Efficacy and Safety of Tamsulosin in Medical Expulsive Therapy for Distal Ureteral Stones with Renal Colic: A Multicenter, Randomized, Double-blind, Placebo-controlled Trial

Ye et al. *Eur Urol* 2017;38(17): 30972–77.

P: Adult patients with distal ureteral stones and renal colic
I: Tamsulosin 0.4 mg daily
C: Placebo
O1: Stone expulsion rate (confirmed by CT) over 28-d surveillance period
O2: Time to stone expulsion, use of analgesics, incidence of adverse events
D: Multicenter, prospective, randomized, double-blind, placebo-controlled trial

What we already know:

- Medical expulsive therapy (MET) refers to the use of alpha-adrenergic receptor antagonists (ex. tamsulosin) to induce smooth muscle relaxation of the ureter, thus promoting stone expulsion
- Previous trials have shown tamsulosin achieves higher stone expulsion rates and lowers analgesic requirements
- Current CUA guidelines recommend that MET with alpha-blockers should be given to patients with distal ureteral stones < 10mm (Level of Evidence 1a, Grade A)
- However, recent high quality RCTs question the effectiveness of alpha-blockers for the management of ureteral stones

Methods:

- Multicenter, prospective, randomized, double-blind, placebo-controlled trial conducted from September 2011 to August 2013 across 30 centers in China
- Computer-generated randomization in 1:1 ratio with allocation concealment and double-blinding – secured study e-packs with identical capsules
- Intervention: tamsulosin 0.4 mg (or placebo pill for control group) daily until stone passage, up to 28d or the need for intervention
    - All pts were seen weekly for repeat non-contrast CT and dispenses of allocated medication
    - All pts instructed to drink 2L water/d, collect urine stone w/ sieve, diclofenac 50 mg PR PRN, diary cards to record reactions to the intervention drug or placebo
- Data collection:
    - Pts with unconsciously expulsed stone, with stone-free ureter on final CT – the date of last positive stone status recorded
    - Failed intervention = unsuccessful stone expulsion within 28d, and discontinuation and intervention prior to end of trial due to pain, adverse events, or desire for stone removal
- *Primary outcome*: stone expulsion rate (confirmed by CT) over 28-d surveillance period
- *Secondary outcomes*: time to stone expulsion, use of analgesics, incidence of adverse events
- Statistical analysis:
    - Sample size ≥ 3100 (95% power, type I error rate 0.01). Enrolled 3450 patients to account for 10% drop out rate.
    - Primary analysis: intention-to-treat (ITT) analysis (excluded pts w/ stone expulsion prior to start of trial, pts withdrew consent, pts lost to follow-up)
    - Pre-specified subgroup comparison (logistic regression analysis for binary outcomes) of the difference in rate of passage for distal ureteral stones to explore effects of age, sex, stone side, and stone size

Inclusion Criteria:

- Adults 18-60 yo admitted to ED for renal colic with a single ureteral stone confirmed by KUB x-ray, US, or non-contrast CT
- Unilateral stone in distal ureter (below SI joint on CT) with largest dimension of 4-7mm

Exclusion Criteria:

- Fever
- Hypotension (SBP <100)
- UTI
- Severe hydronephrosis
- Renal insufficiency (eGFR < 60)
- Abnormal anatomy (ex. solitary kidney, horseshoe kidney, duplex urinary system, urethrostenosis, ureter strictures)
- Diabetes mellitus
- Known or suspected pregnancy
- Current use of alpha-adrenoceptor antagonists or corticosteroids
- Previous history of ipsilateral ureteral surgery, spontaneous stone expulsion, known/suspected allergy to study medications

Results:

- 3450 patients assessed for eligibility
  - 60: Excluded (42 did not meet inclusion criteria, 15 declined participation, 3 other reasons)
- 3390: Randomized and enrolled
  - 1695: Randomized to tamsulosin → 1642 included in primary analysis (22 excluded, 31 lost to f/u)
  - 1695: Randomized to placebo → 1654 included in primary analysis (18 excluded, 23 lost to f/u)
- Demographic and baseline characteristics were similar between the two groups, including average stone size (tamsulosin – 5.8mm, placebo – 5.7mm)
- Primary outcome:
  - Tamsulosin had higher expulsion rate vs. placebo (86% vs. 79%; p<0.001)
- Secondary outcomes:
  - Tamsulosin had shorter time to expulsion vs. placebo (148.3 vs 248.7h; p<0.001)
  - Tamsulosin had less recurrence of renal colic vs. placebo (1.9% vs. 9.4%; p<0.001)
  - Tamsulosin group required less analgesics vs. placebo (89 vs. 236 mg; p<0.001)
  - Adverse events not significantly different between tamsulosin vs. placebo (5.6% vs. 5.1%, p=0.54)
- Subgroup analysis:
  - Tamsulosin had specific therapeutic benefit for large distal ureteral stones >5mm (2.05, 95%CI 1.64-2.54; p<0.01)
  - No subanalysis difference with regards to age, gender, laterality

Strengths:

- Addresses a clinically important, patient-centered question for a common diagnosis in the ED
- Largest multicenter, prospective, randomized, double-blind, placebo-controlled trial to have investigated efficacy of tamsulosin
- One of few trials to use CT imaging to evaluate stone status
- Used a more conventional end point compared to previous trials (ex. 28d expulsion rate, vs. 4wk reintervention rate)
- Compared to recent trials, was adequately powered to evaluate passage of stones >5mm
- Results of study consistent with recent RCT which showed no effect of MET for stone size ≤5mm

Limitations:

- All patients were recruited in China – limits generalization to international populations
- Primarily designed to evaluate difference in larger stones (4-7mm largest dimension)
- Only included distal ureteral stones, cannot extrapolate these results to more proximal stones
- Severe hydronephrosis is an ambiguous exclusion factor that may bias pt selection – stable pts without complicating factors and hydronephrosis can often be managed as outpatients
- Flomax dose chosen based on BPH dosing

Study Conclusions:

- Use of tamsulosin is safe and clinically effective (i.e. higher passage rate, shorter time to expulsion) in pts w/ distal ureteral stones and renal colic, especially for expulsion of stones >5mm
- Tamsulosin does not demonstrate any significant effect on expulsion for stones ≤5mm
- Tamsulosin significantly relieved renal colic, and reduced use of analgesia by 50% compared with placebo

Validity:

- Study conducted across multiple EDs in China, which limits applicability to the Canadian patient population and healthcare system
- However, tamsulosin is the same medication used in Canada for MET in similar dosing

Presenter's Clinical Bottom Line: Tamsulosin is effective for stone expulsion in pts w/ uncomplicated large (>5mm) distal ureteral stones and renal colic. Tamsulosin also significantly decreases recurrence of renal colic and use of analgesia.

An Age-Adjusted D-dimer Threshold for Emergency Department Patients With Suspected Pulmonary Embolus: Accuracy and Clinical Implications

Sharp *et al.,* Ann Emerg Med. 2016 Feb;67(2):249-57

P: Emergency department encounters with patients older than 50 years with suspected PE
I: not applicable
C: not applicable
O_1: Sensitivity, specificity, PPV, NPV of an age-adjusted D-dimer threshold
O_2: (1) Compare age-adjusted limit to standard threshold of 500ng/dL and to 1000ng/dL
(2) Frequency of PE in patients with advanced imaging;
(3) Proportion of patients receiving imaging with negative D-dimer;
(4) Proportion who did not receive imaging with positive D-dimer;
(5) Number of "missed" PEs within 30 days of initial ED visit
D: Retrospective chart review

What we already know:

- Current recommendations are for an initial D-dimer in low to moderate risk patients prior to DI.
- The conventional threshold for a positive test result is <500 ng/dL (<0.50 mg/L in Edmonton)
- Among patients with a positive D-dimer, only a small proportion of these are actually PEs
- Specificity of the D-dimer worsens with age. This leads to more false-positives, more imaging, and potentially more contrast-induced complications.
- Prior reports suggest age-adjusted (age x 10years) D-dimer threshold for patients >50 years. These prior studies have been limited by small sample sizes and referral center bias.
- This study addresses the false negative rate for PE with age adjusted D-dimer in a large sample

Methods:

- 14 EDs within Kaiser Permanente Southern California between 2008 and 2013
- Retrospective chart review of all ED encounters for patients older than 50 who had a D-dimer test with a chief complaint considered relatable to PE (i.e. CP, SOB)
- All the hospitals used a rapid, highly sensitive immunoturbidimetric assay
- *Primary outcome:* Sensitivity, specificity, positive predictive value (PPV), and negative predictive value (NPV) were calculated using age-adjusted D-dimer limits
- *Secondary outcomes:* Proportion of patients receiving advanced imaging (CT pulmonary angiography, VT scan, or chest magnetic resonance angiography), proportion of patients receiving imaging with a (-) D-Dimer, and proportion who did not receive imaging with a (+) D-dimer

- Used *International Classification of Diseases, Ninth Revision (ICD-9)* diagnosis codes to identify patients with a diagnosis of acute pulmonary embolism
- Individualized D-dimer cutoffs were used: patient's age (in years) X 10
- Identified patients who did not receive a diagnosis of PE at initial ED encounter but subsequently received PE diagnosis within 30 days
    - Chart review performed to determine if PE was missed on initial encounter; research team discussed each case. If pt deemed to likely have had PE at initial ED visit then they were subsequently reclassified into PE outcome group for sensitivity/specificity calculations.
- Chart review also performed of patients who received a diagnosis of PE but had no imaging (n=27), 7 patients were found to have no PE
- Provided estimates to predict the number of cases of contrast-induced nephropathy (CIN), episodes of severe renal failure, and deaths related to CIN, using previously published prospective findings.

Inclusion Criteria:
- Age >50
- D-dimer test ordered
- Chief complaints considered related to possible PE

Exclusion Criteria:
- Encounters with Doppler ultrasound for possible deep vein thrombosis
- Encounters without chest related chief complaint
- PE diagnosis in the previous 90 days

Results:
- 31 094 ED patients older than 50 who were evaluated for PE between 2008 and 2013
- Mean age 65, 61% female
- Age-adjusted dimer was 92.9% sensitive and 63.9% specific for detecting PE
    - PPV 4.1%, NPV 99.8%
- Standard threshold (500ng/dL) gave sensitivity of 98.0% and specificity of 54.4%
    - PPV of 3.4% and NPV of 99.9%
- Cut-off of 1000ng/dL gave 84.2% sensitive and 75.4% specific
    - PPV 5.4%, NPV 99.7%
- Number of missed or delayed PE diagnoses (false-negative D-dimer):
    - Age-adjusted cutoff: 36
    - 500ng/dL cutoff: 10
    - 1000ng/dL cutoff: 80
- Among patients with false negative results for each threshold, 1 patient died within 30 days of ED encounter, who was missed in all groups. This patient died in hospice with end-stage HF with a known PE, D-dimer was below 500ng/dL

	% (95% CI)				
Threshold	Sensitivity	Specificity	PPV	NPV	False Negative
500 ng/dL	98.0 (96.4–84.2)	54.4 (53.9–55.0)	3.4 (3.2–3.8)	99.9 (99.9–100)	2.0 (1.0–3.6)
1,000 ng/dL	84.2 (80.8–87.3)	75.4 (74.9–75.9)	5.4 (4.9–5.9)	99.7 (99.6–99.7)	15.8 (12.7–19.3)
Age adjusted	92.9 (90.3–95.0)	63.9 (63.4–64.5)	4.1 (3.7–4.5)	99.8 (99.8–99.9)	7.1 (5.0–9.7)

- Secondary outcomes:
    - 12 486 (40.2%) of patients received diagnostic imaging for PE. Of these, 1323 (10.6%) had a D-dimer <500ng/dL
    - For the 18 608 patients who did not receive DI, 17.6% had a D-dimer >500ng/dL
    - Estimated clinical consequences associated with different D-Dimer thresholds:

Table 3. Estimated clinical consequences associated with different D-dimer thresholds used to prompt imaging in the evaluation of low- to moderate-risk patients with suspected pulmonary embolus.*

	Clinical Consequence (95% CI)					
Threshold	**Diagnosed PE**	**Missed PE**	**Potential CTPAs**	**CIN**	**Severe Renal Failure**	**Death Related to CIN**
500 ng/dL	160 (144–174)	6 (0–16)	4,642 (4,582–4,702)	511 (418–650)	44 (15–92)	29 (7–73)
1,000 ng/dL	137 (115–159)	35 (28–40)	2,556 (2,473–2,639)	283 (230–359)	24 (8–51)	16 (4–40)
Age adjusted†	151 (133–169)	18 (10–26)	3,702 (3,632–3,772)	409 (333–520)	35 (12–74)	23 (6–58)

CTPA, CT pulmonary angiography; *CIN*, contrast-induced nephropathy.
*Estimates are based on the use of the most common mode of diagnostic imaging for PE, CT pulmonary angiography. Our estimates are based on sensitivities and specificities calculated from our sample of 31,094 ED patients aged 50 years or older and evaluated for PE, and on previously reported risks of CIN, severe renal failure, and associated death from CT imaging with contrast.[29] We report expected events per 10,000 suspected PE encounters.
†The age-adjusted threshold is derived by multiplying the patient's age by 10.

Strengths:
- Large trial (n=31 094 patients) at 14 EDs
- Addresses a clinically important, patient-centered question for a common diagnosis in the ED
- Clear explanation of which ICD codes and diagnoses were used in the calculations
- Clear explanation of which chief complaints were considered as a potential PE
- Same D-dimer assay used at all facilities

Limitations:
- Retrospective observational study design: lack of prospective data used to calculate sensitivity/specificity/PPV/NPV
- Chief complaints guided the chart review, which may have missed some patients with a final diagnosis of PE
- Used ICD codes derived from ED diagnosis as primary outcome
- Researchers not blinded
- Review of missed PEs was conducted by the research team who were not blinded to the final PE diagnosis
- Use of chart review as well as claims outside of health system within the 30 days of presentation to identify all missed PEs, but did not elaborate on how this was performed
- Did not incorporate clinical decision-making tools into analysis (i.e. Wells score, PERC, Geneva scores)
- For clinical consequences of DI, this study only estimated risk based on previously published data. They did not compare to actual adverse events.

Study Conclusions:
- Using an age-adjusted D-Dimer was more specific but less sensitive than the conventional threshold. It had a similar NPV and false negative rate (99.8% and 7.1%, respectively) when compared to the previously established 500ng/dL threshold (99.9% and 2.0%); resulted in 20% fewer false positives
- Estimated that using an age-adjusted D-dimer would miss 26 more pulmonary embolisms than the current threshold, but would prevent 322 cases of CIN, 29 cases of severe renal failure, and 18 deaths related to CIN, although this data is based on retrospective chart analysis.
- Need to balance specificity and sensitivity. The current trend is a cut-off that detects minor, nonlife-threatening PEs, which are of uncertain significance.

Validity:
- Unclear if population presenting to EDs in Southern California is applicable to local population
- Retrospective chart review may have missed diagnoses of PE that subsequently presented outside of the Kaiser Permanente catchment area

Presenter's Clinical Bottom Line:
- Using an age-adjusted D-dimer test has a similar false NPV and false negative rate and has higher specificity as compared to the conventional 500ng/dL cutoff, and may reduce the incidence of contrast-related adverse events.

EBM PEARL: Interquartile Range (IQR)

What is it?

- A measure of variability in results to describe statistics of continuous variables
- IQR = Q3 – Q1 (i.e. 75th percentile minus the 25th percentile)
- Reflects the distance taken up by the innermost 50% of the data

Why do we use it?

- Better measure of variation than the regular range (i.e. max value – min value).
- IQR doesn't take outliers into account, rather it cuts them out of the dataset and only focuses on the middle percent of the data.
- Useful when the data are not symmetrically distributed

What do the IQR numbers mean?

- If the IQR is small then you know the data are mostly close to the median
- If the IQR is large then you know the data are spread out from the median

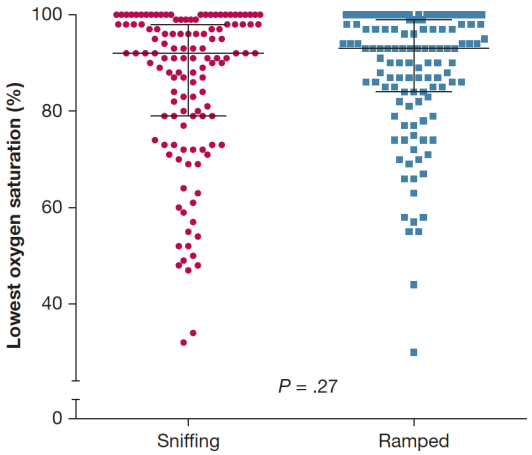

Figure 3 – *Lowest arterial oxygen saturation by study group. The primary outcome of lowest arterial oxygen saturation between induction and 2 minutes after completion of endotracheal intubation (lowest oxygen saturation) is displayed for patients randomized to the sniffing position (circles) and the ramped position (squares). Horizontal bars represent median and interquartile range.*

Checklists and Upright Positioning in Endotracheal Intubation of Critically Ill Patients (Check-UP) Trial: A Multicenter, Randomized Trial of Ramped Position vs Sniffing Position During Endotracheal Intubation of Critically Ill Adults

Semler et al. *Chest* 2017;152(4): 712-722

P: Adult ICU patients undergoing endotracheal intubation (ETI)
I: Intubation in the ramped position (head of the bed elevated to 25 degrees)
C: Intubation in the sniffing position (torso supine, neck flexed, and head extended)
O1: Lowest arterial oxygen saturation measured by pulse oximetry (SpO2) between induction and two minutes after successful intubation
O2: Incidence of hypoxemia (SpO2 <90%), severe hypoxemia (SpO2 <80%), desaturation (SpO2 decrease >3%), Cormack-Lehane grade, difficulty of intubation, time from induction to successful intubation
D: Multicenter, non-blinded, randomized controlled trial

What we already know:

- Hypoxemia is a common complication during ETI of critically ill adults, and is linked to complications including cardiac arrest and death
- Elective ETI in the ramped position improves FRC and laryngeal anatomy, resulting in improved glottic view and decreased time to successful intubation
- Despite the promising data from preoperative studies, the optimal position during emergent intubation outside of the OR remains unclear

Methods:

- 2x2 factorial design (part of "Checklists and Upright Positioning in ETI of Critically Ill Patients (Check-UP) Trial)
- Randomized, multicenter, pragmatic, non-blinded trial conducted from July 2015 to July 2016 at ICUs in 4 tertiary care centers in the US
- Randomized in a 1:1 ratio using computer-generated blocks stratified by study site
- Group allocation was concealed in sealed opaque envelopes until patients qualified
- Interventions:
  - *Intervention (ramped position)*: electronic bed used to elevate HOB to 25 deg while keeping the lower half parallel to the floor (similar to previous studies)
  - *Control (sniffing position)*: bed horizontal with towels/blankets placed under the pt's head to achieve neck flexion and head extension
  - All other aspects of the intubation procedure were at the discretion of the clinical team
- Data collection:
  - Independent observers, with accuracy assurance carried out on a 10% convenience sample
  - Subjective difficulty, glottic view, and complications were reported by the operator
  - Baseline characteristics, pre- and post-laryngoscopy management, and clinical outcomes were collected from medical records by study personnel
- Outcomes:
  - *Primary outcome*: lowest SpO2 between induction and 2 minutes after successful intubation
  - *Secondary outcomes*: incidence of hypoxemia (SpO2 <90%), severe hypoxemia (SpO2 <80%), desaturation (SpO2 decrease >3%), Cormack-Lehane grade, operator-reported difficulty of intubation, number of laryngoscopy attempts, and time from induction to successful intubation
- Statistical analysis:
  - Sample size 260 (80% power, 0.05 α-level to detect an absolute difference in SpO2 of 5%)
  - Primary analysis: intention-to-treat analysis
  - 4 pre-specified secondary analyses: effect of intervention on secondary and tertiary outcomes; subgroup analysis on effect of intervention on primary outcome relative to pre-specified pt and procedural characteristics; per-protocol analysis; linear regression modelling of group assignment and primary outcome

Inclusion Criteria:

- ICU patients ≥ 18 years-old undergoing ETI by critical care or pulmonary fellows
- Use of sedation and neuromuscular blockade

Exclusion Criteria:

- Urgent intubation that precluded randomization
- If treating physicians felt that a specific position was indicated

Results:

- 311 ICU patients assessed for eligibility
  - 2: Did not meet inclusion criteria (1 <18 yrs, 1 for awake intubation)
  - 49: Excluded (43 intubated too urgently, 6 felt to require a specific position)
- 260: Randomized and enrolled
  - 130: Randomized to sniffing position (129 = sniffing position, 1 = ramped position)
  - 130: Randomized to ramped position (128 = ramped position, 2 = sniffing position)
- Group characteristics
  - Similar baseline group characteristics (including APACHE II score, and BMI), active medical conditions at intubation, pre-intubation difficult airway characteristics, pre-oxygenation strategies, induction agents, laryngoscopic device, and operator training
  - In both groups, the lowest SpO2 in 6hrs preceding ETI was 91%, SpO2 at induction was 99%
  - Most common active medical issues: sepsis, ALOC, and pneumonia; with hypoxemic respiratory failure as the indication for intubation in 60% of cases

- *Primary outcome*: no significant difference in the median lowest SpO2 between the sniffing and ramped position groups (p=0.27)
  - Sniffing group: 92% (IQR 79%-98%)
  - Ramped group: 93% (IQR 84%-99%)
- *Secondary outcomes*:
  - The glottic view and intubation difficulty was worse in the ramped group
    - Cormack-Lehane Grade III or IV: Sniffing 11.6% vs Ramped 25.4% (p=0.01)
    - Operator reported "difficult" intubation: Sniffing 4.6% vs Ramped 12.3% (p=0.04)
  - The rate of failed intubation attempts was higher in the ramped group
    - 1st attempt success: Sniffing 85.4% vs Ramped 76.2% (p=0.02)
    - More than 3 attempts at laryngoscopy: Sniffing 2.3% vs Ramped 7.7% (p=0.02)
    - Requiring a bougie: Sniffing 6.2% vs Ramped 19.2% (p=0.002)
    - Requiring a second laryngoscopy device: Sniffing 6.2% vs Ramped 16.2% (p=0.01)
  - There were no significant differences in other oxygenation secondary outcomes
- Secondary analyses:
  - No significant difference in tertiary outcomes of ventilator free days, ICU days, or in-hospital mortality
  - In post-hoc analysis, the operator's previous intubating experience, and prior experience in the ramped position did not alter the primary outcome - although this data was only available for 73.8% of intubations

Strengths:

- Relevant clinical question for EM as data from the preoperative setting doesn't necessarily translate to emergent non-elective situations outside of the OR
- First large multicenter RCT evaluating ramped vs. sniffing position outside of the operative setting
- Minimal deviation from protocol *(3 total)*
- Group characteristics were well matched, including important factors such as: APACHE II score, preoxygenation method, oxygenation status prior to induction, and difficult airway characteristics
- Ramped positioning technique was standardized and well match to similar previous studies

Limitations:

- Factorialised design that evaluated the same primary outcome – potential interaction?
- Absence of blinding due to the nature of the study and intervention
- Not powered to detect differences in pt subgroups (ex. pts with severe hypoxemia)
- No prespecified algorithm for preoxygenation in the study protocol
- Ramping in this study was achieved by raising the HOB rather than using blankets or wedges, which is how we typically ramp in the ED. Raising the HOB to achieve the ramped position could have made intubation more difficult.
- Only 73.8% of cases had data regarding operators' prior intubation experience, and experience in the ramped position
- Study only included trainees (critical care and pulmonary fellows), with the average operator having performed 60 previous intubations
- Ramped position may have been more difficult to maintain compared to studies in the OR setting due to difference in bed construction and ease of airway access

Study Conclusions:

- The ramped position did not significantly improve lowest arterial oxygen saturation in critically ill adult ICU patients requiring emergent intubation, but may actually worsen glottic view, resulting in more difficult intubations that require repeated attempts

Validity:
- Study conducted in ICU setting better approximates practice in the ED compared to previous studies done in the OR (similar bed construction and patient population)
- Operators are critical care and pulmonary fellows with less experience in ramped position, therefore findings may generalize to trainee performed airway management; unclear if results would be similar in experienced operators
- Experience in ramped position may differ between sites depending on specialty and training

Presenter's Clinical Bottom Line: physiologic and anatomic benefits of the ramped position observed in elective ETI were absent and/or worsened in emergent ETI of critically ill patients

Effect of the Pulmonary Embolism Rule-Out Criteria on Subsequent Thromboembolic Events Among Low-Risk Emergency Department Patients: the PROPER Randomized Clinical Trial

Freund *et al*., JAMA. 2018 Feb 13;319(6):559-566.

P: Patients presenting to the ED with a suspicion of PE
I: PERC score of zero followed by no further diagnostic testing
C: Usual care
O1: Thromboembolic event during 3-month follow up
O2: Rate of CTPA, median length of stay in ED, rate of hospital admission
D: Multicenter, crossover cluster-randomized clinical non-inferiority trial

What we already know:
- The diagnostic pathway for PE in the ED is well established, with evaluation of clinical probability, followed by either D-dimer testing or diagnostic imaging.
- The PERC rule was derived in 2004 as a way to rule out PE in patients with low pretest probability in which further diagnostic testing would not be necessary. It is an 8-item set of clinical criteria.
- A meta-analysis of observational studies reported the prevalence of PE in PERC-negative patients to be <1%, but this hasn't been studied in a prospective trial.
- The PERC strategy vs usual diagnostic strategy has not been evaluated in a prospective, randomized study for non-inferiority.
- Nor has there been a randomized study to assess whether the PERC rule reduces the need for D-Dimer or CTPA testing without missing a significant number of PEs.

Methods:
- 14 EDs in France participated in this study for two 6-month periods separated by a 2-month washout period (the EDs switched from control to PERC and vice versa).
- Trial recruitment occurred from August 2015 to September 2016, follow-up ended in December 2016.
- All patients provided signed informed consent before inclusion, and the study reporting followed the CONSORT statement for cluster-randomized trials.
- Computer generated block randomization, with the units of randomization as the EDs.
- Each ED was randomized to start with a 6-month control period (usual care) followed by a 6-month intervention period (PERC-based strategy), or in reverse order. These periods were separated by a 2-month washout period.
- Intervention: diagnostic work-up included initial calculation of PERC score. If PERC score was zero, PE was ruled out without subsequent testing
    - If PERC score positive, usual diagnostic strategy was applied per 2014 European Society of Cardiology guidelines
- Control: After inclusion and classification as low probability by gestalt, age-adjusted D-dimer testing was performed followed by CTPA if positive.

  - CTPA with emboli was considered positive, including isolated sub segmental PE
  - If CTPA inconclusive, patients underwent V/Q or lower leg Doppler ultrasound.
- All patients were observed for 3 months and interviewed by phone at the end of this period using a structured questionnaire. If recurrent or worsening symptoms, they were instructed to return to the same ED.
- *Primary outcome:* occurrence of a symptomatic thromboembolic event during the 3 month follow up period that was not diagnosed during inclusion visit.
- *Secondary outcomes*: proportion of patients investigated with CTPA, rates of CTPA-related adverse events requiring therapeutic intervention, length of stay in ED, rate of hospital admission or readmission, onset of anticoagulation regimen, severe hemorrhage in patients with anticoagulation therapy, and all-cause mortality at 3 months.
- Adjudication committee confirmed occurrence of all suspected thromboembolic events and adjudicated all deaths as to whether or not they were related to a PE. This committee had three blinded experts.
- Statistical analysis:
  - Assumed the primary end point rate in the control group would be 1.5% based on previous diagnostic studies. Non-inferiority margin for the difference of the primary end point between the 2 groups was set at 1.5%.
  - Sample size 1624 (80% power, 0.05 α-level). After taking into account cluster design effect and allowing for 5% nonevaluable patients, a sample size of 1920 patients was required.
  - Primary end point analysis was performed based on the per-protocol population. Non-inferiority was assessed.
  - The secondary endpoints were compared under a superiority hypothesis on the ITT population.

Inclusion Criteria:
- New onset presence or worsening of SOB or CP
- Low clinical probability of PE, estimated by the treating MD's gestalt as an expectation below 15%

Exclusion Criteria:
- Obvious etiology other than PE (pneumothorax, acute coronary syndrome)
- Acute severe presentation (hypotension, SpO2<90%, respiratory distress)
- Contraindication to CTPA: (CrCl <30mL/min, known allergy to IV contrast)
- Pregnancy
- Inability to be followed up
- Pre-existing anticoagulation therapy

Results:
- 1916 patients were recruited during the study period: 962 patients in PERC group and 954 patients in control group

Group characteristics:
- PE was diagnosed initially in 2.7% of the control group versus 1.5% of the PERC group (difference 1.3%, 95% CI -0.1%-2.7%, p=0.052)
- 2 post-hoc sensitivity analysis were completed to adjust for this: one after exclusion of 150 very-low risk patients from PERC group, the other after addition of 175 *simulated* patients with no work-up for PE in the control group

Primary outcome:
- In PERC group, 459 (48%) of patients were PERC-negative
- PE was diagnosed at the initial visit in 40 (2%) of patients overall
  - 14 (1.5%) in PERC group vs 26 (2.7%) in the control group (95% CI -0.1% to 2.7%, p=0.052)
- For PE's diagnosed in follow-up after the initial visit, there was 1 thromboembolic event in the PERC group (0.1%) and none in the control group (95% CI -∞ % to 0.8%)

- Only missed PE was a young male with chest pain and no previous medical history, who was seen the next day with chest pain, positive D-dimer, inconclusive CTPA, and subsequent VQ showing sub segmental defects

- An ITT analysis with worst case scenarios that assumed all lost follow-up patients met the primary end point, resulted in a 0.2% difference in the primary end point (95% CI -∞ % to 1.6%, p=0.12))

Secondary outcomes:

- CTPA performed in 349 (18%) of cases, of which 39 (11%) were positive for PE
- PERC group patients had significantly fewer CTPAs than the control group, 13% vs 23%, (difference 9.7% [95% CI, 6.1% to 13.2%])
- PERC group had significant reduction in median ED length of stay (4h36min vs 5h14min, p <0.001)
- Hospital admission rates: 13% in PERC group vs 16% in control group (95% CI 0.1% to 6.6%)
- No significant difference in all cause-mortality at 3 months (p >0.99), 3 month hospital readmission rate (p=0.051), and no severe hemorrhage or severe adverse events related to CTPA

- In the two post-hoc sensitivity analyses, PERC rule was found to be non-inferior and rate of CTPA was reduced significantly
- Adverse events:
  - 5 deaths, none considered likely to be related to PE (as per adjudication committee)
  - 1 thromboembolic event in PERC group after 3 month follow up (0.1%), none in the control group

Table 3. Main Outcomes in the Study of Pulmonary Embolism Rule-Out Criteria

Characteristics	No. (%) PERC	No. (%) Control	Mean Difference, % (95% CI)	Number Needed to Treat	*P* Value
Intention-to-treat population, No.[a]	962	954			
Thromboembolic event at 3 mo (primary outcome)	32 (3)	29 (3)	0.2 (−∞ to 1.6)[b]		.12
CTPA performed	129 (13)	220 (23)	9.7 (6.1 to 13.2)	10	<.001
Length of ED stay, median (IQR), h:min	4:36 (3:16 to 6:21)	5:14 (3:50 to 7:18)	−00:36 (−1:08 to −0:04)		<.001
Hospital admission	121 (13)	152 (16)	3.3 (0.1 to 6.6)	30	.04
Anticoagulation therapy introduced	21 (2)	33 (3)	1.3 (0.3 to 2.9)	78	.09
Hospital readmission at 3 mo	43 (4)	62 (7)	2.1 (−0.1 to 4.3)	48	.051
All-cause death at 3 mo	3 (0.3)	2 (0.2)	0.1 (−0.5 to 0.7)		>.99
Per-protocol population, No.[a]	847	902			
Thromboembolic event at 3 mo (primary outcome)	1 (0.1)	0	0.1 (−∞ to 0.8)[b]		
CTPA performed	114 (14)	211 (23)	9.9 (6.2 to 13.6)	10	<.001
Length of ED stay, median (IQR), h:min	4:34 (3:12 to 6:14)	5:12 (3:50 to 7:17)	−00:37 (−1:11 to −0:02)		<.001
Hospital admission	101 (12)	139 (15)	3.5 (0.2 to 6.8)	29	.03
Anticoagulation therapy introduced	19 (2)	28 (3)	0.8 (−0.8 to 2.5)	116	.27
Hospital readmission at 3 mo	38 (4)	62 (7)	2.4 (0.1 to 4.7)	42	.03
All-cause death at 3 mo	1 (0.1)	1 (0.1)	0.01 (−0.4 to 0.4)		>.99

Abbreviations: CTPA, computed tomographic pulmonary angiography; ED, emergency department; IQR, interquartile range; PERC, pulmonary embolism rule-out criteria.

[a] Mean difference and its 95% CI. The full analysis set comprised the 1916 patients who were cluster-randomized and included in the study. After the exclusion of wrongly included patients, those lost to follow-up, those with protocol deviations, or those who withdrew consent, the per-protocol population comprised 1749 patients.

[b] One sided 95% CI.

Strengths:

- Multicenter, randomized trial
- Addressed a relevant clinical question for a common rule that we use in the ED
- Each ED participated in both the intervention and control groups
- Patients were followed up at a 3-month period

Limitations:

- Inclusion criteria required physician gestalt, which is difficult to standardize
- Patients were not individually randomized, and bias was introduced by the cluster design
- Study groups were not similar in their baseline rate or PE, so this challenges the statistical analysis
- Simulated patients were used to try and create study and control groups with similar baseline characteristics but arguably simulated patients should not be used to evaluate the safety of a clinical decision making tool

- The cohort of patients in this study were at very low risk of PE (approx. 2%). As a consequence, 48% of the patients in the PERC group were PERC negative, meaning this was a relatively healthy population. Thus, the study may not have ben adequately powered to detect differences in outcomes.
- CTPA was defined positive if it showed an isolated sub-segmental PE. This adds some controversy as these PEs could be left untreated.

Study Conclusions:
- PERC strategy vs conventional strategy did not result in an inferior rate of thromboembolic events over 3 months.
- In the PERC group there are fewer initial PEs diagnosed than the usual care group, with little difference in clinically significant thromboembolic events at 3 months.
- Potential tolerable risk to patient safety as small sub-segmental PEs can often be left untreated

Validity:
- This study had a very low prevalence of PE in low-risk patients. May not be generalizable as there is a higher incidence of PE documented in previous European studies.
- The mean age in their sample was 44 years old, which is younger than many other studies and than many patients in our practice.

Presenter's Clinical Bottom Line:
- PERC strategy is a safe and feasible way to rule out PE in very low-risk, young, and healthy ED patients with no further diagnostic testing.