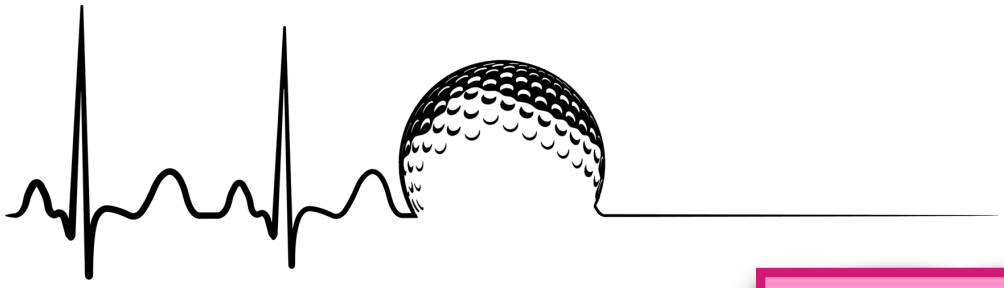
JOURNAL CLUB

The Set Up

Dagnabbit!!! You're back at your desk in the charting room, ready to put in orders for the chest pain patient you just saw. You notice on your computer screen that the patient is 65 years-old - he seemed to be younger than that when you were talking to him. You had already mentally ruled out acute PE with PERC, but that was before you realized the patient's true age. What now? You decide to play the D-dimer game and lose. D-dimer is 950. All the other labs are normal. Chest x-ray and EKG both normal. Double Dagnabbit!!! Well, time for a CTPE you suppose. But wait! What about the IV contrast shortage? What about the radiation? What about the length of ED stay? The patient himself had absolutely no other complaints, and is anxious to leave after his 12-hour wait What to do, what to do?



Article #1

P: Clinical suspicion of PE
P: Low probability for PE, but not PERC (-)
I: YEARS + age-adjusted D-dimer algorithm
C: Age-adjusted D-dimer algorithm
O: Venous thromboembolism at 3-months

Presenters: Drs. Alena Hoover and Benjamin Miller

Journal Club
When?: 05.19.2022
Host: Sarah Herron
846 N. Main St
Naperville, IL 60563
Start 06:30pm

Freund Y et al. Effect of a Diagnostic Strategy Using an Elevated and Age-Adjusted D-Dimer Threshold on Thromboembolic Events in Emergency Department Patients With Suspected Pulmonary Embolism: A Randomized Clinical Trial. *JAMA*. 2021 Dec 7;326(21):2141-2149. doi: 10.1001/jama.2021.20750. **A cluster-randomized, crossover, noninferiority trial in 18 emergency departments (EDs) in France and Spain. Patients (N = 1414) who had a low clinical risk of PE not excluded by the PERC rule or a subjective clinical intermediate risk of PE were included. Each center was randomized for the sequence of intervention periods. In the intervention period (726 patients), PE was excluded without chest imaging in patients with no YEARS criteria and a D-dimer level less than 1000 ng/mL and in patients with 1 or more YEARS criteria and a D-dimer level less than the age-adjusted threshold (500 ng/mL if age <50 years or age in years × 10 in patients ≥50 years). In the control period (688 patients), PE was excluded without chest imaging if the D-dimer level was less than the age-adjusted threshold. The primary end point was venous thromboembolism (VTE) at 3 months. The noninferiority margin was set at 1.35%. At 3 months, VTE was diagnosed in 1 patient in the intervention group (0.15% [95% CI, 0.0% to 0.86%]) vs 5 patients in the control group (0.80% [95% CI, 0.26% to 1.86%]) (adjusted difference, -0.64% [1-sided 97.5% CI, -∞ to 0.21%], within the noninferiority margin). Of the 6 analyzed secondary end points, only 2 showed a statistically significant difference in the intervention group compared with the control group: chest imaging (30.4% vs 40.0%; adjusted difference, -8.7% [95% CI, -13.8% to -3.5%]) and ED median length of stay (6 hours [IQR, 4 to 8 hours] vs 6 hours [IQR, 5 to 9 hours]; adjusted difference, -1.6 hours [95% CI, -2.3 to -0.9]).**

The Set Up Cont…

Despite your best efforts to avoid the CT, you ended up ordering one anyway. Apparently he had a good friend die of a massive PE two years ago, and when he started having chest pain, his main goal was to make sure he didn't have a PE himself. Fine. The patient wants a CT. So be it. And… wouldn't you know it. The CT is positive. You get a call from the radiologist that the patient has a small left subsegmental PE. The patient is subsequently sent for a doppler lower extremity ultrasound, which is negative. It turns out that the patient juggles chainsaws blindfolded on a unicycle for a living and would prefer to avoid systemic anti-coagulation. However, he wants to know what his risk for a recurrent clot is if he doesn't start a DOAC.

Article #2

P: Isolated subsegmental PE
P: Negative bilateral doppler lower extremity ultrasound at time of PE and 1-week later
I: No anti-coagulation
C: N/A
O: Venous thromboembolism at 3-months

Presenters: Drs. Dylan Rupska and Nick Systma

Le Gal G et al. Risk for Recurrent Venous Thromboembolism in Patients With Subsegmental Pulmonary Embolism Managed Without Anticoagulation : A Multicenter Prospective Cohort Study. *Ann Intern Med*. 2022 Jan;175(1):29-35. doi: 10.7326/M21-2981. Epub 2021 Nov 23. **Multicenter prospective cohort study at 18 different sites over 10 years. Enrolled 292 patients with isolated subsegmental PE and no DVT at the time of diagnosis and 1-week later. Patients with ISSPE and no DVT were managed without anti-coagulation. The primary outcome was recurrent DVT within 3-months of follow-up. Recruitment was stopped prematurely because the predefined stopping rule was met after 292 of a projected 300 patients were enrolled. Of the 266 patients included in the primary analysis, the primary outcome occurred in 8 patients, for a cumulative incidence of 3.1% (95% CI, 1.6% to 6.1%) over the 90-day follow-up. The incidence of recurrent venous thromboembolism was 2.1% (CI, 0.8% to 5.5%) and 5.7% (CI, 2.2% to 14.4%) over the 90-day follow-up in patients with single and multiple isolated subsegmental pulmonary embolism, respectively. No patients had a fatal recurrent pulmonary embolism.**

The Set Up Finito…

Six weeks have gone by, and your blind chainsaw juggler is back in the ED for worsening chest pain and an episode of syncope. Luckily we wasn't on his unicycle at the time of symptom onset. Repeat CT now shows a proximal left sided PE. He reluctantly agrees to start a treatment this time. Thing is, the Super Bowl of blind chainsaw unicycle juggling is next Tuesday, and he's got a shot at the title. Can't stop. Won't stop. Beyond the obvious, he wants to know what is his level of risk for bleeding while on the anti-thrombotic.

Article #3

P: Adults with confirmed PE
I: Development and validation of a novel risk score to predict major bleeding
C: VTE-BLEED, RIETE, and BACS models
O: Ability to estimate rates of major bleeding

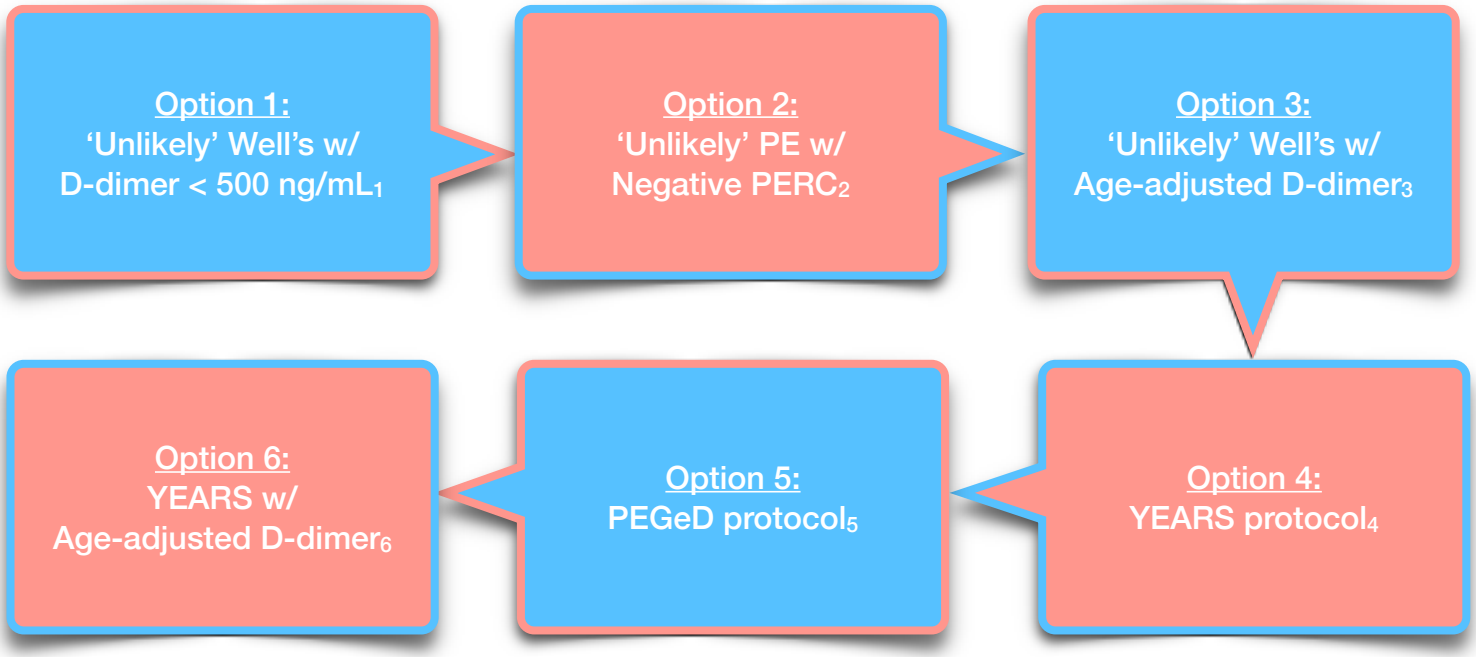
Presenters: Drs. Ramya Kondaveeti and Patsi Whiteside 🎂

Chopard R et al. An Original Risk Score to Predict Early Major Bleeding in Acute Pulmonary Embolism: The Syncope, Anemia, Renal Dysfunction (PE-SARD) Bleeding Score. *Chest*. 2021 Nov;160(5):1832-1843. doi: 10.1016/j.chest.2021.06.048. Epub 2021 Jul 2. **Authors built a risk score to predict early (up to hospital discharge) major bleeding events in acute PE patients. The model was validated internally. Performance of the novel score was compared with that of the VTE-BLEED (Venous Thrombo-Embolism Bleed), RIETE (Registro informatizado de la enfermedad tromboembólica en España; Computerized Registry of Patients with Venous Thromboembolism), and BACS (Bleeding, Age, Cancer, and Syncope) models. Authors identified three predictors for the occurrence of 82 major bleeds (3.0%; 95% CI, 2.39%-3.72%): Syncope (+1.5); Anemia, defined as hemoglobin <12 g/dL (+2.5); and Renal Dysfunction, defined as glomerular filtration rate <60 mL/min (+1 point) (SARD). The PE-SARD bleeding score was calculated by summing all the components. Overall, 52.2% (95% CI, 50.29%-54.11%) of patients were classified as low bleeding-risk (score, 0 point), 35.2% (95% CI, 33.39%-37.04%) intermediate-risk (score, 1-2.5 points), and 12.6% (95% CI, 9.30%-16.56%) high-risk (score >2.5 points). Observed bleeding rates increased with increasing risk group, from 0.97% (95% CI, 0.53%-1.62%) in the low-risk to 8.93% (95% CI, 6.15%-12.44%) in the high-risk group. C-index was 0.74 (95% CI, 0.73-0.76) and Brier score 0.028 in the derivation cohort.**

Pulmonary Embolism: Diagnostic Strategies

It's prerequisite - to be a self respecting emergency medicine physician, the diagnosis of pulmonary embolism must be considered on each and every patient. It's in our marrow. It's part of our essence. Chest pain - What about a PE? Dyspnea - Think about PE. Syncope - Did you think about PE? Dizziness - PE. Upper abdominal pain - PE. Pneumonia - PE. COVID - PE. Cardiac arrest - PE. Peri-arrest - PE. Toothache - PE? PE. PE. PE. PE. PE. PE. PE is all around us. PE is everything and everywhere all at once. PE unites us.

Arggggghhhhhhh!!! Really!??? We're really going to talk about PE again? Didn't we already discuss PE during a journal club this academic year? Yes. Yes we did. Well, why do we have to talk about PE again? I just told you. PE is the fiber of our being. We live to find PE with our every life's breath. Fortunately for us, our rabid, and insatiable appetite for searching for PE currently exists in the golden age of diagnostic strategies for *ruling out* PE. There are sooooo many options currently available to us:



Obviously, we'll be discussing option #6 at journal club, but what are the pearls in regards to the other six options? Before we get into it let's just agree on a few things: #1) the criterion of 'unlikely' Well's is defined by the two-tiered model score of ≤ four; #2) other risk stratification PE scores exist, namely the revised Geneva score; #3) Well's and Geneva are are basically statistically equivalent[7,8]; #4) Well's and the revised Geneva scores have questionable value in the pregnant and postpartum population (Well's AUC 0.67, 95% CI 0.54-0.79; revised Geneva 0.64, 95% CI 0.52-0.76)[9], in critically ill adult patients (Well's AUC 0.634; revised Geneva 0.546)[10], and in patients with COVID (Well's AUC 0.54)[11]; and #5) Comparing the accuracy of good ol' fashioned clinical gestalt the to both the Wells and the revised Geneva score produced AUCs of 0.81 (95% CI 0.78 to 0.84) for gestalt assessment, 0.71 (95% CI 0.68 to 0.75) for Wells,

and 0.66 (95% CI 0.63 to 0.70) for the revised Geneva score[12].

Now that the ground rules are out of the way: Option #1 - 'Unlikely' Well's and a D-dimer of < 500. What does this mean clinically? In 2008, the Christopher group revealed the VTE incidence at 3-months in PE unlikely patients with a negative D-dimer was 0.5%[13]. Further, a meta-analysis including 4 studies (n = 1660 patients) illustrated a pooled incidence of VTE in these such patients as 0.34% (95% CI 0.036-0.96%), resulting in a NPV of 99.7% (95% CI: 99.0-99.9%)[1]. This option is the straight up meat and potatoes classic traditional D-dimer cut-off 1957 Chevrolet Bel-Air.

Well's Criteria for PE

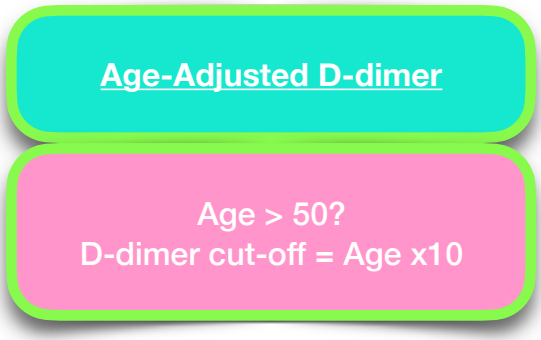
	Points
Signs/Symptoms DVT	3
PE #1 diagnosis	3
HR > 100 bpm	1.5
Immobile/Surgery	1.5
Previous DVT/PE	1.5
Hemoptysis	1
Malignancy w/in 6 mos.	1

Option #2 - 'Unlikely' PE and negative PERC. Get this. The PERC rule was originally derived way back in 2004[14] - even before my old a$$ was a resident! In that original study, the sensitivity of PERC was 96% in low-risk PE patients (defined via gestalt), and 100% very-low risk patients. The 2008 multi-center PERC validation study enrolled ~8000 patients[2]. Clinicians were asked to risk stratify patients based on clinical gestalt assigning a pretest probability estimate for PE as < 15%, 15-40%, or > 40%. Patients were then classified as very low risk if the clinician encoded a gestalt pretest probability of < 15% and were also PERC (-). At initial testing and within 45 days, 561 patients (~7%) were (+) for venous thromboembolism (VTE). In the very low risk group, 1.0% (95% CI 0.6-1.6%) were VTE(+) or died within 45 days. As a diagnostic test, low suspicion plus PERC negative had a sensitivity of 97.4% (95% CI 95.8-98.5%), and a specificity of 21.9% (95% CI 21.0-22.9%). What does it all mean? It means that if a patient is considered low risk PE (via clinical gestalt, or perhaps Wells), and is PERC negative, the chance of PE is < 2% (actually, it is < 1.6%, but keep in mind that it is not 0%!).

PERC

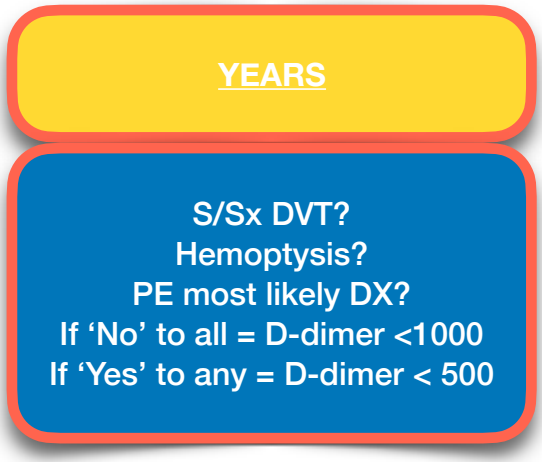
Age ≥ 50?
HR ≥ 100?
O2sat on RA < 95%?
Unilateral leg swelling?
Hemoptysis?
Trauma or Surgery (w/in 4 wks)?
Prior DVT/PE?
Estrogen Use?

Moving on to Option #3 - 'Unlikely' Wells and Age-Adjusted D-dimer. We're now in the mid 2010s, and the ADJUST-PE Study is published in JAMA[3]. In this trial, all ED patients with a suspected PE were risk stratified by Well's or Geneva and had their D-dimer drawn.



In the trial, the age-adjusted D-dimer cutoff was defined as age × 10 in patients 50 years or older. Enrolled patients with a D-dimer value between the conventional cutoff of 500 µg/L and their age-adjusted cutoff had PE ruled-out (e.g.; a 78 year-old patient with a D-dimer of 650 doesn't get a CTPE). The 3-month failure rate in patients who had D-dimer level higher than 500, but below their age-adjusted cutoff was 1 of 331 patients (0.3%; 95% CI, 0.1%-1.7%). Further, in patients that were ≥ 75 years-old, the age-adjusted cutoff increased the proportion of patients in whom PE could be excluded on the basis of D-dimer alone from 6.4% [95% CI, 4.8%-8.5%) to 29.7% [95% CI, 26.4%-33.3%), without any additional false-negative findings.

Similar to ADJUST-PE, the YEARS protocol of option #4 involves differential D-dimer cut-off values[4]. The YEARS rule itself consists of three different items: clinical signs of DVT, hemoptysis, and whether PE is the most likely diagnosis. In patients without any of the YEARS criteria, PE is ruled-out if the D-dimer is < 1000. If ≥ 1 YEARS criteria are present, the traditional D-dimer cut-off of 500 becomes the PE exclusion threshold. In the original YEARS study, CT was not indicated in 48% of YEARS patients versus 34% of patient's assessed via Well's and a traditional D-dimer cuff-off of 500. This lead to 18 missed PEs in ~3000 total study patients (0.61% [95% CI: 0.36-0.96%]) within 3 months. The original YEARS study took place in the Netherlands. However, one year after being published, the protocol was applied to a U.S. population with similar results: using the YEARS adjustment, 67% of patients would not have been referred for CT (vs. 53% via traditional D-dimer cut-off), and 6 PEs would have been missed (0.5%, 95%CI: 0.18-1.1%)[15].



It's worth mentioning that the YEARS protocol has also been studied in pregante, er.. prangent, umm I mean pargant… dang it!!! PREGANANANT patients!! In the Artemis study, 510 pregnant women were screened for PE using YEARS. Twenty patients were diagnosed with PE at baseline. CT was not indicated by YEARS in 39% of patients (95% CI: 35-44%). Of note, the efficiency of YEARS was highest during the first trimester, and lowest during the third trimester - CT pulmonary angiography was avoided in 65% of patients who began the study in their first trimester vs. 32% who began the study in their third[16].

Lastly we come to option #5 - the Pulmonary Embolism Graduated D-dimer (PEGeD) protocol[5]. Basically with PEGeD, pulmonary embolism is ruled out if a patient is low clinical pretest probability via Well's plus has a D-dimer < 1000. Alternatively, the

PEGeD

Well's low risk; D-dimer < 1000

D-dimer cut-off returns to the traditional < 500 if a patient is non-Well's low risk. The PEGeD study enrolled ~ 2,000 patients, of which ~7% had PE. Of the ~1300 patients with low risk or moderate risk Well's score, and a negative D-dimer (< 1000 or < 500, respectively), none had a PE during 3 month follow-up (95% CI 0%-0.29%).

Alright. So them's the options huh? It now begs to question - which of the options available to us is the best? This is where is gets a little tricky, because each option performs differently in different healthcare settings; i.e. in the ED vs. primary health care vs. inpatient hospitalized care. In general, in healthcare settings with a higher prevalence of PE, each diagnostic strategy misses more patients with PE and identifies less patients in whom PE can be ruled out without imaging. In a systematic review and meta-analysis (n ~35K pts) from earlier this year, the PERC algorithm in combination with an 'unlikely' PE per Well's score has a failure rate of 1.12% (95% CI 0.74-1.70%) specifically for "self-referral emergency care" patients (i.e., patients coming to the ED without a referral by a PCP or specialist)[17]. The efficiency of PERC in this patient population was ~20%, which means that in self-referral emergency care patients, the PERC algorithm precludes additional testing for PE in ~ 1 out of every 5 patients. The authors of this study validated only the PERC option in patients coming to the ED on their own accord. But but but, in "referred secondary care" patients (i.e., patients sent to the ED by their primary physician for PE work-up), the Well's (or Geneva) + fixed traditional D-dimer cut-off showed the lowest failure rates (~0.3% [95% CI ~0.2-0.75%]), followed by Well's (or Geneva) + age-adjusted D-dimer (~0.7% [95% CI ~0.4-0.9%]). Failure rates for YEARS (3.06% [95% CI 2.47-3.79%]), and PEGeD (2.95% [95% CI 2.34-3.71]) were much higher in this group of patients. Interestingly, PERC performed poorly in this population with a failure rate of 6.01% (95% CI 4.09 to 8.75%). Further, the efficiency of PERC in this patient population was 10%; i.e, in 1 out of 10 referred patients PERC rules-out PE without any additional testing.

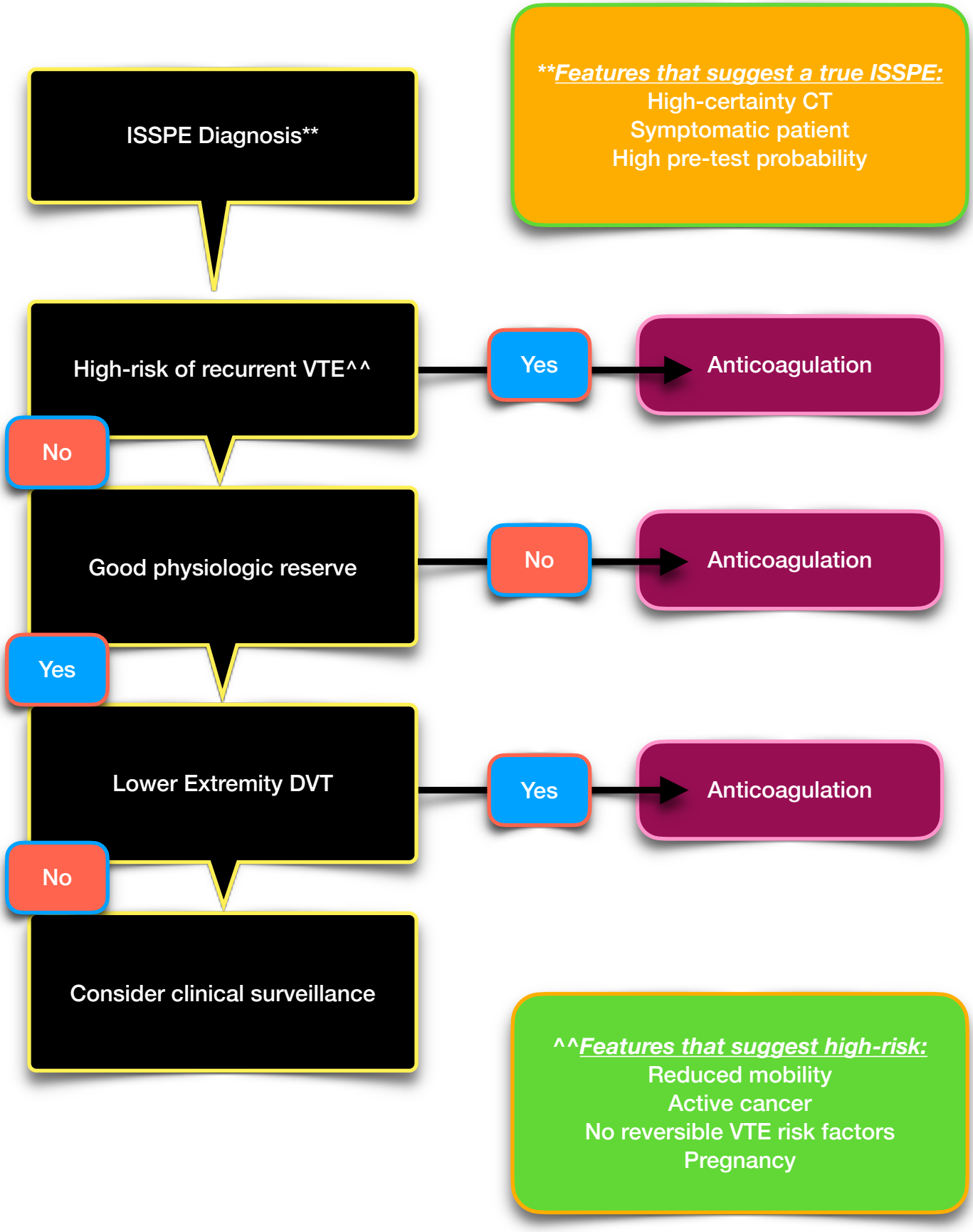
Should you be concerned about these failure rates? Keep in mind that no diagnostic algorithm will ever yield a failure rate of 0%. Actually, even the reference standard CTPE has been shown to a have a failure rate of 1.20% (95% CI 0.48-2.60) for missed VTE at 3-months follow-up[18]. Consequently, it is argued that any diagnostic strategy with a failure rate of ~1-2% is a safe as referring all patient for CTPE[17]. So for us, for now, PERC still seems to reign supreme. But the other strategies still have value with documented sensitivities in the mid 90%s and above[17].

Subsegmental PE Stuff

Say that three times fast. Subsegmental PE Stuff. Subsegmental PE Stuff. Subsegmental PE Stuff. The consensus radiologic definition of isolated subsegmental PE (ISSPE) is: a contrast defect in a subsegmental artery, that is, the first arterial branch division of any segmental artery independent of artery diameter, visible in at least two subsequent axial slices, using a computed tomography scanner with a desired maximum collimator width of ≤1 mm[19]. Right. Okay. Let's just say that a ISSPE is a PE that is confined to the subsegmental pulmonary arteries. Genius. Let's digress. Nowadays, more and more PEs are being diagnosed (an ~ 81% increase following the initial introduction of CTPE[20]), and more patients are staying in the hospital with their PEs, but length of hospitalization, 30-day readmission rates, and mortality rates are all declining[21]. Why? Well, it probably has something to do with ISSPEs. CT technology has advanced to a degree in which ISSPEs are increasingly diagnosed (i.e., from ~ 5% to more than 10% of all PE). So what? Anti-thrombotic therapy for ISSPE may or may not be beneficial because 1) the abnormalities are small and unlikely to adversely effect cardiopulmonary function, and 2) may resolve on their own without therapy. Further, ISSPE are often false-positive findings on CT[22]. Thus, it may be safe to hold refrain from treating ISSPE with anti-thrombotic medications.

What do we know about clinical outcomes of ISSPE? In 2020, the Spanish RIETE (Registro Informatizado Enfermedad TromboEmbólica) investigators (Dios MÍo) used data from their prospectively collected database to investigate outcomes of patients anti-coagulated for their symptomatic PE[23]. ~16K patients were included in the study, with 834 (5.2%) having an ISSPE. Among those patients with an ISSPE, ~25% also had a concomitant lower extremity DVT (~30% had no DVT, and ~50% had no LE ultrasound documented). The main findings of this study was the rate of recurrent PE was twofold higher in patients with subsegmental PE vs in those with segmental (HR, 2.13; 95% CI, 1.16-3.85) or more central PE (HR, 1.89; 95% CI, 1.12-3.13). Further, after stratifying patients with ISSPE according to ultrasound imaging in the lower limbs, the rates of PE recurrences were similar in patients with DVT, in patients without DVT, and in those with no ultrasound imaging. The authors concluded that the risk of PE recurrence was not influenced by anatomic location. Additionally, know that for ISSPE patients on anti-coagulation, the RIETE hombres y mujeres calculated event rates (per 100 patient years) of 2.58 for recurrent PE, 4.83 for major bleeds, and 12.1 deaths.

So what? So what?!!?? So what do we do with these ISSPEs?? According to the Second Update of the CHEST Guideline and Expert Panel for Anti-thrombotic Therapy for VTE Disease[22]: ***"In patients with subsegmental pulmonary embolism and no proximal DVT in the legs, who have a (i) low risk for recurrent VTE, we suggest clinical surveillance over anticoagulation (weak recommendation, low-certainty evidence) or (ii) high risk for recurrent VTE, we suggest anticoagulation over clinical surveillance (weak recommendation, low-certainty of evidence)."*** Easy peasy. Can I get that in flowchart form? Why yes. Yes you can. Basically, the management strategy for ISSPE looks something like this[22, 24]:


**Features that suggest a true ISSPE:
High-certainty CT
Symptomatic patient
High pre-test probability
ISSPE Diagnosis**
High-risk of recurrent VTE^^
Yes
Anticoagulation
No
Good physiologic reserve
No
Anticoagulation
Yes
Lower Extremity DVT
Yes
Anticoagulation
No
Consider clinical surveillance
^^Features that suggest high-risk:
Reduced mobility
Active cancer
No reversible VTE risk factors
Pregnancy

PE and Risk of Major Bleeding

How often do you think about bleeding events as a consequence of anti-thrombotic therapy? It's so easy to just 'click' the order button, and voila, the patient is on heparin. Tisk tisk. The RIETE investigators (¡Órale!) were at it again, this time in regards to providing estimates for case fatality rate of recurrent VTE and major bleeding during anti-coagulation[25]. The study included ~ 42K patients from their registry who received a mean of 7.8 +/- 0.6 months of anti-coagulation. In this study, the overall case fatality rate of recurrent VTE was was 12.1% (95% CI, 10.2-14.2), while that of major bleeding was 19.7% (95% CI, 17.4-22.1)[25]. Note: Major bleeding is defined as 1) fatal bleeding, and/or 2) symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intraarticular or pericardial, or intramuscular with compartment syndrome, and/or 3) Bleeding that causes a fall in hemoglobin level of ≥ 2 g/dL, or leads to transfusion of two or more units of whole blood or red cells[26]. In a recent study of anti-coagulated PE patients, major bleeding was identified as strong predictor of in-hospital (OR 7.7, 95% CI 2.3-25.8) and 1-year mortality (HR 3.6, 95% CI 2.0-6.6)[27].

What are risk factors for major bleeding while on anti-coagulant therapy? The fine folks over at the American College of Chest Physicians defined a whopping eighteen!! These are as follows[28]:

Age > 65	Liver failure	↓ anti-coag control
Age > 75	Thrombocytopenia	Poor functional capacity
Previous bleeding	Previous CVA	Recent surgery
Cancer	Diabetes	Frequent falls
Metastatic cancer	Anemia	EtOH abuse
Renal failure	Anti-platelet Rx	NSAID use

The translation of all of these risk factors into clinical practice is difficult to say the least. As such, several risk scores have been developed to predict the likelihood of major bleeding in stable VTE patients on anti-coagulation. The study we're discussing by Chopard et al compares a novel bleeding score to three previously published scores: VTE-BLEED, RIETE (¡Viva España!), and BACS. We're going to focus here just on VTE-BLEED. Why? Both RIETE and BACS include patients receiving thrombolytic therapy (BACS was actually developed for use *in* patients receiving thrombolysis). So, VTE-BLEED was derived via a post-hoc analysis of the pooled RE-COVER studies, which were two double-blind randomised sister trials that evaluated pradaxa vs. standard treatment in ~ 5K VTE patients. The original VTE-BLEED identified six differently weighted variables: (acti**V**e cancer [2 points], males with uncontrolled hyper**T**ension [1 point], ana**E**mia [1.5 points], history of **BL**eeding [1.5 points], ag**E** ≥60

years [1.5 points] and renal **D**ysfunction [1.5 points]) as predictors of major bleeding in patients with VTE on stable oral anticoagulation with either warfarin or pradaxa. A score of at least two points has been shown to be associated with an odds ratio (OR) of 5.0 (95% CI, 3.5–7.1) and 4.0 (95% CI, 2.5–6.4) for bleeding complications in the pooled derivation RE-COVER studies and the initial external validation (HOKUSAI-VTE study FYI), respectively[29-30]. VTE-BLEED has been further validated in a "real-world" cohort of PE patients that revealed a score of ≥2 points was associated with a similar odds ratio for major bleeding (OR 3.7, 95% CI 1.1–13.0). Additionally, this "real-world" study also described a GFR < 30 (OR 6.0, 95% CI 1.8–19.8) and previous surgery within 4 weeks (OR 3.6, 95% CI 1.4–9.3) as factors associated with major bleeding.

What does this all mean? Well, first of all, you shouldn't send a patient at high risk for bleeding home. So, you can forget about running the patient through the ol' sPESI or HESTIA machine. (Oooooo…wait a second…what's that. That's another journal club all together. That's what that is). Second, bleeding risk has implications for treatment. The Chopard et al discussion has a few suggestions in this regard. The one that I'd like to focus on is low-molecular weight heparin vs. unfractionated heparin. It seems that the go to parenteral anti-coagulant is more often than not UFH. You may be surprised to know that the Cochrane Database of Systematic Reviews first published a paper on this very topic in the year 1999 (*Sings* - I was dreamin' when I wrote this, forgive me if it goes astray. Look it up younglings). The original Cochrane report has since been updated 3 times. The most recent update is from 2017. This review includes 29 total studies (n ~10K pts). After three months, treatment with LMWH vs. UFH resulted in lower rates of recurrent VTE (OR 0.71, 95% CI 0.56-0.99), a greater reduction in thrombus size (OR 0.71, 95% CI 0.61 to 0.82), and less major hemorrhage (OR 0.69, 95% CI 0.50 to 0.95). Additionally, there was a trend in overall improved mortality with LMWH, although this did not reach statistical significance (OR 0.84, 95% CI 0.70 to 1.01)[31] - barely. So, as suggested in the Chopard article, maybe our VTE admits with high-bleeding risks should be started on LMWH initially. Hmmm.

Two More Studies….

Alight ladies and gentlemen. Just two more recent-ish PE related studies that you should know: PROPER[32] and HOME-PE[33]. The PROPER trial is essentially a RCT of the PERC rule. In the trial, 14 different emergency departments in France were randomized to either a PERC-based PE work-up strategy or a "usual care" strategy. Each center participated in their randomized strategy for 6-months then switched to the opposite strategy after a 2-month "wash-out" period. The trial enrolled patients with new onset or worsening chest pain or dyspnea and a low clinical probability of PE per physician gestalt. In the PERC group, PE was excluded without additional testing when the PERC score was zero as per the norm. If PERC was positive, the "usual" diagnostic strategy was applied. The "usual" strategy consisted of an age-adjusted D-dimer followed by CTPE. If the CT was inconclusive, patients underwent V/Q scan and lower extremity doppler ultrasound. Patients were followed for 3-months. The primary outcome was the occurrence of symptomatic VTE not diagnosed during the inclusion visit. This study was of a non-inferiority design which set its margin for the difference

of the primary outcome between the two groups at 1.5%. This meant that if the upper bound of the one-sided CI of the difference between both groups was > 1.5%, the non-inferiority hypothesis would be rejected (see the JC-document from March). A total of 1749 patients completed the trial. Alright. So what did they find? A PE was diagnosed at initial presentation in 26 patients in the control group (2.7%) vs 14 (1.5%) in the PERC group (difference, 1.3% [95% CI, –0.1% to 2.7%]; *P* = .052). In regards to the primary outcome, one PE (0.1%) was diagnosed during follow-up in the PERC group vs none in the control group (difference, 0.1% [95% CI, –∞ to 0.8%]). The lone missed PE was a previously healthy young male with chest pain. The patient was PERC-negative on index visit and initially discharged, but seen again the next day because of persistent pain. When he presented the second time, his D-dimer was positive; however, his CTPE was inconclusive. He was admitted, had negative lower-limb Doppler ultrasound and a V/Q scan which revealed subsegmental defects. He was treated with a DOAC for 6 months, and had a normal scan at follow up after conclusion of his anti-thrombotic therapy - Yay! The authors rightly concluded that ***"Among very low-risk patients with suspected PE, randomization to a PERC strategy vs conventional strategy did not result in an inferior rate of thromboembolic events over 3 months."***

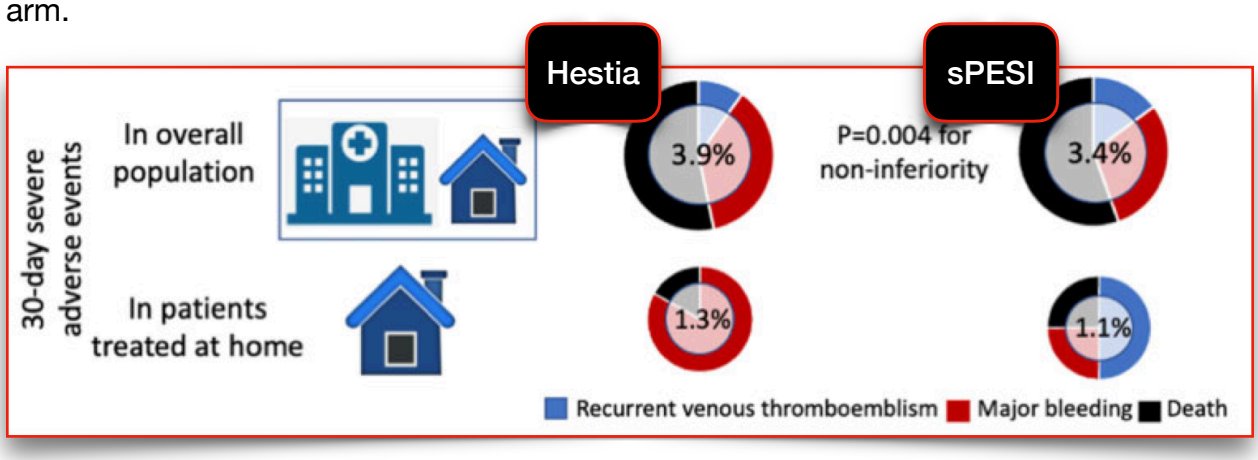
Everyone happy? There's always a catch. You should know that one of the reasons this study was done is that PERC has been challenged in Europe. A previous study in Switzerland reported PERC failure rates of ~5% overall and ~6% in patients with a low pretest probably[34]. Why has PERC performed differently in the US vs across the pond? We touched on this earlier in the document, but it bears repeating. In general, when the prevalence of PE is high, each diagnostic strategy misses more patients with PE. It just so happens that our European brothers and sisters get more PEs. A lot more PEs. Two published reports have both defined an overall PE prevalence of ~4x higher in European ED patients versus those in the US[35,36]. But it is not the higher PE prevalence across the pond that is of interest in PROPER. In fact, it is the opposite. The PE prevalence in each group was ~ 3%. Contrast this to PE prevalence rates of 11-27% in previous European studies[35, 36]. Why so low? Remember, the study enrolled only patients that were already determined to be low risk PE per clinician gestalt. Take a look at the baseline characteristics of these patients (above figure). In general, these patients were young with few co-morbidities. So essentially, the study used a diagnostic strategy to rule out a diagnosis in patients not really at risk for the

Table 1. Baseline Characteristics for Patients Receiving Initial Pulmonary Embolism Rule-Out Criteria vs Standard Treatment (Control)

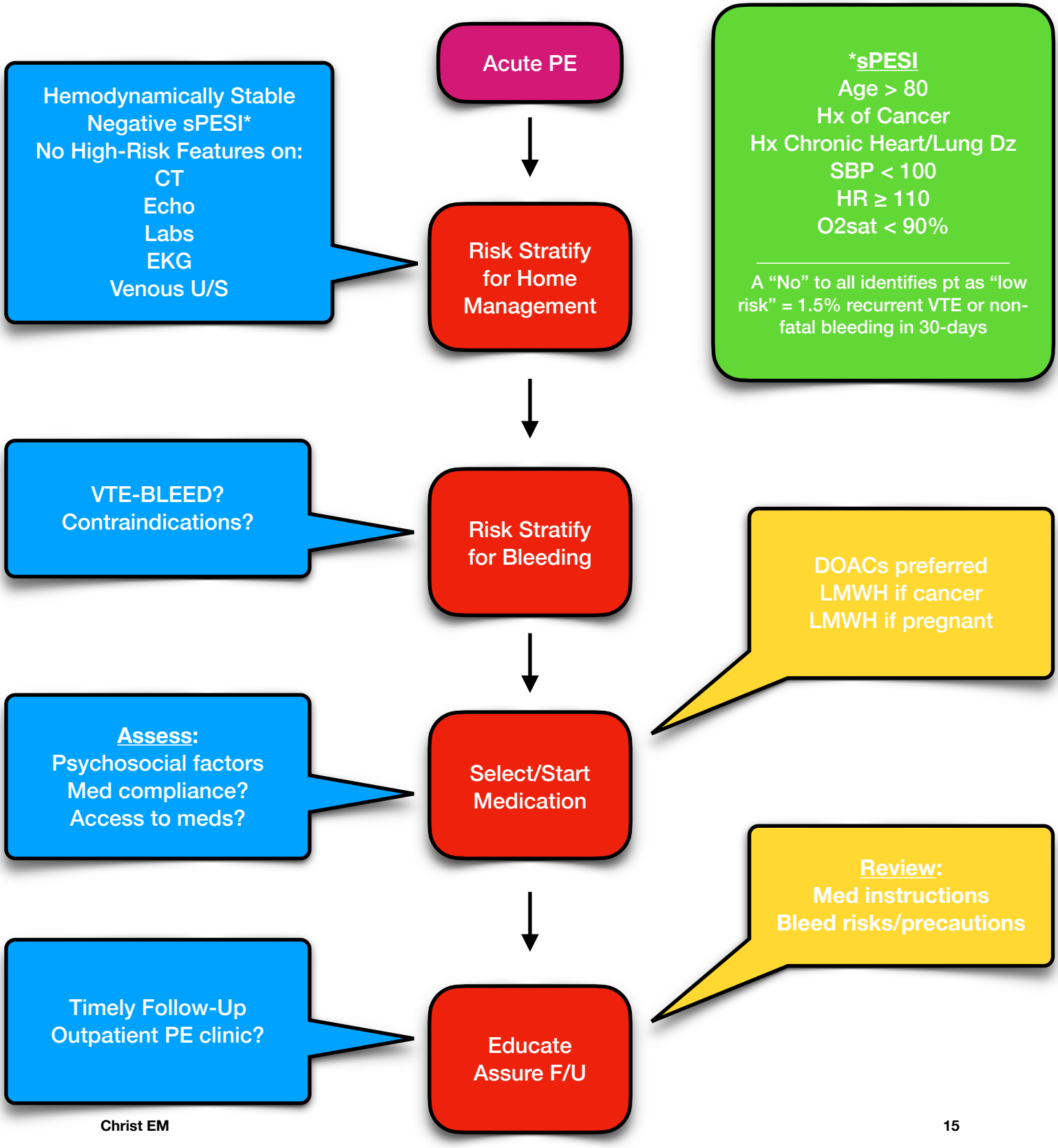
	No. (%)	
Variable	PERC (n = 962)	Control (n = 954)
Age, mean (SD), y	44 (17)	45 (17)
Women	460 (48)	520 (54)
Comorbidities		
Chronic respiratory insufficiency	28 (3)	25 (3)
Chronic heart failure	20 (2)	19 (2)
Stroke	11 (1)	6 (1)
Emergency department presentation		
Chest pain	876 (91)	863 (91)
Shortness of breath	311 (32)	405 (43)
Syncope	12 (1)	19 (2)
Heart rate, mean (SD), beats/min	82 (16)	86 (18)
Heart rate >100 beats/min	128 (13.3)	185 (19.4)
Respiratory rate, mean (SD), breaths/min	18 (4)[a]	18 (5)[b]
Spo_2, median (IQR), %	99 (97-100)[a]	99.0 (97-100)[b]
Spo_2 < 95%	51 (5.3)[a]	49 (5.2)[b]
Systolic blood pressure, mean (SD), mm Hg	136 (19)[a]	137 (21)[b]
Temperature, mean (SD), °C	36.7 (0.5)[a]	36.7 (0.5)[b]
Risk factors for PE		
Estrogen use	62 (7)	98 (10)
Clinical signs of DVT	39 (4)	64 (7)
Past history of PE or DVT	29 (3)	41 (4)
Surgery or trauma requiring immobilization within 1 mo	16 (2)	32 (3)
Hemoptysis	8 (1)	10 (1)
Active malignancy	8 (1)	10 (1)

diagnosis. Of course the study was successful! I'm pretty sure we can PERC out my entire my daughters' second grade class as well. You get what I mean. Always pay attention to the overall prevalence of disease in these types of studies, and how it relates to previously published rates.

Alright, alright, alright. Last study. HOME-PE. The most recent ACEP clinical policy on acute VTE was published in 2018[37]. One of the critical questions asked in this document is whether or not it is safe to initiate anti-coagulation and discharge home adult ED patients diagnosed with acute PE. The writing committee answered with a level C recommendation: **"*Selected patients with acute PE who are at low risk for adverse outcomes as determined by Pulmonary Embolism Severity Index (PESI), simplified PESI (sPESI), or the Hestia criteria may be safely discharged from the ED on anticoagulation, with close outpatient follow-up.*"** Yes!! Yes!!! I mean, a level C recommendation isn't great…. but I'll take it. Acute PE? ✓ Wanna go home? ✓ Which pharmacy do you use? Walgreens in Bridgeview? ✓ Doctor Done. Discharge. See you later! (Actually, let's hope we don't see this person later). Anyway, ACEP recommends using either sPESI or Hestia to risk stratify acute PE patients for discharge. Which strategy is better? Enter the HOME-PE study. This trial was published in August of last year. The trial was conducted in 26 different hospitals in Europe. Included patients had objectively confirmed PEs within 24-hours of enrollment. Patient's were excluded if they had hypotension or couldn't follow-up in 30-days. The patients were randomized to either the Hestia rule or sPESI. If a patient stratified as low risk via either rule, they were discharged home within 24-hours of randomization (Note: ~2/3 patients were admitted observation; ~ 1/3 patients were discharged directly home from ED;). In each group, the evaluating physician could overrule the stratification. The evaluating physicians also took into account the patient's preference via shared decision making. When discharged, the patients received therapeutic anti-coagulation at the discretion of the physician (~85% received a DOAC). The primary outcome was a composite rate of recurrent VTE + major bleeding + all cause mortality within 30 days. The analysis of the primary outcome was via non-inferiority design with a 2.5% risk difference as margin. The study enrolled a total of 1974 patients (n = 984 Hestia; and 986 PESI). The 30-day primary outcome occurred in 3.82% in the Hestia arm and in 3.57% (32/896) in the sPESI arm, for an adjusted absolute difference of 0.20% (upper limit of the one-sided 95% CI 1.43%; P=0.004 for non-inferiority). In the intention-to-treat population, 38.4% of the Hestia patients (378/984) were treated at home vs. 36.6% (361/986) of the sPESI patients (P = 0.41 for superiority), with a 30-day composite outcome rate of 1.33% (5/375) and 1.11% (4/359), respectively. No recurrent or fatal PE occurred in either home treatment arm.



The authors of HOME-PE concluded that either strategy is safe and effective for stratifying acute PE patients for at home treatment. But what would a the framework for managing acute PE patients at home look like? Before I leave you, consider the following as adapted from Kabrhel et al[38]. Thanks for reading. Take care.



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