15, 95% CI 0.03–0.65, $P = .01$), but similar bleeding event rates for both treatments in patients with cancer and renal insufficiency ($P = .47$).[45] Unfractionated heparin is an alternative to LMWH in patients with renal insufficiency.[39]

Distal deep vein thrombosis

VTE in veins distal to the popliteal vein (ie, the peroneal, anterior tibial, and posterior tibial veins) is considered distal deep vein thrombosis.[46] Studies have shown that rates of bleeding and overall survival are similar in patients with isolated distal deep vein thrombosis and proximal deep vein thrombosis, and thus a treatment strategy similar to that for proximal deep vein thrombosis is recommended.[46]

CONCLUSION AND FUTURE DIRECTIONS

VTE leads to a significant health burden in patients with cancer. Anticoagulants such as DOACs and LMWH are the mainstay of treatment. Factor XI inhibitors are being developed in various settings for prevention and treatment of VTE. Abelacimab, a monoclonal antibody that inhibits factor XI activation and activity, is currently being studied in 2 randomized trials (ASTER trial NCT05171049, Magnolia trial NCT051710075) for treatment of acute VTE in patients with active cancer.[47] Overall, drug development and treatment options have increased in the past decade in this setting, reducing the risk of recurrent VTE for patients with cancer. Given these options, treatment needs to be individualized for patients depending on the underlying malignancy burden, risk of bleeding, and patient preferences and values.

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In the January 2024 issue, the article on SGLT-2 inhibitors by Badwan OZ, Braghieri L, Skoza W, Agrawal A, Menon V, and Tang WHW, When should we consider SGLT-2 inhibitors in patients with acute decompensated heart failure? [Cleve Clin J Med 2024; 91(1):47–51. doi:10.3949/ccjm.91a.23034] contained an error in **Figure 1**. The dosage of empagliflozin was given as 10–25 mg twice daily. The correct dosage is 10–25 mg once daily. The corrected version appears below:

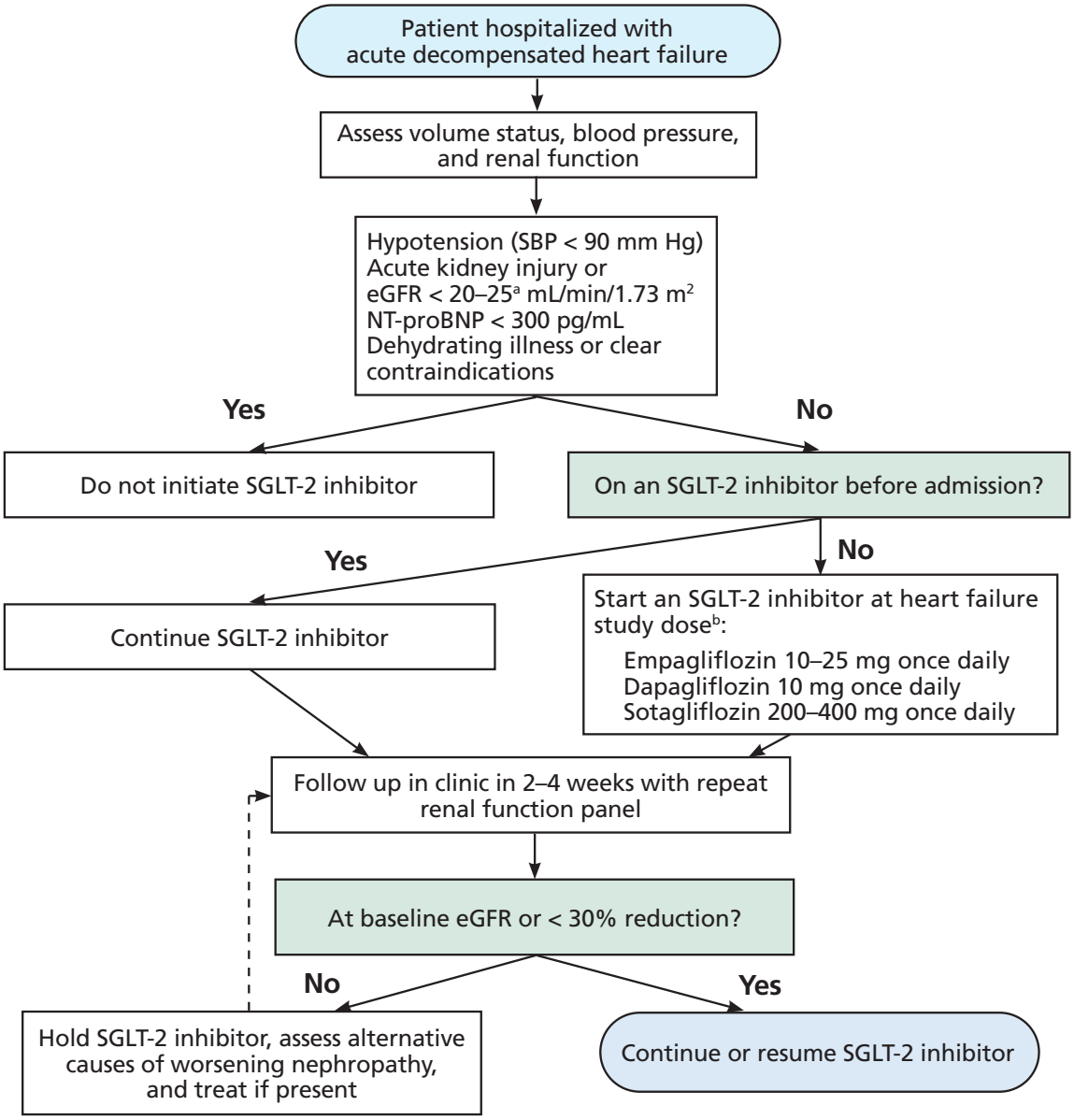

Figure 1. Proposed algorithm for initiating sodium-glucose cotransporter 2 inhibitors in acute decompensated heart failure.

[a]Dapagliflozin: No dosage adjustment for eGFR ≥ 25 mL/min/1.73 m². Manufacturer labeling does not recommend initiation of therapy at eGFR < 25 mL/min/1.73 m². Sotagliflozin is not indicated for patients with eGFR < 25 mL/min/1.73 m². For heart failure, empagliflozin is not indicated for eGFR < 20 mL/min/1.73 m². For type 2 diabetes mellitus, empagliflozin is not indicated for eGFR < 30 mL/min/1.73 m².

[b]Direct evidence on the effects of canagliflozin and ertugliflozin on heart failure outcomes is available only in patients with type 2 diabetes mellitus. It remains to be determined if they have similar effects in patients without type 2 diabetes.

eGFR = estimated glomerular filtration rate; NT-proBNP = N-terminal pro-B-type natriuretic peptide; SBP = systolic blood pressure; SGLT-2 = sodium-glucose cotransporter 2

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von Willebrand disease: A guide for the internist

ABSTRACT

von Willebrand disease (VWD), the most common inherited bleeding disorder, results when patients either do not make enough von Willebrand factor (VWF) or make defective VWF. The pathophysiology of this disorder is complex but needs to be understood to interpret the diagnostic tests. Most patients have mild to moderate symptoms and can be adequately counseled and managed by a general internist, but some need to consult a hematologist. We review the pathophysiology of VWD, its subtypes, common presentations of each subtype, diagnostic testing, and management of mild as well as severe clinical manifestations of VWD.

KEY POINTS

VWD is seen in both inpatients and outpatients. Most patients present with mild to moderate bleeding symptoms and can be adequately managed by a general internist, but in some cases referral to a specialist should be considered.

Specialized diagnostic tests are difficult to interpret and require knowledge of the underlying mechanisms of VWD and its various subtypes.

Treatment of VWD should be tailored to the acuity and severity of the clinical presentation.

VON WILLEBRAND DISEASE (VWD) is an inherited bleeding disorder caused by low levels of or defects in von Willebrand factor (VWF), a key molecule in clotting. It is the most common inherited bleeding disorder and is estimated to affect approximately 1% of the general population.[1] However, only some of those affected ultimately develop clinically significant disease, and many never receive a formal diagnosis. VWD occurs with equal frequency in men and women, although women are more likely to experience symptoms because of increased bleeding during menstruation and pregnancy and after childbirth.[2]

Acquired von Willebrand syndrome is much rarer and occurs when secondary processes lead to a functional impairment of VWF,[3] by either decreasing its quantity or interfering with the hemostatic pathway. Its exact incidence is unknown, but it has been associated with several disease states, including autoimmune disease, hematologic malignancies, solid tumors, metallic heart valves, and high-vascular flow states, such as in patients with ventricular assist devices or receiving extracorporeal membrane oxygenation.[4,5]

Clinical presentations of both acquired and inherited VWD can range from mild mucocutaneous bleeding to severe subcutaneous or intra-articular bleeding. Its diagnosis and management rely on taking an accurate history and interpreting complex diagnostic tests.

This review discusses in detail the clinical, diagnostic, and management considerations for VWD and its various subtypes.

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TABLE 1
International Society of Thrombosis and Haemostasis classification of von Willebrand disease

Type	VWD type 1		VWD type 2				VWD type 3
Subtype	Classic	1C	2A	2B	2M	2N	
Frequency	Common (70% of cases)		Uncommon (25% of cases)				Rare (5% of cases)
Pathophysiology	Mutations result in partial quantitative deficiency of functionally normal VWF		Qualitative defects in VWF				Almost complete quantitative deficiency of VWF
Specific mechanism	Decreased synthesis of VWF due to various genetic mutations	Increased clearance of available VWF in circulation	Mutations result in fewer glycoprotein Ib binding sites and less effective platelet clot formation	Mutations increase affinity of glycoprotein Ib binding site and clearance of high-molecular-weight multimers	Mutations decrease affinity of glycoprotein Ib site or decrease VWF-collagen interaction	Mutation in factor VIII binding site decreases affinity of VWF for factor VIII	
Inheritance	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal dominant	Autosomal recessive	Autosomal recessive
Clinical phenotype	Mild to moderate mucocutaneous bleeding	Mild to moderate mucocutaneous bleeding	Moderate to severe mucocutaneous bleeding	Moderate to severe mucocutaneous bleeding	Severe mucocutaneous bleeding	Hemophilia-like bleeding	Severe mucocutaneous and hemophilia-like bleeding
Response to desmopressin	Very effective in treating minor bleeding episodes	Used to diagnose type 1C (> 30% decrease in VWF 4 hours after infusion) Ineffective in treatment of type 1C VWD	May respond to desmopressin Recommend challenge before therapeutic administration	Desmopressin usually contraindicated due to thrombocytopenia	May respond to desmopressin Recommend challenge before therapeutic administration	May respond to depression Recommend challenge before therapeutic administration	Recommend avoiding desmopressin

VWD = von Willebrand disease; VWF = von Willebrand factor

Data adapted from reference 13.

VWF IS KEY IN CLOTTING

VWF is a glycoprotein synthesized by megakaryocytes and endothelial cells. A disintegrin and metalloprotease with thrombospondin type 1 motif, member 13 (ADAMTS-13) modulates VWF by binding the "ultra-large" VWF multimers initially released from these cells and cleaving them into the normal-sized multimers observed in circulation. High-molecular-weight multimers are hemostatically the most effective conformation of VWF and are elevated in ADAMTS-13 deficiency, leading to formation of platelet thrombi. However, the VWF monomer is the major circulating form and has multiple domains that bind platelets, collagen, and factor VIII.

VWF plays an important role in clotting by binding platelets and subendothelial collagen, aiding in forming an initial platelet plug at the site of endothelial injury. Additionally, it binds and stabilizes coagulation factor VIII, which can activate the coagulation cascade at the site of endothelial injury and result in fibrin clot formation.[6–10]

VWD occurs when a quantitative or qualitative abnormality of VWF leads to defects in primary hemostasis and, depending on the type and severity, to a subsequent factor VIII deficiency similar to hemophilia.

SEVERITY VARIES

Patients with VWD classically present with mild to moderate mucocutaneous bleeding, eg, epistaxis, gingival bleeding, excessive bleeding after dental extractions or minor wounds, easy bruising, abnormal postsurgical or postpartum bleeding, or menorrhagia. However, bleeding frequency and severity vary widely across and even within VWD subtypes (see below). Some

patients may bleed only with hemostatic challenges such as trauma or surgery, while others may have severe or spontaneous bleeding with minor provocation.[11,12]

THREE MAIN TYPES, SEVERAL SUBTYPES

The types and subtypes of inherited VWD recognized by the International Society of Thrombosis and Haemostasis (**Table 1**)[13] are briefly described below, the better to understand the specialized tests done in reference laboratories to diagnose them.

Type 1: Decreased production of VWF

Type 1 accounts for about 70% of all cases of VWD. It is caused by a mutation in the VWF gene that leads to not enough VWF being synthesized, and classically presents as mild mucocutaneous bleeding.[14] Most patients have autosomal dominant missense mutations with incomplete penetrance and variable expression.[15,16] The severity of bleeding is often inversely proportional to the VWF level.

Type 1C: Increased clearance of VWF

Type 1C is a rare subset of type 1 in which there is not enough VWF in circulation because more of it is being cleared, as opposed to synthetic dysfunction.[17]

Type 3: Total or near-total lack of VWF

Type 3 is the rarest and most severe type of VWD. As in type 1, VWF levels are low, but there is a total or near-total lack of the substance. It is typically inherited in an autosomal recessive or compound heterozygous pattern.[18] Patients with type 3 VWD are prone to severe bleeding that often mimics bleeding in hemophilia. Due to their lack of VWF, these patients have low factor VIII levels because factor VIII is not being stabilized in plasma by VWF.[19]

Type 2: Defective VWF variants

In contrast to patients with type 1, type 1C, or type 3 VWD, those with type 2 have normal levels of VWF. However, their VWF has a qualitative defect and does not function as it should.

This is the second most common type of VWD, and it is divided into 4 subtypes (2A, 2B, 2M, and 2N) based on the specific defect.[20] All type 2 subtypes except for 2N have an autosomal dominant inheritance pattern. Notably, type 2N VWD affects the factor VIII binding site of VWF and causes a decrease in factor VIII levels and severe bleeding patterns that mimic hemophilia.

Acquired von Willebrand syndrome

The clinical presentation of acquired von Willebrand syndrome is similar to that of inherited VWD, but patients do not have a family history of bleeding tendencies.[21] Several mechanisms exist, including decreased production of VWF (eg, in hypothyroidism), increased adsorption onto circulating cells (eg, in chronic lymphocytic leukemia), increased antibody-mediated clearance (eg, in lupus), high-flow states leading to increased circulatory clearance of VWF (eg, in patients on left ventricular assist devices), formation of complexes with circulating proteins (eg, in monoclonal gammopathies), and shear destruction (eg, in aortic stenosis).[22,23]

Heyde syndrome is a rare form of acquired von Willebrand syndrome consisting of a triad of aortic stenosis, recurrent gastrointestinal bleeding, and acquired VWF deficiency resulting from destruction of high-molecular-weight multimers of VWF under shear stress due to aortic stenosis.[24]

DIAGNOSTIC APPROACH

The diagnosis of VWD can be nuanced because the clinical bleeding symptoms can vary, and specialized laboratory tests can be difficult to interpret. The diagnosis relies on both thoroughly assessing the bleeding and family history and accurately interpreting the test results. The general approach includes a clinical bleeding assessment, a preliminary laboratory evaluation, a quantitative assessment of VWD levels, a qualitative assessment of VWF function, and, if applicable, specialized tests to determine the subtype of VWD (**Table 2**).[13]

Clinical bleeding assessment

The first step is to obtain an accurate and detailed history of bleeding in the patient and family members. This includes age at symptom onset, frequency of bleeding events, sites of bleeding, triggers for bleeding (spontaneous or after invasive procedures or trauma), exposure to medications associated with bleeding risk, and transfusion history.

Bleeding assessment tools have been developed and validated.[25–27] The 2 most studied are the following:

- The International Society for Thrombosis and Haemostasis Bleeding Score (https://bleedingscore.certe.nl/)
- The Condensed Molecular and Clinical Markers for the Diagnosis and Management of Type 1 VWD Score (https://www.path.queensu.ca/labs/james/bq.htm).

An objective, quantifiable assessment of bleeding symptoms is certainly desirable, but numerous limitations of these tools have been noted in practice: they are time-intensive, they underdiagnose the disease in younger patients, and they rely on prior exposure to

TABLE 2
Diagnostic laboratory criteria for each type of von Willebrand disease

Type	VWD type 1		VWD type 2				VWD type 3
Subtype	**Classic**	**1C**	**2A**	**2B**	**2M**	**2N**	
Ratio of VWF activity to VWF antigen	Normal (about 1)		< 0.6				Markedly low or undetectable VWF activity and antigen levels
Factor VIII levels	Normal or mildly low	Normal or mildly low	Normal or mildly low	Normal or mildly low	Normal or mildly low	Moderately low relative to VWF antigen	Very low
VWF multimer analysis	Full spectrum of multimers, but all at low level	Full spectrum of multimers, but all at low level	Absence of high- and intermediate-molecular-weight multimers	Absence of high-molecular-weight multimers	Normal multimer pattern	Normal multimer pattern	Minimal or complete absence of VWF multimers
Specific testing to diagnose subtype	None	Elevated ratio of VWF propeptide to VWF antigen > 30% decrease in VWF 4 hours after infusion of desmopressin	Genetic testing	Increased ristocetin-induced platelet aggregation Sensitivity to low-dose ristocetin Genetic testing	Decreased ristocetin-induced platelet aggregation Low VWF-collagen binding capacity Genetic testing	Decreased binding of VWF to factor VIII Prolonged partial thromboplastin time Genetic testing	None

VWD = von Willebrand disease; VWF = von Willebrand factor

Data adapted from reference 13.

hemostatic challenges such as trauma or surgery.[28,29] While acknowledging these limitations, recent guidelines recommend using a bleeding-assessment tool rather than a nonstandardized assessment in the primary care setting to screen patients with a low probability of VWD and to determine the need for specialized testing.[13]

Preliminary laboratory evaluation

Preliminary laboratory testing should include a complete blood cell count, blood type and screen, prothrombin time with international normalized ratio, and partial thromboplastin time.[13] While the results of these tests are unremarkable in most forms of VWD, they help to ascertain the extent of bleeding in the patient and to distinguish VWD from other bleeding disorders. Of note, thrombocytopenia may be observed in type 2B VWD, and a prolonged partial thromboplastin time due to reduced factor VIII may be seen in type 2N or type 3.

Specialized tests: preanalytic variables

Specialized tests for VWD require complex assays, and many preanalytic variables can affect their precision and accuracy, including patient age, sex, race, blood group, and comorbid conditions such as recent bleeding, infection, hepatic dysfunction, inflammatory conditions, and renal disease.[30] It is essential to use proper sample-collection technique and to avoid small-gauge needles, prolonged tourniquet application, and inappropriate tube-filling to avoid abnormal results that can be misinterpreted. It is generally recommended that at least 2 separate sets of samples be obtained at different times.

VWF antigen level

The next step is to measure the concentration of VWF protein (antigen) with an immunologic assay, most commonly an enzyme-linked immunosorbent assay or latex-enhanced immunoassay.[31–34] The normal range is between 50 and 200 IU/dL. VWD is diagnosed if the level is lower than 30 IU/dL, or if it is 30 to 50 IU/dL with a positive bleeding history.[13]

The VWF antigen level can be affected by factors such as age, menstrual cycle, contraceptive use, pregnancy, and comorbid conditions.[34] Of note, the

blood type can drastically affect VWF antigen levels. Specifically, patients with type O blood commonly have approximately 25% lower VWF antigen levels than those with type A.[35]

Ristocetin cofactor assay

This test evaluates platelet-dependent VWF activity by assessing the ability of VWF to bind platelet glycoprotein Ib in the presence of the antibiotic ristocetin.[31] The normal range is 50 to 200 IU/dL.[13]

Although the ristocetin cofactor assay has been the gold standard for measuring VWF binding to platelets via glycoprotein Ib, several limitations have been noted, including laboratory variability, error at lower VWF antigen levels (limit of detection 10 IU/dL), and false-positive results associated with polymorphisms commonly found in the general population.[36] New assays have been developed to address these deficiencies, including assays for glycoprotein IbR, glycoprotein IbM, and VWF antibody. Some expert panels recommend these new assays over the ristocetin cofactor assay, but these are conditional recommendations based on low levels of evidence.[13]

Ratio of VWF activity to VWF antigen

The VWF activity assay is a functional test that uses either the ristocetin cofactor assay (described above) or a monoclonal antibody that targets the region of the VWF molecule that binds to the glycoprotein Ib receptor as a measure of VWF activity. The VWF activity-to-antigen ratio helps distinguish quantitative vs qualitative deficiency of VWF (VWD type 1 vs type 2). In type 1 VWD, there is a concordant decrease in both VWF activity and VWF antigen, leading to a ratio greater than 0.7.[13] Type 2 VWD is characterized by a disproportionate reduction of VWF activity compared with VWF antigen levels, leading to a ratio less than 0.7. A notable exception is type 2N disease, in which the ratio is greater than 0.7. However, the joint guideline panel[13] gave this cutoff only a conditional recommendation based on very low certainty in the evidence from diagnostic studies.

VWF multimer analysis

This is a qualitative assessment of the size distribution of VWF multimers in plasma, which helps distinguish the patient's subtype of VWD. The ability of VWF to bind platelets is related to size, with high-molecular-weight multimers showing the greatest activity. Under normal conditions, VWF multimers are distributed evenly across the various sizes. In types 1, 2M, and 2N VWD, all sizes of multimers are seen, while preferential loss of high-molecular-weight multimers is seen in type 2A and type 2B. Type 3 VWD is characterized by almost complete absence of VWF multimers.[37–39]

Factor VIII coagulant assay

The factor VIII coagulant assay is typically used in patients with a substantial bleeding history that is suspicious for hemophilia. It is also integral to the workup of VWD, as a low factor VIII level may be seen with decreased or dysfunctional VWF, which is needed to stabilize factor VIII in plasma. In most types of VWD (1, 2A, 2B, 2M), factor VIII activity is moderately low. A more significant decrease in factor VIII activity suggests type 2N (factor VIII activity 5%–15%) or type 3 VWD (factor VIII activity 1%–10%).[40]

VWF-factor VIII binding assay

This is an enzyme-linked immunoassay that evaluates the ability of VWF to bind recombinant factor VIII. An abnormal result confirms type 2N VWD and helps to distinguish it from hemophilia A.[41]

Low-dose ristocetin-induced platelet aggregation

This assay also measures VWF's affinity for the platelet glycoprotein Ib receptor, but it uses less ristocetin than the ristocetin cofactor assay by exposing platelet-rich plasma from the patient to sequentially lower concentrations of ristocetin. Patients with type 2B VWD (characterized by increased VWF binding to platelet glycoprotein Ib) have platelet aggregation at much lower ristocetin concentrations (< 0.6 mg/mL).[13,42] This assay is also unique in that it can be used to distinguish type 2B VWD from a very rare platelet disorder known as pseudo-type or platelet-type VWD.

VWF-collagen binding capacity

This assay measures the ability of VWF to bind collagen. Though less commonly used than other qualitative assays such as the ristocetin cofactor assay, the VWF-collagen binding capacity can help identify 2M subtypes characterized by defective collagen binding.[21,41]

The VWF propeptide level, and the ratio of VWF propeptide to VWF antigen

This test measures the propeptide of VWF, which is normally synthesized and released in a 1:1 ratio with the VWF monomer.[43] Elevated VWF propeptide relative to VWF antigen suggests increased VWF clearance (type 1C VWD) and helps to distinguish it from complete quantitative deficiencies of VWF (type 3 VWD).

There has been a shift to using desmopressin challenge testing instead of the ratio of VWF propeptide to VWF antigen for patients with suspected type 1C

VWD. However, the guidelines give this a conditional recommendation based on a low level of evidence.[13]

Desmopressin challenge testing

Desmopressin promotes excretion of stored VWF from endothelial cells into plasma. In desmopressin challenge testing, the VWF antigen, VWF activity, and factor VIII levels are measured 1, 2, and 4 hours after desmopressin administration.

An adequate increase in VWF antigen, ristocetin cofactor, and factor VIII levels is seen in most cases of type 1 VWD and in many of type 2. Conversely, in type 2N disease, an initial adequate response is seen but is not appropriately sustained in duration (< 4 hours) because of the increased clearance of factor VIII owing to the impaired stabilization function of VWF.

Desmopressin challenge testing can also be used to diagnose type 1C VWD, as a greater than 30% decrease in VWF from peak concentrations measured 4 hours after the infusion indicates increased VWF clearance, compatible with type 1C VWD.

Of note, desmopressin is contraindicated if type 2B VWD is suspected, as released VWF binds circulating platelets in type 2B, thereby worsening thrombocytopenia.[42,44]

Genetic testing

Genotyping is not required to diagnose VWD and is done only in select clinical scenarios. Genetic analysis in VWD is complicated by the large size and incomplete characterization of the VWF gene as well as by significant genotypic and phenotypic variability. It is not widely available for types 1 and 3 VWD, and it is most useful for diagnosing type 2. Genotyping may be helpful in confirming VWD subtypes (including type 2B, 2M, and 2N disease) when results might affect therapeutic decisions.[21,42] Genetic testing may also be used to screen potential carriers of autosomal recessive forms of VWD.[20]

TREATMENT

We recommend the following approach when treating a bleeding patient with VWD, depending on the acuity and severity of the clinical presentation.

Referral to a hematologist

Though mild forms of VWD can be managed in the primary care setting, several situations may warrant referral to a hematologist or a center with expertise in VWD:

- An abnormal score on a bleeding assessment tool or positive family history
- Testing is not available, or results are needed quickly
- When testing provides results that are borderline, difficult to interpret, or positive for type 2 or type 3 VWD
- Persons with type 1 VWD with a bleeding history, or those with VWD undergoing a hemostatic challenge (ie, major surgery).

Most cases of VWD can be adequately comanaged by primary care physicians with the following treatment strategies.

TREATING MINOR BLEEDING

Local therapies

For minor nasal or oral bleeding, prolonged local pressure can be attempted as a first measure. Topical agents including topical human thrombin, micronized collagen, and fibrin sealants can also be used to control bleeding.[40,44]

Antifibrinolytic agents

When topical agents are ineffective or not practical, antifibrinolytic agents are typically the next-line treatment for minor bleeding in VWD.[42] These drugs inhibit the enzymatic breakdown of fibrin, which cross-links and strengthens clots. Most commonly used are tranexamic acid and epsilon-aminocaproic acid.

These agents are particularly useful in mucocutaneous bleeding including epistaxis, oral bleeding, menstrual bleeding, and postpartum bleeding. They are safe to use in all forms of VWD. Tranexamic acid can be given as an oral capsule, mouthwash, or intravenously, and may be used alone or in combination with desmopressin or VWF-containing products.[42] Antifibrinolytics should be avoided in patients with a history of thromboembolic disease or significant hematuria due to the risk of clot formation and subsequent urinary obstruction.[44]

Desmopressin

Desmopressin is a synthetic derivative of antidiuretic hormone that is useful in treating bleeding episodes in patients with type 1 VWD.[45] It works by inducing the release of endogenous VWF from endothelial cells through agonist activity at vasopressin 2 receptors. Desmopressin is readily available and inexpensive and can be given intranasally, subcutaneously, or intravenously.

Desmopressin is most effective in patients with type 1 VWD but is generally avoided in most patients with types 1C, 2, and 3. A desmopressin challenge should be performed in patients with a history of mild

or moderate bleeding and a diagnosis of VWD to confirm its effectiveness as a potential therapy.

Adverse effects of desmopressin include hyponatremia, headache, vasodilation, hypotension, tachycardia, flushing, and, rarely, thrombosis.[46,47] Another important clinical consideration when using desmopressin is tachyphylaxis, which develops within a few days due to depletion of VWF stores.[46] Desmopressin should be avoided in cases of serious or life-threatening bleeding, as the transient increase in VWF in response to desmopressin is generally insufficient to achieve adequate hemostasis.

Other considerations. Medications that affect platelet function, such as aspirin and nonsteroidal anti-inflammatory drugs, should be avoided in patients with VWD and a history of bleeding.

MAJOR BLEEDING

Patients with severe bleeding or those with mild or moderate VWD undergoing major surgery will not achieve sufficient hemostasis with the aforementioned supportive therapies and should always be comanaged with a hematologist. These patients require exogenous replacement of VWF using plasma-derived or recombinant VWF products. As VWF causes an increase in factor VIII levels, separate factor VIII infusions may not be required depending on the subtype of VWD and the specific treatment used.

These 2 types of VWF products have never been compared head-to-head, though cross-trial comparisons of efficacy and safety do not show appreciable differences.[48] The decision on which product to use is often based on availability and cost.

Plasma-derived VWF

The 3 plasma-derived VWF products approved in the United States—Humate-P, Alphanate, and Wilate—all contain VWF and factor VIII, but at different ratios. Plasma-derived products almost devoid of factor VIII (Wilfactin, Willfact) are available in Europe but not in the United States.

The package inserts for each product provide guidance for dosing. The target VWF level depends on the severity of bleeding if given for trauma, or the complexity of surgery if being used for surgical prophylaxis. In general, replacement is provided to initially reach a peak VWF activity level of 100 IU/dL with a trough of 50 IU/dL. Maintenance doses are then provided for 3 to 7 days depending on the amount of bleeding and patient response.[44]

An important consideration: because plasma-derived VWF products contain factor VIII, separate infusions of factor VIII are generally not required. Repeated dosing may lead to significant elevations of factor VIII (especially for products with a lower VWF-to-factor VIII ratio) and increased risk of thrombosis.[49] The incidence of thrombosis is thought to be relatively small and can be mitigated by closely monitoring factor VIII levels during therapy, with the goal of avoiding factor VIII levels above 150 U/dL.[50]

Recombinant VWF

The first recombinant VWF was approved for adult patients in the United States in 2015 after publication of a landmark phase 3 trial in which it achieved excellent hemostatic efficacy in 97% of bleeding episodes.[50–52] This product contains ultra-large high-molecular-weight multimers, which are the most active form of VWF in attaining primary hemostasis.

Though recombinant VWF replacement will cause a delayed increase in endogenous factor VIII levels, the products themselves are almost devoid of factor VIII.[52] Therefore, factor VIII is often given with recombinant VWF to achieve hemostasis more rapidly, particularly in VWD subtypes with very low endogenous factor VIII levels (types 2N, 3, and severe type 1).

PERIOPERATIVE MANAGEMENT

Careful risk stratification and perioperative management of patients with VWD is required to minimize bleeding risk. Risk stratification depends on the nature of the surgery, the severity of the patient's bleeding history, baseline plasma VWF levels, and responses to previous hemostatic challenges. We recommend a multidisciplinary discussion between the hematology consultant, surgical team, and patient before undertaking a surgical procedure, especially in the case of major surgery or severe VWD.

Consensus is still lacking as to the therapeutic target and assays to be monitored for in the postoperative period. In general, hemostatic levels are maintained until bleeding risk abates (usually 3 to 5 days), depending on the nature of the surgery and the patient's specific phenotype. As a general principle, for emergency surgery, VWF and factor VIII are given together, and for elective surgery, early infusion of VWF replacement therapy alone is sufficient.

TAKE-HOME POINTS

- Despite recent advances, the diagnosis and management of VWD remain challenging.
- A thorough patient history and bleeding assessment are required for prompt diagnosis of VWD.

- Diagnostic testing is crucial to distinguish VWD from other bleeding disorders such as mild factor VIII deficiency and inherited platelet disorders.
- An understanding of the complex pathophysiology and diagnostic testing of VWD can aid in timely diagnosis and referral to a hematologist. Such referral should be considered based on severity of bleeding symptoms, type of VWD, and upcoming hemostatic challenges.
- Treatment of acute bleeding events associated with VWD should be tailored to the acuity and severity of the specific patient's clinical presentation.

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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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