Critical Review Form
Prognosis

PGY-1

Prandoni P, Lensing AW, Prins MH, et al; PESIT Investigators. Prevalence of Pulmonary Embolism among Patients Hospitalized for Syncope. N Engl J Med. 2016 Oct 20;375(16):1524-1531.

Objectives: **"to assess the prevalence of pulmonary embolism in a large number of patients who were hospitalized for a first episode of syncope, regardless of whether there were potential alter- native explanations for the syncope." (p. 1525)**

Methods: **This prospective cross-sectional study was conducted at 11 Italian hospitals (2 academic and 9 nonacademic) between March 2012 and October 2014. Patients older than 18 years with a first episode of syncope being admitted to the hospital were eligible for inclusion. Exclusion criteria were epileptic seizure, stroke or head trauma as the obvious cause for the loss of consciousness; previous episodes of syncope; ongoing anticoagulation therapy; and pregnancy.**

Trained study physicians assessed patients within 48 hours of admission, including medical history, signs/symptoms of lower extremity DVT, and risk factors for thromboembolism. Using this data, a simplified Well's score for PE was calculated for all enrolled patients. Additionally, a d-dimer was sent for all patients. According to a previously validated algorithm (van Belle 2006), patients with a low-risk Well's score and a negative D-dimer underwent no further testing and were felt not to have a PE. Patients with a high (and presumably moderate) Well's score, or an elevated D-dimer, underwent either CT pulmonary angiography or ventilation-perfusion (V/Q) lung scanning. If a patient died before completion of the diagnostic algorithm, an autopsy was requested.

A total of 2584 patients presented to any of the emergency departments for syncope during the study period. Of these, 717 were admitted, of whom 157 were excluded (118 for anticoagulation, 35 for previous syncope, and 4 for lack of consent), leaving 560 patients with a first episode of syncope in the final analysis. The mean age was 76 years and 39.8% were male.

Guide		Comments
I.	**Are the results valid?**	
A.	**Was the sample of patients**	Presumably yes. Although this study was Italian,

	representative? *In other words, how were subjects selected and did they pass through some sort of "filtering" system which could bias your results based on a non-representative sample. Also, were objective criteria used to diagnose the patients with the disorder?*	and hence may represent a different set of comorbidities compared to those seen in the US, risk of PE should be similar. Of note, **this study only included patients admitted to the medical ward** and only patients with a first episode of syncope. As none of the patients were evaluated for PE in the ED, patients with obvious clinical signs of PE (who would normally be diagnosed in the ED) were still included. Details regarding the hospitals involved in the study (percent with cancer referral centers, numbers of cardiology patients) was not provided. While the authors attempted to define syncope using the objective criteria, objective criteria were not necessarily used to diagnose syncope in the ED. Additionally, it is unclear if any measures were taken to ensure that syncope was the primary cause for admission.
B.	**Were the patients sufficiently homogeneous with respect to prognostic risk?** *In other words, did all patients share a similar risk from during the study period or was one group expected to begin with a higher morbidity or mortality risk?*	No. There were clearly certain patients at higher risk of PE, based not only on Well's score but on risk factors. For example, nearly 11% of patients had clinical signs of DVT and 11% had active cancer. Such patients, when presenting with syncope as the chief complaint, are clearly at much higher risk of PE than the average patient presenting to the ED.
C.	**Was follow-up sufficiently complete?** *In other words, were the investigators able to follow-up on subjects as planned or were a significant number lost to follow-up?*	Yes. All patients either had a negative D-dimer with a low-risk Well's score (n = 330), or underwent CT-PE (n = 180), V/Q scan (n = 49), or autopsy (n = 1). Hence, there was no loss to follow-up.
D.	**Were objective and unbiased outcome criteria used?** Investigators should clearly specify and define their target outcomes before the study and whenever possible they should base their criteria on objective measures.	Yes. The authors used a fairly well validated and sensible algorithm to diagnose PE. PE diagnosis was based on the results of CT, V/Q, or autopsy, with specific criteria for CT and V/Q scans. Exclusion of PE required a low-risk Well's score with a negative D-dimer, which is a very sensible approach.
II.	**What are the results?**	
A.	**How likely are the outcomes over time?** *For the defined follow-up period, how likely were subjects to have the outcome of interest.*	Pulmonary embolism was confirmed in 97 of 560 (17.3%, 95% CI 14.2 to 20.5%) patients admitted for syncope. • PE was ruled out in 330 patients with a low-risk Well's score and a negative D-dimer. • Among 180 patients who underwent CT scan, 72 (40%) were found to have a PE.

		○ 30 of these (41.7%) were in the main pulmonary artery, 18 (25.0%) were in a lobar artery, 19 (24.5%) were in a segmental artery, and 5 (6.9%) were in a subsegmental artery. • Among 49 patients who underwent a V/Q scan, 24 (49.0%) were found to have a PE. ○ The perfusion defect involved > 50% of both lungs in 4 patients (16.7%), 26-50% of the area of both lungs in 8 patients (33.3%), and 1-25% of the area of both lungs in 12 patients (50%). • One patient was found to have PE on autopsy.
B.	**How precise are the estimates of likelihood?** *In other words, what are the confidence intervals for the given outcome likelihoods?*	See above. This was a fairly large study with reasonably narrow confidence intervals.
III.	**How can I apply the results to patient care?**	
A.	**Were the study patients and their management similar to those in my practice?**	No. While this study was conducted in Italy, there is no good reason to think that the overall risk of PE would be higher there than it is here. However, healthcare delivery in Italy is quite different from the US, and it is likely that fewer low-risk patients are admitted (or even seen in the ED) in Italy, resulting in a higher risk population included in the study. There was a high incidence of active cancer (11%) in this population a large number of patients with clinical signs of DVT (11%), and a large number of patients with abnormal vitals signs. On closer inspection, this cohort of patients seems to be at a much higher risk of PE based on history and clinical findings than I suspect our patients being admitted for syncope would be. This is based purely on gestalt, and it would be interesting to see this study reproduced in a large, urban, tertiary care center in the US to see rates of risk factors and clinical signs of venous thromboembolism would be similar.
B.	**Was the follow-up sufficiently long?**	Yes and no. All patients underwent evaluation for PE within 48 hours of hospital admission, which should not only catch all cases of PE, but should not included cases of PE unrelated to the reason for admission or potentially a result of the

		immobilization caused by hospital admission. At the same time, no further clinical follow-up was performed, and the clinical significance of those small PEs diagnosed is uncertain.
C.	**Can I use the results in the management of patients in my practice?**	Uncertain. While this study should certainly heighten awareness to the need to consider PE in the differential diagnosis of patients presenting to the ED with syncope, its results should be validated in additional settings prior to implementing routine PE testing for all syncope patients.

Limitations:

1. **Many factors in this study suggest that this was an older population with a much higher risk of PE than patients admitted for undifferentiated syncope in our practice setting (external validity):**
    a. **The median age of the admitted cohort was 80 years, with an 11% incidence of cancer and an 11.6% incidence of recent immobilization, trauma, or surgery.**
2. **It seems that the majority of patients with PE had significant clinical signs of DVT or PE, and yet none were evaluated for PE prior to admission. In our institution, PE work-up would be performed in the ED for those syncope patients felt to be at high for PE. Excluding those patients diagnosed with PE (rather than syncope) would result in a much lower incidence of PE in patients admitted for undifferentiated syncope. Evidence of this includes the following:**
    a. **40% of patients ultimately diagnosed with PE had "Clinical signs of deep-vein thrombosis."**
    b. **Nearly 45% of patients with PE were tachypneic and a third were tachycardic. Unfortunately, the authors do not report the incidence of hypoxemia.**
3. **The clinical significance of those pulmonary emboli diagnosed is uncertain as no further clinical follow-up was performed. Given that 19 PEs diagnosed on CT were segmental and 6 were subsegmental, and that 12 PEs seen on V/Q involved 1-25% of lung, there is a reasonable chance that several of those PEs diagnosed were either false positive or clinically insignificant (and not responsible for syncope).**

Bottom Line:

This prospective, cross-sectional study conducted at 11 hospitals in Italy suggests a high rate of PE in patients being admitted to the hospital for undifferentiated syncope (17.3%, 95% CI 14.2 to 20.5%). Multiple factors suggest that this is a gross overestimation of the rate of PE in truly undifferentiated syncope patients, including the extremely high rate of clinical signs of DVT, tachypnea, and tachycardia, as well as high rates of classic PE risk factors observed among patients with PE. Future studies should attempt to include only patients that would not normally be diagnosed with PE in the ED in order to more closely approximate the risk in truly undifferentiated patients.