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ANTICOAGULATION

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TABATA: HIIT NOT EHIT

This issue of Vein Specialist is like doing a TABATA workout.

Dr. Izumi Tabata, a Japanese scientist, in the early 1990's studied the effectiveness of high intensity exercise. The question asked, "Would shorter maximal bursts of energy followed by even shorter rest intervals condition the body better than continuous moderate exercise?" The study groups were either 1 hour of moderate intensity exercise for 5 days a week or a 4 minute workout 4 days a week at maximal effort; 8 sets of 20 seconds of maximal effort followed by 10 seconds of rest, (8 X 20) + (8 X 10) = 240 seconds or 4 minutes. Overall, the HIIT (High Intensity Interval Training) was better. I discovered Dr. Tabata or now better known as TABATA Training during the early days of COVID when most of us were home and gyms were closed. I have a lot of exercise options in my home. That wasn't the issue. I was looking for something different and up popped TABATA as I perused the Internet. My younger son (age 21) and I with the help of YouTube did some modified TABATA workouts 2 – 3 days a week for 45 – 60 minutes interspersed with moderate intensity exercise on other days. As I said, modified.

–Steve Elias, MD

This issue of Vein Specialist is like doing a TABATA workout: short articles stuffed with information and little rest between each one. We all read journal articles, long journal articles. We digest these as if we are doing moderate intensity exercise for an hour at a slower pace. Our Anticoagulation issue takes a different approach. Most of the articles have been written by our members with what we instructed them to do: Think like Polonius in Shakespeare's Hamlet Act 2, Scene 2, "Brevity is the soul of wit". The articles are short and to the point. We asked them to answer a specific question without the fluff. Their effort resulted in the articles we have here, excellent. You can read them and understand them and remember them in a short period of time. I hope you appreciate the effort and excellence our members are capable of. All of this within a very narrow window. When some of our members wonder what has AVF done lately or what benefits are there for me, this issue and others is the answer. This issue supplies you with answers to many aspects of anticoagulation which can be achieved in 4 minutes of intense, focused reading. TABATA.

Join us at the American Venous Forum's 33rd Annual Meeting!

–Harold Welch, MD

– Harold Welch, MD

I would like to invite all venous practitioners to join us for the 33rd Annual Meeting of the American Venous Forum. The meeting will take place March 17-20, 2021, with the Day of Science leading off on the 17th. The Day of Science, led by Dr. Fedor Lurie and Dr. Jose Diaz, has been a hugely successful addition to the Annual Meeting since its inception five years ago. The next three days will feature research presentations, The David S. Sumner Session led by Dr. Gasparis, The Lionel J. Villavicencio Session led by Dr. Marston, our International Session, as well as poster presentations and informative sessions from our sister societies, AVLS and SVM.

Our Program Committee, led by Dr. Kathleen Ozsvath, is hard at work putting together an educational and interesting program, which will have something for everyone who practices in venous disease

Currently, we are planning a hybrid meeting in San Antonio, with live streaming and video recordings available to those unable to travel to Texas. In the event there is no vaccine for this terrible COVID-19 virus, and travel is still restricted, we have tentative plans for a virtual meeting on the same dates in March 2021.

The Annual Meeting of the AVF is the pre-eminent scientific meeting in venous and lymphatic disease, attracting participants from around the world. We hope you consider joining the AVF to access the many benefits of membership, and hope to see you either in person, or on the screen, in March 2021.

Harold Welch, MD

American Venous Forum
Promoting venous and lymphatic health

COVID-19: Current Clinical Considerations Including The Tangled Web Revisited

–Joseph Caprini, MD

– Joseph Caprini, MD

We have learned that COVID-19 is a very serious pandemic Involving complex pathophysiology in multiple biologic systems. A predominant clinical feature of this disease is venous thromboembolism (VTE) as well as stroke, arterial thrombotic events, and evidence of microvascular thrombosis especially in the lungs, kidneys, and also in other organs.[1] The predominant laboratory findings in most patients include elevated fibrinogen levels and D-dimer levels that frequently are out of proportion compared with documented clinical thrombotic events. Studies have suggested that all hospitalized COVID-19 patients should receive thrombosis prophylaxis using either unfractionated heparin (UHF), or low molecular weight heparin (LMWH). Increasing doses of anticoagulation have been suggested when D-dimer levels are very high. Therapeutic doses have been suggested when clinical symptoms suggest thrombosis, and seriously ill ICU individuals on ventilators. Unfortunately, this practice has not appeared to alter the death rate. Some authorities recommend against this practice. A small subset of individuals have developed a DIC-like clinical picture including consumptive coagulopathy with prolonged clotting tests and low platelet counts and clinical bleeding.

Oscar Ratnoff, a famous hematologist published an article in 1971 entitled "a tangled web: the interdependence of mechanisms of blood clotting, fibrinolysis, immunity, and inflammation."[2] This fascinating thesis described how four experiments done before the turn of the 20th century shows the intra-relationship of these seemingly separate body systems. He concluded that this series of reactions as a whole is a response to injury. Coagulation factor XII, (Hageman factor) discovered by Ratnoff was the pivotal component in this process. He demonstrated that activation of this clotting factor began a chain reaction including activation of platelets and coagulation factors. Thrombosis follows, along with activation of the fibrinolytic system leading to clot lysis and Complement and Kallikrein systems activation leading to increased vascular permeability, vasodilatation, angioedema, and shock. He demonstrated that all of these experiments represented the body's defense against injury from the invasion of foreign substances into the blood. He expressed the opinion that "We wish to separate the mechanisms of defense to suit our experimental convenience, they are enmeshed into a seamless web. It is human characteristic to try to simplify. As a friend of mine used to say -- it is we who are simple, not nature."

Returning the conversation to the present and the COVID-19 pandemic, it is obvious that the body's defense mechanisms have appeared in full force in response to the viral invasion. A number of investigators have described in quite sophisticated terms the inter- relationship of these systems using modern techniques and findings discovered in the 50 years since Ratnoff's original description. One of the prominent features of this disease is the sequence of pathophysiologic changes uniquely affecting the alveolar endothelial interface in the lungs. Vascular thickening in the lungs of these patients has been shown to be a predominant imaging finding that is much more common than in patients with pneumonia who do not have COVID-19. Micro thrombi in various

organs, especially the pulmonary circulation, have been seen in patients dying of the disease and are characteristic thrombotic manifestations of covid-19. Microthrombi help explain the markedly elevated D-dimer levels out of proportion compared with results seen in patients with traditional VTE. Despite these findings, escalation of anticoagulant dose has failed to provide consistent improvement in survival in these patients. It is apparent that the body's inflammatory and immunologic pathways have been activated and cannot be neutralized with anticoagulation alone. Clinical trials are underway using anticoagulants, steroids, anti-inflammatory agents, antiplatelet agents, as well as antiviral therapies to improve outcomes.

We know that the leading preventable cause of death in hospitalized patients is fatal pulmonary embolism. The use of individual thrombosis risk assessment is the key to providing appropriate thromboprophylaxis. Many risk assessment models are available -- Padua score, the IMPROVE score, the Geneva score, the Caprini score, and the British National Health risk assessment document. Thrombosis-related deaths have been shown to decrease with appropriate implementation of the Caprini score or British National Health Assessment document. The Caprini score is the most widely studied and has been used in approximately 180 studies involving five million medical and surgical patients worldwide. The American Society of Hematology recommends either the Padua score or IMPROVE score with bleeding risk assessment to be integrated into clinical decision-making for medical patients. The bottom line consists of using one of these assessment tools as the key to prevention of VTE events including fatal outcomes. There are many roads to Rome and each hospital has to decide which approach works best for their population.

Studies have shown that the risk of VTE is highest during hospitalization but as many as 75% of VTE hospital-related events occur following discharge; about 50% of these are PE events. These recent data agree with data over a decade old indicating that 75% of patients develop their thrombosis after they leave the hospital and about half of them develop after anticoagulation is stopped. There is abundant evidence that standard anticoagulation and several of the new anticoagulants effectively prevent post discharge thrombosis in medical and surgical patients.

Studies in COVID-19 patients demonstrate an increased level of thrombotic risk compared to equivalent patients without the viral infection. The case for individual risk assessment and appropriate thrombosis prophylaxis using anticoagulation has never been greater and should be strictly practiced in patients with COVID-19. The American Venous Forum subcommittee has prepared recommendations that are based on past literature in patients without the viral disease. All patients hospitalized with a positive diagnosis should receive prophylactic anticoagulation with either heparin or low molecular weight heparin. The dose should be adjusted for those who have a BMI of greater than 40, history or family history of thrombosis, heart failure, pulmonary failure, or a combination of comorbidities including insulin dependent diabetes. We know that doubling the dose of anticoagulation in patients without the virus has been beneficial in minimizing the incidence of VTE in very high-risk patents. Preliminary data under review has appeared suggesting modifying the Caprini score according to the presence of the virus, symptomatic disease, and/or positive D-dimer values.[3] Full dose anticoagulation is normally reserved for those with highly probable or proven VTE events. Some investigators resort to full-dose anticoagulation in very seriously ill ICU patients on the respirator, especially when oxygen requirements are severe.

It is important to update the score during hospitalization and record a final score prior to discharge. This principle should be followed with any of the risk assessment scores used in one's hospital. These values can be used to guide six weeks or more of post discharge anticoagulation depending upon the clinical circumstances.[4]

Finally, the current data indicate that elective surgery should be avoided in COVID-19 positive patients unless absolutely necessary unless the delay might cause serious harm to the patient. Death rates of 25% or more as well as VTE rates approaching 50% have been observed following surgical procedures in positive patients. Appropriate postoperative anticoagulation is a must in these individuals.

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DOAC Reversal Agents – Are They Really Necessary?

–Mikel Sadek, MD, FACS

– Mikel Sadek, MD, FACS

Although a seemingly theoretical topic, I recognized that as a vascular specialist I would need some working knowledge of the agents that reverse some of our now most commonly prescribed medications, the direct oral anticoagulants (DOACs). Most of the time we will have very limited use for such reversal agents. Occasionally, our opinion as a consultant might be sought. Medicolegally, they provide some peace of mind. Every once in a blue moon, we will need to know when and how to use one. In short, they are necessary.

The DOACs have dominated our practices and they have been shown to result in less bleeding as compared to Warfarin.[1] This was seen in the randomized controlled trials and substantiated by real-world data.[1,2] Until recently, the Achilles heel for the DOACs was the lack of a reversal agent.

Now we have reversal agents… but with a catch. Their use is, and should be, rather restricted. For this reason, the mainstay reversal agent is time. Nonetheless, major debilitating and life-threatening bleeding still occurs in 3-4% of patients treated with a DOAC.[3-4] In summary, DOAC reversal agents should be used in bleeding that is life-threatening, that compromises an end-organ, or that is refractory to conservative measures.

Non-specific reversal agents

Borne out of necessity, the early experience catalogued the use of non-specific reversal agents. They are prothrombin complex concentrate (PCC) and activated PCC. Four-factor PCC contains factors II, VII, IX and X, and three-factor PCC contains II, IX and X (negligible VII). In two separate studies of four-factor PCC, hemostasis was achieved in 65-69% of patients.[5,6] Ischemic complications occurred in up to 8% of patients. The Anticoagulation Forum recommends a fixed dose of 2000 units of four-factor PCC.[7] Three-factor PCC with fresh frozen plasma (to provide factor VII) may be used, but this has not been validated prospectively.

Activated PCC comprises the vitamin K dependent cofactors, whereby they are "activated" by proteolysis. Hemostasis was achieved in 64% of patients with low ischemia rates. The Anticoagulation Forum recommends a dosage of 50 units / kg.[7,8]

Specific reversal agents

Idarucizumab (dabigatran reversal)

In 2015, the FDA approved idarucizumab (Praxbind, Boehringer Ingelheim). It is a monoclonal antibody against dabigatran.[9] In REVERSE-AD, 203 patients demonstrated a 68% reduction in bleeding, with an average time to hemostasis of 2.5 hours.[10] Fairly predictably, the most common sites of bleeding were intracranial and gastrointestinal. The thrombosis rate was 4.8%, including venous thromboembolic (VTE), stroke and myocardial infarction (MI).

How is it given?

2.5g IV x 2 within 15 minutes (total of 5g), and it may be re-dosed.

Andexanet alfa (apixaban and rivaroxaban reversal)

In 2018, the FDA approved Andexanet alfa (recombinant factor Xa, Portola Pharmaceuticals). Theoretically, it may bind all the direct and indirect factor Xa inhibitors (i.e. enoxaparin and fondaparinux). It is modified recombinant factor Xa that is inactive, and it can bind, sequester, and inactivate factor Xa inhibitors. ANNEXA-4 evaluated 352 patients, the majority having received Rivaroxaban or Apixaban.[11] Bleeding indications were intracranial (64%) and gastrointestinal (26%). Hemostasis was achieved in 80% of patients within 2 hours. There was a 10% thrombosis rate. Consequently, the FDA has a "black box" warning regarding arterial and venous thrombotic events.

How is it given?

Low dose: 400mg bolus followed by 4mg/min

DOAC	*Dosage*	*< 8 hours*	*≥ 8 hours*
Rivaroxaban	*≤ 10mg* *> 10mg or unknown*	*Low dose* *High dose*	*Low dose*
Apixaban	*≤ 5mg* *> 5mg or unknown*	*Low dose* *High dose*	

infusion for 120 minutes.

High dose: 800mg bolus followed by 8mg/min infusion for 120 minutes.

Practical concerns:

Elective or semi-elective procedures:

Adhere to guidelines for peri-procedural DOAC interruption, remembering to extend the interruption period for high-bleeding risk procedures and chronic kidney disease.[12]

Trauma patients:

Routine use is not recommended. Apply the same guidelines as for major bleeding or the need for high-bleeding risk surgery.[13,14]

DOAC overdose:

DOAC overdose is rare and should be managed conservatively, with the usual indications for using a reversal agent.[15,16]

The elephant in the room is cost:

For example, Andexanet alfa may cost up to $49,500 USD (high dose). There are some options for cost mitigation by Centers for Medicare and Medicaid Services (CMS) reimbursement.

Conclusion

We now have access to targeted DOAC reversal agents, and they can save lives under the correct circumstances. There remains a limited published real-world experience.[17,18] The data are also conflicting with some series showing benefit and some showing worsening clinical outcomes.[19-21] Ongoing studies are needed to demonstrate real world safety, efficacy and cost-effectiveness. As it stands, the DOAC reversal agents are necessary.

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COVID 19 & Anticoagulation: The Clot Thickens

–Sri Sharma, MD, PhD[1], Andrea Obi, MD[1], Glenn Jacobowitz, MD[2]

University of Michigan[1], NYU Langone[2]

– Sri Sharma, MD, PhD

– Andrea Obi, MD

– Glenn Jacobowitz, MD

Long before the emergence of the SARs-CoV2 virus (also known as COVID-19), the relationship between pneumonia and an elevated risk of venous thromboembolism (VTE) risk for up to a year following acute illness was well-established in population studies.[1] In this context, it is not unexpected that a hallmark of severe COVID-19 infection and associated acute respiratory distress syndrome (ARDS) is hypercoaguability. The underlying etiology is thought to be immune dysregulation lending to an overwhelming inflammatory response, resulting in aberration of clotting indices (i.e., elevated D-dimer levels and increased prothrombin time), and ultimately clinical thrombosis (VTE, clotting of CRRT filters, MI etc.).[2] The hypercoagulability in SARS-CoV2 patients resembles coagulopathy that was seen in prior viral pneumonia outbreaks including in the 2009 H1N1 influenza pandemic and 2003 SARS pandemic, in which a VTE incidence of 37% and 23-33% was estimated respectively.[3,4] VTE in patients with SARS-CoV2 portends an increased mortality and current practice guidelines including those from the AVF, ISTH and ACCP recommend initiation of thromboprophylaxis for COVID-19 patients after assessment of bleeding risk, especially in the ICU setting, where patients have the highest VTE risk despite prophylaxis.

As the data has grown, so has confusion around the role of therapeutic heparin anticoagulation (Figure). Reports from Europe suggested a high rate of breakthrough VTE (link to Peter Henke's article this month) amongst critically ill COVID-19 patients despite thromboprophylaxis with a thrombotic complication rate of 42.7% and VTE rate of 26-57%.[5,6] This lead to the use of empiric anticoagulation at intermediate or full doses by some large medical centers, our own, University of Michigan and NYU Langone included. Initial data reported from Mount Sinai (NYC) suggested a mortality benefit of pre-emptive therapeutic anticoagulation in critically ill patients but not those confined to the general care ward.[7] However, recent data released from a multihospital collaborative from Boston suggests a lower thromboembolic rate than initial reports: 9.8% amongst the critically ill with a major bleeding rate of 5.4%.[8] The authors suggest that higher doses of anticoagulation should be reserved for patients enrolled in a clinical trial.

Currently there are several randomized control trials registered with the NCT to evaluate the role of heparin

anticoagulation in COVID-19 patients. These are compiled in this edition as our "Trials to Watch" in 2020 (Table). Of particular interest to the AVF readership maybe the ACTIV-4 trial, sponsored by the NHLBI and set to launch in this fall. This trial is unique in that it has an adaptive design, meaning that there are multiple arms of the trial that may be dropped or added as the platform trial progresses and the standard of care is re-defined. The sample size is flexible, although expected to enroll over 1,000 patients and involve an estimated 400 centers. Both prophylactic and therapeutic doses of anticoagulants will be tested stratified by severity of illness: ICU patients, non-ICU patients and outpatients. As we move into the latter half of 2020, the implementation and infrastructure of multiple anticoagulant RCTs will certainly shed light on best practices for prevention of severe viral pneumonia related thrombosis and will be a lasting testament to the collaboration, innovation and fortitude of the scientific community.

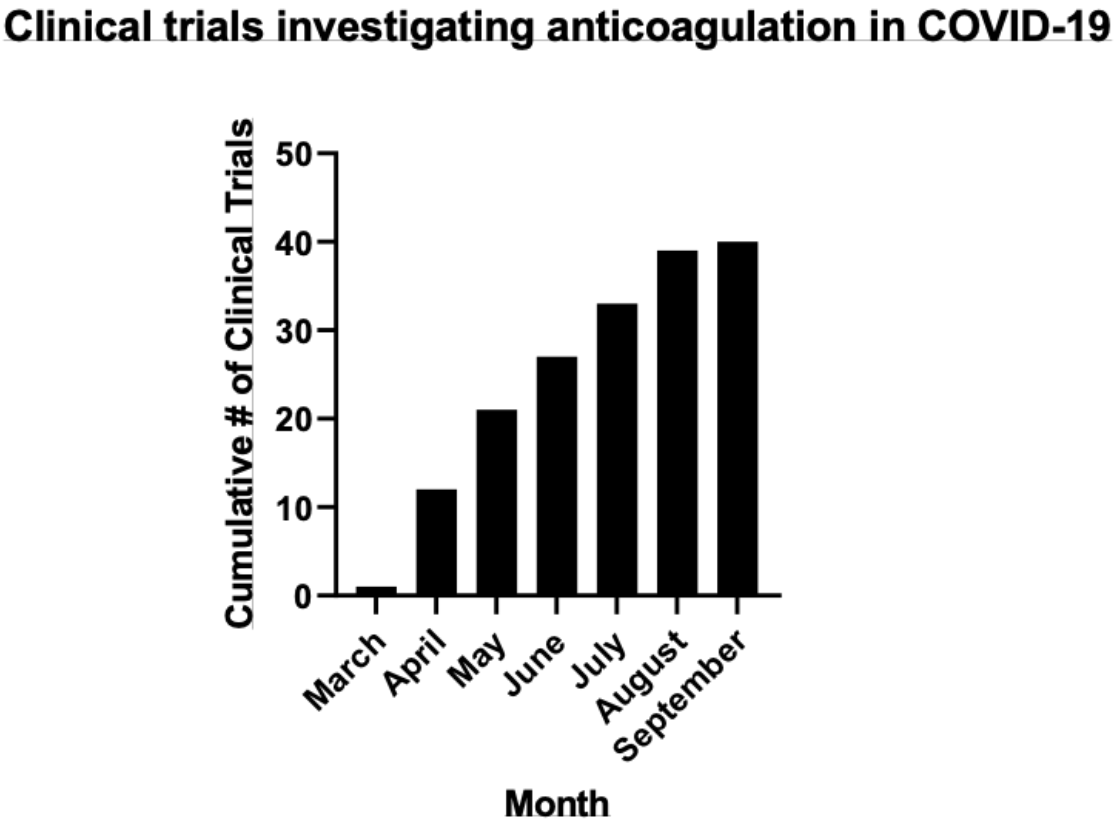

Figure 1. Cumulative number of clinical trials investigating anticoagulants in the setting of COVID-19.

Trial number, expected enrollment	Design, Sponsor	Treatment groups	Primary outcome
NCT04393805 (n=170)	Interventional Clinical Trial, University of Iowa	LMWH (prophylaxis vs. intermediate dose)	Risk of all-cause mortality in first 30 days
NCT04401293 (n=308)	Interventional Clinical Trial, Northwell Health	LMWH (full dose vs. prophylactic or intermediate dose) in high risk COVID-19	Composite of arterial/venous thromboembolic and all-cause mortality at day 30
NCT04345848 (n=200)	COVID-HEP Interventional Clinical Trial, University Hospital, Geneva	Therapeutic LMWH or IV unfractionated heparin vs. Prophylactic LMWH or unfractionated heparin	Composite outcome of arterial or venous thrombosis, DIC and all-cause mortality over 30 days
NCT04367831 (n=100)	IMPROVE Interventional Clinical Trial, Columbia University	Unfractionated heparin (SC vs. infusion) and LMWH (Enoxaparin/Lovenox prophylactic dose vs. Intermediate dose)	Total Number of Patients with Clinically Relevant Venous or Arterial Thrombotic Events in ICU (Discharge from ICU or 30 days)
NCT04359277 (n=1000)	Interventional Clinical Trial, NYU Langone Health	Heparin (higher dose) vs. LMWH (prophylactic dose)	All-cause mortality over one year and many other outcomes such as DVT, MI, etc. over 21 days
NCT04377997 (n=300)	Interventional Clinical Trial, Massachusetts General Hospital	LMWH therapeutic dose v. SOC	Composite endpoint of death, cardiac arrest, symptomatic DVT, PE, arterial thromboembolism, MI, or hemodynamic shock, and major bleeding over 12 weeks
NCT04409834 (n=750)	Interventional Clinical Trial, The TIMI Study Group	Unfractionated Heparin IV target aPTT 1.5-2.5x control, LMWH (enoxaparin 1 mg/kg SC q12h), and Clopidogrel (300 mg PO x 1, then 75 mg PO qD)	Death due to venous or arterial thrombosis, pulmonary embolism, clinically evident DVT, type 1 MI, ischemic stroke, systemic embolism or acute limb ischemia, or clinically silent DVT over 28 days
NCT04416048 (n=400)	COVID-PREVENT Randomized clinical trial, Charite University, Berlin Germany	Rivaroxaban 20 mg daily for at least 7 days vs. Standard of Care (SOC)	Composite endpoint of VTE (DVT and/or fatal or non-fatal PE), arterial thromboembolism, new myocardial infarction, non-hemorrhagic stroke, all-cause mortality or progression to intubation and invasive ventilation 35 days post randomization
NCT04377997 (n=462)	RAPID COVID COAG, St. Michael's Hospital, Toronto, ON	LMWH or UFH v. SOC	Primary composite outcome of ICU admission, non-invasive positive pressure ventilation, invasive mechanical ventilation, or all-cause death up to 28 days.

Table 1. Trials to watch in 2020-2021 to identify the optimal role of anticoagulants in COVID-19 patients.

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DVT Treatment in Special Populations

–Lori Pounds, MD

As a vascular specialist it is common to receive several consults a week for acute DVT treatment / management from primary care or the ER. It is a great teaching opportunity for the residents and fellows to go over the CHEST guidelines that I have set in my memory – using the conveniently laminated flow sheets for reference that we have in our workroom. But a DVT treatment in special populations such as pregnancy still prompt me to check the literature just in case there has be an updated recommendation. For a pregnant woman obviously, the stakes are high as there are two lives at risk. Being pregnant or postpartum has a four to fivefold increased risk of VTE compared to non-pregnant women.[1] This risk increases with each trimester until a zenith in weeks one to three post-delivery, and decreases to normal risk by 12 weeks.[2] In the US, deaths due to pulmonary embolism (PE) account for 9.2% of all pregnancy related deaths – about 1.5 deaths per 100,000 live births.[2] Similar rates are found in the UK and Canada.1 It is more common in cesarean sections and with advanced maternal age along with co-morbidities such as maternal obesity, black race, history of VTE, and known thrombophillas. Confounding factors include decreased venous outflow in the pelvic vasculature due to uterine compression, decreased mobility and vascular injury from complications such as preeclampsia and eclampsia.[2]

The most current CHEST guidelines that addresses antithrombotic therapy and prevention for pregnant patients was in 2012.[3] It established the use of LMWH for the prevention and treatment of VTE instead of unfractionated heparin (Grade 1B), and to avoid Vitamin K antagonists during gestation (Grade 1A and 1B). It also recommended the use of direct thrombin inhibitors rivaroxaban and apixaban (Grade 1C). Interestingly is divided the cesarean deliveries into 3 groups – if no risk factors then no prophylaxis other than early mobilization. If one major or two minor risk factors then LMWH or mechanical (hose OR pneumatic compression), and if very high risk LMWH with compression stockings and/or pneumatic. But that reference

– Lori Pounds, MD

is over eight years old now, and one must wonder if it the most current. Luckily, there are a plethora of more current consensus guidelines from Canada (2014),[4] Britain's Royal College (2015), the American College of Obstetrics and Gynecology - ACOG (2018)[5] and the American Society of Hematology - ASH (2018).[6] The ACOG guideline has a pregnancy specific Caprini scoring system for risk and wonderful tables for ante/postpartum treatment. The 2018 ASH is very specific with just eleven-line items of recommendations. Once again, LMWH is the sole winner for treatment and prophylaxis. They also recommend it for superficial thrombosis over no anticoagulant – the older Canadian guideline was more specific with LMWH treatment for bilateral superficial thrombosis, very symptomatic and if ≤5 cm from the deep system.[4] I would personally have to individualize the patient and am more inclined to use the Canadian guidelines. All guidelines are in consensus against the use of thrombolysis for DVT or PE unless it is a dire situation.

Keeping these updated consensus statements in my peripheral brain (Dropbox) for that special population is necessary to quickly answer consults and provide the best care for two lives.

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Breakthrough VTE: The Devil is in the Details

–Peter Henke, MD

– Peter Henke, MD

Venous thromboembolism (VTE) is a common and potentially deadly disease that has not significantly decreased in incidence over the last several decades. In hospitalized medical and surgical patients, VTE prophylaxis is a standard of care and has gained recognition as an important quality measure.[1] However, prophylaxis is variable with some hospitals and institutions applying this well over 95% and others at much lower levels. Chemoprophylaxis, namely low dose anticoagulation, is generally considered safe and effective for at risk patients. Nonetheless, despite often prescription of optimal VTE prophylaxis, there are many reasons that a VTE may still occur.

'Breakthrough' VTE is defined as a VTE that occurs despite appropriate prescription of prophylaxis. There are multiple factors that may account for this,[2] and I will delineate some of these. First, it is important to accurately risk stratify patients to determine if they're low risk or high risk. This is commonly done with the Caprini Risk Assessment tool in surgical patients and the Padua or Improve scoring tools for medically ill patients. If a patient is deemed low risk, such as a Caprini Risk score <5, they may go without any chemoprophylaxis (Figure 1). However, most patients are high

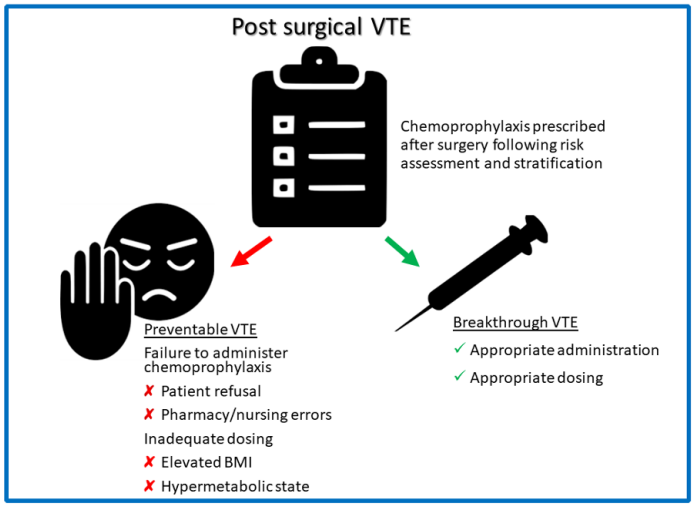

Figure 1. Etiology of postoperative VTE

risk after a major surgical procedure and these patients, in general, will receive chemoprophylaxis and/or mechanical prophylaxis. One scenario in which prophylaxis breaks down is patient refusal of the chemoprophylaxis, often due to the injection regimen. Secondly, it may be that the chemoprophylaxis is not ordered accurately, and the nurse may not give the dose or schedule that is ordered. Thirdly, mechanical prophylaxis such as sequential compression devices, need to be applied to the patient for them to work. Not uncommonly, these are uncomfortable and patients take them off, and thus they are not effective. Lastly, the dose of chemoprophylaxis is that they may be sub therapeutic. Patients who are in a septic hypermetabolic state or those who are morbidly obese may not receive the same therapeutic effect of chemoprophylaxis as compared with a more normal body mass index.

There are those patients who indeed have received a 'defect free' chemoprophylaxis regimen, but still may develop a VTE; this is the biological breakthrough VTE, and likely accounts for about 50% of the total. Factors associated with this include the following history of VTE, age, intraoperative transfusion, and length of stay (unpublished data). These factors bare further study and maybe signals for an even more aggressive empirical anticoagulation approach or use of an alternative agent as outlined in Dr. Wakefield's article.

The use of empirical anticoagulation has recently been highlighted by the COVID-19 epidemic. This was initially observed with H1N1 viral pneumonia at our institution whereby empirical anticoagulation decreased death and pulmonary thrombosis.[3] A similar picture does occur in many of the very ill COVID-19 patients, and we have adopted an aggressive anticoagulation stance with these patients which we believe are beneficial.[4] Early data suggests that bleeding complications have not been significant.

Overall, breakthrough VTE is multifactorial, and solidifying best practices such as ensuring prescription of and receipt of prophylaxis for the patient is the first step (Figure 2). Ultimately, defining the patients at highest biological risk for VTE that may occur despite defect free prophylaxis, and may benefit from empirical anticoagulation, is a critical unanswered question.

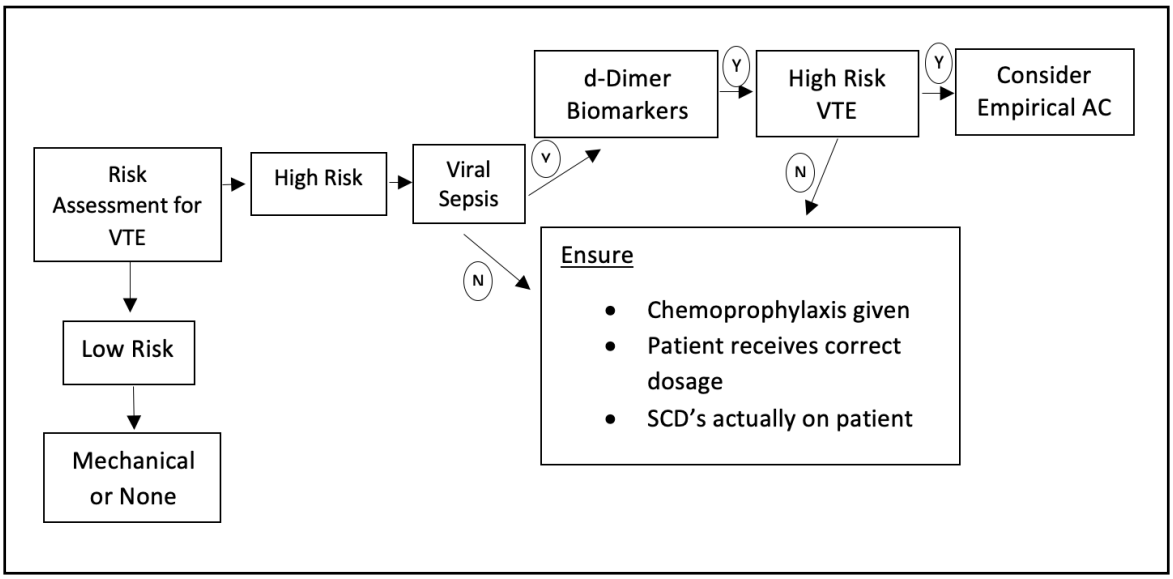

Figure 2. Suggested algorithm for preventing VTE in high risk patients

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Perioperative Anticoagulation for Heparin Induced Thrombocytopenia Patients

–Lakshmi Ayyagari, MD and Maxwell Janosky, MD

Heparin has been widely used for decades for perioperative anticoagulation during vascular surgeries. However, occasionally heparin can cause a paradoxical hypercoagulable syndrome in a minority of patients, called heparin induced thrombocytopenia (HIT). Elective vascular procedures should be postponed at least 100 days after a HIT diagnosis due to the risk of thrombotic complications during this period.

However, urgent vascular intervention may become necessary or the need for elective vascular procedures beneficial. Our current data supports argatroban, an IV direct thrombin inhibitor (DTI), as the de facto substitute in this setting. Other DTIs include bivalirudin and lepirudin, which are renally excreted and are used less frequently. Small retrospective cohort studies demonstrated higher bleeding incidence with lepirudin.

Argatroban reversibly inhibits thrombin, has a short half-life (40-50 min)[A], is hepatically metabolized, and is often given as a continuous IV infusion (CIVI) targeting 1.5-3x the patient's baseline PTT or upper limit of normal starting at 2mcg/kg/min[B]. An argatroban bolus is frequently used in the setting of Percutaneous Coronary Intervention (PCI), is the only drug FDA approved anticoagulant in this setting and for which clear data and guidelines exist.3 Extrapolating this data for use in vascular surgeries may be practical. In PCI, a 350mcg/kg bolus over 3-5 minutes is followed by 25mcg/kg/min CIVI. Activated clotting time (ACT) should be checked 5-10 minutes after completion of the bolus with target ACT 300-450 seconds. If the ACT is <300, an additional 150mcg/kg bolus should be given, and the infusion increased to 30 mcg/kg/min. If low ACTs continue, additional boluses can be given and the infusion increased to a maximum of 40mcg/kg/min. Whereas, if the ACT is >450, the infusion should be decreased to 15mcg/kg/min.

Having a substitute for heparin in cases of HIT, such as argatroban, can enable these patients to safely benefit from vascular interventions.

– Maxwell Janosky, MD

Footnotes

A. half-life up to 3 hour in severe hepatic impairment

B. 0.5mcg/kg/min for hepatic impairment

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Inflammatory Inhibition to Treat DVT The Future is Near

–Thomas Wakefield, MD, Suman Sood, MD, Daniel Myers, DVM

University of Michigan, Ann Arbor, MI

– Thomas Wakefield, MD

– Suman Sood, MD

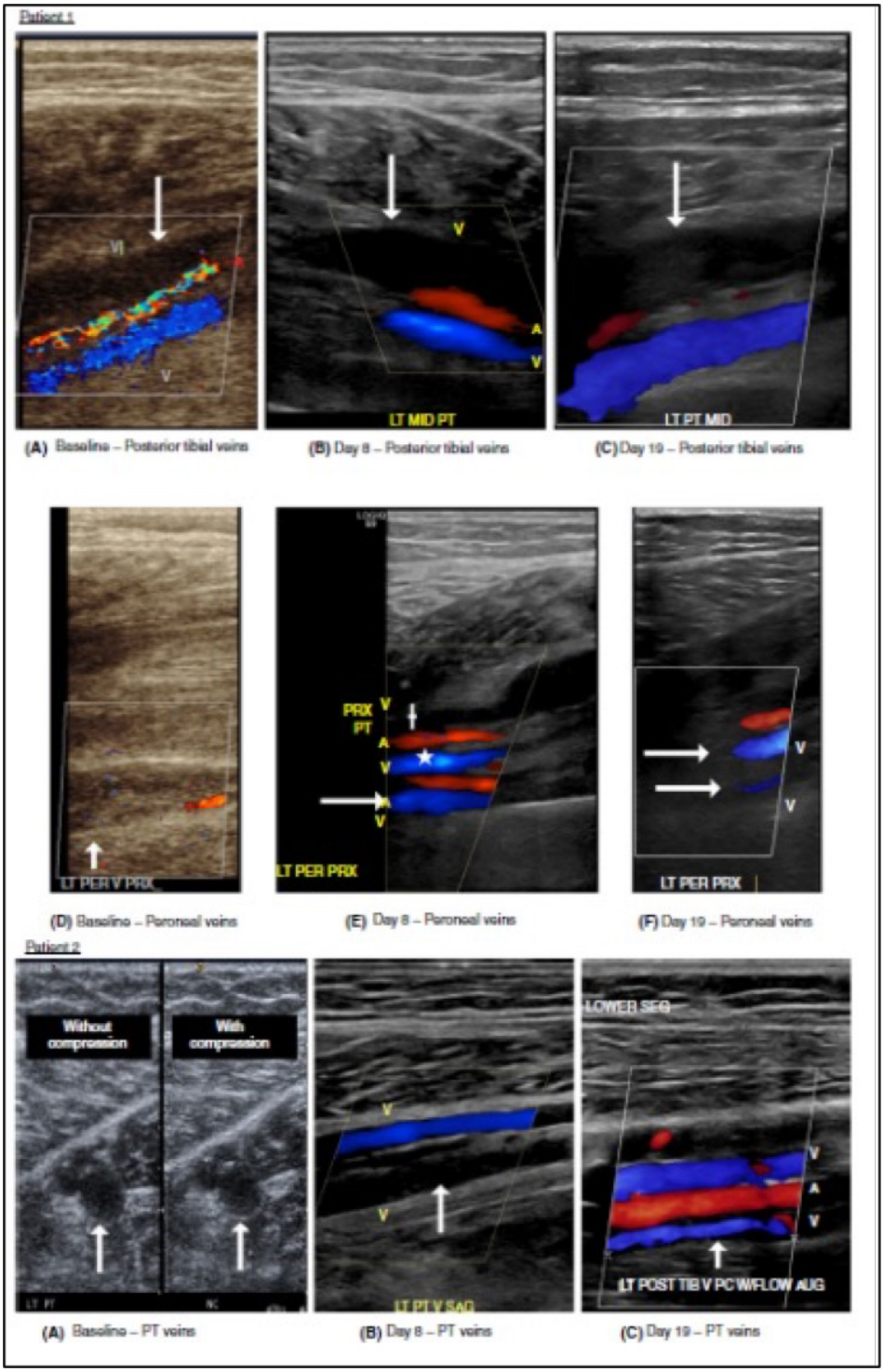
– Daniel Myers, DVM

Venous thromboembolism (VTE) is a very common and deadly problem. It has been estimated that VTE, which includes deep venous thrombosis (DVT) and pulmonary embolism (PE) affects up to 900,000 individuals with 300,000 deaths per year, and the incidence, it seems, has not declined in the recent past and in fact, may be increasing. The current agents that we have available to treat VTE are all based on inhibiting portions of the coagulation pathway and as such, they all can cause bleeding. Additionally, current treatment does not prevent the development of post-thrombotic syndrome, which can occur in up to 40-60% of cases after iliofemoral DVT.

The pathophysiology of venous thrombogenesis has been driven by the concept of Virchow's triad: endothelial injury, circulatory stasis, and blood hypercoagulability. Inflammation was added when it was demonstrated that P-selectin, a glycoprotein, when inhibited decreased thrombosis in a primate AV fistula model. Early work suggested that both P-selectin and E-selectin were critical to the thrombotic process. In 5 studies, vein re-opening was significantly higher with inhibitors to P-selectin and its receptor PSGL-1 compared to saline, and similar to low molecular weight heparin (LMWH). Inflammation as measured by magnetic resonance venography (MRV) using Gadolinium enhancement was significantly decreased in the P-selectin treated groups when compared to saline, with no significant differences to LMWH treated animals. In a further study using an anti-P-selectin aptamer and an aptamer against von Willebrand Factor (vWF), the best recanalization noted was with the anti-P-selectin aptamer, whether given therapeutically (2 days after thrombus initiation) or prophylactically (just before thrombosis). Additionally, P-selectin inhibition resulted in less vein wall fibrosis, without any increase in coagulation times.

E-selectin is also a key regulator of thrombus formation and fibrin content. In studies using an E-selectin inhibitor (GMI-1271) in a stasis mouse model of IVC thrombosis, the inhibitor was equivalent to LMWH for limiting thrombosis, but with a marked decrease in tail vein bleeding time. This and other data led to a clinical study (supported by NIH VITA) in which GMI-1271 was given to normal volunteers in a dose-dependent fashion as a one-time dose, then as a daily dose for 5 consecutive days compared to enoxaparin or saline, and finally to treat calf vein DVT. There were no serious adverse events. GMI-1271 did not affect thromboelastographic parameters, lower levels of sEsel were found in GMI-1271 treated subjects (as expected for on-target effects), and there was lower leukocyte and platelet activation in GMI-1271 treated volunteers (determined by MPO and MAC-1 levels). Two patients with calf

vein DVT were treated with GMI-1271 with a 5-day intravenous course. Both patients had immediate relief of pain and significant increase in vein recanalization by day 19 (Figure 1). The effectiveness of GMI-1271 has been confirmed in a primate model of proximal iliac vein thrombosis, both inhibiting thrombosis and vein wall fibrosis (supported by NIH VITA). This strongly suggests that E-selectin has a significant role in both thrombogenesis and post-thrombotic syndrome after DVT and may be an excellent pharmacologic target.



Patient 1: serial ultrasound results

(A) Baseline longitudinal ultrasound showing the thrombosed posterior tibial vein (arrow). Note the color flow showing the patent paired posterior tibial vein in blue.
(B) Day 8 longitudinal ultrasound again demonstrating the thrombosed posterior tibial vein (arrow). Note the color showing the patent paired posterior tibial vein in blue.
(C) Day 19 longitudinal ultrasound again demonstrating the thrombosed posterior tibial vein (arrow). Note the color showing the patent paired posterior tibial vein in blue.
(D) Baseline longitudinal ultrasound showing the thrombosed paired peroneal veins (arrows). (E) Day 8 longitudinal ultrasound now showing 1 peroneal vein now open (arrow). The open posterior tibial vein is also seen (*), along with the thrombosed posterior tibial vein (+).
(F) Day 19 longitudinal ultrasound showing now both peroneal veins open in the proximal calf (white arrows).

Patient 2: serial ultrasound results

(A) Baseline transverse ultrasound showing thrombosis of one of the 2 paired posterior tibial veins, without (WO) compression and with (W) compression. Arrows demonstrate the thrombus.
(B) Day 8 longitudinal ultrasound showing the thrombosed PT vein (arrow). Note the color flow showing the patent paired posterior tibial vein in blue.
(C) Day 19 longitudinal ultrasound now showing that both posterior tibial veins are patent. Note the reopened posterior tibial vein (arrow) and the second patent posterior tibial vein in blue

From:
Devata S, Angelini DE, Blackburn S, Hawley A, Myers DD, Schaefer JK, Hemmer M, Magnani JL, Thackray HM, Wakefield TW and Sood SL. Use of GMI-1271, an E-selectin antagonist, in healthy subjects and in 2 patients with calf vein thrombosis. Res Pract Thromb Haemost. 2020;4: 193-204.

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Join us at the American Venous Forum's 33rd Annual Meeting!

–Kathleen Ozsvath, MD

– Kathleen Ozsvath, MD
AVF Program Committee Chair

The American Venous Forum looks forward to having your participation at the 2021 meeting in San Antonio Texas.

We are excited about a robust program. We welcome our colleagues locally, nationally and from around the world.

The AVF program committee is committed to providing an experience where experts in the field of venous and lymphatic disease can share their research, debate their opinions, and educate in a collegial, comfortable environment. Abstract presentations will include treatment of superficial disease, deep venous disease, and COVID-19 research as it relates to venous disease. New technology and new techniques will surely bring robust discussion.

Highlights of the program include Scientific Sessions, The Day of Science, The Sumner Session, The International Session, The Villavicencio Session, The Presidents Session and The Eugene Strandness Lecture. We welcome the young career vein specialists and trainees with programming specifically geared to help as they embark on a career that includes the treatment of venous disease.

Safety is our number one priority. We are working closely with the resort team to insure a safe meeting!

We hope to see you in San Antonio 2021!

AVF Advocacy Corner

The American Venous Forum is Now Represented in the American Medical Association!

–Mark Iafrati, MD, BK Lal, MD, Dan Monahan, MD

The long-awaited moment has finally arrived.

As of August 12, 2020, the AVF achieved admittance to AMA representation. This adds yet another benefit of AVF membership, as your voice will now be heard in the AMA as we will advocate for you and your patients. In addition, by 2023, the AVF will join the AMA House of Delegates, and participate in the RBRVS Update (RUC) and CPT Coding Committees, which advise CMS on matters related to physician reimbursements. Needless to say, having a voice in that process will be very important.

Membership in the AMA has been a long-standing goal of the AVF as we have strived to expand our ability to represent our membership in all aspects of venous and lymphatic care, including reimbursement. Last spring, AVF President BK Lal initiated a new attempt to achieve AMA membership leading to RUC status. AVF Executive Director John Forbes and a subgroup of the Health Policy Committee, led by Dan Monahan, pursued the application process. The application was completed on time, and despite pandemic related delays, our admittance was made official in record time. The AVF will now enter the AMA with representatives at the national meetings and will be able to keep our members updated on relevant matters.

It is important for an organization's AMA membership that a (certain percentage?) minimum number of their members be active AMA members. Each AVF member's AMA membership strengthens the AVF's voice in advocating for the interests of our physicians and patients. We encourage all our members to continue or initiate AMA membership, and designate the AVF as your base organization.

Thank you to all our members who have participated in the AMA, and know that it has made, and will continue to make, a difference for the AVF.

– Mark Iafrati, MD

– BK Lal, MD

– Dan Monahan, MD

AVF Member Community

Find a Vein Specialist

The AVF Find a Vein Specialist Directory, located under the Patient tab on the **website**, is a great resource for patients to find a venous specialist. Patients can quickly search for a physician by entering at least one search item like last name, state or zip code. They can also view a complete listing of all Vein Specialists by clicking on *VIEW ALL LISTINGS*.

Being listed in "Find a Vein Specialist" is a valuable benefit for AVF members while helping patients in need. If you are a member of the AVF and haven't enrolled yet, you can do it so quickly and easily at **Vein Specialist Directory**.

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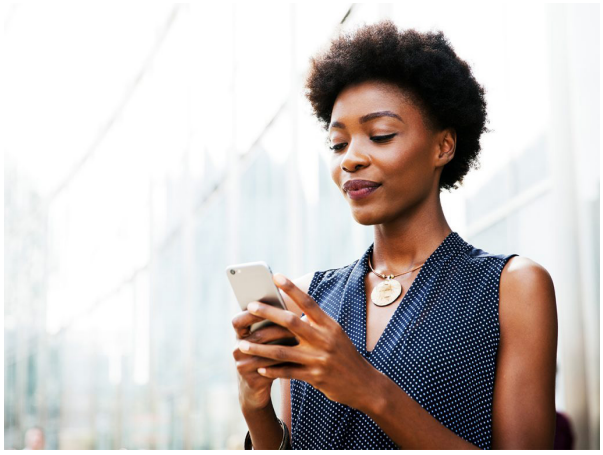

New AVF Members – Welcome to the Community!

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Angela Diamond	*Physician Membership - National, Washington, U.S.*
Hector Pietravallo	*Physician Membership - International, Recoleta, Argentina*
Matthew Pergamo	*Member in Training, New York, U.S.*
Reid Mahoney	*Member in Training, Honolulu, Hawaii*
Daniel Carregal	*Member in Training, Horizonte , Brazil*

AVF Member Community

Social Media Committee

–Nasim Hedayati, MD, FACS, RPVI

– Nasim Hedayati, MD, FACS,

The social media committee of the American Venous Forum has been active for the past two years. The committee members "meet" on a monthly basis and work on discussing content for the various social media platforms of the American Venous Forum to inform members and trainees about upcoming meetings and educational sessions, late breaking studies/abstracts, updated AVF guidelines and news from other societies that our team considers important and of interest to our members. We welcome feedback on content and how we can best serve our members. We hope to reach as many of you as possible. Please follow us on:

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Nasim Hedayati, MD, FACS, RPVI
Chair, Social Media Committee, American Venous Forum
Professor, Department of Surgery
University of California, Davis Medical Center

Journal Watch

–Anil Hingorani, MD

– Anil Hingorani, MD

With the novel coronavirus (COVID-19) sweeping the globe and causing significant morbidity and mortality, urgent clinical questions regarding the prevention, diagnosis and treatment of venous thromboembolism (VTE) in patients have emerged. While new data are forthcoming data everyday, these set of guidelines prepared by an American College of Chest Physicians® (CHEST) panel of experts provides 21 optimal strategies when treating patients with VTE and COVID-19. Read the full text here.

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The Summit, hosted by Stanford University School of Medicine and LE&RN, will feature talks by leading authorities in lymphatic medicine. It will be led by Stanley G. Rockson, M.D., the Allan and Tina Neill Professor of Lymphatic Research and Medicine at Stanford University. Recently announced LE&RN Centers of Excellence will be represented. Attendees will be welcomed by LE&RN Spokesperson and Academy Award winner Kathy Bates.

See the full program of speakers and topics on LE&RN's website.

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American Venous Forum
Promoting venous and lymphatic health

VEIN SPECIALIST PUBLICATION

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American Venous Forum
Promoting venous and lymphatic health

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