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SEEKING A PERFECT RISK-BENEFIT BALANCE IN TREATING VTE

At the dawn of the 21st century, venous thromboembolism (VTE) treatment remained in the dark ages. Backed by an MD and a legacy of paternalistic practice, we convinced patients to do what now seems unthinkable. Unfractionated heparin may come from pigs and cattle, but we infused it like snake oil. Patients spent 5 (or more) days in the hospital chasing partial thromboplastin times and enduring stops and starts with repeated blood draws. Finally, we discharged them on the only drug awful enough to require an eponymous nursing position and clinic.

Our approach to balancing risk-benefit was equally primitive. Patients diagnosed with their first VTE were given the proverbial "trial of life." They generally received 3-6 months of anticoagulation before being advised to stop, with guidance as blithe as it was vague: "If you feel short of breath, go to the emergency room." It mattered not whether their initial clot was a pulmonary embolism or a deep vein thrombosis. Or whether there was comorbid cardiopulmonary disease. If they had a second VTE, assuming they survived it, the initial treatment regimen (including the hospitalization) was repeated.

By 2008, our guidelines had incorporated data showing that for unprovoked events, fixed courses of anticoagulation provided less mitigation than delay. This pushed risk-benefit analysis to the forefront of all things VTE. Physicians, and patients, were forced to balance VTE recurrence with bleeding risk and decide whether to stop treatment after 3 months or continue it indefinitely. Shortly thereafter, the novel blood thinners hit the market, making indefinite anticoagulation slightly more palatable.

Meanwhile, the field continued to refine risk calculations. D-dimer testing had its moment in the sun before being knocked down a notch by the 2016 CHEST VTE guidelines. Lower-extremity ultrasound also helped, but it wasn't quite clear where and how it fit into overall risk after accounting for other factors. Both have given way to more complicated models that perform well in particular situations. There are even online risk calculators to help battle the viscous time scarcity epidemic afflicting all 21st century medicine clinics.

The latest breakthrough reduces bleeding more than VTE recurrence risk. In 2013, the AMPLIFY-EXT trial showed that after 6 months of full-dose treatment, a half dose of apixaban reduced bleeding without increasing recurrence risk. Not to be outdone, these findings were replicated using rivaroxaban in the EINSTEIN CHOICE study. Taken together, AMPLIFY-EXT and EINSTEIN CHOICE provide strong evidence that for those with a first episode of VTE with clinical equipoise (defined as uncertainty as to whether risk-benefit favored continued treatment) after 6 months of

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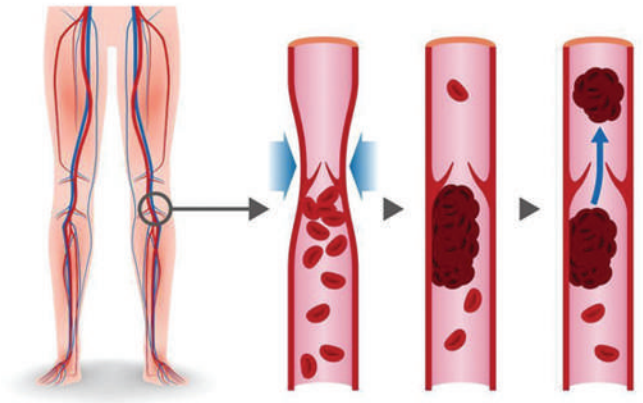
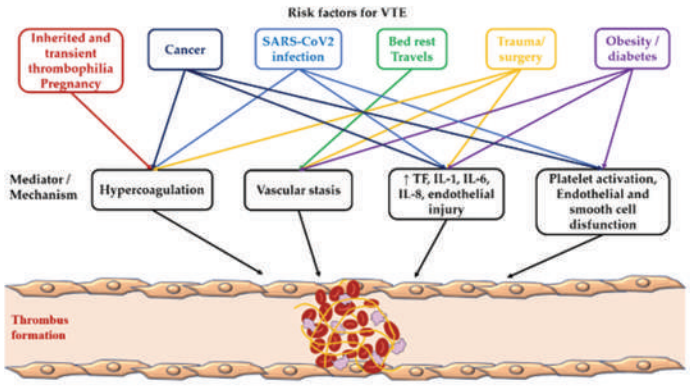
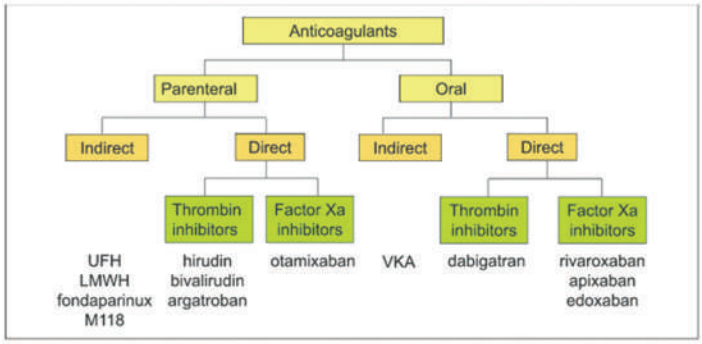
full-dose anticoagulation, reduced doses of apixaban or rivaroxaban are excellent options. The most recent iteration of the CHEST VTE Treatment Guidelines endorses this practice.

Because AMPLIFY-EXT and EINSTEIN CHOICE had the "clinical equipoise" proviso in their inclusion criteria, cancer patients were largely excluded. There's generally not equipoise for them; VTE recurrence risk is expected to remain indefinitely high, requiring indefinite protection. So, the practice of reduced dosing could not be generalized to cancer-related VTE — until now.

The API-CAT investigators recently published reduced-dose data for cancer patients. Turns out, it works! As the accompanying editorial points out, advances in cancer treatment have led to increased survival times. Longer survival with active cancer translates to more cancer-related VTE. The API-CAT data are a critical addition to the literature. The sooner they're incorporated, the better.







CHEST GUIDELINES:

CHEST (the American College of Chest Physicians) develops and publishes clinical practice guidelines for chest diseases, focusing on evidence-based recommendations for diagnosis and treatment.

The American College of Chest Physicians (CHEST) Antithrombotic Therapy for Venous Thromboembolism Disease evidence-based guidelines were recently published and the following are 11 key points about this updated guideline document:

1.For VTE without an associated cancer diagnosis, all direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban) are recommended over vitamin K antagonist (VKA) therapy (all Grade 2B) and VKA therapy is recommended over low molecular weight heparin (LMWH; Grade 2C).

2.For VTE associated with cancer, LMWH is recommended over VKA (Grade 2B) or any direct oral anticoagulants (all Grade 2C).

3.Anticoagulants should stop after 3 months of therapy in patients with an acute, proximal deep venous thrombosis (DVT) provoked by surgery rather than shorter or longer treatment courses (Grade 1B).

4.Anticoagulants should also be stopped after 3 months in patients with a proximal DVT or pulmonary embolism (PE) provoked by a nonsurgical transient risk factor over shorter or longer courses (Grade 1B for high bleeding risk patients, Grade 2B for low or moderate bleeding risk patients).

5.Anticoagulation should be given for 3 months in patients with a first unprovoked VTE and a high risk of bleeding (Grade 1B), but should be extended without a scheduled stop date in patients with a low or moderate risk of bleeding (Grade 2B).

6.For patients with acute VTE who are treated with anticoagulation, the guideline recommends against the use of an inferior vena cava filter (Grade 1B).

7.For patients with an unprovoked proximal DVT or PE who are stopping anticoagulant therapy, the guideline suggests the use of aspirin over no aspirin to prevent recurrent VTE if there are no contraindications to aspirin therapy (Grade 2B).

8.For patients with acute DVT, the guideline recommends against the use of compression stockings routinely to prevent the post-thrombotic syndrome (Grade 2B).

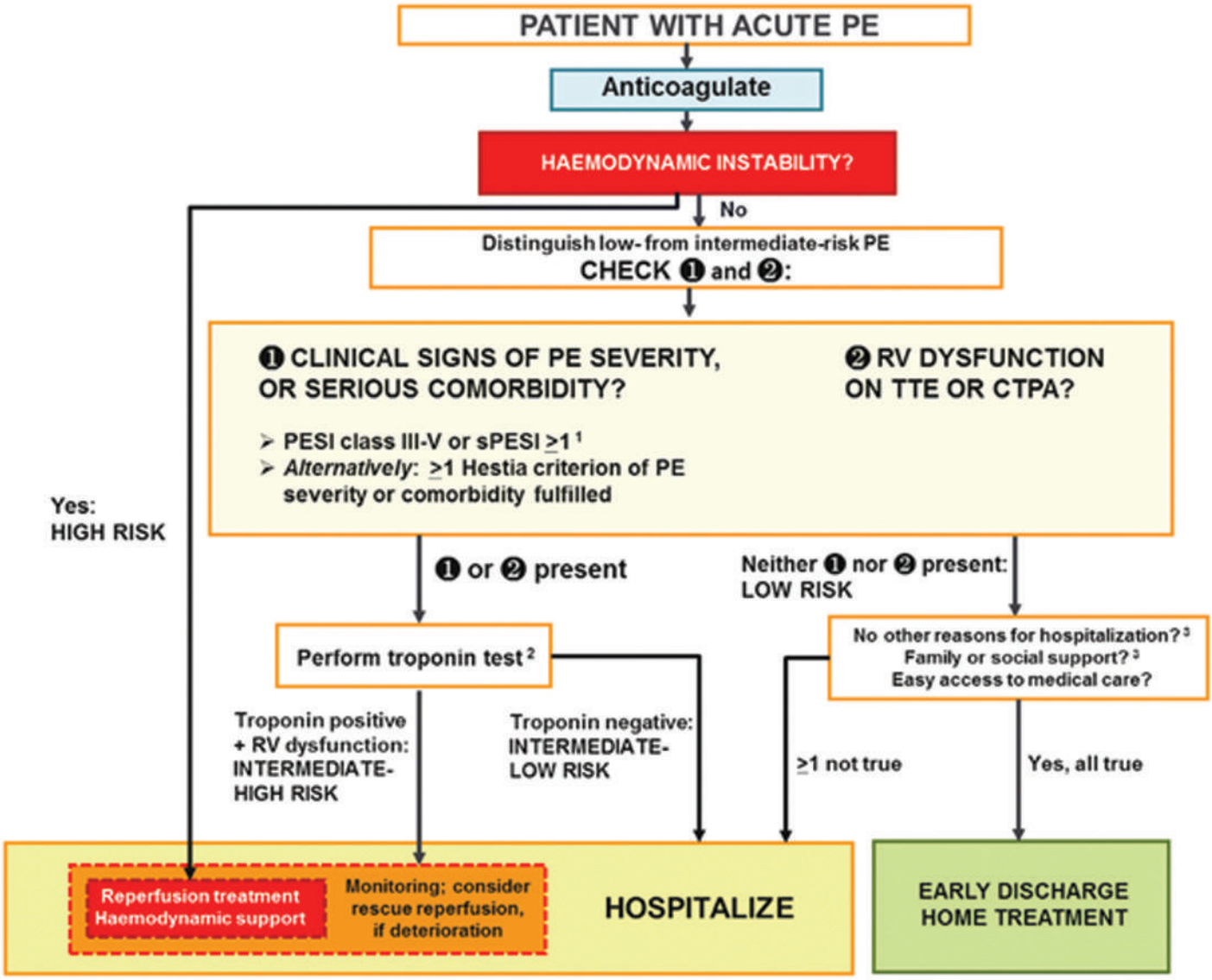
9.For patient with subsegmental PE and no DVT, the guideline suggests clinical surveillance over anticoagulation when the risk of VTE recurrence is low (Grade 2C). The guideline recommends the use of anticoagulation over surveillance when the risk of VTE recurrence is high (Grade 2C).

10. For patients with an acute PE and hypotension (massive PE), the guideline recommends the use of thrombolytic therapy (Grade 2B), preferring systemic therapy over catheter-directed thrombolytic therapy (Grade 2C).

11. For patients with recurrent VTE while treated with a non-LMWH anticoagulant, the guideline recommends changing to LMWH therapy (Grade 2C). If patients suffer a recurrent VTE while on LMWH treatment, the guideline recommends increasing the LMWH dose (Grade 2C).

Drug	CrCl ≥50 mL/min	CrCl 30-49 mL/min	CrCl 15-29 mL/min	CrCl <15 mL/min or ESRD on RRT
VKA	If TTR ≥70%	If TTR ≥70%	If TTR ≥70%	If TTR ≥70%
Dabigatran	150 mg bid[a] (or 110 mg bid)	150 mg bid (or non-US, 110 mg bid)[a]	× (Outside US) 75 mg bid in US[a]	×
Rivaroxaban	20 mg qd	15 mg qd	15 mg qd	×
Apixaban	5 mg bid[b]	5 mg bid[b]	2.5 mg bid	× (Outside US) 5 mg bid in US only[b]
Edoxaban	60 mg qd	30 mg qd	30 mg qd	×

- Closely monitor renal function, especially in NOAC users.
- Schedule for frequent clinical follow-up, look for development of new cardiovascular risk factors, comorbidities.
- Reassess and address bleeding risk factors.



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