SPECIAL SECTION
THROMBOEMBOLIC DISEASE
GUEST EDITOR: KENNETH S. KORR, MD
17 The Evolving Landscape of Thromboembolic Disease: Diagnostic and Management Strategies
KENNETH S. KORR, MD, FACC
GUEST EDITOR

18 Direct Oral Anti-Coagulants (DOACs): Current Status among Distinct Patient Subgroups
PETER RILEY, MD
ABHISHEK MAAN, MD
KENNETH S. KORR, MD, FACC

23 Minimally Invasive Closure of the Left Atrial Appendage: A Non-Pharmacologic Approach to Prevention of Stroke in Patients with Atrial Fibrillation
BRIAN D. MCCAULEY, MD, MPH
ANTONY F. CHU, MD, FHRS, FACC, FACP

27 Pulmonary Embolism in 2017: Increasing Options for Increasing Incidence
WILLIAM PRABHU, MD
PETER A. SOUKAS, MD, FACC, FSVM, FSCAI, FACP

33 The Arm is Not the Leg: Pathophysiology, Diagnosis, and Management of Upper Extremity Deep-Vein Thrombosis
ADAM M. NOYES, MD
JOHN DICKEY, MD

37 Chronic Venous Insufficiency: Novel Management Strategies for an Under-diagnosed Disease Process
OMAR N. HYDER, MD
PETER A. SOUKAS, MD, FACC, FSVM, FSCAI, FACP

On the cover: In patients with non-valvular atrial fibrillation (NVAF), most stroke-causing clots that come from the left atrium form in the left atrial appendage (LAA). The WATCH-MAN implant device closes off the LAA, preventing blood clots from migrating out of it. See Drs. McCauley, Chu article in this issue.
The Evolving Landscape of Thromboembolic Disease: Diagnostic and Management Strategies

KENNETH S. KORR, MD, FACC
GUEST EDITOR

This issue of the Rhode Island Medical Journal focuses on the broad topic of thromboembolic disease, its many and varied clinical presentations, their incidence, symptoms, diagnostic evaluation and, most importantly, their unique management and treatment strategies.

DRS. P. RILEY, A. MAAN and K.S. KORR open with an update on the current status of the Direct-Acting Oral Anticoagulants (DOACs), formerly referred to as new, novel or Non-Vitamin K oral anticoagulants (NOACs). In the brief span of 8 years since their approval, the DOACs are now prescribed more frequently than warfarin both in Europe and North America¹ and are expected to ultimately supplant warfarin due to their relative safety, improved efficacy and ease of use. Moving beyond the initial Randomized Control Trials (RCT) which established the DOACs as non-inferior to warfarin for the prevention of thromboembolism in patients with atrial fibrillation and deep-vein thrombosis, ongoing registry data and real-world experience continue to refine the role of these agents in distinct patient subsets, including those with chronic renal insufficiency, congestive heart failure, distinct ethnic groups and in the elderly.

DRS. B. MCCAULEY and A. CHU discuss the thromboembolic risks of atrial fibrillation, the role of the Left Atrial Appendage (LAA) and an overview of LAA closure devices and techniques as an alternative to anticoagulant therapy for the subset of patients with atrial fibrillation in whom oral anticoagulation is contra-indicated or high risk.

DRS. W. PRABHU and P. SOUKAS provide an update on the risk stratification and management strategies for patients with Pulmonary Embolism (PE) and the emerging role of multi-disciplinary pulmonary embolism response teams (PERT) for optimizing treatment opportunities in patients with intermediate and high-risk PE.

DRS. A. NOYES and J. DICKEY discuss the rising incidence and morbidity of Upper Extremity Deep-Vein Thrombosis (UEDVT) with the increasing prevalence of central venous catheters, PICCs, Ports, and implantable cardiac rhythm devices.

Finally, DRS. O. HYDER and P. SOUKAS present an overview of chronic venous insufficiency, venous ulcers, compression therapy and the role of endovenous ablation and other therapies.

These articles reflect the current state of medical practice in a rapidly changing therapeutic landscape which continues to evolve with the acquisition of real-world data and technologic advancements.


Guest Editor
Kenneth S. Korr, MD, FACC, is Associate Professor of Medicine Emeritus, The Alpert Medical School of Brown University.
Direct Oral Anticoagulants (DOACs):
Current Status Among Distinct Patient Subgroups
PETER RILEY, MD; ABHISHEK MAAN, MD; KENNETH S. KORR, MD, FACC

ABSTRACT
The landscape of anticoagulant therapy for atrial fibrillation and deep-vein thrombosis has evolved considerably in the last decade with the advent of Novel or Direct-Acting Oral Anticoagulants (DOACs). The initial phase III randomized controlled trials established the individual DOACs as viable alternatives to warfarin for thromboprophylaxis but generalizations to the larger population were limited by the small number of protocol subjects with renal insufficiency, congestive heart failure, advanced age and other comorbidities. All the DOACs have some degree of renal excretion and while safe and effective in patients with mild to moderate renal insufficiency, dose adjustment is necessary based on creatinine clearance. Subsequent data registries and real-world experience with DOACs have continued to refine their role in these particular patient subgroups. Off-label use with both under- and overdosing is not uncommon in renal failure and carries increased risk. Their increasing use among the elderly, in patients with heart failure, hepatic and renal insufficiency and among the Asian population has been shown to be relatively safe and effective compared to warfarin. Gaps in our current understanding of this new class of anticoagulants will continue to narrow as additional data becomes available through ongoing registries and real-world experience.

KEYWORDS: DOACs, NOACs, thromboprophylaxis

INTRODUCTION
For almost six decades following its discovery and commercialization in the 1950s, warfarin has been the mainstay of anticoagulant therapy for the prevention of thromboembolic phenomena. Starting in 2009, a new group of potent oral anticoagulants called DOACs [Direct Oral Anti-Coagulants] or NOACs [Non-vitamin K antagonist Oral Anti-Coagulants née Novel Oral Anti-Coagulants] were approved as alternatives to warfarin. Warfarin’s anticoagulant effect is indirect; inhibition of Vitamin K oxide reductase results in decreased levels of pro-coagulant clotting factors in the direct, indirect, and common pathways. By contrast, the DOACs all act on the “Final Common Pathway” of the coagulation cascade.[1-4] Since FDA approval,[1-5] prescribing has rapidly expanded as DOACs replace warfarin, occasionally beyond approved indications. Growing evidence from the Outcomes Registry for Better Informed Treatment of Atrial Fibrillation II (ORBIT-AF II) suggests that off-label use carries increased risk.[6] Current guidelines are limited by the paucity of real-world data with DOACs, and providers often fill gaps in trial data with therapeutic strategies derived from years of experience with warfarin. While meta-analysis of large randomized controlled trial data has shown consistently favorable results with DOACs, it must be applied with caution given the limited real-world data available.[6, 7]

DOACS IN RENAL IMPAIRMENT
Chronic Kidney Disease (CKD) is a frequent comorbidity in patients requiring anticoagulation.[8] CKD may potentiate renally cleared pharmaceuticals without appropriate dose adjustment, and all current DOACs undergo some renal excretion [See Table 1].[9-12] Concern about worsening renal function, lack of readily available anticoagulation reversal agents, and limited real-world experience with DOACs may lead to premature dose-reduction and inadequate thromboprophylaxis. Recent studies of real-world prescription practice suggest significant rates of under-dosing [10%] or over-dosing [3%].[10] Current safety data and renal dosing guidelines were derived from large RCTs that excluded patients with creatinine clearance (CrCl) of <25 mL/min or hemodialysis.[3,11,14] Recently, two large meta-analyses of data from patients with mild-moderate stable CKD suggested that all DOACS may provide a modest reduction of systemic embolization, stroke, and bleeding compared to warfarin, and furthermore, apixaban and edoxaban have significantly lower rates of major bleeding than dabigatran or rivaroxaban.[3,14] Anticoagulant use in subjects with declining renal function was evaluated in a sub-group of 3,000 patients in the ROCKET-AF trial who had a 20% reduction in CrCl from baseline. In this population, the risk of vascular death was significantly higher than in patients with stable renal function, and rivaroxaban significantly decreased embolization without increasing rates of major bleeding as compared to warfarin.[3,13]

Patients with end-stage renal disease (ESRD) were excluded from the Phase III trials for all current DOACs.[14] Apixaban was approved in ESRD-based on pharmacokinetic data;
but no RCT data exists to evaluate its safety, and all other DOACs are contraindicated in ESRD.\[17, 18]\] Despite this, rivaroxaban and dabigatran were prescribed for 6% of patients in a large hemodialysis database, frequently without dose reduction. This was associated with increased rates of bleeding requiring hospitalization and fatal bleeding compared to warfarin.\[14\] Current guidelines recommend warfarin as first-line for thromboprophylaxis in ESRD patients; if warfarin is contraindicated, apixaban may be an acceptable alternative.\[18\] Of note, edoxaban is contraindicated in patients with Cr Cl>95mL/min due to ineffective thromboprophylaxis.

Current DOAC maintenance dosing guidelines for thromboprophylaxis are summarized in Table 1. The maintenance dose for most DOACs is reduced in renal insufficiency to mitigate the effects of reduced excretion and half-life prolongation. Prolonged half-life requires earlier discontinuation of DOACs prior to procedures and current recommendations suggest discontinuation of DOACs 2–3 days prior to surgery and other invasive procedures.

Table 1. Dosing Guidelines for DOACs

<table>
<thead>
<tr>
<th></th>
<th>DABIGATRAN</th>
<th>RIVAROXABAN</th>
<th>APIXABAN</th>
<th>ENDOXABAN</th>
</tr>
</thead>
<tbody>
<tr>
<td>RENAL ELIMINATION</td>
<td>80%</td>
<td>36%</td>
<td>27%</td>
<td>50%</td>
</tr>
<tr>
<td>DOSING</td>
<td>Standard Dose: 150mg BID For eGFR &gt;30 mL/min AND Age &gt;80 years: 110mg BID For eGFR 15-30 mL/min: 75mg BID</td>
<td>Standard Dose: 20mg Daily For eGFR 15-49 mL/min: 15mg Daily</td>
<td>Standard Dose: 5mg BID IF 2 of following present: -Age &gt; 80 yrs -Cr&lt; 1.5 mg/dL -Weight &lt; 60Kg THEN: 2.5mg BID For CrCl 15-29 mL/min: 2.5 mg BID For CrCl &lt;30 mL/min: 2.5mg BID</td>
<td>Standard Dose: 60mg Daily For eGFR 15 to 49 mL/min: 30mg Daily</td>
</tr>
<tr>
<td>CONTRA-INDICATIONS</td>
<td>eGFR &lt;30 mL/min AND use of pGP inhibitor, ESRD-HD, CTP Class C</td>
<td>eGFR &lt;15 mL/min, ESRD-HD, CTP Class B, C</td>
<td>eGFR &lt;15 mL/min, CTP Class C</td>
<td>eGFR &gt;95 mL/min, ESRD-HD, CTP Class B,C</td>
</tr>
<tr>
<td>Cleared by Hemodialysis?</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>Minimally</td>
</tr>
<tr>
<td>HALF-LIFE (HOURS) BASED ON RENAL FUNCTION</td>
<td>CrCl &gt; 80mL/min</td>
<td>14-17</td>
<td>5-9</td>
<td>8-15</td>
</tr>
<tr>
<td>CrCl 50-79 mL/min</td>
<td>16.6 (12-18)</td>
<td>8.7</td>
<td>14.6</td>
<td>No data</td>
</tr>
<tr>
<td>CrCl 30-49 mL/min</td>
<td>18.7 (18-24)</td>
<td>9</td>
<td>17.6</td>
<td>No data</td>
</tr>
<tr>
<td>CrCl &lt;30 mL/min</td>
<td>27.5</td>
<td>9.5</td>
<td>17.3</td>
<td>No data</td>
</tr>
<tr>
<td>When to discontinue before surgery:</td>
<td>2-3 days; if CrCl &lt;50 mL/ min 2-4 days</td>
<td>2-3 days</td>
<td>2-3 days</td>
<td>2-3 days</td>
</tr>
</tbody>
</table>

eGFR – estimated glomerular filtration rate; CrCl – creatinine clearance; ESRD-HD end-stage renal disease- hemodialysis; bid-twice daily; pGP- p Glycoprotein inhibitor (ketoconazole oral or dronedarone); CTP- Child-Turcotte-Pugh Hepatic Impairment Class

DOACS IN HEPATIC IMPAIRMENT

Hepatic impairment and cirrhosis impose unique challenges in patients requiring anticoagulation. Standard laboratory assays for anticoagulant monitoring are rendered unreliable by altered production of pro- and anticoagulant factors, and variation in metabolic kinetics can lead to unpredictable serum drug levels.\[20,21\] DOACs are attractive candidates for patients with liver disease who require anticoagulation due to their independence from laboratory monitoring and lack of pro-coagulant effect seen with initiation of warfarin.\[21-23\] Initial DOAC phase III trials excluded chronic liver disease. Current use is guided by small trials and pharmacokinetic studies suggesting apixaban and dabigatran may be used in CTP class A or B, and rivaroxaban in CTP class A. All DOACs are contraindicated in patients with CTP Class C.\[20,24\] Small retrospective studies of anticoagulants in moderate hepatic impairment have shown DOACs to have non-inferior rates of embolization and reduced rates of bleeding compared to warfarin,\[22,24\] and surveillance data on DOAC...
DOACS IN CONGESTIVE HEART FAILURE

Congestive heart failure (CHF) is a common comorbidity in the atrial fibrillation population, and significantly increases the risk of stroke in these patients.[29-31] There is evidence that CHF constitutes a pro-thrombotic syndrome with low-flow states, biomarker evidence of endothelial dysfunction, and elevated pro-thrombotic biomarkers.[29,32] Risk of thrombosis appears to increase correspondingly with clinical and echocardiographic worsening of CHF and can contribute to the development of left ventricular thrombi.[32,33] Anticoagulation with warfarin has traditionally been used to treat apical thrombi, as well as cardiac structural abnormalities including noncompaction cardiomyopathy.[34,35] The phase III trials evaluating DOACs in nonvalvular AF included many patients with CHF.[1-4] Pooled analysis of data from CHF patients in these trials showed a significant reduction in intra-cranial hemorrhage (ICH) and major bleeding events with dabigatran and apixaban as compared to warfarin. Edoxaban was not included as detailed subgroup data from the ENGAGE-AF trial was not available.[36,37] These findings may be driven by low time in therapeutic range for warfarin in CHF patients. There is evidence that CHF predisposes patients on warfarin to low time in therapeutic range as compared to other comorbidities, and CHF has been associated with higher rates of bleeding in subgroup analyses from large trials of AF patients.[38-40] Together, these results suggest that DOACs are at least as efficacious as warfarin for thromboembolic events in patients with nonvalvular AF and CHF, and may confer a reduction in bleeding as compared to warfarin.

There are no large RCT data available to guide the use of DOACs in treatment of left ventricular thrombi or in cardiomyopathies conferring additional thromboembolic risk; and current evidence is limited to case reports of ventricular thrombi treated successfully with apixaban or rivaroxaban.[41,42] The pathophysiology conferring additional stroke risk in these conditions is mechanistically similar to that of atrial fibrillation and heart failure.[43] There may be a similar role for DOACs in this patient population, however, further study is needed.

The role of prophylactic anticoagulation in CHF patients in sinus rhythm without known thrombus has been extensively studied in large trials.[44] Data from these studies demonstrated a reduction in thromboembolic events with prophylactic anticoagulation with warfarin; however, no survival benefit was seen due to a concomitant increase in bleeding risk. Current guidelines do not recommend prophylactic anticoagulation in patients with heart failure without another primary indication.[44,45] Emerging evidence supports an advantageous bleeding profile of DOACs as compared to warfarin in the CHF population, and CHF as a primary indication for anticoagulation is undergoing re-evaluation in the COMMANDER-HF trial designed to evaluate the efficacy and safety of rivaroxaban in reducing death, MI, or stroke in CHF patients with CAD.[46, 47]

DOACS IN THE ASIAN AND AFRICAN-AMERICAN POPULATIONS

There is growing evidence that optimal management of atrial fibrillation may differ in the Asian patient population compared to Western patients. Data from large global registries indicates that the incidence and mortality of stroke, especially hemorrhagic, is significantly greater in Asian countries as compared to the West,[46-50] and is highest in patients of Japanese ancestry.[51-53] The mechanisms behind this difference are unclear, but differential risk has been shown repeatedly in large international studies, including the phase III trials for dabigatran, apixaban and rivaroxaban.[1,2,54] Subgroup analyses found that a composite clinical outcome of stroke, systemic embolism, pulmonary embolism, myocardial infarction, death, or major bleeding occurs at significantly higher rates in Asian patients on warfarin as compared to non-Asian patients, raising the question of whether anticoagulation with warfarin has a reduced net clinical benefit in the Asian population.[1,2,48] Prescription practice analysis of large international registries suggests that warfarin is prescribed in Asian countries at approximately half the rate of Western countries, and antiplatelet therapy alone is more common for stroke prevention.[55] Meta-analysis of the phase III RCTs for DOACs has demonstrated similar efficacy of embolic prevention in Asian patients treated with DOACs compared to warfarin, but with an overall mortality benefit largely driven by reduced rates of hemorrhagic stroke.[56,57] Furthermore, a recent retrospective cohort study of Taiwanese patients anticoagulated with dabigatran, apixaban, or rivaroxaban, or warfarin found a significant reduction in rates of embolism, ICH, and all-cause mortality in patients anticoagulated with a DOAC compared to warfarin.[58]

African-Americans (AA) have a lower incidence of AF compared to Caucasians but a higher risk of stroke. This may be related to a higher prevalence of other stroke risk factors and limited access to health care among AAs. Warfarin is utilized less frequently among AAs who have a lower time in the therapeutic range and require higher warfarin dosage to maintain therapeutic INRs. Racial subgroups were under-represented in Phase III RTCs of DOACs and limited subgroup analyses have been published. However, the DOACs compared to warfarin were similar for outcomes of stroke, systemic embolization and bleeding and may be preferable agents in the AA population.[63]
DOACS IN THE GERIATRIC POPULATION

Advanced age increases risk of stroke and also increases risk of ICH due to increased fragility of cerebral bridging veins, increased frailty and falls. Thus, the risk/benefit ratio of anticoagulation for thromboprophylaxis is less clear in the elderly population. Sub-group analysis of patients over age 75 in the Phase III RCTs suggested that DOACs were noninferior to warfarin for thromboembolism prophylaxis. Rivaroxaban carried equivalent hemorrhagic risk compared to warfarin, and dabigatran, apixaban, and edoxaban were all found to have lower risk of ICH or major bleeding, despite an increased risk of GI bleed with dabigatran.[59,60] Emerging evidence from subsequent RCTs and real-world practice observational studies supports these findings. A sub-group analysis of approximately 2,000 patients over age 75 from a trial comparing aspirin to apixaban found significantly improved thromboprophylaxis with apixaban, without significant difference in bleeding rates.[61] A cohort study drawn from Medicare data of 118,000 patients over age 65, on dabigatran or rivaroxaban found that rivaroxaban usage had higher rates of ICH and major bleeding compared to dabigatran; however, renal function data was not available and dose-reduced regimens were not studied.[62]

CONCLUSIONS

The landscape of anticoagulation has evolved considerably in the last decade. The initial phase III RCTs established the DOACs as viable alternatives to warfarin. Subsequent data registries and real-world experience have shed light on potential differences in outcomes in certain subpopulations. In patients with renal impairment, there is mounting evidence that DOACs are safe, and may reduce ischemia and major bleeding in patients with stable mild-moderate CKD as compared to warfarin. Apixaban undergoes the least renal excretion of DOACs and may have lower bleeding risks than other DOACs in CKD. There is also limited evidence that apixaban may be useful in ESRD when warfarin is specifically contraindicated, while edoxaban, rivaroxaban, and dabigatran are contraindicated in ESRD, and may increase bleeding risk as compared to warfarin in this population. Current guidance for the use of DOACs in patients with hepatic impairment is driven by pharmacokinetic data and small studies suggesting that most DOACs are safe in mild-moderate hepatic impairment, though rivaroxaban should not be used in Class B impairment and all DOACs are contra-indicated in CTP Class C.

In patients with CHF, meta-analysis of pooled RCT data demonstrates that apixaban, dabigatran, and rivaroxaban are non-inferior to warfarin for thromboprophylaxis and may carry reduced risk of bleeding, therefore DOACs may be preferable first-line agents. Current guidelines do not recommend prophylactic anticoagulation for patients with heart failure, however, this concept is undergoing re-evaluation in the COMMANDER-HF trial. The Asian population is known to have elevated rates of stroke and hemorrhage with warfarin thromboprophylaxis and a growing body of evidence suggests that use of DOACs in place of warfarin carries reduced rates of hemorrhage and overall clinical benefit in this subgroup. Among the elderly, DOACs are non-inferior to warfarin for thromboprophylaxis, and dabigatran, apixaban, and edoxaban may confer reduced rates of major bleeding and ICH. Emerging evidence suggests rivaroxaban may carry a higher bleeding risk. However, until robust real-world outcomes data is available, caution must be exercised in extrapolating from RCTS, as even now available registry data suggests inappropriate dosing occurs at not-significant rates and is associated with adverse outcomes. Still, this emerging signal suggests an opportunity to improve outcomes in certain subpopulations and the picture will undoubtedly become clearer as data from ongoing registries and newer trials fill gaps in our knowledge.

References


References 26–63
Minimally Invasive Closure of the Left Atrial Appendage: A Non-Pharmacologic Approach to Prevention of Stroke in Patients with Atrial Fibrillation

BRIAN D. McCauley, MD, MPH; ANTONY F. CHU, MD, FHRS, FACC, FACP

ABSTRACT

Atrial Fibrillation’s (AF) role in the pathogenesis of thromboembolic stroke has been well established, with estimates from trials of approximately 15-20% of all strokes in the U.S. Research shows more than 90% of atrial thrombi originate from the left atrial appendage (LAA). Traditionally, oral anticoagulants (OACs) have been the cornerstone of management for AF in reducing the risk of thromboembolic stroke. However, OACs also pose a non-negligible risk of bleeding with between 30-50% of eligible patients not receiving OACs due to absolute contraindications or perceived increased bleeding risk. New technologies aimed at isolating the LAA through ligation, exclusion, or occlusion are attempting to mitigate the embolic risk posed by LAA thrombi while simultaneously reducing the bleeding risk associated with OAC. In this review, we discuss the safety, efficacy, and clinical utility of these technologies as alternatives to OACs.

KEYWORDS: Atrial fibrillation, Lariat, Left atrial appendage closure, stroke, Watchman

INTRODUCTION

Atrial Fibrillation’s (AF) role in the pathogenesis of thromboembolic stroke has been well established. Currently, in the United States, stroke ranks as the fifth leading cause of death. There are approximately 795,000 strokes annually with one occurring every 40 seconds [1]. Estimates from numerous trials, including the local Framingham trial, attribute approximately 15-20% of all strokes to AF [2-3]. The mere presence of AF carries with it a five-fold increased risk for embolic stroke [4]. Research has shown that more than 90% of atrial thrombi originate from the left atrial appendage (LAA). Strokes originating from the LAA tend to be more severe with a 70% chance of death or permanent disability [5]. Traditionally, oral anticoagulants (OACs) have been the cornerstone of management for AF and embolic strokes, with relative overall success. In fact, a meta-analysis in 2014, showed a 64% embolic stroke reduction with a 26% mortality reduction with OAC use [6,7]. While OACs have demonstrated an ability to reduce embolic stroke, they are also associated with a non-negligible risk of bleeding. Unfortunately, between 30-50% of eligible patients do not receive OACs due to absolute contraindications or perceived increased bleeding risk [8]. Bleeding risk takes several forms, from increased risk of spontaneous intraparenchymal hemorrhage to the complications of surgical procedures. Hence, current clinical guidelines for OAC balance the risk of stroke using risk assessment tools such as the CHA2DS2-VASc score against the patient’s native bleeding risk via HAS-BLED score. New technologies aimed at isolating the LAA through ligation, exclusion, or occlusion are attempting to mitigate the embolic risk posed by LAA thrombi while simultaneously reducing the bleeding risk associated with OAC. As with most percutaneous procedures in modern cardiology, these LAA occluder technologies have evolved from cardiothoracic surgical techniques traditionally used to isolate the LAA from the systemic circulation.

DEVICES FOR CLOSURE OF THE LAA

Broadly the devices used for closure of the LAA can be classified into two primary categories, epicardial and endocardial. The epicardial devices include the LARIAT suture delivery device [SentreHEART, Palo Alto, CA, USA] and the BELIEF trial. The LARIAT physically isolates the LAA by ligation through a combination of pericardial and transseptal access. Individuals with a history of pericarditis, cardiac surgery, recent myocardial infarction, or pectus excavatum are not candidates for the LARIAT [9] approach. The BELIEF trial utilized radiofrequency ablation to isolate the pulmonary veins while rendering the LAA inert, adding rhythm control to LAA exclusion. The BELIEF trial showed the possible benefit of radiofrequency isolation of the LAA in maintaining consistent rhythm control [10]. The obvious advantage of both of these epicardial techniques is that there are no retained endovascular devices. The endocardial devices currently available include Amplatzer Amulet [St. Jude Medical, St. Paul, MN, USA] and the Watchman device [Boston Scientific, Plymouth, MN, USA]. Both of these devices are percutaneously delivered occluders which remain with the L.A. Of all the percutaneous devices available for LAA occlusion, the Watchman has been the most thoroughly investigated with extensive trials and follow-up registry data. See Figures 1 & 2.

PERCUTANEOUS LAA OCCLUSION

Percutaneous left atrial appendage occlusion (LAAO) via the Watchman device has been extensively studied. The Percutaneous Closure of the Left Atrial Appendage Versus Warfarin
Thromboembolic Disease

Therapy for the Prevention of Stroke in Patients with Atrial Fibrillation [PROTECT-AF] trial was a large, non-blinded, randomized trial utilizing the Watchman device in a non-inferiority comparison to standard warfarin therapy [11]. It was a multi-center, open-label trial involving 707 patients with non-valvular AF randomly assigned in a 2:1 ratio to either Watchman implantation or long-term warfarin (INR 2.0-3.0). Patients in the device group were given warfarin for 45 days to facilitate device endothelialization, a timeline chosen from canine experience. After 45 days, warfarin was discontinued and a follow-up transesophageal echocardiogram (TEE) showed either an acceptable residual per-device flow with a jet <5mm or complete LAAO. After discontinuation of warfarin, clopidogrel and aspirin were given for 6 months, followed by aspirin alone. The control arm received warfarin with a target INR between 2.0-3.0, which was only accomplished two-thirds of the time despite close INR monitoring. Implant success rate was 91%. Primary outcomes of stroke, systemic embolism, and cardiovascular death were measured at 18 months and the event rate was similar in both arms [3.0 vs. 4.9 events per 100 patient-years]. The PROTECT-AF study successfully demonstrated non-inferiority of the Watchman device compared to standard warfarin therapy. Subsequently, several subset analyses were conducted, and while being constrained by the limitations inherent to subset analysis, some notable findings were discovered. One analysis of the PROTECT-AF trial assessed quality-of-life parameters in a subset of 547 patients [361 device and 186 control] [12]. This demonstrated that patients with AF at risk for stroke who underwent LAAO had favorable quality-of-life changes at 12 months compared to patient treated with warfarin. At face value this makes sense, warfarin patients require frequent blood-test monitoring, which places a burden on a patient’s time. A post-hoc analysis of the PROTECT-AF and its long-term monitoring registry, the Continuous Access Protocol, assessed the net clinical benefit (NCB) of LAAO. They looked for rates of thromboembolism, intracranial hemorrhage, major adverse events, and death while objectively comparing Watchman implantation to warfarin. This study showed that the NCB of LAAO was highest for those at highest risk for stroke, but also reported that this benefit increased over time. As with most device trials, the NCB favored the control arm in the initial 6-month period; however, by 6–9 months, the NCB changed favorably toward the intervention arm. In the early phase, those receiving the device had procedural-related complications to deal with such as cardiac tamponade or procedure-related stroke. Additionally, this study showed that operator experience might have some bearing on the procedural complication rate.

The ASA Plavix Feasibility Study with Watchman Left Atrial Appendage Closure Technology [ASAP] Registry demonstrated that all-cause stroke and systemic embolization risk was 2.3% per year. Also, the observed ischemic stroke rate was 77% lower than expected by the CHA2DS2-VASc predictive model [13]. In 2014, the long-term follow-up data from the PROTECT-AF trial were published [14]. With a mean follow-up of 3.8 years, the primary efficacy rate (combined end-point consisting of strokes, cardiovascular death or unexplained death, and systemic embolism) was lower in the Watchman group (2.3%) than in the control arm (3.8%), reflecting a 40% relative risk (RR) reduction, and a 96% probability of superiority. In 2016, the results from the Registry on WATCHMAN Outcomes in Real-Life Utilization [EWOLUTION] were released. In this large, prospective, multicenter registry a total of 1025 subjects from 47 centers in 13 countries were enrolled. Interestingly, their CHA2DS2-VASc risk scores were 4.5 +/- 1.6 with almost half the subjects having either a history of TIA (10.7%), ischemic stroke (19.7%), or hemorrhagic stroke (15.0%), classifying this population as high-risk. Additionally, 62% of patients were deemed unsuitable for OAC by their physician based
on factors such as inability to adhere to OAC use, bleeding history, or high risk for bleeding as dictated by their elevated HAS-BLED score. The EWOLUTION (15) registry demonstrated high procedural success rate (98.5%) with a low 7-day serious adverse event rate (2.8%). An interesting feature of this trial was the inclusion of patients who would have been OAC candidates, in contrast to the PROTECT-AF and PREVAIL trials in the U.S., which restricted enrollment to patients deemed unsuitable for OAC administration. The flexibility regarding enrolling individuals who are OAC candidates was made possible by current European Society of Cardiology (ESC) guidelines for AF. Under current ESC guidelines, LAAO is given a Class IIb, Level of Evidence B recommendation (8).

PERCUTANEOUS LAA LIGATION AND LAA ABLATION

Percutaneous LAA ligation devices such as the LARIAT offer a method of LAA exclusion by ligation, utilizing a novel pericardial and transseptal process. See Figure 3. While less well-studied than the LAAO devices, the benefit of the LARIAT lies in the establishment of tissue-to-tissue exclusion of the LAA from the circulation and the lack of an implantable device with a risk of embolization. The downside of the LARIAT stems from its procedural complexity and the exclusion of individuals with a history of pericarditis, cardiothoracic surgery, recent myocardial infarction, or a prior embolic event within 30 days of the procedure. The first single-center trial of the LARIAT device was done in Poland. It included 89 patients, mean age 62 years and a mean CHA2DS2-VASc score of 2.8. Technical success was achieved in 96%, with 2 epicardial complications and 1 transseptal complication. Major post-operative adverse events included severe pericarditis in 2 patients, 1 late pericardial effusion, 2 unexplained sudden deaths, and 2 late strokes (9). While complete closure was verified by TEE one year later, only 65 of the 89 patients underwent follow-up TEE. In 2013, the results from the U.S. Transcatheter LAA Ligation Consortium, a multi-center retrospective analysis of 154 LARIAT procedures (16) were published. Their findings included a procedural time of 76.6 minutes, a technical success rate of 94%, and procedural success rate of 86%. Major adverse events included significant pericardial effusion requiring intervention in 10.64%, bleeding requiring transfusion 4.5%, and emergent cardiac surgery 2.0%. Their median follow-up was 112 days with TEE performed in 63 patients demonstrating residual leak in 20%, and presence of thrombus in 4.8%. The U.S. experience showed that technical success is possible, but not without concerning pericardial bleeding and effusion.

The application of radiofrequency energy to achieve electrical isolation of the LAA represents a departure from implantable device or surgical exclusion therapies. In the BELIEF Trial, a randomized trial of patients with long-standing persistent AF (LSPAF), patients underwent two different ablative strategies: an extended pulmonary vein (PV) antrum ablation plus non-PV trigger ablation (Group 1) versus standard ablation plus non-PV trigger ablation plus empiric LAA isolation (Group 2) (10). The primary endpoint of the study was freedom from atrial arrhythmia, defined as atrial fibrillation, atrial flutter, and atrial tachycardia lasting >30 seconds. The secondary endpoints assessed at a <12-month interval included stroke, death, and rehospitalization. Patients were followed at 12- and 24-month intervals with no patients lost to follow-up. If the patients had breakthrough arrhythmia at their 12-month evaluation, they were rescheduled for another ablation. Individuals in the BELIEF trial underwent an average of 1.3 procedures and all were followed out to 24 months. At 24 months, the cumulative success rates were 76% and 56% in Group 1 and Group 2 respectively. Four patients (4.5%) in Group I suffered a stroke but there were no strokes or TIsAs among Group 2 patients at the 24 month follow-up. While the success rates for complete electrical isolation are relatively low, the lack of stroke or TIA in the electrically isolated LAA remains an interesting finding. Larger studies will need to be done to see if electrical isolation of the LAA remains a viable alternative to device-based or suture-mediated LAA exclusion.

CONCLUSION

Exclusion of the LAA as a nidus for thromboembolic stroke in patients with AF stands as a viable alternative therapy, especially in light of the risks posed by OAC. Leading the charge in excluding the LAA, the Watchman device is well studied, touting efficacy data from PROTECT-AF and further bolstered by

Figure 3. LARIAT (SentreHEART Inc.) Left Atrial Appendage Ligation Device showing transeptal and epicardial delivery catheters and ligation being deployed at the neck of the left atrial appendage.
long-term registries such as PREVAIL(17) and CAP. Currently, the Watchman device is FDA-approved for patients with non-valvular AF at increased risk for stroke, recommended for OACs, and have an appropriate reason for seeking an alternative to OACs. Emerging devices and technologies, such as the LARIAT and LAA isolation via ablative strategies clearly warrant further investigation and are currently only available through clinical trials and registries but are not currently approved alternatives to either OAC or the Watchman device.

References

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Pulmonary Embolism in 2017:
Increasing Options for Increasing Incidence

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ABSTRACT

Scope of the problem – An increasing burden of disease

Acute pulmonary embolism (PE) is a problem encountered by a majority of medical and surgical specialties in their scope of practice. Acute PE is currently the 3rd leading cause of cardiovascular death in the United States, resulting in 100,000 deaths annually as estimated by the Centers for Disease Control (CDC) [1]. There is a paucity of data and a broad range of estimates for both incidence and morbidity due to acute PE. The mortality of all patients presenting with acute PE is estimated between 10-30% at 90 days utilizing current treatment regimens [2]. The incidence of acute symptomatic PE seems to be increasing from 3/100 to more than 6.5/100 in the past 15 years [2]. The increasing burden of disease has led to a period of intense investigation into new therapies and strategies to treat acute PE.

KEYWORDS: pulmonary embolism, pulmonary embolism response team, catheter-directed thrombolysis, RV to LV ratio, PESI

PULMONARY EMBOLISM - MORTALITY RISK

Pulmonary embolism has a wide morbidity range, from the asymptomatic and incidentally discovered where mortality is less than 1%, to massive acute PEs that often lead to progressive shock and death. The difficulty lies in stratifying patients into categories based on risk. Only recently has increased research begun to codify categories of acute PE based on risk. Acute PE in 2017 is currently divided into 3 categories of low, moderate and high risk. The mortality for low-risk patients is approximately 1% and this represents 40% of all presenting pulmonary embolism [4,5]. Another 5-15% of presenting pulmonary embolisms have shock and hemodynamic compromise representing a high-risk cohort. Even with systemic tPA thrombolysis the mortality for these patients exceeds 30%. The third category is the sub-massive or moderate-risk patient population, and makes up the remaining 40-45% of presenting PEs. These patients have a large central thrombus burden and signs of RV failure or compromise without frank shock. These intermediate-risk patients have a high risk of degeneration to shock and death. Depending on the exact definitions, the mortality in this subgroup of patients ranges from 5-20% [4].

STRATEGY FOR RISK STRATIFICATION AND THERAPY SELECTION

Given that PE requires expertise from pulmonology, radiology, non-invasive and interventional cardiology, and cardiothoracic surgery, a multi-disciplinary team approach has been adopted at many institutions to help better serve patients with acute PE. The success of multi-disciplinary teams in the arenas of complicated coronary disease and aortic stenosis have served as a model for PE. PE response teams or PERT are gaining traction at many large medical centers that offer advanced therapies available to patients with acute PE. Engaging specialists from different backgrounds using telemedicine allows timely and efficient discussion of treatment options and provides immediate advice and therapy for patients with massive and sub-massive PE.

Prognostic scoring systems incorporate clinical, laboratory and radiographic parameters. The original and simplified pulmonary embolism severity index (PESI) scores utilize clinical variables that predict mortality [Figure 1]. The modified Miller index uses the CTPA clot burden to predict prognosis. These scores have variable accuracy in predicting morbidity and mortality [6,7,8,9,10]. Laboratory markers of RV dysfunction include BNP or N-terminal-proBNP, which reflect the severity of hemodynamic compromise and RV dysfunction in PE and predict adverse outcome [8,12,13]. They may be an effective tool for triaging patients in the ED for admission to the ICU, step-down or floor units but they do not take into account RV parameters such as RV to LV ratio or RV size and systolic function that are important decision points when considering advances therapies and refining risk stratification.

THE RVS THE PROBLEM

Mortality in acute pulmonary embolism is caused by acute RV failure from acute pressure overload in the setting of a large volume of thrombus. Multiple registries have shown a strong association with RV dysfunction and subsequent death from acute PE [12, 13, 14, 15, 16]. The difficulty lies in which RV parameter seems to best correlate with poor outcomes. Current data suggests that an RV to LV ratio greater than 1 appears to be the best predictor of morbidity and mortality [15, 16]. The RV to LV ratio has been validated both on CT imaging, which is typically the modality through which acute PE is diagnosed, as well as via 2-D...
TRANSTHORACIC ECHOCARDIOGRAM (Figure 2). Combining PE-related risk and patient’s clinical status and co-morbidities predicts early outcomes and may be used to guide treatment decision-making (Figure 4).

EMERGING THERAPIES WITH A PAUCITY OF DATA

The standard therapy for acute pulmonary embolism remains parenteral anticoagulation with the addition of high dose (100 mg) bolus systemic thrombolysis for cases of shock [currently defined as a SBP less than 90 mmHg]. These both have level 1 evidence supporting their use in acute PE but are based on decades-old data with small sample sizes. A meta-analysis of trials in patients with massive PE showed a reduction in the composite of recurrent PE and death in systemic lysis patients versus heparin (19). The PEITHO trial demonstrated reduced composite endpoint of death and hemodynamic collapse in intermediate-risk patients (2.6% vs. 5.6%), but no mortality benefit and at the expense of a higher bleeding risk [17,18,19]. The MOPPET trial randomized moderate-risk patients to half-dose alteplase (50 mg over 2 hours) anticoagulation with lower pulmonary artery pressure at 28 months and no major bleeding (23). These studies collectively demonstrate that systemic fibrinolysis in patients with massive and sub-massive PE leads to improved hemodynamic stabilization and possibly lower risk of recurrent PE and death but with a higher risk of severe bleeding and intracranial hemorrhage (ICH).

Catheter-based therapies to relieve obstruction quickly and restore pulmonary blood flow and improve RV dysfunction may improve cardiac output and stabilize hemodynamics. Delivery of fibrinolytics directly into the clot may allow for increased clot dissolution, shorter treatment...
times and reduced risk of bleeding complications. Catheter-directed infusion of tPA plus ultrasound for clot separation is currently the only FDA-approved therapy for PE treatment. The smaller studies supporting EKOS catheter directed thrombolytic therapy include the randomized controlled ULTIMA trial which examined patients with intermediate or sub-massive PE vs traditional anticoagulation therapy or catheter-directed thrombolysis and the single arm Seattle II PE trial.

**ULTIMA AND SEATTLE II PE TRIALS (20, 21, 22)**

The Ultima trial showed rapid improvement of RV function and reduced pulmonary artery pressures within 24 hours when compared to standard anticoagulation in patients with sub-massive acute PE. This benefit was no longer statistically significant at 90 days of follow-up. Bleeding rates were no higher in the treatment arm and led to the approval of catheter-directed thrombolytic therapy for this moderate-risk population. The US based Seattle II PE trial, of which the Miriam Hospital was a site, was a prospective, single arm safety and efficacy trial that confirmed improvement in RV function using catheter directed thrombolytic therapy. (See case example of EKOS CDT, Figure 3.) It also confirmed no major bleeding events as a result of lower dose catheter-directed thrombolytic therapy, (like ULTIMA, a total of 24 mg of tPA). Although proven safe and effective there has yet to be a randomized controlled trial showing benefit for clinical endpoints in acute pulmonary embolism using catheter-directed therapy (CDT). The pivotal trial for moderate risk PE patients, PE TRACT, hopes to recruit over 500 patients and randomize to anticoagulation with or without catheter-directed thrombolysis. Long-term clinical endpoints should answer this critical clinical equipoise question.
Clinical suspicion of PE

Shock / hypotension?

Yes

Diagnostic algorithm as in Figure 3

PE confirmed

Intermediate risk

Consider further risk stratification

RV function (echo or CT)\(^a\)
Laboratory testing\(^b\)

Both positive

High risk

Primary reperfusion

A/C; monitoring; consider rescue reperfusion\(^d\)

Intermediate–high risk

Hospitalization; A/C\(^a\)

Intermediate–low risk

Low risk\(^c\)

No

Diagnostic algorithm as in Figure 4

PE confirmed

Assess clinical risk (PESI or \(s\)PESI)

PESI class III–IV or \(s\)PESI \(\geq 1\)

PE class I–II or \(s\)PESI \(= 0\)

One positive or both negative

Low risk\(^c\)

Consider early discharge and home treatment, if feasible\(^c\)

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\(A/C\) = anticoagulation; CT = computed tomographic pulmonary angiography; PE = pulmonary embolism; PESI = pulmonary embolism severity index; RV = right ventricular; \(s\)PESI = simplified pulmonary embolism severity index.

\(^a\)If echocardiography has already been performed during diagnostic work-up for PE and detected RV dysfunction, or if the CT already performed for diagnostic work-up has shown RV enlargement (RV/LV [left ventricular] ratio \(>0.9\)), a cardiac troponin test should be performed except for cases in which primary reperfusion is not a therapeutic option (e.g., due to severe comorbidity or limited life expectancy of the patient).

\(^b\)Markers of myocardial injury (e.g., elevated cardiac troponin I or T concentrations in plasma), or of heart failure as a result of (right) ventricular dysfunction (elevated natriuretic peptide concentrations in plasma). If a laboratory test for a cardiac biomarker has already been performed during initial diagnostic work-up (e.g., in the chest pain unit) and was positive, then an echocardiogram should be considered to assess RV function, or RV size should be reassessed on CT.

\(^c\)Patients in the PESI Class I–II, or with \(s\)PESI of 0, and elevated cardiac biomarkers or signs of RV dysfunction on imaging tests, are also to be classified into the intermediate–low risk category. This might apply to situations in which imaging or biomarker results become available before calculation of the clinical severity index. These patients are probably not candidates for home treatment.

\(^d\)Thrombolysis, if (and as soon as) clinical signs of haemodynamic decompensation appear; surgical pulmonary embolectomy or percutaneous catheter-directed treatment may be considered as alternative options to systemic thrombolysis, particularly if the bleeding risk is high.

\(^e\)Monitoring should be considered for patients with confirmed PE and a positive troponin test, even if there is no evidence of RV dysfunction on echocardiography or CT.

\(^f\)The simplified version of the PESI has not been validated in prospective home treatment trials; inclusion criteria other than the PESI were used in two single-arm (non-randomized) management studies.
The AngioVac thrombectomy device utilizes a 22F venous catheter that can remove large volume thrombus using a centrifugal pump and venous reinfusion, and is designed to remove thrombus from iliac veins, IVC, RA and PA. The need for a 26F sheath and a perfusionist limits its use. The Inari FlowTriever device is a 22F venous sheath aspiration system that utilizes an aspiration guide catheter and a catheter composed of three self-expanding nitinol disks to entrain and remove thrombi. Limitations include the large access sheath and difficulty manipulating the guide catheter into the pulmonary artery. The Penumbra thrombectomy device provides 29 mmHg vacuum aspiration with an 8F device that uses a separator wire to clear the system of thrombus.

OTHER PE THERAPIES

In high-risk patients with shock from acute PE who fail or have a contraindication to systemic thrombolytic therapy, several options remain. Extracorporeal membrane oxygenation (ECMO) therapy can unload the RV and provide oxygenation to allow for recovery. It is being used more frequently for critically ill patients with high expected mortality but vascular complications from large bore sheaths remain the current limitation to this promising therapy. Data is only available through small registry and single-center data with regards to the efficacy of ECMO in the acute PE patient. Surgical embolectomy remains an important option for critically ill patients for whom high dose thrombolytics have failed or are contraindicated, and they must have proximal disease that is accessible through a median sternotomy. IVC filter use has fallen out of favor due to its high complication rate and low efficacy rate, and is only indicated in patients with an absolute contraindication to anticoagulation. Both the American and European guidelines do not recommend routine use of IVC filters in patients with PE.

Due to the complexities of assigning risk and choosing therapy for acute PE patients in a rapid manner, we’ve taken the burden of PE head-on in an effort to improve outcomes for patients. At Rhode Island and The Miriam Hospitals we offer advanced therapy for intermediate- and high-risk PE that include percutaneous catheter-directed thrombolysis, aspiration thrombectomy, surgical embolectomy and ECMO therapies. In order to rapidly triage patients to the appropriate therapy, we have created a pulmonary embolism response team to provide a multi-disciplinary approach to the management of acute PE. A call placed from the pulmonary fellow rapidly assembles a team including pulmonary critical care, interventional and non-invasive cardiology, interventional radiology and a cardiothoracic surgeon. The case is presented by the pulmonary critical care fellow, including access to all relevant imaging data and a discussion is held to determine the best care for the patient. We are currently collecting clinical data to compare our efforts pre- and post-initiation of the PERT team in a prospective trial dubbed Providence PE.

MORE WORK TO BE DONE

Definitive randomized controlled trials are currently in the early phases of approval so 3-5 years will lapse before any decisive data is available to guide treatment of acute PE patients. In the interim we are using guideline-based therapies and the PERT in an effort to maximize benefit for this common and highly morbid condition. Until appropriate studies fill knowledge gaps, we suggest utilization of multi-disciplinary PERTs and collection of data both locally and nationally through the PERT Consortium. (Figure 4. Suggested PE Treatment Algorithm, adapted from the ESC 2015 Guidelines)

References

14. Wolde M, Sohne M, Quak E, Mac Gillavry MR, Buller HR. Prog-


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The Arm is Not the Leg: Pathophysiology, Diagnosis, and Management of Upper Extremity Deep Venous Thrombosis

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ABSTRACT

Upper extremity deep venous thrombosis (UEDVT) involves thrombosis of the deep veins of the arm as they enter the thorax. They are increasing in frequency, largely due to the rising use of central venous catheters and implantable cardiac devices, and represent more than 10% of all DVT cases. Upper extremity deep venous thrombosis has been historically misunderstood when compared to lower extremity deep vein thrombosis (LEDVT). Their associated disease states may carry devastating complications, with mortality rates often higher than that of LEDVT. Thus, education on recognition, classification and management is critical to avoid long-term sequelae and mortality from UEDVT.

KEYWORDS: Upper extremity deep vein thrombosis, catheter associated deep vein thrombosis, pacemaker associated deep vein thrombosis, thoracic outlet syndrome, Paget-von Schröetter syndrome

INTRODUCTION

Upper extremity deep venous thrombosis (UEDVT) accounts for more than 10% of all cases of deep venous thrombosis (DVT). UEDVT is about 1/5 as common as lower-extremity deep vein thrombosis (LEDVT) (0.19 vs 0.96 per 100,000 hospitalizations). The subclavian vein is most often affected, with the internal jugular, brachial, and basilic veins involved in approximately 4–30% of patients. Complications, such as pulmonary embolism (PE) as well as mortality are more frequent and more severe when UEDVT involves the axillary or more proximal veins than if thrombosis is confined to the brachial vein. As such, the term “UEDVT” is typically used only when referring to thrombosis involving axillary and more proximal veins. In addition, UEDVT has associated under-recognized and distinct disease states, which are often misunderstood when compared to LEDV Ts. Prompt recognition and appropriate management of UEDVT is vital due to the significant risk of PE, mortality, and observable long-term sequelae.

In this article, we review the pathogenesis, diagnosis, classification, and clinical characteristics of the different forms of UEDVT as well as treatment and management.

ANATOMY OF THE VEINS OF THE UPPER EXTREMITY

The superficial veins of the arm include the cephalic, basilic, and median cubital veins. These veins drain into the deep veins, which are the radial and ulnar veins in the forearm and the brachial, axillary, and subclavian veins in the upper arm and shoulder. The subclavian vein continues, joining with the internal jugular vein and eventually emptying into the superior vena cava [SVC].

CLASSIFICATION AND PATHOGENESIS

The mechanism of DVTs was first described by Rudolf Virchow as a triad of factors thought to contribute to thrombosis: hypercoagulability, hemodynamic stasis or turbulence, and endothelial dysfunction. From this, the mechanism of UEDVT can be further characterized as primary, or “spontaneous,” and secondary.

Primary Upper Extremity Deep Venous Thrombosis

A DVT of the arm veins without apparent predisposing factors in the patient’s history is classified as primary UEDVT and accounts for up to 33% of all thromboses involving the upper extremities. Classifying an UEDVT as primary requires thorough evaluation for predisposing anatomic and hematologic abnormalities. Primary UEDVT can be further classified into effort thrombosis, otherwise referred to by the eponym Paget-von Schröetter Syndrome (PSS), and idiopathic thrombosis.

Paget-von Schröetter Syndrome is the most common form of primary UEDVT and typically occurs in young and otherwise healthy individuals with a male to female ratio of approximately 2:1. UEDVT occurs in the dominant arm after strenuous, repetitive or unusual physical activity, such as lifting weights, playing tennis, pitching a baseball, or performing repetitive overhead activities such as painting. Patients with PSS have an underlying anatomic abnormality involving the thoracic outlet. The repetitive physical activity leads to damage to the subclavian vein intima with subsequent fibrosis and activation of the coagulation cascade. This elicits effort-related thrombosis due to compression of the subclavian vein from anatomic abnormalities within the anterior portion of the thoracic outlet triangle leading to the formation of the venous thoracic outlet syndrome (VTOS).

The subset of primary UEDVT where there are no evident predisposing factors or underlying VTOS is identified as...
idiopathic. However, occult malignancies in this subgroup of patients have been reported in up to 25% of cases, and the prevalence of coagulation abnormalities appears to be even higher in patients with idiopathic thrombosis than in those with PSS thrombosis or other forms of secondary thrombosis. Patients with PSS generally have good functional status with longer life expectancies than that of idiopathic UEDVT.

Secondary UEDVT
Secondary UEDVT accounts for up to 80% of UEDVT and is defined as any UEDVT related to a predisposing factor, such as central venous catheters (CVC), implantable cardiac rhythm devices, malignancy, or insertion of other prosthetic or foreign material. Compared to primary UEDVT, there is increased mortality in patients with secondary UEDVT, usually related to the underlying disease state. The incidence of secondary UEDVT is increasing due to growing use of medical devices, particularly use of central venous catheters, which have been reported in 25–50% of UEDVT. The internal jugular, subclavian or axillary veins can be involved, and the risk of thrombosis is equal, regardless of vascular access site. The risk of developing catheter-related thrombosis depends on an individual patient’s profile, and is as high as 66% in cancer patients with CVCs.

UEDVTs occurred in 23% of patients following implantation of a permanent pacemaker, while peripherally inserted central catheters were associated with UEDVT in 9% of patients. Other related risk factors include personal or family history of thrombosis and thrombophilia (11–60%), surgery, trauma or immobilization of the arm, pregnancy and oral contraceptive use. Malignancy is an independent risk factor for secondary UEDVT and is present in approximately 33% of cases, particularly ovarian and lung adenocarcinoma. Catheter-related risk factors such as technically difficult or left-sided catheter placement, location of the catheter tip not at the atriocaval junction, prior CVC, and large-lumen catheters also pose increased risk.

CLINICAL PRESENTATION AND DIAGNOSIS
The most common clinical features of UEDVT are unilateral arm erythema, edema and discomfort, and dilated superficial veins, dyspnea, low-grade fever and failure to withdraw blood from a catheter may also be present. In cases where there is central vein obstruction or occlusion, SVC syndrome may be seen. When PSS is present, venous distention was reported in all cases, with edema of the arm (93%), cyanosis (77%) and pain with exercise (66%) also occurring. Compression of the brachial plexus can lead to paresthesias and arm pain, which worsens with hyperabduction of the shoulder when VTOS is associated with PSS. The incidence of symptomatic and asymptomatic UEDVT following CVC placement is 2–6% and 11–19%, respectively.

Clinical probability scores have a sensitivity of 78% and specificity of 64% for diagnosing UEDVT. Furthermore, 13% of patients with low probability scores were later diagnosed with UEDVT; thus, scores alone should not be used to rule out the likelihood of UEDVT. In contrast to LEDVT, D-dimer testing has not been prospectively tested and cannot be used to exclude UEDVT with one study showing a specificity of 14%. The mainstay in diagnosis of UEDVT is imaging. Duplex ultrasonography (US) is commonly used as the initial study and should be considered the first-line diagnostic imaging procedure for UEDVT. It is readily available, portable, non-invasive, inexpensive, and without radiation exposure. Ultrasound has 97% sensitivity and 96%

Figure 1. Greyscale image (A) of subclavian vein (arrows) with intraluminal PICC line (arrowhead) surrounded by heterogeneous echodensity filling the vessel consistent with thrombus. Color Doppler (B) shows flow (blue) between the vessel wall and thrombus demonstrating near-occlusive thrombus.
specificity for the diagnosis of UEDVT. Applying pressure to compress the visualized vein should easily collapse the vessel under normal conditions, with lack of expected venous collapse indicating presence of a thrombus. This technique cannot be used for centrally located veins, such as the SVC, where manual compression is not possible. Echogenicities visualized within the vessel lumen may represent acute or age indeterminate thrombus. Pulsed wave- and color-flow Doppler US can further assess dynamics of venous blood flow. Absence of flow, or conversion of the normal biphasic flow pattern into a non-pulsatile, continuous flow signal suggests venous obstruction and the presence of a DVT.14

Figure 2. Greyscale image (A) showing axillary vein (AV) and artery (AA). The vein is dilated and filled with heterogeneous echogenic material consistent with spontaneous thrombosis. Color Doppler (B) showing no flow within the vein demonstrating complete occlusion of the vessel. Red color in the axillary artery consistent with normal arterial flow.

Contrast venography has the ability to visualize the entire deep venous system and can define complex and difficult anatomy not otherwise visualized with US. It is utilized infrequently and is typically reserved for these situations or if there is a disparity between US and clinical findings. Contrast venography is invasive and exposes the patient to iodinated contrast and radiation. When contrast is injected into the venous system, a non-filling venous segment suggests thrombosis.14

Additionally, contrast-enhanced computed tomography and magnetic resonance venography are potential diagnostic tests for UEDVT, though limited evidence exists to guide their use. Sensitivity of magnetic resonance venography has been reported at 71%,41 and the value of computed tomography venography has not been systematically evaluated.14 However, both computed tomography and magnetic resonance imaging are useful not only to confirm UEDVT but also to diagnose concomitant pathologies, including cancer, adenopathy, or anatomic abnormalities suggestive of VTOS and have largely supplanted contrast venography.1

TREATMENT AND PREVENTION

Goals of therapy can be divided into the acute treatment phase, defined as the first three months following diagnosis, and the secondary prevention phase, which refers to therapy beyond three months.11,42 In the acute treatment phase, the optimal treatment duration and intensity has not been determined in randomized controlled trials. However, a small prospective cohort study has shown low rates of recurrent DVT, PE, and episodes of major bleeding when acute UEDVT is treated similarly to LEDVT.43 The 2012 consensus guidelines of the American College of Chest Physicians11 recommend anticoagulation therapy with low molecular weight heparin (LMWH), unfractionated heparin, or fondaparinux followed by 3 months of vitamin K antagonists for idiopathic UEDVT involving the axillary and more proximal veins.11 Anticoagulation for isolated brachial vein thrombosis is not well studied, but is recommended if the thrombus is symptomatic or involves a CVC. In contrast to idiopathic LEDVT, anticoagulation therapy beyond 3 months is generally not recommended after a first episode of idiopathic UEDVT.11

In UEDVT associated with malignancy, treatment with LMWH monotherapy for 3-6 months is preferred over the administration of vitamin K antagonists and should continue as long as the cancer remains active and the event was not related to a CVC.11 In patients with catheter-associated UEDVT (with or without cancer), anticoagulation therapy can be discontinued after at least 3 months if the CVC is removed. If the catheter is not removed, anticoagulation therapy should be continued as long as the catheter remains.11 In most patients with CVC-associated UEDVT, it is recommended that the catheter not be removed if it is functional and there is an ongoing need for central access.11
The use of direct thrombin inhibitors and Xa inhibitors over vitamin K antagonists or LMWH for the long-term treatment of UEDVT is not recommended as their use has not been studied.11

Criteria for placement of SVC filters are similar to those in LEDVT, and should only be considered in patients with contraindications to anticoagulant treatment and PE.11

In patients with UEDVT due to PSS, physical therapy may reduce symptoms. If symptoms persist with evidence of residual subclavian vein stenos is by positional venography, surgical decompression should be considered.13

PROGNOSIS AND FOLLOW-UP

Mortality rates are significantly higher with UEDVT compared to LEDVT [7.6% vs. 4.2%; p<0.001],4 and two- and 12-month mortality rates following diagnosis of UEDVT have been reported at 30 and 40%, respectively.4, 11 Pulmonary embolism is a dire complication and drives mortality in both UEDVT and LEDVT, although rates in one large retrospective study showed a lower incidence of PE in UEDVT compared to LEDVT [5.4% vs. 27.9%; p<0.001]. Nonetheless, the prevalence of hemodynamically unstable PE was higher among patients with UEDVT than LEDVT [5.2% vs. 3.6%; p<0.001].4 Another analysis reported the rate of PE to be 6% in primary UEDVT, 13% in secondary UEDVT and 17% in catheter-related UEDVT.17

Post-thrombotic syndrome (PTS) of the arm, a condition characterized by persistent pain, edema, and functional limitation due to persistent obstruction and valvular insufficiency, has been reported in up to 20% of patients after treatment for UEDVT.11 In contrast to LEDVT, use of compression therapy to prevent PTS of the arm is not recommended due to lack of evidence of efficacy in this population and a difference in the suspected pathophysiology of PTS in the upper extremity.11 Additionally, there is no evidence or recommendations to support the practice of serial US imaging in UEDVT.11

CONCLUSION

The clinician’s understanding and recognition of UEDVT is essential in avoiding PE. Mortality is elevated in patients with UEDVT, and prompt identification of thrombosis and initiation of anticoagulation is essential. Specific differences exist between the various types of UEDVT and can alter approaches to treatment. Further research should focus on use of novel anticoagulants given the anticipated increase in UEDVT incidence due to increasing use of CVC.

References 17–45

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Chronic Venous Insufficiency: Novel Management Strategies for an Under-diagnosed Disease Process
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ABSTRACT
Chronic venous insufficiency is an often-missed diagnosis that results in a variety of clinical manifestations that may severely compromise quality of life. Prompt recognition is important to provide symptomatic relief and prevent disease progression. Most patients can be treated with a comprehensive plan of conservative measures. However, it is important for providers to recognize those patients who require referral to a vascular specialist for more invasive therapies. Over the past 2 decades, a variety of endovenous strategies have demonstrated effective and lasting results in treatment of severe symptomatic venous insufficiency.

KEYWORDS: Venous insufficiency, venous ulcer, radiofrequency ablation, endovenous laser therapy, phlebectomy

BACKGROUND
Chronic venous disease is often underdiagnosed and consequently undertreated in a variety of healthcare settings. An estimated 25 million Americans are affected by some degree of chronic venous insufficiency. Manifestations of chronic venous disease range from asymptomatic varicose veins in 30% of screened individuals, to more advanced disease in 10% of patients. Varicose veins have an estimated prevalence of 5-30% in adults with a female-to-male preponderance of 3:1. Non-healing and healed venous ulcers occur in approximately 1% of the US adult population. Risk factors associated with chronic venous disease including increasing age, female gender, family history of venous insufficiency, obesity, pregnancy and prior leg injury or surgery. Furthermore, occupations that require prolonged standing predispose individuals to development of chronic venous insufficiency. Disability secondary to severe venous ulcers results in 2 million workdays lost. Moreover, an estimated $1 billion are spent annually in the treatment of chronic venous ulcers.

The superficial venous system above the muscular fascial layer is composed of the great saphenous vein (GSV), the small saphenous vein (SSV) as well as several accessory veins. Along with the superficial venous system, the deep venous system and perforating veins serve as both a reservoir and conduit to return blood to the heart. Normal venous return depends on patency of the venous system as well as proper functioning of a series of 1-way bicuspid valves. In addition, lower extremity muscular function must be adequate in order to ensure central venous return. When the venous system is functioning correctly, every movement of the lower extremity moves blood inward and upward past competent valves that ensure that the hydrostatic pressure is near zero. In patients with venous insufficiency, incompetent valves remain in an open configuration, resulting in an unbroken column of blood from head to foot with a subsequent high hydrostatic pressure.

Failure of superficial venous valves occurs most commonly from weak vein walls that dilate under normal venous pressures, resulting in secondary valve failure. In addition, direct injury from superficial phlebitis, as well as congenital abnormalities, can result in primary valve failure. Finally, normal valves can be excessively distensible under the influence of hormones as in pregnancy. The common pathway of these states leads to an inability to prevent backflow and venous pooling.

The CEAP classification (Figure 1) is commonly utilized to reliably and reproducibly grade severity of venous insufficiency. Furthermore, therapy can be tailored to the severity of venous insufficiency.

Figure 1. CEAP classification

| Clinical | C₀ – No clinical signs
| C₁ – Small varicose veins
| C₂ – Large varicose veins
| C₃ – Edema
| C₄ – Skin changes without ulceration
| C₅ – Skin changes with healed ulceration
| C₆ – Skin changes with active ulceration
|
| Etiology | E₁ – Congenital
| E₂ – Primary
| E₃ – Secondary
|
| Anatomy | A₀ – Superficial
| A₁ – Deep
| A₂ – Perforating
|
| Pathophysiology | Pᵣ – Reflux
| Pₒ – Obstruction |
PRESENTATION

Early clinical manifestations of chronic venous insufficiency include the reporting of subjective symptoms. The characteristic ache of venous insufficiency comes on after prolonged standing and is described as pain, pressure, burning, itching or heaviness in the affected limb. Importantly, episodic symptoms may occur temporally, related to hormonal changes during pregnancy. Symptoms are alleviated by walking and leg elevation unlike in peripheral arterial disease. As the disease process advances, damage to the capillary basement membrane results in leg edema. The characteristic appearance of lipodermatosclerosis results from the breakdown of red blood cells and the subsequent deposition of hemosiderin in the skin. In the most advanced cases, non-healing ulcers are noted around the medial malleolus where venous pressure is maximal. Unlike typical arterial ulcers, the wound of chronic venous insufficiency is shallow, superficial, irregular in shape and associated with painful edema.

DIAGNOSIS

Venous duplex imaging is the simplest and most commonly used technique for establishing the diagnosis of venous insufficiency. Furthermore, duplex imaging is usually sufficient enough to guide therapy and management. Presence of venous reflux is confirmed by determining direction of blood flow. This is evaluated by placing the patient in reverse Trendelenburg position, and assessing blood flow direction during a Valsalva maneuver or after augmenting blood flow with more proximal limb compression. An alternative method requires venous duplex interrogation following a rapid cuff inflation-deflation technique while the patient is standing. The presence of significant reflux is determined by the presence of reverse flow towards the feet for a significant amount of time: ≥ 0.5 seconds for superficial veins and ≥ 1.0 seconds for deep veins. A longer duration of reflux corresponds with more severe disease but not necessarily with clinical manifestations.

Venous duplex imaging is often more than sufficient in diagnosing and managing patients with venous insufficiency. Air plethysmography is utilized occasionally to determine the relative contribution of venous reflux, as opposed to venous obstruction or muscle pump dysfunction, to the clinical syndrome. Computed tomography (CT) and magnetic resonance (MR) are rarely utilized to evaluate venous disease. The utility of advanced imaging modalities is mainly to diagnose both intrinsic and extrinsic compression of the venous system by surrounding structures. Invasive contrast venography is very rarely utilized if surgical intervention is considered.

TREATMENT OF CHRONIC VENOUS INSUFFICIENCY

Compression therapy between 20–50 mmHg remains the cornerstone of any treatment plan for chronic venous insufficiency. Graded external compression to the leg opposes the hydrostatic pressure that results in venous hypertension. The presence of compression grades is essential as non-graded ACE wraps and stockings cause a tourniquet effect that in turn exacerbates venous insufficiency. Compliance with 30-50 mmHg compression therapy is sufficient in the vast majority of patients to alleviate symptoms of chronic venous insufficiency as well as improve mobility. Even in more severe disease, compression therapy has been associated with complete venous ulcer healing at 5 months.

The most common compression stocking prescribed is for knee-high garments. A general rule of tension prescription that correlates with disease severity would be 20–30 mmHg for C2-C3 disease, 30-40 mmHg for C4-C6 and 40–50 mmHg for recurrent ulcers. Stockings should be worn daily and removed only at night for maximal benefit. Any compression garment should be replaced every 6 to 9 months.

In addition to compression therapy, calf muscle exercises should be performed as part of any treatment plan. In very small studies, coumarins, flavonoids, saponosides and other plant extracts have demonstrated mild improvement in edema-related symptoms. However, currently, there are no pharmacological agents approved in the United States for treatment of chronic venous insufficiency. Although diuretics are commonly used to treat edema for short periods of time, it is important to understand that chronic venous insufficiency is not a state of volume overload. As a result, the benefit of temporary relief must be balanced with the metabolic and renal side effects of long-term diuretic usage.

Interventional therapy of chronic venous insufficiency includes both venous ablation as well as sclerotherapy. Endovenous ablation involves the application of thermal energy, either radiofrequency (RF) or laser (EVLT), to the vein wall which in turn leads to thrombosis followed by fibrosis of the treated segment. In the case of GSV ablation, both RF and EVLT procedures involve ultrasound-guided placement of a 7 Fr sheath in the GSV with subsequent passage of a catheter to the level of the saphenofemoral junction. Radiofrequency ablation of the greater saphenous vein has resulted in successful venous closure in 85% of patients with a 10% rate of recanalization at 2 years. A very rare complication (< 1%) of RF is deep-vein thrombosis and subsequent pulmonary embolism. Laser treatments have reported rates of closure as high as 95% at 2 years with no major complications. At present venous ablation, by either laser or RF, has a higher rate of success compared to sclerotherapy and lower rate of co-morbidity compared to traditional surgical ligation and stripping. Endovenous ablation is performed almost exclusively with local tumescent anesthesia which prevents skin burns and reduces any pain associated with the procedure.

Although most commonly utilized in the treatment of GSV insufficiency, endovenous ablative techniques have also been utilized in treatment of perforator reflux in the case of non-healing ulcers.

A variety of sclerosing agents have been utilized to treat
telangiectasias, varicose veins and smaller segments of venous reflux. In addition, sclerotherapy has been used to treat spider veins, bleeding varicosities and cavernous hemangiomas. Currently in the United States, the only approved sclerosing agents are detergents including sodium tetradecyl sulfate, polidocanol, glycerin and sodium morrhuate. Generally, all agents have to be diluted with air or saline in order to avoid tissue inflammation and necrosis. The most common complication of any sclerotherapy is skin hyperpigmentation of surrounding tissue from hemosiderin degradation.

Endovenous deep-system therapy has become an important part of restoring venous outflow from the lower extremities. In the case of deep venous insufficiency from obstruction, venous balloon angioplasty followed by stenting has evolved as an alternative to surgical bypass surgery which is now very infrequently performed. Primary patency rates of 80% at 6 years for non-thrombotic and 60% for thrombotic disease have been reported\(^1\). The success of iliac stenting for venous ulcers has proved to be effective with 90% of patients free from recurrent ulceration at 5 years\(^12\).

Surgical therapy is reserved for those individuals with venous insufficiency symptoms refractory to compression and endovenous therapy. High ligation at the level of the saphenofemoral junction followed by excision of the GSVs ameliorate symptoms and possibly improves ulcer healing\(^13\). Following vein stripping or endovenous ablation, symptomatic varicose veins can be removed with stab phlebectomy. Surgical intervention on incompetent perforator veins for non-healing ulcers can be especially challenging, given pre-existing tissue damage. However, when performed, endoscopic perforator surgery is associated with a high rate of ulcer healing and low rate of recurrence at 2 years when performed in conjunction with GSV ablation\(^14\).

**SUMMARY**

Chronic venous insufficiency is a common medical problem. Adequate screening and recognition of its various manifestations are important to appropriately treat patients. Conservative measures including compression therapy, leg elevation and calf exercises are usually sufficient for most patients. In cases refractory to conservative therapy, interventional modalities including radiofrequency and laser ablation as well as sclerotherapy are effective at alleviating symptoms and venous ulcer healing. Rarely, surgical therapy may be required if ablation is ineffective.

**References**


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Direct Oral Anticoagulants (DOACs): Current Status Among Distinct Patient Subgroups


46. Zannad, F., et al., Rationale and design of a randomized, double-blind, event-driven, multicentre study comparing the efficacy and safety of oral rivaroxaban with placebo for reducing the risk of death, myocardial infarction or stroke in subjects with heart failure and significant coronary artery disease following an exacerbation of heart failure: the COMMANDER HF trial. European Journal of Heart Failure, 2015. 17(7): p. 735-742.


The Arm is Not the Leg: Pathophysiology, Diagnosis, and Management of Upper Extremity Deep Vein Thrombosis


18. Virchow RC. Cellular Pathology as based upon physiological and pathological history. [Tr. from the 2nd ed. of the original by Frank Chance.] Birmingham, Grynophod Editions, Ltd, 1978.


